# Hexamethylene diisocyanate

**EC Number: 212-485-8**

**CAS Number: 822-06-0**

**IUPAC name: 1,6-diisocyanatohexane**

# IUCLID Endpoint Summary Information

The information compiled in this document consists mainly of the IUCLID endpoint summaries regarding environmental and health hazards and the rationale for DNEL and PNEC derivation. This information is included in the REACH registration dossier for 1,6-diisocyanatohexane but is currently not disseminated on the ECHA website. However, this information is deemed necessary to comprehend the conclusions as derived in the REACH registration dossier for 1,6-diisocyanatohexane.

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# 1. PHYSICAL AND CHEMICAL PROPERTIES

**Molecular Weight:** 168.2 g/mol

**Molecular formula:** $C_8H_{12}N_2O_2$

**Appearance/physical state/colour:** Clear, colourless liquid with an pungent odour

**Melting / freezing point:** approx. -67 °C

**Boiling point:** 255 °C at 1013 hPa

**Mass density:** 1.047 g/cm3 at 20 °C

**Vapour pressure:** 0.007 hPa at 20 °C

**Water solubility:** Hydrolytically unstable (half-life 0.23 hour (23 °C)

**Partition coefficient n-octanol/water (log value):** 3.2 (calculated with Epiwin). Test cannot be performed, as the substance decomposes in water.

**Flash point:** 130 °C (closed cup)

**Self-ignition temperature:** 454 °C

**Stability in organic solvents:** Isocyanates are known to react rapidly with protic solvents like methanol or ethanol. They are stable to aprotic solvents like hexane, toluene, and dioxane.

**Dynamic viscosity:** 2.40 mPa*s (20 °C)

# 2. ENVIRONMENTAL FATE PROPERTIES

The main conclusions in this chapter have been prepared in accordance with the draft SIDS initial assessment report OECD (2001).

## 2.1. Hydrolysis

The half-life of hexamethylene diisocyanate (HDI) in the acetonitrile/water solution is approx. 0.23 hour at room temperature (23 °C). The concentration of the test substance in the acetonitrile solution without addition of water was stable over the measurement time (Bayer AG, 1999).

In a test on the stability of hexamethylene diisocyanate (HDI) in drinking water initial concentrations of 2 and 200 mg/l were tested at 20 °C. The reduction of the substance was 90 % after a reaction period of 50 min and 30 min., respectively. The half life in dependence of the initial concentration varied between 5 and 10 min. (Sopac, 1974).

Hydrolysis products have not been elucidated. However similar substances containing several isocyanate groups like MDI are known to react rapidly with water forming insoluble oligomeric and polymeric ureas.

In addition to the findings for the decrease of NCO groups (Bayer 1999), Sopac & Boltromejuk (1974) have reported in detail, that three main findings determine the results:

1. HDI is not soluble in the low mg/l range in water without another solvent. It forms oily droplets in water.

2. The diisocyanate ends of HDI react with water forming the amine and CO2.

3. The diisocyanate ends of HDI can also react with an amine end of an already hydrolysed (former HDI-) molecule, forming oligo-and polyureas. Depending on the use of a solvent or not, the size of the drops when direct weight is used, and the speed of a magnetic stirrer or of ultrasonic if used, determine the quantitative proportion of the hydroxylation products HDA and polyurea.

## 2.2. Phototransformation in air

The calculated half-life ($t_{1/2}$) of hexamethylene diisocyanate (HDI) in air due to indirect photodegradation is

approx. 48 h (Currenta, 2009). As HDI hydrolyses rapidly, also the hydrolysis product hexamethylene diamine (HDA) (CAS-No. 124-09-4) was estimated with AOPWIN v. 1.92. The atmospheric half live of approx 6 hrs was calculated (Currenta, 2009).

## 2.3. Biodegradation

Hexamethylene diisocyanate (HDI) is not readily biodegradable. After 28 days only 42 % of the test substance had been degraded in a manometric respiratory test (Directive 92/69/EEC, C.4-D) (Bayer AG, 2000).

Because of its expected reactivity with water in moist soil to form amine or polyurea derivatives, monomeric hexamethylene diisocyanate (HDI) is not likely to be found in soil in significant concentrations except near sources of release. Small amounts of HDI that have become encapsulated in water-insoluble polyurea agglomerates may persist in soils and sediments.

## 2.4. Bioaccumulation

The direct and indirect exposure of the aquatic compartment is unlikely because hexamethylene diisocyanate (HDI) hydrolysis completely in water within far less than 1 hour at environmental relevant concentrations. For this reason, an experimental study is not useful, and calculated values can be used. Bioconcentration factors (BCF) of 58 and 3 for hexamethylene diisocyanate (HDI) and its hydrolysis product hexamethylene diamine (HDA) (CAS 124-09-4) were obtained. Also the hydrolysis product with a bioconcentration factor of 3 does not have high bioaccumulation potential.

## 2.5. Adsorption

Hexamethylene diisocyanate (HDI) is characterized by a KOC of 5861 being calculated with PCKOCWIN v. 1.66 (Currenta, 2009). According to the method of Gerstl (1990) the KOC of 1665 accounts for hexamethylene diisocyanate (HDI) (Currenta, 2009e).

As hexamethylene diisocyanate (HDI) hydrolyses rapidly, the BCF of the hydrolysis product was calculated, too. The hydrolysis product of hexamethylene diisocyanate (HDI) is characterized by a KOC of 286 being calculated with PCKOCWIN v. 1.66 (Currenta, 2009e). According to the method of Gerstl (1990) the KOC of 5 accounts for HDA (CAS 124-09-4) (Currenta, 2009f).

However, while hexamethylene diisocyanate shows moderate sorption to soil and sediment, slow migration potential to groundwater its hydrolysis product has only a negligible sorption potential to soil and sediment.

## 2.6. Distribution modelling

Because of the relatively rapid reaction of hexamethylene diisocyanate (HDI) with hydroxyl radicals in the atmosphere and the rapid hydrolysis in other media , significant concentrations would not be expected to occur in air, water, or sediment and soil, except near potential emission sources of this substance (e.g., industrial waste streams, hazardous waste sites, occupational settings, environmental spills). Small amounts of unreacted hexamethylene diisocyanate (HDI) may persist in water, or sediment and soil, if encapsulated in water-insoluble polyurea crusts formed during hydrolysis.

# 3. ENVIRONMENTAL HAZARD ASSESSMENT

The main conclusions in this chapter have been prepared in accordance with the draft SIDS initial assessment report OECD (2001).

# 3.1. Aquatic compartment (including sediment)

**Summary and discussion**

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

## 3.1.1. Short-term toxicity to fish

**Discussion**

Disregarded study:

For fish (Danio rerio) a LC 50 > 22 mg/l after 96 h was obtained. The study was conducted according to the German standard "Letale Wirkung beim Zebrabaerbling (Brachydanio rerio) LC0, LC50, LC100, 48-96h", UBA-Verfahrensvorschlag, Mai 1984 (Bayer AG, 1992). This study is not regarded as being reliable. In all tests, the temperature is stated to be higher then recommended in the test guideline. After 1 hour of stirring the hydrolysis process was still ongoing at least in the vessels with the higher hexamethylene diisocyanate (HDI) concentrations as was obvious by “remaining oily droplets (HDI) at the water surface”. Therefore the lethal effects might not be caused by HDI itself but by the matter of fact that non-dissolved particles in the test substance impinged on the gill breathing of fish.

The following information is taken into account for acute fish toxicity for the derivation of PNEC:

The acute toxicity has been determined for fish with 96 h-LC0 of >= 82.8 mg/l (Brachydanio rerio). The test result refers to concentration of the test substance which was calculated directly from analytically determined TOC-value. The test was conducted according to Council Directive 92/69/EEC C.1 (1992) (Bayer AG, 2000b). A water accommodated fraction was prepared for testing by stirring the substance in water with Ultra turrax 60 sec/8000 rpm, 24 hours magnetic stirrer and filtration. Only one concentration was tested. The pH of the test solution was around 8.

## 3.1.2. Long-term toxicity to fish

**Data waiving**

**Reason:** other justification

**Justification:** According to column 2 of Reach Annex VII-X, a long-term ecotox study should be proposed by the registrant if the chemical safety assessment indicates the need to further investigate the effects on those organisms.

