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:
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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:
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   • 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

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* BUA (GDCh-Beratergremium fuer Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)
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/m³ 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 LC₅₀-values (4 h, rat) of approximately 40 mg/m³ and 31 mg/m³, 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/m³, 1 x 6 h). The dermal LD₅₀ 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 LD₅₀-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/m³ 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/m³; 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/m³ (histopathological changes in nasal cavity and larynx). At 4.1 mg/m³ 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/m³.

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/m³. Tests 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/m³, and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m³ it seems quite unlikely that this substance might have critical effects on testsis 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/m³. A dose of 4.536 mg/m³ 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/m³ 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/m³. The NOAEL for both maternal toxicity and developmental toxicity was 0.929 mg/m³.

**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/cm³ 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 m³/mol.
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLICYCLOHEXYL ISOcyanate

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 m³/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 KOW of 0.99 which indicates a low bioaccumulation potential.

For bacteria (activated sludge of a predominantly domestic sewage) an EC₅₀ (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 PNECₐqua 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): LC₅₀ (96h) = 110 mg/l;
Daphnia magna (Directive 92/69/EEC, static): EC₅₀ (48 h) = 23 mg/l;
Desmodesmus subspicatus (Directive 88/302/EEC): E₉₅₀ (72 h) > 50 mg/l; E₉₅₁₀ = 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): E₉₅₁₀ (72 h) = 11 mg/l; E₉₅₁₀ = 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 PNECₐqua 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
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.
SIDS Initial Assessment Report

1 IDENTIFY

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_{2}O_{2}

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

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>liquid</td>
<td>Sax and Lewis (1987)</td>
</tr>
<tr>
<td>Melting point</td>
<td>-60°C</td>
<td>Sax and Lewis (1987)</td>
</tr>
<tr>
<td>Density</td>
<td>1.058 g/cm³ (20°C)</td>
<td>Auer (1989), INRS (1988)</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>0.0635 Pa (20°C)</td>
<td>Bayer AG (1994)</td>
</tr>
<tr>
<td>Water solubility</td>
<td>ca. 15 mg/l (23°C)</td>
<td>Infracor GmbH (2000)</td>
</tr>
<tr>
<td>Partition coefficient n-octanol/water (log KOW)</td>
<td>4.75 (calc.) (rapid hydrolysis)</td>
<td>Degussa AG (2006)</td>
</tr>
<tr>
<td>Henry’s law constant</td>
<td>0.941 Pa m³/mol (calc.)</td>
<td>Degussa AG (2006)</td>
</tr>
<tr>
<td>Soil sorption constant (log Koc)</td>
<td>4.562 (calc.)</td>
<td>Degussa AG (2006)</td>
</tr>
</tbody>
</table>

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 KOW 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:

\[
\text{NH}_2\text{-C}_{10}\text{H}_{18}\text{-NH}_2 + 2 \text{ COCl}_2 \rightarrow \text{OCN-C}_{10}\text{H}_{18}\text{-NCO} + 4 \text{ HCl}
\]

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):

\[
\text{NH}_2\text{-C}_{10}\text{H}_{18}\text{-NH}_2 + 2 \text{ NH}_2\text{CONH}_2 + 2 \text{ R-OH} \rightarrow \text{R-O-CO-NH-C}_{10}\text{H}_{18}\text{-NH-CO-OR} + 4 \text{ NH}_3
\]

\[
\text{R-O-CO-NH-C}_{10}\text{H}_{18}\text{-NH-CO-OR} \rightarrow \text{OCN-C}_{10}\text{H}_{18}\text{-NCO} + 2 \text{ R-OH}
\]
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 worldwide, 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 $8.8 \times 10^{-12} \text{ cm}^3/(\text{molecule x s})$ corresponding to a half-life of 1.8 days based on a tropospheric OH radical concentration of $5 \times 10^5$ 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:

$$\text{OCN-C}_{10}\text{H}_{18}\text{-NCO} + 2 \text{H}_2\text{O} \rightarrow \text{HOOCNH-C}_{10}\text{H}_{18}\text{-NHCOOH}$$

$$\text{HOOCNH-C}_{10}\text{H}_{18}\text{-NHCOOH} \rightarrow \text{NH}_2\text{-C}_{10}\text{H}_{18}\text{-NH}_2 + 2 \text{CO}_2$$
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/m³ (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/m³ (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/m³) 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/m³) (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/m³.

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/m³. 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 m³ exposure chamber to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate concentrations of 0.0121, 0.0177, and 0.0507 mg/m³ 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/m³ 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 LC₅₀ determination. Only two of the available inhalation LC₅₀ 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/m³ (analytical: 2.09; 7.5; 26 mg/m³). 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 ≥ 8 mg/m³. 2/18 rats died at 25 mg/m³. At 8 mg/m³ 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/m³ (6.2 and 9.1°C below control, respectively). Lung weights were increased only in the high dose group (25 mg/m³) 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 LC₅₀ 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/m³. 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/m³ 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 ≥ 73.8 mg/m³ 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 LC₅₀ (4 h) stated in this study (Bayer AG, 1995 a, b, c) is approximately 40 mg/m⁵ for both sexes.

In the OECD TG 403 study of RCC (1988), a four-hour LC₅₀ of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (purity > 99%) to male and female Wistar rats of 31 mg/m³ was determined. The no-observed-effect level was less than 18 mg/m³. 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/m³. 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 LD₅₀ 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 irritant” (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/m³ (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/m³ (3 h) (Mobay Chemical Corporation, 1984 a) or 6.0 mg/m³ (3 min), 4.0 mg/m³ (10 min) and 3.0 mg/m³ (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/m³ the odor was just perceptible; at 0.64 mg/m³ slight irritation of the mucous membranes of the eyes and nose were observed; at 1.37 mg/m³ 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/m³ 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 hyperresponsive 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 dermatitis 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 pneumopathies.
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/m³ (corresponding to analytical means of 0.24; 1.05; 4.1 mg/m³). Exposure was dynamic directed-flow nose-only and vapor saturation was reported to be about 4 – 11 mg/m³ 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/m³ (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/m³ 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/m³ (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/m³; 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/m³ (histopathological changes in nasal cavity and larynx). At 4.1 mg/m³ 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/m³.

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 β-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/m³. 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/m³. Testes and ovary weights were also not affected. The NOAEL for general toxicity is 0.24 mg/m³. 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/m³ despite the fact that already at 1.05 mg/m³ 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/m³ and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m³ 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/m³ (0.206, 0.929, 4.536 mg/m³ 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/m³ 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/m³, 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/m³ 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/m³. Reduction of fetal weight at the 4 mg/m³ 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/m³ 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/m³, while slightly retarded descensus testis could not be completely excluded at the maternally toxic 4 mg/m³ exposure level. 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. All signs of developmental toxicity observed at the 4 mg/m³ 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/m³ (nominal; analytical: 0.929 mg/m³) (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/m³. 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/m³; 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/m³ (histopathological changes in nasal cavity and larynx). At 4.1 mg/m³ 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/m³.

