SIDS Initial Assessment Report

For

SIAM 23

Jeju (Korea), October 17-20, 2006

1. Chemical Name:	3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
2. CAS Number:	4098-71-9
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D-53048 Bonn
4. Shared Partnership with:	Bayer MaterialScience AG: Dr. J. Brück (Germany) Bayer MaterialScience LLC: Robin Ruppel-Kerr (USA) Degussa North America: Alex Bell (USA) Rhodia Operations: Dr. Bernard Hendrickx (France)
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	Degussa AG, Germany Contact person: Dr. R. Ebert Bennigsenplatz 1 D-40474 Duesseldorf
• Process used	see next page
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Program?	by ICCA initiative
7. Review Process Prior to the SIAM:	last literature search (update): 26 April 2006 (Human Health): databases Biosis, Embase, Medline, Toxline, Scisearch; search profile CAS-No. and special search terms 31 March 2006 (Ecotoxicology): databases Beilstein, Chemlist and Chemical Abstracts; search profile CAS-No. and special search terms
8. Quality check process:	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA. 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: 13 September 2006
10. Date of last Update:	-

11. Comments: -

OECD/ICCA - The BUA* Peer Review Process

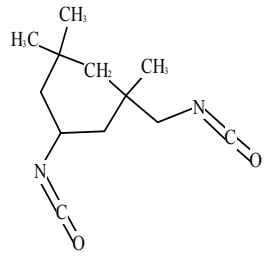
Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

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

In case of data gaps, review of testing plan or rationale for not test

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	4098-71-9
Chemical Name	3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The only information available on the toxicokinetics of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate results from a test chamber exposure of three volunteers to concentrations of 0.0121, 0.0177 and 0.0507 mg /m^3 for 2 hours at day 1, 3, and 5, respectively. After hydrolysis of blood and urine samples the corresponding amine, 3-aminomethyl-3,5,5-trimethylcyclohexylamine, was detected in urine but not in plasma. The average urinary excretion was 27 % and urinary elimination half-time was 2.8 hours. No 3-aminomethyl-3,5,5-trimethylcyclohexylamine was observed in samples without hydrolysis from exposed persons.

Assessment of the acute inhalation toxicity data indicates that effects caused by exposure to respirable aerosols of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate were confined predominantly to the respiratory tract. Clinical signs (serous nasal discharge, bradypnea, stridor) indicated respiratory distress. There are two studies according to OECD TG 403 with LC_{50}-values (4 h, rat) of approximately 40 mg/m^3 and 31 mg/m^3, respectively. Special investigations with male rats revealed airway rather than pulmonary irritation, which became evident after exposure of a concentration causing some lethality (25 mg/m^3, 1 x 6 h). The dermal LD_{50} determined in compliance with OECD TG 402 was > 7000 mg/kg bw for rats. Non-specific, transient signs of intoxication (sedation, ataxia) and obvious skin irritation at the application site were reported. The available studies revealed a low oral toxicity with LD_{50}-values (rat) of 4814 - 5490 mg/kg bw. Toxic symptoms after oral administration included decreased activity, piloerection, and diarrhea.

In two studies performed according to OECD TG 404, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be corrosive to the rabbit skin. Strong irritation was observed in rabbit eyes when tested according to OECD TG 405. The toxicity studies indicate that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate vapor causes irritation of the upper respiratory tract. In a study with volunteers, a perception threshold for irritation of 0.64 mg/m^3 was determined for short-term (1-5 minutes) exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be skin sensitizing in the Buehler test according to or equivalent to the EU Directive, in the guinea pig maximization test comparable or according to OECD TG 406, in the mouse ear swelling test, and in the open epicutaneous test. Skin sensitization was also observed in humans. One case report describes respiratory hypersensitivity after occupational exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. No validated animal model is available to assess the potential for respiratory sensitization or asthma in humans, and one animal study did not show respiratory tract sensitization when exposed by inhalation (challenge) following intradermal induction. However, due to the well known reactivity of diisocyanates, respiratory sensitization is likely to occur.

No repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (0.24, 1.05, and 4.1 mg/m^3; 6 hours/day, 5 days/week, 4 weeks; OECD TG 412) with male and female Wistar rats indicates the respiratory tract to be the target organ. Clinical signs of respiratory tract irritation (nostrils: red encrustations, stridor, nasal discharge, breathing sounds, hypothermia) are restricted to the high concentration rats.

The LOAEL is 1.05 mg/m^3 (histopathological changes in nasal cavity and larynx). At 4.1 mg/m^3 also the pharynx, trachea, and lungs are affected but the lesions are reversible within the four weeks of recovery with regard to the lung and trachea. However, lesions in the nasal cavity, the pharynx, and the larynx still occurred in some animals with minimal or slight degree. The most relevant systemic effects were a slight decrease in body weight gain in the high dose group and an increased leukocyte count in the peripheral blood in mid and high dose groups. The NOAEL is 0.24 mg/m^3.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was not genotoxic in bacterial systems *in vitro* (Ames test). Neither *Salmonella typhimurium* TA 102 nor *Escherichia coli* WP2 were tested in these Ames tests, however, this is an acceptable restriction because it can be assumed that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate has no oxidizing or cross-linking potential which may be detected by *S. typhimurium* TA 102 or *E. coli* WP2. In a chromosomal aberrations test performed on Chinese hamster ovary cells according to OECD TG 473, results were positive both with and without metabolic activation. *In vivo*, no mutagenic activity was detectable in a micronucleus assay on mice according to OECD TG 474 using the inhalation route of administration**.** However, as the micronucleus test only covers systemic genotoxic effects and given the well known high local reactivity of the substance local genotoxic effects cannot be excluded.

No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Histopathological results of a subacute 28-day inhalation study in rats according to OECD TG 412 showed no effects regarding the reproductive organs in concentrations up to 4.1 mg/m^3. Testes and ovary weights were also not affected. Taking into account the knowledge about the mode of action of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (local effects at sites of immediate contact clearly predominant), the lack of effect on the reproductive organs at 4.1 mg/m^3, and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m^3 it seems quite unlikely that this substance might have critical effects on testis in this low dose range.

In a nose-only inhalation study performed in accordance with OECD TG 414, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate had no adverse effects on the development of rats up to and including a dose level of 0.929 mg/m^3. A dose of 4.536 mg/m^3 was maternally toxic as evidenced by effects on respiratory tract and fur as well as decreased feed intake and impaired body weight gain. All signs of developmental toxicity observed at the 4.536 mg/m^3 exposure level, i.e. reduced fetal weights, delayed descensus testis, and slightly retarded ossification, were indicative of delayed fetal development and were only seen in the presence of maternal toxicity and thus considered secondary effects. There was no treatment related effect on incidence and type of fetal malformations up to and including 4.536 mg/m^3. The NOAEL for both maternal toxicity and developmental toxicity was 0.929 mg/m^3.

Environment

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is a colorless to yellowish, water sensitive liquid with a melting point of –60 °C, a boiling point (with decomposition) of approximately 310 °C at 1013 hPa, a water solubility of approximately 15 mg/l at 23 °C, a density of 1.058 g/cm^3 at 20 °C, and a vapor pressure of 0.064 Pa at 20 °C. The calculated log K_{OW} is 4.75. The most important values for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) concerning environmental behavior and ecotoxicity are a melting point of 10 °C, a vapor pressure of ca. 2 Pa at 20 °C, a measured log K_{OW} of 0.99 at 23 °C, and miscibility with water. This hydrolysis product was already evaluated in the OECD HPV Chemicals Program.

In the atmosphere, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is photodegraded by reaction with hydroxyl radicals with a calculated half-life of 1.8 days. For 3-aminomethyl-3,5,5-trimethylcyclohexylamine a half-life of 0.2 days is estimated. In water, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is expected to hydrolyze with a half-life of approximately 1 hour under environmental conditions, forming at high concentrations a white polymer, which is insoluble in water, or at low concentrations 3-aminomethyl-3,5,5-trimethylcyclohexylamine. Photolytic degradation in surface waters is expected to be of minor importance due to the absence of relevant chromophores in the chemical structure.

Biodegradation of the substance itself, which was not observed in a manometric respiratory test according to Directive 92/69 EEC, is irrelevant as a primary degradation step because hydrolysis is much faster. The hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine is not readily biodegradable (OECD 301A: 8 % degradation after 28 days). However, in a simulation test with activated, non-adapted sludge, a degradation of 42 % (including a minor, though not negligible contribution by adsorption to sludge) was measured after a contact time of 6 hours.

Distribution modeling according to Mackay Level I indicates that the main target compartments will be soil and sediment with approximately 43 % each, followed by water with about 10 %. A calculated log K_{OC} of 4.562 indicates very high adsorption to the organic phase of soils and sediments. For the hydrolysis product a log K_{OC} of 2.532 corresponds to a moderate potential for geoaccumulation. An estimated Henry's law constant of 0.000446 Pa m^3/mol

for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine indicates also very low volatility. Due to the rapid hydrolysis of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, volatilization will not be an important fate process for the environment. The calculated Henry's law constant of 0.941 Pa m^3/mol indicates low volatility from aqueous solution. Environmental distribution considerations for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate are of little relevance because the reaction with water is expected to eliminate the substance from the environment with a half-life of approximately 1 hour. The target compartment for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) is water (99.8 %) as outlined in separate documentation on this compound (the chemical was already evaluated in the OECD HPV Chemicals Program).

A calculated bioconcentration factor of 910 is irrelevant because rapid hydrolysis inhibits bioconcentration. The hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a log K_{OW} of 0.99 which indicates a low bioaccumulation potential.

For bacteria (activated sludge of a predominantly domestic sewage) an EC_{50} (3 h) of 263 mg/l (nominal) 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was determined according to OECD TG 209. The aquatic effects of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate relevant in the environment will be those of its hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine. For this substance, the $PNEC_{aqua}$ was derived in separate documentation (SIAM 18). For 3-aminomethyl-3,5,5-trimethylcyclohexylamine the lowest valid acute test results of aquatic testing determined for fish, daphnids, and algae were as follows:

Leuciscus idus (Directive 84/449/EEC, semistatic):	LC_{50} (96h) = 110 mg/l;
Daphnia magna (Directive 92/69/EEC, static):	EC_{50} (48 h) = 23 mg/l;
Desmodesmus subspicatus (Directive 88/302/EEC):	E_rC_{50} (72 h) > 50 mg/l; E_bC_{50} = 37 mg/l.

Long-term aquatic toxicity data for 3-aminomethyl-3,5,5-trimethylcyclohexylamine were available for two trophic levels:

Daphnia magna (OECD TG 202, semistatic):	NOEC (21 d) = 3.0 mg/l;
Desmodesmus subspicatus (Directive 88/302/EEC, static):	E_rC_{10} (72 h) = 11 mg/l; E_bC_{10} = 3.0 mg/l.

According to the EU Technical Guidance Document, an assessment factor of 50 was applied to the lower of two long-term results covering two trophic levels, i.e. NOEC for *Daphnia* = 3.0 mg/l. Thus a $PNEC_{aqua}$ of 60 µg/l for aquatic organisms was calculated for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

Exposure

Commercial 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is manufactured from 3-aminomethyl-3,5,5-trimethylcyclohexylamine by reaction with either phosgene or urea, the urea route requiring additionally an aliphatic alcohol and a thermal cleavage step where the alcohol is eliminated again and recycled into the process. The global production volume is about 25 000 to 35 000 tons annually, approximately 2/3 thereof in Germany (one production site). Two other production sites are located in the U.S.A. and a fourth one in France.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is exclusively used as an intermediate or monomer for polyurethanes or other polymers comprising urethane functions in various applications, particularly coatings, varnishes and impregnation for e.g. cars, floors, leather, cans and coils, and special (waterborne or hot melt) adhesives. 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is mainly not employed as such but used for the manufacture of polyurethane coating raw materials like pre-polymers and polyisocyanates.

By the formation of the polymer a high degree of conversion is required for an efficient cross-linking, which will bind at least one of the two isocyanate functions to the polymer. So exposure to the aquatic environment is not likely to occur from these uses.

In European product registers numerous products containing 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate for such purposes can be found, some of which are consumer products. In the consumer products, the concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is mostly below 1 %, while in products for professional use it may exceed 50 %.

Releases into the environment may occur during production of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, during formulation and use of formulations as well as from its use as a monomer for the production of polymers or other downstream products. In the Sponsor country, the annual release to the atmosphere from production is below 25 kg and there is no release to other compartments of the environment. Direct releases to the

hydrosphere can be excluded because the substance is produced and used in the absence of water.

The most probable human exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is through dermal contact or inhalation during manufacture or use. In the Sponsor country, exposure is controlled in occupational settings, and the substance could not be identified in the latest occupational exposure monitoring studies at a detection level of 0.001 mg/m^3. In the French production plant ten occupational exposure analyses have been performed between 2002 and 2005 and all concentrations were below 0.01 mg/m^3. In the U.S. production plant, the maximum concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate during the years 2003, 2004, and 2005 was 0.024 mg/m^3.

In an extensive occupational exposure survey for the German paper industry, the concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was always below the detection limit of 20 µg/m^3. In analyses in two car repair workshops, the maximum concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in air was 39 µg/m^3.

Consumers may occasionally be exposed to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate when using paint, varnish, or lacquers products including this substance. The frequency and duration of such operations are expected to be low, and the generally low concentration of the substance in such products will keep the doses low. Consumer use is expected to decrease as a consequence of recommendations of the producers since the producers have agreed to recommend in their safety data sheets that handling the substance "requires appropriate protective measures. These products may therefore be used only in industrial or trade applications. They are not suitable for use in homeworker (DIY) applications."

Because of the reactions of the chemical aquatic exposure to the environment will be very limited from these uses.

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

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute inhalation toxicity [target: respiratory tract], skin corrosion and serious eye damage, skin sensitization and predicted to be a respiratory tract sensitizer because it is a diisocyanate, genotoxicity in vitro). Based on data presented by the Sponsor country (relating to production by one producer which accounts for more than 50 % of global production and relating to the use pattern in several OECD countries), occupational and consumer exposure is anticipated to be low. Adequate risk management decisions are in place regarding the workplace. 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.

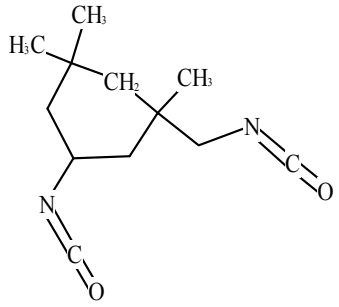
Environment: The chemical is currently of low priority for further work. The chemical (including its hydrolysis product) possesses properties indicating a hazard for the environment (acute aquatic toxicity to invertebrates). Based on the data presented by the Sponsor country (relating to production of one producer which accounts for more than 50 % of the 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: 4098-71-9
IUPAC Name: 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
Molecular Formula: $C_{12}H_{18}N_2O_2$
Structural Formula:



Molecular Weight: 222.29 g/mol
Synonyms: Isophorone diisocyanate
IPDI
1-(Isocyanatomethyl)-5-isocyanato-1,3,3-trimethylcyclohexane
1-Isocyanato-3,3,5-trimethyl-5-(isocyanatomethyl)cyclohexane
1-Isocyanato-3-(isocyanatomethyl)-3,5,5-trimethylcyclohexane
1-Isocyanato-3-isocyanatomethyl-3,5,5-trimethylcyclohexane
1-Isocyanato-5-(isocyanatomethyl)-3,3,5-trimethylcyclohexane
1,3,3-Trimethyl-1-(isocyanatomethyl)-5-isocyanatocyclohexane
3-(Isocyanatomethyl)-3,5,5-trimethylcyclohexyl isocyanate
3,3,5-Trimethyl-5-(isocyanatomethyl)cyclohexyl isocyanate
5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane
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The substance has two chiral centers on carbon atoms no. 1 and 3. Thus it is likely to be composed of two enantiomers.

1.2 Purity/Impurities/Additives

Purity: 99 - 100% (w/w)

Impurities: < 200 ppm hydrolyzable chlorine

< 400 ppm total chlorine

Additives: none

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

Property	Value	Reference
Physical state	liquid	Sax and Lewis (1987)
Melting point	-60°C	Sax and Lewis (1987)
Boiling point	ca. 310°C (1013 hPa, decomposition)	Auer (1989), INRS (1988)
Density	1.058 g/cm^3 (20°C)	Auer (1989), INRS (1988)
Vapor pressure	0.0635 Pa (20°C)	Bayer AG (1994)
Water solubility	ca. 15 mg/l (23°C) (rapid hydrolysis)	Infracor GmbH (2000)
Partition coefficient n-octanol/water (log K_{ow})	4.75 (calc.) (rapid hydrolysis)	Degussa AG (2006)
Henry's law constant	0.941 Pa m^3/mol (calc.)	Degussa AG (2006)
Soil sorption constant (log $K_{oc)}$	4.562 (calc.)	Degussa AG (2006)

The most important values for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) concerning environmental behavior and ecotoxicology are a melting point of 10°C, a vapor pressure of ca. 2 Pa at 20°C, a measured log K_{OW} of 0.99 at 23°C, and miscibility with water (OECD, 2004). This hydrolysis product was evaluated at SIAM 18 in 2004 and a SIAP is available.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Commercial 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate manufacturing can be done by phosgenation of 3-aminomethyl-3,5,5-trimethylcyclohexylamine:

NH_2-$C_{10}H_{18}$-NH_2 + 2 $COCl_2$ → OCN-$C_{10}H_{18}$-NCO + 4 HCl

This procedure is employed in the Sponsor country. During the phosgenation process hydrochloric acid is stripped and recycled to yield chlorine for the phosgene production. The isocyanate is subsequently purified by distillation (Bayer MaterialScience AG, 2006).

With the so-called urea route, which is used in the USA, the use of phosgene can be avoided. Instead of phosgene, urea plus excess aliphatic alcohol are reacted with the diamine leading to the corresponding diurethane. The diurethane is subsequently thermally cleaved leading to the originally employed alcohol, which is recycled into the process, plus the desired diisocyanate (Degussa North America, 2006):

NH_2-$C_{10}H_{18}$-NH_2 + 2 NH_2CONH_2 + 2 R-OH → R-O-CO-NH-$C_{10}H_{18}$-NH-CO-OR + 4 NH_3

R-O-CO-NH-$C_{10}H_{18}$-NH-CO-OR → OCN-$C_{10}H_{18}$-NCO + 2 R-OH

The urea route requires higher effort for purification due to the less specific reactivity of the urea molecule as compared to the phosgene molecule.

The production volume of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is estimated to be in the order of 25 000 to 35 000 tones annually world wide, approximately 2/3 thereof in Germany. The substance is manufactured in closed systems. Two production sites are in the EU (France, Germany) and two others in the U.S.A. (Bayer MaterialScience AG, 2006; Degussa North America, 2006; Rhodia Operations, 2006).

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is exclusively used as an intermediate or monomer for polyurethanes or other polymers comprising urethane functions in various applications, particularly coatings, varnishes and impregnation for e.g. cars, floors, leather, cans and coils, and special (waterborne or hot melt) adhesives. 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is mainly not employed as such but used for the manufacture of polyurethane coating raw materials like pre-polymers and polyisocyanates. As a cycloaliphatic diisocyanate it meets all important requirements for the manufacture of light-stable and weather-resistant polyurethanes (Danish Product Register, 2002; Degussa AG, 2001; Swiss Product Register, 2001).

The product registers of Denmark (151 products), Sweden (65 products) and Switzerland (285 products) report numerous products containing 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate for such purposes, some of which are consumer products (Sweden: 13; Switzerland 13). For Sweden no concentrations are given, in Switzerland for 12 out of 13 products the 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate concentration is reported to be below 1%. The concentrations in products for professional use may exceed 50% (Danish Product Register, 2002; Swedish Product Register, 2002; Swiss Product Register, 2001).

In order to avoid harm that may be caused when 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is used by private consumers, the producers have agreed to recommend in their safety data sheets that handling the substance “requires appropriate protective measures. These products may therefore be used only in industrial or trade applications. They are not suitable for use in homeworker (DIY) applications.” (Bayer MaterialScience AG, 2006; Degussa North America, 2006).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases into the environment may occur during production of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, during formulation and use of formulations as well as from its use as a monomer for the production of polymers or other downstream products. Information on environmental releases from production is available for 3 sites:

France: There is no release to atmosphere or water at this site. Solid waste from the production of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is incinerated in a specialized center (Rhodia PPMC, 2002).

Germany: The annual release to the atmosphere is below 25 kg. There is no release to other compartments of the environment (water, soil, biota) (Bayer MaterialScience AG, 2006).

U.S.A.: There is no contact with water. Fugitive emissions amount to 122 kg/year. Two drums of miscellaneous plant waste/month are disposed of off site (Degussa North America, 2006).

No further information on environmental exposure is available.

For releases of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate to the environment, it is expected that the following requirements are fulfilled: Direct releases to the hydrosphere can be excluded because the substance is produced and used in the absence of water. Any waste waters contaminated with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate would be expected to be subject to treatment processes where hydrolysis and adsorption would leave negligible 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate concentrations. The main route of releases to the environment is fugitive emissions, and on this route 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate will reach the hydrosphere at concentrations low enough to exclude polymerization. The consequence is that the aquatic effects of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in the environment will be those of its hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

2.2.2 Photodegradation

There are no experimental data available on the stability of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate and of its hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

In the atmosphere, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is photodegraded by reaction with hydroxyl radicals with a calculated rate constant of 8.8 x 10^{-12} cm^3/(molecule x s) corresponding to a half-life of 1.8 days based on a tropospheric OH radical concentration of 5 x 10^5 molecules cm^{-3} as a 24-h average (Degussa AG, 2006). Under the same conditions 3-aminomethyl-3,5,5-trimethylcyclohexylamine is rapidly photodegraded leading to a calculated half-life of 0.2 days. In view of the absence of chromophores in the structure, it is expected that photolytic degradation in surface waters will be of minor importance.

2.2.3 Stability in Water

Bayer AG (1999) studied the hydrolysis of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate under GLP standards using acetonitrile as solubilizer at the minimum concentration required to obtain a clear solution, i.e. 40%. They monitored the concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate at 23°C and at 11 minute intervals by GC/FID. The resulting half-life was 50 minutes.

Infracor GmbH (2000) investigated the hydrolysis rate of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate using a simplified preliminary test based on OECD TGs 105 (water solubility) and 111 (hydrolysis as a function of pH) as well as on corresponding EU methods. The half-life determined is below 7.2 hours, and a white, water-insoluble oligomer / polymer was observed as reaction product. The authors concluded that the water solubility of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is too low for an analytical monitoring of the test substance concentration which would be required to comply fully with OECD TG 111, even when a solubilizer is used. The observations reported are compatible with the results of Bayer AG (1999) described above.

At very low concentrations of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in water, the hydrolysis reaction can be described by the following equation:

$OCN\text{-}C_{10}H_{18}\text{-}NCO + 2\ H_2O \rightarrow HOOCNH\text{-}C_{10}H_{18}\text{-}NHCOOH$

$HOOCNH\text{-}C_{10}H_{18}\text{-}NHCOOH \rightarrow NH_2\text{-}C_{10}H_{18}\text{-}NH_2 + 2\ CO_2$

For the hydrolysis product less than 10% degradation was observed after 5 days at 50°C and pH 4, 7, and 9, corresponding to a $t_{1/2}$ of > 1 year at 25°C (OECD, 2004).

2.2.4 Transport between Environmental Compartments

The Henry's law constant governing the distribution of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate between aqueous solutions and air was calculated from water solubility and vapor pressure, see Table 1. An estimated value of 0.941 Pa m^3/mol (Degussa AG, 2006) indicates low volatility from aqueous solution according to the criteria of Thomas (1990). Due to the rapid hydrolysis volatilization will not be an important fate process for the environment. An in the same way estimated value of 0.000446 Pa m^3/mol for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine indicates very low volatility from aqueous solution (OECD, 2004).

A (calculated) log K_{OC} of 4.562 indicates very high adsorption to soil and sediment (Degussa AG, 2006). Due to the (calculated) log K_{OC} of 2.532, the hydrolysis product is expected to have a moderate potential for geoaccumulation (OECD, 2004).

Distribution modeling using Mackay, Level I (V 2.11) and based on the physico-chemical properties listed in Table 1 indicates that the main target compartments will be soil and sediment with approximately 43% each, followed by water with about 10% (Degussa AG, 2006).

All these considerations are of little relevance because the reaction of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate with water (see chapter 2.2.3) is expected to eliminate the substance from the environment before equilibrium can be attained. The target compartment for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) is water (99.8%) as outlined in separate documentation on this compound (OECD, 2004).

2.2.5 Biodegradation

No ready biodegradation was observed in a manometric respiratory test performed with domestic, non-adapted activated sludge according to Directive 92/69/EEC, C.4-D (Bayer AG, 2000). Due to the rapid hydrolysis characterized above, biodegradation is irrelevant as a primary degradation step of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate because in aqueous media 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate will be degraded abiotically within hours.

The hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2), which was evaluated at SIAM 18 in 2004, is not readily biodegradable (OECD 301A: 8% after 28 days). However, in a simulation test with activated, non-adapted sludge, a degradation of 42% (including a minor, though not negligible contribution by adsorption onto sludge) was measured after a contact time of 6 hours (OECD, 2004).

2.2.6 Bioaccumulation

From the calculated log K_{OW} of 4.75 (see Table 1), a bioconcentration factor of 910 was derived (Degussa AG, 2006), which would indicate a high bioaccumulation potential. In view of the rapid hydrolysis, however, bioaccumulation of the substance itself can be excluded, and the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a log K_{OW} of 0.99 which indicates a low bioaccumulation potential (OECD, 2004).

2.3 Human Exposure

2.3.1 Occupational Exposure

Because 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is produced in closed systems, there is no direct contact during production. Occupational exposure may occur via inhalation or dermal contact with airborne substance. Workplace measurements were performed by producers in Germany, France and the United States. In four analyses of 3 hour samples performed in 2004 and 2005, the workplace concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in the German production plant was always below the detection limit of 0.001 mg/m^3 (Bayer MaterialScience AG, 2006). In the French production plant ten occupational exposure analyses have been performed between 2002 and 2005 and all concentrations were below 0.01 mg/m^3 (Rhodia Operations, 2006). In the U.S. production plant, the maximum concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was 0.0026 ppm (0.024 mg/m^3) 8 hour-time weighted average for eight determinations performed during the years 2003, 2004, and 2005 (Degussa North America, 2006). Occupational exposure is well below the MAK- or TLV-value of 0.005 ppm (0.046 mg/m^3) (ACGIH, 2004; DFG, 2005).

Ahrens and Jöckel (1997) studied occupational exposure in the paper industry. Exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was expected only in the impregnation and coating work area. All 33 analyses were negative, i.e. 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was always below the detection limit of 0.02 mg/m^3.

Karlsson et al. (2000) investigated occupational exposure during grinding, cutting, and welding operations in two car repair workshops, where isocyanates can be formed by thermal degradation of polyurethane coatings, particularly during cutting and welding operations. The maximum concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in air was 0.039 mg/m^3. No further concentration values for this substance are reported.

Further data on occupational exposure are not available except for the case studies reported in chapter 3, which indicate that there has been some exposure.

In accordance with the principles of Responsible Care and Sustainable Development, in the Sponsor Country (Germany) the exposure of workers is reduced to the lowest technically practicable level. Surveys of the 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, any organic solvents used, and 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate under relevant work situations, and application of appropriate control measures (Bayer MaterialScience AG, 2006).

To protect workers from exposure during production, 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 in advance. 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)). Downstream users of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate are informed by way of a material safety data sheet on the recommended safety measures (as characterized above) (Bayer MaterialScience AG, 2006).

2.3.2 Consumer Exposure

According to information reported in chapter 2.1, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate occurs as a component in consumer products in Sweden and Norway up to 2004. There are no data given on the current number of consumer products (SPIN, 2006). 13 consumer products were listed in the Swedish Product Register in 2002 and the in the Swiss Product Register in 2001 (Swedish Product Register, 2002; Swiss Product Register, 2001). Available information for Switzerland indicates that concentrations are very low, mostly below 1%. For Sweden and Norway no concentrations are given. However, consumer exposure can be expected to be negligible, and the extent is depending on appropriate use of such products. 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate may be formed in thermal degradation of polyurethanes. Thus Karlsson et al. (2000) found occupational exposure in car repair workshops (see chapter 2.3.1). However, relevant regular exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate from such sources is not expected.

Further information on consumer exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is not available. As noted above, the producers have agreed to recommend in their safety data sheets that handling the substance "requires appropriate protective measures. These products may therefore be used only in industrial or trade applications. They are not suitable for use in homeworker (DIY) applications." (Bayer MaterialScience AG, 2006; Degussa North America, 2006).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

There are no data available on the metabolic fate of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in experimental animals. (With regard to its fate in aqueous systems, see chapter 2.2.3).

Studies in Humans

Three healthy male volunteers were exposed in a 5.6 m^3 exposure chamber to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate concentrations of 0.0121, 0.0177, and 0.0507 mg/m^3 for 2 hours at day 1, 3, and 5, respectively. All urine was collected for 16 days, and blood samples were taken before and half an hour after exposure, and daily on exposure-free days. After hydrolysis 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was determined as 3-aminomethyl-3,5,5-trimethylcyclohexylamine.When working up samples from exposed persons without hydrolysis, no 3-aminomethyl-3,5,5-trimethylcyclohexylamine was seen. This indicates that the test substance was available in the urine only as conjugates. Hydrolysis had to split the conjugates and convert any residual isocyanate functions that might have been stabilized by conjugation, to amine functions. The average urinary elimination half-time was 2.8 hours. The average urinary excretion of the corresponding amine was 27% (range 19 -46%). An association between the estimated inhaled dose and the total excreted amount was seen. No 3-aminomethyl-3,5,5-trimethylcyclohexylamine was found in hydrolyzed plasma (Tinnerberg et al., 1995).

Conclusion

The only information available on the toxicokinetics of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate results from a test chamber exposure of three volunteers to concentrations of 0.0121, 0.0177 and 0.0507 mg /m^3 for 2 hours at day 1, 3, and 5, respectively. After hydrolysis of blood and urine samples the corresponding amine, 3-aminomethyl-3,5,5-trimethylcyclohexylamine, was detected in urine but not in plasma. The average urinary excretion was 27% and urinary elimination half-time was 2.8 hours. No 3-aminomethyl-3,5,5-trimethylcyclohexylamine was observed in samples without hydrolysis from exposed persons.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is a liquid with a low vapor pressure under ambient conditions. Based on these characteristics, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is expected to occur at temperatures close to room temperature as vapor at low concentrations and as liquid aerosol droplets at higher concentrations. With the vapor, exposure of the respiratory tract should be relatively uniform. In contrast, exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate aerosols may result in an unequal distribution and higher local concentrations in the respiratory tract at the site of deposition which depends on particle size.

These considerations lead to some requirements for adequately testing the inhalation toxicity of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. The particle-size distribution of aerosols generated in inhalation studies should allow exposure of all relevant regions of the respiratory tract, since damage to and/or deposition in any region of the respiratory tract may induce lethality. An aerosol bracketing a particle-size mass distribution of mass median aerodynamic diameter (MMAD) 1 to 4 µm, as recommended by Society of Toxicology (1992) and a geometric standard deviation (GSD) in the range of 1.5 to 3.0 µm therefore appear to be appropriate for LC_{50} determination. Only two of the available inhalation LC_{50} studies give consideration to these exposure and analysis requirements, which are essential for a reliable quantitative assessment of inhalation toxicity. These studies will be presented here in more detail.

Particular attention was paid to the location of effects in the study of Pauluhn (2004). Both the concentration- and time dependence of parameters in the bronchoalveolar lavage fluid (BALF) following a single 6 hours exposure to the aerosolized 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was analyzed. Male rats were exposed in direct-flow nose-only exposure chambers to conditioned air or target concentrations of 2, 8, and 25 mg 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate/m^3 (analytical: 2.09; 7.5; 26 mg/m^3). The test substance was applied as an aerosol with high respirability (MMAD 1.6 µm; GSD approx. 1.8 µm) at the high level group. No particle size analyses were performed in the low and mid dose group because these concentrations were in the range of the vapor saturation concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. BALF was analyzed for protein as an index of air-blood barrier permeability. Lactate dehydrogenase (LDH) was taken as indicator of cell injury. These endpoints were determined on postexposure days 1, 3, and 7. Clinical signs of respiratory distress were observed at 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate concentrations $\geq$ 8 mg/m^3. 2/18 rats died at 25 mg/m^3. At 8 mg/m^3 and higher body weight retardation was observed, which was statistically significant only in the high dose group (21% below control on day 7). Rectal temperature was statistically significantly decreased at 8 and

25 mg/m^3 (6.2 and 9.1°C below control, respectively). Lung weights were increased only in the high dose group (25 mg/m^3) not until at day 7 (+24.3%) as were protein (+291%; also significant on day 1, not on day 3) and LDH (+151%) in BALF. The time course of changes can be associated with features reminiscent of upper airway rather than pulmonary irritation.

The inhalation LC_{50} of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (purity > 99%) was determined by Bayer AG (1995 a, b, c) by exposing Wistar rats in six groups, each containing 5 males and 5 females according to the method of OECD TG 403. Each group was nose only exposed to conditioned air or aerosol concentrations of the test substance. After exposure (4 hours) the animals were observed for four weeks. The actual mean concentrations of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate were 20.4, 53.3, 73.8, 104.6 and 410.3 mg/m^3. The test substance aerosol exhibited a particle-size indicating that this aerosol was of adequate respirability (83% of the particle mass was < 3 µm; MMAD approx. 1.6 – 2.1 µm; GSD approx. 1.7 µm). Rats exposed to ≥ 20.4 mg/m^3 experienced signs of respiratory tract distress (i.e. tachypnea, bradypnea, stridor). Body weight gain and rectal temperature were depressed significantly in all exposed groups. Exposure to a concentration of 53.3 mg/m^3 induced mortality in 6 of 10 animals. This mortality was observed between days 16 and 28. Exposure to concentrations of ≥ 73.8 mg/m^3 was lethal for all exposed animals and increased exposure concentrations clearly induced a speeding up of mortality. With the exception of a less collapsed lung and some focal discolorations of the lung, which are sporadically observed, survivors showed no substance-induced macroscopic, extrapulmonary alterations. Animals that died during or following exposure showed nose/muzzle with red incrustations, mucous membrane of nose with reddening, pleural cavity filled with liquid, lung less collapsed emphysematous, and spongy, which are considered to reflect local irritant effects to the respiratory tract. The LC_{50} (4 h) stated in this study (Bayer AG, 1995 a, b, c) is approximately 40 mg/m^3 for both sexes.

In the OECD TG 403 study of RCC (1988), a four-hour LC_{50} of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (purity > 99%) to male and female Wistar rats of 31 mg/m^3 was determined. The no-observed-effect level was less than 18 mg/m^3. The animals were exposed flow-past nose-only to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate aerosol and observed for up to 17 days after exposure. Applied analytical concentrations were 18, 22, 70 and 450 mg/m^3. The data on particle size distribution showed that all particles were below 4.6 µm and approximately 90% w/w of the particles had diameters ≤ 2.13 µm at the three lowest exposure concentrations. The predominant clinical signs were breathing difficulty, piloerection and stagger. Necropsy findings were red foci on lung lobes, or reddish lungs (in decedent animals only). There was no body weight gain during the first week.

Dermal

A test performed according to OECD TG 402 with male and female rats (Hüls AG, 1985) demonstrated the low acute dermal toxicity of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. No animal (= 0/10) died after 24 hours occlusive application of 7000 mg/kg. Non-specific transient signs of intoxication (sedation, ataxia) and obvious skin irritation at the application site were observed in all animals.

Oral

Kimmerle (1968) reported LD_{50} values (with 14 days post observation period) of > 2645 mg/kg bw each for 15 male Wistar rats and for 15 male CF1 mice. In the study with rats no animal died and no signs of intoxication or change of behavior could be observed at any dose up to 2645 mg/kg bw. In the study with mice two animals died at 2645 mg/kg bw on the first day, symptoms of intoxication were uncharacteristic. While in this study unspecified oil was used as vehicle, no vehicle was employed in the other oral toxicity studies:

Similarly low acute oral toxicities in Wistar rats were determined by IBR (1976) and Thyssen (1976), with LD_{50} values of 4814 mg/kg bw and above. Clinical signs observed in the former study were a decrease in activity, diarrhea, piloerection, in the higher dose groups also tremor, the symptoms beginning 20 minutes after dosing and lasting for about 24 hours. Growth rates were transiently reduced but returned to normal by the end of the post exposure observation period. Mortalities occurred within 3 days after dosing. Necropsy findings were reddening of stomach and intestinal mucosa of dead animals, and loss of hair at the perineum of survivors.

Conclusion

Assessment of the acute inhalation toxicity data indicates that effects caused by exposure to respirable aerosols of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate were confined predominantly to the respiratory tract. Clinical signs (serous nasal discharge, bradypnea, stridor) indicated respiratory distress. There are two studies according to OECD TG 403 with LC_{50}-values (4 h, rat) of approximately 40 mg/m^3 and 31 mg/m^3, respectively. Special investigations with male rats revealed airway rather than pulmonary irritation, which became evident after exposure of a concentration causing some lethality (25 mg/m^3, 1 x 6 h). The dermal LD_{50} determined in compliance with OECD TG 402 was > 7000 mg/kg bw for rats. Non-specific, transient signs of intoxication (sedation, ataxia) and obvious skin irritation at the application site were reported. The available studies revealed a low oral toxicity with LD_{50}-values (rat) of 4814 - 5490 mg/kg bw. Toxic symptoms after oral administration included decreased activity, piloerection, and diarrhea.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Two studies on the skin irritating properties of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate were performed according to OECD TG 404. Undiluted test substance was applied in both studies. In one study with three rabbits per sex exposed occlusively for four hours, the result was, with regard to the irritation index (6.87 of max. 8.0), described as “highly irritating” (Hüls AG, 1984 a). The overall result was “corrosive” because of extensive irreversible tissue damage such as necrosis, ulceration, or scarring within the observation period (14 days) in all animals. This overall assessment was confirmed by another study performed according to OECD TG 404 with one rabbit exposed semiocclusively for four hours, the result was “corrosive” with an irritation index of 4.5 of max. 8.0 (Krötlinger, 1994).

Eye Irritation

Studies in Animals

Conflicting results ranging from “not irritating” (Hüls AG, 1984 b) to “highly irritating” (Schreiber, 1981) were reported for the effects of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate on rabbit eyes in studies performed according to OECD TG 405. The exudation observed in the study of Hüls AG (1984 b) may have contributed to the avoidance of damage to the eye. The irritation index was 9.96 of max. 110. Ten days after treatment with 0.1 ml undiluted test substance all animals in this study showed loss of hair around the eye and incrustation at the eyelid, mostly associated with thickening on day 13, which is not reflected in the scores. In the study of Schreiber (1981), where both eyes were treated (0.1 ml undiluted per eye) and only one eye was rinsed, severe irritation of the conjunctiva was observed. There was a constantly high degree of chemosis throughout the 8 days observation period both on rinsed and non-rinsed eyes, and slight cornea

damage, to a lesser degree on the rinsed eye, with significant retrogression within 8 days. The irritation score was 36.4/110 (not rinsed) or 26.4/110 (rinsed eye).

Respiratory Tract Irritation

Studies in Animals

Some studies were performed to determine the concentration causing a 50% decrease in respiration rate. This effect, which is thought to reflect the respiratory tract irritation, was observed at 11.1 mg/m³ (30 min), 10.3 mg/m^3 (1 h) and 4.7 mg/m³ (3 h) in rats (Mobay Chemical Corporation, 1984 b) and at 11.1 mg/m³ (30 min), 6.0 mg/m³ (1 h) and 2.0 mg/m^3 (3 h) (Mobay Chemical Corporation, 1984 a) or 6.0 mg/m³ (3 min), 4.0 mg/m³ (10 min) and 3.0 mg/m^3 (30 min) (E.I. du Pont de Nemours and Company, 1987) in mice.

Studies in Humans

Henschler (1972) published results of experiments with volunteers exposed for 1 - 5 minutes to an aerosol (with regard to the vapor saturation concentration at ambient temperature the particle concentration should be negligible in relation to vapor atmosphere) of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. At 0.25 mg/m^3 the odor was just perceptible; at 0.64 mg/m^3 slight irritation of the mucous membranes of the eyes and nose were observed; at 1.37 mg/m^3 there was strong, intolerable irritation of the mucous membranes of the eyes and the breathing passages.

Conclusion

In two studies performed according to OECD TG 404, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be corrosive to the rabbit skin. Strong irritation was observed in rabbit eyes when tested according to OECD TG 405. The toxicity studies indicate that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate vapor causes irritation of the upper respiratory tract. In a study with volunteers, a perception threshold for irritation of 0.64 mg/m^3 was determined for short-term (1-5 minutes) exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

3.1.4 Sensitization

Studies in Animals

Skin

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be sensitizing in numerous studies. Positive results were obtained in the Buehler test performed according or equivalent to the corresponding EU Directive (Zissu, Binet and Limasset, 1998; American Cyanamid Company, 1987), in the guinea pig maximization test comparable or according to OECD TG 406 (Hüls AG 1983, Bayer AG, 1984; Vohr, 1993), in the mouse ear swelling test (Dearman, Spence and Kimber, 1992), and in the open epicutaneous test (Biosphere Research Center Inc., 1991).

