3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (Isophorone diisocyanate)

EC Number: **223-861-6**

CAS Number: **4098-71-9**

IUPAC name: **5-Isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane**

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 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (Isophorone diisocyanate) 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 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (Isophorone diisocyanate).

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1. PHYSICAL AND CHEMICAL PROPERTIES

Molecular weight range: 222.28

Molecular formula: C12H18N2O2

Appearance/physical state/colour: light yellowish liquid; Odour: pungent

Melting / freezing point: According to available publications the melting point of isophorone diisocyanate is -60 °C. A new study does not need to be conducted according to REACH Annex VII, 7.2, column 2.

Boiling point: According to well established data collections, the boiling point of isophorone diisocyanate at normal pressure (1013 hPa) is 310 °C. Decomposition is observed at temperatures below the normal boiling point, beginning at approximately 260 °C.

Relative density: 1.058 g/cm3 at 20 °C

Vapour pressure: 0.000635 hPa at 20 °C

Water solubility: approximately 15 mg/l at 23 °C

Partition coefficient n-octanol/water (log value): The octanol-water partition coefficient of isophorone diisocyanate was calculated using a well established QSAR method at log Kow = 4.75. The partition coefficient n-octanol/water of isophorone diamine, which is the monomeric hydrolysis product of isophorone diisocyanate, is log Kow = 1.67 at 20 °C (shake-flask method, OECD TG 107 / EU method A.8). Experimental verification of the QSAR value is hardly possible because of the rapid hydrolysis of the test substance.Also due to hydrolysis, the partition coefficient of the hydrolysis product, for which isophorone diamine may be considered as a surrogate, is relevant for evaluating the environmental behavior of isophorone diisocyanate.

Flash point: 150.5 °C at 1013 hPa (Pensky-Martens method; closed cup).

Flammability: The test substance is a liquid. The EU method is not applicable for liquids.
Experimental experience, in particular from studies on flash point and water solubility, shows that isophorone diisocyanate is neither pyrophoric nor flammable in contact with water. Upon hydrolysis carbon dioxide (mineral) and very unvolatile organic substances are formed.

Explosive properties: As 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl-isocyanate was neither shock sensitive nor thermally sensitive (AQura, 2009), according to the criteria of the EC test method A.14 it is not representing an explosive hazard and has not to be considered to present a danger of explosion.

Self-ignition temperature: According to several data collections, autoignition of isophorone diisocyanate at atmospheric pressure was observed at 430 °C. Experimental details have not been reported.

Oxidising properties: Based on the chemical structure, the substance is incapable of reacting exothermically with combustible materials. The substance contains oxygen atoms (no halogen atoms), but the oxygen atoms are not bonded directly to nitrogen atoms or other oxygen atoms. Therefore, according to REACH Annex VII, 7.13, column 2 testing is not required.

Stability in organic solvents: The stability of the substance is not considered to be critical. The substance is completely miscible with esters, ketones, ethers, and aromatic and aliphatic hydrocarbons. Therefore testing is not required according to REACH Annex IX, 7.15, column 1.

Dissociation constant: The substance is hydrolytically unstable (half-life less than 12 hours). Therefore, a test is not required according to REACH Annex IX, 7.16, column 2.

Viscosity: A testing proposal is submitted to ECHA for this endpoint according to OECD Test Guideline 114 (Viscosity of Liquids).

2. ENVIRONMENTAL FATE PROPERTIES

General discussion of environmental fate and pathways:

Releases into the environment may occur during production ofisophorone diisocyanate, during formulation and use of formulations as well as from its use as a monomer for the production of polymers or other downstream products.

Distribution modelling 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 %. The calculated Henry's law constant of 0.941 Pa m3/mol (vapor pressure x molecular weight / water solubility) at 20-23 °C indicates low volatility from aqueous solution. Both Henry's law constant and adsorption / desorption constant cannot be studied due to rapid hydrolysis of isophorone diisocyanate. Environmental distribution considerations for isophorone diisocyanate are of little relevance because the reaction with water is expected to eliminate the substance from the environment rapidly.

The rate constant of the OH radical sensitized indirect photodegradation of isophorone diisocyanate corresponds to a half-life of 1.8 days at a 24 hour mean OH radical concentration of 500,000 molecule/cm³, which is typical of Central Europe. A preliminary hydrolysis test resulted in a dissipation half-life of 0.84 hours (approx. 50 minutes) at 23 °C. No ready biodegradation (0% degradation within 28 days) was observed in a manometric respiratory test performed with domestic, non-adapted activated sludge according to Directive 92/69/EEC, C.4-D. Biodegradation of the substance itself is irrelevant as primary degradation step because hydrolysis is much faster.

Rapid hydrolysis of the substance makes approximation of equilibrium in the environment impossible resulting in a low potential for bioaccumulation.

2.1. Hydrolysis

Discussion

According to experience with the substance itself as well as with similar diisocyanates, the amines formed in the initial hydrolysis step, which is associated with elimination of carbon dioxide, have a high reactivity towards unreacted isocyanate. The consequence is that in the hydrolysis of isophorone diisocyanate predominantly polyurea molecules are formed. They are insoluble in water. Their formation was observed in the study of Infracor GmbH (2000) who reported that droplets settled on the bottom of the test vessel and became increasingly coated with a white layer.

Beside these insoluble main hydrolysis products minor amounts of other hydrolysis products having a low to moderate molecular weight and being more or less water soluble (e. g. isophorone diamine). They were determined by unspecific TOC analysis in aqueous phases of ecotoxicity studies where their potential for adverse environmental effects was investigated (see section 6.1).

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

A preliminary hydrolysis test was conducted by Bayer AG (1999) in order to determine the dissipation half-life of isophorone diisocyanate. The test medium was 30 % acetonitrile / 70 % water (no buffer) at 23 °C. Samples of the test solution were taken every 11 minutes and analysed by GC/FID. Approx. 84 % of the test substance were found to dissipate within a period of 121 minutes. The dissipation half-life was determined as 0.84 hours (approx. 50 minutes). Degradation products have not been analysed.

The observed half-life is in agreement with the results of Infracor GmbH (2000) who performed a preliminary study in unbuffered aqueous solution. The results show that the half-life at 23 °C is below 7.2 hours.

2.2. Phototransformation in air

Discussion

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

The rate constant of the OH radical sensitized indirect photodegradation of isophorone diisocyanate has been calculated using a well established QSAR method (AOP Computer Program, Vers. 1.90) as 8.8248E-12 cm^3/(molecule*sec). This corresponds to a half-life of 1.8 days at a 24 hour mean OH radical concentration of 500,000 molecule/cm^3, which is typical of Central Europe.