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was not genotoxic in bacterial systems in vitro. 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/m³. 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/m³, and as the NOAEL for repeated dose toxicity is set at 0.24 mg/m³ 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/m³. A dose of 4.536 mg/m³ 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/m³ 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/m³. The NOAEL for both maternal toxicity and developmental toxicity was 0.929 mg/m³.
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): \( \text{LC}_{50} \ (96 \text{ h}): > 208 \text{ mg/l} \) (Hüls AG, 1996)

*Danio rerio* (Directive 92/69/EEC, static): \( \text{LC}_{50} \ (96 \text{ h}): > 72 \text{ mg/l} \) (Bayer AG, 2000)

*Daphnia magna* (Directive 92/69/EEC, static): \( \text{EC}_{50} \ (48 \text{ h}): 27 \text{ mg/l} \) (Hüls AG, 1995)

*Daphnia magna* (Directive 92/69/EEC, static): \( \text{EC}_{50} \ (48 \text{ h}): 35 \text{ mg/l} \) (Bayer AG, 2000; Bayer Industry Services, 2006)
OECD 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

*Chaetogammarus marinus* (other method, semi-static):  EC$_{50}$ (96 h): 4 mg/l (Adema, 1982)
*Desmodesmus subspicatus* (Directive 92/69/EEC, static):  E$_{C50}$ and E$_{B50}$ (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$_{C50}$ (72 h) > 50 mg/l;
\[ E_{B50} = 37 \text{ mg/l.} \]

**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$_{C10}$ (72 h) = 11 mg/l;  E$_{B10}$ = 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/cm³ at 20°C, and a vapor pressure of 0.064 Pa at 20°C. The calculated log Kᵪ₂ 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 Kᵪ₂ 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 Kᵪ₂ of 4.562 indicates very high adsorption to the organic phase of soils and sediments. For the hydrolysis product a log Kᵪ₂ of 2.532 corresponds to a moderate potential for geoaccumulation. An estimated Henry’s law constant of 0.000446 Pa m³/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 m³/mol indicates low volatilization 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 Kᵪ₂ of 0.99 which indicates a low bioaccumulation potential.

For bacteria (activated sludge of a predominantly domestic sewage) an EC₅₀ (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<sub>aqua</sub> 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): \( E_{95} C_{50} \) (72 h) > 50 mg/l; \( E_{65} C_{50} \) = 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): \( E_{10} C_{10} \) (72 h) = 11 mg/l; \( E_{6} C_{10} \) = 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<sub>aqua</sub> 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.


Danish Product Register (2002). Communication to BUA.


Swedish Product Register (2002). Communication to BUA.

Swiss Product Register (2001). Communication to BUA.


1. GENERAL INFORMATION

**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: C\textsubscript{12}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}

**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

**Contact person**
- Dr. Jochen Brück

**Date**
- 01.01.2006

**Street**
- Building E 1-2

**Town**
- 51368 Leverkusen

**Country**
- Germany

**Phone**
- +49 214 30-71970

**Telefax**
- +49 214 30-52973

**Telex**
- 

**Cedex**
- 

---

35
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

1. GENERAL INFORMATION

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<tr>
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02.06.2006

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<tr>
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<tr>
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1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

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1.0.3 IDENTIFY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

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

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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

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

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

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

Isophorone diisocyanate

IPDI
1. GENERAL INFORMATION
ID: 4098-71-9
DATE: 16-APR-2007

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-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

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12.06.2006

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12.06.2006
1. GENERAL INFORMATION

OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

ID: 4098-71-9
DATE: 16-APR-2007

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)

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

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: 

40
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."

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 (February 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)
1. GENERAL INFORMATION

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 light-stable 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 Type: Synthesis
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 Type: Synthesis
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)

12.06.2006 (31) (32)

Origin of substance Type: Synthesis
Method: Manufacturing of isophorone diisocyanate by phosgenation of isophorone
1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

<table>
<thead>
<tr>
<th>Type of limit</th>
<th>MAK (DE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limit value</td>
<td>.046 mg/m³</td>
</tr>
<tr>
<td>Short term exposure limit value</td>
<td>1</td>
</tr>
</tbody>
</table>

Remark : 0.005 ppm

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

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
1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

<table>
<thead>
<tr>
<th>Type</th>
<th>thermal breakdown products</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS-No</td>
<td>74-90-8</td>
</tr>
<tr>
<td>EC-No</td>
<td>200-821-6</td>
</tr>
<tr>
<td>EINECS-Name</td>
<td>hydrogen cyanide</td>
</tr>
<tr>
<td>IUCLID Chapter</td>
<td></td>
</tr>
</tbody>
</table>

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

**Source of exposure**: Human: exposure by production

**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

**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

**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

**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.

**Source of exposure**
- Environment: exposure from production

**Exposure to the**
- Substance

**Remark**
- Release from production

**Result**
- Release to the atmosphere is below 25 kg/year.
- Release to water or other environmental media is zero.

13.06.2006

Source of exposure
- Environment: exposure from production

Exposure to the
- Substance

Remark
- Release from production

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

Source of exposure
- Human: exposure through intended use

Exposure to the
- Substance

Remark
- 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 virtually 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

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.
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

1. GENERAL INFORMATION  ID: 4098-71-9

DATE: 16-APR-2007

<table>
<thead>
<tr>
<th>Type of search</th>
<th>External</th>
</tr>
</thead>
<tbody>
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<td>Chapters covered</td>
<td>3, 4</td>
</tr>
<tr>
<td>Date of search</td>
<td>31.03.2006</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Type of search</th>
<th>Internal and External</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapters covered</td>
<td>5</td>
</tr>
<tr>
<td>Date of search</td>
<td>26.04.2006</td>
</tr>
</tbody>
</table>

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

13.06.2006

1.13  REVIEWS
## 2. PHYSICO-CHEMICAL DATA

### 2.1 MELTING POINT

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Decomposition</th>
<th>Sublimation</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
<th>Reliability</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>-60 °C</td>
<td>no, at</td>
<td>no</td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td>(2) valid with restrictions</td>
<td>17.07.2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>°C</td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td>Data from peer reviewed handbook</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>-60 °C</td>
<td>no, at</td>
<td>no</td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td>(2) valid with restrictions</td>
<td>17.07.2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>°C</td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td>Data from handbook or collection of data</td>
<td>(1) (7) (43) (64) (80)</td>
</tr>
</tbody>
</table>

### 2.2 BOILING POINT

<table>
<thead>
<tr>
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<th>Value</th>
<th>Decomposition</th>
<th>Sublimation</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
<th>Reliability</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>310 °C at 1013 hPa</td>
<td>yes</td>
<td></td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td>(2) valid with restrictions</td>
<td>17.07.2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td>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</td>
<td>(7) (64)</td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>310 °C at 1000 hPa</td>
<td>yes</td>
<td></td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>217 °C at 133 hPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 2. PHYSICO-CHEMICAL DATA