For example, in the Buehler test performed by Zissu, Binet and Limasset (1998), after occlusive epicutaneous induction with 0.5 ml of a solution of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in petrolatum at 5% (w/v), 16/20 guinea pigs showed positive response upon occlusive epicutaneous challenge with 1% test substance. This characterizes the test substance as a strong sensitizer. Similarly, in the Guinea pig maximization test performed by Vohr (1993) using 0.1 ml of a 5% solution in olive oil for intracutaneous induction, 15/20 guinea pigs from the test group displayed a positive response upon semiocclusive rechallenge at 0.1%. However, in this study skin

reactions were also observed in control animals, though at a lower incidence as compared to the test group, which is why a second challenge was performed.

Respiratory Tract

Respiratory tract sensitization of guinea pigs following intradermal induction (1%, 100 µl) was studied by Bayer AG (1996) in accordance with the exposure criteria defined in OECD TG 403. High titer IgG1 antibody observed proved that successful sensitization had occurred. However, when challenged by nose only inhalation of aerosol at varying concentrations, the incidence of immediate-onset respiratory reactions was roughly the same in all groups. No delayed-onset reactions, deaths or anaphylactic reactions were observed. Challenge with acetylcholine did not show specific respiratory responses indicating that the animals were hyperrespondive to cholinergic acetylcholine stimuli. Severe reactions were observed with trimellitic anhydride (CAS No. 552-30-7) when investigated with the current animal model, using the equivalent induction and challenge.

Studies in Humans

Skin

A glue, mainly based on dicyclohexylmethane-4,4'-diisocyanate (70%), was suspected of being the cause of an outbreak of severe eczema at a factory manufacturing medical equipment from August 1999 to April 2001 (Frick et al., 2003). 16 out of approximately 100 persons working in the relevant department were referred to medical consultation. When patch tested with a standard series, an isocyanate series, and work material, 4 of these 16 persons reacted to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

Two Italian women who worked with polyurethane materials made of diisocyanates other than 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (diphenylmethane-4,4'-diisocyanate in one case, dicyclohexylmethane-4,4'-diisocyanate in the other) developed distinct contact dermatitis. When patch tested with the North American Contact Dermatitis Group (NACDG) standard series and with a second series including in one case 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (1% in petrolatum), a weakly positive response towards 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was observed beside positive responses to other isocyanate materials (Militello et al., 2004).

Twenty poorly documented cases of occupational dermatoses observed between the end of 1970 and mid 1974 were reported in East Germany (Rothe, 1976). Appropriate concentrations for patch epicutaneous challenge testing were determined by self-application of medical staff. 1% solutions of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in acetone as well as test solutions of other isocyanates were then applied to workers who were suspected to be sensitized by polyurethane chemicals. Readings were done at 24, 48, and 72 hours (some also at 96 hours). Four persons turned out to be sensitized towards 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. The main symptoms in these cases were follicular nodules. Symptoms had appeared after an accidental spill with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate even in two of the above mentioned persons that had previously no contact with this substance, but with toluene diisocyanate and diphenylmethane diisocyanate. The skin of the sensitized workers returned to a stable healthy state after avoiding contact with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

In the same poorly documented study, single-dose self-application of medical staff with undiluted 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate caused follicular papules after 10 days in 2 out of 3 persons. Sensitization was confirmed by challenge with 1% 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in acetone. Control tests in 6 non-exposed persons with eczema were negative (Rothe, 1976).

Cross-sensitivity between 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate and the corresponding diamine 3-aminomethyl-3,5,5-trimethylcyclohexylamine was studied by Lachapelle and Lachapelle-Ketelaer (1979). Two workers who were allergic to the diamine and two volunteers who had been sensitized also to the diamine were patch tested 1 month later with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (1% in ethanol); the patches were removed after 48 hours, and read at 48 and 96 hours. Five adult volunteers were patch tested with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate as controls. The tests were strongly positive in the 4 patients. None of the control subjects was positive. Since 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is hydrolyzed (see chapter 2.2.3), which initially leads to the diamine (see chapter 3.1.1), traces of 3-aminomethyl-3,5,5-trimethylcyclohexylamine are expected to occur in patch tests with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate and may trigger symptoms of sensitization in persons who are allergic towards 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

Non-occupational skin sensitization towards 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was identified by Belsito (2003). Three out of 70 patients with allergic-appearing foot dermatitis, of which 23 were found to have allergic contact dermatitits from shoes, showed positive response when challenged with 1% 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in petrolatum. The source of exposure appeared to be the foam rubber padding in athletic shoes, though migration from glues into the padding could not be excluded.

Respiratory Tract

A 50-year old spray painter developed severe asthma soon after introduction of a new paint containing 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. His asthma was associated with an abnormal chest X-ray, blood eosinophilia, normal IgE level, negative skin prick tests and no precipitins to Aspergillus fumigatus. After successful initial therapy, the person was left in an enclosed room for 30 minutes each on three days, followed by spirometry at hourly intervals for nine hours. Exposure conditions in the enclosed room were as follows:

Day 1: Sitting

Day 2: Painting a chair without 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in the spraying enamel

Day 3: Painting a chair with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in the spraying enamel

Exposure was not quantified. On day 3, the patient required treatment 3 hours 35 minutes after cessation of challenge. A very large reduction in forced expiratory volume was observed on that day (Clarke and Aldons, 1981).

Germanaud et al. (2003) published a case of occupational hypersensitivity pneumoapathy, which according to the investigators is rarely caused by isocyanates. A 50 year old man had worked in the production of polyurethane foams and polyurethane coatings for 32 years with a generally low exposure. He then was engaged more closely in a polyurethane synthesis from 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Few hours after the beginning of this new occupational exposure, which was not defined any more specifically, he showed dyspnea, fever (39°C), and crepitant rales. Further investigations revealed ground glass appearance on the thoracic CT scan and lymphocytosis in the broncho-alveolar lavage. Effects were confirmed by transbronchial biopsy. Only the functional assessment (airflow obstruction and absence of marked reduction in CO transfer) was atypical for hypersensitivity pneumapathies.

A poorly documented case is also reported by Tyrer (1979): In 1974, a sprayer in a firm of motor body repairers used for some months intermittently a two-pack paint containing 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (not quantified), toluene and xylene, with no ill-effects. The spraying was done in a large, completely enclosed booth with effective downdraught through the floor. He then developed tightness of the chest and dyspnea, which disappeared when he took a few days off, but recurred, shortly after his return to work. The sprayer who took his place had similar symptoms in a milder form, which lasted only a few hours. A causal relationship between the asthmatic symptoms and a specific substance was not established in this mixed exposure case.

Conclusion

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be skin sensitizing in the Buehler test according to or equivalent to the EU Directive, in the guinea pig maximization test comparable or according to OECD TG 406, in the mouse ear swelling test, and in the open epicutaneous test. Skin sensitization was also observed in humans. One case report describes respiratory hypersensitivity after occupational exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. No validated animal model is available to assess the potential for respiratory sensitization or asthma in humans, and one animal study did not show respiratory tract sensitization when exposed by inhalation (challenge) following intradermal induction. However, due to the well known reactivity of diisocyanates, respiratory sensitization is likely to occur.

3.1.5 Repeated Dose Toxicity

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

In a study performed according to OECD TG 412, groups of ten male and ten female Wistar rats were exposed for six hours/day on five days/week for four consecutive weeks to target 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate concentrations of 0.25, 1 or 4 mg/m^3 (corresponding to analytical means of 0.24; 1.05; 4.1 mg/m^3). Exposure was dynamic directed-flow nose-only and vapor saturation was reported to be about 4 – 11 mg/m^3 at 20 – 25°C. A concurrent control group was exposed to air only, under otherwise identical conditions. Recovery was studied after approximately four further weeks in two additional, identical groups, one of them a control group, the other one exposed to the highest test concentration.

No mortality was observed in this study. No treatment-related effects were observed in urinalysis, ophthalmoscopic examination, clinical chemistry, gross pathology and examination of reflexes. Clinical signs were mild and transient signs of respiratory tract irritation (nostrils: red encrustations, stridor, nasal discharge, breathing sounds, hypothermia) in most rats only at 4.1 mg/m^3 (signs in 18/20 males, 18/20 females). Body weights were slightly decreased in the high dose group (day 28: males -5.1%, statistically significant; females -3.4%, not significant) and returned rapidly to normal during the recovery period. The only relevant hematological finding was an increased leukocyte count in the peripheral blood in mid (males +46%, significant; females +82%, not significant) and high dose (males +55%, significant; females +16%, not significant) groups. Other statistical significances (none in high dose animals except prothrombin time for females +7.6%) were considered to be of no pathodiagnostic relevance. Statistically significant findings in high dose group organ weights were a reduced absolute liver weight in females (-9.7%) and an increased relative lung weight in males (+12.6%). Only the latter finding was conclusive. Histopathology revealed in rats exposed at 1.05 and 4.2 mg/m^3 a significantly increased incidence of inflammatory as well as epithelial changes occurring in the airways of the entire respiratory tract (nasal cavity, pharynx, larynx, trachea, lungs) with typical anterior-posterior gradient in intensity. Recovery after the post observation period was incomplete in nasal cavity, pharynx, larynx, and complete in

trachea and lung. The lesions were thus considered to be reversible with no evidence of fibroproliferative effects. There was no effect on extrapulmonary organs. Determination of the rectal temperatures indicated hypothermia in the high dose group, which was statistically significant on day 0 (males 34.6 vs. 37.4°C in control, females 35.6 vs. 37.3°C) but not towards the end of the exposure period (day 22). The NOAEL (histopathological changes in nasal cavity and larynx) was 0.24 mg/m^3 (Bayer AG, 2003).

Conclusion

No repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (0.24, 1.05, and 4.1 mg/m^3; 6 hours/day, 5 days/week, 4 weeks; OECD TG 412) with male and female Wistar rats indicates the respiratory tract to be the target organ. Clinical signs of respiratory tract irritation (nostrils: red encrustations, stridor, nasal discharge, breathing sounds, hypothermia) are restricted to the high concentration rats. The LOAEL is 1.05 mg/m^3 (histopathological changes in nasal cavity and larynx). At 4.1 mg/m^3 also the pharynx, trachea, and lungs are affected but the lesions are reversible within the four weeks of recovery with regard to the lung and trachea. However, lesions in the nasal cavity, the pharynx, and the larynx still occurred in some animals with minimal or slight degree. The most relevant systemic effects were a slight decrease in body weight gain in the high dose group and an increased leukocyte count in the peripheral blood in mid and high dose groups. The NOAEL is 0.24 mg/m^3.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

In an Ames test performed according to Directive 84/449/EEC B.14 (1984) with *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100, test substance concentrations of up to 5000 µg/plate (without preincubation) and up to 1000 µg/plate (with preincubation) were employed in the presence and absence of Aroclor-induced rat liver S9 mix. A significant increase in mutant frequency was not observed. Cytotoxicity was observed at 1000 µg/plate (+/- S9 without preincubation) and at 1000 or 500 µg/plate (+/- S9, with preincubation) (Hüls AG, 1993 a). Neither *Salmonella typhimurium* TA 102 nor *Escherichia coli* WP2 were tested in these Ames tests, as it was not required by the EC guideline in 1984 when these studies were performed. This is an acceptable restriction compared to OECD TG 471 because it can be assumed that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate has no oxidizing or cross-linking potential which may be detected by *S. typhimurium* TA 102 or *E. coli* WP2. A negative result was also obtained by Mortelmans et al. (1986) in the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 using the preincubation method and concentrations up to 33 000 µg/plate both with and without Aroclor 1254-induced Wistar rat Syrian hamster liver S9 mix, respectively. Concentrations above 10 000 µg/plate were cytotoxic.

In a test performed according to OECD TG 473 (1997), 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate induced dose dependent chromosomal aberrations in Chinese hamster ovary cells both in the presence and absence of S9 homogenate prepared from Sprague-Dawley rat livers, induced with phenobarbital and ß-naphthoflavone. Test concentrations were 0.625; 1.25; 2.50; 5.0; 10.0; 20.0; 40.0; 80.0 µg/ml, and cytotoxicity was observed at ca. 40 µg/ml and higher (RTC, 2003). Appropriate reference substances were used as positive controls in these *in vitro* studies and showed the expected genotoxic result.

In vivo Studies

In order to further clarify the relevance of the positive findings in the *in vitro* chromosomal aberrations test, an *in vivo* micronucleus test according to OECD TG 474 was performed. 18 (main study) plus 5 (satellite for respiratory function measurements) male NMRI mice per dose group were exposed once for six hours by nose-only inhalation (vapor/aerosol) to target concentrations of 0, 5, 15, or 40 mg/m^3. Sampling times for bone marrow were 24, 48, and 72 hours after test substance administration. No indication of a clastogenic effect was observed. The positive control, cyclophosphamide, caused a clear increase in the number of polychromatic erythrocytes with micronuclei (Bayer HealthCare AG, 2006).

Studies in Humans

There are no data available.

Conclusion

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was not genotoxic in bacterial systems *in vitro* (Ames test). Neither *Salmonella typhimurium* TA 102 nor *Escherichia coli* WP2 were tested in these Ames tests, however, this is an acceptable restriction because it can be assumed that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate has no oxidizing or cross-linking potential which may be detected by *S. typhimurium* TA 102 or *E. coli* WP2. In a chromosomal aberrations test performed on Chinese hamster ovary cells according to OECD TG 473, results were positive both with and without metabolic activation. *In vivo*, no mutagenic activity was detectable in a micronucleus assay on mice according to OECD TG 474 using the inhalation route of administration**.** However, as the micronucleus test only covers systemic genotoxic effects and given the well known high local reactivity of the substance local genotoxic effects cannot be excluded.

3.1.7 Carcinogenicity

There are no data available.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. However, relevant information can be found in studies on different endpoints. Histopathological results of a subacute 28-day inhalation study in rats according to OECD TG 412 (adjusted to fulfill both the TSCA § 798.2250 as well as EU Guideline 92/69/EEC) showed no effects on the reproductive organs (ovaries, oviducts and testes) at tested concentrations of up to 4.1 mg/m^3. Testes and ovary weights were also not affected. The NOAEL for general toxicity is 0.24 mg/m^3. For further details on general toxicity see chapter 3.1.5. (Bayer AG, 2003).

Based on the results there are no indications for specific adverse effects on the reproductive organs following 28-day treatment with up to 4.1 mg/m^3 despite the fact that already at 1.05 mg/m^3 the substance leads to a significantly increased incidence of inflammatory as well as epithelial changes occurring in the airways of the entire respiratory tract (nasal cavity, pharynx, larynx, trachea, lungs) with typical anterior-posterior gradient in intensity. Taking into account the knowledge about the mode of action of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (local effects at sites of

immediate contact clearly predominant) the lack of effect on the reproductive organs at 4.1 mg/m^3 and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m^3 it seems quite unlikely that this substance might have critical effects on testis in this low dose range.

Developmental Toxicity

The developmental toxicity of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was investigated by Klaus (2004) in a vapor inhalation study conducted according to OECD TG 414 (2001). Groups of 27 female Wistar rats were exposed to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate via nose-only inhalation, 6 hours/day on gestation days 6 to 19 at target concentrations of 0.25, 1.0 or 4.0 mg/m^3 (0.206, 0.929, 4.536 mg/m^3 analytical). The study was terminated by cesarean section on day 20. No maternal mortalities were reported. Treatment with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate at the 4 mg/m^3 exposure level affected the respiratory tract and the fur of the females and comprised bradypnea, labored breathing, breathing sounds, reddish encrusted nostrils, serous nasal discharge and rough fur. Effects on water intake and excretion of urine and feces were not observed at an exposure level up to and including 4 mg/m^3, while decreased feed intake (–14.7%), reduced corrected body weight (–9.2%) and impaired body weight gain (relative to initial weight: –21.7%) was evident in the 4 mg/m^3 exposure group as compared to control. Necropsy revealed no treatment related gross pathological findings in any group.

Intrauterine development, gestation rate, postimplantation loss, mean litter size, fetal sex distribution, and placental appearance were not affected by treatment with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate at exposure levels up to and including 4 mg/m^3. Reduction of fetal weight at the 4 mg/m^3 exposure level was 6.8% ($p < 0.01$), and impairment of placental weight (–6.6%, not statistically significant but slightly below historical control data range) could not be completely excluded at this exposure level. A marginally higher number of common eye malformations in the 4 mg/m^3 group (1% of the fetuses and 7.7% of litters affected vs. 0.4% of fetuses and 4.2% of litters in control), well within the range of historical control data (up to 1.8% of fetuses and 20% of litters affected), was considered to be either incidental or secondary (reduced oxygen supply to offspring by maternal bradypnea). Further incidence and type of fetal malformations were unaffected by treatment. An adverse effect on incidence and type of external and visceral deviations was not evident at an exposure level up to and including 1 mg/m^3, while slightly retarded descensus testis could not be completely excluded at the maternally toxic 4 mg/m^3 exposure level. Statistically significant fetal skeletal findings at the 4 mg/m^3 exposure level included retarded ossification of distal and proximal phalanges of digits and toes, of metacarpal bones, 6th sternal segment, 7th cervical vertebral body, sacral and caudal vertebral arches, and caudal vertebral bodies. All signs of developmental toxicity observed at the 4 mg/m^3 exposure level, i.e. reduced fetal weights, delayed descensus testis, and slightly retarded ossification, were indicative of delayed fetal development and were only seen in the presence of maternal toxicity and thus considered secondary effects. The NOAEL for both maternal toxicity and developmental toxicity was 1 mg/m^3 (nominal; analytical: 0.929 mg/m^3) (Klaus, 2004).

Studies in Humans

There are no data available.

Conclusion

No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Histopathological results of a subacute 28-day inhalation study in rats according to OECD TG 412 showed no effects regarding the reproductive organs in concentrations up to 4.1 mg/m^3. Testes and ovary weights were also not affected. Taking into account the knowledge about the mode of action of 3-isocyanatomethyl-3,5,5-

trimethylcyclohexyl isocyanate (local effects at sites of immediate contact clearly predominant), the lack of effect on the reproductive organs at 4.1 mg/m^3, and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m^3 it seems quite unlikely that this substance might have critical effects on testis in this low dose range.

In a nose-only inhalation study performed in accordance with OECD TG 414, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate had no adverse effects on the development of rats up to and including a dose level of 0.929 mg/m^3. A dose of 4.536 mg/m^3 was maternally toxic as evidenced by effects on respiratory tract and fur as well as decreased feed intake and impaired body weight gain. All signs of developmental toxicity observed at the 4.536 mg/m^3 exposure level, i.e. reduced fetal weights, delayed descensus testis, and slightly retarded ossification, were indicative of delayed fetal development and were only seen in the presence of maternal toxicity and thus considered secondary effects. There was no treatment related effect on incidence and type of fetal malformations up to and including 4.536 mg/m^3. The NOAEL for both maternal toxicity and developmental toxicity was 0.929 mg/m^3.

3.2 Initial Assessment for Human Health

The only information available on the toxicokinetics of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate results from a test chamber exposure of three volunteers to concentrations of 0.0121, 0.0177 and 0.0507 mg /m^3 for 2 hours at day 1, 3, and 5, respectively. After hydrolysis of blood and urine samples the corresponding amine, 3-aminomethyl-3,5,5-trimethylcyclohexylamine, was detected in urine but not in plasma. The average urinary excretion was 27% and urinary elimination half-time was 2.8 hours. No 3-aminomethyl-3,5,5-trimethylcyclohexylamine was observed in samples without hydrolysis from exposed persons.

Assessment of the acute inhalation toxicity data indicates that effects caused by exposure to respirable aerosols of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate were confined predominantly to the respiratory tract. Clinical signs (serous nasal discharge, bradypnea, stridor) indicated respiratory distress. There are two studies according to OECD TG 403 with LC_{50}-values (4 h, rat) of approximately 40 mg/m^3 and 31 mg/m^3, respectively. Special investigations with male rats revealed airway rather than pulmonary irritation, which became evident after exposure of a concentration causing some lethality (25 mg/m^3, 1 x 6 h). The dermal LD_{50} determined in compliance with OECD TG 402 was > 7000 mg/kg bw for rats. Non-specific, transient signs of intoxication (sedation, ataxia) and obvious skin irritation at the application site were reported. The available studies revealed a low oral toxicity with LD_{50}-values (rat) of 4814 - 5490 mg/kg bw. Toxic symptoms after oral administration included decreased activity, piloerection, and diarrhea.

In two studies performed according to OECD TG 404, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be corrosive to the rabbit skin. Strong irritation was observed in rabbit eyes when tested according to OECD TG 405. The toxicity studies indicate that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate vapor causes irritation of the upper respiratory tract. In a study with volunteers, a perception threshold for irritation of 0.64 mg/m^3 was determined for short-term (1-5 minutes) exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was found to be skin sensitizing in the Buehler test according to or equivalent to the EU Directive, in the guinea pig maximization test comparable or according to OECD TG 406, in the mouse ear swelling test, and in the open epicutaneous test. Skin sensitization was also observed in humans. One case report describes respiratory hypersensitivity after occupational exposure to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. No validated animal model is available to assess the potential for

respiratory sensitization or asthma in humans, and one animal study did not show respiratory tract sensitization when exposed by inhalation (challenge) following intradermal induction. However, due to the well known reactivity of diisocyanates, respiratory sensitization is likely to occur.

No repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (0.24, 1.05, and 4.1 mg/m^3; 6 hours/day, 5 days/week, 4 weeks; OECD TG 412) with male and female Wistar rats indicates the respiratory tract to be the target organ. Clinical signs of respiratory tract irritation (nostrils: red encrustations, stridor, nasal discharge, breathing sounds, hypothermia) are restricted to the high concentration rats. The LOAEL is 1.05 mg/m^3 (histopathological changes in nasal cavity and larynx). At 4.1 mg/m^3 also the pharynx, trachea, and lungs are affected but the lesions are reversible within the four weeks of recovery with regard to the lung and trachea. However, lesions in the nasal cavity, the pharynx, and the larynx still occurred in some animals with minimal or slight degree. The most relevant systemic effects were a slight decrease in body weight gain in the high dose group and an increased leukocyte count in the peripheral blood in mid and high dose groups. The NOAEL is 0.24 mg/m^3.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was not genotoxic in bacterial systems *in vitro* (Ames test). Neither *Salmonella typhimurium* TA 102 nor *Escherichia coli* WP2 were tested in these Ames tests, however, this is an acceptable restriction because it can be assumed that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate has no oxidizing or cross-linking potential which may be detected by *S. typhimurium* TA 102 or *E. coli* WP2. In a chromosomal aberrations test performed on Chinese hamster ovary cells according to OECD TG 473, results were positive both with and without metabolic activation. *In vivo*, no mutagenic activity was detectable in a micronucleus assay on mice according to OECD TG 474 using the inhalation route of administration**.** However, as the micronucleus test only covers systemic genotoxic effects and given the well known high local reactivity of the substance local genotoxic effects cannot be excluded.

No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Histopathological results of a subacute 28-day inhalation study in rats according to OECD TG 412 showed no effects regarding the reproductive organs in concentrations up to 4.1 mg/m^3. Testes and ovary weights were also not affected. Taking into account the knowledge about the mode of action of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (local effects at sites of immediate contact clearly predominant), the lack of effect on the reproductive organs at 4.1 mg/m^3, and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m^3 it seems quite unlikely that this substance might have critical effects on testis in this low dose range.

In a nose-only inhalation study performed in accordance with OECD TG 414, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate had no adverse effects on the development of rats up to and including a dose level of 0.929 mg/m^3. A dose of 4.536 mg/m^3 was maternally toxic as evidenced by effects on respiratory tract and fur as well as decreased feed intake and impaired body weight gain. All signs of developmental toxicity observed at the 4.536 mg/m^3 exposure level, i.e. reduced fetal weights, delayed descensus testis, and slightly retarded ossification, were indicative of delayed fetal development and were only seen in the presence of maternal toxicity and thus considered secondary effects. There was no treatment related effect on incidence and type of fetal malformations up to and including 4.536 mg/m^3. The NOAEL for both maternal toxicity and developmental toxicity was 0.929 mg/m^3.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

In view of the low solubility in water (see chapter 1.3) and the liability towards hydrolysis (see chapter 2.2.3) of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, exposure to well-defined aquatic concentrations is difficult to achieve. Routine analytical methods such as determination of dissolved organic carbon (DOC) will not distinguish between the test substance and its dissolved hydrolysis products. Test organisms will be affected by both 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate and its reaction products, and the total concentration may exceed the water solubility of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. The acute fish toxicity tests are presented here in more detail to show the ways how these problems were handled.

In the environment, however, hydrolysis will convert 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate rapidly into its main hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine, and aquatic organisms will be exposed to this latter substance. In this report, the studies with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate are presented first, and thereafter the key studies from the separate documentation on 3-aminomethyl-3,5,5-trimethylcyclohexylamine (OECD, 2004) will be cited and used for deriving the $PNEC_{aqua}$.

Acute Toxicity Test Results

In a semi-static acute fish toxicity test according to Directive 92/69/EEC, Hüls AG (1996) observed no mortalities in *Cyprinus carpio* within 96 hours of exposure to concentrations up to the maximum possible concentration of 208 mg/l (arithmetic mean of analyses for four days). For the daily preparation of the test solutions, 1 g test substance/l was stirred for approximately 18 hours in water, filtered and diluted. Hydrolysis was expected but not quantified. DOC analysis after 24 hours indicated that evaporative losses were insignificant (< 20%).

In an earlier study performed in this laboratory which cannot be verified because no report exists while results were communicated (Hüls AG, 1993 b; Hüls AG, 1994), a 48 h-LC_{50} of 1.8 mg/l was determined in *Leuciscus idus* according to the German Standard DIN 38412 part 15 (static). An emulsifier was used but there is no information available on its concentration as well as on other important test conditions like test substance purity and preparation of stock and test solutions.

Bayer AG (2000) first determined the water solubility under the test conditions. The 1.3 fold amount (100 mg/l) of the maximum water solubility of the test substance in the preliminary test (70 mg/l) was weighed into water, treated for 60 seconds at 8000 rpm with an ultra-turrax and afterwards stirred on a magnetic stirrer for 24 hours. The resulting emulsion was filtered using a folded filter of pore size 7 - 12 µm. A static acute 96-hour fish toxicity limit test according to Directive 92/69/EEC was performed with *Danio rerio*. No mortalities and normal swimming were observed. The analytical test concentration, which was determined daily by DOC measurements, was 72.3 mg/l.

The following valid studies (including those detailed above) for aquatic toxicity have been performed with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate:

Cyprinus carpio (Directive 92/69/EEC, semistatic):	LC_{50} (96 h): > 208 mg/l (Hüls AG, 1996)
Danio rerio (Directive 92/69/EEC, static):	LC_{50} (96 h): > 72 mg/l (Bayer AG, 2000)
Daphnia magna (Directive 92/69/EEC, static):	EC_{50} (48 h): 27 mg/l (Hüls AG, 1995)
Daphnia magna (Directive 92/69/EEC, static):	EC_{50} (48 h): 35 mg/l (Bayer AG, 2000; Bayer Industry Services, 2006)

Chaetogammarus marinus (other method, semi-static): EC_{50} (96 h): 4 mg/l (Adema, 1982)
Desmodesmus subspicatus (Directive 92/69/EEC, static): E_rC_{50} and E_bC_{50} (72 h): > 70 mg/l (Bayer AG, 2000)

Among these valid studies, the highest sensitivity was observed in the test with the most restrictions, i.e. the study of Adema (1982): No standard protocol, no standard organism, no data on test substance purity, no analytical monitoring. In particular, daily renewal of the test solution is not adequate for testing a rapidly hydrolyzing substance, and addition of a solvent (0.1 ml/l = 110 mg/l) is expected to have increased the solubility of the test substance in the test solutions and thus its bioavailability. An even higher ecotoxicity, i.e. a 48-LC_{50} of 1.8 mg/l, was found in the above mentioned study in *Leuciscus idus*, which, however, cannot be considered valid. Although in both studies an increased bioavailability of the poorly soluble test substance has to be assumed due to the presence of a solubilizer, they give an indication that unhydrolyzed 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate probably has a significantly higher ecotoxicity than its hydrolysis products.

As mentioned above, the aquatic effects of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate relevant in the environment will be those of its hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine. For this substance (CAS No. 2855-13-2), the $PNEC_{aqua}$ was derived in separate documentation (OECD, 2004). The lowest valid acute test results of aquatic testing determined for fish, daphnids, and algae with 3-aminomethyl-3,5,5-trimethylcyclohexylamine were as follows:

Leuciscus idus (Directive 84/449/EEC, semistatic): LC_{50} (96 h) = 110 mg/l;
Daphnia magna (Directive 92/69/EEC, static): EC_{50} (48 h) = 23 mg/l;
Desmodesmus subspicatus (Directive 88/302/EEC, static): E_rC_{50} (72 h) > 50 mg/l; E_bC_{50} = 37 mg/l.

Chronic Toxicity Test Results

There are no data available for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

For its hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine, long-term aquatic toxicity data were available for two trophic levels (OECD, 2004):

Daphnia magna (OECD TG 202, semistatic): NOEC (21 d) = 3.0 mg/l;
Desmodesmus subspicatus (Directive 88/302/EEC, static): E_rC_{10} (72 h) = 11 mg/l; E_bC_{10} = 3.0 mg/l.

Determination of $PNEC_{aqua}$

According to the EU Technical Guidance Document (ECB, 2003), an assessment factor of 50 was applied to the lower of two long-term results covering two trophic levels, i.e. NOEC for *Daphnia* = 3.0 mg/l. Thus a $PNEC_{aqua}$ of 60 µg/l for aquatic organisms was calculated for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (OECD, 2004).

Toxicity to Microorganisms

In a test comparable to OECD TG 209, Bayer AG (2000) determined a 3 h-EC_{50} of 263 mg/l, based on nominal concentrations, in activated sludge of a predominantly domestic sewage.

4.2 Terrestrial Effects

There are no data available.

4.3 Other Environmental Effects

There are no data available.

4.4 Initial Assessment for the Environment

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is a colorless to yellowish, water sensitive liquid with a melting point of –60°C, a boiling point (with decomposition) of approximately 310°C at 1013 hPa, a water solubility of approximately 15 mg/l at 23°C, a density of 1.058 g/cm^3 at 20°C, and a vapor pressure of 0.064 Pa at 20°C. The calculated log K_{OW} is 4.75. The most important values for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) concerning environmental behavior and ecotoxicity are a melting point of 10°C, a vapor pressure of ca. 2 Pa at 20°C, a measured log K_{OW} of 0.99 at 23°C, and miscibility with water. This hydrolysis product was already evaluated in the OECD HPV Chemicals Program.

In the atmosphere, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is photodegraded by reaction with hydroxyl radicals with a calculated half-life of 1.8 days. For 3-aminomethyl-3,5,5-trimethylcyclohexylamine a half-life of 0.2 days is estimated. In water, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is expected to hydrolyze with a half-life of approximately 1 hour under environmental conditions, forming at high concentrations a white polymer, which is insoluble in water, or at low concentrations 3-aminomethyl-3,5,5-trimethylcyclohexylamine. Photolytic degradation in surface waters is expected to be of minor importance due to the absence of relevant chromophores in the chemical structure.

Biodegradation of the substance itself, which was not observed in a manometric respiratory test according to Directive 92/69 EEC, is irrelevant as a primary degradation step because hydrolysis is much faster. The hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine is not readily biodegradable (OECD 301A: 8% degradation after 28 days). However, in a simulation test with activated, non-adapted sludge, a degradation of 42% (including a minor, though not negligible contribution by adsorption to sludge) was measured after a contact time of 6 hours.

Distribution modeling according to Mackay Level I indicates that the main target compartments will be soil and sediment with approximately 43% each, followed by water with about 10%. A calculated log K_{OC} of 4.562 indicates very high adsorption to the organic phase of soils and sediments. For the hydrolysis product a log K_{OC} of 2.532 corresponds to a moderate potential for geoaccumulation. An estimated Henry's law constant of 0.000446 Pa m^3/mol for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine indicates also very low volatility. Due to the rapid hydrolysis of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, volatilization will not be an important fate process for the environment. The calculated Henry's law constant of 0.941 Pa m^3/mol indicates low volatility from aqueous solution. Environmental distribution considerations for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate are of little relevance because the reaction with water is expected to eliminate the substance from the environment with a half-life of approximately 1 hour. The target compartment for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine (CAS No. 2855-13-2) is water (99.8%) as outlined in separate documentation on this compound (the chemical was already evaluated in the OECD HPV Chemicals Program).

A calculated bioconcentration factor of 910 is irrelevant because rapid hydrolysis inhibits bioconcentration. The hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a log K_{OW} of 0.99 which indicates a low bioaccumulation potential.

For bacteria (activated sludge of a predominantly domestic sewage) an EC_{50} (3 h) of 263 mg/l (nominal) 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was determined according to

OECD TG 209. The aquatic effects of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate relevant in the environment will be those of its hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine. For this substance, the $PNEC_{aqua}$ was derived in separate documentation (SIAM 18). For 3-aminomethyl-3,5,5-trimethylcyclohexylamine the lowest valid acute test results of aquatic testing determined for fish, daphnids, and algae were as follows:

Leuciscus idus (Directive 84/449/EEC, semistatic): LC_{50} (96 h) = 110 mg/l;
Daphnia magna (Directive 92/69/EEC, static): EC_{50} (48 h) = 23 mg/l;
Desmodesmus subspicatus (Directive 88/302/EEC, static): E_rC_{50} (72 h) > 50 mg/l; E_bC_{50} = 37 mg/l.

Long-term aquatic toxicity data for 3-aminomethyl-3,5,5-trimethylcyclohexylamine were available for two trophic levels:

Daphnia magna (OECD TG 202, semistatic): NOEC (21 d) = 3.0 mg/l;
Desmodesmus subspicatus (Directive 88/302/EEC, static): E_rC_{10} (72 h) = 11 mg/l; E_bC_{10} = 3.0 mg/l.

According to the EU Technical Guidance Document, an assessment factor of 50 was applied to the lower of two long-term results covering two trophic levels, i.e. NOEC for *Daphnia* = 3.0 mg/l. Thus a $PNEC_{aqua}$ of 60 µg/l for aquatic organisms was calculated for the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

5 RECOMMENDATIONS

Human Health:

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute inhalation toxicity [target: respiratory tract], skin corrosion and serious eye damage, skin sensitization and predicted to be a respiratory tract sensitizer because it is a diisocyanate, genotoxicity in vitro). Based on data presented by the Sponsor country (relating to production by one producer which accounts for more than 50% of global production and relating to the use pattern in several OECD countries), occupational and consumer exposure is anticipated to be low. Adequate risk management decisions are in place regarding the workplace. 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 is currently of low priority for further work. The chemical (including its hydrolysis product) possesses properties indicating a hazard for the environment (acute aquatic toxicity to invertebrates). Based on the data presented by the Sponsor country (relating to production of one producer which accounts for more than 50% of the 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.

6 REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists) (2004). TLVs and BEIs, Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. Cincinnati, OH; ACGIH.

Adema DMM (1982). Tests and desk studies carried out by MT-TNO during 1980-1981 for annex II of marpol 1973. (Rep.No. CL82/14, 52 pp). TNO, Delft (NL).

Ahrens W and Jöckel KH (1997). Exposure to hazardous agents in the paper and pulp industry. Zentralbl. Arbeitsmed., Arbeitsschutz Ergon. 47, 390-401.

American Cyanamid Company (1987). A closed-patch repeated insult dermal sensitization study in guinea pigs with TDI, MDI, p-TMXDI, IPDI, m-TMXDI, HMDI and m-TMI, Project No. 4971-84. NTIS/OTS Microfiche 0515234, Doc 86-870000795.

Auer (1989). Auer-Technikum, Ausgabe 12, 380-385. Auer-Gesellschaft mbH, Berlin.

Bayer AG (1984). Isophorondiisocyanat (IPDI) - Untersuchungen zur sensibilisierenden Wirkung an der Meerschweinchenhaut (modif. "Maximierungstest" mit nur intrakutaner Induktion). Bayer AG (Wuppertal) Report No. 13041 (unpublished).

Bayer AG (1994). Bestimmung von physikalisch-chemischen Stoffdaten - Dampfdruck. Report No. 94/121 B (unpublished).

Bayer AG (1995 a). Isophorondiisocyanat - study on acute inhalation toxicity in rats according to OECD No. 403 (English translation from the German). NTIS/OTS Microfiche 0558208, Doc 86-960000068.

Bayer AG (1995 b). Isophorondiisocyanat - study on acute inhalation toxicity in rats according to OECD 403. Report No. 24245. Bayer AG, Wuppertal (unpublished).

Bayer AG (1995 c). Support: isophorondiisocyanat - study on acute inhalation toxicity in rats according to OECD No. 403. NTIS/OTS Microfiche 0537597-1, Doc 86-960000012.

Bayer AG (1996). IPDI (Isophorondiisocyanat), evaluation of respiratory sensitization in guinea-pigs following intradermal induction. Report No. 24967, 1458 pp., also on NTIS/OTS Microfiche 0558691, Doc 86-960000490 (1996).

Bayer AG (1999). Decrease of NCO-content in water - Desmodur I. Report No. N 99/0050/01 LEV (unpublished).

Bayer AG (2000). Investigation of the ecological properties of DESMODUR I. Bayer AG (Leverkusen) Report No. 860 A/99 with attachments (unpublished).

Bayer AG (2003). Isophorondiisocyanate (IPDI) subacute inhalation toxicity on rats, study no. T0071598. Report No. AT00440, 398 pp (unpublished).

Bayer HealthCare AG (2006). Isophorone diisocyanate - micronucleus test on male mouse after inhalative exposure for 6 hours. Bayer HealthCare Report No. AT03075 (unpublished).

Bayer Industry Services (2006). Re-evaluation of effect concentrations to *Daphnia magna* for Desmodur I (CAS: 4098-71-9) (unpublished).

Bayer MaterialScience AG (2006). Bayer isophorone diisocyanate exposure questionnaire (unpublished) and EU safety data sheet.

Belsito DV (2003). Common shoe allergens undetected by commercial patch-testing kits: dithiodimorpholine and isocyanates. Am. J. Contact Dermatitis 14, 95-96.

Biosphere Research Center Inc. (1991). Dermal sensitization study of compound number 11583B15 and isophorone diisocyanate. Report No. 81-149. Biosphere Research Center Inc. (BRC), New City (NY, USA).

Clarke CW and Aldons PM (1981). Isophorone diisocyanate induced respiratory disease (IPDI). Aust. N.Z. J. Med. 11, 290-292.

Danish Product Register (2002). Communication to BUA.

Dearman RJ, Spence LM, Kimber I (1992). Characterization of murine immune responses to allergenic diisocyanates. Toxicol. Appl. Pharmacol. 112, 190-197.

Degussa AG (2001). VESTANAT(R) IPDI - isophorone diisocyanate - 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Degussa Coatings & Colorants information sheet 43.13.018e / 12.01.

Degussa AG (2006). Unpublished calculations using standard methods / equations.

Degussa North America (2006). Degussa North America isophorone diisocyanate exposure questionnaire (unpublished) and EU safety data sheet.

DFG (Deutsche Forschungsgemeinschaft, Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe) (2005). MAK- und BAT-Werte-Liste 2005, Mitteilung 41. Wiley-VCH (Weinheim, Germany).

ECB (2003). Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on risk assessment of new notified substances, Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Part II. European Commission Joint Research Centre. EUR 20418 EN/2.

E.I. du Pont de Nemours and Company (1987). Mouse sensory irritation. NTIS/OTS Microfiche 0514930, Doc 86-870001028.

Frick M, Björkner B, Hamnerius N and Zimerson E (2003). Allergic contact dermatitis from dicyclohexylmethane-4,4'-diisocyanate. Contact dermatitis 48, 305-309.

Germanaud J, Proffit V, Janvoie B, Lemarie E and Lasfargues G (2003). Pneumopathy due to isocyanate hypersensitivity: recognition as an occupational disease. Rev. Mal. Respir. 20, 443-449.

Henschler D (1972). Isophorondiisocyanat - Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten. Verlag Chemie.

Hüls AG (1983). 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat - Prüfung auf sensibilisierende Eigenschaften am Meerschweinchen nach B. Magnusson und A.M. Kligman (gemäß OECD Richtlinien). Report 2-5-120-83 (unpublished). IBR International Bio-Research (Walsrode).

Hüls AG (1984 a). Prüfung der akuten Hautreizwirkung von Isophorondiisocyanat (IPDI). Report No. 0290 (unpublished).

Hüls AG (1984 b). Prüfung der akuten Augen- und Schleimhautreizwirkung von Isophorondiisocyanat (IPDI). Report No. 0291 (unpublished).

Hüls AG (1985). Akute dermale Toxizität von Isophorondiisocyanat (IPDI) für Ratten. Report No. 0385 (unpublished).

Hüls AG (1993 a). Mutagenitätsuntersuchung von Isophorondiisocyanat (IPDI) mit Hilfe des Salmonella typhimurium / Mikrosomen-Mutagenitäts-Tests nach Ames. Report No. 84/25 (unpublished).