2.3 Biodegradation

2.3.1. Biodegradation in water and sediment

Discussion (screening testing)

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

No ready biodegradation (0% degradation within 28 days) 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).

2.3.2. Biodegradation in soil

Discussion

As no biodegradation (0%) was observed in a study on ready biodegradability it is not expected that significant degradation would occur in a soil degradation test. The test substance is considered as non-biodegradable in surface water and sediment compartment. Moreover, biodegradation is irrelevant as primary degradation step because immediate hydrolysis takes place.

2.3.3. Summary and discussion of degradation

Abiotic degradation

The rate constant of the OH radical sensitized indirect photodegradation of isophorone diisocyanate corresponds to a half-life of 1.8 days at a 24 hour mean OH radical concentration of 500,000 molecule/cm^3, which is typical of Central Europe. A preliminary hydrolysis test resulted in a dissipation half-life of 0.84 hours (approx. 50 minutes) at 23 °C.

Biotic degradation

No biodegradation (0% degradation within 28 days) 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). Biodegradation of the substance itself is irrelevant as primary degradation step because hydrolysis is much faster. As no degradation occurred in the test on ready biodegradability it is not expected that a significant degradation would occur in a simulation test (water and soil). The test substance is considered as non-biodegradable in surface water, sediment and soil. However, biodegradation is considered as irrelevant as primary degradation step anyway because immediate hydrolysis takes place.

2.4. Environmental distribution

2.4.1. Adsorption/desorption

Discussion

Under the test conditions required for covering this endpoint, the primary degradation product will react further. Therefore its adsorption / desorption cannot be measured. Quantifying the adsorption / desorption of the resulting polymer is technically not feasible because of its inhomogeneous composition, its low mobility inhibiting equilibration, and analytical limitations.

The following information is taken into account for any environmental exposure assessment:

According to REACH Annex VII, 9.3.1, column 2 the adsorption/desorption study does not need to be conducted as the substance and its relevant degradation products decompose rapidly.

2.4.2. Volatilisation

Discussion

Due to hydrolysis the Henry's law constant cannot be measured. Environmental distribution considerations for isophorone diisocyanate are of little relevance because the reaction with water is expected to eliminate the substance from the environment rapidly.

The following information is taken into account for any environmental exposure assessment:

The calculated Henry's law constant of 0.941 Pa m3/mol (vapour pressure x molecular weight / water solubility) at 20-23 °C indicates low volatility from aqueous solution.

2.4.3. Summary and discussion of environmental distribution

Releases into the environment may occur during production of isophoronedi 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.

Distribution modelling 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 %. The calculated Henry's law constant of 0.941 Pa m3/mol (vapour pressure x molecular weight / water solubility) at 20-23 °C indicates low volatility from aqueous solution. Both Henry's law constant and adsorption / desorption constant cannot be studied due to rapid hydrolysis of isophorone diisocyanate. Environmental distribution considerations for isophorone diisocyanate are of little relevance because the reaction with water is expected to eliminate the substance from the environment rapidly.

2.5. Bioaccumulation

Rapid hydrolysis of the substance makes approximation of equilibrium in the environment impossible resulting in a low potential for bioaccumulation.

2.5.1 Aquatic bioaccumulation

According to REACH Annex IX, 9.3.2, column 2 the bioaccumulation study does not need to be conducted if the substance has a low potential for bioaccumulation. Rapid hydrolysis of the substance makes approximation of equilibrium in the environment impossible resulting in a low potential for bioaccumulation

According to experience with the substance itself as well as with similar diisocyanates, the amines formed in the initial hydrolysis step, which is associated with elimination of carbon dioxide, have a high reactivity towards unreacted isocyanate. The consequence is that in the hydrolysis of isophorone diisocyanate predominantly

polyurea molecules are formed. They are insoluble in water. Their formation was observed in the hydrolysis study of Infracor GmbH (2000) (see 5.1.2) who reported that droplets settled on the bottom of the test vessel and became increasingly coated with a white layer.

The polyurea molecules cannot bioaccumulate due to the absence of sufficient mobility. Therefore not only the substance itself but also its hydrolysis products have a low potential for bioaccumulation.

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

According to REACH Annex IX, 9.3.2, column 2 the bioaccumulation study does not need to be conducted if the substance has a low potential for bioaccumulation. Rapid hydrolysis of the substance makes approximation of equilibrium in the environment impossible resulting in a low potential for bioaccumulation. For the bioaccumulation potential of the hydrolysis products see the discussion below.

2.5.2 Terrestrial bioaccumulation
There are no data on terrestrial bioaccumulation available

2.5.3 Secondary poisoning

Based on the available information, there is no indication of a bioaccumulation potential and, hence, secondary poisoning is not considered relevant (see CSR chapter 7.5.3 "Calculation of PNECoral (secondary poisoning) ".

Justification for no PNEC oral derivation: There are no results from long-term bird or mammal studies reporting on dietary or oral exposure available. Hence a determination of the PNEC oral is not possible. However, considering that direct or indirect exposure of the soil compartment is unlikely and that hydrolysis is the dominating degradation process in the aquatic environment (no bioaccumulation) secondary poisoning is not determined to be a relevant exposure route for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

3. ENVIRONMENTAL HAZARD ASSESSMENT

3.1. Aquatic compartment (including sediment)

3.1.1. Toxicity test results

3-Isocyanatomethyl-3,5,5 -trimethylcyclohexyl isocyanate hydrolyses upon contact with water. The diisocyanate groups of the substance react by forming amines (i. e. 3-aminomethyl-3,5,5-trimethylcyclohexylamine) and CO2. The amines formed may react further with unreacted diisocyanate groups of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate resulting in oligo- and subsequently polyurea components.

Test substance solutions of 3-isocyanatomethyl-3,5,5 -trimethylcyclohexyl isocyanate were prepared at nominal concentrations that were some orders of magnitude higher than the maximum water solubility. The solutions were stirred for 18 to 24 hours and insoluble particles were filtered off. Substance concentrations were determined as DOC/TOC and were back-calculated to the parent compound. For long-term toxicity to aquatic invertebrates a Daphnia reproduction test with 3-aminomethyl-3,5,5-trimethylcyclohexylamine (hydrolysis product) was taken into account. The lowest toxicity values were derived for Daphnia magna. The EC50, 48 hours was 27 mg/L (parent substance) and the NOEC, 21 days was 3.0 mg/L (hydrolysis product).