**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

<table>
<thead>
<tr>
<th>Value</th>
<th>Decomposition</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
<th>Reliability</th>
<th>Remark</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 158 °C at 13 hPa</td>
<td>no</td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td>(2) valid with restrictions</td>
<td>Data from handbook or collection of data</td>
<td>13.06.2006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Value</th>
<th>Decomposition</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
<th>Reliability</th>
<th>Remark</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 153 °C</td>
<td>no</td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td>(2) valid with restrictions</td>
<td>Data from handbook or collection of data</td>
<td>13.06.2006</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Type</th>
<th>Value</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
<th>Reliability</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>density</td>
<td>= 1.056 g/cm³ at °C</td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td>(2) valid with restrictions</td>
<td>17.07.2006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Value</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
<th>Reliability</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>density</td>
<td>= 1.056 g/cm³ at °C</td>
<td>other: no data</td>
<td></td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate, purity not specified</td>
<td>(2) valid with restrictions</td>
<td>17.07.2006</td>
</tr>
</tbody>
</table>
2. PHYSICO-CHEMICAL DATA

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

<table>
<thead>
<tr>
<th>Value</th>
<th>Decomposition</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000635 hPa at 20 °C</td>
<td>no</td>
<td>other (measured): Comparable to OECD Guideline 104 (1981) - vapor pressure balance</td>
<td>1994</td>
<td>yes</td>
<td>other TS: Isophorone diisocyanate of Bayer AG, coded as DEA 232-I; purity not reported</td>
</tr>
</tbody>
</table>

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
- 0.000215 hPa at 12.9 °C; regression: 0.000264 hPa
- 0.000278 hPa at 12.8 °C; regression: 0.000261 hPa
- 0.000383 hPa at 12.7 °C; regression: 0.000258 hPa
- 0.000479 hPa at 13.0 °C; regression: 0.000268 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
Resulting Antoine regression equation:

\[ VP \ [hPa] = 10^{(31.84 - 23124/(T+639.99)} \]

\( T \) = temperature \(^\circ\)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 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

Value:

\( \text{hPa at 20 °C} \) = 0.00093 hPa

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

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Vapor Pressure [hPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 °C</td>
<td>0.000089</td>
</tr>
<tr>
<td>10 °C</td>
<td>0.000300</td>
</tr>
<tr>
<td>20 °C</td>
<td>0.00093</td>
</tr>
</tbody>
</table>
### 2. PHYSICO-CHEMICAL DATA

**OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE**

**ID:** 4098-71-9  
**DATE:** 16-APR-2007

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Vapor Pressure (hPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>0.0026</td>
</tr>
<tr>
<td>40</td>
<td>0.0069</td>
</tr>
<tr>
<td>50</td>
<td>0.017</td>
</tr>
<tr>
<td>60</td>
<td>0.039</td>
</tr>
<tr>
<td>70</td>
<td>0.085</td>
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<td>80</td>
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<td>90</td>
<td>0.35</td>
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<tr>
<td>100</td>
<td>0.66</td>
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<tr>
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<td>120</td>
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<td>200</td>
<td>67.6</td>
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<td>94</td>
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<tr>
<td>220</td>
<td>129</td>
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<tr>
<td>230</td>
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<td>240</td>
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<td>260</td>
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<td>270</td>
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<td>290</td>
<td>795.3</td>
</tr>
<tr>
<td>300</td>
<td>987.5</td>
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</tbody>
</table>

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

**17.07.2006**

- **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**

- **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**

- **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

**Value:**

**Decomposition:**

**Method:**

**Year:**

**GLP:**

**Test substance:** other TS: Isophorone diisocyanate, purity not specified
### 2. PHYSICO-CHEMICAL DATA

#### 2.5 PARTITION COEFFICIENT

| Reliability | (4) not assignable  
|             | Manufacturer/producer data without proof |
| Value       | 0.00055 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 |
| Value       | 0.009 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 |
| Value       | 0.0009 hPa at 50 °C |
| Decomposition | no |
| Method      | other (measured): no data |
| Year        | |
| GLP         | no data |
| Test substance | other TS: Isophorone diisocyanate, purity not specified |

| 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 |

#### 2.6.1 SOLUBILITY IN DIFFERENT MEDIA

| Solubility in | Water |
| Value         | ca. 15 mg/l at 23 °C |
2. PHYSICO-CHEMICAL DATA

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>value</td>
</tr>
<tr>
<td></td>
<td>concentration at °C</td>
</tr>
<tr>
<td>Temperature effects</td>
<td>Examine different pol.</td>
</tr>
<tr>
<td>pKa</td>
<td>at 25 °C</td>
</tr>
<tr>
<td>Description</td>
<td>of low solubility</td>
</tr>
<tr>
<td>Stable</td>
<td>no</td>
</tr>
<tr>
<td>Deg. product</td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>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</td>
</tr>
<tr>
<td>Year</td>
<td>2000</td>
</tr>
<tr>
<td>GLP</td>
<td>no</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate of Degussa AG, purity 99.8 %</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Solubility in</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH value</td>
<td>ca. 6.052 mg/l at 25 °C</td>
</tr>
<tr>
<td>Temperature effects</td>
<td>Examine different pol.</td>
</tr>
<tr>
<td>pKa</td>
<td>at 25 °C</td>
</tr>
<tr>
<td>Description</td>
<td>of very low solubility</td>
</tr>
<tr>
<td>Stable</td>
<td>no</td>
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<tr>
<td>Deg. product</td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>other: SRC WSKOW v1.40 Computer Program, integrated in U.S. EPA's EPI program Vers. 3.10</td>
</tr>
<tr>
<td>Year</td>
<td>2002</td>
</tr>
<tr>
<td>GLP</td>
<td></td>
</tr>
<tr>
<td>Test substance</td>
<td></td>
</tr>
</tbody>
</table>

**Reliability**
(2) valid with restrictions
Accepted calculation method

<table>
<thead>
<tr>
<th>Solubility in</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>at °C</td>
</tr>
</tbody>
</table>
2. PHYSICO-CHEMICAL DATA

- **pH value**: at °C
- **Temperature effects**: Examine different pol.
- **pKa**: at 25 °C
- **Description**: of very low solubility
- **Stable**: no
- **Deg. product**: other: no data
- **Method**: no
- **Year**: other TS: Isophorone diisocyanate, purity not specified
- **GLP**: other TS: Isophorone diisocyanate, purity not specified
- **Remark**: Vigorous exothermal reaction with water, formation of carbon dioxide and isocyanate vapors
- **Reliability**: (3) invalid

### Solubility in Organic Solvents
- **pH value**: 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**: other: no data
- **Deg. product**: other: no data
- **Method**: no
- **Year**: other TS: Isophorone diisocyanate, purity not specified
- **GLP**: other TS: Isophorone diisocyanate, purity not specified
- **Reliability**: (2) valid with restrictions

### SURFACE TENSION

#### 2.6.2 SURFACE TENSION

- **Value**: 155 °C
- **Type**: other: no data
- **Method**: other
- **Year**: no
- **GLP**: no
- **Test substance**: other TS: Isophorone diisocyanate, purity not specified
- **Reliability**: (2) valid with restrictions