Hüls AG (1993b). Internal communication concerning ecotoxicity and biodegradation of isophorone diisocyanate, 23.12.1993.

Hüls AG (1994). Internal communication concerning ecotoxicity and biodegradation of isophorone diisocyanate, 26.05.1994.

Hüls AG (1995). Bestimmung der Auswirkungen von Vestanat IPDI auf das Schwimmverhalten von *Daphnia magna*. Report No. DK-654 (unpublished).

Hüls AG (1996). Bestimmung der akuten Wirkungen von Vestanat IPDI gegenüber Fischen. Report No. FK 1369 (unpublished).

IBR (International Bio-Research) (1976). Akute Toxizitätsprüfung von "3-Isocyanatomethyl-3.5.5-trimethylcyclohexyl isocyanat" nach oraler Applikation an der Ratte. Report 1 - 4 - 382/1 - 76 (unpublished).

Infracor GmbH (2000). Löslichkeits- und Abbauverhalten von Isophorondiisocyanat (IPDI) in Wasser. Communication Dr. W. Schleich to Degussa AG dated 26 June 2000 (unpublished).

INRS (Institut national de recherche et de sécurité), Paris (1988). Diisocyanate d'isophorone. Fiche Toxicologique 166, 1-4.

Karlsson D, Spanne M, Dalene M and Skarping G (2000). Airborne thermal degradation products of polyurethane coatings in car repair shops. J. Environ. Monit. 2, 462-469.

Kimmerle G (1968). Isophorondiisocyanat - toxikologische Untersuchungen. Report 908 (unpublished). Bayer AG (Wuppertal).

Klaus AM (2004). Isophorondiisocyanat (IPDI) - developmental toxicity study in rats after inhalation. Report No. T7072620 (unpublished). Bayer AG (Wuppertal).

Krötlinger F (1994). Isophorondiisocyanat, study for skin irritation/corrosion in rabbits. Report No. 22961 (unpublished). Bayer AG (Wuppertal).

Lachapelle JM and Lachapelle-Ketelaer MJ (1979). Cross-sensitivity between isophorone diamine (IPD) and isophorone diisocyanate (IPDI). Contact Dermatitis 5, 55.

Militello G, Sasseville D, Ditre C and Brod BA (2004). Allergic contact dermatitis from isocyanates among sculptors. Dermatitis 15, (3), 150-153.

Mobay Chemical Corporation (1984 a). Sensory irritation of isophorone diisocyanate (IPDI) to mice, study number 82-341-01. Report 538. Mobay Chemical Corporation (Metcalf, Stilwell, KS, USA).

Mobay Chemical Corporation (1984 b). Sensory irritation with isophorone diisocyanate (IPDI) in rats. Report No. 540. NTIS/OTS Microfiche 0515439, Doc 86-870001280.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E (1986). Salmonella mutagenicity tests: II. results from the testing of 270 chemicals. Environ. Mutagen. Suppl. 8, 1-119.

OECD (2004). SIAP 3-aminomethyl-3,5,5-trimethylcyclohexylamine, approved at SIAM 18, Paris April 2004.

Pauluhn J (2004). Analysis of bronchoalveolar-lavage following acute inhalation toxicity in rats (exposure: 1 x 6 hours). Bayer HealthCare AG Report No. AT01428 (unpublished).

RCC (Research & Consulting Company Ltd.) (1988). 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat - 4-hour acute inhalation toxicity study in rats. Report No. 094320 (Hüls AG, unpublished).

Rhodia PPMC (2002). Isophorone diisocyanate exposure questionnaire (unpublished).

Rhodia Operations (2006). Isophorone diisocyanate exposure questionnaire (unpublished).

Rothe A (1976). Zur Frage arbeitsbedingter Hautschädigungen durch Polyurethanchemikalien. Berufsderm. 24, 7-24.

RTC (Research Toxicology Centre) (2003). IPDI chromosome aberrations in Chinese hamster ovary cells in vitro. Report No. 8148 (unpublished). RTC (Rome).

Sax NI and Lewis RJ (1987) in Hawley's Condensed Chemical Dictionary, 11th ed., 659. Van Nostrand Reinhold Co. (New York).

Schreiber G (1981). Data of FhG, Bericht über die Prüfung von Isophorondiisocyanat auf Schleimhautreizwirkung. Communication of April 2, 1981 (at the request of Bayer AG).

Society of Toxicology (Technical Committee of the Inhalation Specialty Section) (1992). Recommendations for the conduct of acute inhalation limit tests. Fund. Appl. Toxicol. 18, 321-327.

SPIN (2006). Substances in Preparations in Nordic Countries. (http://www.spin2000.net)

Swedish Product Register (2002). Communication to BUA.

Swiss Product Register (2001). Communication to BUA.

Thomas RG (1990). Volatilization from water. **In:** Handbook of chemical property estimation methods; Lyman WJ, Reehl WF and Rosenblatt DH (Eds.), McGraw-Hill Book Company, New York, p15-16.

Thyssen (1976). Bestimmung der akuten Toxizität (LD50), Substanz 3-Isocyanatomethyl-3,5,5-trimethylcyclohexylisocyanat (IPDI). Bayer AG short report, July 23, 1976 (unpublished).

Tinnerberg H, Skarping G, Dalene M, and Hagmar L (1995). Test chamber exposure of humans to 1,6-hexamethylene diisocyanate and isophorone diisocyanate. Int. Arch. Occup. Environ. Health 67, 367-374.

TRGS 402 (1997). Technische Regeln für Gefahrstoffe 402: Ermittlung und Beurteilung der Konzentrationen gefaehrlicher Stoffe in der Luft in Arbeitbereichen http://www.baua.de/prax/ags/trgs402.pdf.

TRGS 430 (2004). Isocyanate –Exposition und Ueberwachung http://www.baua.de/prax/index.htm

TRGS 900 (2004). Technische Regeln für Gefahrstoffe 900: Limit values relating to air in the workplace, http://www.baua.de/prax/ags/trgs900.pdf.

Tyrer FH (1979). Hazards of spraying with two-pack paints containing isocyanates. J. Soc. Occup. Med. 29, 22-24.

Vohr HW (1993). Isophorondiisocyanat - Untersuchungen auf hautsensibilisierende Wirkung bei Meerschweinchen (Maximierungstest nach Magnusson und Kligman). Report No. 22645 (unpublished). Bayer AG (Wuppertal).

Zissu D, Binet S, Limasset JC (1998). Cutaneous sensitization to some polyisocyanate prepolymers in guinea pigs. Contact Dermatitis 39, 248-251.

I U C L I D

Data Set

Existing Chemical	:	ID: 4098-71-9
CAS No.	:	4098-71-9
EINECS Name	:	3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
EC No.	:	223-861-6
TSCA Name	:	Cyclohexane, 5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethyl-
Molecular Formula	:	C12H18N2O2

Producer related part

Company	:	Degussa AG
Creation date	:	07.09.2001

Substance related part

Company	:	Degussa AG
Creation date	:	07.09.2001
Status	:	
Memo	:	Submission to ICCA
Printing date	:	16.04.2007
Revision date	:	31.05.2006
Date of last update	:	16.04.2007
Number of pages	:	116
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	cooperating company
Name	:	Bayer MaterialScience AG
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Telefax	:	+49 214 30-52973
Telex	:	
Cedex	:	

Email : jochen.brueck@bayermaterialscience.com
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02.06.2006

Type : cooperating company
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Contact person : Robin Ruppel-Kerr
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Homepage : www.bayermaterialscience.com

Type : cooperating company
Name : Degussa AG
Contact person : Dr. Michael Weiß, Marl
Date : 01.01.2002
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Town : 40474 Duesseldorf
Country : Germany
Phone : +49 2365 49 4607
Telefax : +49 2365 49 7275
Telex :
Cedex :
Email : michael.weiss@degussa.com
Homepage : www.degussa.com

Type : cooperating company
Name : Degussa North America
Contact person : Alex Bell
Date : 01.10.2002
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Email : alex.bell@degussa.com
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Type : cooperating company
Name : Rhodia Operations
Contact person : Bernard Hendrickx
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Country : France
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Telefax : +33 1 5356 5160
Telex :
Cedex :

Email : bernard.hendrickx@eu.rhodia.com
Homepage :

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type : manufacturer
Name of plant : Bayer MaterialScience AG
Street :
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Country : Germany
Phone : +49 214 30-71970
Telefax : +49 214 30-52973
Telex :
Cedex :
Email :
Homepage : www.bayermaterialscience.com

(18)

Type : manufacturer
Name of plant : Bayer MaterialScience LLC
Street :
Town : Baytown, TX
Country : United States
Phone : +1 412 777-2285
Telefax : +1 412 777-7484
Telex :
Cedex :
Email :
Homepage : www.bayermaterialscience.com

Type : manufacturer
Name of plant : Degussa North America
Street : 4301 Degussa Road
Town : 36582 Theodore, AL
Country : United States
Phone : +1 251-443-3462
Telefax : +1 251-443-3607
Telex :
Cedex :
Email :
Homepage : www.degussa.com

(32)

Type : manufacturer
Name of plant : Rhodia Operations, Usine du Pont de Claix
Street : Rue Lavoisier, BP 17
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Country : France
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Telefax : +33 1 5356 5160
Telex :
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Email : Laura.planel@eu.rhodia.com
Homepage :

(88)

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : ca. 99.8 - 100 % w/w
Colour : light yellowish
Odour : pungent smell

Remark : Company (site): Bayer MaterialScience AG, Leverkusen (Germany)
12.06.2006 (18)

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : ca. 50 - 100 % w/w
Colour : colorless to yellowish
Odour : stinging

Remark : Company (site): Degussa North America, Theodore (AL, USA)
Result : Pure substance as well as a variety of formulations with the trimer and other derivatives are produced.
12.06.2006 (32)

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : 100 % w/w
Colour :
Odour :

Remark : Company (site): Rhodia Operations, Usine du Pont de Claix (France)
(88)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Cyclohexane, 5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethyl-

Isophorone diisocyanate

IPDI

1-(Isocyanatomethyl)-5-isocyanato-1,3,3-trimethylcyclohexane

1-Isocyanato-3,3,5-trimethyl-5-(isocyanatomethyl)cyclohexane

1-Isocyanato-3-(isocyanatomethyl)-3,5,5-trimethylcyclohexane

1-Isocyanato-3-isocyanatomethyl-3,5,5-trimethylcyclohexane

1-Isocyanato-5-(isocyanatomethyl)-3,3,5-trimethylcyclohexane

1,3,3-Trimethyl-1-(isocyanatomethyl)-5-isocyanatocyclohexane

3-(Isocyanatomethyl)-3,5,5-trimethylcyclohexyl isocyanate

3,3,5-Trimethyl-5-(isocyanatomethyl)cyclohexyl isocyanate

5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane

Desmodur I

12.06.2006

VESTANAT IPDI

12.06.2006

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name : total chlorine
Molecular formula :
Value : < .04 % w/w

Remark : Product specification. Company (site): Bayer MaterialScience AG, Leverkusen (Germany)

12.06.2006 (29) (52)

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name : hydrolyzable chlorine
Molecular formula :
Value : < .02 % w/w

Remark : Product specification. Company (site): Bayer MaterialScience AG, Leverkusen (Germany)

12.06.2006 (29) (52)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 25000 - 35000 tonnes produced in 2005

Remark : Worldwide annual production, including production volume of the Sponsor country (approximately 2/3)

15.09.2006 (18) (32) (88)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits : yes
Symbols : T, N, ,
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
(51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases : (26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(28) After contact with skin, wash immediately with plenty of soap and 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)
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

Remark : Index No. 615-008-00-5
Nota 2
Specific limits:
C >= 25 %: T, N; R23-36/37/38-42/43-51/53
20 % <= C < 25 %: T; R23-36/37/38-42/43-52/53
2.5 % <= C < 20 %: T; R23-42/43-52/53
2 % <= C < 2.5 %: T; R23-42/43
0.5 % <= C < 2 %: Xn; R20-42/43

18.07.2006

1.6.2 CLASSIFICATION

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

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 : Use in closed system

Remark : Company (site): Bayer MaterialScience AG, Leverkusen (Germany)
Company (site): Degussa North America, Theodore (AL, USA)
Company (site): Rhodia Operations, Usine du Pont de Claix (France)
Result : The producers have agreed to recommend in their safety data sheets that handling the substance "requires appropriate protective measures. These products may therefore be used only in industrial or trade applications. They are not suitable for use in homeworker (DIY) applications."
(18) (32) (88)

Type of use : type
Category : Non dispersive use

Result : Denmark (February 2002):
Total number of products = 151
Total tonnage = 10 t/year
Consumer or professional products not distinguished
Various concentrations, 3 products > 50%
Sweden (Februar 2002):
Total number of products = 65
Number of consumer products = 13
Concentrations not reported
Switzerland (December 2001):
Total number of products = 285
Number of consumer products = 13
concentration range < 1% except 1 product 1-10%
Number of products for professional use = 272;
various concentrations, 4 products > 50%
12.06.2006 (26) (99) (100)

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

12.06.2006 (18) (32) (88) (97)

Type of use : industrial
Category : Polymers industry

Result : The substance is a monomer for polyurethanes in various applications, particularly coatings, varnishes and impregnation for e.g. cars, floors, leather, cans and coils, and special (waterborne or hot melt) adhesives. Isophorone diisocyanate is mainly used for the manufacture of polyurethane coating raw materials like prepolymers. As a cycloaliphatic diisocyanate it meets all important requirements for the manufacture of lightstable and weather-resistant polyurethanes.
12.06.2006 (26) (29) (97) (100)

Type of use : industrial
Category : Paints, lacquers and varnishes industry

12.06.2006 (88) (97) (99) (100)

Type of use : use
Category : Intermediates

Remark : Intermediate in the manufacture of polyisocyanates and polyurethanes
12.06.2006 (18) (32) (88) (97)

Type of use : use
Category : Process regulators

Remark : Crosslinking agent = Hardener
Sweden (February 2002):
Hardeners, paints, various products for construction
12.06.2006 (97) (99)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Method : Manufacturing of isophorone diisocyanate by phosgenation of isophorone diamine (CAS RN 2855-13-2) in a closed system continuous process. Water is used only in cleaning operations.
Remark : Company (site): Bayer MaterialScience AG, Leverkusen (Germany)
12.06.2006 (15) (18)

Origin of substance : Synthesis
Type : Production

Method : Isophorone diisocyanate is produced in a closed system continuous process using the urea route. Water is used neither in the production process nor in cleaning the system.
Remark : Company (site): Degussa North America, Theodore (AL, USA)
(31) (32)

Origin of substance : Synthesis
Type : Production

Method : Manufacturing of isophorone diisocyanate by phosgenation of isophorone

diamine (CAS RN 2855-13-2), purification by distillation. No water is involved in the production process or in cleaning the system.

Remark : Company (site): Rhodia PPMC, Usine du Pont de Claix (France)

(89)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value : .046 mg/m3
Short term exposure limit value
Limit value : 1
Time schedule :
Frequency : times

Remark : 0.005 ppm

(33)

Type of limit : TLV (US)
Limit value : .045 mg/m3

Remark : 0.005 ppm
Test condition : Analogy to the TLV-TWA for toluene-2,4-diisocyanate (TDI)

(1)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 2 (water polluting)

Remark : Classification according to Annex 2 of the Administrative Regulation of Substances Hazardous to Water (VwVwS). No. 1203 in catalogue.

18.07.2006 (105)

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

Classified by : other: Bayer AG
Labelled by : other: Bayer AG
Number : other: 5.2.5 organic substances
Class of danger :

Remark : Organic substances in the exhaust shall not exceed the limit value of 0.10 kg/h or the concentration of 20 mg/m3.

13.06.2006 (20) (22)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

Type	:	thermal breakdown products
CAS-No	:	74-90-8
EC-No	:	200-821-6
EINECS-Name	:	hydrogen cyanide
IUCLID Chapter	:	
Result	:	When heated to decomposition temperature, isophorone diisocyanate emits irritating, corrosive, and/or toxic fumes of nitrogen oxides, hydrogen cyanide, carbon monoxide, and isocyanate vapor.

13.06.2006 (18) (20) (32)

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Source of exposure	:	Human: indirect exposure
Exposure to the	:	Substance
Method	:	Collection and derivatization of air samples in impinger flask with di-n-butylamine in toluene and glass-fibre filter in series; quantification by liquid chromatotraphy / mass spectrometry
Remark	:	Occupational exposure data: heating of polyurethanes This study indicates a potential for occupational exposure to isocyanates from heating of polyurethanes. Since the isocyanates detected were formed only at elevated temperatures, their release from finished products under environmental conditions is not expected.
Result	:	Study a) = Thermal degradation: Up to 1 % of the total sample weight was emitted as different isocyanates. At temperatures < 350 degree C, diisocyanate monomers dominated. At higher temperatures, monoisocyanates dominated. Study b) = Workplace exposure: The maximum concentration of isophorone diisocyanate in air was 39 µg/m3. No further concentration values for this substance are reported.
Test condition	:	Two studies: 1a) 69 different polyurethane coating samples were heated to temperatures in the range 100-500 degree C; 1b) Occupational exposure in 2 car repair shops (24 + 1 samples) was determined during grinding, cutting, and welding operations. Isocyanates were formed by thermal degradation of polyurethanes, particularly during cutting and welding operations. 2) Particles smaller than about 1.5 µm passed through the impinger and were collected on the filter. After sampling, they were also reacted with dibutylamine. 3) Concentrations of isocyanates from impinger flask and from filter were determined separately.
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment

13.06.2006 (66)

Source of exposure	:	Human: indirect exposure

Exposure to the : Substance

Remark : Occupational exposure in paper and pulp industry
Result : Exposure to isophorone diisocyanate was expected only in the impregnation and coating work area. All 33 analyses were negative, i.e. isophorone diisocyanate was below the detection limit (< 0.02 mg/m3).
Test condition : All available occupational exposure data gathered by the German paper professional association between 1974 and 1993 were evaluated for various chemical substances and dust. Data were assigned to work areas. From a total of 3946 individual values, 33 values from 5 plants were for isophorone diisocyanate.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
13.06.2006 (3)

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

Method : ISOLOGGER
Remark : Occupational exposure from production
Company (site): Rhodia Operations, Usine du Pont de Claix (France)
Result : - 10 Occupational exposure have been performed between 2002 and 2005. Samples were collected for durations ranging from 2 minutes up to 2 hours with the Isologger method. All concentrations were below 0.01 mg/m3.
13.06.2006 (88)

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

Method : Absorption on glass wadding which is soaked in a nitro reagent / described in TRGS 402 (DFG No. 1)
Remark : Occupational exposure from production
Company (site): Bayer MaterialScience AG, Leverkusen (Germany)
Result : In 2004 and 2005, all concentrations (4 measurements) were below the detection limit of 1 µg/m3.
Exposure during production is only possible in case of accidental spillage.
13.06.2006 (18)

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

Method : Occupational exposure: OSHA PV 2034: Integrated active sampling using a cassette filter 225/9002 at a flow rate of 1000 ml/min
Remark : Occupational exposure from production
Company (site): Degussa North America, Theodore (AL, USA)
Result : Occupational exposure is possible by skin contact and inhalation: Results ranged from non detectable to 0.0026 ppm (24 µg/m3) 8 hour-time weighted average.
Test condition : Eight Industrial Hygiene measurements were performed during the years 2003, 2004, 2005.
Actual sampling time varied from 1 to 2 hours with results extrapolated to an 8hr time weighted average (TWA).
13.06.2006 (32)

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

Remark : Release from production
Company (site): Rhodia Operations, Usine du Pont de Claix (France)
Result : - There is no release to atmosphere or water at this site.
- Solid waste from the production of isophorone diisocyanate is incinerated.

The total annual quantity including wastes from the manufacture of hexane-1,6-diisocyanate amounts to 40 t.

13.06.2006 (88)

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

Remark : Release from production
Company (site): Bayer MaterialScience AG, Leverkusen (Germany)
Result : Release to the atmosphere is below 25 kg/year.
Release to water or other environmental media is zero.

13.06.2006 (18)

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

Remark : Release from production
Company (site): Degussa North America, Theodore (AL, USA)
Result : Release to the environment:
- Air: 122 kg/year
- Water: None (no contact with water)
- Solid waste: 2 drums of miscellaneous plant waste/month is disposed of off site.

13.06.2006 (32)

Source of exposure : Human: exposure through intended use
Exposure to the : Substance

Remark : Release from use in outdoor deck coating process
Result : Isophorone diisocyanate was not detected at a detection limit of 0.54 µg/g wet product. Based on concentrations of other components it was concluded that emissions are virutally complete after 5 hours.
Test condition : - Test substance: Commercial coating formulation with isophorone diisocyanate (Polyglaze AL Brown), diisocyanate concentration not reported.
- Test vessel: Sample chamber simulating an outdoor deck coating process
- Test temperature: 21 °C
- Sampling: Air with 50 percent relative humidity was passed over a freshly applied coating at 1.0 l/min into a reaction vessel containing 1-(2-methoxyphenyl)piperazine as a derivatizing agent for up to 15 hours.
- Analysis: Removal of residual derivatizing agent by reaction with acetic anhydride; drying; solution in methanol; sonication; filtration; HPLC/UV (254 nm).
Reliability : (4) not assignable
Documentation insufficient for assessment

(65)

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : External
Chapters covered : 2
Date of search : 31.03.2006

Remark : Environmental chemistry and ecotoxicity search performed by BUA: CAS number search in external databases; e.g. Registry, Beilstein, Chemlist and Chemical Abstracts.

13.06.2006

Type of search : External
Chapters covered : 3, 4
Date of search : 31.03.2006

Remark : Environmental chemistry and ecotoxicity search performed by BUA: CAS number search in external databases; e.g. Registry, Beilstein, Chemlist and Chemical Abstracts.

13.06.2006

Type of search : Internal and External
Chapters covered : 5
Date of search : 26.04.2006

Remark : CAS number search by BUA in external and internal databases; e.g. Biosis, Embase, Toxline, Scisearch.

13.06.2006

1.13 REVIEWS

2.1 MELTING POINT

Value : = -60 °C
Decomposition : no, at °C
Sublimation : no
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from peer reviewed handbook
17.07.2006 (92)

Value : = -60 °C
Decomposition : no, at °C
Sublimation : no
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
17.07.2006 (1) (7) (43) (64) (80)

2.2 BOILING POINT

Value : 310 °C at 1013 hPa
Decomposition : yes
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Remark : Decomposition above 260 degree C
Reliability : (2) valid with restrictions
Data from handbook or collection of data, reported in several references and in good agreement with other data on the boiling point of the substance
17.07.2006 (7) (64)

Value : 310 °C at 1000 hPa
Decomposition : yes
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Remark : Decomposition above 260 degree C
Reliability : (2) valid with restrictions
Data from handbook or collection of data, reported in several references and in good agreement with other data on the boiling point of the substance
17.07.2006 (80)

Value : 217 °C at 133 hPa
Decomposition :

Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
13.06.2006 (72)

Value : = 158 °C at 13 hPa
Decomposition : no
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
13.06.2006 (1) (64) (92)

Value : = 153 °C at
Decomposition :
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Remark : This value is probably invalid due to not mentioning a reduced pressure.
Reliability : (3) invalid
Data from handbook or collection of data, not peer reviewed and in conflict with other data on the boiling point of the substance
13.06.2006 (43)

2.3 DENSITY

Type : density
Value : = 1.058 g/cm³ at 20 °C
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data, reported in several references and in good agreement with other data
14.09.2006 (7) (64) (80)

Type : density
Value : = 1.056 g/cm³ at °C
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from peer reviewed handbook or collection of data, but no value of temperature given
17.07.2006 (92)

Type : density
Value : = 1.062 g/cm³ at 20 °C
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
13.06.2006 (1) (72) (73)

Type : density
Value : = 1.058 - 1.064 g/cm³ at °C
Method :
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
17.07.2006 (43)

Type : density
Value : = 1.058 - 1.064 g/cm³ at °C
Method : other: DIN 51757 and ASTM D 2111
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (4) not assignable
Manufacturer/producer data without proof
17.07.2006 (29) (52)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .000635 hPa at 20 °C
Decomposition : no
Method : other (measured): Comparable to OECD Guideline 104 (1981) - vapor pressure balance
Year : 1994
GLP : yes
Test substance : other TS: Isophorone diisocyanate of Bayer AG, coded as DEA 232-I; purity not reported

Result : Measured values vs. corresponding results of regression calculation:
0.000173 hPa at 9.5 °C; regression: 0.000173 hPa
0.000191 hPa at 9.9 °C; regression: 0.000181 hPa
0.000383 hPa at 12.7 °C; regression: 0.000258 hPa
0.000278 hPa at 12.8 °C; regression: 0.000261 hPa
0.000215 hPa at 12.9 °C; regression: 0.000264 hPa
0.000479 hPa at 13.0 °C; regression: 0.000268 hPa
0.000377 hPa at 15.5 °C; regression: 0.000365 hPa
0.000379 hPa at 15.7 °C; regression: 0.000374 hPa
0.000399 hPa at 17.4 °C; regression: 0.000462 hPa
0.000300 hPa at 17.5 °C; regression: 0.000468 hPa
0.000912 hPa at 19.3 °C; regression: 0.000583 hPa

0.00105 hPa at 19.5 °C; regression: 0.000598 hPa
0.000751 hPa at 21.0 °C; regression: 0.000716 hPa
0.000642 hPa at 21.2 °C; regression: 0.000734 hPa
0.00570 hPa at 25.6 °C; regression: 0.00125 hPa
0.00417 hPa at 25.7 °C; regression: 0.00127 hPa
0.00197 hPa at 30.7 °C; regression: 0.00230 hPa
0.00199 hPa at 30.9 °C; regression: 0.00235 hPa
0.00711 hPa at 31.1 °C; regression: 0.00241 hPa
0.00794 hPa at 32.5 °C; regression: 0.00280 hPa
0.00296 hPa at 34.6 °C; regression: 0.00366 hPa
0.00316 hPa at 34.8 °C; regression: 0.00375 hPa
0.0105 hPa at 36.7 °C; regression: 0.00466 hPa
0.00993 hPa at 37.9 °C; regression: 0.00535 hPa
0.00655 hPa at 37.9 °C; regression: 0.00535 hPa
0.00755 hPa at 38.0 °C; regression: 0.00541 hPa
0.00854 hPa at 38.0 °C; regression: 0.00541 hPa
0.00508 hPa at 39.0 °C; regression: 0.00607 hPa
0.00506 hPa at 39.4 °C; regression: 0.00635 hPa
0.00973 hPa at 43.9 °C; regression: 0.0107 hPa
0.0101 hPa at 44.1 °C; regression: 0.0109 hPa
Resulting Antoine regression equation:
VP [hPa] = 10**(31.84-23124/(T+639.99)
T = temperature [°C]
Correlation coefficient R = 0.99881
Mean deviation (absolute): 28.70 % of measured value
Regression data reported for key temperatures:
0.000635 hPa at 20 °C
0.00117 hPa at 25 °C
0.0212 hPa at 50 °C

Test condition : - Determination of 43 vapor pressure data between 4.5 and 52.9 °C with vapor pressure balance
- Calibration with reference substance di-(2-ethylhexyl) phthalate
- Exclusion of 12 initial values (too high due to vaporization of residual material from previous measurements by heating)
- Exclusion of too low values (possible precipitation, not applicable in present test)
- Regression fit of Antoine equation
- Consideration of sources of error below 0.01 Pa and above 1 Pa

Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions: Insufficient characterization of test substance (identity, purity), significant scattering of results.
Evidence for the reliability of this study comes from:
- QSAR check with MpBpWin v1.41 from the EPIWIN software suite (v3.11) predicts 0.00115 Torr (0.0015 hPa) at 25 °C, which is in satisfactory agreement.

13.06.2006 (8)

Value : = .00093 hPa at 20 °C
Decomposition : no
Method : other (measured)
Year : 1989
GLP : no
Test substance : other TS: Isophorone diisocyanate of Bayer AG / Hüls AG, minimum purity 99 %

Result : Vapor pressure as a function of temperature

0 °C:	0.000089 hPa
10 °C:	0.00030 hPa
20 °C:	0.00093 hPa

30 °C: 0.0026 hPa
40 °C: 0.0069 hPa
50 °C: 0.017 hPa
60 °C: 0.039 hPa
70 °C: 0.085 hPa
80 °C: 0.18 hPa
90 °C: 0.35 hPa
100 °C: 0.66 hPa
110 °C: 1.20 hPa
120 °C: 2.16 hPa
130 °C: 3.66 hPa
140 °C: 6.00 hPa
150 °C: 9.56 hPa
160 °C: 14.8 hPa
170 °C: 22.4 hPa
180 °C: 33.0 hPa
190 °C: 47.7 hPa
200 °C: 67.6 hPa
210 °C: 94 hPa
220 °C: 129 hPa
230 °C: 174 hPa
240 °C: 230.5 hPa
250 °C: 302 hPa
260 °C: 391.4 hPa
270 °C: 501 hPa
280 °C: 634.4 hPa
290 °C: 795.3 hPa
300 °C: 987.5 hPa

Reliability : (4) not assignable
Manufacturer/producer data without proof
17.07.2006 (52)

Value : = .0004 hPa at 20 °C
Decomposition : no
Method : other (measured): no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
20.07.2006 (1) (7) (43) (64) (80)

Value : = .0004 hPa at 20 °C
Decomposition : no
Method : other (measured): no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from peer reviewed handbook
14.09.2006 (92)

Value : = .0004 hPa at 20 °C
Decomposition : no
Method : other (measured): no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (4) not assignable
Manufacturer/producer data without proof
14.09.2006 (52)

Value : = .00055 hPa at 30 °C
Decomposition : no
Method : other (measured): no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
13.06.2006 (7)

Value : = .009 hPa at 50 °C
Decomposition : no
Method : other (measured): no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data, in conflict with other data at the same temperature
13.06.2006 (1) (64) (80)

Value : = .0009 hPa at 50 °C
Decomposition : no
Method : other (measured): no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
13.06.2006 (7)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : ca. 4.75 at °C
pH value :
Method : other (calculated): SRC Kowwin v1.67 Computer Program, integrated in U.S. EPA's EPI program Vers. 3.11
Year : 2004
GLP :
Test substance :

Remark : Isocyanates hydrolyze ... estimate questionable!
Reliability : (2) valid with restrictions
Accepted calculation method
(30)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : ca. 15 mg/l at 23 °C

pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	of low solubility
Stable	:	no
Deg. product	:	
Method	:	other: Simplified preliminary tests based on OECD Test Guidelines 105 (water solubility) and 111 (hydrolysis as a function of pH) as well as on corresponding EU methods
Year	:	2000
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Degussa AG, purity 99.8 %
Result	:	- TEST 1: Droplet formation was observed. The droplets settled on the bottom of the test vessel and became increasingly coated with a white layer. 14 mg test substance/l water were determined in the analysis after 1 hour. - TEST 2: Droplet formation was observed. 16 mg test substance/l water were determined in the analysis after 1 hour. < 10 mg/l were determined after 24 hours. After this time instead of droplets finely distributed white solids were observed.
Test condition	:	TEST 1: Approximately 1 g test substance was dissolved in 10 ml acetonitrile (CAS RN 75-05-8) and stirred into 1000 ml of purified water. Stirring was discontinued. After 1 hour a sample was taken from the centre of the solution and analyzed. TEST 2: Approximately 100 mg test substance was dissolved in 10 ml acetonitrile and stirred into 1000 ml of purified water. Stirring was continued for 24 hours except for sampling after 1 hour and 24 hours. After settling of droplets, samples were taken from the centre of the solution.
Conclusion	:	OECD Test Guideline 105 (water solubility) is not applicable because the test substance is not sufficiently stable to obtain equilibrium.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles, acceptable for assessment; Restriction: Presence of solubilizer (1 % v/v) slightly increases water solubility.

13.06.2006 (63)

Solubility in	:	Water
Value	:	ca. 6.052 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	of very low solubility
Stable	:	no
Deg. product	:	
Method	:	other: SRC WSKOW v1.40 Computer Program, integrated in U.S. EPA's EPI program Vers. 3.10
Year	:	2002
GLP	:	
Test substance	:	
Reliability	:	(2) valid with restrictions Accepted calculation method

(30)

Solubility in	:	Water
Value	:	at °C

pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : of very low solubility
Stable : no
Deg. product :
Method : other: no data
Year :
GLP : no
Test substance : other TS: Isophorone diisocyanate, purity not specified

Remark : Vigorous exothermal reaction with water, formation of carbon dioxide and isocyanate vapors
Reliability : (3) invalid
Data from handbook or collection of data (not peer reviewed) in obvious conflict with observations in other water behavior and ecotoxicity studies
14.06.2006 (43)

Solubility in : Organic Solvents
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : other: completely miscible with esters, Ketones, ethers, and aromatic and aliphatic hydrocarbons
Stable :
Deg. product :
Method : other: no data
Year :
GLP : no
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
14.06.2006 (92)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 155 °C
Type : other: no data
Method : other
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
17.07.2006 (64) (81)

Value : = 155 °C
Type : closed cup
Method : other

Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
17.07.2006 (7) (43)

2.8 AUTO FLAMMABILITY

Value : = 430 °C at
Method : other: Ignition temperature, no further data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
14.06.2006 (7) (43) (64) (80)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Result : other: Explosive limit: Lower 1.0 % v/v
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
14.06.2006 (64)

Result : other: Explosive limits: Lower 1.0 % v/v, upper 4.5 % v/v
Method : other: no data
Year :
GLP : no data
Test substance : other TS: Isophorone diisocyanate, purity not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
14.06.2006 (7)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Test type : other: no data
Test procedure :

Value	:	13 - 15 mPa s (dynamic) at 23 °C
Result	:	
Method	:	other: DIN EN ISO 3219
Year	:	
GLP	:	no data
Test substance	:	other TS: Isophorone diisocyanate of Hüls AG, minimum purity 99 %
Reliability	:	(4) not assignable Manufacturer data without proof

17.07.2006 (29)

2.14 ADDITIONAL REMARKS

Memo	:	Index of refraction
Result	:	Isophorone diisocyanate of Hüls AG, minimum purity 99 %, Nd at 25 °C: 1.483
Reliability	:	(4) not assignable Manufacturer data without proof

17.07.2006 (29)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	ca. .0000000000088248 cm³/(molecule*sec)
Degradation	:	ca. 50 % after 1.8 day(s)
Deg. product	:	
Method	:	other (calculated): AOP Computer Program, Vers. 1.90, integrated in U.S. EPA's EPI program Vers. 3.10
Year	:	2002
GLP	:	
Test substance	:	
Reliability	:	(2) valid with restrictions Accepted calculation method

(30)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
t1/2 pH	:	ca. 50 minute(s) at 23 °C
Deg. product	:	
Method	:	other: See Test Conditions
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Desmodur I = Isophorone diisocyanate of Bayer AG, Batch no. 1.5/8-73 sampled 07 May 1999, purity not reported.
Remark	:	Preparations with a lower content of acetonitrile were cloudy and inhomogenous due to the low water solubility of the test substance.
Result	:	- Stock solution in acetonitrile: Stable over the time of the experiment. - Time-concentration data of test solution: Concentration Ct at time t as percent of initial concentration Co: 0 seconds: 100.0 % 664 seconds: 88.8 % 1317 seconds: 77.0 % 1980 seconds: 70.4 % 2634 seconds: 69.4 % 3298 seconds: 67.7 % 3959 seconds: 55.4 % 4615 seconds: 45.4 % 5275 seconds: 41.6 % 5933 seconds: 29.5 % 6594 seconds: 22.4 % 7252 seconds: 15.9 % - Rate constant k = [ln (Co/Ct)] / (t-to) = 2.30319E-4 1/s Half-life = ln(2)/k = 3009 s = 50.15 min r = -0.95722
Test condition	:	- Initial test: Minimum concentration of acetonitrile to obtain a clear solution = 40 %.

- Preparation of test solution:
Dissolve 1 g test substance in acetonitrile, total volume 100 ml.
Concentration: 10 g/l
Take 10 ml of this solution, add 30 ml acetonitrile and fill up with water to 100 ml. Concentration: 1 g/l
- Test temperature: 23 °C
- Analysis: GC/FID analysis every 11 minutes

Reliability : (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards, documentation not very detailed.

14.06.2006 (13)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
t1/2 pH : < 7.2 hour(s) at 23 °C
Deg. product : not measured
Method : other: Simplified preliminary tests based on OECD Test Guidelines 105 (water solubility) and 111 (hydrolysis as a function of pH) as well as on corresponding EU methods
Year : 2000
GLP : no
Test substance : other TS: Isophorone diisocyanate of Degussa AG, purity 99.8 %

Result : - TEST 1: Droplet formation was observed. The droplets settled on the bottom of the test vessel and became increasingly coated with a white layer. 14 mg test substance/l water were determined in the analysis after 1 hour.
- TEST 2: Droplet formation was observed. 16 mg test substance/l water were determined in the analysis after 1 hour. < 10 mg/l were determined after 24 hours. After this time instead of droplets fine distributed and white solids were observed.
- Half-life: The half-life of < 7.2 hours is based on a decrease from 100 mg/l to < 10 mg/l within 24 hours in TEST 2.

Test condition : - TEST 1: Approximately 1 g test substance was dissolved in 10 ml acetonitrile (CAS RN 75-05-8) and stirred into 1000 ml of purified water. Stirring was discontinued. After 1 hour a sample was taken from the centre of the solution and analyzed.
- TEST 2: Approximately 100 mg test substance was dissolved in 10 ml acetonitrile and stirred into 1000 ml of purified water. Stirring was continued for 24 hours except for sampling after 1 hour and 24 hours. After settling of droplets, samples were taken from the centre of the solution.
- Half-life derived assuming pseudo-first order degradation kinetics.

Conclusion : OECD Test Guideline 111 (hydrolysis as a function of pH) is not applicable because the water solubility is too low for analytical monitoring of the test substance concentration, even when a solubilizer is used.
OECD Test Guideline 105 (water solubility) is not applicable because the test substance is not sufficiently stable to obtain equilibrium.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles, acceptable for assessment; Restriction: Presence of solubilizer (1 % v/v) slightly increases water solubility.