3.1.2. Short-term toxicity to fish

Discussion

The LC50 values for Danio rerio and Cyprinus carpio were determined as >72 mg/L and >208 mg/L, respectively. In view of the low solubility in water (see chapter 4.9) and the liability towards hydrolysis (see chapter 5.1.2) of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, exposure to well-defined aquatic concentrations is difficult to achieve. Due to fast hydrolysis, the observed effect is expected to be the effect of the hydrolysis product. In the aquatic environment, only the chemically less reactive hydrolysis product is expected to be relevant. The methods used for the determination of the test substance concentration (DOC or TOC) do not differentiate between parent substance and hydrolysis product. Hence the analytical results should be treated with caution.

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

A static acute 96-hour fish toxicity limit test according to Directive 92/69/EEC was performed with Danio rerio (Bayer AG, 2000). No mortalities or abnormal swimming behaviour were observed. The analytical test concentration, which was determined daily by DOC measurements, was 72.3 mg/l. In a semi-static acute fish toxicity test according to Directive 92/69/EEC, Hüls AG (1996) no mortalities in Cyprinus carpio within 96 hours of exposure to concentrations up to the maximum possible concentration of 208 mg/l were observed.

3.1.3. Long-term toxicity to fish

Discussion

The following information is taken into account for long-term fish toxicity for the derivation of PNEC:

According to Annex IX, 9.1, column 2 of the REACH regulation long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. As Daphnia magna was observed to be the most sensitive species (parent substance: EC50, 48 hours: 27 mg/L; hydrolysis product: NOEC, 21 days: 3.0 mg/L) no long-term toxicity testing with fish is needed.

3.1.4. Short-term toxicity to aquatic invertebrates

Discussion

Among the two valid freshwater studies, the highest sensitivity was observed in the test which was conducted by Hüls AG (1995) and therefore this test was determined as key study. The test conducted with the marine crustacean *Chaetogammarus marinus* (Adema 1982) was also determined as key study, but its reliability is limited by several restrictions: no standard protocol, no standard organism, no analytical monitoring, use of a solubilizer.
In view of the low solubility in water (see chapter 4.9) and the liability towards hydrolysis (see chapter 5.1.2) of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, exposure to well-defined aquatic concentrations is difficult to achieve. Due to fast hydrolysis, the observed effect is expected to be the effect of the hydrolysis product. In the aquatic environment, only the chemically less reactive hydrolysis product is expected to be relevant. The methods used for the determination of the test substance concentration (DOC or TOC) do not differentiate between parent substance and hydrolysis product. Hence the analytical results should be treated with caution.

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

Daphnia magna were exposed to the test substance in a static test conducted by Hüls AG (1995) according to EU method C.2. Five concentrations ranging from 5.2 to 73 mg/L were tested over a period of 48 hours. The EC50 (48 hours) was determined as 27 mg/L. A second freshwater test with Daphnia magna was conducted by Bayer AG (2000) with an EC50 of 35 mg/L. Another study was conducted with the marine crustacean Chaetogammarus marinus (Adema 1982). The study was not well documented and was characterised by some deficiencies (e. g. no standard protocol, no analytical monitoring, etc.). The EC50 (96 hours) was determined as 4.0 mg/L.

3.1.5. Long-term toxicity to aquatic invertebrates

Discussion

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

The long-term toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine on Daphnia magna was investigated over a test period of 21 days according to OECD 202, part 2 (1984). As the mentioned substance is the main

hydrolysis product of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate this substance can be used as supporting substance for a read-across purposes. The reproduction rate and the mortality of the parent animals were monitored at nominal concentrations ranging from 0.1 to 30.0 mg/L. The long-term NOEC for reproduction (21 days) was determined as 3 mg/L and the LOEC (reproduction) as 10 mg/L.

3.1.6. Algae and aquatic plants

Discussion

Effects on algae / cyanobacteria

In view of the low solubility in water and the liability towards hydrolysis of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, exposure to well-defined aquatic concentrations is difficult to achieve. Due to fast hydrolysis, the observed effect is expected to be the effect of the hydrolysis product. In the aquatic environment, only the chemically less reactive hydrolysis product is expected to be relevant. The method for the determination of the test substance concentration (TOC) does not differentiate between parent substance and hydrolysis product. Hence the analytical results should be treated with caution.

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

The toxic effects of isophorone diisocyanate on Scenedesmus subspicatus were investigated by Bayer AG (2000) according to EU method C.3. Seven concentrations ranging from 1.1 to 70.0 mg/L were tested over a period of 72 hours. The EC50 (72 hours, growth rate) was determined as >70 mg/L and the NOEC as 4.4 mg/L.

3.1.7. Sediment organisms

Data waiving

Justification: Long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment indicate the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment (compare column 2, Annex X of the REACH regulation). The CSA does not indicate the need for any long-term tests on sediment organisms.

3.1.8. Predicted No Effect Concentration (PNEC)

3.1.8.1. PNEC water

PNEC	Assessment factor	Remarks/Justification
PNEC aqua (freshwater): 0.06 mg/L	50	Extrapolation method: assessment factor An assessment factor of 50 was applied to the lowest 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 was calculated for the hydrolysis product 3-aminomehtyl-3,5,5-trimethylcyclohexylamine.
PNEC aqua (marine water): 0.006 mg/L	500	Extrapolation method: assessment factor The lowest result of two long-term studies was 3.0 mg/L (NOEC Daphnia magna reproduction test) and thus an AF of 500 was applied for the PNEC aqua (marine).
PNEC aqua (intermittent releases): 0.04 mg/L	100	Extrapolation method: assessment factor There is no information available about the intermittent release of the substance. Nevertheless a PNEC for intermittent releaese was calculated from the acute aquatic data. The most sensitive organism for short term

		aquatic toxicity is Chaetogammarus marinus (LC50 (96h): 4 mg/l). Data for three species are avaiable thus an assessment factor of 100 was applied.

3.1.8.2. PNEC sediment

PNEC	Assessment factor	Remarks/Justification
PNEC sediment (freshwater): 218.92 mg/kg sediment dw		Extrapolation method: partition coefficient There are no test results available for sediment dwelling freshwater organisms. The PNEC for sediment was derived by using the equilibrium partitioning method.
PNEC sediment (marine water): 21.89 mg/kg sediment dw		Extrapolation method: partition coefficient There are no test results available for sediment dwelling marine organisms. The PNEC for sediment was derived by using the equilibrium partitioning method.

3.2. Terrestrial compartment

According to Annex IX, column 2 of the REACH regulation no data on terrestrial organisms are needed, if direct or indirect exposure of the soil compartment is unlikely. There is no indication that there is a relevant route of exposure with respect to soil.