For the risk characterisation of the aquatic compartment, a PNEC has been derived on the basis of three acute aquatic toxicity data. According to the CSA, the risk characterisation yields a PEC/PNEC ratio smaller than 1. Further test are not necessary as the risk is sufficiently described based on the already available data.

## 3.1.3. Short-term toxicity to aquatic invertebrates

**Discussion**

Disregarded study:

In an earlier IUCLID dataset a test result was erroneously reported as a 24 -h EC0 < 0.33 mg/l (Bayer AG, 1989). No relation of concentration to effect-level was observed. So as a result of this test the advice was to test at first the hydrolysis behaviour of hexamethylene diisocyanate (HDI). However, according to international standard methods an exposure duration of 48 hours follows the state-of-the-art of science.

The following information is taken into account for short-term toxicity to aquatic invertebrates for the derivation of PNEC:

For acute toxicity of HDI to Daphnia magna a 48 h-EC0 of >= 89.1 mg/l has been determined (92/69/EEC C.2 (1992)) proceeding in the same way as described in the first fish test above. The pH of the test solution was 7.8 (Bayer AG, 2000b).

## 3.1.4. Long-term toxicity to aquatic invertebrates

**Data waiving**

**Reason:** other justification

**Justification:** According to column 2 of Reach Annex VII-X, a long-term ecotox study should be proposed by the registrant if the chemical safety assessment indicates the need to further investigate the effects on those organisms.

For the risk characterisation of the aquatic compartment, a PNEC has been derived on the basis of three acute aquatic toxicity data. According to the CSA, the risk characterisation yields a PEC/PNEC ratio smaller than 1. Further test are not necessary as the risk is sufficiently described based on the already available data.

## 3.1.5. Algae and aquatic plants

**Discussion**

**Effects on algae / cyanobacteria**

In an algae growth inhibition test, 7 test concentrations of HDI (1.5 to 78 mg/l) were exposed to Desmodesmus subspicatus. Nominal values were confirmed analytically with TOC. No acute effects have been observed up to the highest concentration of 78 mg/l. Results were expressed in measured values.

The following information is taken into account for effects on algae / cyanobacteria for the derivation of PNEC:

Concerning the algal toxicity, a test with Desmodesmus subspicatus in the presence of hexamethylene diisocyanate (HDI) was performed according to the Directive 92/69/EEC, C.3 (Bayer AG, 2000).

The arithmetic mean of the analytical values showed a 72 h-EC50 value for the growth rate to be > 77.4 mg/l. With the Dunett test the 72 h-NOEC and 72 h-LOEC for the growth rate was estimated to be 11.7 mg/l and 12.6 mg/l resp.

## 3.1.6. Sediment organisms

**Data waiving**

**Reason:** study scientifically unjustified

**Justification:** According to section 1 of Reach Annex XI, performing of a test is scientifically unjustified. Reach guidance document R7b states that a log Pow should be used as a trigger value for assessing sediment toxicity. For the substance, a log Kow of 3.2 was calculated. However, HDI hydrolyses rapidly to either oligomeric or polymeric ureas or to 1,6-diaminohexane. The ureas are insoluble in water and therefore not bioavailable. 1,6-diaminohexane has a very low log Pow of 0.02 indicating that distributed mainly in the aquatic compartment and not absorbed to sediment.

For the risk characterisation of the sediment compartment, a PNEC sediment has been derived on the basis of the equilibrium partition theory from aquatic toxicity data. As the risk characterisation yields a PEC/PNEC ratio smaller than 1, a test towards sediment dwelling organisms is not necessary as the risk towards the sediment compartment is sufficiently described based on the already available data.

## 3.1.7. Predicted No Effect Concentration (PNEC)

### 3.1.7.1. PNEC water

| | Value | Assessment factor | Remarks/Justification |
|---|---|---|---|
| PNEC aqua - freshwater (mg/L) | >0.0774 | 1000 | No effects have been observed in any of the acute ecotox studies. Therefore the PNEC was derived on the highest concentration tested and should read >0.0744 mg/l. Thus, it is regarded as provisional. The lowest endpoint from the 3 acute tests covering 3 trophic levels was derived for algae: 72 h-EC 50 > 77.4 mg/l (Scenedesmus subspicatus). |
| PNEC aqua - marine water (mg/L) | >0.00774 | 10000 | For the marine compartment no tests are available. For PNEC derivation, short-term toxicity results from three species representing three trophic levels (fish, daphnia and algae) for the freshwater compartment are taken into account. An assessment factor of 10000 is applied using the effect concentration, which was obtained for the lowest endpoint (algae). For the same reasons as stated for PNEC aqua the PNEC marine should read >0.0074 mg/l and it is regarded as provisional. |
| PNEC aqua - intermittent releases (mg/L) | >0.774 | 100 | Short-term toxicity results are available from three species representing three trophic levels (fish, daphnia and algae). The default assessment factor of 100 is applied using the effect concentration, which was obtained for algae. For the same reasons as stated for PNEC aqua the PNEC intermittent release should read >0.774 mg/l and it is regarded as provisional. |

### 3.1.7.2. PNEC sediment

| | Value | Assessment factor | Remarks/Justification |
|---|---|---|---|
| PNEC sediment (mg/kg d.w.) | >0.01334 | | extrapolation method<br><br>extrapolation method<br>The PNEC sediment was derived on the basis of aquatic toxicity data applying the Equilibrium Partitioning Theory (EPT) as no data is available covering sediment organisms. For the same reasons as stated for PNEC aqua the PNEC sediment should read >0.01334 mg/kg (de) or >0.0029 mg/kg (w.wt)and it is regarded as provisional.<br>To derive the PNECsediment on the basis of EPT, the Koc, the Henry's Law Constant as well as the PNECaqua are crucial. Following values have been used for hexamethylene diisocyanate (HDI):<br>Koc**= 1665 (calc. acc. to method of Gerstl)<br>HLC= 5 Pa*m³/mole (calc. acc. to EPIWIN)<br>PNECaqua= 0.0774 mg/L<br>Due to dissociating properties, the adsorption/desorption behaviour, expressed as Koc, is characterized by a range rather than a single value. Describing processes in the sediment, lower values are linked to a lower sorption potential, what in turn means higher concentrations in the pore water. As effects towards sediment organisms are assumed to be caused by the fraction dissolved in the pore water, lower Koc values are synonymous with a higher exposure of sediment organisms and were thus used to calculate the PNECsediment. |

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| | | | ** If released to the environment, hexamethylene diisocyanate (HDI) will be rapidly degraded by hydrolysis. The hydrolysis product has only a small to medium tendency for adsorption. Therefore the lowest Koc-value of HDI was used for the derivation of PNEC-sediment, which is even higher then the highest, calculated KOC-value of its hydrolysis product (Currenta, 2009b). |
| PNEC marine sediment (mg/kg d.w.) | >0.001334 | | extrapolation method<br><br>extrapolation method<br>The PNEC sediment was derived on the basis of aquatic toxicity data applying the Equilibrium Partitioning Theory (EPT) as no data is available covering sediment organisms. For the same reasons as stated for PNEC aqua the PNEC sediment should read >0.001334 mg/kg (de) or >0.00029 mg/kg (w.wt)and it is regarded as provisional.<br>To derive the PNECsediment on the basis of EPT, the Koc, the Henry's Law Constant as well as the PNECaqua are crucial. Following values have been used for hexamethylene diisocyanate (HDI):<br>Koc**= 1665 (calc. acc. to method of Gerstl)<br>HLC= 5 Pa*m³/mole (calc. acc. to EPIWIN)<br>PNECaqua= 0.0774 mg/L<br>Due to dissociating properties, the adsorption/desorption behaviour, expressed as Koc, is characterized by a range rather than a single value. Describing processes in the sediment, lower values are linked to a lower sorption potential, what in turn means higher concentrations in the pore water. As effects towards sediment organisms are assumed to be caused by the fraction dissolved in the pore water, lower Koc values are synonymous with a higher exposure of sediment organisms and were thus used to calculate the PNECsediment.<br>** If released to the environment, hexamethylene diisocyanate (HDI) will be rapidly degraded by hydrolysis. The hydrolysis product has only a small to medium tendency for adsorption. Therefore the lowest Koc-value of HDI was used for the derivation of PNEC-sediment, which is even higher then the highest, calculated KOC-value of its hydrolysis product (Currenta, 2009b). |

## 3.2. Terrestrial compartment

### 3.2.1. Toxicity to soil macro-organisms

**Data waiving**

**Information requirement:** Toxicity to soil macro-organisms except arthropods

**Reason:** exposure considerations

**Justification:** According to column 2 of Reach Annex VII-X, these studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. A test towards soil macroorgansims is not proposed by the registrant as the chemical safety assessment indicates the need to further investigate the effects on terrestrial organisms.