20.07.2006 (63)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2004

Remark : Rapid hydrolysis makes attaining equilibrium in the environment impossible.
Result : Air: 3.2113 %
Water: 9.7034 %
Soil: 43.1462 %
Sediment: 43.6256 %
Susp. Sediment: 0.2802 %
Fish: 0.0273 %
Aerosol: 0.0061 %
Test condition : Data used:
Molecular weight: 222.29 g/mol
log Pow: 4.75
Vapour pressure: 0.0635 Pa
Water solubility: 0.015 g/l
Melting point: -60 degree C
Temperature: 20 degree C

Volumes, densities, and organic carbon / fat concentration:
Air: 6 000 000 000 m3, 1.206 kg/m3
Water: 7 000 000 m3, 1000 kg/m3
Soil: 45 000 m3, 1500 kg/m3, 2 % OC
Sediment: 21 000 m3, 1300 kg/m3, 5 % OC
Susp. sediment: 35 m3, 1500 kg/m3, 16.7 % OC
Fish: 7 m3, 1000 kg/m3, 5 % fat
Aerosol: 0.12 m3, 1500 kg/m3
Reliability : (2) valid with restrictions
Accepted calculation method

14.06.2006 (30)

Media : water - soil
Method : other (calculation): PCKowWin Version 1.66 as integrated in EpiWin Version 3.11 (first-order molecular connectivity index (1-MCI) method), Syracuse Research Center / U.S. EPA
Year : 2004

Remark : Rapid hydrolysis makes approximation of equilibrium in the environment impossible. Thus the calculated "very high" geoaccumulation potential has no practical relevance.
Result : Koc = 36,450; log Koc = 4.562
"very high" potential for geoaccumulation (Blume scale)
Reliability : (2) valid with restrictions
Accepted calculation method

14.06.2006 (30)

Media : water - air
Method : other (calculation): Vapour pressure x molecular weight / water solubility = 0.0635 Pa x 222.29 g/mol / (15 g/m3)
Year : 2006

Remark : Rapid hydrolysis makes approximation of equilibrium in the environment impossible.
Result : Henry's Law Constant = 0.941 Pa m3/mol
Reliability : (2) valid with restrictions
Accepted calculation method

14.06.2006 (30)

Media : water - air
Method : other (calculation): HENRYWIN v3.10
Year : 2006

Remark : The calculated value reflects the properties of the unhydrolysed molecule without taking into account the sensitivity of isophorone diisocyanate towards hydrolysis.
Result : Henry's Law Constant:
- Bond method: 6.57E-5 atm m3/mol * 101325 Pa/atm = 6.66 Pa m3/mol
- Group method: Incomplete
Reliability : (2) valid with restrictions
Accepted calculation method

14.06.2006 (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 : 28 day(s)
Degradation : = 0 (±) % after 28 day(s)
Result : under test conditions no biodegradation observed
Kinetic of testsubst. : 4 day(s) = 0 %
14 day(s) = 0 %
%
%
%
Control substance : Benzoic acid, sodium salt
Kinetic : 4 day(s) = 69 %
14 day(s) = 88 %
Deg. product :
Method : Directive 92/69/EEC, C.4-D
Year : 2000
GLP : yes
Test substance : other TS: Desmodur I = isophorone diisocyanate of Bayer AG, purity > 99.5 %, Article number 00416258, Batch number 1,5/8-73

Remark : The used concentrations of the test substance did not show toxic effects to bacteria. In a toxicity control a mean degradation of 55 % was achieved after 28 days.
Test condition : INOCULUM/TEST ORGANISM
- Species/strain: mixed population
- Sampling site: WWTP of Wupper area water authority, sampled 09 Aug 1999

- Pretreatment: none
TEST SYSTEM
- Number of culture flasks per concentration: 3 each for test substance, blank control and reference substance; 2 for toxicity control
METHOD OF PREPARATION OF TEST SOLUTION: direct weighing
ANALYTICAL PARAMETER: Dissolved oxygen
SAMPLING: days 4, 6, 8, 12, 14, 18, 20, 22, 26, 28
TEST CONDITIONS
- Test temperature: 20 +/- 1 degree C
- Concentration of suspended solids: 30 mg/l
CONTROLS: blank control, toxicity control, reference substance

Reliability : (1) valid without restriction
Guideline study

14.06.2006 (14)

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : 20 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : = 62 (±) % after 28 day(s)
Result :
Deg. product :
Method : other: OECD Guideline 301 E (1981) and Directive 84/449/EEC, C.3
Year :
GLP : no
Test substance : other TS: Isophorone diisocyanate of Bayer AG, no further information

Reliability : (4) not assignable
Secondary quotation/Documentation insufficient for assessment

17.07.2006 (37) (54) (55)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : other: QSAR estimate
Exposure period : at °C
Concentration :
BCF : = 910
Elimination :
Method : other: calculation with BCFWIN v2.15 as integrated in EPIWIN v3.11, Syracuse Research Center / U.S. EPA
Year : 2006
GLP :
Test substance : other TS: Isophorone diisocyanate (CAS No. 4098-71-9)

Remark : Rapid hydrolysis makes approximation of equilibrium in the environment impossible. Thus the calculated bioaccumulation potential has no practical relevance.
Reliability : (2) valid with restrictions
Accepted calculation method

21.06.2006 (30)

Species : other: QSAR estimate
Exposure period : at °C
Concentration :
BCF : = 2078

Elimination	:	
Method	:	other: calculation with Advanced Chemistry Development (ACD/Labs) Software V8.14 ((C) 1994-2006 ACD/Labs)
Year	:	
GLP	:	
Test substance	:	other TS: Isophorone diisocyanate (CAS No. 4098-71-9)
Remark	:	Database search performed in 2006. Rapid hydrolysis makes approximation of equilibrium in the environment impossible. Thus the calculated bioaccumulation potential has no practical relevance.
Reliability	:	(4) not assignable Secondary quotation

19.06.2006 (23)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 208
LC50	:	> 208
Limit test	:	no
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.1
Year	:	1996
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG, purity 99.9 % (gas chromatogram area), sample No. 1486/940804, ID No. 0637/81645
Result	:	RESULTS: - Nominal/measured concentrations: nominal: 28; 46; 81; 139; 231 mg/l 0 h (first analysis): 25; 45; 81; 134; 231 mg/l 0 h (second analysis): 27; 44; 78; 138; 178 mg/l 24 h (single analysis): 25; 48; 84; 147; 251 mg/l - Effect data (mortality): no deaths in exposed or control animals
Test condition	:	TEST ORGANISMS - Supplier: Bio International B.V., Someren (NL) - Age/size/weight/loading: length 2-3 cm, weight approx. 0.36 g - Feeding: approx. 1 % of body weight daily - Pretreatment: 14 days quarantine - Feeding during test: no STOCK AND TEST SOLUTION AND THEIR PREPARATION - Other procedures: 1 g test substance was stirred for approx. 18 hours in water and filtered. Test solutions were prepared daily. STABILITY OF THE TEST CHEMICAL SOLUTIONS: Hydrolysis was expected but not quantified. TOC analysis after 24 hours indicated that losses were insignificant (less than 20 % compared to nominal concentrations). DILUTION WATER - Source: drinking water (Gelsenwasser AG) - Aeration: continuously during test - Hardness: approx. 11 degree (German hardness) TEST SYSTEM - Concentrations: 28; 46; 81; 139; 231 mg/l (nominal) 28; 46; 81; 139; 208 mg/l (used for evaluation) The maximum concentration of 231 mg/l could not be achieved every day. Thus the mean of the highest test concentrations was used for evaluation. - Renewal of test solution: daily - Exposure vessel type: approx. 20 l aquaria with 10 l test solution - Number of replicates, fish per replicate: one replicate with 10 fish - Test temperature: 18.1-21.5 degree C, mean 20 degree C - Dissolved oxygen: 88-100 % saturation - pH: 7.7-8.3 - Adjustment of pH: no - Photoperiod: 16 / 8 hours MONITORING OF TEST SUBSTANCE CONCENTRATION: TOC-500 infrared analysis after 0 hours (twice) and 24 hours (single determination)
Reliability	:	(2) valid with restrictions

Guideline study with acceptable restrictions: Test substance not stable under test conditions

(57)

Type	:	static
Species	:	other: Danio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 72
LC50	:	> 72
Limit test	:	yes
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.1
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG (Desmodur I), purity > 99.5 %, article number 00416258, batch number 1,5/8-73

Result :

RESULTS:
- Nominal/measured concentrations:
nominal: 70 mg/l; arithmetic mean analytical 72.3 mg/l
analytical TOC at
0 h: 48 mg/l; 24 h: 49 mg/l; 48 h: 48 mg/l;
72 h: 47 mg/l; 96 h: 49 mg/l
control: always < 2 mg/l
- Effect data (Mortality): no mortality
- Other effects: normal swimming (observation at 2, 24, 48, 72, and 96 hours)
TOC has to be multiplied with 1.5 to correspond with test substance.

Test condition :

TEST ORGANISMS
- Strain: Danio rerio (formerly Brachydanio rerio) HAMILTON BUCHANAN
- Supplier: Bio International B.V. (The Netherlands)
- Age/size/weight/loading:
age 6 months 23 days,
total weight of 10 fish at test end 3.62 g (10 control fish: 4.83 g),
length 2.5 - 3.5 cm
- Pretreatment: no medical pretreatment
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: A 1.3 fold amount (100 mg/l) of the maximum water solubility of the test substance in the preliminary test (70 mg/l) was weighed into water, treated for 60 seconds at 8000 rpm with an ultra-turrax and afterwards stirred on a magnetic stirrer for 24 hours. The resulting emulsion was filtered using a folded filter of pore size 7-12 um.
- Vehicle, solvent: none
DILUTION WATER
- Hardness: 14.0 degree German hardness
- Holding water: Synthetic fresh water in accordance with ISO
TEST SYSTEM
- Concentration: 70 mg/l
- Control: Synthetic fresh water in accordance with ISO
- Exposure vessel type: 300 x 135 x 200 mm with 5 l test medium, ventilated
- Number of replicates, fish per replicate: 1 replicate with 10 fish each for exposed and control
- Test temperature: 21.4-21.5 (control: 21.4-21.7) degree C
- Dissolved oxygen: 8.2-8.5 = 95.1-98.7 % saturation
(control: 8.3-8.4 mg/l = 96.3-97.4 % saturation)
- pH: 7.6-8.0 (control: 7.7-8.1)
- Photoperiod: 16 hours light / 8 hours dark
TEST PARAMETER: mortality and visible effects (swimming behavior)
MONITORING OF TEST SUBSTANCE CONCENTRATION: TOC, daily

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: Test substance not stable under test conditions
21.06.2006 (14)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC0 : = 1
LC50 : = 1.8
Limit test : no
Analytical monitoring : no
Method : other: German Standard DIN 38412 part 15
Year :
GLP : no
Test substance : other TS: Isophorone diisocyanate, no further information

Test condition : An emulsifier was used.
Reliability : (4) not assignable
Documentation insufficient for assessment
21.06.2006 (37) (54) (55)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC0 : = 18
EC50 : = 27
EC100 : > 65
Limit Test : no
Analytical monitoring : yes
Method : Directive 92/69/EEC, C.2
Year : 1995
GLP : yes
Test substance : other TS: Isophorone diisocyanate of Hüls AG (VESTANAT IPDI), purity 99.9 % (gas chromatogram area), sample No. 1486/940804, ID No. 0637/81645

Result : RESULTS:
- Nominal/measured concentrations:
nominal: 5.2; 8.6; 15; 26; 43; 73 mg/l
0 h analysis: 2.8; 5.7; 9.8; 17.7; 34.2; 67.4 mg/l
48 h analysis: 3.6; 5.9; 10.5; 18.0; 32.0; 62.2 mg/l
evaluation (geometric mean of measured concentrations): 3.2; 5.8; 10.0; 18.0; 33.0; 65.0 mg/l
- Effect data (Immobilization):
control; 3.2 mg/l; 5.8 mg/l: no immobilization
10 mg/l: 0 % after 24 hours, 5 % after 48 hours
18 mg/l: 0 % after 24 and 48 hours
33 mg/l: 20 % after 24 hours, 75 % after 48 hours
65 mg/l: 70 % after 24 hours, 95 % after 48 hours
- Concentration / response curve:
24 h-EC50 = 49 mg/l (33-65 mg/l)
48 h-EC50 = 27 mg/l (18-33 mg/l)
The EC0 was defined as the highest test concentration with an effect <= 10 %.
RESULTS: TEST WITH REFERENCE SUBSTANCE

- Concentrations: 1 mg/l; 2 mg/l
- Results: 40 %; 100 % immobilization after 24 hours

Test condition : TEST ORGANISMS
- Strain: Daphnia magna STRAUS clone 5
- Source/supplier: Hüls AG (inhouse)
- Breeding method: in 1 l jars with dechlorinated drinking water, water renewal each 2-3 days, isolation of juveniles for further breeding each approx. 4 weeks
- Age: < 24 hours
- Feeding: Desmodesmus subspicatus, as much as consumed
- Pretreatment: Filtration of adults 24 h prior to testing
- Feeding during test: no
- Control group: blank synthetic freshwater

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Other procedures: 1 g/l test substance was stirred for approx. 18 hours in synthetic freshwater and filtered. DOC 279 mg/l = 430 mg test substance/l.

STABILITY OF THE TEST CHEMICAL SOLUTIONS: Hydrolysis was expected but not quantified.

REFERENCE SUBSTANCE: potassium dichromate, CAS No. 7778-50-9

DILUTION WATER
- Source: Synthetic:
  $CaCl_2 \times 2 H_2O$: 294 mg/l
  $MgSO_4 \times 7 H_2O$: 123 mg/l
  $NaHCO_3$: 63 mg/l
  KCl: 5.5 mg/l
- Ca/Mg ratio: 4:1
- Na/K ratio: 10:1
- Aeration: no

TEST SYSTEM
- Concentrations: 5.2; 8.6; 15; 26; 43; 73 mg/l (nominal)
- Exposure vessel type: glass jars with 10 ml test solution
- Number of replicates, individuals per replicate:
  4 replicates with 5 animals each (including control)
- Test temperature: 20 +/- 1 degree C
- Dissolved oxygen: 8.4-8.6 mg/l
- pH: 7.8-8.0
- Adjustment of pH: no
- Photoperiod: darkness

MONITORING OF TEST SUBSTANCE CONCENTRATION: TOC-500 infrared analysis after 0 and 24 hours

STATISTICAL METHODS:
- EC50 values were calculated by graphic interpolation

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: Test substance not stable under test conditions

19.06.2006 (56)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	= 19
EC50	:	= 35
EC100	:	= 73
Limit Test	:	no
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.2
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG (DESMODUR I), purity > 99.5 %, article number 00416258, batch number 1,5/8-73

Result :

RESULTS:
- Nominal/measured concentrations:

nominal / 0 hours	48 hours	evaluation
test s. / TOC	TOC	/ test s.
control / <2	<2	/ 0 mg/l
18.5 / 12	13	/ 19 mg/l
37 / 24	25	/ 37 mg/l
74 / 47	50	/ 73 mg/l

TOC has to be multiplied with 1.5 to correspond with test substance. The arithmetic means of the two analytical values were used for the evaluation.

- Effect data (Immobilization):

nominal / analytical	24 hours	48 hours
control / 0 mg/l	/ 0 %	/ 0 %
18.5 / 19 mg/l	/ 0 %	/ 0 %
37 / 37 mg/l	/ 0 %	/ 60 %
74 / 73 mg/l	/ 70 %	/ 100 %

EC0 (highest concentration without effect): 37 mg/l (24 h); 19 mg/l (48 h)
EC50: not determined (24 h); 35 mg/l (48 h) (95 % confidence interval: 30.9 - 39.7 mg/l)
EC100 (lowest concentration with 100 % effect): >73 mg/l (24 h); 73 mg/l (48 h)
EC50 (48 h) was determined by probit analysis using nominal concentrations, since recovery rates of the analytical results were > 80 %. For this calculation, inhibitions of 0 % and 100 % were replaced by 0.1 % and 99.9 %, respectively.

Test condition :

TEST ORGANISMS
- Strain: Daphnia magna STRAUS, parthenogenetic females
- Source/supplier: Origin German Federal Health Office (BGA); laboratory bred inhouse
- Age: 0-24 hours
- Control group: M4-Medium according to Elendt and BGA (1992)

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: ultra-turrax treatment for 60 seconds at 8000 rpm, followed by stirring with a magnetic stirrer for 24 hours and filtration (folded filter) at pore size 7-12 um
- Vehicle, solvent: none
- Other procedures: 120 mg/l stock solution

DILUTION WATER
- Hardness: 14.2 degree German hardness
- Holding water: M4-Medium according to Elendt and BGA (1992)

TEST SYSTEM
- Concentrations: 18.5; 37; 74 mg/l
- Renewal of test solution: no
- Exposure vessel type: cylindrical test vessels, 4.0 cm diameter, 6.5 cm height, with 20 ml test medium
- Number of replicates, individuals per replicate: 2 replicates with 10 individuals each
- Test temperature: 20.0-20.4 degree C (at 48 hours)
- Dissolved oxygen: 8.1-8.4 mg/l (at 48 hours)
- pH: 7.9-8.0 (at 48 hours)
- Photoperiod: 16 hours light / 8 hours dark

TEST PARAMETER: number of immobile daphnids
MONITORING OF TEST SUBSTANCE CONCENTRATION: at test start and after 48 hours of exposure, TOC determination

Reliability : (2) valid with restrictions

Guideline study with acceptable restrictions: Test substance not stable under test conditions

19.06.2006 (14) (17)

Type	:	semistatic
Species	:	other: Chaetogammarus marinus (Crustacea, marine)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= .56
EC50	:	= 4
Limit Test	:	no
Analytical monitoring	:	no
Method	:	other: see Reference / Test Conditions
Year	:	1980
GLP	:	no data
Test substance	:	other TS: Isophorone diisocyanate of Fluka AG, "pract." grade, no data on purity
Remark	:	Daily renewal of the test solution causes over-representation of the effects of the unreacted test compound. In the environment only the chemically and biologically less reactive hydrolysis product is expected to be relevant.
Result	:	RESULTS: EXPOSED - Effect data (Immobilization): 24 h-EC50 = 6.9 mg/l (confidence interval 6.0-7.9) 48 h-EC50 = 5.5 mg/l (confidence interval 5.0-6.1) 72 h-EC50 = 4.8 mg/l (confidence interval 4.3-5.5) 96 h-EC50 = 4.0 mg/l (confidence interval 3.5-4.5) - Other effects: 96 h NOEC (condition of test animals compared to controls, visual estimation): 0.56 mg/l
Test condition	:	TEST ORGANISMS - Breeding method: laboratory culture - Age: young gammarids, 5 +/- 1 mm long - Feeding: Fucus sp. - Feeding during test: some Fucus sp. and/or Tetramin; reason: to prevent cannibalism - Control group: (1) blank seawater; (2) solvent in seawater STOCK AND TEST SOLUTION AND THEIR PREPARATION - Solvent: dimethyl sulfoxide, CAS No. 67-68-5 - Concentration of solvent: max. 0.1 ml per l DILUTION WATER - Source: natural seawater from Eastern Scheldt (NL), filtered through sand, activated charcoal, and 0.2 um millipore filter - Aeration: no - Salinity: 28 o/oo TEST SYSTEM - Concentrations: 0.18; 0.32; 0.56; 1.0; 1.8; 3.2; 5.6; 10 mg/l - Renewal of test solution: once a day - Exposure vessel type: 1 l glass beaker, covered with watch glass - Number of replicates, individuals per replicate: 2, 10 - Test temperature: 15 degree C - Dissolved oxygen: "almost saturated for the whole duration" - pH: approx. 8 (between 7.8 and 8.3) - Adjustment of pH: no DURATION OF THE TEST: 96 hours
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles. Restrictions: No analytical monitoring, no consideration of hydrolysis and effects due to temporary reactive test components, no international standard method. In particular, daily renewal of the test solution is not adequate for testing a rapidly hydrolyzing substance.

18.07.2006 (2)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	= 84
Limit Test	:	no
Analytical monitoring	:	yes
Method	:	other: German Standard DIN 38412 part 11
Year	:	1988
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, no further information
Test condition	:	STOCK AND TEST SOLUTION AND THEIR PREPARATION - Probably saturated stock solution, no details (stirring time, filtration) reported. - Analytical monitoring: DOC determination at beginning of test. Based on DOC analysis, the concentration in the saturated solution is reported as 225 mg/l, which indicates that significant hydrolysis of the less soluble test substance to more soluble substances had occurred.
Reliability	:	(4) not assignable Documentation insufficient for assessment

18.07.2006 (51)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other algae: Desmodesmus subspicatus
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= 4.4
LOEC	:	= 8.8
EC50	:	> 70
Limit test	:	no
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.3
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG (DESMODUR I), purity > 99.5 %, article number 00416258, batch number 1,5/8-73
Remark	:	After 2 days of undisturbed growth, cell counts suddenly stayed constant (17.5 mg/l nominal) or even dropped markedly (> 17.5 mg/l nominal) leading to an inhibition of growth rate of 8.3 % at 17.5 mg/l and higher concentrations compared to 0 % inhibition at all lower concentrations. In total, however, EC50 values are beyond the highest test concentration based on both biomass (area under the growth curve) and growth rate. The report uses the species name Scenedesmus subspicatus which has since then been replaced by Desmodesmus subspicatus.
Result	:	- Nominal/measured concentrations: nominal / 24 hours / 72 hours test s. / TOC / TOC 4.4 3 5 mg/l 8.8 6 7 mg/l 17.5 12 18 mg/l 35 25 24 mg/l 70 48 45 mg/l TOC has to be multiplied with 1.5 to correspond with test substance. - Effect data / endpoints: EC50 (biomass as well as growth rate) > highest

test concentration (70 mg/l nominal/measured), NOEC / LOEC (growth rate) = 4.4 / 8.8 mg/l, NOEC / LOEC (biomass) >= 70 / > 70 mg/l
- Cell density data:
concn. / biomass / % inhibition / growth rate (% inhibition)
control / 426000 / 0.0 / 1.2/d (0.0)
1.1 / 481000 / -12.9 / 1.2/d (0.0)
2.2 / 445000 / -4.5 / 1.2/d (0.0)
4.4 / 416000 / 2.3 / 1.2/d (0.0)
8.8 / 356000 / 16.4 / 1.2/d (0.0)
17.5 / 455000 / -6.8 / 1.1/d (8.3)
35 / 427000 / -0.2 / 1.1/d (8.3)
70 / 436000 / -2.3 / 1.1/d (8.3)

Test condition : TEST ORGANISMS
- Strain: Desmodesmus subspicatus CHODAT
- Source/supplier: Institute of Plant Physiology, University of Göttingen
- Method of cultivation: In a light chamber at 23 +/- 2 °C and with a quantum flux which equals 120 uE/m2 x s
- Controls: Inoculum in nutrient medium and dilution water
- Initial cell concentration: 10 000 cells/ml
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: ultra-turrax treatment for 60 seconds at 8000 rpm, followed by stirring with a magnetic stirrer for 24 hours and filtration (folded filter) at pore size 7-12 µm
- Vehicle, solvent: none
- Other procedures: 125 mg/l stock solution
DILUTION WATER
- Source: deionized water
TEST SYSTEM
- Concentrations: 1.1; 2.2; 4.4; 8.8; 17.5; 35; 70 mg/l
- Renewal of test solution: no
- Exposure vessel type: 300 ml Erlenmeyer flasks with stoppers with 100 ml of test medium; light chamber with shaker
- Number of replicates: 3 (control: 6)
- Test temperature: 23 +/- 2 degree C
- pH: 8.0-8.1 at 0 hours; 9.5-10.2 at 72 hours
control: 7.8 at 0 hours; 10.2 at 72 hours
- Intensity of irradiation: 120 uE/m2 x s
TEST PARAMETER: Counting with microcellcounter Sysmex F-300 Digitana at every 24 hours
MONITORING OF TEST SUBSTANCE CONCENTRATION: TOC determination at test start and after 72 hours of exposure for concentrations >= 4.4 mg/l
STATISTICAL METHODS: Williams test for NOEC, LOEC

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: Test substance not stable under test conditions

21.06.2006 (14)

Species : other algae: Desmodesmus subspicatus
Endpoint : growth rate
Exposure period : 72 hour(s)
Unit : mg/l
EC10 : = 19
EC50 : = 119
EC90 : = 750
Limit test : no
Analytical monitoring :
Method : other: German Umweltbundesamt draft procedure (1984)
Year : 1988
GLP : no
Test substance : other TS: Isophorone diisocyanate, no further information

Result	:	The results reported are based on two performances of the test with stock solution concentrations of 290 mg/l and 201 mg/l, respectively.
Test condition	:	TEST ORGANISMS - Strain: Desmodesmus subspicatus Chodat former name (used in report): Scenedesmus subspicatus Chodat STOCK AND TEST SOLUTION AND THEIR PREPARATION - Saturated solution STATISTICAL METHODS - Probit analysis
Reliability	:	(4) not assignable Documentation insufficient for assessment

20.06.2006 (50)

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	:	= 263
Analytical monitoring	:	no
Method	:	Directive 87/302/EEC, part C, p. 118 "Biodegradation: Activated sludge respiration inhibition test"
Year	:	1999
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG (DESMODUR I), purity > 99.5 %, article number 00416258, batch number 1,5/8-73
Method	:	The method is actually according Directive 88/302/EEC, not Directive 87/302/EEC.
Result	:	Concentration: Inhibition 100 mg/l: 17.4 % 180 mg/l: 17.4 % 320 mg/l: 52.1 % 560 mg/l: 95.7 % 1000 mg/l: 96.5 %
Test condition	:	The test method corresponds for the most part to OECD Test Guideline 209 INOCULUM/TEST ORGANISM - Species/strain: mixed population of different microorganisms - Sampling site: WWTP of Wupper area water authority - Pretreatment: none INITIAL TEST SUBSTANCE CONCENTRATION: 100; 180; 320; 560; 1000 mg/l (nominal) METHOD OF PREPARATION OF TEST SOLUTION: The test substance was added to deionized water, treated 3-4 h by ultrasound and stirred overnight before testing (equilibration phase) DURATION OF THE TEST: 5-9 min; preincubation 3 hours ANALYTICAL PARAMETER: Oxygen consumption TEST CONDITIONS - Test temperature: 20 +/- 1 degree C - pH value: 6.7 before addition of test substance; 7.9-8.3 in test solutions (controls: 7.8-7.9; reference substance: 7.8-8.0) at study termination - Aeration of dilution water: permanent during preincubation - Concentration of suspended solids: 320 mg sludge/l REFERENCE SUBSTANCE: 3,5-dichlorophenol STATISTICAL METHODS: Probit analysis
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions: Test substance not stable under test conditions

19.06.2006 (14)

Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	6 hour(s)
Unit	:	mg/l
EC10	:	= 554
Analytical monitoring	:	no
Method	:	other: Test for inhibition of oxygen consumption by Pseudomonas putida (Hüls Method), 5-6 h
Year	:	
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, no further information
Test condition	:	An emulsifier was used.
Reliability	:	(4) not assignable Documentation insufficient for assessment

21.06.2006 (37) (54)

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

Remark : See "Biological monitoring in urine" chapter 5.10

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 4814 mg/kg bw
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 10
Vehicle : other: no vehicle
Doses : 4.21; 5.29; 6.67; 8.40; 10.58 g/kg bw
Method : other: Based on "Appraisal of the safety of chemicals in foods, drugs and cosmetics" by the staff of the Division of Pharmacology, FDA (1959), complies with OECD Guideline 401 (1981)
Year : 1976
GLP : no
Test substance : other TS: Isophorone diisocyanate of Veba-Chemie AG, Gelsenkirchen (Germany); purity not reported

Result : MORTALITY:
- Time of death: within 3 days
- Number of deaths at each dose:
3.98 ml/kg: 2/10
5.00 ml/kg: 8/10
higher: 10/10 each
LD50 (24 hours) = 7.10 ml/kg = 7512 mg/kg
confidence interval: 6.02 - 8.38 ml/kg
LD50 (7 days, 14 days) = 4.55 ml/kg = 4814 mg/kg
confidence interval: 4.06 - 5.10 ml/kg

CLINICAL SIGNS: decrease in activity, diarrhea, piloerection, in higher dose groups also tremor (beginning 20 min after dosing, lasting 24 hours)
- Growth rates returned to normal by the end of the post exposure observation period.

NECROPSY FINDINGS: reddening of stomach and intestinal mucosa of dead animals, loss of hair at perineum of survivors

Test condition : TEST ORGANISMS:
- Source: Winkelmann, Paderborn (Germany)
- Weight at study initiation: 110-140 g

ADMINISTRATION:
- Doses: calculated from volume
- Doses per time period: single dose (gavage)
- Volume administered or concentration: undiluted test substance, 3.98; 5.00; 6.30; 7.94; 10.00 ml/kg bw
* 1.058 = 4.21; 5.29; 6.67; 8.40; 10.58 g/kg bw
- Post dose observation period: 14 days

EXAMINATIONS: central nervous system, lung, heart, heart sac, stomach, large intestine, small intestine, liver, spleen, kidneys, serosa, lymph nodes, gonads, perineum
- LD50 calculation: according to Litchfield and Wilcoxon, in connection with the Gauß integral

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

16.09.2006 (59)

Type : LD50
Value : = 5490 mg/kg bw

Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	10
Vehicle	:	other: no vehicle
Doses	:	2500; 4000; 5000; 6000; 7500; 10000 mg/kg bw
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, no data on purity
Result	:	MORTALITY: - Number of deaths and time of death at each dose: 2500 mg/kg: 0/10 - 4000 mg/kg: 1/10 1 d 5000 mg/kg: 4/10 1-2 d 6000 mg/kg: 6/10 1-2 d 7500 mg/kg: 9/10 1-3 d 10000 mg/kg: 10/10 1 d - Confidence interval of LD50: 4850-6215 mg/kg CLINICAL SIGNS: All animals showed impairment of general condition up to 8 days after administration of the test substance
Test condition	:	ADMINISTRATION: - Post dose observation period: 14 days EXAMINATIONS: - clinical symptoms - LD50 calculation: according to Lichtfield and Wilcoxon, J. Pharmacol. Exper. Therap. 96, 99 (1949)
Reliability	:	(2) valid with restrictions Study documentation sufficient (short report), meets generally accepted scientific principles, acceptable for assessment (102)

Type	:	LD50
Value	:	> 2645 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	15
Vehicle	:	other: Oil, not specified
Doses	:	265; 529; 1058; 2645 mg/kg bw
Method	:	other: Bayer AG
Year	:	1968
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, "technically pure"
Result	:	MORTALITY: No animal died CLINICAL SIGNS: No signs of intoxication or change of behaviour could be observed at any dose. Body weight increase was normal.
Test condition	:	TEST ORGANISMS: - Source: Winkelmann, Kirchborchen (Germany) - Weight at study initiation: 190-200 g ADMINISTRATION: - Route: gavage - Doses: 0.25; 0.5; 1.0; 2.5 ml/kg bw x 1058 mg/ml = 265; 529; 1058; 2645 mg/kg bw - Volume administered or concentration: 0.2 % of body weight - Post dose observation period: 14 days - LD50 calculation: according to Litchfield and Wilcoxon
Reliability	:	(2) valid with restrictions Study documentation sufficient (short report), meets generally accepted

scientific principles, acceptable for assessment

(67)

Type	:	LD50
Value	:	> 2645 mg/kg bw
Species	:	mouse
Strain	:	other: CF1
Sex	:	male
Number of animals	:	15
Vehicle	:	other: Oil, not specified
Doses	:	1058; 2645 mg/kg bw
Method	:	other: Bayer AG
Year	:	1968
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, "technically pure"
Result	:	MORTALITY: No animal died in the low dose group. Two animals died in the high dose group on the first day. CLINICAL SIGNS: No signs of intoxication or change of behaviour could be observed at the low dose. Symptoms of intoxication in the high dose group were uncharacteristic.
Test condition	:	TEST ORGANISMS: - Source: Winkelmann, Kirchborchen (Germany) - Weight at study initiation: 18-23 g ADMINISTRATION: - Route: gavage - Doses: 1.0; 2.5 ml/kg bw x 1058 mg/ml = 1058; 2645 mg/kg bw - Volume administered or concentration: 0.2 % of body weight - Post dose observation period: 14 days
Reliability	:	(2) valid with restrictions Study documentation sufficient (short report), meets generally accepted scientific principles, acceptable for assessment

(67)

Type	:	LD50
Value	:	= 1185 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	5
Vehicle	:	other: no vehicle
Doses	:	2.116; 1.058; 0.529 mg/kg bw
Method	:	other: "Standard"
Year	:	1967
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, submitted by P.G. Naylor, Division Chemicals and Plastics Research and Development, South Charleston, W.Va. (USA); sponsor's ID 38-MPW-105 / 29-DS-10-5; internal ID 30-182, no data on purity
Result	:	MORTALITY: - Number of deaths at each dose: 2.0 ml/kg: 4/5 within 1 day 1.0 ml/kg: 2/5 within 1 day 0.5 ml/kg: 1/5 within 2 days CLINICAL SIGNS: not reported, body weight change observed NECROPSY FINDINGS: Congestion throughout the lungs and the abdominal viscera (no information available whether these findings were restricted to the animals found dead) LD50: 1.12 (0.52-2.41) ml/kg = 1185 (550-2550) mg/kg
Test condition	:	TEST ORGANISMS:

- Source: inhouse
- Age: 3-4 weeks
- Weight at study initiation: 90-120 g
ADMINISTRATION: single dose, stomach intubation
- Doses: 2.0; 1.0 and 0.5 ml/kg bw
= 2.116; 1.058; 0.529 mg/kg bw
- Post dose observation period: 14 days
- Calculation of LD50: moving average method

Reliability : (3) invalid
While the study documentation may be regarded as sufficient (short report) the statistical evaluation is less reliable due to low number of animals and only 3 dose levels.

14.06.2006 (106)

Type : LD50
Value : > 1058 mg/kg bw
Species : cat
Strain : other: no specific strain
Sex : male/female
Number of animals : 2
Vehicle : other: Oil, not specified
Doses : 1058 mg/kg bw
Method : other: Bayer AG
Year : 1968
GLP : no
Test substance : other TS: Isophorone diisocyanate, "technically pure"

Result : MORTALITY: No animal died.
CLINICAL SIGNS: No signs of intoxication could be observed.

Test condition : TEST ORGANISMS:
- Weight at study initiation: 3000 and 3200 g
ADMINISTRATION:
- Route: gavage
- Doses: 1.0 ml/kg bw x 1058 mg/ml = 1058 mg/kg bw
- Volume administered or concentration: 0.2 % of body weight
- Post dose observation period: 14 days

Reliability : (3) invalid
Useful only for screening purposes because only two animals were treated (67)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : ca. 40 mg/m³
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 10
Vehicle : other: no vehicle
Doses : 0; 20.4; 53.3; 73.8; 104.6; 410.3 mg/m3 (analytical)
Exposure time : 4 hour(s)
Method : other: Directive 92/69/EEC;93/21/EEC, B.2 and OECD Test Guideline 403 (1981)
Year : 1994
GLP : yes
Test substance : other TS: Isophorone diisocyanate of Bayer AG, batch no. 1.5/3-28, purity > 99 %

Result : MORTALITY:
- Time of death:

Concentration: No. and time span (males) / (females)

20.4 mg/m3: no mortalities / no mortalities
53.3 mg/m3: 3 (16 d - 28 d) / 3 (11 d - 25 d)
73.8 mg/m3: 5 (1 d - 12 d) / 5 (3 d - 9 d)
104.6 mg/m3: 5 (1 d - 10 d) / 5 (1 d - 20 d)
410.3 mg/m3: 5 (<= 4 h) / 5 (<= 4 h - 6 h)
control: no mortalities / no mortalities
CLINICAL SIGNS:
control: no signs
20.4 mg/m3: reduced motility, piloerection, ungroomed coat, bradypnea, labored breathing, rales, sluggishness, nose and/or muzzle with red incrustations, reddening of nose
additional observations in higher dose groups: tachypnea, irregular breathing pattern, serous nasal discharge, cyanosis, emaciation, extreme breathing difficulties, sneezing, death
OTHER OBSERVATIONS:
- Reflexes: With the exception of a depressed righting response observed nearly exclusively in moribund group 4 and 5 animals, reflexes were normal in all groups.
- Body weights: Significant depression in b.w. gain in all exposed groups
- Rectal temperature: Concentration dependent decrease after exposure in treated groups
NECROPSY FINDINGS:
- Survivors: Except for a less collapsed lung and some focal discolorations of the lung, which was only sporadically observed, survivors showed no substance-induced macroscopic alterations.
- Animals that died within the exposure / observation period: Nose and/or muzzle with red incrustations, mucous membrane of nose with reddenings; pleural cavity filled with liquid; lung less collapsed, with dark-red foci or diffusely black-red, emphysematous, spongy, and with escape of liquid at the cut part; small intestine with reddenings and yellowish and/or reddish content; liver pale, spotted, and with distinct lobular pattern; spleen pale; kidneys pale, pelvis of kidneys with reddenings.
Findings of the nose/muzzle, pleural cavity, and lung are considered to reflect irritant effects to the respiratory tract.
POTENTIAL TARGET ORGANS:
respiratory tract (severe irritation)
SEX-SPECIFIC DIFFERENCES: not ascertained

Test condition **:**

TEST ORGANISMS:
- Strain: SPF bred Wistar rats, strain Hsd/Win:WU (formerly BOR:WISW (SPF-Cpb))
- Source: Harlan-Winkelmann, Borchen, Germany
- Age: 2-3 months
- Weight at study initiation: 193 g (males mean), 177 g (females mean)
- Number of animals: 5 per sex and dose group (incl. control)
- Controls: air
ADMINISTRATION:
- Type of exposure: nose-only using the dynamic directed-flow principle
- nominal concentration (calculated from the ratio of the quantity of test substance sprayed into the baffle and the total throughput of air through the inhalation chamber): 115, 289, 462, 379, 1514 mg/m3
- gravimetric concentration: 18, 55, 85, 105, 410 mg/m3
- Particle size:
Mass Median Aerodynamic Diameter (MMAD) 1.6 - 2.1 µm
geometric standard deviation: approx. 1.7 µm
- Type or preparation of particles: aerosol, generated using a two-component nozzle with conditioned compressed air
- post-exposure observation period: 4 weeks
EXAMINATIONS:
- clinical signs: several times on day of exposure and twice daily (morning and evening) thereafter (morning only on weekends)

- mortality: time recorded as precisely as possible
- body weight: before exposure, on days 3 and 7, thereafter weekly, at death if applicable
- rectal temperature: 15 to 30 min after exposure
- gross pathology of all animals after sacrifice of surviving animals
CALCULATION OF LC50: Since only test concentration (53.3 mg/m3) was within 0 % and 100 % lethality, the geometric mean of the next concentrations (20.4 and 73.8 mg/m3) was chosen.

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: exposure concentrations spaced suboptimal

(9) (10) (11)

Type	:	LC50
Value	:	= 31 mg/m³
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: no vehicle
Doses	:	18; 22; 70; 450 mg/m3 (analytical)
Exposure time	:	4 hour(s)
Method	:	other: OECD Guideline 403 (1981) and Sachsse et al. (1973, 1976)
Year	:	1988
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Hüls AG, batch no. 87/07/11 SM1, purity > 99 %

Result :
MORTALITY: LC50 = 31 (28-35) mg/m3
- Time of death: The LC50 is based on observation for 17 days. One female of the 22 mg/m3 group died on day 19.
18 mg/m3: no mortalities
22 mg/m3: 3/5 males on test days 2, 8, and 9; 1/5 females on test day 19.
70 mg/m3: 5/5 males overnight (day 1/2), 4/5 females between test days 5 and 9; 1 female survived in poor condition until test day 27.
450 mg/m3: 3/5 males and 3/5 females during exposure, all other animals within 24 hours after begin of exposure.
CLINICAL SIGNS:
All groups: Breathing difficulty, piloerection and stagger following exposure (for several days); no body weight gain during first week.
22 mg/m3: Salivation, sedation.
>= 22 mg/m3: Nose bleeding
NECROPSY FINDINGS: Red foci on all lung lobes, or reddish lungs were observed in all decedent animals except in 4 females of the 22 mg/m3 group. No abnormal findings were observed in surviving animals.
POTENTIAL TARGET ORGANS: Respiratory tract

Test condition :
TEST ORGANISMS: KFM-Han., outbred, SPF quality
- Source: KFM Kleintierfarm Madoerin AG, Füllinsdorf (Switzerland)
- Age at study initiation: males 10-11 weeks, females 13-14 weeks
- Weight at study initiation: males 221.8-326.8 g, females 202.2-266.4 g
- Number of animals: 5 males + 5 females per dose group
- Controls: none
ADMINISTRATION:
- Type of exposure: flow-past nose-only inhalation
- gravimetric concentrations: 14, 23, 69, 548 mg/m3
- Particle size:
18 mg/m3: 100 % <= 4.6 µm; 99.7 % <= 3 µm; 92.4 % <= 2.13 µm
22 mg/m3: 100 % <= 4.6 µm; 99.3 % <= 3 µm; 94.4 % <= 2.13 µm
70 mg/m3: 100 % <= 4.6 µm; 97.2 % <= 3 µm; 87.1 % <= 2.13 µm
450 mg/m3: 100 % <= 4.6 µm; 81.3 % <= 3 µm; 61.1 % <= 2.13 µm
- Type or preparation of particles: Hospitak No. 950 nebulizer and dilution

system (clean air), symmetrical top-down flow of aerosol to animals' noses and further
- Post dose observation period (including day of exposure as day 1):
18 mg/m3: 17 days
22 mg/m3: 21 days
70 mg/m3: 27 days
450 mg/m3: 24 hours (all dead)
EXAMINATIONS:
- Analysis of test atmosphere:
Sampling close to the animals' noses with Gelman A/E 47 mm diameter glass fiber filters; monitoring of relative aerosol concentration using a RAM-1 light scattering type aerosol monitor.
In addition, collection of test atmosphere in three bottles filled with ethyl acetate and cooled with dry ice, subsequent analysis with gas chromatography
- Particle size (gravimetric): Once during each exposure
- Concentration (gravimetric): At regular intervals during each exposure
- Concentration (analytic): Three times during each exposure
- Oxygen content, humidity, temperature: Once during each exposure
- Air flow rate: Monitored indirectly during the exposure period
- Mortality/viability: At least four times on test day 1 and twice daily thereafter.
- Body weights
18 mg/m3: test days 1, 7, 14
22 mg/m3: test days 1, 8, 15, 21
70 mg/m3: test days 1, 7, 14
450 mg/m3: test day 1
- Symptoms: At least four times on test day 1 and twice daily thereafter. During exposure only grossly abnormal signs could be noted, due to the animals being in restraint tubes. General behavior, motor susceptibility, body position, motility, respiration, skin / fur, eyes, and nose were characterized in addition to potential emaciation, poor condition, salivation, crying, diarrhea and distended abdomen.
- Necropsies of all animals

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: no air control animals; exposure concentrations spaced suboptimal

(87)

Type	:	other: Pulmonary irritant potency study
Value	:	
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	18
Vehicle	:	other: no vehicle
Doses	:	2.1; 7.5; 26 mg/m3
Exposure time	:	6 hour(s)
Method	:	other: OECD Guideline 403 (1981), adjusted to fulfill 92/69/EEC;93/21/EEC B.2 and FIFRA § 81-2 (1984)
Year	:	2004
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG, batch no. LL48/3-55, purity >= 99.5 %

Result : TEST ATMOSPHERE:
- Target concentrations: 0 / 2 / 8 / 25 mg/m3
- Nominal concentrations: 0 / 8.5 / 31.8 / 106 mg/m3
- Analytical concentrations: - / 2.09 / 7.5 / 26 mg/m3
The difference between nominal and analytical concentrations is mainly due to the removal of high-size particles. The exposure conditions were

temporally stable over the exposure period.
MORTALITY:
- Number of deaths at each dose: 2/18 rats of the high concentration group died.
- Time of death: days 1 and 2 after treatment
CLINICAL SIGNS:
- Number of animals: 6/18 control rats, 11/18 low concentration rats, all mid and high concentration rats
- Control and low concentration groups: Ungroomed hair-coat
- Mid concentration group: Bradypnea; labored breathing patterns; irregular breathing patterns; breathing sounds; ungroomed hair-coat; piloerection; nasal discharge (serous); nose reddened; red incrustations of nose, muzzle, nostrils; stridor in muzzle; reduced motility; limp; high-legged gait.
- High concentration group: All signs observed in mid concentration group plus dyspnea; tremor; blepharospasm; muzzle reddened and enlarged; cyanosis.
- Rectal temperatures: Statistically significant decrease in mid and high concentration rats:
Mean values were 37.6 / 37.3 / 31.4 / 28.5 °C in control / low / mid / high concentration groups.
- Body weights: On day 1 after treatment there was a dose-related decrease in body weights. By the end of the study, the mean weights of low and mid concentration rats were similar to those of the controls while the mean body weight of the high concentration rats was still below the initial value:
0 mg/m3: 222.1 / 217.9 / 252.8 g (days 0 / 1 / 7)
2.1 mg/m3: 221.7 / 214.0 / 253.7 g (days 0 / 1 / 7)
7.5 mg/m3: 220.3 / 203.6 / 254.8 g (days 0 / 1 / 7)
26 mg/m3: 219.7 / 190.4 / 199.6 g (days 0 / 1** / 7**)
** p<0.01
NECROPSY FINDINGS:
- In all exposure groups an increased incidence of macroscopic alterations of the respiratory tract was found.
0 mg/m3: Dark-red foci in the lungs of 4/18 animals
2.1 mg/m3: Similar to control plus few gray foci in the lungs of 2/6 animals at 1 day sacrifice
7.5 mg/m3: Similar to control plus red discharge or red encrustations in the noses of 3/6 animals at 1 day sacrifice
26 mg/m3, 1 day sacrifice: Findings in 5/6 animals: Noses with red encrustations (3/6) and/or colorless discharge (2/6), intestines bloated (2/6) and/or with yellowish-foamy content (2/6), lungs less collapsed (1/6) and/or light colored (3/6).
26 mg/m3, 3 day sacrifice (incl. 2 mortalities): Findings in 7/7 animals: Noses with colorless or yellow discharge (4/7) or red encrustations (1/7), lungs less collapsed (3/7) and/or light or dark red colored (6/7), stomach bloated (1/7) and mucosa reddened (2/7), intestines bloated with reddish-mucous content (2/7), spleen light-colored (2/7), few other findings confined to 1/7 animals
26 mg/m3, 7 day sacrifice: Findings in 5/5 animals: Noses with red encrustations(3/5), lungs light-colored or otherwise discolored including foci (5/5) and less collapsed (2/5), trachea with colorless viscous content (2/5), few other findings confined to 1/7 animals
- The relative lung weight was significantly increased (p<0.01) in the high concentration group (day 1: +11.9 %; day 3: +17.3%; day 7: +60.9%), which is mainly a secondary effect caused by the loss in body weight.
- The absolute lung weight in this group was similar to that in the control group on post-treatment days 1 and 3 (-1.7% and -5.0%, respectively) but significantly increased on day 7 (+24.3%).
POTENTIAL TARGET ORGANS: Statistically significant results (* p<0.05; ** p<0.01) of the BALF analysis were
- Total cell count:
+31 % * day 3, mid concentration group

+48 % ** day 3, high concentration group
- Lactate dehydrogenase:
+151 % * day 7, high concentration group
- Total protein:
+68 % ** day 1, high concentration group
+ 5.3% (insignificant) day 3, high concentration group
+291 % ** day 7, high concentration group
- alpha-2-macroglobulin (mg/l; significance not reported)
low concentration: -5.3% / -80.2% / -59.8% (days 1 / 3 / 7)
mid concentration: -43.4% / -84.7% / -96.1 % (days 1 / 3 / 7)
high concentration: -96.1% / -96.3% / -51.0% (days 1 / 3 / 7)

Test condition : TEST ORGANISMS:
- Strain: Hsd Cpb:WU (formerly BOR:WISW (SPF-Cpb))
- Source: Harlan Winkelmann GmbH, Borchen (Germany)
- Age: approximately 2 months
- Weight at study initiation: 202-234 g, mean 221 g
- Number of animals: 18 per test concentration
- Controls: concurrent conditioned air
ADMINISTRATION:
- Type of exposure: directed-flow nose-only inhalation
- Particle size: 26 mg/m3: MMAD 1.6 µm;
other concentrations: below vapor saturation, no particles expected
- Type or preparation of particles: Nebulization of test substance in binary nozzle maintained at 30 °C with conditioned compressed air, removal of larger particles with pre-separator / baffle system, adjustment of concentration with additional airflows in dilution cascade.
- Determination of concentrations:
Nominal: Mass of substance sprayed / throughput of air
Analysis: Scavenging of test substance from air samples with nitro reagent in glass powder filled tubes followed by HPLC analysis; 3 samples / exposure from vicinity of breathing zone
- Test temperature: 22.1 - 22.6 °C
- Post dose observation period: 1, 3, or 7 days (each 6 rats per test concentration)
EXAMINATIONS:
- Clinical signs and mortality: Several times on day of exposure, at least once daily thereafter, including changes in skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system, and somatomotor activity and behavior pattern.
- Sampling of bronchoalveolar lavage fluid (BALF) 3 hours after exposure and on post exposure days 1, 3, 7 (two lavages each of the excised lungs with two 5 ml aliquots of saline solution at 37 °C); analysis for
- total protein (index of air-blood barrier permeability),
- lactate dehydrogenase (LDH) (indicator of cell injury),
- alpha-2-macroglobulin
- Gross pathology on all rats with focus on respiratory tract

Conclusion : The author concludes that the acute inhalation toxicity of the test substance appears to be governed by effects occurring in the airway rather than pulmonary region. Thus a threshold for pulmonary irritation cannot be calculated.