3.2.1. Toxicity to soil macro-organisms

Data waiving

Information requirement: Toxicity to soil macro-organisms except arthropods

Justification: According to Annex IX, column 2 of the REACH regulation no data on terrestrial organisms are needed, if direct or indirect exposure of the soil compartment is unlikely. There is no indication that there is a relevant route of exposure with respect to soil.

Information requirement: Toxicity to terrestrial arthropods

Justification: According to Annex IX, column 2 of the REACH regulation no data on terrestrial organisms are needed, if direct or indirect exposure of the soil compartment is unlikely. There is no indication that there is a relevant route of exposure with respect to soil.

3.2.2. Toxicity to terrestrial plants

Data waiving

Justification: According to Annex IX, column 2 of the REACH regulation no data on terrestrial organisms are needed, if direct or indirect exposure of the soil compartment is unlikely. There is no indication that there is a relevant route of exposure with respect to soil.

3.2.3. Toxicity to soil micro-organisms

Data waiving

Justification: According to Annex IX, column 2 of the REACH regulation no data on terrestrial organisms are needed, if direct or indirect exposure of the soil compartment is unlikely. There is no indication that there is a relevant route of exposure with respect to soil.

3.2.4. Predicted No Effect Concentration (PNEC soil)

PNEC	Assessment factor	Remarks/Justification
PNEC soil: 44.01 mg/kg soil dw		Extrapolation method: partition coefficient There are no test results available for soil organisms. The PNEC for soil was derived by using the equilibrium partitioning method.

3.3. Atmospheric compartment

Direct data on biotic and abiotic effects of isophorone diisocyanate 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, there are no indications that isophorone diisocyanate 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:

The effects of isophorone diisocyanate on the inhibition of the respiration rate of activated sludge (from a STP treating predominantly domestic sewage) was investigated by Bayer AG (2000) according to EU method C.11. The oxygen content was measured at five concentrations ranging from 100 to 1000 mg/L over a period of 3 hours. The EC50 (3 hours contact time) was determined as 263 mg/L.

3.4.2. PNEC for sewage treatment plant

Value	Assessment factor	Remarks/Justification
PNEC STP: 10.6 mg/L	10	Extrapolation method: assessment factor An AF of 10 is to be applied to the NOEC/EC10 of a sludge respiration test. The EC10 of the sludge respiration test was 106 mg/L and thus a PNEC of 10.6 mg/L was obtained.

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

3.5.1. Toxicity to birds

Data waiving

Justification: The risk for secondary poisoning is considered to be negligible because the substance has a low potential for bioaccumulation. Rapid hydrolysis of the substance makes approximation of equilibrium in the environment impossible resulting in a low potential for bioaccumulation.

Discussion

The following information is taken into account for effects on birds for the derivation of PNEC:

There are no results from long-term bird or mammal studies reporting on dietary or oral exposure available. Hence a determination of the PNEC oral is not possible. However, considering that direct or indirect exposure of the soil compartment is unlikely and that hydrolysis is the dominating degradation process in the aquatic environment (no bioaccumulation) secondary poisoning is not determined to be a relevant exposure route for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

3.5.2. Toxicity to mammals

There are no data on mammals available.

3.5.3. PNECoral (secondary poisoning)

PNEC	Assessment factor	Remarks/Justification
No potential for bioaccumulation		There are no results from long-term bird or mammal studies reporting on dietary or oral exposure available. Hence a determination of the PNEC oral is not possible. However, considering that direct or indirect exposure of the soil compartment is unlikely and that hydrolysis is the dominating degradation process in the aquatic environment (no bioaccumulation) secondary poisoning is not determined to be a relevant exposure route for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

3.6. Conclusion on the environmental hazard assessment and on classification and labelling

Environmental classification justification

Directive 67/548/EEC:
According to Directive 67/548/EEC annex 1, the test substance is classified as "R51/53 Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment". However, considering the chronic aquatic toxicity data from a Daphnia reproduction study with the hydrolysis product 3 -aminomethyl-3,5,5 -trimethylcyclohexylamine (the test substance has a half-life <12 hours) it is proposed that the test substance is not environmentally classified.

GHS:
According to Annex VI of the CLP regulation the test substance has to be classified as “Hazardous to the aquatic environment, chronic 2”(Hazard statement H411: Toxic to aquatic life with long lasting effects.).However, considering the chronic aquatic toxicity data from a Daphnia reproduction study with the hydrolysis product 3 -aminomethyl-3,5,5 -trimethylcyclohexylamine (the test substance has a half-life <12 hours) it is proposed that the test substance is not environmentally classified.

4. HUMAN HEALTH HAZARD ASSESSMENT

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

Basic toxicokinetics

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

Studies in Animals

"There are no data available on the metabolic fate of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate in experimental animals. "

Studies in Humans

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

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

Cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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. "

4.2. Acute toxicity

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

Studies in Animals

Inhalation

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

These considerations lead to some requirements for adequately testing the inhalation toxicity of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. The particle-size distribution of aerosols generated in

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

Particular attention was paid to the location of effects in the study of Pauluhn (2004). Both the concentration- and time dependence of parameters in the bronchoalveolar lavage fluid (BALF) following a single 6 hours exposure to the aerosolized 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate was analyzed. Male rats were exposed in direct-flow nose-only exposure chambers to conditioned air or target concentrations of 2, 8, and 25 mg 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate/m^3(analytical: 2.09; 7.5; 26 mg/m^3). The test substance was applied as an aerosol with high respirability (MMAD 1.6 µm; GSD approx. 1.8 µm) at the high level group. No particle size analyses were performed in the low and mid dose group because these concentrations were in the range of the vapor saturation concentration of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. BALF was analyzed for protein as an index of air-blood barrier permeability. Lactate dehydrogenase (LDH) was taken as indicator of cell injury. These endpoints were determined on postexposure days 1, 3, and 7. Clinical signs of respiratory distress were observed at 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate concentrations$\geq$ 8 mg/m^3. 2/18 rats died at 25 mg/m^3. At 8 mg/$m^3$and higher body weight retardation was observed, which was statistically significant only in the high dose group (21% below control on day 7). Rectal temperature was statistically significantly decreased at 8 and 25 mg/m^3(6.2 and 9.1°C below control, respectively). Lung weights were increased only in the high dose group (25 mg/m^3) not until at day 7 (+24.3%) as were protein (+291%; also significant on day 1, not on day 3) and LDH (+151%) in BALF. The time course of changes can be associated with features reminiscent of upper airway rather than pulmonary irritation. "