For the risk characterisation of the terrestrial compartment, a PNEC soil has been derived on the basis of the equilibrium partition theory from aquatic toxicity data. As the risk characterisation yields a PEC/PNEC ratio smaller than 1, a test towards soil macroorganisms is not necessary as the risk towards the terrestrial compart-

ment is sufficiently described based on the already available data.

**Information requirement:** Toxicity to terrestrial arthropods

**Reason:** exposure considerations

**Justification:** According to section 3 of Reach Annex XI, these studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. A test towards terrestrial arthropods is not proposed by the registrant as the chemical safety assessment indicates the need to further investigate the effects on terrestrial organisms.

For the risk characterisation of the terrestrial compartment, a PNEC soil has been derived on the basis of the equilibrium partition theory from aquatic toxicity data. As the risk characterisation yields a PEC/PNEC ratio smaller than 1, a test towards terrestrial arthropods is not necessary as the risk towards the terrestrial compartment is sufficiently described based on the already available data.

## 3.2.2. Toxicity to soil micro-organisms

**Data waiving**

**Reason:** exposure considerations

**Justification:** According to section 3 of Reach Annex XI, these studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. A test towards soil microorgansims is not proposed by the registrant as the chemical safety assessment indicates the need to further investigate the effects on terrestrial organisms.

For the risk characterisation of the terrestrial compartment, a PNEC soil has been derived on the basis of the equilibrium partition theory from aquatic toxicity data. As the risk characterisation yields a PEC/PNEC ratio smaller than 1, a test towards soil microorganisms is not necessary as the risk towards the terrestrial compartment is sufficiently described based on the already available data.

## 3.2.3. Predicted No Effect Concentration (PNEC soil)

| | Value | Assessment factor | Remarks/Justification |
|---|---|---|---|
| PNEC soil (mg/kg. dw.) | >0.0026 | | The PNEC soil was derived on the basis of aquatic toxicity data applying the Equilibrium Partitioning Theory (EPT) as no data is available covering soil organisms. For the same reasons as stated for PNEC aqua the PNEC soil should read >0.0026 mg/kg (dw) or >0.0023 mg/kg (wwt) and it is regarded as provisional.<br>To derive the PNECsoil on the basis of EPT, the Koc, the Henry's Law Constant as well as the PNECaqua are crucial. Following values have been used for hexamethylene diisocyanate (HDI):<br>Koc**= 1665 (calc. acc. to method of Gerstl)<br>HLC= 5 Pa*m³/mole (calc. acc. to EPIWIN)<br>PNECaqua= 0.0774 mg/L<br>Due to dissociating properties, the adsorption/desorption behaviour, expressed as Koc, is characterized by a range rather than a single value. Describing processes in the soil, lower values are linked to a lower sorption potential, what in turn means higher concentrations in the pore water. As effects towards sediment organisms are assumed to be caused by the fraction dissolved in the pore water, lower Koc values are synonymous with a higher exposure of sediment organisms and were thus used to calculate |

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|---|---|---|---|
| | | | the PNECsoil.<br>** If released to the environment, hexamethylene diisocyanate (HDI) will be rapidly degraded by hydrolysis. The hydrolysis product has only a small to medium tendency for adsorption. Therefore the lowest Koc-value of HDI was used for the derivation of PNEC-sediment, which is even higher then the highest, calculated KOC-value of its hydrolysis product (Currenta, 2009b). |

### 3.2.4. Toxicity to terrestrial plants

**Data waiving**

**Reason:** exposure considerations

**Justification:** According to section 3 of Reach Annex XI, these studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. A test towards terrestrial plants is not proposed by the registrant as the chemical safety assessment indicates the need to further investigate the effects on terrestrial organisms.

For the risk characterisation of the terrestrial compartment, a PNEC soil has been derived on the basis of the equilibrium partition theory from aquatic toxicity data. As the risk characterisation yields a PEC/PNEC ratio smaller than 1, a test towards terrestrial plants is not necessary as the risk towards the terrestrial compartment is sufficiently described based on the already available data.

## 3.3. Atmospheric compartment

Direct data on biotic and abiotic effects of hexamethylene diisocyanate (HDI) in the atmospheric compartment are not available. On one hand, it is nearly impossible to obtain reliable data for risk assessment on the biotic effects of chemical substance in air, due to lack of well developed methods. On the other hand, no indications suggest that hexamethylene diisocyanate (HDI) causes abiotic hazard in air compartment.

## 3.4. Microbiological activity in sewage treatment systems

### 3.4.1. Toxicity to aquatic micro-organisms

**Discussion**

The following information is taken into account for effects on aquatic micro-organisms for the derivation of PNEC:

Concerning the acute toxicity of hexamethylene diisocyanate (HDI) to activated sludge a study was conducted according to Directive 88/302/EEC Part C. The 3 h-EC50 estimated by Probit analysis gave a value of 842 mg/l (Bayer AG, 2000b).

### 3.4.2. PNEC for sewage treatment plant

| | Value | Assessment factor | Remarks/Justification |
|---|---|---|---|
| $PNEC_{stp}$ (mg/L) | 8.42 | 100 | The PNEC STP is derived from the EC50 value of a toxicity study with activated sludge: 3 h-EC 50 842 mg/l |

## 3.5. Non compartment specific effects relevant for the food chain (secondary poisoning)

### 3.5.1. Toxicity to birds

**Data waiving**

**Information requirement:** Toxicity to birds

**Reason:** study scientifically unjustified

**Justification:** According to section 1 of Reach Annex XI, there is no need for testing taking into account the mammalian dataset that is available for the substance.

### 3.5.2. Toxicity to mammals

No data.

### 3.5.3. PNEC oral (secondary poisoning)

| | Value | Assessment factor | Remarks/Justification |
|---|---|---|---|
| PNEC oral (mg/kg food) | | | Hexamethylene diisocyante (HDI) hydrolysis rapidly. The hydrolysis product hexamethylene diamine has a measured partition coefficient log Kow=0.02. Therefore no bioaccumulation potential is expected. Thus, no risk characterisation for secondary poisoning is carried out and the deviation of a PNEC oral is scientifically unjustified. |

## 3.6. Conclusion on the environmental classification and labelling

**Classification and labelling according to aquatic toxicity data**

Justification for classification or non classification

Three acute tests have been performed with fish, daphnia and algae. No effects have been observed up to the highest concentrations tested (algae: 77 mg/l, fish: 83 mg/l, daphnia: 90 mg/l). Therefore, a classification related to risk phrases R50, 51, 52 can be ruled out.

**Classification and labelling according to degradation and bioconcentration**

Justification for classification or non classification

Hexamethylene diisocyanate is not readily biodegradable and has a logPow of 3.2 (calculated). However, the substance hydrolysis rapidly within 1 hour. The hydrolysis product is - beside insoluble oligomeric and polymeric ureas - the corresponding hexamethylene diamine. The latter has a logPow of 0.02 (measured). Therefore, a classification related to risk phrase R53 is not required

# 4. HUMAN HEALTH HAZARD ASSESSMENT

## 4.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

**Basic toxicokinetics**

The following remarks on the toxicokinetics of HDI are based on experimental toxicokinetic studies in animals and volunteers. In addition, physico-chemical properties of the compound as well as toxicological data were

taken into account.