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

14.09.2006 (83) (84)

Type : other: RD50 (sensory irritation)
Value : = 4.7 mg/m³
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals : 4
Vehicle :
Doses : 0.83; 2.31; 4.71; 14.3; 28.6 mg/m3

Exposure time	:	3 hour(s)
Method	:	other: The concentration associated with a 50 % decrease in respiration rates was determined (RD50).
Year	:	1982
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Mobay Chemical Corporation, commercial grade; Batch No. 150-2-7, no data on purity
Result	:	RD 50: after 30 min. exposure = 11.1 mg/m3 (1.20 ppm), after 1 h = 10.3 mg/m3 (1.12 ppm), after 3 h = 4.7 mg/m3 (0.51 ppm); - Mortality: 25 % at highest concentration (28.6 mg/m3 = 3.09 ppm) - Clinical signs: nasal and ocular irritation during exposure and post-exposure; reduced activity (some animals); all surviving animals appeared normal on day 1. - Recovery following exposure was slow. - Body weights: Decrease on day 1 followed by increase in three lowest concentration groups and further decrease in higher concentration groups; mean weight in highest concentration group still below initial weight on day 7 - Gross pathology: gross lesions only in highest concentration group (28.6 mg/m3 = 3.09 ppm), e.g. white foci in the liver; reddened lungs and cervical lymph nodes in dead animal - Microscopic examination: no results reported
Test condition	:	TEST ORGANISMS: - Source: Sasco Inc., Omaha, Nebraska (USA) - Age: young adult - Weight at study initiation: 211-252 g - Controls: pre-exposure respiration rate ADMINISTRATION: - Type of exposure: head only - Concentrations: 0.09; 0.25; 0.51; 1.55; 3.09 ppm = 0.83; 2.31; 4.71; 14.3; 28.6 mg/m3 Analysis: Sampling at 1.5 l/min from animals' breathing zone through a series of midget impingers followed by HPLC - Duration: 10 minutes pre-exposure, 3 hours exposure, 30 minutes recovery - Preparation of test concentrations: Air bubbled through a smog bubbler, which was filled with the test substance and kept at 27 °C, was diluted with room air. EXAMINATIONS: respiration rate; additional: - Mortality and clinical signs: continuously during exposure, at 0.5, 1.0, 1.5, 3.6 hours thereafter, then twice daily for 7 days (except 0.09 ppm: 6 days). - Body weights: prior to exposure and on days 1, 2, 3, 4, 7 (0.09 ppm: day 6 instead of day 7) - Pathology: sacrifice on day 7 (0.09 ppm: day 6), gross necropsy and microscopic examination
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment

14.06.2006 (77)

Type	:	other: RD50 (sensory irritation)
Value	:	= 3 mg/m³
Species	:	mouse
Strain	:	CD-1
Sex	:	male
Number of animals	:	4
Vehicle	:	
Doses	:	

Exposure time	:	30 minute(s)
Method	:	other: See Test Conditions
Year	:	1981
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Thorson Chemical Corp., New York; no data on purity
Result	:	RD50 after 3 min. of exposure = 0.006 mg/l (0.7 ppm), after 10 min. = 0.004 mg/l (0.43 ppm), after 30 min. = 0.003 mg/l (0.35 ppm); Recovery began immediately after end of exposure but was not complete within the 5 min. observation period.
Test condition	:	TEST ORGANISMS: - Weight at study initiation: 25-30 g - Controls: respiration rate prior to exposure ADMINISTRATION: - Type of exposure: Air was bubbled through a midget impinger containing 7 ml IPDI and diluted with ambient air to vary the concentration. EXAMINATIONS: RD50 = 50 % decrease in respiration rate - Determination of respiration rate initial five-minute control period: each minute; exposure period: after 1, 2, 3, 5, 10, 20, 30 minutes five-minute recovery period: each minute
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment

14.06.2006 (35) (36)

Type	:	other: RD50 (sensory irritation)
Value	:	= 2.01 mg/m³
Species	:	mouse
Strain	:	Swiss Webster
Sex	:	male
Number of animals	:	4
Vehicle	:	
Doses	:	0.157; 0.638; 1.02; 3.23; 8.96; 12.66 mg/m3
Exposure time	:	3 hour(s)
Method	:	other: The concentration associated with a 50 % decrease in respiration rates was determined (RD50).
Year	:	1982
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Mobay Chemical Corporation, commercial grade; Batch No. 150-2-7, no data on purity
Result	:	RD50 = 11.1 mg/m3 (1.2 ppm), 30 min. 5.95 mg/m3 (0.644 ppm), 1 h 2.01 mg/,3 (0.218 ppm), 3 h NOEL = 0.16 mg/m3 (0.017 ppm) - Mortality: 50 % at highest concentration (1.37 ppm = 12.66 mg/m3) - Clinical signs: reduced activity; none observed at 0.069 and 0.017 ppm; tremors in two animals of highest dose group; all animals appeared normal on day 1. - Recovery following exposure was slow. - Body weights: Decrease on day 1; further decrease in 0.35 and 1.37 ppm groups on day 2; subsequent trend toward recovery - Gross pathology: No compound-related gross lesions - Microscopic examination: no results reported
Test condition	:	TEST ORGANISMS: - Source: Charles River Breeding Laboratories, Wilmington, Massachusetts (USA) - Weight at study initiation: 24-30 g

- Controls: pre-exposure respiration rate
ADMINISTRATION:
- Type of exposure: head only
- Concentrations: 0.017; 0.069; 0.11; 0.35; 0.97; 1.37 ppm
= 0.157; 0.638; 1.02; 3.23; 8.96; 12.66 mg/m3
Analysis: Sampling at 1 l/min from animals' breathing zone through a series of midget impingers followed by HPLC
- Duration: 10 minutes pre-exposure, 3 hours exposure, 30 minutes post exposure
EXAMINATIONS: respiration rate; additional:
- mortality and clinical signs: continuously during exposure, one to three times within 1 to 2.5 hours thereafter, then twice daily for 7 days (except 0.35 ppm: once on days 4, 5, 6, 7; and 0.97 ppm: once on day 3).
- body weights: prior to exposure and on days 1, 2, 3, 4, 7
- pathology: sacrifice on day 7 (0.35 ppm: day 8), gross necropsy and microscopic examination

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

14.06.2006 (76)

Type : LC50
Value : = 41.4 mg/m³
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 20
Vehicle : other: no vehicle
Doses : 9.2; 18.5; 46; 69; 92 mg/m3 (nominal)
Exposure time : 4 hour(s)
Method : other: acute inhalation toxicity
Year : 1977
GLP : no
Test substance : other TS: Isophorone diisocyanate of Veba-Chemie AG, Gelsenkirchen (Germany); purity not reported

Result : MORTALITY: LC50 = 4.48 (3.88-5.08) ml/m3 = 41 (36-47) mg/m3
LC50 (24 h observation) = 7.09 (6.31-7.87 ml/m3 = 66 (58-73) mg/m3
- Number of deaths at each dose:
1.0 ml/m3: 0/20 (24 hours), 1/20 (14 days)
2.0 ml/m3: 0/20 (24 hours), 5/20 (14 days)
5.0 ml/m3: 5/20 (24 hours), 9/20 (14 days)
7.5 ml/m3: 11/20 (24 hours), 14/20 (14 days)
10 ml/m3: 11/20 (24 hours), 17/20 (14 days)
CLINICAL SIGNS: During exposure animals showed moderate increase of respiratory rate. Following exposure the respiratory rate was decreased, and apathy, asynchronism and ruffled fur were observed. Appearance, reflexes and excretion of the surviving animals were normal after 24 hours.
NECROPSY FINDINGS:
- 1.0 - 5.0 ml/m3: No macroscopically visible changes except for rare hemorrhages in the lungs.
- 7.5 ml/m3: Bronchial hemorrhages in the two animals that died first and in two others; redness in mucosa of stomach and duodenum of several animals.
- 10 ml/m3: Bronchial hemorrhages in all animals; redness in mucosa of stomach and duodenum of several animals.
POTENTIAL TARGET ORGANS: Respiratory tract
OTHER: The body weight of the surviving animals in the high dose group was decreased at the end of the study.

Test condition : TEST ORGANISMS:
- Source: Winkelmann, Paderborn (Germany)

- Weight at study initiation: 160-270 (mean 203) g
- Number of animals: 10 males + 10 females per dose group
- Controls: no
ADMINISTRATION:
- Type of exposure: nose-only inhalation followed by cleaning of heads
- Concentrations: nominal as "mass of test substance / (air flow rate x time)"
Original values: 1.0, 2.0, 5.0, 7.5, 10 ppm
- Particle size: approximately 2-5 µm
- Type or preparation of inhalation atmosphere: aerosol generated with compressed air and nozzle
- Post dose observation period: 14 days
EXAMINATIONS: Clinical signs (18 parameters), body weights, gross necropsy (central nervous system, lung, heart with heart sac, stomach, large and small intestine, liver, spleen, kidneys, serous membranes and vessels, lymph nodes, gonads)

Reliability : (4) not assignable
Documentation insufficient for assessment: Incomplete characterization of test atmosphere (no analytical concentrations, no data on particle size distribution); no information about LC50 calculation

14.06.2006 (61)

Type : LC50
Value : ca. 100 mg/m³
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 10
Vehicle : other: no vehicle
Doses : 42; 111; 622; 1,615; 4,368 mg/m3 (gravimetric)
Exposure time : 4 hour(s)
Method : other: OECD Guideline 403 (1981)
Year : 1985
GLP : yes
Test substance : other TS: Isophorone diisocyanate, purity > 99 %

Result : MORTALITY:
- Number of deaths at each dose:
42 mg/m3: 0 %
111 mg/m3: 70 % after regular postobservation period,
90 % after 22 days
>= 622 mg/m3 and higher: 100 %
- Time of death:
111 mg/m3: within 4 hours (3 males), 24 hours (2 males), 4, 12, 16, and 20 days (1 female each)
622 mg/m3: within 4 hours (all)
> 622 mg/m3: withing 2 hours (all)
- LC50 nominal: 670 (350-1010) mg/m3;
based on mortality after 22 days: 570 (220-970) mg/m3
- LC50 analytical: ca. 100 mg/m3
CLINICAL SIGNS:
- 42 mg/m3: Sedation, dyspnea, ruffled fur; recovery within 5 days
- 111 mg/m3: Sedation, dyspnea, inspiration noise, nose with red crusts, ventral body position, ruffled fur, stiff movements (female), emaciation (females)
- >= 622 mg/m3: death
NECROPSY FINDINGS:
- 42 mg/m3: no pathologic changes
- 111 mg/m3, surviving: no pathologic changes
- 111 mg/m3, dead: foam excretion from the nose (5), lung not collapsed (5), foam excretion (5), dark-red (8), intestines / stomach reddened or with

reddish contents (3), severe emaciation (2)
- >= 622 mg/m3: lung not collapsed; dark-red; severe foam excretion from the bronchi; nose swollen; foam excretion

Test condition : TEST ORGANISMS:
- Source: Kleintierfarm Mandoerin, Fuellinsdorf (CH)
- Age: 8-13 weeks
- Weight at study initiation:
males 230-305 g; females: 190-257 g
- Controls: no
ADMINISTRATION:
- Type of exposure: nose only exposure to aerosol (generated with nozzle)
- Concentrations:
calculated from: volume of test substance consumed x density of test substance / (air flow rate x time)
= nominal: 340; 670; 3,530; 10,600; 53,000 mg/m3
and determined gravimetrically on selectron filters
= gravimetric: 42; 111; 622; 1,615; 4,368 mg/m3
- Particle size:
Concentration: < 1 um / 1-3 um / 3-7 um / > 7 um
0.34 mg/l : 18.8 % / 26.2 % / 36.1 % / 10.9 %
0.67 mg/l : 9.8 % / 24.1 % / 26.7 % / 39.3 %
3.53 mg/l : 8.7 % / 24.9 % / 43.1 % / 23.3 %
10.6 mg/l : 6.5 % / 28.1 % / 52.7 % / 12.7 %
53.0 mg/l : 5.8 % / 23.8 % / 41.5 % / 28.9 %
EXAMINATIONS:
- Post dose observation period:
Up to 22 days
- Symptoms: 4 times during the first day and daily thereafter (several aspects each of general behavior, respiration, eyes, nose, motility, body position, motor susceptibility, skin and others)
- Mortality: 4 times during the first day, daily thereafter
- Body weights: Days 1 (exposure), 8, 15, 22
- Concentration: Five times during exposure
- Oxygen content, humidity, temperature: Eight times during exposure
- Air flow rate: continuously during exposure
- Necropsy: All animals (survivors sacrificed)
- LC50 calculation: Estimated with LOGIT model

Reliability : (3) invalid
Significant methodological deficiencies: No air control; no analytical determination of exposure concentrations in the vicinity of the breathing zone; particle sizes too high

(58) (86)

Type : LC50
Value : = 123 mg/m³
Species : rat
Strain : Wistar
Sex : male
Number of animals : 20
Vehicle : other: DMSO (CAS RN 67-68-5)
Doses :
Exposure time : 4 hour(s)
Method : other: Bayer AG
Year : 1968
GLP : no
Test substance : other TS: Isophorone diisocyanate, "technically pure"

Result : MORTALITY:
- 1 hour exposure:
measured: 61; 126; 256; 580 mg/m3
dead: 0/20; 2/20; 3/20; 19/20

LC50 ca. 260 mg/m3
- 4 hour exposure:
measured: 11; 21; 52; 75; 112; 150; 228 mg/m3
dead: 0/20; 0/20; 1/20; 7/20; 9/20; 16/20; 17;20
LC50 ca. 123 mg/m3
CLINICAL SIGNS: Irritation of the mucosae of the nose and the eyes
NECROPSY FINDINGS: Pulmonary changes

Test condition : TEST ORGANISMS:
- Source: Winkelmann, Kirchborchen (Germany)
- Weight at study initiation: 170-190 g
ADMINISTRATION:
The compound was dissolved in DMSO and applied as aerosol.
- Doses 1 hour exposure:
nominal: 500; 1000; 1750; 2500 mg/3
measured: 61; 126; 256; 580 mg/m3
- Doses 4 hour exposure:
nominal: 100; 250; 350; 500; 750; 1000; 1500 mg/m3
measured: 11; 21; 52; 75; 112; 150; 228 mg/m3
- Post observation period: 28 days

Reliability : (3) invalid
Unsuitable test system: Use of vehicle; whole body inhalation; generation of test atmosphere and analytical procedure do not comply with current standards.

(67)

Type : LC50
Value : = 135 - 160 mg/m³
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 10
Vehicle : other: See test conditions
Doses : 62; 72; 131; 200; 211; 285 mg/m3
Exposure time : 4 hour(s)
Method : other: See test conditions
Year : 1976
GLP : no
Test substance : other TS: Isophorone diisocyanate, 100 % pure, NCO content approx. 38 %

Result : MORTALITY:
- Time of death: 1-14 days
- Number of deaths at each dose:
62 mg/m3: 0/10 males, 0/10 females
72 mg/m3: 2/10 males, 1/10 females
131 mg/m3: 4/10 males, 5/10 females
200 mg/m3: 5/10 males, 6/10 females
211 mg/m3: 6/10 males, 10/10 females
285 mg/m3: 10/10 males, 10/10 females
CLINICAL SIGNS: breathing difficulties
NECROPSY FINDINGS: edema in lungs, pneumonia
POTENTIAL TARGET ORGANS: lung
SEX-SPECIFIC DIFFERENCES:
- males LC50 = 160 (120-215) mg/m3
- females LC50 = 135 (98-185) mg/m3

Test condition : TEST ORGANISMS:
- Source: Winkelmann, Borchen, Germany
- Weight at study initiation: 170-190 g
- Controls: no
ADMINISTRATION:
- Type of exposure: nose only

- Vehicle: 40 % solution of test substance in 1:1 mixture of
  xylene (CAS RN 1330-20-7) and
  2-ethoxyethanol acetate (CAS RN 111-15-9);
  0.05 % of colorant "oil red" was added for the analysis:
  the aerosol was adsorbed, dissolved, and the light absorption of the colorant was determined at 525 nm
- Type or preparation of particles: nozzle at 10 l/min, dilution with air to obtain desired concentration

EXAMINATIONS:
- post exposure observation period: 4 weeks

Reliability : (3) invalid
Unsuitable test system: Use of vehicle; whole body inhalation; generation of test atmosphere and analytical procedure do not comply with current standards.

(68)

Type : LC50
Value : = 118 mg/m³
Species : guinea pig
Strain : other: English smooth-haired
Sex : male/female
Number of animals : 10
Vehicle :
Doses : 81; 92; 100; 165; 364 mg/m3
Exposure time : 1 hour(s)
Method : other: See Test Conditions
Year : 1982
GLP : yes
Test substance : other TS: Isophorone diisocyanate of American Cyanamid Co., Stanford, Connecticut; no data on purity

Result : MORTALITY:
- Time of death: within two days of exposure
- Number of deaths at each dose (day of exposure + following day):
  control: males 0 + 0, females 0 + 1 (by injury to ear)
  81 mg/m3: males 1 + 2, females 0 + 1
  92 mg/m3: males 1 + 1, females 0 + 1
  100 mg/m3: males 1 + 0, females 0 + 0
  165 mg/m3: males 4 + 1, females 4 + 1
  364 mg/m3: males 5 + 0, females 4 + 1
- LC50 confidence interval: 100-140 mg/m3
- Body weight: Losses occurred in all treated groups, but group mean body weights of survivors in treated groups were similar to those of the control group by the end of the recovery period.

CLINICAL SIGNS: Lethargy, gasping or rales, discharge from the nose or mouth, and pallor of the skin
NECROPSY FINDINGS: Swollen, reddened, rubbery lungs and lung congestion were observed in treated animals that died. Swelling, reddening and increased consistency of the lungs were observed at termination in survivors.
POTENTIAL TARGET ORGANS: lung

Test condition : TEST ORGANISMS:
- Source: Hilltop Laboratory Animals, Scottdale, PA (USA)
- Age: 4-5 weeks
- Weight at study initiation: 250-300 g
- Number of animals: 5 per sex and group, total 30 per sex
- Controls: air

ADMINISTRATION:
- Type of exposure: whole-body aerosol exposure
- Concentrations (in chronological order of exposure):
  air control; 364; 81; 165; 92; 100 mg/m3

- Particle size: The count median diameter was always less than 2 µm although the small size of the particles observed often prevented the calculation of an exact value.
- Type or preparation of particles: Use of a concentric jet glass atomizer supplied with pre-dried compressed air
- Analytical methods:
Gravimetric determination of weight increase of Gelman glass fibre filter paper positioned near the breathing zone of the animals
Collection of test substance in liquid traps containing toluene followed by GC/FID analysis
Particle size analysis with May Cascade Impactor followed by an optical counting and sizing procedure
EXAMINATIONS:
- Clinical signs: during and immediately after exposure and at least twice daily during 14-day recovery period
- Body weights: day of exposure, days 2, 3, 4, 7, and 14
- Antibody analysis: Prior to treatment and at termination
- Gross pathology: All surviving animals were given a "detailed gross pathology examination".

Reliability : (3) invalid
Unsuitable test system: Whole-body aerosol exposure

(6)

Type : other: Inhalation hazard test
Value :
Species : rat
Strain :
Sex :
Number of animals : 6
Vehicle :
Doses : 125 mg/m3
Exposure time : 8 hour(s)
Method : other: see Method and Test Condition
Year : 1967
GLP : no
Test substance : other TS: Isophorone diisocyanate, submitted by P.G. Naylor, Division Chemicals and Plastics Research and Development, South Charleston, W.Va. (USA); sponsor's ID 38-MPW-105 / 29-DS-10-5; internal ID 30-182

Method : Concentrated vapor is generated in a gas washing bottle by passing dried air at 2.5 liters/min. through a fritted glass disc immersed to a depth of at least 1-1/2 inches in the chemical which is delivered to rats in a 9-liter glass exposure chamber. Mean vapor concentration is calculated from the loss in weight of the liquid.

Result : MORTALITY:
- Number of deaths at each dose: no deaths
NECROPSY FINDINGS: "nothing remarkable"

Test condition : ADMINISTRATION:
- Concentrations: Reported as 0.125 mg/l or 14 ppm (substantially saturated vapor at approx. 22 degree C), concentration measured from weight loss of liquid
- Type or preparation of test atmosphere: ca. 20 ml of sample in a small bubbler with 2.5 l/min of air

Reliability : (3) invalid
Poor documentation and significant methodological deficiencies: No analytical determination of exposure concentrations.

(106)

Type : other: Inhalation hazard test
Value :
Species : rat

Strain	:	other: CD
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	approximately saturated atmosphere
Exposure time	:	8 hour(s)
Method	:	other: See Test Conditions
Year	:	1978
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of VEBA-Chemie AG, purity > 99 %
Result	:	MORTALITY: - Number of deaths at each dose: no deaths CLINICAL SIGNS: - during exposure: mild, non specific irritation (ptyalism); gasping vasodilatation; brown staining of the fur of the snout and head (females worse than males) - during observation period: noisy respiration during the first 2 days; loss of body weight and depression of food and water consumption on the day following exposure NECROPSY FINDINGS: mild subpleural congestion in 4/10 females POTENTIAL TARGET ORGANS: respiratory tract SEX-SPECIFIC DIFFERENCES: clinical signs were more intensive in female rats; see also necropsy findings
Test condition	:	TEST ORGANISMS: - Source: Charles River (UK) Ltd., Manston, Kent - Controls: Air ADMINISTRATION: - Type of exposure: Whole body exposure, dynamic, minimum flow. Air was passed through a wash bottle immersed in a water bath at 20 °C. - Concentration: Nominal: Results were unsatisfactory due to problems of weighing accurately the very small (order of a few milligrams) loss in weight of the vaporizer filled with the test substance (about 400 g). Analytical: None of the methods available was successful at the levels of vapor used in the study, thus no analysis was possible. Theoretical: According to the vapor pressure data used by the authors, saturation corresponds to 0.4 ppm = 3.6 mg/m3. EXAMINATIONS: - Post exposure observation: 14 days - Clinical signs: frequently during exposure, at least twice daily thereafter - Body weights: daily - Food & water consumption: daily - Gross pathology: macroscopic examination included opening the thoracic and abdominal cavities. The respiratory tract was removed and given a detailed examination. The lungs were dissected clear of surrounding tissue and weighed.
Reliability	:	(3) invalid Significant methodological deficiencies: Insufficient characterization of exposure atmosphere

(44)

Type	:	other: Inhalation hazard test
Value	:	
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	12
Vehicle	:	other: no vehicle
Doses	:	atmosphere saturated at 20 °C
Exposure time	:	8 hour(s)

Method	:	other: Draft version for Directive 84/449/EEC, B.2
Year	:	1978
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Veba-Chemie AG, Gelsenkirchen (Germany); purity not reported
Result	:	MORTALITY: - Time of death: hours 6-8 of exposure - Number of deaths at each dose: 2/6 males + 3/6 females CLINICAL SIGNS: During and some hours following exposure animals showed moderate increase of respiratory rate, irritability and agitation, slight decrease of abdominal tension and of cutaneous turgor. Appearance, reflexes and excretion were normal after 24 hours. NECROPSY FINDINGS: - Animals that died during the study: Hemorrhage throughout the lungs - Terminal sacrifice: No macroscopically visible changes POTENTIAL TARGET ORGANS: Lung OTHER: The mean body weight of the surviving animals at the end of the study was normal (230 g).
Test condition	:	TEST ORGANISMS: - Weight at study initiation: 190-210 (mean 198.6) g - Number of animals: 6 males + 6 females - Controls: no ADMINISTRATION: - Type of exposure: whole-body exposure in inhalation chamber followed by cleaning of heads - Concentrations: not quantified - Type or preparation of inhalation atmosphere: 200 l air/hour were blown through the test substance at 20 °C. - Post dose observation period: 14 days EXAMINATIONS: Clinical signs (27 parameters), body weights, gross necropsy (central nervous system, lung, heart with heart sac, stomach, large and small intestine, liver, spleen, kidneys, serous membranes and vessels, lymph nodes, gonads)
Reliability	:	(3) invalid Significant methodological deficiencies: Insufficient characterization of exposure atmosphere

(62)

Type	:	other: requirements for adequately testing the inhalation toxicity of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate
Value	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: Isophorone diisocyanate, essentially pure
Result	:	The particle-size distribution of aerosols generated in inhalation studies should allow exposure of all relevant regions of the respiratory tract, since damage to and/or deposition in any region of the respiratory tract may induce lethality. An aerosol bracketing a particle-size mass distribution of mass median aerodynamic diameter (MMAD) 1 to 4 µm, as recommended by Society of Toxicology (1992) and a geometric standard deviation (GSD) in the range of 1.5 to 3.0 therefore appear to be appropriate for LC50

determination.

14.06.2006 (96)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 7000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: no vehicle
Doses	:	7000 mg/kg bw
Method	:	other: OECD Guideline 402 (1981)
Year	:	1985
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Hüls AG, purity > 99 %
Result	:	MORTALITY: - Number of deaths at each dose: no deaths CLINICAL SIGNS: 5/5 females and 5/5 males showed signs of intoxication for up to 72 hours: After 24 hours most animals showed piloerection, sedation, ataxia, hypothermia, hunched position, irritations at application site. Reduced body weight was observed after 1 week. NECROPSY FINDINGS: hyperemia of stomach and intestinal mucosa, pale kidneys with dark spots, incrustation and cicatrization at application site (number of affected animals not reported)
Test condition	:	TEST ORGANISMS: - Source: Winkelmann, Borchen (Germany) - Weight at study initiation: males 265 g, females 208 g (mean) ADMINISTRATION: - Occlusion: yes - Removal of test substance: with warm water after 24 hours EXAMINATIONS: - Clinical observation and mortality: for 6 hours on day of exposure, daily thereafter - Body weights: Before exposure and on days 1, 7 and 14 after treatment - Gross pathology: After observation period (14 days)
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions: Kind of limit test with unusual dose, no rationale for dose selection reported

(49)

Type	:	LD50
Value	:	= 1275 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: no vehicle
Doses	:	1000; 1250; 1990 mg/kg bw
Method	:	other: OECD Guideline 402 (1981)
Year	:	1984
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Hüls AG, purity > 99 %
Remark	:	The test was repeated in a follow-up study applying occlusion of the test substance. The follow-up study is presented as a separate entry in this chapter. The difference in test results indicates a significant effect of occlusion on the effects.

Result : MORTALITY:
- Number of deaths at each dose and time of death:
1000 mg/kg: 3/5 males (within 26 hours); 0/5 females
1250 mg/kg: 3/5 males, 1/5 females (within 6 days)
1990 mg/kg: 5/5 males, 4/5 females (within 96 hours)
LD50 = 1275 (1028-1581) mg/kg
CLINICAL SIGNS: bleeding noses, ruffled fur, slight sedation and ataxia, reduced weight gain / loss of weight, irritations at application side
NECROPSY FINDINGS: incrustation and cicatrization at application site, hyperemia and swelling of stomach and intestinal mucosa

Test condition : TEST ORGANISMS:
- Source: Winkelmann, Borchen (Germany)
- Weight at study initiation: males 214 g, females 193 g (mean)
ADMINISTRATION:
- Occlusion: no
- Removal of test substance: no (or not reported)
- Other: A collar made of cardboard was fixed to the animals' necks for the first six hours after test substance administration. Each animal had its individual cage.
EXAMINATIONS:
- Clinical observation and mortality: for 6 hours on day of exposure, daily thereafter
- Body weights: Before exposure and on days 1, 7 and 14 after treatment
- Gross pathology: After observation period (14 days)

Reliability : (3) invalid
Significant methodological deficiencies: no occlusion (required by the OECD TG to "ensure that the animals cannot ingest the test substance").

23.09.2006 (46)

Type : LD50
Value : ca. 529 mg/kg bw
Species : rat
Strain : Wistar
Sex : male
Number of animals : 5
Vehicle : other: Oil, not specified
Doses : 106; 264; 529; 793; 1058 mg/kg bw
Method : other: Bayer AG
Year : 1968
GLP : no
Test substance : other TS: Isophorone diisocyanate, "technically pure"

Result : MORTALITY:
- Number of deaths at each dose:
0.10 ml/kg: 0/5
0.25 ml/kg: 1/5
0.50 ml/kg: 2/5
0.75 ml/kg: 5/5
1.00 ml/kg: 5/5
CLINICAL SIGNS: Symptoms of intoxication were not characteristic.

Test condition : TEST ORGANISMS:
- Source: Winkelmann, Kirchborchen (Germany)
- Weight at study initiation: 200-230 g
ADMINISTRATION:
- Area covered: 2-3 cm2
- Occlusion: no
- Concentration in vehicle: 50 %
- Doses: 0.1; 0.25; 0,5; 0.75; 1 ml/kg bw x 1058 mg/ml = 106; 264; 529; 793; 1058 mg/kg bw
- Removal of test substance: no
EXAMINATIONS: test period 7 days

Reliability	:	(3) invalid Significant methodological deficiencies; no occlusion, application of test substance diluted in oil, no data on purity of test substance.
14.06.2006		(67)
Type	:	LD50
Value	:	ca. 1058 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	5
Vehicle	:	other: Oil, not specified
Doses	:	264; 529; 1058 mg/kg bw
Method	:	other: Bayer AG
Year	:	1968
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, "technically pure"
Result	:	MORTALITY: - Number of deaths at each dose: 0.25 ml/kg: 0/5 0.50 ml/kg: 0/5 1.00 ml/kg: 2/5 CLINICAL SIGNS: Symptoms of intoxication were not characteristic.
Test condition	:	TEST ORGANISMS: - Source: Winkelmann, Kirchborchen (Germany) - Weight at study initiation: 200-230 g ADMINISTRATION: - Area covered: 2-3 cm2 - Occlusion: no - Concentration in vehicle: 50 % - Doses: 0.25; 0,5; 1 ml/kg bw x 1058 mg/ml = 264; 529; 1058 mg/kg bw - Removal of test substance: with water and soap after 4 hours EXAMINATIONS: post observation period 7 days
Reliability	:	(3) invalid Unsuitable test system: Substance was applied onto the abdomen whereas the rats were fixed supine for 4 hours. No occlusion. No data on purity of test substance.
14.06.2006		(67)
Type	:	LD50
Value	:	= 4780 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	4
Vehicle	:	other: no vehicle
Doses	:	6771 and 3386 mg/kg bw
Method	:	other: "standard"
Year	:	1967
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate submitted by P.G. Naylor, Division Chemicals and Plastics Research and Development, South Charleston, W.Va. (USA); sponsor's ID 38-MPW-105 / 29-DS-10-5; internal ID 30-182
Method	:	Rabbits are immobilized during the 24-hour contact period with the compound retained under impervious sheeting on the clipped intact skin of the trunk. Thereafter, excess fluid is removed to prevent ingestion. Maximum dosage that can be retained is 20 ml/kg.
Result	:	MORTALITY: - Number of deaths at each dose:

6.4 ml/kg: 3/4 on days 0, 4, 6
3.2 ml/kg: 1/4 on day 2
CLINICAL SIGNS: not reported
Skin irritation: not reported
NECROPSY FINDINGS: Congestion throughout the lungs and the abdominal viscera (no information available whether these findings are restricted to the animals that died; no information available how many animals showed these findings.)
LD50 = 4.52 (2.08-9.87) ml/kg = 4780 (2200-10440) mg/kg

Test condition : TEST ORGANISMS:
- Age: 3-5 months
ADMINISTRATION: single dose
- Occlusion: VINYLITE covering
- Doses: 6.4 and 3.2 ml/kg = 6771 and 3386 mg/kg bw
- Post observation period: 14 days

Reliability : (3) invalid
While the study documentation may be regarded as sufficient (short report) the statistical evaluation is less reliable due to low number of animals and only 2 dose levels.

19.06.2006 (106)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	222 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	female
Number of animals	:	5
Vehicle	:	other: no vehicle
Doses	:	106; 212; 423; 846 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other: "standard"
Year	:	1967
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate submitted by P.G. Naylor, Division Chemicals and Plastics Research and Development, South Charleston, W.Va. (USA); sponsor's ID 38-MPW-105 / 29-DS-10-5; internal ID 30-182

Result : MORTALITY:
- Number of deaths at each dose:
0.8 ml/kg: 5/5 within less than 1 day
0.4 ml/kg: 3/5 within 1 day
0.2 ml/kg: 4/5 within 1 day
0.1 ml/kg: 0/5
CLINICAL SIGNS: slight tremors, heavy breathing
NECROPSY FINDINGS: congestion throughout the lungs and the abdominal viscera
LD50 = 0.21 (0.13-0.35) ml/kg = 222 (138-370) mg/kg

Test condition : TEST ORGANISMS:
- Weight at study initiation: 180-260 g
ADMINISTRATION:
- Doses: 0.1; 0.2; 0.4; 0.8 ml/kg bw = 106; 212; 423; 846 mg/kg bw

Reliability : (3) invalid
While the study documentation may be regarded as sufficient (short report) the statistical evaluation is less reliable due to low number of animals.

14.06.2006 (106)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	other: no vehicle
PDII	:	6.87
Result	:	corrosive
Classification	:	
Method	:	other: OECD Guideline 404 (1981)
Year	:	1984
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, purity > 99%
Result	:	AVERAGE SCORE - Erythema: 3.61/4.0 (6th Amendment = 79/831/EEC) - Edema: 3.33/4.0 (6th Amendment = 79/831/EEC) - Overall: 6.87/8.0 (OECD TG) OTHER EFFECTS: necrosis after 4 hours, not after 3 minutes
Test condition	:	TEST ANIMALS: - Strain: New Zealand white - Sex: male/female - Source: Dr. Karl Thomae GmbH, Biberach (Germany) - Weight at study initiation: 3.8-5.3 kg ADMINISTRATION/EXPOSURE - Area of exposure: ca. 6 cm2 - Total volume applied: 0.5 ml - Postexposure period: 14 days - Removal of test substance: with warm water EXAMINATIONS - Scoring system: OECD Guideline; Annex VI of 79/831/EEC (6th Amendment) - Examination time points: 1; 24; 48; 72 hours and 6; 8; 10; 14 days after removal of patch and test substance; the first 4 readings were scored in the OECD system.
Reliability	:	(1) valid without restriction Guideline study

16.09.2006 (47)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	1
Vehicle	:	
PDII	:	4.5
Result	:	corrosive
Classification	:	
Method	:	other: OECD Guideline 404 (1981)
Year	:	1994
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG, Leverkusen, Batch/lot no. 1.5 / 3.-20, Purity > 99 %
Result	:	AVERAGE SCORE - Erythema: 2.7/4.0 - Edema: 1.7/4.0 OTHER EFFECTS: 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 and in this area a wound (1 x 1 cm) with incrustation was observed.

Test condition : TEST ANIMALS:
- Strain: HC:NZW
- Sex: female
- Source: Interfauna U.K. Ltd., Wyton, Huntingdon, England
- Weight at study initiation: 3.2 kg
- Controls: deionized water on contralateral skin area

ADMINISTRATION/EXPOSURE
- Area of exposure: ca. 6 cm2
- Total volume applied: 0.5 ml
- Postexposure period: 14 days
- Removal of test substance: yes

EXAMINATIONS
- Scoring system: 83/467/EEC; Draize scores
- Examination time points:
  after ca. 1; 24; 48; 72 hours, 7 and 14 days

Reliability : (1) valid without restriction
Guideline study

16.09.2006 (70)

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 30 minute(s)
Number of animals : 2
Vehicle : other: cellulose
PDII :
Result : corrosive
Classification :
Method : other: See Test Conditions
Year : 1968
GLP : no
Test substance : other TS: Isophorone diisocyanate, "technically pure"

Result : Strong reddening and swelling with successive cauterization of the skin was observed. The irritational effect of the substance visibly reached beyond the skin areas treated.