#### 2.7 FLASH POINT

- **Value**: 155 °C
- **Type**: closed cup
- **Method**: other
- **Year**: no
- **GLP**: no
- **Test substance**: other TS: Isophorone diisocyanate, purity not specified
- **Reliability**: (2) valid with restrictions

17.07.2006

*Data from handbook or collection of data (not peer reviewed) in obvious conflict with observations in other water behavior and ecotoxicity studies*
2. PHYSICO-CHEMICAL DATA

<table>
<thead>
<tr>
<th>Test type</th>
<th>Test procedure</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
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<td>2.8 AUTO FLAMMABILITY</td>
<td></td>
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<td>Year</td>
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<tr>
<td>Method</td>
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<td>Data from handbook or collection of data</td>
</tr>
<tr>
<td>Year</td>
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</tr>
<tr>
<td>GLP</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test substance</td>
<td></td>
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</table>
### 2. PHYSICO-CHEMICAL DATA

**ID:** 4098-71-9  
**DATE:** 16-APR-2007

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<th>Property</th>
<th>Details</th>
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<tbody>
<tr>
<td>Value</td>
<td>13 - 15 mPa s (dynamic) at 23 °C</td>
</tr>
<tr>
<td>Method</td>
<td>other: DIN EN ISO 3219</td>
</tr>
<tr>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>GLP</td>
<td>no data</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate of Hüls AG, minimum purity 99 %</td>
</tr>
<tr>
<td>Reliability</td>
<td>(4) not assignable</td>
</tr>
<tr>
<td></td>
<td>Manufacturer data without proof</td>
</tr>
<tr>
<td>17.07.2006</td>
<td></td>
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</table>

**2.14 ADDITIONAL REMARKS**

<table>
<thead>
<tr>
<th>Memo</th>
<th>Index of refraction</th>
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</thead>
<tbody>
<tr>
<td>Result</td>
<td>Isophorone diisocyanate of Hüls AG, minimum purity 99 %, Nd at 25 °C:</td>
</tr>
<tr>
<td></td>
<td>1.483</td>
</tr>
<tr>
<td>Reliability</td>
<td>(4) not assignable</td>
</tr>
<tr>
<td></td>
<td>Manufacturer data without proof</td>
</tr>
<tr>
<td>17.07.2006</td>
<td></td>
</tr>
</tbody>
</table>
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. 0.000000000088248 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

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.

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: 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.

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.
3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

<table>
<thead>
<tr>
<th>Media</th>
<th>air - biota - sediment(s) - soil - water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Calculation according Mackay, Level I</td>
</tr>
<tr>
<td>Year</td>
<td>2004</td>
</tr>
</tbody>
</table>

**Remark**: Rapid hydrolysis makes attaining equilibrium in the environment impossible.

**Result**

<table>
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<tr>
<th>Media</th>
<th>%</th>
</tr>
</thead>
<tbody>
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<td>3.2113</td>
</tr>
<tr>
<td>Water</td>
<td>9.7034</td>
</tr>
<tr>
<td>Soil</td>
<td>43.1462</td>
</tr>
<tr>
<td>Sediment</td>
<td>43.6256</td>
</tr>
<tr>
<td>Susp. Sediment</td>
<td>0.2802</td>
</tr>
<tr>
<td>Fish</td>
<td>0.0273</td>
</tr>
<tr>
<td>Aerosol</td>
<td>0.0061</td>
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</table>

**Test condition**

<table>
<thead>
<tr>
<th>Data used:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight: 222.29 g/mol</td>
</tr>
<tr>
<td>log Pow: 4.75</td>
</tr>
<tr>
<td>Vapour pressure: 0.0635 Pa</td>
</tr>
<tr>
<td>Water solubility: 0.015 g/l</td>
</tr>
<tr>
<td>Melting point: -60 degree C</td>
</tr>
<tr>
<td>Temperature: 20 degree C</td>
</tr>
</tbody>
</table>

Volumes, densities, and organic carbon / fat concentration:

<table>
<thead>
<tr>
<th>Media</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>6 000 000 000 m³, 1.206 kg/m³</td>
</tr>
<tr>
<td>Water</td>
<td>7 000 000 m³, 1000 kg/m³</td>
</tr>
<tr>
<td>Soil</td>
<td>45 000 m³, 1500 kg/m³, 2 % OC</td>
</tr>
<tr>
<td>Sediment</td>
<td>21 000 m³, 1300 kg/m³, 5 % OC</td>
</tr>
<tr>
<td>Susp. sediment</td>
<td>35 m³, 1500 kg/m³, 16.7 % OC</td>
</tr>
<tr>
<td>Fish</td>
<td>7 m³, 1000 kg/m³, 5 % fat</td>
</tr>
<tr>
<td>Aerosol</td>
<td>0.12 m³, 1500 kg/m³</td>
</tr>
</tbody>
</table>

**Reliability**: (2) valid with restrictions

Accepted calculation method

14.06.2006

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 |

**Reliability**: (2) valid with restrictions

Accepted calculation method

14.06.2006
3. ENVIRONMENTAL FATE AND PATHWAYS

### 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

14.06.2006

### 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

14.06.2006

### 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
- Directive 92/69/EEC, C.4-D

#### Method
- Yes

#### 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
3. ENVIRONMENTAL FATE AND PATHWAYS

ID: 4098-71-9
DATE: 16-APR-2007

- 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:
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
### 3. ENVIRONMENTAL FATE AND PATHWAYS

**ID:** 4098-71-9  
**DATE:** 16-APR-2007

| **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 |
| **19.06.2006** | Secondary quotation |

### 3.8 ADDITIONAL REMARKS
4. ECOTOXICITY

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

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
4. ECOTOXICITY

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>static</td>
</tr>
<tr>
<td>Species</td>
<td>Daphnia magna (Crustacea)</td>
</tr>
<tr>
<td>Exposure period</td>
<td>48 hour(s)</td>
</tr>
<tr>
<td>Unit</td>
<td>mg/l</td>
</tr>
<tr>
<td>EC0</td>
<td>= 18</td>
</tr>
<tr>
<td>EC50</td>
<td>= 27</td>
</tr>
<tr>
<td>EC100</td>
<td>&gt; 65</td>
</tr>
<tr>
<td>Limit Test</td>
<td>no</td>
</tr>
<tr>
<td>Analytical monitoring</td>
<td>yes</td>
</tr>
<tr>
<td>Year</td>
<td>1995</td>
</tr>
<tr>
<td>GLP</td>
<td>yes</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate of Hüls AG (VESTANAT IPDI), purity 99.9 % (gas chromatogram area), sample No. 1486/940804, ID No. 0637/81645</td>
</tr>
</tbody>
</table>

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:
  CaCl2 x 2 H2O: 294 mg/l
  MgSO4 x 7 H2O: 123 mg/l
  NaHCO3: 63 mg/l
  KCl: 5.5 mg/l
- Ca/Mg ratio: 4:1
- Na/K ratio: 10:1
- 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
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

- 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

- 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
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