The inhalation LC_{50}of3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate(purity > 99%) was determined by Bayer AG (1995) 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 of3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanatewere 20.4, 53.3, 73.8, 104.6 and 410.3 mg/m^3. The test substance aerosol exhibited a particle-size indicating that this aerosol was of adequate respirability (83% of the particle mass was< 3 µm; MMAD approx. 1.6 – 2.1 µm; GSD approx. 1.7 µm). Rats exposed to >= 20.4 mg/m^3experienced signs of respiratory tract distress (i. e. tachypnea, bradypnea, stridor). Body weight gain and rectal temperature were depressed significantly in all exposed groups. Exposure to a concentration of 53.3 mg/m^3induced mortality in 6 of 10 animals. This mortality was observed between days 16 and 28. Exposure to concentrations of >= 73.8 mg/$m^3$was lethal for all exposed animals and increased exposure concentrations clearly induced a speeding up of mortality. With the exception of a less collapsed lung and some focal discolorations of the lung, which are sporadically observed, survivors showed no substance-induced macroscopic, extrapulmonary alterations. Animals that died during or following exposure showed nose/muzzle with red incrustations, mucous membrane of nose with reddening, pleural cavity filled with liquid, lung less collapsed emphysematous, and spongy, which are considered to reflect local irritant effects to the respiratory tract. " The LC_{50}(4 h) stated in this study (Bayer AG, 1995) is approximately 40 mg/$m^3$for both sexes.

"In the OECD TG 403 study of RCC (1988), a four-hour LC_{50}of3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate(purity > 99%) to male and female Wistar rats of 31 mg/$m^3$was determined. The no-observed-effect level was less than 18 mg/m^3. The animals were exposed flow-past nose-only to3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate aerosol and observed for up to 17 days after exposure. Applied analytical concentrations were 18, 22, 70 and 450 mg/m^3. The data on particle size distribution showed that all particles were below 4.6 µm and approximately 90% w/w of the particles had diameters$\leq$ 2.13 µm at the three lowest exposure concentrations. The predominant clinical signs werebreathing difficulty, piloerection and stagger. Necropsy findings were red foci on lung lobes, or reddish lungs (in decedent animals only). There was no body weight gain during the first week.

Dermal

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

Oral

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

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

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

Cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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. "

Justification for classification or non classification

The substance 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is classified according to the criteria of EC Directive 67/548/EEC (Annex I) as follows: "Toxic by inhalation" (T, R 23)

4.3. Irritation

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

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). "The overall result was “corrosive” because of extensive irreversible tissue damage such as necrosis, ulceration, or scarring within the observation period (14 days) in all animals. This overall assessment was confirmed by another study performed according to OECD TG 404 with one rabbit exposed semiocclusively for four hours, the result was “corrosive” with an irritation index of 4.5 of max. 8.0 (Krötlinger, 1994). "

Eye Irritation

Studies in Animals

Conflicting results ranging from “not irritating” (Hüls AG, 1984) 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) may have contributed to the avoidance of damage to the eye. "The irritation index was 9.96 of max. 110. Ten days after treatment with 0.1 ml undiluted test substance all animals in this study showed loss of hair around the eye and incrustation at the eyelid, mostly associated with thickening on day 13, which is not reflected in the scores. In the study of Schreiber (1981), where both eyes were treated (0.1 ml undiluted per eye) and only one eye was rinsed, severe irritation of the conjunctiva was observed. There was a constantly high degree of chemosis throughout the

8 days observation period both on rinsed and non-rinsed eyes, and slight cornea damage, to a lesser degree on the rinsed eye, with significant retrogression within 8 days. The irritation score was 36.4/110 (not rinsed) or 26.4/110 (rinsed eye). "

Respiratory Tract Irritation

Studies in Animals

Some studies were performed to determine the concentration causing a 50% decrease in respiration rate. This effect, which is thought to reflect the respiratory tract irritation, was observed at 11.1 mg/m³ (30 min), 10.3 mg/m^3(1 h) and 4.7 mg/m³ (3 h) in rats (MobayChemical Corporation, 1984) and at 11.1 mg/m³ (30 min), 6.0 mg/m³ (1 h) and 2.0 mg/m^3(3 h) (MobayChemical Corporation_2, 1984) or 6.0 mg/m³ (3 min), 4.0 mg/m³ (10 min) and 3.0 mg/m^3(30 min) (E. I. du Pont de Nemours and Company, 1987 and 1990) in mice (see chapter 7.2.2 of IUCLID 5 data set).

Studies in Humans

"Henschler (1972) published results of experiments with volunteers exposed for 1 - 5 minutes to an aerosol (with regard to the vapor saturation concentration at ambient temperature the particle concentration should be negligible in relation to vapor atmosphere) of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. At 0.25 mg/m^{3}the odor was just perceptible; at 0.64 mg/m^{3}slight irritation of the mucous membranes of the eyes and nose were observed; at 1.37 mg/m^{3}there was strong, intolerable irritation of the mucous membranes of the eyes and the breathing passages. " (see chapter 7.10.5 of IUCLID data set)

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

Cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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" (see chapter 7.2.2 and 7.5.3 of IUCLID5 data set). "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. " (see chapter 7.10.5 of IUCLID5 data set)

Justification for classification or non classification

The substance 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is classified according to the criteria of EC Directive 67/548/EEC (Annex I) as follows: "Irritating to eyes, respiratory system and skin" (Xi; R 36/37/38)

4.4. Sensitisation

Skin sensitisation

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

Studies in Animals

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 (IBR/Huels AG 1983, Schmidt/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., 1981).

"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. "

Studies in Humans

"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'-diisocyanatein the other) developed distinct contact dermatitis. When patch testedwith 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 of SIAR), which initially leads to the diamine (see chapter 3.1.1 of SIAR), traces of 3-aminomethyl-3,5,5-trimethylcyclohexylamine are expected to occur in patch tests with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate and may trigger symptoms of sensitization in persons who are allergic towards 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

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

Liippo and Lammintausta (2008) describe patch testing with isophorone diisocyanate in 433 dermatology patients. 8 patients from 433 tested patients showed positive reactions (1.8% of the tested patients). Cross reactivity between isophorone diamine (IPDA) and isophorone diisocyanate was apparent for two of the patients. In general according to the investigated patients the association with current dermatitis was not apparent in all cases.

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

Cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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. "

Respiratory sensitisation

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

Studies in Animals

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

The study of Plitnick et al. (2005) is based on the hypothesis on the idea that respiratory sensitizers can be identified based on relativly high expression of cytokines characteristic of Th2 cells. Thus, cytokine profiling may be an effective way to detect respiratory sensitizers. After exposure with the stest item Isophorone Diisocyanate auricular lymph nodes were removed from the animals, the total RNA was extracted and Cytokine mRNA was analysed. Response after exposure with the test item Isophorone Diisocyanate was variable but was comparatively weaker as for strong respiratory sensitizers used in this study. Biological relevance of this results are still under discussion but in general as the result of this study the authors conclude that the test item Isophorone Diisocyanate has at least respiratory sensitizing potential under the conditions of the study.