Test condition : TEST ANIMALS:
- Strain: no specific strain
- Sex: male/female

ADMINISTRATION/EXPOSURE
- Occlusion: no details reported
- Total volume applied: 0.5 ml
  The substance was trickled onto cellulose and placed inside the pinna

Reliability : (3) invalid
Borderline validity. Test system not according to Guideline

(67)

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 4 hour(s)
Number of animals : 6
Vehicle :
PDII : 3.71
Result : corrosive
Classification :

Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1981
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, no data on purity
Remark	:	The original test report was submitted to the sponsor with cover letter dated 02 April 1981. Thus it cannot have been performed according to the adapted OECD Test Guideline. Probably a late / final draft was used.
Result	:	AVERAGE SCORE - Erythema: 1.71/4.0 - Edema: 2.00/4.0 OTHER EFFECTS: high degree of irritation of the skin with severe thickening and fissured surface hardening after 8 days
Test condition	:	TEST ANIMALS: - Strain: New Zealand white - Sex: Male - Source: Lippische Versuchstierzucht, Extertal (Germany) - Weight at study initiation: 2.3 kg (average) ADMINISTRATION/EXPOSURE - Area of exposure: 2.5 cm x 2.5 cm flank skin on both sides; 8 cm x 8 cm shaved 24 hours in advance - Occlusion: PVC film - Total volume applied: 0.5 ml per application site - Postexposure period: 8 days - Removal of test substance: washing with water EXAMINATIONS - Scoring system: maximum 4 scores each for erythema and scab formation and edema formation; average of 24 h and 72 h readings - Examination time points: immediately after removal = 4 hours; 24, 48, 72 hours; 8 days
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment
16.09.2006		(79) (94)
Species	:	rabbit
Concentration	:	undiluted
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	highly irritating
Classification	:	
Method	:	other: See Test Conditions
Year	:	1968
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, no data on purity
Result	:	abdomen: marked edema and deep necrosis, not healing to any great extent after 15 d; ear: edema and necrosis, healing after 10 d with no scarring
Test condition	:	TEST ANIMALS: - Sex: male ADMINISTRATION/EXPOSURE - Area of exposure: abraded and unabraded area of the abdomen (with occlusion for 24 hours); uncovered area of the ear - Postexposure period: 15 days or more - Removal of test substance: not reported

Reliability : (4) not assignable
Documentation insufficient for assessment

14.09.2006 (34)

Species : rabbit
Concentration : undiluted
Exposure : Open
Exposure time : no data
Number of animals : 5
Vehicle :
PDII :
Result :
Classification :
Method : other: "standard"
Year : 1967
GLP : no
Test substance : other TS: Isophorone diisocyanate submitted by P.G. Naylor, Division Chemicals and Plastics Research and Development, South Charleston, W.Va. (USA); sponsor's ID 38-MPW-105 / 29-DS-10-5; internal ID 30-182

Method : Chemical is applied in 0.01 ml amounts to clipped intact skin of 5 rabbit bellies. Ten grades are recognized based on appearance of moderate or marked capillary injection, erythema, edema, necrosis within 24 hours. No injury from undiluted = Grade 1.
Result : - uncovered application of undiluted substance: marked necrosis in 2 animals and moderate capillary injection in one;
- uncovered application of a 10 % solution in acetone: marked necrosis in 3 animals and moderate erythema in 2 others;
- uncovered application of a 1 % solution in acetone: moderate to marked erythema in 5 animals tested
- Result: "Grade 7"; maximum: 10
Reliability : (4) not assignable
Documentation insufficient for assessment

(106)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time :
Comment : not rinsed
Number of animals : 6
Vehicle : none
Result : not irritating
Classification :
Method : other: OECD Guideline 405 (1981)
Year : 1984
GLP : no
Test substance : other TS: Isophorone diisocyanate, purity > 99%

Result : AVERAGE SCORE
- Cornea: 0.33
- Iris: 0.17
- Conjuntivae (Redness): 1.61
- Conjuntivae (Chemosis): 0.67
- Overall irritation score: 9.96/110
OTHER EFFECTS: Significant exsudation was observed at the 1 hour and 24 hour inspections. Ten days after treatment all animals showed loss of hair around the eye and incrustation at the eyelid, mostly associated with

thickening on day 13, which is not reflected in the scores.

Test condition : TEST ANIMALS:
- Strain: New Zealand white
- Sex: male/female
- Source: Dr. Karl Thomae GmbH, Biberach (Germany)
- Weight at study initiation: 3.7-5.4 kg
- Controls: untreated eye

EXAMINATIONS
- Ophtalmoscopic examination: 1; 24; 48; 72 hours and 6; 8; 10; 13; and 15 days after treatment
- Scoring system: Draize (1959); Annex VI of 79/831/EEC (6th Amendment)
- Tool used to assess score: sodium fluorescein plus ophthalmic lamp

Reliability : (1) valid without restriction
Guideline study

02.06.2006 (48)

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time :
Comment :
Number of animals : 6
Vehicle : none
Result : corrosive
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1981
GLP : no
Test substance : other TS: Isophorone diisocyanate, no data on purity

Remark : The original test report was submitted to the sponsor with cover letter dated 02 April 1981. Thus it cannot have been performed according to the adapted OECD Test Guideline. Probably a late / final draft was used.

Result : AVERAGE SCORE (not rinsed / rinsed)
- Cornea (opacity): 1.0 / 0.9 (max. 4)
- Cornea (area): 2.9 / 1.6 (max. 4)
- Iris: 0.6 / 0.1 (max. 1)
- Conjunctivae (Redness): 2.8 / 2.7 (max. 3)
- Conjunctivae (Chemosis): 3.9 / 3.9 (max. 4)
- Conjunctivae (Exsudation): 2.8 / 2.3 (max. 3)
- Overall irritation score: 36.4 / 26.4 (max. 110)

OTHER EFFECTS:
Severe irritation of the conjunctiva: high degree of chemosis with unchanged condition after 8 d both on rinsed and non-rinsed eye; slight cornea damage, to a lesser degree on the rinsed eye, with significant retrogression within 8 d

Test condition : TEST ANIMALS:
- Strain: New Zealand white
- Sex: male
- Source: Lippische Versuchstierzucht, Extertal (Germany)
- Weight at study initiation: 2.3 kg (average)
- Controls: no

ADMINISTRATION/EXPOSURE
- Administration of test substance: both eyes; eyes closed for 1 s after administration
- Amount of substance instilled: 0.1 ml into each eye
- Rinsing: right eye after 30 s for 3 min with physiol. sodium chloride solution
- Postexposure period: 8 days

EXAMINATIONS

- Ophtalmoscopic examination: 1; 24; 48; 72 hours; 8 days
- Scoring system: maximum 110 scores (Draize)
- Observation period: 8 days
- Tool used to assess score: ophthalmoscope; fluorescein

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

21.06.2006 (78) (95)

Species : rabbit
Concentration : undiluted
Dose : .05 ml
Exposure time :
Comment : no data
Number of animals : 1
Vehicle : none
Result : corrosive
Classification :
Method : other: See Test Conditions
Year : 1968
GLP : no
Test substance : other TS: Isophorone diisocyanate, "technically pure"

Result : Heavy damage of the conjunctivae and sclerae: reddening, swelling, cauterization; turbidity of the cornea
Test condition : TEST ANIMALS:
- Strain: no specific strain

ADMINISTRATION/EXPOSURE
The substance placed onto the conjunctiva of a rabbit's eye

Reliability : (4) not assignable
Documentation insufficient for assessment

14.06.2006 (67)

Species : rabbit
Concentration : undiluted
Dose : .5 ml
Exposure time :
Comment :
Number of animals : 5
Vehicle : none
Result :
Classification :
Method : other: "standard"
Year : 1967
GLP : no
Test substance : other TS: Isophorone diisocyanate submitted by P.G. Naylor, Division Chemicals and Plastics Research and Development, South Charleston, W.Va. (USA); sponsor's ID 38-MPW-105 / 29-DS-10-5; internal ID 30-182

Method : Eyes not staining with 5% fluorescein in 20 seconds contact are accepted. Single instillations of 0.005, 0.02, 0.10 or 0.5 ml undiluted are made into conjunctival sac of 5 rabbits. Read within one hour unstained and after fluorescein at 24 hours, with ten grades recognized. Trace or no injury from 0.5 ml undiluted = Grade 1.
Result : 0.5 ml caused trace corneal injury in 2 of 5 eyes with swelling and injection of the lids. There was no corneal injury in three eyes from 0.005 ml of the undiluted material.
Reliability : (4) not assignable
Documentation insufficient for assessment

14.06.2006 (106)
Species : rabbit

Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	other: one eye rinsed
Number of animals	:	
Vehicle	:	none
Result	:	highly irritating
Classification	:	
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Dow Resins Research, purity not reported
Result	:	The test material produced immediate indications of severe pain. The pain persisted for only a few minutes and was reduced by washing. The material produced immediate conjunctival response with severe swelling and reddening. This effect was severe in both treated and untreated eyes and persistde for more than 15 days. The cornea showed almost immediate response showing opaque areas of 50 % in the unwashed eye and 25 % in the washed eye, which both stained with fluorescein but cleared in 8 days.
Reliability	:	(4) not assignable Documentation insufficient for assessment

14.06.2006 (34)

5.3 SENSITIZATION

Type	:	Buehler Test
Species	:	guinea pig
Concentration	:	1st: Induction 5 % occlusive epicutaneous 2nd: Challenge 1 % occlusive epicutaneous 3rd:
Number of animals	:	20
Vehicle	:	petrolatum
Result	:	sensitizing
Classification	:	sensitizing
Method	:	Directive 84/449/EEC, B.6 "Acute toxicity (skin sensitization)"
Year	:	1998
GLP	:	no data
Test substance	:	other TS: Isophorone diisocyanate of Hüls AG, commercial, purity >= 99 %
Result	:	RESULTS OF PILOT STUDY: see test concentrations RESULTS OF TEST - Sensitization reaction: test group treated with test substance 16/20 animals positive = strong sensitization test group treated with vehicle: all animals negative (0-1 scores) control groups: no irritation or sensitization
Test condition	:	TEST ANIMALS: - Strain: Dunkin-Hartley - Sex: female - Source: Charles River (France) - Weight at study initiation: 350 g on average - Controls: 10 animals; vehicle during induction ADMINISTRATION/EXPOSURE - Induction schedule: not reported; see guideline - Concentrations used for induction: 5 % (w/v); 0.5 ml - Challenge schedule:

14 days after end of induction: patch treatment
approx. 30 hours after patch application: assessment of skin reactions
- Concentrations used for challenge: 1 % (w/v); 0.5 ml
- Positive control: neomycin sulfate (CAS RN 1405-10-3)
EXAMINATIONS
- Grading system: Magnusson/Kligman
0 = no visible change
1 = discrete or patchy erythema
2 = moderate and confluent erythema
3 = intense erythema and swelling
only scores of 2 and/or 3 considered positive;
histopathological examination in cases of doubt
Characterization of sensitization potential in 5 groups according to the number of positive animals
- Pilot study: determination of test concentrations for induction (mild to moderate dermal response or 100 %) and challenge (no dermal response)

Reliability : (2) valid with restrictions
Guideline study without detailed documentation

02.06.2006 (111)

Type : Buehler Test
Species : guinea pig
Concentration : 1st: Induction occlusive epicutaneous
2nd: Challenge occlusive epicutaneous
3rd:
Number of animals : 15
Vehicle : other: 1:1 mixture of olive oil and acetone (anhydrous)
Result : sensitizing
Classification : sensitizing
Method : other: Closed patch test; modified Buehler method, Buehler EV (1965). Arch. Dermatol 91, 171-175; Ritz HL and Buehler EV (1980). In: Drill VA and Lazar P (eds.): Current Concepts in Coutaneous Toxicity, Academic Press, 25-40.
Year : 1984
GLP : no
Test substance : other TS: Isophorone diisocyanate of American Cyanamid Co., Bound Brook N.J. (USA), purity not reported

Result : RESULTS OF PILOT STUDY: Dose selection. Consequence: The low and mid concentrations used for induction were non-irritating, the high concentration was minimally irritating.
RESULTS OF TEST
- Sensitization reaction: The three lowest challenge concentrations did not induce skin reactions, and minimal effects were observed with the fourth challenge concentration level. The highest challenge concentration induced skin reactions for all induction concentration levels with 10/15 animals positive + 4/15 animals equivocal for highest induction concentration.
- Clinical signs: No substance-related abnormalities were observed. Dermal scores after the third induction exposure were generally higher than after the first exposure. Their severity and incidence was concentration-dependent.
- Cross-challenge:
In the whole test with 7 isocyanates the cross-challenge response was generally low. Cross-challenge was observed with p-tetramethylxylene diisocyanate (CAS RN 2778-41-8), 3-(2-propenyl)-1-(2-propyl-2-isocyanato) benzene (2094-99-7), isophorone diisocyanate (4098-71-9), m-tetramethylxylene diisocyanate (CAS RN 2778-42-9), and 4,4'-methylenedicyclohexyl diisocyanate (5124-30-1), not with toluene diisocyanate (1321-38-6) and 4,4'-methylenediphenyl diisocyanate (101-68-8).
Induction with the present test substance, challenge with:

- p-tetramethylxylene diisocyanate (2778-41-8): 6/15 animals positive or ambiguous
- m-tetramethylxylene diisocyanate (2778-42-9): 2/15 animals positive or ambiguous
- 4,4'-methylenedicyclohexyl diisocyanate (5124-30-1): 2/15 animals positive or ambiguous
- 3-(2-propenyl)-1-(2-propyl-2-isocyanato) benzene (2094-99-7): 0/15 animals positive or ambiguous

Challenge with the present test substance after induction with:
- p-tetramethylxylene diisocyanate (2778-41-8): 1/15 animals positive or ambiguous
- m-tetramethylxylene diisocyanate (2778-42-9): 4/15 animals positive or ambiguous
- 4,4'-methylenedicyclohexyl diisocyanate (5124-30-1): 2/15 animals positive or ambiguous
- 3-(2-propenyl)-1-(2-propyl-2-isocyanato) benzene (2094-99-7): 1/15 animals positive or ambiguous

Test condition : TEST ANIMALS:
- Strain: Hartley
- Sex: male/female
- Source: Hazelton-Dutchland Laboratory Animals, Denver (PA, USA)
- Age: 5-6 weeks
- Weight at study initiation:
males 307-480 g; females 299-462 g
- Number of animals per treatment group: 7 or 8 males + 8 or 7 females
- Controls: 3 males + 3 females; treatment at challenge only; similar control group with cross-challenge

ADMINISTRATION/EXPOSURE
- Preparation of test substance for induction: 1 mol/l stock solution in vehicle, avoiding any moisture
- Induction schedule: once weekly for 3 weeks, 50 µl, removal of patch and excess substance after 6 hours
- Concentrations used for induction:
3 groups: 30, 90, or 300 mMol/l
Dermal evaluation before and approx. 24 hours after treatment
- Challenge schedule: 14 days after last induction exposure
Dermal evaluation before and approx. 24 and 48 hours after treatment
- Concentrations used for challenge: 25 µl of solutions of 90; 30; 9; 0.9; 0.09 mMol/l to opposite side relative to induction, removal of patch and excess material after 6 hours
- Cross-challenge: 7 days after challenge the high dose group was challenged at previously untreated sites with 4 structurally similar substances. Similarly the high dose animals from parallel tests with structurally similar substances were challenged with (among others) the present test substance.
Dermal evaluation before and approx. 24 and 48 hours after treatment
- Positive control: no / other substances tested simultaneously

EXAMINATIONS
- Grading system: possible scores 0 - 3 plus indication of edema, necrosis, and eschar formation
- Pilot study: range finding; 6 animals were treated topically (occlusive) with 30 µl of 1.0; 0.3; 0.1; 0.03; 0.01; 0.003 mol/l solutions in olive oil or in a 1:1 mixture of olive oil and anhydrous acetone; removal of patch and excess material after 6 hours, observations after 24 and 48 hours and on days 4, 5, and 6

Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions: Purity of test substance not reported

(4)

Type : Guinea pig maximization test
Species : guinea pig

Concentration : 1st: Induction 5 % intracutaneous
2nd: Induction .05 % occlusive epicutaneous
3rd: Challenge .5 % semiocclusive
Number of animals : 20
Vehicle : other: olive oil; 2nd challenge: olive oil + acetone 1:1
Result : sensitizing
Classification : sensitizing
Method : other: OECD Guideline 406 (1992) and Directive 84/449/EEC, B.6
Year : 1993
GLP : no
Test substance : other TS: Isophorone diisocyanate of Bayer AG, Batch 1.5/3-20, purity > 99 %

Result : RESULTS OF PILOT STUDY:
A) Weals at all injection sites. 0 %: red and fading; other concentrations: grey, red borderline appearing at 48 hours
B) Edema: In all animals at >= 25 %, in no animal at <= 12 %
Erythema: In all animals at >= 3 %, in >= 2 animals at >= 0.05 %, in 1 animal at 0.025 %.
C) Edema were not observed. Grade 1 erythema were observed in 2 out of 5 animals at the 2 lower concentrations and in only 1 animal at the 2 higher concentrations.
RESULTS OF TEST
- Sensitization reaction: Incidence of skin reaction 24 hours (48 hours) after patch removal

Chall. Concn.	Test group Test subst.	Test group Vehicle	Control group Test subst.	Control group Vehicle
0.5 %	16(16)/20	15(11)/20	8(7)/10	7(7)/10
0.1 %	11(8)/20	14(7)/20	9(8)/10	7(7)/10

Rechallenge:

0.5 %	19(17)/20	7(3)/20	8(6)/10	3(0)/10
0.1 %	15(8)/20	6(3)/20	4(2)/10	4(3)/10

From the difference between test and control in the severity of skin reactions, which was more pronounced at rechallenge than at the first challenge, the authors concluded that the test substance is sensitizing.
- Clinical signs: No symptoms and no mortalities were observed.
ADDITIONAL INFORMATION:
The mean body weight increase was not affected:
Test group: 161 g (24 days), 245 g (38 days)
Control group 1: 157 g (24 days)
Control group 2: 195 g (24 days), 251 g (38 days)

Test condition : TEST ANIMALS:
- Strain: Dunkin-Hartley, Pirbright White (Hsd/Win:DH) (SPF)
- Sex: male
- Source: Harlan Winkelmann, Borchen (Germany)
- Age: 4-8 weeks
- Weight at study initiation: 296-426 g (mean 368 g)
- Number of animals:
Total 58; 20 in test group; 10 each in 2 control groups;
1 for topical dose finding; 3 x 4 for skin irritation;
5 for challenge dose finding
- Controls: vehicle without test substance
ADMINISTRATION/EXPOSURE
- Preparation of test substance for induction: Mixing with vehicle immediately prior to each application, continuous stirring until end of the application

- Induction schedule:
Day 1: Injection
Day 7: Clipping of injection area
Day 8: 48 hours occlusive patch treatment of injection area with 0.5 ml of 0.05 % test substance in vehicle (controls: 0.5 ml vehicle)
Day 10: Removal of patch and residual test material (with sterile physiol. NaCl)
- Injection details: 0.1 ml each at 6 positions in clipped scapular region:
2 x Freund's Complete Adjuvant (FCA) / sterile physiol. NaCl (50:50)
2 x test substance 5 % in vehicle
2 x test substance 5 % in 50:50 mixture of FCA and vehicle
pairwise and symmetrical administration of each solution / suspension
controls: Vehicle instead of test substance
- Challenge schedule:
Day 21: Clipping of hair from backs and flanks
Day 22: 24 hour patch treatment with each 0.5 ml of 0.1 % and 0.5 % test substance (left flank) and vehicle (right flank) of both test group and first control group
Day 23: Removal of patches and residual substance
Days 24 and 25: Assessment for challenge reaction 24 and 48 hours after patch removal; first assessment preceded by clipping of hair in application area 3 hours in advance
Day 36: Rechallenge with identical concentrations on identical flanks as on day 22 except:
- vehicle olive oil + acetone 1:1 instead of olive oil alone
- different positions on flanks
- other (second) control group
Day 37: Removal of patches and residual substance
Days 38 and 39: Assessment for challenge reaction 24 and 48 hours after patch removal; first assessment preceded by clipping of hair in application area 3 hours in advance
- Positive control: 2-mercaptobenzothiazole in physiol. NaCl, 80 % positive
EXAMINATIONS
- Grading system:
Skin reaction according to Draize et al. (1944). J. Pharmacol. Exp. Ther. 82, 377-390.
Sensitization = Incidence and severity of skin reactions higher in test group than in control group
- Pilot study: Dose finding for topical and dermal induction and for challenge
A) 1 animal, duplicate injection of each 0.1 ml with 0 %; 1 %; 2.5 %; 5 %, assessment after 24 and after 48 hours.
B) Three series with 4 animals each, 4 different concentrations per animal in occlusive 24 hour patches (100 %; 50 %; 25 %; 12 % in series 1; 6 %; 3 %; 1 %; 0.5 % in series 2; 0.25 %; 0.1 %; 0.05 %; 0.025 % in series 3); Draize scoring 24 and 48 hours after removal of patch and residual substance; first assessment preceded by clipping of hair in application area 3 hours in advance.
C) 5 animals were treated identical to test group animals during the induction period (days 1-10). On day 15, 4 occlusive 24 hour patches per animal were applied (0.05 %; 0.025 %; 0.0125 %; 0.00625 %). Draize scoring 24 and 48 hours after removal of patch and residual substance; first assessment preceded by clipping of hair in application area 3 hours in advance.

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: The observations are not completely conclusive due to effects at low concentrations and even in controls.

(107)

Type : Guinea pig maximization test
Species : guinea pig

Concentration	:	1st: Induction 10 % intracutaneous 2nd: Induction undiluted occlusive epicutaneous 3rd: Challenge undiluted occlusive epicutaneous
Number of animals	:	20
Vehicle	:	other: Paraffin oil (DAB 6)
Result	:	sensitizing
Classification	:	sensitizing
Method	:	other: OECD Guideline 406 (1981)
Year	:	1983
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Hüls AG, purity not reported
Result	:	RESULTS OF PILOT STUDY: no irritation at any concentration RESULTS OF TEST - Sensitization reaction: 24 hours after challenge: 17/20 animals positive, overall mean score 1.15 48 hours after challenge: 16/20 animals positive, overall mean score 0.85 24 or 48 hours after challenge: 19/20 animals with positive reaction = extreme sensitization, interpreted as "slight sensitization" by the authors Control group: 0/20 animals positive at both 24 and 48 hours
Test condition	:	TEST ANIMALS: - Strain: Dunkin-Hartley, Pirbright White, Hoe: DHPK (SPF - LAC.) /Boe. - Sex: no data - Source: Lippische Versuchstierzucht Hagemann, Extertal (Germany) - Weight at study initiation: mean 350 g - Controls: 20 animals, concurrent vehicle ADMINISTRATION/EXPOSURE - Induction schedule: Day 0: Injection Days 7-9: 48 hours closed patch treatment of injection sites (0.5 ml; control: vehicle) - Injection details: pairwise injections of 0.05 ml each on shoulders: 2 x test substance 10 % in vehicle (control: vehicle) 2 x test substance 10 % in 50:50 mixture of Freund's Complete Adjuvant (FCA) / oleum arachidis (control: vehicle instead of test substance) 2 x FCA / distilled water (50:50) (control: FCA undiluted) - Challenge schedule: Days 21-22: 24 hour closed patch treatment with test substance (left flank) / vehicle (right flank) Days 22-23: Readings at patch removal and 24 hours later - Concentrations used for challenge: 100 % (0.5 ml) - Rechallenge: no - Positive control: none EXAMINATIONS - Grading system: 0 = no skin reaction 0.5 = slight and spotted erythema 1 = slight and regular, or moderate and spotted erythema 2 = moderate erythema 3 = severe erythema or edema - Pilot study: range finding (skin irritation) Test substance undiluted; 75 %; 50 % in vehicle tested in 2 animals per concentration Single dermal treatment with 0.5 ml, probably (not reported) 24 hour occlusive patch Observation period 4 days after test substance administration
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions: Purity of test substance not

reported

(60)

Type	:	Mouse ear swelling test
Species	:	mouse
Concentration	:	1st: Induction open epicutaneous 2nd: Challenge .5 % open epicutaneous 3rd:
Number of animals	:	6
Vehicle	:	other: acetone+olive oil, 4:1
Result	:	sensitizing
Classification	:	sensitizing
Method	:	other: no data
Year	:	1992
GLP	:	no data
Test substance	:	other TS: Isophorone diisocyanate of Aldrich, Gillingham (UK); purity not reported
Result	:	Sensitization reaction: maximum at 1.0 % challenge concentration; reduced activity at higher concentrations possibly due to local toxicity
Test condition	:	TEST ANIMALS: - Strain: BALB/c - Sex: female - Source: Barriered Animal Breeding Unit, Alderley Park (UK) - Age: 8-12 weeks - Controls: vehicle ADMINISTRATION/EXPOSURE - Induction schedule: 50 ul on each shaved flank - Concentrations used for induction: 0; 0.1; 0.25; 0.5; 1.0, 2.5 % w/v - Challenge schedule: 5 days after induction; 25 ul to the dorsum of both ears EXAMINATIONS: ear thickness before and 24 h after challenge
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment

14.06.2006 (28)

Type	:	Open epicutaneous test
Species	:	human
Number of animals	:	
Vehicle	:	other: Acetone, CAS RN 67-64-1
Result	:	sensitizing
Classification	:	
Method	:	other: See Test Conditions
Year	:	1976
GLP	:	no
Test substance	:	other TS: Commercial isophorone diisocyanate, purity not reported, used within 6 weeks, dissolved in water free acetone.
Country	:	East Germany (GDR)
Result	:	- Four persons revealed sensitization towards isophorone diisocyanate. - Main symptoms in these cases were follicular nodules. - Symptoms had appeared after an accidental spill with isophorone diisocyanat even in two of the above mentioned persons that previously had no contact with this substance but with toluene diisocyanate and diphenylmethane diisocyanate. - Single-dose self-application of medical staff with undiluted isophorone diisocyanate caused follicular papules after 10 days in 2 out of 3 persons. Sensitization was confirmed by challenge with 1 % isophorone diisocyanate in acetone.

- Control tests in 6 non-exposed persons with eczema were negative.
- The skin of the sensitized workers returned to a stable healthy state after avoiding contact with isophorone diisocyanate.

Test condition : - Twenty cases of occupational dermatoses observed between the end of 1970 and mid 1974 were reported.
- Appropriate concentrations for patch epicutaneous challenge testing were determined by self-application of medical staff.
- The following tests were performed only with workers sensitized by polyurethane chemicals:
1 % solutions of isophorone diisocyanate in acetone as well as test solutions of other isocyanates were applied to the workers.
Readings were done at 24, 48, and 72 hours (some also at 96 hours).

Reliability : (4) not assignable
Documentation insufficient for assessment

16.09.2006 (90)

Type : Open epicutaneous test
Species : guinea pig
Concentration : 1st: Induction 8 % open epicutaneous
2nd:
3rd:
Number of animals : 10
Vehicle : other: olive oil
Result : sensitizing
Classification : sensitizing
Method : other: Standard Operating Procedures of Biosphere Research Center, Inc., 216 Congers Road, New City, New York 10956
Year : 1981
GLP : yes
Test substance : other TS: Isophorone diisocyanate, commercial sample from Veba-Chemie AG

Result : RESULTS OF PILOT STUDY: skin reaction in 2/5 animals:
- First animal: maximum grade 1 after 24 hours (test site treated with 0.1%), normal after 48 hours;
- Second animal: after 24 hours grade 1 even with vehicle only and up to 0.025%, maximum grade 2 (0.1 and 0.05%); after 48 hours all 1 grade less
RESULTS OF TEST
- Sensitization reaction: contact sensitization was evident at initial challenge. Skin reactions were observed at 24 and 48 hours at 0.00625% and above.
- Clinical signs: not reported. Between challenge and rechallenge, one male animal was found dead. The cause of death could not be determined. Fluid was around the nose and mouth, urine had soaked the fur, and the stomach, duodenum, jenunum and ileum were distended with air.
- Rechallenge: contact sensitization was negligible. Very slight skin reactions were observed at 24 and 48 hours at 0.05% and above.

Test condition : TEST ANIMALS:
- Strain: Hartley
- Sex: male/female (5 males/5 females)
- Source: Elm Hill Breeding Laboratories, Chelmsford (Mass., USA)
- Weight at study initiation: 327-498 g
- Controls: vehicle challenge
ADMINISTRATION/EXPOSURE
- Induction schedule:
single induction, 25 ul each to both sides of the animals
- Challenge schedule: 5 days after induction treatment
- Concentrations used for challenge: 25 µl of 0.0; 0.00625; 0.0125; 0.025; 0.05; 0.1 % in olive oil open epicutaneously on 6 previously untreated sites per animal
- Rechallenge: 9 days after first challenge 25 µl of 0.0; 0.00625; 0.0125;

0.025; 0.05; 0.1 % in olive oil open epicutaneously on 6 previously untreated sites per animal
- Positive control: Isophorone diisocyanate was used as the positive control in a test on a different substance.
EXAMINATIONS
- Grading system: Draize; evaluation ca. 24 and 48 hours after pilot study treatment, challenge, or rechallenge
- Pilot study: Primary skin irritation; 2 males, 3 females:
25 ul of 0.0; 0.00625; 0.0125; 0.025; 0.05; 0.1 % in olive oil open epicutaneously on 6 sites per animal

Reliability : (2) valid with restrictions
Small number of animals, not according to guideline, no data on purity of test substance, however test procedure in accordance with generally accepted scientific standards and described in sufficient detail

16.09.2006 (21)

Type : other: Bronchial challenge test
Species : human
Number of animals :
Vehicle :
Result : sensitizing
Classification :
Method : other
Year : 1981
GLP : no
Test substance : other TS: Isophorone diisocyanate, no further data

Method : A 50-year old spray painter developed severe asthma soon after introduction of a new paint containing isophorone diisocyanate. His asthma was associated with an abnormal chest X-ray, blood eosinophilia, normal IgE level, negative skin prick tests and no precipitins to Aspergillus fumigatus. After successful initial therapy, the person was left in an enclosed room for 30 minutes each on three days, followed by spirometry at hourly intervals for nine hours. Exposure conditions in the enclosed room were as follows:
Day 1: Sitting
Day 2: Painting a chair without isophorone diisocyanate in the spraying enamel
Day 3: Painting a chair with isophorone diisocyanate in the spraying enamel
Exposure was not quantified.

Remark : Enquiries failed to reveal any other workers at his worksop with similar symptoms.

Result : On day 3, the patient required treatment 3 hours 35 minutes after cessation of challenge. A very large reduction in forced expiratory volume was observed on that day.

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

16.09.2006 (25)

Type : other: Patch-test for cross-sensitization
Species : human
Concentration : 1st: Challenge 1 % occlusive epicutaneous
2nd:
3rd:
Number of animals :
Vehicle : other: ethanol
Result : sensitizing
Classification :
Method : other: See Test Conditions

Year : 1981
GLP : no
Test substance : other TS: Isophorone diisocyanate, no data on purity

Result : The tests were strongly positive in the 4 patients. None of the control subjects was positive.
Test condition : Two workers who were allergic to isophorone diamine and two volunteers who had been sensitized to isophorone diamine were patch tested 1 month later with isophorone diisocyanate (1% in ethanol); the patches were removed after 48 h, and read at 48 and 96 h.
Five adult volunteers were patch tested with isophorone diisocyanate as controls.
Conclusion : Cross-sensitivity can occur between isophorone diamine (CAS No. 2855-13-2) and isophorone diisocyanate.
Reliability : (4) not assignable
Documentation insufficient for assessment

16.09.2006 (71)

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction 10 % intracutaneous
2nd: Induction 100 % intracutaneous
3rd: Challenge 1 % occlusive epicutaneous
Number of animals : 20
Vehicle : other: paraffin oil (DAB 7)
Result : sensitizing
Classification : sensitizing
Method : other: Modified maximization test:
- Second induction intracutaneous
- Challenge treatment only 6 instead of 24 hours
Year : 1984
GLP : no
Test substance : other TS: Isophorone diisocyanate of Bayer AG, no data on purity

Result : RESULTS OF PILOT STUDY:
0.03 %: 1 animal (No. 192) with score 1 only at 24 hours
0.1 %: no skin reaction
0.3 %: 1 animal (No. 192) with score 1 only at 24 hours
1.0 %: 2 animals with score 1 only at 24 hours; 1 animal (No. 192) with score 2 at 24 hours and score 1 both at 48 and 72 hours
RESULTS OF TEST
- Sensitization reaction: Number of test animals with skin reactions at

	Challenge		Rechallenge	
Reading	0.3 %	1.0 %	0.3 %	1.0 %
8 hours	1/18	4/18	7/18	11/18
24 hours	8/18	12/18	10/18	13/18
48 hours	12/18	15/18	8/18	11/18
72 hours	3/18	8/18	1/18	10/18

The maximum intensity was observed 24-48 hours after patch application. No skin reaction was observed in any of the 10 control animals including rechallenge. According to the criteria applied, the number of positive animals was
0.3 %: 8/18 (challenge), 10/18 (rechallenge)
1.0 %: 13/18 (challenge), 13/18 (rechallenge)
- Clinical signs, other observations:
2 animals died after the 2nd induction treatment showing signs of allergic shock: heavy breathing, salivation, spontaneous release of urine and feces, foam at snouts and noses; necropsy revealed lungs covered with dark red areas.

Sedation was observed the day after the 2nd induction treatment.
Decreased body weight gain in treated group (214 g vs 241 g in control groups)

Test condition : TEST ANIMALS:
- Strain: Pirbright white
- Sex: female
- Source: Lippische Versuchstierzucht Hagemann, Exteral (Germany)
- Weight at study initiation: 225-292 g; 259 g (mean test), 268 g (mean control)
- Controls: 2 groups, each 10 animals

ADMINISTRATION/EXPOSURE
- Preparation of test substance for induction: Mixing (stirring) with vehicle on day of application to obtain the desired concentrations (v/v)
- Induction schedule:
Day 0: 1st injection
Day 7: 2nd injection: 2 injections of each 0.025 ml in area of 1st injection; controls: untreated
- Injection details day 0: 0.1 ml each at 6 positions in clipped scapular region:
2 x Freund's Complete Adjuvant (FCA) / water for injection (50:50)
2 x test substance 10 % in vehicle
2 x test substance 10 % in FCA
pairwise and symmetrical administration of each preparation
controls: Vehicle instead of test substance
- Challenge schedule:
Day 21 (1st control group): 6 hour occlusive patch with 0.3 % (left) or 1.0 % (right) test substance on clipped flanks; assessment of skin reaction 8, 24, 48, and 72 hours after begin of treatment
Day 36 (2nd control group): 6 hour occlusive patch with 0.3 % (right) or 1.0 % (left) test substance on clipped flanks; assessment of skin reaction 8, 24, 48, and 72 hours after begin of treatment
- Concentrations used for challenge: 0.3 and 1.0 %
- Rechallenge: Day 36 with switched flank / concentration assignment, see above
- Positive control: no

EXAMINATIONS
- Grading system:
0 = no skin reaction
1 = patchy and slight erythema
2 = distinct and diffuse erythema
3 = intense erythema and/or edema
skin reaction at >= 2 readings = positive
positive without indications of primary or unspecific effects = sensitized
- Pilot study: threshold of primary irritation:
pretreatment with FCA and paraffin oil;
0.2 ml each of 0.03; 0.1; 0.3; 1.0 % solutions in paraffin oil;
applied to each of 4 animals in 24 hours occlusive patches;
readings 24, 48, and 72 hours after begin of treatment.

Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions: Slight deviations in Method, no positive control

14.06.2006 (93)

Type : Mouse ear swelling test
Species : mouse
Number of animals : 4
Vehicle : other: 1 part olive oil + 4 parts acetone
Result : sensitizing
Classification :
Method : other: based on the method described by Gad et al., Toxicol. App.l Pharmacol. 84, 93 (1986)
Year : 1986

GLP	:	no data
Test substance	:	other TS: Isophorone diisocyanate of Aldrich Chemical Co., purity ca. 99 %
Result	:	A statistically significant response was observed in mice using the induction concentration of 1 % and a challenge concentration of 3.0 %. Although the treated ears demonstrated significant changes in thickness, the mean change in thickness of the untreated ears was never more than 0.1 mm.
Test condition	:	TEST ANIMALS: - Strain: B6C3F1 - Sex: female - Source: Taconic Farms, Germantown (New York, USA) - Age: >= 8 weeks - Weight at study initiation: 17-20 g - Number of animals: 4 per group in pilot study, probably also in main study - Controls: vehicle, irritancy, and positive controls ADMINISTRATION/EXPOSURE - Induction schedule: 20 µl direct dermal application on each of 5 subsequent days - Concentrations used for induction: 0.1; 0.3; 1.0 % - Challenge schedule: rest period 7 days - Concentrations used for challenge: 3.0 % - Rechallenge: no - Positive control: 1-Fluoro-2,4-dinitrobenzene (DNFB) EXAMINATIONS - Pilot study: primary irritancy study; test concentrations 0.1; 0.3; 1.0; 3.0; 10.0; 30 %; 4 mice/concentration; 20 µl direct dermal application on each of 5 subsequent days
Reliability	:	(2) valid with restrictions Borderline validity: small number of animals, however study well documented

(98)

Type	:	other: Respiratory tract sensitization following intradermal induction
Species	:	guinea pig
Concentration	:	1st: Induction .1 % intracutaneous 2nd: Challenge other: nose only inhalation of aerosol 3rd:
Number of animals	:	8
Vehicle	:	other: corn oil
Result	:	
Classification	:	
Method	:	other: exposure criteria of OECD Guideline 403 (1981) and Directive 84/449/EEC, B.6 fulfilled
Year	:	1994
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Bayer AG, Batch No. 1.5 / 3-20, purity > 99 %
Method	:	Directive 84/449/EEC; OECD Test Guideline 403; Pauluhn J and Eben A (1991). Validation of a non-invasive technique to assess immediate- or delayed-onset of airway hyperreactivity in guinea-pigs. J. Appl. Toxicol. 11, 423-431; Pauluhn J (1994). Validation of an improved nose-only exposure system for rodents. J. Appl. Toxicol. 14, 55-62.
Remark	:	Severe reactions were observed with trimellitic anhydride (CAS RN 552-30-7) when investigated with the current animal model, using the same induction and challenged.
Result	:	RESULTS OF PILOT STUDY: see test concentration RESULTS OF TEST

- Sensitization reaction: High titer IgG1 antibody observed proved that successful sensitization had occurred. However, when challenged, the incidence of immediate-onset respiratory reactions was roughly the same in all groups. No delayed-onset reactions, deaths or anaphylactic reactions were observed. Challenge with acetylcholine did not evoke group specific respiratory responses.
- Clinical signs: No clinical signs or specific abnormalities were observed at necropsy.

Test condition : TEST ANIMALS:
- Strain: Hartley [Crl:(HA)BR]
- Sex: female
- Source: Charles River Wiga, Sulzbach (Germany)
- Age: ca. 2 months
- Weight at study initiation: 237-273 g; mean 256 g
- Number of animals: 8 (treated)
- Controls: vehicle; 8 animals

ADMINISTRATION/EXPOSURE
- Induction schedule: days 0, 2, 4 (100 ul each)
- Challenge schedule: 4 subgroups, 4 animals each
  days 21/22/28 (control subgroup a)
  days 22/23/29 (treated subgroup a)
  days 23/24/30 (control subgroup b)
  days 24/25/31 (treated subgroup b)
- Concentrations used for challenge:
  first day: 10.2 mg/m3 test substance 30 min nose-only
  second day: 0.05; 0.15; 0.5 % Acetylcholine for 15 min each
  last day: 35.5 mg/m3 conjugate of test substance with guinea pig serum albumin

EXAMINATIONS
- During sacrifice the trachea, lung and lung associated lymph nodes were fixed and subjected to histopathological evaluation. Lung weights were also determined
- Pilot study: assessment of the approximate irritant threshold concentration

Reliability : (1) valid without restriction
Guideline study

22.09.2006 (12)

Type : other: TINA (Tierexperimenteller Nachweis) Test
Species : guinea pig
Concentration : 1st: Induction .5 % intracutaneous
2nd: Induction 30 % other: i.m.
3rd: Induction undiluted occlusive epicutaneous
Number of animals : 25
Vehicle : other: acetone
Result : sensitizing
Classification : sensitizing
Method : other: A modification of the method described by Polak & Turk, Clin. exp. Immunol. 7., 739 - 744 (1970), during the induction exposure the testsubstance is applied in 3 different ways (i.m.; i.d. and epicutaneously)
Year : 1976
GLP : no
Test substance : no data

Remark : - The TINA test was determined to be the most sensitive method among six variations of the guinea pig maximization test.
- The only method in which isophorone diisocyanate was applied was the TINA test; all other conclusions were drawn from test with other test substances.
- The methods with the longest exposure time gave the highest sensitization rates.

- The potentiating effect of Freund's Complete Adjuvant was confirmed.
- Sensitization rates were reduced in diseased animals.
- Sensitization rates were practically identical in males and females.