4. ECOTOXICITY  ID: 4098-71-9

DATE: 16-APR-2007

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

19.06.2006

<table>
<thead>
<tr>
<th>Type</th>
<th>semistatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>other: Chaetogammarus marinus (Crustacea, marine)</td>
</tr>
<tr>
<td>Exposure period</td>
<td>96 hour(s)</td>
</tr>
<tr>
<td>Unit</td>
<td>mg/l</td>
</tr>
<tr>
<td>NOEC</td>
<td>0.56</td>
</tr>
<tr>
<td>EC50</td>
<td>4.0</td>
</tr>
<tr>
<td>Limit Test</td>
<td>no</td>
</tr>
<tr>
<td>Analytical monitoring</td>
<td>no</td>
</tr>
<tr>
<td>Method</td>
<td>other: see Reference / Test Conditions</td>
</tr>
<tr>
<td>Year</td>
<td>1980</td>
</tr>
<tr>
<td>GLP</td>
<td>no data</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate of Fluka AG, &quot;pract.&quot; grade, no data on purity</td>
</tr>
</tbody>
</table>

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

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

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
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:
- 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: other: German Umweltbundesamt draft procedure (1984)
Method: Year: 1988
GLP: no
Test substance: other TS: Isophorone disocyanate, 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:

- 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

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
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:
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
### 4. ECOTOXICITY

**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**

<table>
<thead>
<tr>
<th>Date</th>
<th>(14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.06.2006</td>
<td></td>
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<tr>
<td>21.06.2006</td>
<td>(37) (54)</td>
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#### 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

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

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: Winkelmman, 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

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

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Value</th>
<th>Species</th>
<th>Strain</th>
<th>Number of animals</th>
<th>Vehicle</th>
<th>Doses</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Value</td>
<td>Species</td>
<td>Strain</td>
<td>Number of animals</td>
<td>Vehicle</td>
<td>Doses</td>
<td>Method</td>
<td>Year</td>
<td>GLP</td>
<td>Test substance</td>
</tr>
<tr>
<td>LD50</td>
<td>&gt; 2645 mg/kg bw</td>
<td>mouse</td>
<td>other: CF1</td>
<td>15</td>
<td>other: Oil, not specified</td>
<td>1058; 2645 mg/kg bw</td>
<td>other: Bayer AG</td>
<td>1968</td>
<td>no</td>
<td>other TS: Isophorone diisocyanate, &quot;technically pure&quot;</td>
</tr>
<tr>
<td>LD50</td>
<td>= 1185 mg/kg bw</td>
<td>rat</td>
<td>Wistar</td>
<td>5</td>
<td>other: no vehicle</td>
<td>2.116; 1.058; 0.529 mg/kg bw</td>
<td>other: &quot;Standard&quot;</td>
<td>1967</td>
<td>no</td>
<td>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</td>
</tr>
</tbody>
</table>

**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

**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
5. TOXICITY

- 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**
- 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

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)
**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:
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

5. TOXICITY  ID: 4098-71-9
DATE: 16-APR-2007

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)
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOXYANATE

5. TOXICITY

DATE: 16-APR-2007

ID: 4098-71-9

- 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

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

**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

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)
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 viscus 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
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+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:

- 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

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:
- RD50: 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

14.06.2006
Study well documented, meets generally accepted scientific principles, acceptable for assessment
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

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
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

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ADMINISTRATION:
- Controls: pre-exposure respiration rate
- 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
- 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

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)
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

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

**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/m³
    - 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.

---

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

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**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.

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

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<td>8 hour(s)</td>
</tr>
<tr>
<td>Method</td>
<td>other: see Method and Test Condition</td>
</tr>
<tr>
<td>Year</td>
<td>1967</td>
</tr>
<tr>
<td>GLP</td>
<td>no</td>
</tr>
<tr>
<td>Test substance</td>
<td>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</td>
</tr>
</tbody>
</table>

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:
- 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.
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:
- 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)
### Method
- Draft version for Directive 84/449/EEC, B.2

### Year
- 1978

### GLP
- no

### Test substance
- 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

### 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
- 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.
5.1.3 ACUTE DERMAL TOXICITY

<table>
<thead>
<tr>
<th>Type</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>&gt; 7000 mg/kg bw</td>
</tr>
<tr>
<td>Species</td>
<td>rat</td>
</tr>
<tr>
<td>Strain</td>
<td>Wistar</td>
</tr>
<tr>
<td>Sex</td>
<td>male/female</td>
</tr>
<tr>
<td>Number of animals</td>
<td>10</td>
</tr>
<tr>
<td>Vehicle</td>
<td>other: no vehicle</td>
</tr>
<tr>
<td>Doses</td>
<td>7000 mg/kg bw</td>
</tr>
<tr>
<td>Year</td>
<td>1985</td>
</tr>
<tr>
<td>GLP</td>
<td>no</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate of Hül's AG, purity &gt; 99 %</td>
</tr>
</tbody>
</table>

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

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.
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

5. TOXICITY  
ID: 4098-71-9  
DATE: 16-APR-2007

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

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

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:
5. TOXICITY

ID: 4098-71-9

DATE: 16-APR-2007

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Species</strong></td>
<td>rabbit</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td>undiluted</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Occlusive</td>
</tr>
<tr>
<td><strong>Exposure time</strong></td>
<td>4 hour(s)</td>
</tr>
<tr>
<td><strong>Number of animals</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Vehicle</strong></td>
<td>other: no vehicle</td>
</tr>
<tr>
<td><strong>PDII</strong></td>
<td>6.87</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>corrosive</td>
</tr>
<tr>
<td><strong>Classification</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>other: OECD Guideline 404 (1981)</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td>1984</td>
</tr>
<tr>
<td><strong>GLP</strong></td>
<td>no</td>
</tr>
<tr>
<td><strong>Test substance</strong></td>
<td>other TS: Isophorone diisocyanate, purity &gt; 99%</td>
</tr>
</tbody>
</table>

**Result**

- 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

**Administrative/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

---

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure time: 4 hour(s)
Number of animals: 1
Vehicle: other: no vehicle
PDII: 4.5
Result: corrosive
Year: 1994
GLP: yes
Test substance: other TS: Isophorone diisocyanate of Bayer AG, Leverkusen, Batch/lot no. 1.5 / 3.-20, Purity > 99 %