De Jong et al. (2009) and Arts et al. (2008) reported an induction of cytokine IL-4 after inhalation exposure of IPDI in an inhalative LLNA study, which is discussed to be an indicator of respiratory sensitizers.

Further studies examined cytokine profiles, serum antibodies and respirative responses after dermal exposure with IPDI followed by intranasal challenge with IPDI (Farraj et al. 2007) or followed by inhalation of metacholine (Selgrade et al. 2006)

in order to predict and screen for a respiratory sensitizing potential by using the dermal route of exposure. Although the results were ambigous and further experimental work is needed the authors conclude that IPDI appears to have some potential to induce respiratory hypersensitivity.

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

Day 1: Sitting

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

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

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

Germanaud et al. (2003) published a case of occupational hypersensitivity pneumoapathy, which according to the investigators is rarely caused by isocyanates. A 50 year old man had worked in the production of polyurethane foams and polyurethane coatings for 32 years with a generally low exposure. He then was engaged more closely in a polyurethane synthesis from 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. Few hours after the beginning of this new occupational exposure, which was not defined any more specifically, he

showed dyspnea, fever (39°C), and crepitant rales. Further investigations revealed ground glass appearance on the thoracic CT scan and lymphocytosis in the broncho-alveolar lavage. Effects were confirmed by transbronchial biopsy. Only the functional assessment (airflow obstruction and absence of marked reduction in CO transfer) was atypical for hypersensitivity pneumapathies.

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

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

Cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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. "

Justification for classification or non classification

The substance 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is classified according to the criteria of EC Directive 67/548/EEC (Annex I) as follows: "May cause sensitization by inhalation and skin contact (R 42/43).

4.5. Repeated dose toxicity

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

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

Subacute 28 day inhalation study

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

No mortality was observed in this study. No treatment-related effects were observed in urinalysis, ophthalmoscopic examination, clinical chemistry, gross pathology and examination of reflexes. Clinical signs were mild and transient signs of respiratory tract irritation (nostrils: red encrustations, stridor, nasal discharge, breathing sounds, hypothermia) in most rats only at 4.1 mg/m^3(signs in 18/20 males, 18/20 females). Body weights were slightly decreased in the high dose group (day 28: males -5.1%, statistically significant; females -3.4%, not significant) and returned rapidly to normal during the recovery period. The only relevant hematological finding was an increased leukocyte count in the peripheral blood in mid (males +46%, significant; females +82%, not significant) and high dose (males +55%, significant; females +16%, not significant) groups. Other statistical significances (none in high dose animals except prothrombin time for females +7.6%) were considered to be of no pathodiagnostic relevance. Statistically significant findings in high dose group organ weights were a reduced absolute liver weight in females (-9.7%) and an increased relative lung weight in males (+12.6%). Only the latter finding was conclusive. Histopathology revealed in rats exposed at 1.05 and 4.2 mg/m^3a 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 NOAEC (histopathological changes in nasal cavity and larynx) was 0.24 mg/m^3(Bayer AG, 2003).

Subchronic 90 day inhalation study

A subcronic 13 week inhalation study with Isophorone Diisocyanate has been conducted in young adult Wistar rats (Pauluhn, 2008). 10 male and 10 female rats per group were exposed (dynamic directed-flow, nose-only) 6 hours/day on five days/week for 13 weeks to following concentrations of the test substance: 0 (air control), 0.05, 0.27 and 1.1 mg/m3. Additional animals of the control and high-level exposure group (10/sex/group) were allowed to recover over an exposure-free time period of approximately 4 weeks. This subchronic 13 week inhalation study demonstrates that rats exposed up to 1.1 mg/m3 of the test substance did not display any substance-induced clinical effects, changes in reflexes and body temperature, conclusively affected body weights or food/water consumption. There was no evidence of hematological effects. Clinical pathology and urinanalysis were unobtrusive. There were no statistically significant or conclusive dose-dependend changes in absolute or relative organ weights. The histopathological evaluation of the nasal cavity and the larynx revealed minimal or slight epithelial changes at 1.1 mg/m3. After a four week recovery period minimal epithelial metaplasia could still be detected; however clear evidence of recovery existed. This study demonstrated that the test substance was tolerated without any systemic adverse effects or clinical findings suggestive of respiratory tract irritation at any exposure level. Taking all findings into account, 0.27 mg/m3 constitutes a No-Observed-Adverse-Effect-Concentration (NOAEC).

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

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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 LOAEC 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 NOAEC is 0.24 mg/m3.

A subchronic 13 week inhalation study demonstrates that rats exposed up to 1.1 mg/m3 of the test substance Isophorone Diisocyanate did not display any substance-induced clinical effects, changes in reflexes and body temperature, conclusively affected body weights or food/water consumption. There was no evidence of hematological effects. Clinical pathology and urinanalysis were unobtrusive. There were no statistically significant or conclusive dose-dependend changes in absolute or relative organ weights. The histopathological evaluation of the nasal cavity and the larynx revealed minimal or slight epithelial changes at 1.1 mg/m3. After a four week recovery period minimal epithelial metaplasia could still be detected; however clear evidence of recovery existed. This study demonstrated that the test substance was tolerated without any systemic adverse effects or...

Justification for classification or non classification

Regarding repeated dose toxicity the substance 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is not classified according to the criteria of EC Directive 67/548/EEC.

4.6. Mutagenicity

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

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). "Neither *Salmonella typhimurium* TA 102 nor *Escherichia coli* WP2 were tested in these Ames tests, as it was not required by the EC guideline in 1984 when these studies were performed. This is an acceptable restriction compared to OECD TG 471 because it can be assumed that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate has no oxidizing or cross-linking potential which may be detected by *S. typhimurium* TA 102 or *E. coli*WP2. A negative result was also obtained by Mortelmans et al. (1986) in the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 using the preincubation method and concentrations up to 33 000 µg/plate both with and without Aroclor 1254-induced Wistar rat Syrian hamster liver S9 mix, respectively. Concentrations above 10 000 µg/plate were cytotoxic.

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

The substance Isophorone Diisocyanate was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells in vitro (Schulz and Landsiedel, 2007). Four independent experiments were carried out with and without the addition of Aroclor-induced rat liver S9 mix. On the basis from the results of the present study, the test substance did not cause any increase in the mutant frequencies without and with S9 mix in four experiments performed independently of each other. Thus, under the experimental conditions of this study, Isophorone Diisocyanate has no mutagenic activity in vitro in the CHO/HPRT forward mutation assay neither in the absence nor in the presence of metabolic activation.