Result : RESULTS OF PILOT STUDY: see test concentrations
RESULTS OF TEST
- Sensitization reaction: 6/16 animals positive = 37.5 %; results for control group not reported

Test condition : TEST ANIMALS:
- Sex: male/female
- Weight at study initiation: 300-550 g
- Number of animals: test 25, control 10, dose finding 5 per concentration; conflicting data: 16 test animals in table with results
- Controls: Freunds Complete Adjuvant (induction 1); vehicle (other inductions)
ADMINISTRATION/EXPOSURE
- Induction schedule:
Day 1: intramuscular, with FCA
2, 3, 4, and 5 weeks later intradermal + epicutaneous after pretreatment with dimethyl sulfoxide or sodium lauryl sulfate
- Concentration in Freunds Complete Adjuvant (FCA):
equal volumes of FCA and substance solution
- Challenge schedule: 7 days after last induction, occlusive epicutaneous for 24 hours, readings thereafter plus on following three days
- Concentrations used for challenge: 1 %
- Rechallenge: no
EXAMINATIONS
- Grading system:
0 - 8%: allergenicity unlikely
9 - 28%: mild allergens
29 - 64%: moderate allergens
> 64%: strong allergens
- Pilot study: Dose finding experiment

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, however, test system not established

14.09.2006 (38) (110)

Type :
Species : guinea pig
Concentration : 1st: Induction .1 % active substance intracutaneous
2nd: Challenge .1 % active substance intracutaneous
3rd:
Number of animals : 15
Vehicle : physiol. saline
Result : sensitizing
Classification :
Method : other: FDA (1959)
Year : 1968
GLP : no
Test substance : other TS: Isophorone diisocyanate, "technically pure"

Result : Re-injection caused a swelling, which was visibly heavier than after pre-injection

Test condition : TEST ANIMALS:
- Strain: Pirbright white
- Sex: male
- Source: Winkelmann, Kirchborchen (Germany)
- Weight at study initiation: 300-500 g
ADMINISTRATION/EXPOSURE
- Preparation of test substance: 0.1 % solution / suspension in vehicle
- Induction schedule: Every other day or three times weekly, total 10

injections in an area of the back and upper flanks; first injection 0.05 ml, other injections 0.10 ml
- Challenge schedule: Two weeks after last injection of induction phase, 0.05 ml freshly prepared test substance solution / suspension in an adjacent area
EXAMINATIONS: 24 hours after all injections readings of diameter, height, and color of reaction
- Grading system (for erythema): 0 = no effect / 1 = very slight / 2 = slight / 3 = moderate / 4 = severe effect
- Sensitizing if reaction after challenge > average reaction after 10 inductions.

Reliability : (3) invalid
Incomplete documentation, no positive control, not according to todays standard, no validated test system

(67)

Type : other: radioisotopic assay
Species : mouse
Number of animals : 4
Vehicle : other: 1 part olive oil + 4 parts acetone
Result : sensitizing
Classification :
Method : other
Year : 1989
GLP : no data
Test substance : other TS: Isophorone diisocyanate of Aldrich Chemical Co., purity ca. 99 %

Method : 20 ul by direct dermal application, for 5 days, to sites prepared by shaving, dermabrading and, in some mice, with intra dermal injection of complete Freund's adjuvant. The rest period was 7 days. Measurement of the contact hypersensitivity response in mice was by radioisotopic assay two days after challenge.

Result : A statistically significant dose-related hypersensitivity response was elicited in mice using a sensitizing concentration of 1 % and a challenge concentration of 3 %.

Test condition : TEST ANIMALS:
- Strain: B6C3F1
- Sex: female
- Source: Taconic Farms, Germantown (New York, USA)
- Age: >= 8 weeks
- Weight at study initiation: 17-20 g
- Number of animals: 4 per group in pilot study, probably also in main study
- Controls: vehicle, irritancy, and positive controls;
2 groups each, one with and one without FCA, total 6 groups
ADMINISTRATION/EXPOSURE
- Induction schedule: 5 days
- Concentrations used for induction: 0.1; 0.3; 1.0 %
- Concentration in Freunds Complete Adjuvant (FCA):
- Challenge schedule: rest period 7 days
- Concentrations used for challenge: 3.0 %
- Rechallenge: no
- Positive control: 1-Fluoro-2,4-dinitrobenzene (DNFB)
- On the day before challenge, 125-I-IUDR (0,2 ml, 10 µCi/ml) was injected i.v. into the tail vein. 48 h after challenge mice were sacrificed, biopsied and counted in a gamma counter
EXAMINATIONS
- Grading system:
- Pilot study: primary irritancy study; test concentrations 0.1; 0.3; 1.0; 3.0; 10.0; 30 %; 4 mice/concentration; 20 µl direct dermal application on each of 5 subsequent days

Reliability : (2) valid with restrictions

Borderline validity: small number of animals, however study well documented

16.09.2006 (98)

Type	:	other: Cytokine induction in the draining lymph node
Species	:	mouse
Concentration	:	1st: Induction 2 % open epicutaneous 2nd: Induction 2 % open epicutaneous 3rd:
Number of animals	:	
Vehicle	:	other: acetone:olive oil (4:1 v/v)
Result	:	
Classification	:	
Method	:	other:
Year	:	2005
GLP	:	no data
Test substance	:	other TS

Method : In search for a test method to identify chemicals with respiratory sensitization potential, it was tested if respiratory sensitizers might be distinguished from contact sensitizers by their induction of relatively high expression of cytokines characteristic of Th2 cells (IL-4, IL-10 and IL-13), unlike contact sensitizers, which favor Th1 responses.

Result : General: Results are reported only graphically.

Main study:
As expected, (1) TDI and (2) MDI induced message for the Th2 cytokines IL-4, IL-10 and IL-13. However, the mRNA for these cytokines was also elevated in response to the other four test substances. Based on the magnitude of the response, the authors differentiated into two distinct groups:
High responders: (1) TDI, (2) MDI, (5) HMDI
Low responders: (3) TMI, (4) TMXDI, (6) IPDI
There were no statistically significant changes in IL-2, IL-3, IL-5, IL-9, IL-15, and IFN-gamma relative to vehicle controls.

Satellite LLNA: The doses used in the main study were immunologically equivalent based on similar SI.

Follow-up study: Levels of IL-4, IL-10 and IL-13 were higher for both (3) TMI, (4) TMXDI than for DNCB, though not statistically significant for IL-4 in the case of (4) TMXDI.

Test condition : TEST ANIMALS:
- Strain: BALB/c
- Sex: female
- Source: Charles River Breeding Laboratories (Raleigh, NC, USA or Kingston, NY, USA)
- Age: 8-12 weeks
- Number of animals: 5-6 per group
- Controls: Concurrent vehicle control. Additional DNCB control (1 %) in follow-up study. DNCB (1-chloro-2,4-dinitrobenzene) is a potent contact sensitizer which is generally used as a negative control in respiratory sensitization studies.

ADMINISTRATION/EXPOSURE
- Study type: RPA (ribonuclease protection assay) analysis
- Induction schedule:
Days 0 and 5: Dermal application of 100 µl chemical on both flanks
Days 10, 11 and 12: Dermal application of 12.5 µl chemical to each side of both ears
- Concentrations used for induction:
(1) TDI: 1 %

(2) MDI: 2 %
(3) TMI: 1 %
(4) TMXDI: 1 %
(5) HMDI: 2 %
(6) IPDI: 2 %
- Challenge schedule: On day 14 animals were euthanized, auricular lymph nodes were removed and total RNA was extracted from these tissues and subject to RPA analysis using commercial assay systems.
- Positive control: thought to be included in set of test substances
EXAMINATIONS
- Grading system: not yet established
- Satellite study: Local lymph node assay (LLNA), in part conducted with female CBA/JHsd mice (7-12 weeks old) from Harlan Sprague-Dawley (Frederick, MD, USA), done for four of the six test substances:
(2) MDI: BALB/c; 0.02 / 0.2 or 2 %
(3) TMI: CBA/JHsd; 0.25 / 0.5 / 1 %
(4) TMXDI: CBA/JHsd; 0.25 / 0.5 / 1 %
(6) IPDI: BALB/c; 0.02 / 0.2 or 2 %
The purpose was to determine whether the doses chosen induced similar levels of proliferation, thus suggesting immunological equivalence and allowing direct comparison of chemicals in the RPA main test.
- Follow-up study: RPA analysis as described above for two substances: (3) TMI, (4) TMXDI

Test substance : Commercial grades (purities not reported) of the following substances
- Two isocyanates known to be respiratory sensitizers:
(1) TDI = toluene diisocyanate
(2) MDI = diphenylmethane-4,4'-diisocyanate
- Two isocyanates with no records of inducing respiratory sensitivity in humans:
(3) TMI = p-tolyl isocyanate
(4) TMXDI = m-tetramethylxylylene diisocyanate
- Two isocyanates for which there are conflicting reports with respect to respiratory sensitization:
(5) HMDI = dicyclohexylmethane-4,4'-diisocyanate
(6) IPDI = isophorone diisocyanate

Reliability : (2) valid with restrictions
Study without detailed documentation but in good agreement with generally accepted scientific principles.

(85)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	4 weeks
Frequency of treatm.	:	5 days/week, 6 hours/day
Post exposure period	:	ca. 4 weeks (additional control and high-dose groups of identical size)
Doses	:	0.25; 1; 4 mg/m3 (target) = 0.24; 1.05; 4.1 mg/m3 (analytical mean)
Control group	:	other: yes, concurrent air, otherwise identical
NOAEL	:	= .24 mg/m³
LOAEL	:	= 1.05 mg/m³
Method	:	other: OECD Guide-line 412 (1981), adjusted to fulfill both the TSCA § 798.2250 as well as EU Guideline 92/69/EEC
Year	:	2003
GLP	:	yes

Test substance : other TS: Isophorone diisocyanate of Bayer Polymers, batch no. 4.4/1-110; sample no./yr: 1060313/2002; purity 99.6 % (determined by titration with dibutylamine)

Result : TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: No mortality was observed.
- Clinical signs: Mild and transient signs of respiratory tract irritation (nostrils: red encrustations, stridor, nasal discharge, breathing sounds, hypothermia) in most rats at 4.1 mg/m3 (signs in 18/20 males, 18/20 females); no clinical signs in other groups
- Body weight gain: body weights were slightly decreased in the high dose group (day 28: males -5.1 %, statistically significant; females -3.4 %, not significant) and returned rapidly to normal during the recovery period.
- Ophthalmoscopic examination: No conclusive evidence of exposure-induced changes in the dioptric media or in the fundus
- Clinical chemistry: No evidence of concentration dependent effects
- Haematology: Increased leukocyte count in the peripheral blood in mid and high dose groups:
  males mid dose +46%, high dose +55%, both significant;
  females mid dose +82%, high dose +16%, none significant.
  Other statistical significances (none in high dose animals except Hepatoquick (prothrombin time) for females +7.6%) were considered to be of no pathodiagnostic relevance.
- Urinalysis: No effects considered to be of pathodiagnostic relevance.
- Organ weights: No statistically significant or conclusive changes in absolute or relative organ weights except slight increase of lung weight in high dose males. Statistically significant findings in high dose group:
  absolute liver weight (females) -9.7%
  relative (to body) lung weight (males) +12.6%
  none in recovery groups and in relative to brain weights
- Gross pathology: No evidence of treatment-related organ damage
- Histopathology: Significantly increased incidence of inflammatory as well as epithelial changes occurring in the airways of the entire respiratory tract (nasal cavity, pharynx, larynx, trachea, lungs) with typical anterior-posterior gradient in intensity. Recovery after the postobservation period was incomplete in nasal cavity, pharynx, larynx, and complete in trachea and lung. The lesions were thus considered to be reversible with no evidence of fibroproliferative effects. There was no effect on extrapulmonary organs.
- Other:
  Examination of REFLEXES did not reveal any differences between the groups.
  Determination of the RECTAL TEMPERATURES indicated hypothermia in the high dose group, which was statistically significant on day 0 (males 34.6 vs. 37.4 °C in control, females 35.6 vs. 37.3 °C) but not towards the end of the exposure period (day 22).
  No mortality occurred in the one-week inhalation PILOT STUDY. Observations in this pilot study demonstrate that the test substance induced a concentration-dependent respiratory tract irritation with signs that are suggestive of an anterior-posterior gradient of irritation occurring with the respiratory tract, NOAEL = 1.04 mg/m3.

Test condition : TEST ORGANISMS
- Strain: Hsd Cpb:WU (SPF) Wistar rats
- Source: Harlan-Winkelmann, Borchen (Germany)
- Age: 2 months at study initiation
- Weight at study initiation:
  males 207-237 (mean 223) g
  females 157-183 (mean 169) g
- Number of animals: 10 per sex and dose group

ADMINISTRATION / EXPOSURE
- Type of exposure: dynamic directed-flow nose-only

- Particle size: Vapor saturation is reported to be about 4-11 mg/m3 at 20-25 degree C, i.e. no particles are expected at the test concentrations.

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: before and after each exposure, once a day on exposure-free days; additional observations during exposure where indicated by e.g. spasms, abnormal movements, severe respiratory signs, hemorrhage
- Mortality: (if applicable) time recorded as precisely as possible during observations
- Body weight: Mondays and Fridays during exposure period, once per week during postexposure period
- Ophthalmoscopic examination: prior to first exposure and towards end of exposure period with indirect ophthalmoscope five minutes after treatment with mydriatic: changes in the retina, vitreous humor, lens, cornea, external eye surface
- Haematology: End of exposure period (samples from non-fasted animals): hematocrit, hemoglobin, leukocytes, erythrocytes, mean corpuscular hemoglobin, thrombocyte count, reticulocytes, Heinz' bodies, aspartate aminotransferase (optimized, GOT/AST), alanine aminotransferase (optimized, GPT/ALT), glutamate dehydrogenase (GLDH), lactate dehydrogenase (LDH), alkaline phosphatase (APh), creatine kinase (CK), albumin, bilirubin, creatinine, total protein, triglycerides, cholesterol, clotting time (Hepatoquick), sodium, potassium, calcium, magnesium, phosphate, chloride
- Urinalysis: for 5 animals per group and gender, 16 hour overnight sampling during last week of study, semiquantitative determination of pH, protein, glucose, blood, bilirubin, urobilinogen, ketone bodies
- Other:
Rectal temperatures: twice during the exposure period, within 1/2 hour after cessation of exposure
Reflexes on days 3 and 21: visual placing response and grip strenghth on wire mesh, abdominal muscle tone, corneal and pupillary reflexes, pinnal reflex, righting reflex, tail-pinch response, startle reflex (finger snapping and touch on back)

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: not listed separately in test report
- Weights: absolute, relative to body weight and relative to weight of brain for adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus
- Microscopic:
All groups including recovery groups: nasal cavity, larynx, lungs, pharynx, trachea;
All groups excluding recovery groups: adrenal glands, aorta, esophagus, eyes, eyelids, exorbital lacrimal glands, heart, duodenum, kidneys, liver, mesenteric lymph nodes, lung assoc. lymph nodes, optic nerves, ovaries, oviducts, skin (mammary region and muzzle), spleen, stomach (fore- and glandular), testes, thymus, organs and tissues with macroscopic findings;
Prepared but not evaluated: brain, epididymides, femur, Harderian glands, head, jejunum, ileum, caecum, colon, rectum, remaining intestine, mandibular lymph nodes, pancreas, pituitary gland, prostate, salivary glands, sciatic nerve, seminal vesicles, skeletal muscle (tigh), spinal cord, sternum, thyroid glands (with parathyroids), tongue, ureters, urethra, urinary bladder, uterus (with cervix), vagina, Zymbal's glands

OTHER EXAMINATIONS: Test conditions were selected based on an acute inhalation toxicity study (cited above) and a one-week repeated inhalation study (1.04; 4.08; 15.3 mg/m3, 6 h/day, 5 days).

STATISTICAL METHODS:
- Descriptive analysis: all variables that are not dichotomous

- Others depending on prior experience:
Dunnett test: where approximately normal distribution with equal variances across treatments was anticipated
p value adjusted Welch test: where heteroscedasticity appeared to e more likely
Kruskal-Wallis test followed by adjusted MWW tests (U tests): where the assumptions for a parametric analysis of variance were questionable

Reliability : (1) valid without restriction
Guideline study

02.06.2006 (16)

Type	:	Sub-acute
Species	:	rat
Sex	:	male
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	4 weeks
Frequency of treatm.	:	4 hours/day, 5 days/week
Post exposure period	:	24 hours
Doses	:	0.25; 0.64; 1.37 mg/3
Control group	:	no data specified
NOAEL	:	.64 mg/m³
LOAEL	:	1.37 mg/m³
Method	:	other: See Test Conditions
Year	:	1968
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, "technically pure"
Remark	:	Significant deviations between nominal and measured concentrations
Result	:	TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality and time to death: no deaths reported - Clinical signs: no signs of intoxication in any group - Body weight gain: reduced in highest dose group (compared to lowest dose group: 58.6 vs. 77.7% increase) - Clinical chemistry: In tests of liver activity no effects were observed - Haematology: no effects observed - Urinalysis: no pathological effects observed - Organ weights: In the highest dose group, the absolute weights of liver (-8.8%) and spleen (-13.2%) were lower, the absolute (+9.3%) and relative (+7.3%) weights of lungs were higher when compared to the lower dose groups (numerical values refer to lowest dose group). - Gross pathology: Except for slightly edematous lungs in the highest dose group, no exposure-related changes were observed.
Test condition	:	TEST ORGANISMS - Weight at study initiation: 190-210 g - Number of animals: 20 ADMINISTRATION / EXPOSURE - Type of exposure: aerosol - Vehicle: A solution in DMSO (CAS RN 67-68-5) was sprayed CLINICAL OBSERVATIONS AND FREQUENCY: - Clinical signs: daily - Mortality: daily - Body weight: weekly - Haematology: end of study, 5 rats per group - Biochemistry: end of study, 10 rats per group - Urinalysis: end of study, 10 rats per group ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC): - Macroscopic (surviving animals): no details on visual inspection reported; weights determined for liver, spleen, kidneys, suprarenal gland, thyroid gland, testicles, lung

Reliability	:	(3) invalid Unsuitable test system, use of vehicle, whole body inhalation, generation of test atmosphere and analytical procedure do not comply with current standard.

14.09.2006 (67)

Type	:	
Species	:	rat
Sex	:	male
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	5 days
Frequency of treatm.	:	4 hours/day
Post exposure period	:	28 days
Doses	:	0.525; 0.84; 3.57; 33 mg/m3
Control group	:	no data specified
NOAEL	:	.525 mg/m³
LOAEL	:	.84 mg/m³
Method	:	other: See Test Conditions
Year	:	1968
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate, "technically pure"
Remark	:	Significant deviations between nominal and measured concentrations
Result	:	ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX - Concentrations: nominal: 10; 25; 50; 300 mg/m3 measured: 0.525; 0.84: 3.57; 33 mg/m3 TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality and time to death: 0.525 mg/m3: 0/20 0.84 mg/m3: 0/20 3.57 mg/m3: 1/20 (after 8 days) 33.0 mg/m3: 4/20 (after 4-10 days)
Test condition	:	TEST ORGANISMS - Weight at study initiation: 190-210 g - Number of animals: 20 ADMINISTRATION / EXPOSURE - Type of exposure: aerosol - Vehicle: A solution in DMSO (CAS RN 67-68-5) was sprayed
Reliability	:	(3) invalid Unsuitable test system, use of vehicle, whole body inhalation, generation of test atmosphere and analytical procedure do not comply with current standard.

19.06.2006 (67)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Chromosomal aberration test
System of testing	:	Chinese hamster ovary (CHO) cells
Test concentration	:	0; 10.0; 20.0; 40.0 mg/l (+/- S9); additionally 5 mg/l (- S9)
Cycotoxic concentr.	:	ca. 40 mg/l (+/- S9)
Metabolic activation	:	with and without
Result	:	positive
Method	:	other: OECD Guideline 473 (1997) and Directive 2000/32/EC, B.10
Year	:	2003
GLP	:	yes
Test substance	:	other TS: Isophorone diisocyanate of Degussa AG, Batch No. 1103211, purity > 99.5 %

Result : GENOTOXIC EFFECTS:
- With metabolic activation: Dose related increase in chromosomal aberrations
- Without metabolic activation: Dose related increase in chromosomal aberrations
CHROMOSOMAL ABERRATIONS (excluding gaps):

Concentration	% Chromosomal aberrations	
- Experiment # 1	with S9	without S9
untreated	0.0	0.5
Solvent	0.5	0.5
10 mg/l IPDI	0.0	1.5
20 mg/l IPDI	5.5 *	2.5
40 mg/l IPDI	8.5 ***	10.5 ***
0.3 mg/l MMC	-	57.0 ***
15 mg/l CPA	32.0 ***	-
- Experiment # 2	with S9	without S9
untreated	0.5	0.0
Solvent	1.5	1.0
5 mg/l IPDI	-	0.5
10 mg/l IPDI	3.5	3.5
20 mg/l IPDI	4.0	12.0 ***
40 mg/l IPDI	19.5 ***	-
0.3 mg/l MMC	-	27.0 ***
15 mg/l CPA	42.0 ***	-

IPDI = isophorone diisocyanate (test substance)
MMC = mitomycin-C (positive control)
CPA = cyclophosphamide (positive control)
Significance: * p<0.05; ** p<0.01; *** p<0.001

PRECIPITATION CONCENTRATION: Solubility in DMSO at 500 g/l. Precipitation at > 62.5 g/l upon addition to Ham's F10.
MITOTIC INDEX:

Concentration	% relative cell growth	
- Experiment # 1	with S9	without S9
untreated	122	106
Solvent	100	100
10 mg/l IPDI	97	85
20 mg/l IPDI	80	55
40 mg/l IPDI	76	26
0.3 mg/l MMC	-	71
15 mg/l CPA	53	-
- Experiment # 2	with S9	without S9
untreated	107	99
Solvent	100	100
5 mg/l IPDI	-	86
10 mg/l IPDI	71	71
20 mg/l IPDI	73	65
40 mg/l IPDI	21	-
0.3 mg/l MMC	-	66
15 mg/l CPA	66	-

OTHER OBSERVATIONS: pH and osmolality of the treatment media were not obviously affected by the test substance.

Test condition : SYSTEM OF TESTING
- Species/cell type: CHO cells as described by Kao and Puck (1968),

obtained from Dr. A.T. Natarajan (State University of Leiden, Netherlands)
- Metabolic activation system:
S9 homogenate prepared from male Sprague-Dawley rat livers, co-induced with phenobarbital and betanaphthoflavone. Batches No. 2002/9 and 2002/14
- No. of metaphases analyzed:
100 / culture except 50 for positive controls with chromosomal aberration rates > 50 % (excl. gaps)
ADMINISTRATION:
- Dosing:
0.625; 1.25; 2.50; 5.0; 10.0; 20.0; 40.0; 80.0 mg/l (+/- S9)
Doses selected for scoring:
10; 20; 40 mg/l (Experiment 1 +/- S9; Experiment 2 + S9)
5; 10; 20 mg/l (Experiment 2 - S9)
- Number of replicates: 2
- Application:
Approx. 300,000 cells each seeded in 25 cm2 flasks approx. 20 hours before treatment
Treatment time 3 hours, harvest time 20 hours (approx. 1.5 cell cycles)
Addition of 0.2 mg/l colcemid for last 3 hours
- Positive and negative control groups and treatment:
negative: DMSO (dimethyl sulfoxide, CAS RN 67-68-5)
positive -S9: 0.30 or 0.45 mg mitomycin C/l
positive +S9: 15 and 23 mg cyclophosphamide/l
CRITERIA FOR EVALUATING RESULTS:
(i) statistically significant increases in the incidence of cells bearing aberrations at any dose-level over the concurrent control, AND
(ii) the increases must exceed the historical control values, AND
(iii) the increases are reproduced in both replicate cultures

Reliability : (1) valid without restriction
Guideline study

(91)

Type : Ames test
System of testing : Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, TA 100
Test concentration : up to 1000 µg/plate (pre-incubation); up to 5000 µg/plate (without pre-incubation)
Cycotoxic concentr. : 500 µg/plate in pre-incubation test -S9; 1000 µg/plate otherwise
Metabolic activation : with and without
Result : negative
Method : Directive 84/449/EEC, B.14
Year : 1984
GLP : no
Test substance : other TS: Isophorone diisocyanate of Hüls AG, purity not reported

Result : GENOTOXIC EFFECTS:
- With metabolic activation: None
- Without metabolic activation: None
Precipitation at 1000 and 5000 µg/plate led to additional particles counted as colonies, thus leading to treated/control ratios > 2 falsely indicating mutagenicity in some strains.
PRECIPITATION CONCENTRATION: 1000 µg/plate
CYTOTOXIC CONCENTRATION (including effects on background lawn):
all strains: 500 µg/plate in pre-incubation test -S9; 1000 µg/plate otherwise

Test condition : SYSTEM OF TESTING
- Metabolic activation system:
Aroclor 1254 induced rat S9 liver, male Bor: WISW (SPF/Cpb) rats
ADMINISTRATION:
- Dosing:
main test: 10/50/250/1000/5000 µg/plate (+/- metabolic activation)

pre-incubation test: 10/50/250/500/1000 µg/plate (+/- metabolic activation)
- Number of replicates: 3
- Application: solvent dimethyl sulfoxide (CAS No. 67-68-5)
- Positive and negative control groups and treatment:
positive controls not reported
negative: water + solvent controls
activity of metabolic system: aminoanthracene / TA 100
- Pre-incubation: 30 minutes at 30 +/- 1 °C
incubation ca. 96 hours at ca. 37 °C
CRITERIA FOR EVALUATING RESULTS:
mutagenic effects (i.e ratio of revertant rates treated/control >= 2) at <= 5000 µg/plate with generally positive dose-response relationship in any strain

Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions: No testing in E. coli WP2 uvrA / E. Coli WP2 uvrA (pKM101) / S. typhimurium TA 102; poor documentation

(53)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	:	0; 300; 1000; 3300; 10000; 33000 µg/plate
Cycotoxic concentr.	:	> 10000 µg/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: See Test Conditions
Year	:	1982
GLP	:	no data
Test substance	:	other TS: Isophorone diisocyanate of Fluka Chemical Co., Purity: "Pract"

Test condition : SYSTEM OF TESTING
- Metabolic activation system: Aroclor 1254-induced Sprague-Dawley rat and Syrian hamster metabolic activation systems
ADMINISTRATION:
- Dosing: Pretest with TA 100 and max. 10 000 ug/plate; main test with at least one toxic dose
- Number of replicates: 3
- Positive and negative control groups and treatment:
sodium azide for TA 1535 and TA 100
4-nitro-o-phenylenediamine for TA 98
9-aminoacridine for TA 1537
2-aminoanthracene for all strains
potassium chloride as negative control
- Pre-incubation time: 20 min; incubation time 48 h
DESCRIPTION OF FOLLOW UP REPEAT STUDY: retested in all strains after no less than one week
CRITERIA FOR EVALUATING RESULTS:
positive: dose-related, reproducible increase over background
questionable: not dose-related, not reproducible, insufficient magnitude

Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions: No testing in E. coli WP2 uvrA / E. Coli WP2 uvrA (pKM101) / S. typhimurium TA 102

14.06.2006 (82)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, TA 100
Test concentration	:	10 to 1000 µg/plate
Cycotoxic concentr.	:	not reported
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Ames BN et al. (1975). Mutat. Res. 31, 347-364

Year	:	1981
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Hüls AG, purity not reported
Test condition	:	SYSTEM OF TESTING - Metabolic activation system: Aroclor induced rat S9 liver homogenate, male Wistar/TNO/W 74 rats ADMINISTRATION: - Solvent: Dimethyl sulfoxide (CAS No. 67-68-5) or methanol (67-56-1) - Number of replicates: 2 - Pre-incubation: With and without CRITERIA FOR EVALUATING RESULTS: Mutagenic effects (i.e ratio of revertant rates treated/control >= 2) with generally positive dose-response relationship in any strain
Reliability	:	(4) not assignable Abstract

(45)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration	:	7; 15; 30; 60; 120; 250; 500 µg/plate; TA 98 only >= 60 µg/plate
Cycotoxic concentr.	:	depending on strain, see Results for details
Metabolic activation	:	without
Result	:	negative
Method	:	other: Ames BN et al. (1975). Mutat. Res. 31, 347-364
Year	:	1979
GLP	:	no
Test substance	:	other TS: Isophorone diisocyanate of Chemische Werke Hüls AG, purity not reported
Result	:	GENOTOXIC EFFECTS: None CYTOTOXIC CONCENTRATION: TA 98: >= 250 µg/plate TA 100: >= 120 µg/plate TA 1535: >= 60 µg/plate TA 1537: >= 30 µg/plate TA 1538: >= 60 µg/plate
Test condition	:	ADMINISTRATION: - Number of replicates: 3 - Application: Solvent dimethyl sulfoxide (CAS No. 67-68-5) - Positive and negative control groups and treatment: Negative: Blank Positive: None (except simultaneous test of several substances including one positive result) - Incubation: 72 hours at 37 °C CRITERIA FOR EVALUATING RESULTS: Mutagenic effects (i.e ratio of revertant rates treated/control >= 2) at <= 500 µg/plate
Reliability	:	(2) valid with restrictions Comparable to guideline study with acceptable restrictions: TA 102 or E.coli WP2 were not tested, no test with metabolic activation

(24)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male
Strain	:	NMRI
Route of admin.	:	other: nose-only inhalation (vapor/aerosol)

Exposure period : 1 x 6 hours
Doses : 0, 5, 15, 40 mg/m³ (target concentration)
Result : negative
Method : other: OECD Guideline 474 (1997)
Year : 2006
GLP : yes
Test substance : other TS: Isophorone diisocyanate of Bayer MaterialScience AG, batch no.LL48/3-55, purity: 99.8%

Result : ISOPHORONE DIISOCYANATE EXPOSURE
- Target Concentration (mg/m³): 5, 15, 40
- Nominal Concentration (mg/m³): 33, 94.2, 212
- Gravimetric Concentration (mg/m³): 2.2, 15.9, 44.0
- Analytical Concentration (mg/m³): 4.3, 16.1, 39.6
- The Mass Median Aerodynamic Diameters (MMAD) was <4 µm (MMAD 1.3 µm, Geometric Standard Deviation 2). At the lowest concentration IPDI atmospheres consisted of vapor rather than aerosol to an appreciable extent.
PARAMETERS ASSESSED:
- Mortality: did not occur at any exposure level:
- Clinical Observations:

Target Concentration (mg/m³)	Deaths/signs/total	Onset and Duration of Signs
0	0 / 0 / 18	-- --
5	0 / 18 / 18	0d - 3d
15	0 / 18 / 18	0d - 3d
40	0 / 18 / 18	0d - 3d

0d = day of exposure.
3d: terminal sacrifice
Values given in the 'Deaths/signs/total' column are as follows:
1st number = number of dead animals
2nd number = number of animals with signs after exposure cessation
3rd number = number of animals exposed

0 mg/m³: All mice tolerated the exposure/dosing without signs.
5 mg/m³: Bradypnea, labored breathing patterns, stridor, motility reduced, high-legged gait, piloerection, eyelids closed.
15 mg/m³: Bradypnea, labored breathing patterns, breathing sounds, stridor, motility reduced, high-legged gait, piloerection, hair-coat ungroomed, eyelids closed, blepharospasm.
40 mg/m³: Bradypnea, labored breathing patterns, breathing sounds, stridor, motility reduced, high-legged gait, piloerection, hair-coat ungroomed, eyelids closed, blepharospasm, tremor, prostration, salivation, cyanosis.

- Body weights: Marked, concentration-dependent decrease in body weights which was most pronounced at 15 mg/m³ and 40 mg/m³.
- Body temperature: The mean body temperatures were significantly decreased at the end of the 6-h exposure period in all test material-exposure groups.
0 mg/m³: 38.1 °C
5 mg/m³: 33.3* °C
15 mg/m³: 27.9** °C
40 mg/m³: 25.6** °C
* = $p < 0.05$, ** = $p < 0.01$
Subcutaneously measured body temperatures were consistent with rectal temperatures. The subcutenously measured values showed that the duration of hypothermia was more pronounced in 40 mg/m³-group as

compared to 15 mg/m³-group.

- Respiratory function measurements (satellite groups):
Moderate effects on respiration were observed in 5 mg/m³, whilst in 15 mg/m³-group and 40 mg/m³-group a maximal depression of respiration was observed. This was caused specifically by increases in the bradypnoic period (pause between end inspiration and start of expiration).

CONDUCT OF THE MICRONUCLEUS TEST
- As may be seen from the tables below, the ratio of polychromatic to normochromatic erythrocytes in males was altered by the treatment with Isophorone diisocyanate for all sacrifice times at all concentration groups.
- As may be further deduced from the tables below, no biologically important or statistically significant variations existed for males between the negative control and the groups treated by inhalation with isophorone diisocyanate, with respect to the incidence of micronucleated polychromatic erythrocytes.
- Similarly, there could be no biologically significant variation between the negative control and Isophorone diisocyanate groups in the number of micronucleated normochromatic erythrocytes, since normochromatic erythrocytes originated from polychromatic ones. As expected, relevant variations were not observed.
- The positive control, cyclophosphamide, caused a clear increase in the number of polychromatic erythrocytes with micronuclei. The incidence of micronucleated cells represents biologically relevant increases in comparison to the negative control.

SUMMARY OF RESULTS OF 24 HOURS INTERVAL

Experimental groups	number of evaluated	number of MNNCE per 2000 NCE	MNNCE per 2000 PCE	MNPCE per 2000 PCE
	PCE		(1s range)	(1s range) (1s range)
negative control	12000	1988 (412)	2.3 (2.3)	2.0 (0.6)
5 mg/m³	12000	3117 (997)	2.1 (1.2)	1.7 (0.8)
15 mg/m³	12000	4598* (1617)	3.0 (1.0)	3.0 (0.6)
40 mg/m³	12000	3679 (1959)	2.8 (3.3)	4.5 (2.2)
positive control	10000	2515 (768)	1.9 (0.8)	26.2** (12.4)

SUMMARY OF RESULTS OF 48 HOURS INTERVAL

Experimental groups	number of evaluated	number of MNNCE per 2000 NCE	MNNCE per 2000 PCE	MNPCE per 2000 PCE
	PCE		(1s range)	(1s range) (1s range)
negative control	12000	1682 (154)	2.4 (1.6)	4.3 (2.3)
5 mg/m³	12000	2039	2.8	2.2

(635) (2.5) (1.5)

15 mg/m³ 12000 3874 2.1 3.3
(2810) (0.9) (2.3)

40 mg/m³ 12000 4236* 2.5 3.5
(1568) (0.6) (1.4)

SUMMARY OF RESULTS OF 72 HOURS INTERVAL

Experimental groups	number of evaluated PCE	number of NCE per 2000 PCE	MNNCE per NCE 2000 PCE (1s range)	MNPCE per 2000 PCE (1s range)
negative control	12000	1353	3.2 (209)	2.3 (1.8)
5 mg/m³	12000	1800	1.7 (541)	1.8 (2.5)
15 mg/m³	2000	3387	2.4 (2810)	3.7 (0.9)
40 mg/m³	12000	7168**	2.6 (2577)	4.5 (0.7)

*P < 0.05 in non-parametric Wilcoxon ranking test
**P < 0.01 in non-parametric Wilcoxon ranking test

Test condition : ISOPHORONE DIISOCYANATE EXPOSURE:
- Mice were assigned to four exposure groups and were exposed to the aerosolized test substance to target concentrations of 0 (air), 5, 15 and 40 mg/m³ (1 x 6 hr).
- number of animals per concentration: 18 (main study) and additionally 5 (satellite mice for respiratory function measurements)

PARAMETERS ASSESSED
- Clinical observations: several times on the day of exposure and at least once daily thereafter
- Body weights: daily
- Body temperature: rectal body temperature directly after cessation of exposure; subcutaneous body temperature (transponders) during exposure (at intervals of 30 min.) up to 3 hours after ceasing exposure
- Respiratory function measurements (restricted to the satellite mice)

CONDUCT OF THE MICRONUCLEUS TEST
- Experimental Group Target Concentration Sacrifice Time

	(mg/m³)	(hours)
Negative Control	0	24
Isophorone Diisocyanate	5	24
Isophorone Diisocyanate	15	24
Isophorone Diisocyanate	40	24
Positive Control		
Cyclophosphamide	20 mg/kg	
Negative Control	0	48
Isophorone Diisocyanate	5	48
Isophorone Diisocyanate	15	48
Isophorone Diisocyanate	40	48

Negative Control	0	72
Isophorone Diisocyanate	5	72
Isophorone Diisocyanate	15	72
Isophorone Diisocyanate	40	72

number of animals in the positive control group: 5
2000 polychromatic erythrocytes were counted per animal

BIOMETRY:
- Per sacrifice time the Isophorone diisocyanate group with the highest mean (provided this superceded the negative control mean) and the positive control were checked by Wilcoxon's non-parametric rank sum test with respect to the number of polychromatic erythrocytes having micronuclei and the number of normochromatic erythrocytes. A variation was considered statistically significant if its error probability was below 5% and the treatment group figure was higher than that of the negative control.
- The rate of normochromatic erythrocytes containing micronuclei was examined if the micronuclear rate for polychromatic erythrocytes was already relevantly increased. In this case, the group with the highest mean was compared with the negative control using the one-sided chi2-test. A variation was considered statistically significant if the error probability was below 5% and the treatment group figure was higher than that of the negative control.
- In addition, standard deviations (1s ranges) were calculated for all the means.
ASSESSMENT CRITERIA:
- A test was considered positive if there was at any time point a biologically relevant and statistically significant increase in the number of polychromatic erythrocytes showing micronuclei in comparison to the negative control.
- A test was considered negative if there was no relevant or significant increase in the rate of micronucleated polychromatic erythrocytes. A test was also considered negative if there was a significant increase in that rate which, according to the laboratory's experience was within the range of historical negative controls.
- In addition, a test was considered equivocal if there was an increase of micronucleated polychromatic erythrocytes above the range of attached historical negative controls, provided the increase was not significant and the result of the negative control was not closely related to the data of the respective treatment group. A test was also considered equivocal, if its result was implausible. In both case, normally a second test will be performed.

Conclusion : There was no indication of a clastogenic effect after inhalative exposure of Isophorone diisocyanate in the micronucleus test on the male mouse. Analytical monitoring data of the exposure conditions, clinical signs of respiratory tract irritation, hypothermia and respiratory depression appear to suggest adequate bioavailability by this route.