HDI is a clear colourless liquid with a low vapour pressure under normal ambient conditions (0.007hPa at 20°C), therefore inhalation exposure to the vapour is expected to be low. After 1 hr exposure of guinea pigs to vapour concentrations ≥ 0.034 mg/m3 14C-HDI the uptake of radiolabelled HDI into blood was immediate and increased linearly to a 2-4 hr post exposure peak (Kennedy et al., 1990). The14C-activity was cleared from the blood rapidly (no date) to a nanomolar level which persisted after 72 hr regardless of initial dose. Acute inhalation of HDI (vapour + condensation aerosol) to rats did not reveal signs of systemic toxicity at the maximum concentration of 151 mg/m3 (Pauluhn, 1997). Exposure to 55 mg/m3 and higher were followed by concentration-dependent signs suggestive of irritation of the respiratory tract. At concentrations of 107 mg/m3and above increased mortality was observed. Even life-time inhalation of HDI vapour to rats revealed no signs of systemic toxicity (Shiotsuka, 1989).

In controlled studies in human volunteers 1,6-hexamethylene diamine (HDA) could be detected in the urine of HDI exposed persons (inhalation exposure) after acid hydrolysis as a biomarker for excretion of HDI or HDI-metabolites (Brorson et al., 1990; Dalene et al., 1990; Rosenberg and Savolainen, 1986). In a study with three volunteers each exposed to 0.012, 0.020 and 0.022 mg/m3for 2 hours (2 days each between the exposures) the average urinary elimination half-time for HDA in hydrolysed urine was 2.5 hr (Tinnerberg et al., 1995). No HDA could be found in hydrolysed plasma during the exposure days (before and half an hour after exposure). Due to the analytical method using acid hydrolysis these studies give some insight in potential absorption and elimination, but not on metabolism.

At ambient temperature HDI is hydrolytically unstable (half-life in acetonitrile/water solution 0.23 hour; Bayer AG, 1999). HDA and carbon dioxide are found to be the main degradation products after contact with water (Sopac and Boltromejuk, 1974). Due to hydrolytic instability of HDI in aqueous solutions neither water solubility nor log Pow value were determinable. Under physiological conditions it is expected that HDI decomposes in the GI tract mainly into HDA and carbon dioxide. Therefore intestinal absorption of HDI subsequent to oral ingestion may be limited. Acute oral toxicity in rats revealed clinical symptoms at 263 mg/kg HDI as well as deaths at 788 mg/kg HDI within the first day of treatment (Kimmerle et al., 1970), possibly caused by the decomposition product HDA.

Due to a molecular weight of 168.2 g/mol and a calculated log Pow of 3.2 dermal absorption is conceivable. Furthermore, after contact of HDI with the surface moisture of the skin hydrolysis to HDA and carbon dioxide can be expected as well as reaction with nucleophiles like, NH- or SH-groups. HDI revealed corrosive properties to the skin (Schreiber, 1981). Damage to the skin surface may enhance penetration of HDI and/or HDA. The assumption of a dermal absorption is confirmed by the data on acute dermal toxicity and skin sensitization. In the acute dermal toxicity study in rabbits hyperemia and swelling of the gastric mucosa as well as distinct hyperemia of the small intestine mucosa, peritineum, pleura, diaphragm and pancreas were seen macroscopically in all animals at 7000 mg/kg (Mürmann, 1985). In a guinea pig maximization test (GPMT) a strong skin sensitization potential could be detected for HDI (Schmidt and Bomhard, 1983).

Based on the results of two in vitro genotoxicity tests (negative with and without metabolic activation in an Ames test (Wagner and Klug, 1998) and in a HGPRT test (San and Clarke, 1998)) it is concluded that DNA-reactive metabolites of HDI will most probably not be generated in mammals in the course of hepatic biotransformation. This conclusion is confirmed by a negative result in a mouse micronucleus test in vivo with vapour inhalation of HDI (Gudi and Krsmanovic, 1998).

## 4.2. Acute toxicity

**Acute toxicity: oral**

The LD50 resulting from a single oral (gavage) administration ranged from 746 to approximately 959 mg/kg bw for the male rat (Smyth et al., 1969; Union Carbide Corp., 1964; Kimmerle et al., 1970). Soon after dosing the animals appeared to be extremely sluggish. All deaths occurred within the first day.

**Acute toxicity: dermal**

The acute dermal toxicity of HDI was low with an LD50 value > 7000 mg/kg bw for male and female rats according to OECD TG 402 (Mürmann, 1985). Single occlusive administration of 7000 mg/kg bw for 24 hours was tolerated without mortalities. The animals showed clinical signs (rough hair, crusts and scars in application area) up to the end of the 14-day observation period. Body weight gain was transiently inhibited. Gross necropsy revealed hyperemia and swelling of the gastric mucosa as well as distinct hyperemia of the small intestine mu-

cosa, peritoneum, pleura, diaphragm and pancreas in all animals.

**Acute toxicity: inhalation**

The inhalation LC50 in rats of both sexes was determined to be 124 mg/m3 for 4 hours of exposure to HDI vapour according to OECD TG 403 (Pauluhn, 1997). Exposures to concentrations of 55 mg/m3 and above were followed by a concentration-dependent signs indicative of respiratory tract irritation, such as bradypnea, dyspnea, laboured breathing pattern, rales, nostrils/muzzle with red encrustations, cyanosis, prostration (lying on belly), reduced motility, ungroomed haircoat, hypothermia, decreased body weights, and piloerection. Gross necropsy revealed less collapsed, discolorated (dark-red) lungs with serous mucus in trachea. The lung associated lymph nodes were enlarged. Clinical observations and necropsy findings support the conclusion that a causal relationship between lethality and lung damage existed.

Two sensory irritation studies with HDI vapour revealed 30-minute RD50 values (50 % inhibition of respiration) of 9.93 mg/m3 in male rats (Sangha, 1982) and of 2.45 mg/m3 in male mice (Sangha et al., 1981). In rats, time-response relationships showed a fast onset of the response and development of tolerance after five minutes of exposure. However, fast recovery after short exposure and slow recovery after longer exposure were observed in mice.

**Justification for classification or non classification**

**Acute toxicity: oral**

Not classified under Annex I of Directive 67/548/EEC or Annex VI-1 of Regulation (EC) No 1272/2008. Differing from this oral LD50 values of 746-959 mg/kg bw for the male rat lead to the following classification according to Annex I of Regulation (EC) No 1272/2008: Category 4 (H302: Harmful if swallowed).

**Acute toxicity: dermal**

Not classified under Annex I of Directive 67/548/EEC. According to Annex I of Regulation (EC) No 1272/2008 no classification is required for acute dermal toxicity (LD50: > 7000 mg/kg bw).

**Acute toxicity: inhalation**

Classified under Annex I of Directive 67/548/EEC with R23 (toxic by inhalation). This classification corresponds to Category 3* (minimum classification: toxic if inhaled) according to Annex VI-1 of Regulation (EC) No 1272/2008. Differing from this the LC50 value of 124 mg/m3 (vapour) for rats leads to the following classification according to Annex I of Regulation (EC) No 1272/2008: Category 1 (H330: Fatal if inhaled as vapour).

Classification of acute inhalation toxicity with regard to Specific Target Organ Toxicity - Single Exposure (STOT-SE):

Due to respiratory irritation effects HDI was classified under Annex I of Directive 67/548/EEC with R37 (irritating to respiratory system). This classification corresponds to STOT-SE Category 3 (H335: May cause respiratory irritation) according to Annex VI-1 of Regulation (EC) No 1272/2008.

## 4.3. Irritation / Corrosivity

**Skin irritation**

In a dermal irritation/corrosion study HDI was corrosive to the skin of rabbits according to OECD TG 404 (Schreiber, 1981). Immediately after patch removal all treated animals showed severe edema and erythema (grade 4). 24 hours after patch removal induration and necrosis at the application site of all animals were seen. No reversibility could be observed at the end of the post-observation period of 8 days.

**Eye irritation**

In an acute eye irritation/corrosion study HDI was corrosive to the eyes of rabbits according to OECD TG 405 (Schreiber, 1981). The examination of the eyes showed 1 hour after instillation severe effects in all animals with

regard to cornea, iris and conjunctivae (left eye not rinsed). All effects had a tendency to get worse during the 8-day post-observation period. Damage to the eye was already observed 30 seconds after instillation (right eye rinsed with saline 30 sec. after instillation).