In vivo Studies

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

Studies in Humans

"There are no data available. "

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

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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. "

The test substance Isophorone Diisocyanate has no mutagenic activity in vitro in the CHO/HPRT forward mutation assay neither in the absence nor in the presence of metabolic activation under the experimental conditions of this study.

"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. "

Justification for classification or non classification

Regarding genetic toxicity the substance 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is not classified according to the criteria of EC Directive 67/548/EEC.

4.7. Carcinogenicity

There are no data available.

4.8. Toxicity for reproduction

4.8.1. Effects on fertility

Data waiving

Justification: According to section 1.2 of Annex XI, the study need not be done if there is a weight of evidence to conclude the substance does not have a particular property, and further testing on vertebrate animals may be omitted. The toxicological database for inhaled 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (isophorone diisocyanate; IPDI) demonstrates consistently that toxicityis associated only with the portal of entry (respiratory tract), any other manifestations of toxicity are secondary to this. While no fertility study is available for IPDI, sub-chronic study shows toxicity confined to the respiratory tract. Fertility studies with the similar diisocyanates H12MDI and HDI show no effects on reproductive parameters, all effects are confined to the respiratory tract. Hence the databases for other aliphatic diisocyanates all show that primary toxicity for diisocyanates is to the respiratory tract, other effects, such as fetotoxicity in developmental studies, are secondary to this. This relationship applies to H12MDI and HDI when tested in fertility studies in the rat and is considered to apply equally to IPDI, i. e., if any effects were to be seen in a fertility study, these would occur only as a secondary effect of the toxicity to the respiratory system of the exposed rats. Protection against respiratory tract toxicity will protect against any secondary effects. A full and detailed text "Rationale for Waiving Additional Animal Studies on Reproductive Toxicity for Aliphatic Diisocyanate Monomers and their Polyisocyanates" elaborating this data waiver is attached to this record. Using the weight of evidence, it is concluded that reproductive toxicity is not an endpoint of concern for IPDI and additional toxicity testing is not necessary.

Discussion

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

Studies in Animals

"No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. However, relevant information can be found in studies on different endpoints. Histopathological results of a subacute 28-day inhalation study in rats according to OECD TG 412 (adjusted to fulfill both the TSCA § 798.2250 as well as EU Guideline 92/69/EEC) showed no effects on the reproductive organs (ovaries, oviducts and testes) at tested concentrations of up to 4.1 mg/m^3. Testes and ovary weights were also not affected. " The NOAEC for general toxicity is 0.24 mg/m^3. For further details on general toxicity see chapter 7.5.3 (Bayer AG, 2003).

"Based on the results there are no indications for specific adverse effects on the reproductive organs following 28-day treatment with up to 4.1 mg/m^3despite the fact that already at 1.05 mg/$m^3$the substance leads to a significantly increased incidence of inflammatory as well as epithelial changes occurring in the airways of the entire respiratory tract (nasal cavity, pharynx, larynx, trachea, lungs) with typical anterior-posterior gradient in intensity. " Taking into account the knowledge about the mode of action of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (local effects at sites of immediate contact clearly predominant) the lack of effect on the reproductive organs at 4.1 mg/$m^3$and as the NOAEC for repeated dose toxicity is set at 0.24 mg/m^3it seems quite unlikely that this substance might have critical effects on testis in this low dose range.

Additionally a subchronic 13 week inhalation study with Isophorone Diisocyanate has been conducted in young adult Wistar rats according to OECD Guideline 413 (Pauluhn, 2008), which showed no substance induced effects on the reproductive organs (ovaries, oviducts and testes) at tested concentrations up to 1.1 mg/m3. Additionally there were no statistically significant or conclusive dose-dependend changes in absolute or relative organ weights of the examined reproductive organs. Based on the results there are no indications for specific adverse effects on the examined reproductive organs following 13 week treatment with up to 1.1 mg/m^3

For further details on general toxicity see chapter 7.5.3 of IUCLID 5 data set (Pauluhn, 2008)

The toxicological database for inhaled Isophorone Diisocyanate (IPDI) demonstrates consistently that toxicity is associated only with the portal of entry (respiratory tract), any other manifestations of toxicity are secondary to this. While no fertility study is available for IPDI, sub-chronic and subacute studies all show toxicity confined to the respiratory tract. Fertility studies with other aliphatic diisocyanates (H12MDI and HDI) show no effects on reproductive parameters, all effects are confined to the respiratory tract. Hence the databases for other aliphatic diisocyanates all show that primary toxicity for diisocyanates is to the respiratory tract, other effects, such as fetotoxicity in developmental studies, are secondary to this. This relationship applies to H12MDI and HDI when tested in fertility studies in the rat and is considered to apply equally to IPDI, i. e., if any effects were to be seen in a fertility study, these would occur only as a secondary effect of the toxicity to the respiratory system of the exposed rats. Protection against respiratory tract toxicity will protect against any secondary effects.

Using the weight of evidence, it is concluded that reproductive toxicity is not an endpoint of concern for IPDI and additional toxicity testing is not necessary.

Studies in Humans

"There are no data available. "

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

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate. " A data waiver is claimed. "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 NOAEC 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.

Additionally a subchronic 13 week inhalation study with Isophorone Diisocyanate has been conducted in young adult Wistar rats according to OECD Guideline 413, which showed no substance induced effects on the examined reproductive organs (ovaries, oviducts and testes) at tested concentrations up to 1.1 mg/m3. (see Chapter 7.5.3 of IUCLID 5 data set)

4.8.2. Developmental toxicity

Discussion

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

Studies in Animals

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

Intrauterine development, gestation rate, postimplantation loss, mean litter size, fetal sex distribution, and placental appearance were not affected by treatment with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate at exposure levels up to and including 4 mg/m^3. Reduction of fetal weight at the 4 mg/m^3exposure level was 6.8% ($p < 0.01$), and impairment of placental weight (–6.6%, not statistically significant but slightly below historical control data range) could not be completely excluded at this exposure level. A marginally higher

number of common eye malformations in the 4 mg/m^{3}group (1% of the fetuses and 7.7% of litters affected vs. 0.4% of fetuses and 4.2% of litters in control), well within the range of historical control data (up to 1.8% of fetuses and 20% of litters affected), was considered to be either incidental or secondary (reduced oxygen supply to offspring by maternal bradypnea). Further incidence and type of fetal malformations were unaffected by treatment. An adverse effect on incidence and type of external and visceral deviations was not evident at an exposure level up to and including 1 mg/m^3, while slightly retarded descensus testis could not be completely excluded at the maternally toxic 4 mg/m^{3}exposure level. Statistically significant fetal skeletal findings at the 4 mg/m^{3}exposure level included retarded ossification of distal and proximal phalanges of digits and toes, of metacarpal bones, 6thsternal segment, 7thcervical vertebral body, sacral and caudal vertebral arches, and caudal vertebral bodies. All signs of developmental toxicity observed at the 4 mg/m^{3}exposure level, i. e. reduced fetal weights, delayed descensus testis, and slightly retarded ossification, were indicative of delayed fetal development and were only seen in the presence of maternal toxicity and thus considered secondary effects. " The NOAEC for both maternal toxicity and developmental toxicity was 1 mg/m^3(nominal; analytical: 0.929 mg/m^3) (Klaus, 2004).