Reliability : (1) valid without restriction
Guideline study

16.09.2006 (42)

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: inhalation (nose-only)
Exposure period	:	days 6 through 19 post coitum
Frequency of treatm.	:	6 hours/day, daily
Duration of test	:	cesarean section on day 20
Doses	:	0.25; 1.0; 4.0 mg/m3 nominal = 0.206; 0.929; 4.536 mg/m3 analytical
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1 mg/m³
NOAEL teratogen.	:	= 4 mg/m³
NOAEL Embryotoxicity	:	= 1 - mg/m³
Result	:	not teratogenic
Method	:	other: OECD TG 414 (2001); 88/302/EEC (1988); U.S. OPPTS 870.0300 (1998); Japanese MAFF guidelines (2000, amended 2001).
Year	:	2003
GLP	:	yes
Test substance	:	other TS: isophorone diisocyanate of Bayer Polymers, batch no. LL48/3-55, purity 99.8 %, sampled 07 Aug 2003

Result :

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX: Chemical analyses demonstrated satisfactory stability and agreement between nominal and actual concentrations of the test material.
MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
- Mortality and day of death: No mortalities were reported.
- Description, severity, time of onset and duration of clinical signs: decreased respiratory rate (bradypnea), labored breathing, breathing sounds, reddish encrusted nostrils, serous nasal discharge, rough fur (4 mg/m3 group). Effects on breathing as well as nasal discharge were not observed in the other groups, while effects on nose and nostrils were rare (maximum 2 females/group) and likely related to restraint. Rough fur occurred in some females of all study groups, including the control group, but showed a sharp increase in incidence with the 4 mg/m3 group.
- Food/water consumption: Decreased feed intake throughout the exposure period was observed in the 4 mg/m3 group (14.7 % below control; $p < 0.01$) and during the last interval (days 18-20) in the 0.25 mg/m3 group ($p < 0.05$, not dose related). After start of inhalation, reduced feed intake was observed in all study groups including control, most probably due to the inhalation procedure. Beyond this, feed intake was normal. No effects on water intake and on excretion of urine and feces were observed in any group.
- Body weight: The body weight in the 4 mg/m3 group from day 0 to day 20 was lower by 7.9 %, the corrected body weight (body weight minus unterine weight) was lower by 9.2 %. The body weight gain in the 4 mg/m3 group from day 0 to day 20 was lower by 23.5 % (absolute; relative to initial weight: -21.7 %; corrected: -91.3 %; compared to control; $p < 0.01$). After start of inhalation, body weight loss was observed in all study groups including control, most probably due to the inhalation procedure. Beyond this, body weight development was normal.
- Gross pathology incidence and severity: There were no treatment related gross pathological findings in any group.
- Number pregnant per dose level: control: 24/27; 0.25 mg/m3: 23/27; 1 mg/m3: 24/27; 4 mg/m3: 26/27
- Number of implantations: control 11.9; 0.25 mg/m3: 11.9; 1 mg/m3: 13.0, 4 mg/m3: 12.0 (mean per female with implantation sites) = no significant differences
- Pre and post implantation loss: control: 1.7 / 0.8; 0.25 mg/m3: 2.1 / 0.7; 1 mg/m3: 1.2 / 0.7; 4 mg/m3: 1.4 / 0.5 (mean pre- / postimplantation loss per

female with implantation sites) = no significant differences
- Number of corpora lutea: control: 13.6; 0.25 mg/m3: 14.0; 1 mg/m3: 14.1, 4 mg/m3: 13.4 (mean per female with implantation sites) = no significant differences
- Number aborting: No abortion in any group
- Number of resorptions: There were no females with total resorption in any group.
- Duration of pregnancy: determined by cesarean section on day 20
- Other findings: Placental weights were marginally decreased at the 4 mg/m3 level (-6.6 %, not statistically significant but slightly below historical control data range).
FETAL DATA:
- Litter size and weights: mean fetal weight in control: 3.51 g; 0.25 mg/m3: 3.49 g; 1 mg/m3: 3.46 g; 4 mg/m3: 3.27 g, i.e. reduction of fetal weight in 4 mg/m3 group (-6.8 %; $p < 0.01$)
- Number viable: control: 11.1; 0.25 mg/m3: 11.2; 1 mg/m3: 12.3; 4 mg/m3: 11.5, i.e. no treatment related findings
- Sex ratio: control: 49.3; 0.25 mg/m3: 48.3; 1 mg/m3: 50.0; 4 mg/m3: 52.0 % males, i.e. no treatment related findings
- Grossly visible abnormalities: There is no evidence for treatment relation. A marginally higher number of common eye malformations in the 4 mg/m3 group (1 % of the fetuses and 7.7 % of litters affected vs. 0.4 % of fetuses and 4.2 % of litters in control), which is well within the range of historical control data (up to 1.8 % of fetuses and 20 % of litters affected), is considered to be either incidental or secondary (reduced oxygen supply to offspring by maternal bradypnea).
control: 1.1 % of fetuses / 12.5 % of litters showed malformations
0.25 mg/m3: 1.6 % of fetuses / 13.0 % of litters showed malformations
1.0 mg/m3: 2.0 % of fetuses / 20.8 % of litters showed malformations
4.0 mg/m3: 1.7 % of fetuses / 11.5 % of litters showed malformations
- External abnormalities: External deviations were not observed in this study.
- Soft tissue abnormalities: Statistical significance was only evident for reduced number of tracheal findings (membraneous part of trachea slightly folded, lying in tracheal lumen; possibly of artefactual origin) in the 1 mg/m3 and 4 mg/m3 groups and for reduced total number of fetuses with deviations in the 1 mg/kg exposure group. Based on lack of dose relationship (control: 23; 0.25 mg/m3: 11; 1 mg/m3: 6; 4 mg/m3: 10 %), highest incidence of the tracheal finding in the actual control group and lack of pathological significance per se for a reduced number, these findings were considered incidental. Other deviations observed during visceral evalution were either common or without dose relationship. In conclusion, an effect on incidence and type of external and visceral deviations was not evident at an exposure level up to and including 1 mg/m3, while slightly retarded descensus testis (4 % of fetuses and 38.5 % of litters vs. 2.2 % of fetuses and 25 % of litters in the control group) was observed at the maternally toxic 4 mg/m3 exposure level. In relation to decreased fetal weights treatment relationships could not be totally excluded, although the individual alterations lay well in the range of historical data and statistical significance was not evident.
control: 27.0 % of fetuses / 95.8 % of litters showed deviations
0.25 mg/m3: 24.4 % of fetuses / 87.0 % of litters showed deviations
1.0 mg/m3: 17.0 % of fetuses / 87.5 % of litters showed deviations
4.0 mg/m3: 23.0 % of fetuses / 96.2 % of litters showed deviations
- Skeletal abnormalities: Fetal skeletal including cartilaginous tissue evaluation for degree of ossification and incidence of variations relealed no toxicologically relevant effects at an exposure level up to and including 1 mg/m3. Dose relation was missing for all findings at 0.25 and 1 mg/m3, and statistical significance was absent either on a fetus base, or on a litter base, or for both. Statistically significant fetal skeletal findings at the 4 mg/m3 exposure level included retarded ossification of distal and proximal phalanges of digits and toes, of metacarpal bones, 6th sternal segment, 7th

cervical vertebral body, sacral and caudal vertebral arches and caudal vertebral bodies. Incidence of findings at the proximal phalanges of digits and distal phalanges of toes, of metacarpals, and sacral and caudal vertebrae lay outside the range of recent historical control data on a fetal basis, and although statistical significance on a litter basis was restricted to delayed ossification of proximal phalanges of digits, treatment relationship was assumed for retarded ossification of these localizations in relation to as well impaired fetal weight. Other findings in the 4 mg/m3 group were considered to be of no toxicological relevance.

Test condition : TEST ORGANISMS
- Source: Hsd Cpb:WU from Harlan-Winkelmann GmbH, Borchen (Germany)
- Age: between 14 and 17 weeks
- Weight at study initiation: 201 - 244 g
- Number of animals: 27 per dose / control group
MATING PROCEDURES: Two females and one male were placed in a cage overnight. If sperm was detected in the vaginal smear taken in the morning, this day was regarded as day 0 of gestation.
PARAMETERS ASSESSED DURING STUDY:
- Mortality: daily on days 0 through 5 and 20, twice daily on days 6 through 19
- Clinical signs: daily on days 0 through 5 and 20, twice daily on days 6 through 19
- Body weight gain: Weighing on days 0 and 6 through 20, correction for weight of uterus on day 20
- Food consumption: Cumulative on days 3, 6, 9, 12, 15, 18, and 20; water consumption 3 times/week
- Examination of uterine content: Number of corpora lutea, number of implantations (in females without visible implantation sites after staining with 10 % ammonium sulfide solution), uterine weights, individual weight and appearance of the placentas, number of early resorptions (only implantation sites visible), number of late resorptions (fetal or placental remnant visible), number of dead fetuses (i.e. without signs of life, without maceration), number of live fetuses
- Examination of fetuses: sex, individual weight, external malformations or other findings deviating from normal, visceral malformations and other findings deviating from normal (Wilson technique), findings in abdominal, pelvic, and thoracic organs as well as skeletal and cartilage findings (modified Dawson technique) with the addition of cartilage staining: evisceration, cartilage staining with alcian blue GX, clearing of the fetuses with diluted potassium hydroxide solution, staining of the skeletal system with alizarin red S and evaluation of the skeletal system including cartilaginous findings. Every other fetus within a litter was prepared for either skeletal or visceral evaluation with generally the first fetus of each litter assigned to skeletal analysis.
STATISTICAL METHODS:
- Females without implanatation sites were excluded. Skeletal localizatins with mechanical damage in single fetuses were ecluded from the calculation of percentages of affected localizations but reported in the tables of individual skeletal findings.
- Analysis of variance, and in case of significant results Dunnett's test for: feed consumption; body weights (incl. gains and corrections); uterine weights; number of corpora lutea, of implantations, of live fetuses (incl. percentages) per female; placental and fetal weights per female.
- 2 by N Chi(square) test, and in case of significant differences Fisher's exact test with Bonferroni correction for: fertility and gestation rate; number of implantations per group; number of preimplantation losses per group; number of postimplantation losses, early resorptions, late resorptions, or dead fetuses per group; number of live fetuses per group in percent of implantations; number of male or female fetuses or fetuses with undeterminable sex per group; number of fetuses or litters with external, visceral, and skeletal findings; number of fetuses or litters with

malformations.
- Kruskal-Wallis test, and in case of significant differences Dunn's test for: number of preimplantation losses, postimplantation losses, early resorptions, late resorptions or dead fetuses per female; number of male or female fetuses or fetuses with undeterminable sex per female; proportion of placental, fetal external, and fetal visceral findings per female.
- Chi(square) test (correction according to Yates) for: number of fetuses or litters with cartilaginous tissue observations.

Reliability : (1) valid without restriction
Guideline study

16.09.2006 (69)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human

Remark : Biological monitoring in urine

Result : The average urinary elimination half-time was 2.8 hours. The average urinary excretion was 27 % (range 19-46%). An association between the estimated inhaled dose and the total excreted amount was seen.
The detection limit was about 0.1 µg/l in urine and < 0.1 µg/l in plasma.
No isophorone diamine was found in hydrolyzed plasma.
When working up samples from exposed persons without hydrolysis, no isophorone diamine was seen.

It has been implied that isophorone diisocyanate conjugates or reacts with biological molecules in the lung, which then enter the systemic circulation. Hydrolysis releases the adducted isocyanate as amine. The analytical methods used would not distinguish between isocyanate and amine.

Test condition : - Three healthy male volunteers were exposed simultaneously in a 5.6 m3 exposure chamber to concentrations of 12.1 (Tuesday), 17.7 (Thursday), and 50.7 (Saturday) ug isophorone diisocyanate/m3 for 2 hours per concentration level.
- The inhaled doses were estimated by pulmonary ventilation x exposure level x duration of exposure.
- All urine was collected for 16 days.
- Blood samples were taken before and half an hour after exposure plus daily on exposure-free days.
- Samples were hydrolyzed, i.e. conjugates were split and any residual isophorone diisocyanate was converted to isophorone diamine (CAS No. 2855-13-2).
- This diamine was determined as its pentafluoropropionic amide by liquid chromatography / mass spectrometry.

Reliability : (2) valid with restrictions
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

23.09.2006 (103)

Type of experience : Direct observation, clinical cases

Result : 3 patients (13 % of those with allergic contact dermatitis, 4.3 % of all) were allergic to isophorone diisocyanate. The source of exposure appeared to be the foam rubber padding in athletic shoes, though migration from glues into the padding could not be excluded.

Isophorone diisocyanate had not previously been reported as a causative allergen in shoe dermatitis.

Test condition : During an 8-year period, 70 patients with allergic-appearing foot dermatitis, of which 23 were found to have allergic contact dermatitits from shoes, were patch tested with commercially available diagnostic sets and some additional substance preparations.

Test substance : Induction: Not identified.
Challenge: 1 % isophorone diisocyanate in petrolatum (Chemotechnique Diganostics, Malmö, Sweden)

Reliability : (4) not assignable
Documentation insufficient for assessment

22.09.2006 (19)

Type of experience : Direct observation, clinical cases

Remark : Occupational contact dermatitis

Result : - 13 patients reacted to dicyclohexylmethane-4,4'-diisocyanate
9 patients reacted to hexane-1,6-diisocyanate
5 patients reacted to bis-(4-aminocyclohexyl)methane
5 patients reacted to bis-(4-aminophenyl)methane
** 4 patients reacted to isophoronediisocyanate **
0 patients reacted to diphenylmethane-4,4'-diisocyanate or toluene diisocyanate

Test condition : - A glue, mainly based on dicyclohexylmethane-4,4'-diisocyanate (70 %), was suspected of being the cause of an outbreak of severe eczema at a factory manufacturing medical equipment from August 1999 to April 2001. 16 out of approximately 100 persons working in the relevant department were referred to medical consultation.
- These 16 workers with recent episodes of eczema were patch tested with a standard series, an isocyanate series, and work material.

Reliability : (2) valid with restrictions
Limited documentation

14.06.2006 (39)

Type of experience : Direct observation, clinical cases

Remark : Occupational contact dermatitis
The authors state that allergic contact dermatitis from isocyanates is rare.

Result : CASE 1:
- While working with the polyurethane foam, the patient developed a dermatitis involving her arms and face and occasional bouts of periorbital edema. Frequent relapses occurred in spite of treatment with moderate-strength topical steroids.
- 96 hours after patch application, the patient had
a ++ reaction to 4,4'-methylenedianiline and epoxy resin and
a + reaction to isophorone diisocyanate and diphenylmethane-4,4'-diisocyanate.
CASE 2:
- After an entire day of work on a large polyurethane block, during which her forearms, thighs, face, neck, and work clothes were contaminated, the woman developed within 2 days a severe and intensely pruritic dermatitis involving all areas that had been exposed. This reaction was accompanied by considerable edema, especially of the face and eyelids.
- 96 hours after patch application, the patient had
a + reaction to isophorone diisocyanate, 4,4'-methylene-dianiline, diphenylmethane-4,4'-diisocyanate, toluene diisocyanate, and hexamethylenediisocyanate. dicyclohexylmethane-4,4'-diisocyanate was not tested.

Test condition : CASE 1:
- A 21-year-old woman was exposed to various materials including a polyurethane foam with diphenylmethane-4,4'-diisocyanate. The patient did

report wearing protective gloves that covered her up to her proximal forearms while working in an unventilated area.
- She was patch-tested with the North American Contact Dermatitis Group (NACDG) standard series and with an isocyanate series including isophorone diisocyanate (1 % in petrolatum)
CASE 2:
- A 31-year-old woman designed and created various objects required by the performers of a circus. Besides work with various other materials, she often poured and cured a liquid polyurethane product and sculpted the resulting blocks with a high-speed electrical drill in an open-space workshop. The product used is 75-85 % dicyclohexylmethane-4,4'-diisocyanate and 15-25 % polyurethane polymer.
- She was patch-tested with the NACDG standard series and with a glues, plastics, and adhesives series.

Reliability : (2) valid with restrictions
Limited documentation

19.06.2006 (75)

Type of experience : Direct observation, clinical cases

Remark : Occupational hypersensitivity pneumoapathy
The investigators state that hypersensitivity pneumoapathies from isocyanates are rare (49 cases betwen the first observation in 1976 and submission for publication of this report in 2002).

Result : Few hours after the beginning of this new occupational exposure, which was not defined any more specifically, he showed dyspnea, fever (39 °C), and crepitant rales. Further investigations revealed ground glass appeareance on the thoracic CT scan and lymphocytosis in the broncho-alveolar lavage. Effects were confirmed by transbronchial biopsy. Only the functional assessment (airflow obstruction and absence of marked reduction in CO transfer) was atypical for hypersensitivity pneumapathies.

Test condition : A 50 year old man had worked in the production of polyurethane foams and polyurethane coatings for 32 years with a generally low exposure. He then was engaged more closely in a polyurethane synthesis from isophorone diisocyanate.

Reliability : (2) valid with restrictions
Limited documentation

16.04.2007 (40)

Type of experience : Direct observation, clinical cases

Remark : Effects from occupational spraying with two-pack paints
In the other cases reported in this reference, other or unidentified isocyanates were used.

Result : He then developed tightness of the chest and dyspnoea, which disappeared when he took a few days off, but recurred shortly after his return to work.
The sprayer who took his place had similar symptoms in a milder form which lasted only a few hours.

Test condition : In 1974, a sprayer in a firm of motor body repairers used for some months intermittently a two-pack paint containing the test substance (not quantified), toluene and xylene, with no ill-effects.
The spraying was done in a large, completely enclosed booth with effective downdraught through the floor.

Reliability : (4) not assignable
Documentation insufficient for assessment

14.06.2006 (104)

Type of experience : Human

Remark : Sensory irritation in humans

With regard to the vapor saturation concentration at ambient temperature the particle concentration should be negligible in relation to vapor atmosphere

Result : 0.25 mg/m3: odor just perceptible;
0.64 mg/m3: slight irritation of the mucous membranes of the eyes and nose;
1.37 mg/m3: strong irritation of the mucous membranes of the eyes and the breathing passages, intolerable

Test condition : Experiments with voluntary test persons (1-5 minutes aerosol exposure)

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

14.06.2006 (41)

Type of experience : Direct observation, clinical cases

Remark : The authors mention the possibility of a cross reaction with diphenylmethane diisocyanate, which is a constituent of a glue used in playground fitting. This raises the question why no positive reaction with diphenylmethane diisocyanate was observed in the present case. No further information which might be helpful to answer this question could be found in the publication.

Result : Positve reactions were observed on days 2 and 4 with
- cyclohexylthiophthalimide (1 % pet.)
- isophoronediisocyanate (no details reported).
He subsequently avoided contact with the rubber material and his symptoms have cleared.

Test condition : A 45-year-old British playground fitter had developed dermatitis on his palms and finger tips after 12 months working with (among other materials) rubber tiles made from recycled car tyres, which were laid as flooring around the playground equipment.
Symptoms cleared with topical corticosteroids or during prolonged time off working but returned after turning to work and spread out to his forearms.
He was patch tested to the European standard series as well as to a rubber and isocyanate series (further details available only for positive reactions).

Reliability : (4) not assignable
Documentation insufficient for assessment

17.11.2006 (74)

Type of experience : Health records, other

Remark : Occupational asthma
No relationship between the effects observed and a specific substance was established. Particularly, exposure to isophorone diisocyanate was not confirmed.

Result : Occupational asthma was confirmed in six of the 51 subjects.

Test condition : - Persons: All 51 workers (including 39 spray painters) of a set of four paint shops of a large airplane assembly plant participated.
- Paints containing different types of isocyanates were applied in spray painting in these paint shops; isophorone diisocyanate is not among the four examples listed.
- All were interviewed using a respiratory questionnaire.
- Spirometry was performed.
- Workers with certain symptoms were selected for a follow-up clinical study by the occupational health physician.
- The clinical study included a further questionnaire, spirometry and assessment of responsiveness to inhaled histamine, skin tests and specific inhalation challenges.

Conclusion : A prevalence of 11.8 % for occupational asthma in spray paint shops was reported.

Reliability : (4) not assignable
Documentation insufficient for assessment

(101)

Type of experience : other: Sensitization in vitro

Method : This in vitro test system simulates the in vivo interaction with mucosal surface proteins. The hypothesis was that there ought to be a correlation between the ability of a substance to react with proteins and its potential to induce respiratory tract dysfunction.

Remark : Sensitization (in vitro)

Result : Isophorone diisocyanate was positive (ca. 50 % reaction of LTL) and is therefore suggested to have the potential to act as a hapten and cause respiratory tract dysfunction when inhaled.

Test condition : - Isophorone diisocyanate was allowed to react with a lysine containing peptide (L-lysyl-L-tyrosyl-L-lysine . 2 formate = LTL) in buffered solution at 37 °C for 10 minutes.
- After 1 additional minute in a 20 °C water bath, the mixtures was analyzed by HPLC.
- The percentage of peptide reacted was determined by comparison of the peptide peak intensity with that in a blank test, i.e. without isocyanate.

Reliability : (4) not assignable
Study well documented but test system not validated

13.02.2007 (108)

5.11 ADDITIONAL REMARKS

Type : Immunotoxicity

Method : The immunologic evaluation of allergenic hapten-protein conjugates with isophorone diisocyanate (IPDI) was reported. The specificity of the IPDI-ovalbumine was verified with antiserum by ELISA. The reactivity of guinea-pig sera to an IPDI-ovalbumine conjugate after aerosol- or intradermal exposure of donor animals to IPDI was tested using ELISA optical density at 490 nm.

Result : 7/8 intradermally injected guinea-pigs were positive for IgG1-antibody to IPDI. 4 had titer greater than 1/1000. None of 16 guinea-pigs exposed to IPDI aerosol showed a positive reaction (optical density > 0.22, dilution 1/20).

Test condition : TEST ANIMALS: guinea pigs
- Strain: English smooth haired
- Sex: female
- Source: Hilltop Lab Animals, Scottdale (PA, USA)
- Weight at study initiation: 250-300 g
- Number of animals: 4

ADMINISTRATION/EXPOSURE
- Preparation of test substance for induction:
conjugation with guinea pig serum albumin (GPA)
- Induction schedule: multiple intradermal injections for 3-5 months, total dose ca. 250 µl
- Concentration in Freunds Complete Adjuvant (FCA):
IPDI-GPA conjugate applied emulsified in FCA
- Challenge schedule: subcutaneous injection 5 days before being bled of animals

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

(5)

Method : The working hypothesis is that chemicals which have a potential to induce

respiratory sensitization preferentially activate murine T helper cells TH2, resulting in the production of Interleukin IL-4 with the consequence of promotion of the IgE response.

Result : RESULTS OF PILOT STUDY: Topical exposure of mice to IPDI caused a lymphocyte proliferative response in lymph nodes draining the site of application, i.e. the substance was immunogenic at the concentration of the main test.
RESULTS OF TEST
- Sensitization reaction: Exposure did not induce any change in the concentration of serum IgE. Promotion of antibodies of IgG2a isotype, which according to preliminary studies also correlates with respiratory sensitization, was not observed either.

Test condition : TEST ANIMALS:
- Strain: BALB/c
- Sex: female
- Source: Barriered Animal Breeding Unit, Alderley Park (UK)
- Age: 8-12 weeks
- Controls: vehicle
ADMINISTRATION/EXPOSURE
- Vehicle: acetone+olive oil, 4:1
- Induction schedule: 50 ul on each shaved flank
- Concentrations used for induction: 2 %
- Challenge schedule: 7 days later 25 ul diluted 1:1 with vehicle to dorsum of both ears
EXAMINATIONS: Determination of serum IgE
- Pilot study: Measurement of lymph node cell proliferation

Test substance : Isophorone diisocyanate of Aldrich, Gillingham (UK); purity not reported

Conclusion : Isophorone diisocyanate has no or very limited potential to cause respiratory allergy.

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

(27) (28)

Type : Immunotoxicity

Method : Chemicals that bind to protein may lead to immunological responses that include respiratory responses mediated by IgE anbitodies.

Result : Treated mice had statistically higher concentrations of serum IgE than control animals.

Test condition : BALB/c mice were exposed dermally to 3 and 6 % isophorone diisocyanate in olive oil:acetone on days 1 and 7. Serum IgE was evaluated 14 days after the first administration.

Reliability : (4) not assignable
Abstract

(109)

(1) ACGIH (American Conference of Governmental Industrial Hygienists) (2004). TLVs and BEIs, Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. Isophorone diisocyanate (2 pp). Cincinnati (OH, USA).

(2) Adema DMM (1982). Tests and desk studies carried out by MT-TNO during 1980-1981 for annex II of marpol 1973. Rep.No. CL82/14, 52 pp. TNO, Delft (NL).

(3) Ahrens W and Jöckel KH (1997). Exposure to hazardous agents in the paper and pulp industry. Zentralbl. Arbeitsmed. Arbeitsschutz Ergon. **47**, 390-401.

(4) American Cyanamid Co. (1987a). A closed-patch repeated insult dermal sensitization study in guinea pigs with TDI, MDI, p-TMXDI, IPDI, m-TMXDI, HMDI and m-TMI, Project No. 4971-84. NTIS/OTS Microfiche 0515234, Doc 86-870000795.

(5) American Cyanamid Co. (1987b). Preparation and immunologic evaluation of allergenic hapten-protein conjugates. NTIS/OTS Microfiche 0515218, Doc 86-870000779.

(6) American Cyanamid Co. / Bio-Research Laboratories Ltd. (1992). The acute toxicity of inhaled isophorone diisocyanate in the guinea pig. NTIS/OTS Microfiche 0543418, Doc 86-930000052.

(7) Auer (1989). Auer-Technikum, Ausgabe 12, 380-385. Auer-Gesellschaft mbH, Berlin.

(8) Bayer AG (1994). Bestimmung von physikalisch-chemischen Stoffdaten - Dampfdruck. Report No. 94/121 B (unpublished).

(9) Bayer AG (1995a). Isophorondiisocyanat - study on acute inhalation toxicity in rats according to OECD No. 403 (English translation from the German). NTIS/OTS Microfiche 0558208, Doc 86-960000068.

(10) Bayer AG (1995b). Isophorondiisocyanat - study on acute inhalation toxicity in rats according to OECD 403. Report No. 24245. Bayer AG, Wuppertal (unpublished).

(11) Bayer AG (1995c). Support: isophorondiisocyanat - study on acute inhalation toxicity in rats according to OECD No. 403. NTIS/OTS Microfiche 0537597-1, Doc 86-960000012.

(12) Bayer AG (1996). IPDI (Isophorondiisocyanat), evaluation of respiratory sensitization in guinea-pigs following intradermal induction. Report No. 24967, 1458 pp., also on NTIS/OTS Microfiche 0558691, Doc 86-960000490 (1996).

(13) Bayer AG (1999). Decrease of NCO-content in water - Desmodur I. Report No. N 99/0050/01 LEV (unpublished).

(14) Bayer AG (2000). Investigation of the ecological properties of DESMODUR I. Bayer AG (Leverkusen) Report No. 860 A/99 with attachments (unpublished).

(15) Bayer AG (2002). Bayer isophorone diisocyanate exposure questionnaire (unpublished).

(16) Bayer AG (2003). Isophorondiisocyanate (IPDI) subacute inhalation toxicity on rats, study no. T0071598. Report No. AT00440, 398 pp (unpublished).

(17) Bayer Industry Services (2006). Re-evaluation of effect concentrations to Daphnia magna for Desmodur I (CAS: 4098-71-9) (unpublished).

(18) Bayer MaterialScience AG (2006). Bayer isophorone diisocyanate exposure questionnaire (unpublished).

(19) Belsito DV (2003). Common shoe allergens undetected by commercial patch-testing kits: dithiodimorpholine and isocyanates. Am. J. Contact Dermatitis **14**, 95-96.

(20) BGIA (Berufsgenossenschaftliches Institut für Arbeitsschutz) (2006). GESTIS-database on hazardous substances. www.hvbg.de/bgia/stoffdatenbank

(21) Biosphere Research Center Inc. (1981). Dermal sensitization study of compound number 11583B15 and isophorone diisocyanate. Report No. 81-149. American Cyanamid Company Wayne (NJ, USA).

(22) BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit, Germany) (2002). Technische Anleitung zur Reinhaltung der Luft (2002-07-24). http://www.bmu.de.

(23) BUA (2006). Registry database search performed 31.03.2006.

(24) Chemische Werke Hüls AG (1979). Ames-Test - getestete Substanzen TMD, MNDA, Isophoron, Diaminodurol, IPD, IPDI. Internal report (unpublished).

(25) Clarke CW and Aldons PM (1981). Isophorone diisocyanate induced respiratory disease (IPDI). Aust. N.Z. J. Med. **11**, 290-292.

(26) Danish Product Register (2002). Communication to BUA.

(27) Dearman RJ, Basketter DA and Kimber I (1992). Variable effects of chemical allergens on serum IgE concentration in mice. Preliminary evaluation of a novel approach to the identification of respiratory sensitizers. J. Appl. Toxicol. **12**, 317-323.

(28) Dearman RJ, Spence LM and Kimber I (1992). Characterization of murine immune responses to allergenic diisocyanates. Toxicol. Appl. Pharmacol. **11**2, 190-197.

(29) Degussa AG (2001). VESTANAT® IPDI - isophorone diisocyanate - 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Degussa Coatings & Colorants information sheet 43.13.018e / 12.01.

(30) Degussa AG (2006). Unpublished calculations using standard methods / equations.

(31) Degussa Corporation (2002). Degussa Corp. isophorone diisocyanate exposure questionnaire (unpublished).

(32) Degussa North America (2006). Degussa Corp. isophorone diisocyanate exposure questionnaire (unpublished).

(33) DFG (Deutsche Forschungsgemeinschaft, Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe) (2005). MAK- und BAT-Werte-Liste 2005, Mitteilung 41. Wiley-VCH (Weinheim, Germany).

(34) Dow Chemical Company (1987). Preliminary toxicology information - isophorone diisocyanate. NTIS/OTS Microfiche 0517013, Doc 86-870002233.

(35) E.I. du Pont de Nemours and Company (1987). Mouse sensory irritation. NTIS/OTS Microfiche 0514930, Doc 86-870001028.

(36) E.I. du Pont de Nemours and Company (1990). Laboratory report on cyclohexane, 5-isocyanate-1-(isocyanatomethyl)-1,3,3-trimethyl. NTIS/OTS Microfiche 0530170, Doc 86-910000412S.

(37) ECB (European Commission - European Chemicals Bureau) (2000). IUCLID Dataset on 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, 18th February 2000.

(38) Fiss J (1976). Diss. Akademie für ärztl. Fortbildung der DDR, Berlin. Cited in: Ziegler V and Süss E (1985): The TINA test. Curr. Probl. Derm. **14**, 172-192.

(39) Frick M, Björkner B, Hamnerius N and Zimerson E (2003). Allergic contact dermatitis from dicyclohexylmethane-4,4'-diisocyanate. Contact dermatitis **48**, 305-309.

(40) Germanaud J, Proffit V, Janvoie B, Lemarie E and Lasfargues G (2003). Pneumopathy due to isocyanate hypersensitivity: recognition as an occupational disease. Rev. Mal. Respir. **20**, 443-449.

(41) Henschler D (1972). Isophorondiisocyanat - Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten. Verlag Chemie.

(42) Herbold B (2006). Isophorone diisocyanate - micronucleus test on the male mouse after inhalative exposure for 6 hours. Bayer HealthCare Report No. AT03075 (unpublished).

(43) Hommel G (1991). Handbuch der gefährlichen Güter, Merkblatt 917. 2. neubearbeitete Auflage. Springer Verlag (Berlin).

(44) Huntingdon Research Centre (1978). IPDI and TMDI - acute inhalation toxicity, Report VBC 1/78994, Veba-Chemie AG (Gelsenkirchen, Germany, unpublished).

(45) Hüls AG (1981). Mutagenitätsuntersuchung von Isophorondiisocyanat mit Hilfe des Salmonella typhimurium/Mikrosomen-Mutagenitäts-Tests nach Ames. Report No. 8134 (unpublished).

(46) Hüls AG (1984a). Akute dermale Toxizität von Isophorondiisocyanat (IPDI) für Ratten. Report No. 0289 (unpublished).

(47) Hüls AG (1984b). Prüfung der akuten Hautreizwirkung von Isophorondiisocyanat (IPDI). Report No. 0290 (unpublished).

(48) Hüls AG (1984c). Prüfung der akuten Augen- und Schleimhautreizwirkung von Isophorondiisocyanat (IPDI). Report No. 0291 (unpublished).

(49) Hüls AG (1985). Akute dermale Toxizität von Isophorondiisocyanat (IPDI) für Ratten. Report No. 0385 (unpublished).

(50) Hüls AG (1988). Algenwachstumshemmtest nach UBA (Stand Feb. 1984) - Scenedesmus subspicatus, Produkt Isophorondiisocyanat. Report No. AW 145/1+2 (unpublished, 1 p).

(51) Hüls AG (1988). Daphnientest nach DIN 38412 Teil 11, Produkt Isophorondiisocyanat. Report No. D-310a (unpublished, 1 p).

(52) Hüls AG (1989). Product information and unpublished vapour pressure curve "IPDI - isophorone diisocyanate". Edition 43.03.018e/08.89.

(53) Hüls AG (1993a). Determination of the mutagenicity of isophorone diisocyanate (IPDI) in the Ames Salmonella/mammalian microsomes mutagenicity test complying with Directive 84/449/EEC B.14. Report No. AM-84/25 (unpublished).

(54) Hüls AG (1993b). Internal communication concerning ecotoxicity and biodegradation of isophorone diisocyanate, 23.12.1993.

(55) Hüls AG (1994). Internal communication concerning ecotoxicity and biodegradation of isophorone diisocyanate, 26.05.1994.

(56) Hüls AG (1995). Bestimmung der Auswirkungen von Vestanat IPDI auf das Schwimmverhalten von Daphnia magna. Report No. DK-654 (unpublished).

(57) Hüls AG (1996). Bestimmung der akuten Wirkungen von Vestanat IPDI gegenüber Fischen. Report No. FK 1369 (unpublished).

(58) Hüls America Inc. (1990). 4-Hour acute inhalation toxicity study with 3-isocyanatomethyl-3,5,5-trimethylcyclohexylisocyanate in rats with cover letter. NTIS/OTS Microfiche 0530239, Doc 86-910000493.

(59) IBR (International Bio-Research) (1976). Akute Toxizitätsprüfung von "3-Isocyanatomethyl-3.5.5-trimethylcyclohexyl isocyanat" nach oraler Applikation an der Ratte. Report 1 - 4 - 382/1 - 76 (Veba-Chemie AG, unpublished).

(60) IBR (International Bio-Research) (1983). 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat - Prüfung auf sensibilisierende Eigenschaften am Meerschweinchen nach B. Magnusson und A.M. Kligman (gemäß OECD Richtlinien). Report 2-5-120-83 (Hüls AG, unpublished).

(61) IBR International Bio-Research (1978a). Akute Inhalationstoxizität von 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat (IPDI) bei der Ratte. Report No. 1-4-325-77 (Veba-Chemie AG, unpublished).

(62) IBR International Bio-Research (1978b). Akute Inhalationstoxizität von Isophorondiisocyanat "(IPDI)" im Zeitsättigungstest bei der Ratte. Report No. 1-4-79-78 (Veba-Chemie AG, unpublished).

(63) Infracor GmbH (2000). Löslichkeits- und Abbauverhalten von Isophorondiisocyanat (IPDI) in Wasser. Communication Dr. W. Schleich to Degussa AG dated 26 June 2000 (unpublished).

(64) INRS (Institut national de recherche et de sécurité), Paris (1988). Diisocyanate d'isophorone. Fiche Toxicologique 166, 1-4.

(65) Jarand CW, Akapo SO, Swenson LJ and Kelman BJ (2002). Diisocyanate emission from a paint product: A preliminary analysis. Appl. Occup. Environ. Hyg. **17**, 491-494.

(66) Karlsson D, Spanne M, Dalene M and Skarping G (2000). Airborne thermal degradation products of polyurethane coatings in car repair shops. J. Environ. Monit. **2**, 462-469.

(67) Kimmerle G (1968). Isophorondiisocyanat - toxikologische Untersuchungen. Report 908 (unpublished). Bayer AG (Wuppertal).

(68) Kimmerle G (1976). Akute Inhalationstoxizität von Diisocyananaten, polymeren Isocyanaten und Lacksystemen an Ratten. Report No. 6200 (unpublished). Bayer AG (Wuppertal).

(69) Klaus AM (2004). Isophorondiisocyanat (IPDI) - developmental toxicity study in rats after inhalation. Report No. T7072620 (unpublished). Bayer AG (Wuppertal).

(70) Krötlinger F (1994). Isophorondiisocyanat, study for skin irritation/corrosion in rabbits. Report No. 22961 (unpublished). Bayer AG (Wuppertal).

(71) Lachapelle JM and Lachapelle-Ketelaer MJ (1979). Cross-sensitivity between isophorone diamine (IPD) and isophorone diisocyanate (IPDI). Contact Dermatitis **5**, 55.

(72) Lewis RJ (2000) Sax's Dangerous Properties of Industrial Materials. Wiley Interscience Publication, New York, 10th ed., 2145-2146.

(73) Lide DR (2003). CRC handbook of chemistry and physics, 84th edition 2003-2004. Page 3-342, entry 6457. CRC Press, Boca Raton (Fla, USA).

(74) Loffeld A and Foulds IS (2004). Allergic contact dermatitis from N-(cyclohexlthio)phthalimide in a playground fitter. Contact Dermatitis **51**, 212-213.

(75) Militello G, Sasseville D, Ditre C and Brod BA (2004). Allergic contact dermatitis from isocyanates among sculptors. Dermatitis **15**, (3), 150-153.

(76) Mobay Chemical Corporation (1984a). Sensory irritation of isophorone diisocyanate (IPDI) to mice, study number 82-341-01. Report 538. Mobay Chemical Corporation (Metcalf, Stilwell, KS, USA).

(77) Mobay Chemical Corporation (1984b). Sensory irritation with isophorone diisocyanate (IPDI) in rats. Report No. 540. NTIS/OTS Microfiche 0515439, Doc 86-870001280.

(78) Mobay Chemical Corporation (1987a). The evaluation of isophorone diisocyanate for mucous membrane irritation in rabbits. NTIS/OTS Microfiche 0515404, Doc 87-870001245.

(79) Mobay Chemical Corporation (1987b). The evaluation of isophorone diisocyanate for primary skin irritation in rabbits, NTIS/OTS Microfiche 0515403, Doc 86-870001244.

(80) Morel C, Gendre M, Cavigneaux A and Protois JC (1982). Fiche toxicologique No 166: diisocyanate d'isophorone. Cah. Notes Doc. 106, 151-154.

(81) Morel, C. et al., Fiche toxicologique No. 166, Cah. Notes Doc. 106, 151-154 (1982)

(82) Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, and Zeiger E (1986): Salmonella mutagenicity tests: II. results from the testing of 270 chemicals. Environ. Mutagen. Suppl. 8, 1-119.

(83) Pauluhn J (2004a). Analysis of bronchoalveolar-lavage following acute inhalation toxicity in rats (exposure: 1 x 6 hours). Bayer HealthCare AG Report No. AT01428 (unpublished).

(84) Pauluhn J (2004b). Pulmonary irritant potency of polyisocyanate aerosols in rats: comparative assessment of irritant threshold concentrations by bronchoalveolar lavage. J. Appl. Toxicol. **24**, 231-247.

(85) Plitnick LM, Loveless SE, Ladics GS, Holsapple MP, Smialowicz RJ, Woolhiser MR, Anderson PK, Smith C and Selgrade MJK (2005). Cytokine mRNA profiles for isocyanates with known and unknown potential to induce respiratory sensitization. Toxicology **207**, 487-499.

(86) RCC (Research and Consulting Company AG) (1985). 4-Hour acute aerosol inhalation toxicity (LC50) study with 3-isocyanatomethyl 3.5.5 trimethylcyclohexylisocyanat in rats. Report No. 038676 (Hüls AG, unpublished).

(87) RCC Research & Consulting Company Ltd. (1988). 3-Isocyanatomethyl-3.5.5-trimethylcyclohexylisocyanat - 4-hour acute inhalation toxicity study in rats. Report No. 094320 (Hüls AG, unpublished).

(88) Rhodia Operations (2006). Isophorone diisocyanate exposure questionnaire (unpublished).

(89) Rhodia PPMC (2002). Isophorone diisocyanate exposure questionnaire (unpublished).

(90) Rothe A (1976). Zur Frage arbeitsbedingter Hautschädigungen durch Polyurethanchemikalien. Berufsderm. **24**, 7-24.

(91) RTC (Research Toxicology Centre) (2003). IPDI chromosome aberrations in Chinese hamster ovary cells in vitro. Report No. 8148 (unpublished). RTC (Rome).

(92) Sax NI and Lewis RJ (1987) in Hawley's Condensed Chemical Dictionary, 11th ed., 659. Van Nostrand Reinhold Co. (New York).

(93) Schmidt WM (1984). Isophorondiisocyanat (IPDI) - Untersuchungen zur sensibilisierenden Wirkung an der Meerschweinchenhaut (modif. "Maximierungstest" mit nur intrakutaner Induktion). Bayer AG (Wuppertal) Report No. 13041 (unpublished).

(94) Schreiber G (1981a). Data of FhG, Bericht über die Prüfung von Isophorondiisocyanat auf primäre Hautreizwirkung. Communication of April 2, 1981 (at the request of Bayer AG).

(95) Schreiber G (1981b). Data of FhG, Bericht über die Prüfung von Isophorondiisocyanat auf Schleimhautreizwirkung. Communication of April 2, 1981 (at the request of Bayer AG).

(96) Society of Toxicology, Technical Committee of the Inhalation Specialty Section (1992). Recommendations for the conduct of acute inhalation limit tests. Fund. Appl. Toxicol. **18**, 321-327.

(97) SPIN (2006). Substances in Preparations in Nordic Countries. CAS 4098-71-9 www.spin2000.net/spin.html.

(98) Stern ML, Brown TA, Brown RD, and Munson AE (1989). Contact hypersensitivity response to isophorone diisocyanate in mice. Drug Chem. Toxicol. **12,** 287-296.

(99) Swedish Product Register (2002). Communication to BUA.

(100) Swiss Product Register (2001). Communication to BUA.

(101) Séguin P, Allard A, Cartier A and Malo JL (1987). Prevalence of occupational asthma in spray painters exposed to several types of isocyanates, including polymethylene polyphenylisocyanate. J. Occup. Med. **29**, 340-344.

(102) Thyssen (1976). Bestimmung der akuten Toxizität (LD50), Substanz 3-Isocyanatomethyl-3,5,5-trimethylcyclohexylisocyanat (IPDI). Bayer AG short report, July 23, 1976 (unpublished).

(103) Tinnerberg H, Skarping G, Dalene M, and Hagmar L (1995). Test chamber exposure of humans to 1,6-hexamethylene diisocyanate and isophorone diisocyanate. Int. Arch. Occup. Environ. Health **67**, 367-374.

(104) Tyrer FH (1979). Hazards of spraying with two-pack paints containing isocyanates. J. Soc. Occup. Med. **29**, 22-24.

(105) UBA (Umweltbundesamt) (2006). Katalog wassergefährdender Stoffe. Database search for CAS-Nr. 4098-71-9, state of 24 March 2006.

(106) Union Carbide Corp. (1987). Isophorone diisocyanate - 1-Isocyanato-3-isocyanatomethyl-3,5,5-trimethylcyclohexane - range finding toxicity studies. NTIS/OTS Microfiche 0515604, Doc 86-870001442.

(107) Vohr HW (1993). Isophorondiisocyanat - Untersuchungen auf hautsensibilisierende Wirkung bei Meerschweinchen (Maximierungstest nach Magnusson und Kligman). Bayer AG (Wuppertal) Report No. 22645 (unpublished).

(108) Wass U and Belin L (1990). An in vitro method for predicting sensitizing properties of inhaled chemicals. Scand. J. Work Environ. Health **16**, 208-214.

(109) Wederbrand KS and Potter DW (1993). Assessment of serum IgE concentrations in BALB/C mice after dermal exposure to chemicals. Toxicologist **13**, 42.

(110) Ziegler V and Süss E (1985). The TINA test. Curr. Probl. Derm. **14**, 172-192.

(111) Zissu D, Binet S and Limasset JC (1998). Cutaneous sensitization to some polyisocyanate prepolymers in guinea pigs. Contact Dermatitis **39**, 248-251.