**Respiratory / sensory irritation**

Sensory irritation studies using laboratory animal models demonstrated evidence of sensory irritation but no evidence of pulmonary irritation to HDI. In a sensory irritation study with HDI vapour Sangha et al. (1981) reported a 3-hour RD50 (concentration required to reduce respiratory rate by 50 %) of 1.19 mg/m3 using male Swiss Webster mice. Exposure duration between 0.17-3 hours and concentrations between 1.19 -6.71 mg/m3 caused a time and concentration dependent decrease of the respiration rate. Fast recovery after short exposure and slow recovery after longer exposure were observed. A comparable study using male Fisher 344 rats resulted in a 30-minute RD50 of 9.93 mg/m3 (Sangha, 1982). HDI vapour exposure (head-only) of female Sprague-Dawley rats revealed a 3-hour RD50 of 11.83 mg/m3 (1.69 ppm) (Shiotsuka 1987a). In a study to assess the effects of repeated exposures on respiratory rate, female Sprague-Dawley rats were head-only exposed 3 hours/day for 6 days (5 consecutive days and 2 days later for an additional day) to a mean HDI vapour concentration of 8.19 mg/m3 (1.17 ppm). The daily decrease in respiratory rate of 50 to 63 %, relative to pre-exposure mean for day 1, showed that repeated exposures did not produce a cumulative effect on respiratory rate depression during daily exposures (Shiotsuka, 1987b).

**Value used for CSA:**

Skin irritation / corrosion: corrosive

Eye irritation: corrosive

**Justification for classification or non classification**

**Skin irritation**

Classified under Annex I of Directive 67/548/EEC with R38 (irritating to skin). This classification corresponds to Category 2 (causes skin irritation) according to Annex VI-1 of Regulation (EC) No 1272/2008. Differing from this the irreversible damage to the skin of rabbits leads to the following classification according to Annex I of Regulation (EC) No 1272/2008: Category 1C (H314: Causes severe skin burns and eye damage).

**Eye irritation**

Classified under Annex I of Directive 67/548/EEC with R36 (irritating to eye). This classification corresponds to Category 2 (causes serious eye irritation) according to Annex VI-1 of Regulation (EC) No 1272/2008. Differing from this the irreversible damage to the eyes of rabbits leads to the following classification according to Annex I of Regulation (EC) No 1272/2008: Category 1 (H318: Causes serious eye damage).

**Respiratory irritation**

Classified under Annex I of Directive 67/548/EEC with R37 (irritating to respiratory system). This classification corresponds to STOT-SE Category 3 (H335: May cause respiratory irritation) according to Annex VI-1 of Regulation (EC) No 1272/2008.

## 4.4. Sensitisation

**Skin sensitisation**

In a guinea pig maximization test (GPMT) similar to OECD TG 406 1,6-hexamethylene diisocyanate (HDI) revealed a strong skin sensitizing potential. At the topical challenges (4 and 6 weeks after the first induction treatment) 16/17 or 17/17 animals reacted with erythema according to a contact allergy after application of a 0.3 or a 1.0 % HDI formulation in petrolatum (Schmidt and Bomhard, 1983). A Buehler test in guinea pigs showed a strong skin sensitizing potential of HDI (1 % induction conc., 70 % incidence of sensitization) according to EU method B.6 (Zissu et al., 1998). In a mouse local lymph node assay (LLNA) equivalent to OECD TG 429 HDI revealed a clear skin sensitizing potential (Hilton et al., 1995). In addition, HDI was found to be positive in

mice using the mouse ear swelling test (MEST; Gad et al., 1986; Thorne et al., 1987).

In summary, HDI was found to induce dermal sensitization in animals.

**Value used for CSA:** sensitising

**Respiratory sensitisation**

A lung sensitization test in guinea pigs provides clear evidence that 1,6-hexamethylene diisocyanate (HDI) is a respiratory sensitizer.

When animals that were sensitized intradermally (three injections, one per day) or by inhalation (5 x 3 hours per day) and were subsequently challenged by inhalation with the respective hapten of HDI no conclusive immediate-onset responses were observed. As a result of challenge with the respective conjugate of the hapten conclusive immediate-onset responses occurred. Additional evidence of a lung sensitizing potential was provided by the histopathological examination which revealed an increased eosinophilia of airways and lung associated lymph nodes as well as specific IgG1-antibody (Pauluhn, 1996). In a modified local lymph node assay (LLNA) on male mice high stimulation indices (SIs) were observed in mandibular lymph nodes (SI = 9.8) and in auricular lymph nodes (SI = 109) after 6-hour vapour inhalation of 7.5 mg/m3 for three consecutive days. HDI inhalation induced positive responses of IL-4 and IL-10 in the mandibular lymph nodes, whereas for IL-12 and IFN-gamma no dose-response in mandibular lymph nodes was found (Arts et al., 2008; De Jong et al., 2009).

In summary, HDI was found to induce respiratory sensitization in animals.

**Value used for CSA:** sensitizing

**Justification for classification or non classification**

**Skin sensitisation**

Classified under Annex I of Directive 67/548/EEC with R43 (may cause sensitization by skin contact). This classification corresponds to Category 1 (H317: May cause an allergic skin reaction) according to Annex VI-1 of Regulation (EC) No 1272/2008.

**Respiratory sensitisation**

Classified under Annex I of Directive 67/548/EEC with R42 (may cause sensitization by inhalation). This classification corresponds to Category 1 (H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled) according to Annex VI-1 of Regulation (EC) No 1272/2008.

## 4.5. Repeated dose toxicity

Inhalation exposure is the most appropriate route for assessing occupational risk in humans. Effects from repeated exposure of animals to 1,6-hexamethylene diisocyanate (HDI) are limited to effects on the respiratory tract caused by local irritation.

The most relevant evaluation of repeated dose toxicity comes from a 2-year chronic toxicity and oncogenicity study in rats according to OECD TG 453 (Shiotsuka, 1989). The animals were whole-body exposed to 0, 0.005, 0.025 and 0.164 ppm (0, 0.035, 0.175 and 1.15 mg/m3) of HDI vapour. The exposure regimen was 6 hours/day, 5 days/week for one year (chronic toxicity assessment) or two years (toxicity and oncogenicity assessment). There were no compound-related effects on mortality, ophthalmology, clinical biochemistry, urinalysis and organ weights after 2-year inhalation with vapour concentrations up to and including 0.164 ppm. Those effects determined to be compound-related were transient ocular irritation in males, small but consistent decrease in body weight of females (particularly during the second year of exposure) and slight anemia in females at 0.164 ppm. There were no compound-related gross lesions. Histopathologically, compound-related non-neoplastic changes were limited to the nasal cavity and the lungs.

Changes in the nasal cavity were observed in both sexes at 0.005 ppm and above (except males of the lowest dose group) and characterized by a non-specific epithelial tissue reaction to irritation at all exposure concentrations. The following nasal lesions were observed: hyperkeratosis, hyperplasia of the squamous epithelium, chronic active inflammation, squamous metaplasia, mucus secretory cell or goblet cell hyperplasia, hyaline

droplet degeneration and minimal degeneration of the olfactory epithelium. Lung lesions were noted as epithelialization, interstitial pneumonia or alveolar macrophage accumulation in both sexes at 0.025 ppm and above after two years of exposure. No evidence of compound-related oncogenicity was found. The highest concentration of 0.164 ppm is regarded as a Maximum Tolerated Dose (MTD) based on a slight decrease in body weight and slight anemia of females and microscopic changes in the nasal cavity of both sexes. The lowest concentration of 0.005 ppm is considered to be a NOEC after one year of exposure since the changes observed occurred only in one sex, were qualitatively similar to those seen in controls and did not show any concentration-dependent increase in degree. After two years of exposure to the lowest concentration (0.005 ppm), indications of a protective response to non-specific irritation was observed (NOAEC).

Analysis of the results from the principal study revealed that compound-related effects were limited to histopathology in the nasal passages. Although some lesions were noted in the nasal tract of animals from all exposure groups, Foureman et al. (1994) concluded that the olfactory epithelial degeneration should be considered as the significant effect in this study, with a NOAEC of 0.005 ppm and a LOAEL of 0.025 ppm, because it followed a concentration-response relationship for both incidence and severity. The data for this lesion show its absence at the lowest concentration with parallel increases in both incidence and severity at the two highest concentrations. For the other lesions, including chronic inflammation, mucus cell hyperplasia, epithelial hyperplasia, hyaline droplet degeneration, and squamous metaplasia no concordance in incidence and severity was found. In response to an irritant, the character of lesions in the nasal tract such as squamous metaplasia, mucus cell hyperplasia, and hyaline droplet formation appears to be more adaptive than adverse.