Result

- Erythema: 2.7/4.0
- Edema: 1.7/4.0

**Other Effects:** On the exposed skin strongly 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

**Species**
- rabbit

**Concentration**
- undiluted

**Exposure**
- Occlusive

**Exposure time**
- 30 minute(s)

**Number of animals**
- 2

**Vehicle**
- other: cellulose

**PDII**
- 3.71

**Result**
- corrosive

**Classification**
- other: See Test Conditions

**Year**
- 1968

**GLP**
- no

**Test substance**
- other TS: Isophorone diisocyanate, "technically pure"

---

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

**Species**
- rabbit

**Concentration**
- undiluted

**Exposure**
- Occlusive

**Exposure time**
- 4 hour(s)

**Number of animals**
- 6

**Vehicle**
- other: cellulose

**PDII**
- 3.71

**Result**
- corrosive

**Classification**
- other: See Test Conditions
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

5. TOXICITY

<table>
<thead>
<tr>
<th>Method</th>
<th>OECD Guide-line 404 &quot;Acute Dermal Irritation/Corrosion&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>1981</td>
</tr>
<tr>
<td>GLP</td>
<td>no</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate, no data on purity</td>
</tr>
<tr>
<td>Remark</td>
<td>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.</td>
</tr>
<tr>
<td>Result</td>
<td>AVERAGE SCORE</td>
</tr>
<tr>
<td></td>
<td>- Erythema: 1.71/4.0</td>
</tr>
<tr>
<td></td>
<td>- Edema: 2.00/4.0</td>
</tr>
<tr>
<td>OTHER EFFECTS:</td>
<td>high degree of irritation of the skin with severe</td>
</tr>
<tr>
<td></td>
<td>thickening and fissured surface hardening after 8 days</td>
</tr>
<tr>
<td>Test condition</td>
<td>TEST ANIMALS:</td>
</tr>
<tr>
<td></td>
<td>- Strain: New Zealand white</td>
</tr>
<tr>
<td></td>
<td>- Sex: Male</td>
</tr>
<tr>
<td></td>
<td>- Source: Lippische Versuchstierzucht, Extertal (Germany)</td>
</tr>
<tr>
<td></td>
<td>- Weight at study initiation: 2.3 kg (average)</td>
</tr>
<tr>
<td>ADMINISTRATION/EXPOSURE</td>
<td>- 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</td>
</tr>
<tr>
<td></td>
<td>- Occlusion: PVC film</td>
</tr>
<tr>
<td></td>
<td>- Total volume applied: 0.5 ml per application site</td>
</tr>
<tr>
<td></td>
<td>- Postexposure period: 8 days</td>
</tr>
<tr>
<td></td>
<td>- Removal of test substance: washing with water</td>
</tr>
<tr>
<td>EXAMINATIONS</td>
<td>- Scoring system: maximum 4 scores each for erythema and scab formation and edema formation; average of 24 h and 72 h readings</td>
</tr>
<tr>
<td></td>
<td>- Examination time points: immediately after removal = 4 hours; 24, 48, 72 hours; 8 days</td>
</tr>
<tr>
<td>Reliability</td>
<td>(2) valid with restrictions</td>
</tr>
<tr>
<td></td>
<td>Study well documented, meets generally accepted scientific principles, acceptable for assessment</td>
</tr>
<tr>
<td>16.09.2006</td>
<td>(79) (94)</td>
</tr>
<tr>
<td>Species</td>
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<td>Concentration</td>
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<td>Exposure</td>
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<tr>
<td>Exposure time</td>
<td></td>
</tr>
<tr>
<td>Number of animals</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td></td>
</tr>
<tr>
<td>PDII</td>
<td></td>
</tr>
<tr>
<td>Result</td>
<td>highly irritating</td>
</tr>
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<td>Classification</td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>other: See Test Conditions</td>
</tr>
<tr>
<td>Year</td>
<td>1968</td>
</tr>
<tr>
<td>GLP</td>
<td>no</td>
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<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate, no data on purity</td>
</tr>
<tr>
<td>Result</td>
<td>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</td>
</tr>
<tr>
<td>Test condition</td>
<td>TEST ANIMALS:</td>
</tr>
<tr>
<td></td>
<td>- Sex: male</td>
</tr>
<tr>
<td>ADMINISTRATION/EXPOSURE</td>
<td>- Area of exposure: abraded and unabraded area of the abdomen (with occlusion for 24 hours); uncovered area of the ear</td>
</tr>
<tr>
<td></td>
<td>- Postexposure period: 15 days or more</td>
</tr>
<tr>
<td></td>
<td>- Removal of test substance: not reported</td>
</tr>
</tbody>
</table>
5. TOXICITY

<table>
<thead>
<tr>
<th>Reliability</th>
<th>(4) not assignable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation</td>
<td>insufficient for assessment</td>
</tr>
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</table>

14.09.2006

<table>
<thead>
<tr>
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<tbody>
<tr>
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</tr>
<tr>
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<td>Open</td>
</tr>
<tr>
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<td>no data</td>
</tr>
<tr>
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</tr>
<tr>
<td>Vehicle</td>
<td></td>
</tr>
<tr>
<td>PDII</td>
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<tr>
<td>Result</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Method</td>
<td>other: &quot;standard&quot;</td>
</tr>
<tr>
<td>Year</td>
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</tr>
<tr>
<td>GLP</td>
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<td>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</td>
</tr>
</tbody>
</table>

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

5.2.2 EYE IRRITATION

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<tr>
<td>Dose</td>
<td>.1 ml</td>
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<tr>
<td>Comment</td>
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<tr>
<td>Number of animals</td>
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<td>Vehicle</td>
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<tr>
<td>Result</td>
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<tr>
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</tr>
<tr>
<td>Method</td>
<td>other: OECD Guideline 405 (1981)</td>
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<tr>
<td>Year</td>
<td>1984</td>
</tr>
<tr>
<td>GLP</td>
<td>no</td>
</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate, purity &gt; 99%</td>
</tr>
</tbody>
</table>

Result

AVERAGE SCORE
- Cornea: 0.33
- Iris: 0.17
- Conjunctivae (Redness): 1.61
- Conjunctivae (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**
- Ophthalmoscopic 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

**02.06.2006**

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<thead>
<tr>
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<tr>
<td>Comment</td>
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<td>Number of animals</td>
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<td>Vehicle</td>
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<tr>
<td>Result</td>
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<tr>
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<tr>
<td>Year</td>
<td>1981</td>
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<tr>
<td>GLP</td>
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</tr>
<tr>
<td>Test substance</td>
<td>other TS: Isophorone diisocyanate, no data on purity</td>
</tr>
</tbody>
</table>

**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**
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

5. TOXICITY

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- Ophthalmoscopic 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:
Number of animals: 1
Vehicle: none
Result: corrosive
Classification: other: See Test Conditions
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 persisted 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
Documention insufficient for assessment

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:
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

5. TOXICITY

ID: 4098-71-9

DATE: 16-APR-2007

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:
  - Induction: occlusive epicutaneous
  - Challenge: occlusive epicutaneous
Number of animals: 15
Vehicle: other: 1:1 mixture of olive oil and acetone (anhydrous)
Result: sensitizing
Classification: sensitizing
Method:
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'-methylene diclohexyl diisocyanate (5124-30-1), not with toluene diisocyanate (1321-38-6) and 4,4'-methylene diphenyl diisocyanate (101-68-8).
  Induction with the present test substance, challenge with:
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

5. TOXICITY

ID: 4098-71-9
DATE: 16-APR-2007

- 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'-methylene diclohexyl 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'-methylene diclohexyl 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

Type: Guinea pig maximization test
Species: guinea pig
Concentration:
1st: Induction 5% intracutaneous
2nd: Induction 0.05% occlusive epicutaneous
3rd: Challenge 0.5% semiocclusive