In a 21-day inhalation study in rats (Sangha, 1984) with HDI vapour concentrations up to 0.3 ppm no mortality was observed during the study at all concentrations. Signs of toxicity were concentration-related and were observed at concentrations of 0.0175 ppm and above. The signs included ocular and nasal irritation and were observed on the exposure days only. Body weights, feed consumption, blood chemistry, urinalysis and hematology showed no biologically significant differences from the control group. Only liver and kidney weights (absolute and/or relative) showed a concentration-related effect. No compound-related gross lesions were observed. Microscopic examination of the tissues demonstrated concentration-related effects on the respiratory mucosa and nasal cavity at 0.15 and 0.30 ppm concentration levels. The effects noted at 0.0175 ppm were equivocal, and there was no effect at 0.005 ppm. The changes were characterized by squamous metaplasia. In the larynx and trachea the changes included accumulation of mixed inflammatory cells in the submucosa and a minimal to mild hyperplasia of the epithelium. Recovery at 0.0175 and 0.15 ppm concentrations was suggested. The NOEC was 0.005 ppm.

In a 90-day inhalation study in rats (OECD TG 413; Shiotsuka, 1988) with HDI vapour concentrations of 0, 0.01, 0.04 and 0.14 ppm the only compound-related clinical sign was ocular irritation which was observed at all three concentrations. There were no mortalities and no compound-related effects on the following parameters: body weight, clinical chemistry, hematology, urinalysis, gross pathology, organ weight and organ to body weight ratios. The compound-related histopathologic lesions were observed at all three concentrations and were generally located in the cranial nasal cavity anterior to the nasal papilla. Hyperplasia and/or squamous metaplasia of the respiratory epithelium were considered to be the most important compound-related lesions in both sexes. Keratin was often present covering the metaplastic epithelium in the mid- and high-dose rats. Mucous cell hyperplasia predominantly of the respiratory epithelium and inflammatory cell infiltrate principally within subepithelial tissues were also considered to be compound- related. The concentration of 0.01 ppm was considered to approximate a threshold for respiratory tract lesions, but a clear NOEC was not established for this study.

**Value used for CSA (route: inhalation):**

NOAEC 0.035 mg/m³ air

Target organs: respiratory: nose; respiratory: lung

**Justification for classification or non classification**

**Repeated dose toxicity**

Not classified under Annex I of Directive 67/548/EEC. According to Annex I of Regulation (EC) No 1272/2008 no classification is required for repeated dose toxicity.

Remark: A classification with STOT-RE is not justified due to lack of cumulative toxicity. This is in accordance with the ECHA Guidance on the Application of the CLP Criteria (2009), which notes on page 365: Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it

may be concluded that the toxicity is essentially an acute (i. e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate.

## 4.6. Mutagenicity

In an Ames test with the S. typhimurium strains TA 1535, TA 1537, TA 98 and TA 100 1,6-hexamethylene diisocyanate (HDI; vapour-phase exposure) revealed no mutagenic activity in the absence and in the presence of a metabolic activation system (Wagner and Klug, 1998; Wagner et al., 2000). Using vapor-phase exposure HDI did not induce mutagenic effects in the in vitro gene mutation assay (HGPRT test) with Chinese hamster ovary (CHO) cells in the presence and absence of a metabolic activation system (San and Clarke, 1998; Wagner et al., 2000).

In a micronucleus test (MNT) equivalent to OECD TG 474 male and female mice were once whole-body exposed for 6 hours to HDI vapour concentrations of 0.14, 0.80 and 1.47 ppm. No significant increase in micronucleated polychromatic erythrocytes in test substance treated groups relative to the respective air control group was observed in male or female mice at 24 or 48 hours after exposure. Therefore, HDI was concluded to be negative in the mouse micronucleus assay after inhalation exposure (Gudi and Krsmanovic, 1998; Wagner et al., 2000).

**Value used for CSA:** Genetic toxicity: negative

**Justification for classification or non classification**

Genetic toxicity (in vitro and in vivo)

Not classified under Annex I of Directive 67/548/EEC. According to Annex I of Regulation (EC) No 1272/2008 no classification is required for genetic toxicity.

## 4.7. Carcinogenicity

In a combined chronic toxicity and oncogenicity study in rats according to OECD TG 453 HDI revealed no carcinogenic potential after 2-year inhalation (whole-body) with vapour concentrations of 0.005, 0.025, 0.164 ppm (0.035, 0.175, 1.15 mg/m3). A Maximum Tolerated Dose (MTD) was established at the highest concentration tested (Shiotsuka, 1989).

**Value used for CSA (route: inhalation):**

NOAEL: 1.150 mg/m³ air

**Justification for classification or non classification**

Carcinogenicity

Not classified under Annex I of Directive 67/548/EEC. According to Annex I of Regulation (EC) No 1272/2008 no classification is required for carcinogenicity.

## 4.8. Toxicity for reproduction

**Effects on fertility**

In a combined reproductive/developmental/neurotoxicity study (OECD TG 422) with 1,6-hexamethylene diisocyanate (HDI) rats were exposed, via whole-body exposure, to HDI vapour concentrations of 0, 0.005, 0.050, or 0.300 ppm for 6 hours/day during a 14-day premating phase, up to a 14-day mating phase, and a 21-day gestation phase (Astroff, 1999; Astroff et al., 2000). Analytically confirmed overall (for the entire study) mean HDI vapour concentrations were 0.005, 0.053 and 0.299 ppm. Following the gestation phase the dams were transferred to nesting cages and permitted to deliver. The dams and their litters were maintained for a 4-day lactation phase during which exposure to HDI was discontinued. HDI demonstrated toxicity at vapour concentrations of 0.050 and 0.300 ppm resulting in microscopic alterations in the nasal cavity (primarily epithelial hyperplasia, squamous metaplasia, chronic-active inflammation, and more seriously, degeneration of the olfac-

tory epithelium). No effects were observed in the 0.005 ppm group, and no effects on hematology, clinical chemistry, or neurologic parameters were observed with any concentration. There were no statistically significant effects on the mating, fertility, or gestation indices. There were no effects observed on the days to insemination, gestation length, or total number of implantation sites. There were no statistically significant effects on litter size, total number of pups born, sex distribution, mean weight of viable pups, mean number of viable pups or number of stillborn pups. No statistically significant effects were observed on the live birth, viability, lactation, or birth indices.

Therefore, the no-observed-effect-level (NOEL) for reproduction (including neonatal development) as well as for hematology, clinical chemistry, and neurotoxicity was 0.300 ppm (2.03 mg/m3) and the overall NOEL was 0.005 ppm (0.034 mg/m3).

**Value used for CSA (route: inhalation):** NOAEC: 2.030 mg/m³ air

**Developmental toxicity**

In a developmental toxicity study (OECD TG 414) with 1,6-hexamethylene diisocyanate (HDI) rats were exposed, via whole-body exposure, to HDI vapour concentrations of 0, 0.005, 0.050, or 0.300 ppm for 6 hours/day on days 0 through 19 of gestation (Astroff, 1999; Astroff et al., 2000). Analytically confirmed overall (for the entire study) mean HDI vapour concentrations were 0.005, 0.052 and 0.308 ppm. Maternal toxicity was demonstrated in the 0.300 and to a lesser extent in the 0.050 ppm exposure groups. No maternal effects were noted in the 0.005 ppm dose group. Test compound-related maternal effects were restricted to histopathological findings, and included acanthosis, hyperkeratosis, inflammation of the nasal turbinates, and more seriously, degeneration of the olfactory epithelium. No pathological alterations were noted in the larynx, trachea, or lungs in any dose group. No test compound-related effects were observed on any reproductive parameters, or any embryonic endpoints, including pre/post-implantation loss and resorptions. There were no effects on litter size or the number of fetuses per implantation site and no effects on fetal or placental weights were observed. No test compound-related fetal external, visceral, or skeletal findings were observed. No effect on the fetal or litter incidence of total malformations or variations was observed and there was no difference in the incidence of malformations between males and females.

In summary, HDI produced maternal effects (nasal turbinate histopathology) at concentrations of 0.050 and 0.300 ppm. No developmental toxicity was observed at any concentration level. Therefore, the maternal no-observed-effect-level (NOEL) was 0.005 ppm (0.034 mg/m3) and the developmental NOEL was 0.300 ppm (2.1 mg/m3).