Number of animals: 20

Vehicle:
other: olive oil; 2nd challenge: olive oil + acetone 1:1

Result:
sensitizing

Classification:
sensitizing

Method:

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

<table>
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<th>Conc.</th>
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<th>Vehicle</th>
<th>Test subst.</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td>0.5 %</td>
<td>16(16)/20</td>
<td>15(11)/20</td>
<td>8(7)/10</td>
<td>7(7)/10</td>
</tr>
<tr>
<td>0.1 %</td>
<td>11(8)/20</td>
<td>14(7)/20</td>
<td>9(8)/10</td>
<td>7(7)/10</td>
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Rechallenge:

<table>
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<th>Test subst.</th>
<th>Vehicle</th>
<th>Test subst.</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 %</td>
<td>19(17)/20</td>
<td>7(3)/20</td>
<td>8(6)/10</td>
<td>3(0)/10</td>
</tr>
<tr>
<td>0.1 %</td>
<td>15(8)/20</td>
<td>6(3)/20</td>
<td>4(2)/10</td>
<td>4(3)/10</td>
</tr>
</tbody>
</table>

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.

Type : Guinea pig maximization test
Species : guinea pig
**Concentration**
- 1\( ^{st} \): Induction 10 % intracutaneous
- 2\( ^{nd} \): Induction undiluted occlusive epicutaneous
- 3\( ^{rd} \): Challenge undiluted occlusive epicutaneous

**Number of animals** : 20

**Vehicle** : other: Paraffin oil (DAB 6)

**Result** : sensitizing

**Classification** : sensitizing


**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
### Toxicity

**ID:** 4098-71-9  
**DATE:** 16-APR-2007

<table>
<thead>
<tr>
<th>Type</th>
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<tr>
<td><strong>Concentration</strong></td>
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</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;: Induction</td>
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</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;: Challenge</td>
<td>.5 % open epicutaneous</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;:</td>
<td></td>
</tr>
<tr>
<td><strong>Number of animals</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Vehicle</strong></td>
<td>other: acetone+olive oil, 4:1</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>sensitizing</td>
</tr>
<tr>
<td><strong>Classification</strong></td>
<td>sensitizing</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>other: no data</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td>1992</td>
</tr>
<tr>
<td><strong>GLP</strong></td>
<td>no data</td>
</tr>
<tr>
<td><strong>Test substance</strong></td>
<td>other TS: Isophorone diisocyanate of Aldrich, Gillingham (UK); purity not reported</td>
</tr>
</tbody>
</table>

**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: Bariered 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  

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**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. 1% solutions of isophorone diisocyanate in acetone as well as test solutions of other isocyanates were applied to the workers.
  2. Readings were done at 24, 48, and 72 hours (some also at 96 hours).

**Reliability**
(4) not assignable
Documentation insufficient for assessment

**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, jejunum 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 µl 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: V
Vehicle: 
Result: 
Classification: 
Method: 
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 workshop 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: V
Vehicle: other: ethanol
Result: sensitizing
Classification: 
Method: other: See Test Conditions
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE
5. TOXICITY  ID: 4098-71-9
DATE: 16-APR-2007

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 disocyanate (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 disocyanate 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 disiocyanate 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**

**Type**

- Mouse ear swelling test

**Species**

- mouse

**Number of animals**

- 4

**Vehicle**

- other: 1 part olive oil + 4 parts acetone

**Result**

- sensitizing

**Classification**

- 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

Type: other: Respiratory tract sensitization following intradermal induction
Species: guinea pig
Concentration:
1st: Induction 0.1 % intracutaneous
2nd: Challenge 3rd: other: nose only inhalation of aerosol

Number of animals: 8
Vehicle: other: corn oil
Result:
Classification:
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:

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

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 tests substance 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: Freund's 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 Freund's 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

Type: guinea pig
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

Type: other: radioisotopic assay
Species: mouse
Number of animals: 4
Vehicle: other: 1 part olive oil + 4 parts acetone
Result: sensitizing
Classification: other
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

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 %
5. TOXICITY

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 sensitzers:
  (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.

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 strength on wire mesh, abdominal muscle tone, corneal and pupillary reflexes, pinna 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 parathyrds), 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
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

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/m³
Control group: no data specified
NOAEL: 0.64 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
5. TOXICITY

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

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
- 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

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)
Cytotoxic concentr.: ca. 40 mg/l (+/- S9)
Metabolic activation: with and without
Result: positive
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):**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>% Chromosomal aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment # 1</strong></td>
<td></td>
</tr>
<tr>
<td>untreated</td>
<td>0.0</td>
</tr>
<tr>
<td>Solvent</td>
<td>0.5</td>
</tr>
<tr>
<td>10 mg/l IPDI</td>
<td>0.0</td>
</tr>
<tr>
<td>20 mg/l IPDI</td>
<td>5.5</td>
</tr>
<tr>
<td>40 mg/l IPDI</td>
<td>8.5 ***</td>
</tr>
<tr>
<td>0.3 mg/l MMC</td>
<td>-</td>
</tr>
<tr>
<td>15 mg/l CPA</td>
<td>32.0 ***</td>
</tr>
<tr>
<td><strong>Experiment # 2</strong></td>
<td></td>
</tr>
<tr>
<td>untreated</td>
<td>0.5</td>
</tr>
<tr>
<td>Solvent</td>
<td>1.5</td>
</tr>
<tr>
<td>5 mg/l IPDI</td>
<td>-</td>
</tr>
<tr>
<td>10 mg/l IPDI</td>
<td>3.5</td>
</tr>
<tr>
<td>20 mg/l IPDI</td>
<td>4.0</td>
</tr>
<tr>
<td>40 mg/l IPDI</td>
<td>19.5 ***</td>
</tr>
<tr>
<td>0.3 mg/l MMC</td>
<td>-</td>
</tr>
<tr>
<td>15 mg/l CPA</td>
<td>42.0 ***</td>
</tr>
</tbody>
</table>

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

**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

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)
Cytotoxic 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)
### 5. TOXICITY

**OECD SIDS** 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLICYCLOHEXYL ISOCYANATE  

**ID:** 4098-71-9  
**DATE:** 16-APR-2007

#### SYSTEM OF TESTING

<table>
<thead>
<tr>
<th>Test condition</th>
<th>System of testing</th>
<th>Test concentration</th>
<th>Metabolic activation</th>
<th>Result</th>
<th>Method</th>
<th>Year</th>
<th>GLP</th>
<th>Test substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-incubation test: 10/50/250/500/1000 µg/plate (+/- metabolic activation)</td>
<td>Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537</td>
<td>0; 300; 1000; 3300; 10000; 33000 µg/plate</td>
<td>with and without</td>
<td>negative</td>
<td>other: See Test Conditions</td>
<td>1982</td>
<td>no data</td>
<td>other TS: Isophorone diisocyanate of Fluka Chemical Co., Purity: &quot;Pract&quot;</td>
</tr>
</tbody>
</table>