**Value used for CSA (route: inhalation):** NOAEC: 2.100 mg/m³ air

**Justification for classification or non classification**

Toxicity to reproduction (fertility, developmental toxicity / teratogenicity)

Not classified under Annex I of Directive 67/548/EEC. According to Annex I of Regulation (EC) No 1272/2008 no classification is required for toxicity to reproduction.

## 4.9. DNEL(s) / DMEL(s)

**Available dose-descriptor(s) per endpoint for the submission substance as a result of its hazard assessment**

| Endpoint | | Dose descriptor | Qualitative assessment | Remarks on study |
|---|---|---|---|---|
| Irritation / Corrosivity | skin | | corrosive | |
| Irritation / Corrosivity | eye | | corrosive | |
| Sensitisation | skin | | sensitising | |
| Sensitisation | respiratory tract | | sensitising | |
| Repeated dose toxicity: sub-acute / sub-chronic / chronic | inhalation | NOAEC: 0.035 mg/m³<br><br>Target organs: respiratory: nose; respiratory: lung | | |
| Mutagenicity | in vitro / in vivo | | Genetic toxicity: negative | |
| Carcinogenicity | inhalation | NOAEC: 1.15 mg/m³ | | |
| Reproductive toxicity: fertility impairment | inhalation | NOAEC: 2.03 mg/m³ | | |
| Reproductive toxicity: developmental toxicity | inhalation | NOAEC: 2.1 mg/m³ | | |

## DN(M)ELs for workers

| Exposure pattern | Route | Descriptor | DNEL / DMEL | (Corrected) Dose descriptor *) | Most sensitive endpoint | Justification |
|---|---|---|---|---|---|---|
| Acute - systemic effects | Dermal | | | | sensitisation (respiratory tract) | HDI appears to have some potential to induce respiratory hypersensitivity and there is evidence from both human experience and animal studies, which indicate that effective sensitization of the respiratory tract can result from dermal contact with a chemical respiratory allergen. Because there are currently no available methods to determine thresholds and DNELs for respiratory sensitizers, therefore a quantitative risk assessment for this endpoint (= leading health effect after dermal contact) is not possible. |
| Acute - systemic effects | Inhalation | DNEL (Derived No Effect Level) | 0.07 mg/m³ | | irritation (respiratory tract) | see "Discussion" |
| Acute - local effects | Dermal | | | | sensitisation (respiratory tract) | HDI appears to have some potential to induce respiratory hypersensitivity and there is evidence from both human experience and animal studies, which indicate that effective sensitization of the respiratory tract can result from dermal contact with a chemical respiratory allergen. Because there are currently no available methods to determine thresholds and DNELs for respiratory sensitizers, therefore a quantitative risk assessment for this endpoint (= leading health effect after dermal contact) is not possible. |
| Acute - local effects | Inhalation | DNEL (Derived No Effect Level) | 0.07 mg/m³ | | irritation (respiratory tract) | see "Discussion" |
| Long-term - systemic effects | Dermal | | | | sensitisation (respiratory tract) | HDI appears to have some potential to induce respiratory hypersensitivity and there is evidence from both human experience and animal studies, which indicate that effective sensitization of the respiratory tract can result from dermal contact with a chemical respiratory allergen. Because there |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | are currently no available methods to determine thresholds and DNELs for respiratory sensitizers, therefore a quantitative risk assessment for this endpoint (= leading health effect after dermal contact) is not possible. |
| Long-term - systemic effects | Inhalation | DNEL (Derived No Effect Level) | 0.035 mg/m³ | | irritation (respiratory tract) | see "Discussion" |
| Long-term - local effects | Dermal | | | | sensitisation (respiratory tract) | HDI appears to have some potential to induce respiratory hypersensitivity and there is evidence from both human experience and animal studies, which indicate that effective sensitization of the respiratory tract can result from dermal contact with a chemical respiratory allergen. Because there are currently no available methods to determine thresholds and DNELs for respiratory sensitizers, therefore a quantitative risk assessment for this endpoint (= leading health effect after dermal contact) is not possible. |
| Long-term - local effects | Inhalation | DNEL (Derived No Effect Level) | 0.035 mg/m³ | | irritation (respiratory tract) | see "Discussion" |

**) The (corrected) dose descriptor starting points have been automatically calculated by multiplying the values of the fields "D(N)MEL" and "Assessment factor" provided in the Endpoint summary of IUCLID section 7. Toxicological information. It reflects the value after any corrections, e.g. route-to-route extrapolation. See column "Justification" for the rationale behind such modifications and the use of assessment factors.*

**Discussion**

Inhalation exposure is typically the most relevant route for assessing occupational risk in humans. Effects from repeated exposure of animals to hexamethylene diisocyanate (HDI) are limited to effects on the respiratory tract caused by local irritation. In a 2-year chronic toxicity and carcinogenicity study with vapour exposure of HDI to rats a NOAEC of 0.035 mg/m3 (0.005 ppm) was determined (Shiotsuka, 1989). Neither indications of systemic toxicity nor evidence of a carcinogenic potential were found in rats. Tests assessing the mutagenic potential of HDI in vitro and in vivo provide no evidence of mutagenic or genotoxic activity.

According to the ECHA Guidance on information requirements and chemical safety assessment - chapter R.8 (May 2008) a national occupational exposure limit (OEL) was used as a surrogate for a DNEL. For HDI the German MAK Commission established an OEL (MAK value) of 0.005 ppm (0.035 mg/m3) referring to an 8-hour exposure period. This OEL is used as a surrogate DNEL for long-term exposure. A ceiling limit value of 0.01 ppm (0.07 mg/m3) was settled. This ceiling limit is used as a surrogate DNEL for short-term exposure. The justification of these OELs is given in the published HDI evaluation of the German MAK Commission (DFG, 1996) [1] with the following statements (inofficial translation from German into English; for official and complete rationale see DFG 1996):

Both in humans and in animals the irritating and sensitising effects of HDI on the respiratory tract are in the foreground. However, the present experiences in man are not suitable for the derivation of a MAK value since they always refer practically to mixed exposures with HDI prepolymers, other diisocyanates or solvents and the real exposure levels were usually not determined quantitatively. In the subacute inhalation study the NOEC for rats was 0.005 ppm (0.035 mg/m3). Concentrations above 0.15 ppm (1.05 mg/m3) led to distinct changes in the nasal mucosa (squamous metaplasia). The same changes as well as initial clinical signs of ocular irritation were observed in the 13 -week study at the lowest test concentration of 0.011 ppm (0.08 mg/m3) already. In the 2-year inhalation study in rats concentrations of 0.005 ppm (0.035 mg/m3) and above lead to metaplasia/hyperplasia and hyaline droplet degeneration of respiratory epithelium and mucus secreting glands. In addition, hyperkeratosis of the respiratory epithelium and degeneration of the olfactory epithelium were observed at 0.025 ppm (0.175 mg/m3) and above. Since the findings described at 0.005 ppm increased with rising concentrations only with regard to incidence, but not with regard to severity and comparable alterations also occurred spontaneously, they were evaluated as an adaptive response (Foureman et al., 1994) [2]. Such adaptive reactions are frequently observed in rodents after exposure to gaseous irritants (Monticello et al., 1990) [3]. Thus, a NOAEC of 0.005 ppm was established for the long-term inhalation study in rats. The MAK value for HDI is therefore reduced to 0.005 ppm (0.035 mg/m3). The limited human experiences also indicate that irritation effects are not longer expected at this concentration. However, this does not apply to persons with a non-specific bronchial hyperreactivity or an allergic hypersensitivity to HDI since with these persons minimal concentrations can already provoke bronchospastic conditions.

The German OEL for HDI is in agreement with the threshold limit value (TLV-TWA: 0.005 ppm (0.034 mg/m3)) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2001) and no additional information became available in the meantime that would influence the respective assessment.

No comparative DNELs for systemic effects (short-term and long-term exposure) are calculated since no indications of systemic toxicity were observed in the repeated dose toxicity studies by the inhalation route. The toxicological database for inhaled HDI demonstrates consistently that toxicity is associated only with the portal of entry (respiratory tract).