#### Metabolic System

- Activity of metabolic system: aminoantracene / 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

---

### 14.06.2006

**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

**Metabolic activation**

with and without

**Result**

negative

**Method**


---

There is no data available for GLP.
**OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLICYCLOHEXYL ISOCYANATE**

**5. TOXICITY**

**ID:** 4098-71-9  
**DATE:** 16-APR-2007

---

**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**

**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  
**Cytotoxic 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**

- 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

---

**5.6 GENETIC TOXICITY ‘IN VIVO’**

**Type:** Micronucleus assay  
**Species:** mouse  
**Sex:** male  
**Strain:** NMRI  
**Route of admin.:** other: nose-only inhalation (vapor/aerosol)
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

5. TOXICITY

DATE: 16-APR-2007

Exposure period: 1 x 6 hours
Doses: 0, 5, 15, 40 mg/m³ (target concentration)
Result: negative
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:

<table>
<thead>
<tr>
<th>Target Concentration (mg/m³)</th>
<th>Deaths/signs/total</th>
<th>Onset and Duration of Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 / 0 / 18</td>
<td>-- --</td>
</tr>
<tr>
<td>5</td>
<td>0 / 18 / 18</td>
<td>0d - 3d</td>
</tr>
<tr>
<td>15</td>
<td>0 / 18 / 18</td>
<td>0d - 3d</td>
</tr>
<tr>
<td>40</td>
<td>0 / 18 / 18</td>
<td>0d - 3d</td>
</tr>
</tbody>
</table>

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 subcutaneously 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

<table>
<thead>
<tr>
<th>Experimental number of</th>
<th>number of MNNCE per</th>
<th>number of MNPCE per</th>
</tr>
</thead>
<tbody>
<tr>
<td>groups</td>
<td>evaluated of NCE per</td>
<td>2000 NCE 2000 PCE</td>
</tr>
<tr>
<td>PCE</td>
<td>2000 PCE</td>
<td>(1s range) (1s range)</td>
</tr>
<tr>
<td>(1s range) (1s range) (1s range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative control</td>
<td>12000</td>
<td>1988</td>
</tr>
<tr>
<td>(412)</td>
<td>(2.3)</td>
<td>(0.6)</td>
</tr>
<tr>
<td>5 mg/m³</td>
<td>12000</td>
<td>3117</td>
</tr>
<tr>
<td>(997)</td>
<td>(1.2)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>15 mg/m³</td>
<td>12000</td>
<td>4598*</td>
</tr>
<tr>
<td>(1617)</td>
<td>(1.0)</td>
<td>(0.6)</td>
</tr>
<tr>
<td>40 mg/m³</td>
<td>12000</td>
<td>3679</td>
</tr>
<tr>
<td>(1959)</td>
<td>(3.3)</td>
<td>(2.2)</td>
</tr>
<tr>
<td>positive control</td>
<td>10000</td>
<td>2515</td>
</tr>
<tr>
<td>control</td>
<td>(768)</td>
<td>(0.8)</td>
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SUMMARY OF RESULTS OF 48 HOURS INTERVAL

<table>
<thead>
<tr>
<th>Experimental number of</th>
<th>number of MNNCE per</th>
<th>number of MNPCE per</th>
</tr>
</thead>
<tbody>
<tr>
<td>groups</td>
<td>evaluated of NCE per</td>
<td>2000 NCE 2000 PCE</td>
</tr>
<tr>
<td>PCE</td>
<td>2000 PCE</td>
<td>(1s range) (1s range)</td>
</tr>
<tr>
<td>(1s range) (1s range) (1s range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative control</td>
<td>12000</td>
<td>1682</td>
</tr>
<tr>
<td>(154)</td>
<td>(1.6)</td>
<td>(2.3)</td>
</tr>
<tr>
<td>5 mg/m³</td>
<td>12000</td>
<td>2039</td>
</tr>
</tbody>
</table>
SUMMARY OF RESULTS OF 72 HOURS INTERVAL

Experimental number of number of MNNCE per MNPCE per groups evaluated of NCE per 2000 NCE 2000 PCE
PCE 2000 PCE
(1s range) (1s range) (1s range)

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>negative</td>
<td>12000</td>
<td>1353</td>
<td>3.2</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(209)</td>
<td>(2.3)</td>
<td>(1.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg/m³</td>
<td>12000</td>
<td>1800</td>
<td>1.7</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>(541)</td>
<td>(2.5)</td>
<td>(1.0)</td>
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<td>3387</td>
<td>2.4</td>
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<tr>
<td>(2810)</td>
<td>(0.9)</td>
<td>(2.3)</td>
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<tr>
<td>40 mg/m³</td>
<td>12000</td>
<td>7168**</td>
<td>2.6</td>
<td>4.5</td>
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<tr>
<td>(2577)</td>
<td>(0.7)</td>
<td>(1.8)</td>
<td></td>
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</table>

*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)

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<table>
<thead>
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<tbody>
<tr>
<td>Negative Control</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Isophorone Diisocyanate</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>Isophorone Diisocyanate</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Isophorone Diisocyanate</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>Positive Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>20 mg/kg</td>
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</table>

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<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Control</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>Isophorone Diisocyanate</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>Isophorone Diisocyanate</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>Isophorone Diisocyanate</td>
<td>40</td>
<td>48</td>
</tr>
</tbody>
</table>
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 superseded 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  

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
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 uterine 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).
- External abnormalities: External deviations were not observed in this study.
- Soft tissue abnormalities: Statistical significance was only evident for reduced number of tracheal findings (membranous 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 evaluation 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.
- Skeletal abnormalities: Fetal skeletal including cartilaginous tissue evaluation for degree of ossification and incidence of variations revealed 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
OECD SIDS 3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLICYCLOHEXYL ISOCYANATE

5. TOXICITY

ID: 4098-71-9

DATE: 16-APR-2007

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 implantation sites were excluded. Skeletal localizations with mechanical damage in single fetuses were excluded 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

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human

Remark
Result : Biological monitoring in urine
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 addeducted 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

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 dermatitis 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

**Type of experience**
- Direct observation, clinical cases

**Remark**
- Occupational contact dermatitis

**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**
- A 21-year-old woman was exposed to various materials including a polyurethane foam with diphenylmethane-4,4'-diisocyanate. The patient did...
CASE 1:
- A 47-year-old woman reported 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 between 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 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 bronchoalveolar 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 pneumoapathies.

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

**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

**Type of experience**

Direct observation, clinical cases

**Remark**

The authors mention the possibility of a cross reaction with
derphenylmethane diisocyanate, which is a constituent of a glue used in
playground fitting. This raises the question why no positive reaction with
derphenylmethane 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**

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
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

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
- Source: Hilltop Lab Animals, Scottdale (PA, USA)
- Weight at study initiation: 250-300 g
- Number of animals: 4
- 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
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: Barrired 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 antibodies.

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)
OECD SIDS  3-ISOCYANATOMETHYL-3,5,5-TRIMETHYLCYCLOHEXYL ISOCYANATE

6. REFERENCES

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