No DNEL for skin sensitization is calculated as the relationship between skin dose and response is not clear. There is no validated method of DNEL calculation for skin sensitization. According to the potency categorisation approach HDI is classified as a moderate to strong skin sensitizer (Category 1) based on a guinea pig maximization test (GPMT: 10 % induction conc., $\geq$ 94 % incidence of sensitization; Schmidt and Bomhard, 1983) and a Buehler test (1 % induction conc., 70 % incidence of sensitization; Zissu et al., 1998), respectively. The results of a local lymph node assay with HDI (LLNA: calculated EC3 value of 0.03 %; Hilton et al., 1995) were not considered for the potency categorisation on skin sensitization since this test is also sensitive against respiratory sensitizers and irritants (De Jong et al., 2009) [4] and does not allow differentiation of antigen-specific immune responses from non-specific inflammatory reactions (McGarry, 2007) [5]. Therefore, LLNA results with HDI are deemed to be overpredictive.

A lung sensitization test in guinea pigs (Pauluhn, 1996) as well as a modified LLNA in mice (Arts et al. 2008; De Jong et al., 2009) provides clear evidence that HDI is a respiratory sensitizer (Category 1). Since there are currently no available methods to determine thresholds and DNELs for respiratory sensitizers, a quantitative risk assessment for this endpoint is not possible. Substances with the R-phrase R42 (Category 1) have to be allocated to the high hazard category. There is evidence from both human and animal studies, which indicate that effective sensitization of the respiratory tract can result from dermal contact with a chemical respiratory allergen

(ECHA Guidance on information requirements and chemical safety assessment - Part E: Risk characterisation (May 2008)).

For HDI no repeated dose toxicity studies by the dermal route are available. As mentioned above exposure to HDI via the air does not lead to systemic toxicity, therefore systemic toxicity is covered by the respective DNELs for inhalation exposure. As there is no indication that dermal contact could lead to principally different and more severe systemic effects compared to inhalation exposure, a DNEL for systemic toxicity (short-term and long-term) after dermal contact is not required. Regarding local effects the corrosive potential as well as the sensitization potential needs to be considered in the selection of the respective risk management measures (RMMs) at the workplaces.

The DNEL for long-term exposure covers also reproductive toxicity, as HDI is not a reproductive toxicant and the local effects at the respiratory tract covered by the DNEL for long-term exposure are the most sensitive effects also in the reproduction/developmental toxicity screening test and the developmental toxicity study.

[1]Deutsche Forschungsgemeinschaft (DFG, 1996): Hexamethylendiisocyanat. In: Gesundheitsschädliche Arbeitsstoffe - Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. DFG, Nachtrag 23. Lieferung 1996

[2]Foureman GL et al. (1994): Evaluation of nasal tract lesions in derivation of the inhalation reference concentration for hexamethylene diisocyanate. Inhalation Toxicology 6 (Suppl.): 341-355

[3]Monticello TM et al. (1990): Nonneoplastic nasal lesions in rats and mice. Environ. Health Perspect. 85: 249-274

[4]De Jong WHet al. (2009): Contact and respiratory sensitizers can be identified by cytokine profiles following inhalation exposure. Toxicology 261: 103-111

[5]McGarry HF (2007): The murine local lymph node assay - Regulatory and potency considerations under REACH. Toxicology 238: 71-89

### DN(M)ELs for the general population

**Discussion**

The substance is not used in the public domain and exposure of consumers is thus not to be expected.

# 5. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

## 5.1. Explosivity

The following information is taken into account for any hazard / risk assessment:

Performing of a test is scientifically not necessary. According to United Nations (2003) (Annex 6, Table 6.1), hexamethylene diisocyante (HDI) does not contain a chemical moiety suggesting a potential for explosivity.

## 5.2. Flammability

The following information is taken into account for any hazard / risk assessment:

(a) No flammability in contact with water: The substance contains no metals or metalloids and therefore will not release flammable gases in contact with water.

(b) Pyrophic properties: Experience in production or handling; substance is known to be stable at room temperature.

(c) Performing of a study according to EG A10 is technically not feasible, as the substance is a liquid.

**Flash point**

Reference:

Eisenmann, 1977

Guideline:

German standard method DIN 51758

The following information is taken into account for any hazard / risk assessment:

130 °C (closed cup)

## 5.3. Oxidising potential

The following information is taken into account for any hazard / risk assessment:

Performing of a test is scientifically not necessary. According to United Nations (2003) (Annex 6, Table 6.1), hexamethylene diisocyanate (HDI) does not contain a chemical moiety suggesting an oxidising potential.

# 6. PBT AND VPVB ASSESSMENT

## 6.1. Assessment of PBT/vPvB Properties - Comparison with the Criteria of Annex XIII

| Criterion | PBT criteria | vPvB criteria | property | Criterion fulfilled? |
|---|---|---|---|---|
| P | Half-life in marine water > 60 d, or<br>half-life in fresh- or estuarine water > 40 d, or<br>half-life in marine sediment > 180 d, or<br>half-life in fresh- or estuarine water sediment > 120 d, or<br>half-life in soil > 120 d | Half-life in marine, fresh or esturarine water > 60 d, or<br><br>Half-life in marine, fresh or esturarine sediment > 180 d, or<br><br>half-life in soil > 180 d | Not readily biodegradable (Bayer AG 2000a) but abiotic degradation; Half-life in fresh water < 12 hours. | Preliminary yes |
| B | BCF > 2000 | BCF > 5000 | No bioaccumulation potential | no |
| T | Long-term NOEC for marine or freshwater organisms < 0.01 mg/l | Not applicable. | 72h-NOEC 11.7 mg/l for algae (Bayer AG 2000b) | no |
| T | CMR | Not applicable. | Not classified as CMR | no |
| T | Other evidence of chronic toxicity, as identified by the classifications: T, R48, or Xn, R48 according to Directive 67/548/EEC | Not applicable | Not classified as T, R48, or Xn, R48 according to Directive 67/548/EEC | no |

### 6.1.1. Persistence Assessment

Hexamethylene disiocyanate (HDI) is not readily biodegradable with 42 % biodegradation in 28 days (Bayer AG, 2000). However, biodegradation is irrelevant as primary degradation step because of immediate hydrolysis takes place. The hydrolysis products are polyurea components and hexamethylene diamine. Polyurea is known to be inert and is probably due to its molecular size not bioavailable. Moreover, polyurea is considered insoluble in water and is characterised by limited mobility. Based on these considerations, HDI is classified as *preliminary* persistent according to screening criteria

### 6.1.2. Bioaccumulation Assessment

Measured bioconcentration factors (BCF) for hexamethylene diisocyanate (HDI) are not available.
Hexamethylene diisocyanate (HDI) hydrolyses rapidly in the presence of water with a half life of 0.23 hours. Therefore a risk estimation regarding the bioaccumulation potential of hexamethylene diisocyanate (HDI) on the basis of a log Kow, determined by QSAR, is misleading. A calculated theoretical log Kow value of 3.2 reflects the unreacted molecule without influence of water.
The hydrolysis product, hexamethylene diamine (HDA) is also not bioaccumulative. With a measured log Kow (OECD 107) of 0.02 (BASF 1978, not validated), a BCF of 3.2 was calculated with BCFWIN Program (v2.17)) (Currenta 2009f).
On the basis of these information it can not be expected that bioaccumulation of hexamethylene diisocyanate (HDI) occurs. Therefore the B criterion is not fulfilled.

### 6.1.3. Toxicity Assessment

There is one aquatic toxicity test for algae available which counts as a chronic test. The NOEC was 11.7 mg/l. Furthermore, the substance is not classified as carcinogenic, mutagenic or toxic for reproduction or R48. For these reasons, the substance does not meet the T-criterion.

### 6.1.4. Summary and overall Conclusions on PBT or vPvB Properties

A substance only is identified as a PBT substance if it fulfils all criteria described above. According to information summarized above, only the P criterion was preliminarily fulfilled and hence hexamethylene diisocyanate is not a PBT or a vPvB substance.

A substance only is identified as a vPvB substance if it fulfils both vPvB criteria described above.
The P criterion is preliminary fulfilled, the B criterion is not fulfilled.

## 6.2. Emission Characterisation

It is concluded that HDI does not fulfill the PBT/vPvB criteria. An emission characterisation is therefore not required.

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