Studies in Humans

"There are no data available. "

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

Partly cited from SIAR for SIAM 23 (Jeju, Korea, October 17-20, 2006):

"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 NOAEC for both maternal toxicity and developmental toxicity was 0.929 mg/m3 (analytical).

Justification for classification or non classification

Regarding toxicity to reproduction the substance 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is not classified according to the criteria of EC Directive 67/548/EEC.

4.9. Derivation of DNEL(s) / DMEL(s)

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)	IPDI 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					Exposure to IPDI via the air does not lead to systemic toxicity, therefore any potential systemic toxicity effects are covered by the respective DNELs for inhalation expousre, local effects (DNEL = 0.0453 mg/m³).
Acute - local effects	Dermal				sensitisation (respiratory tract)	IPDI 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. Furthermore the substance is corrosive to the skin and no DNEL can be derived for this effect.
Acute - local effects	Inhalation	DNEL (Derived No Effect Level)	0.0453 mg/m³	NOAEC: 0.1359 mg/m³ (based on AF of 3)	irritation (respiratory tract)	Justification for applied assessment factor: see Discussion in Chapter 5.11.2 of the Chemical Safety Report
Long-term - systemic effects	Dermal				sensitisation (respiratory	IPDI appears to have some potential to induce respiratory hypersensitivity and there is evidence

					tract)	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					Exposure to IPDI via the air does not lead to systemic toxicity, therefore any potential systemic toxicity effects are covered by the respective DNELs for inhalation expousre, local effects (DNEL = 0.0453 mg/m³).
Long-term - local effects	Dermal				sensitisation (respiratory tract)	IPDI 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. According to the potency categorisation approach isophorone diisocyanate is classified as a moderate skin sensitizer based on a Guinea Pig Maximization Test (10 % induction conc., 85 % incidence of sensitization; Hüls/IBR, 1983).
Long-term - local effects	Inhalation	DNEL (Derived No Effect Level)	0.0453 mg/m³	NOAEC: 0.1359 mg/m³ (based on AF of 3)	irritation (respiratory tract)	Justification for applied assessment factor: see Discussion in Chapter 5.11.2 of the Chemical Safety Report

**) 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

For workers, which are exposed via inhalation, relevant DNELs for acute and long-term inhalation effects of 3-Isocyanatomethyl-3.5.5-trimethylcyclohexyl isocyanate (syn. isophorone diisocyanate) have to be derived. Additionally, the sensitization potential after skin contact to 3-Isocyanatomethyl-3.5.5-trimethylcyclohexyl isocyanate has to be assessed.

For repeated dose toxicity a subacute and a subchronic inhalation study with aerosol exposure of 3-Isocyanatomethyl-3.5.5-trimethylcyclohexyl isocyanat to rats are available (Bayer AG, 2003 and Pauluhn, 2008). The obtained LOAECs were 1.05 mg/m³ (subacute study) and 1.1 mg/m³ (subchronic study), respectively, for effects governed by irritation of the respiratory tract. No indications of systemic toxicity effects were found within the studies.

Histopathological changes in the respiratory tract were related to portal-of-entry, local irritant effects, i. e. epithelial metaplasia and inflammatory changes predominantly in the upper respiratory tract (larynx). For the subchronic study the NOAEC relating to these changes was set 0.27 mg/m³ (Pauluhn, 2008). The result of a developmental toxicity test (NOAEC: 0.929 mg/m³ analytical concentration for developmental and maternal toxicity; developmental toxicity considered to be a secondary effect as a result of maternal toxicity; maternal toxicity predominantly caused by irritative effects on respiratory tract; Klaus, 2004) is in line with the NOAEC of 0.27 mg/m³ based on the subchronic inhalation study. Therefore 0.27 mg/m³ was used as a starting point for the derivation of a $DNEL_{long\text{-}term}$ for long-term local effects for inhalation.

$DNEL_{long\text{-}term}$ for workers for inhalation route (local effects):

For rats exposed to the substance 6 h/d 5 d/w for 13 weeks NOAEC = 0.27 mg/m³

Correction of dose-descriptors (ECHA Guidance, part B, chapter R.8.4):

In case of workers 8h/day exposed:

$$\text{corrected NOAEC} = \text{inhalatory NOAEC} * \frac{\text{exp. cond. rat}}{\text{exp. cond. human}}$$

$$\text{corrected NOEAC} = \text{inhalatory NOAEC} * \frac{6\ \text{h/d}}{8\ \text{h/d}} * \frac{6.7\ \text{m}^3\ (8\text{h})}{10\ \text{m}^3\ (8\text{h})}$$

corrected NOAEC = inhalatory NOAEC * 0.5025

corrected NOAEC = 0.136 mg/m³

According to ECHA Guidance "Guidance on information requirements and chemical safety assessment; Chapter R.8: Characterisation of dose [concentration]-response for human health" chapter R.8.4 a series of assessment factors (AF) were applied to the NOAEC from rats and are summarized in the table below.

Assessment	**Assessment Factor**
[1]For interspecies differences rat vs. human (allometric scaling)	1
[2]For remaining interspecies differences	1
[3]For intraspecies differences in workers	3
[4]Differences in duration of exposure	1
[5]Dose-response relationship	1
[6]Quality of whole Database	1
Overall Assessment Factor	3

[1]According to the ECHA TGD allometric scaling should not be applied for local effects, since local effects are independent of the basal metabolic rate, therefore AF 1 is chosen.

[2]A factor 2.5 is suggested by the ECHA TGD for remaining interspecies differences, but justified deviations are possible. Rodents like the rat are in general more sensitive compared to humans as the rat's ventilation frequency is higher. Therefore, as a general rule a factor of 1 for remaining interspecies differences provides sufficient protection.

[3]For intraspecies variability, the default assessment factor of 5 is recommended for workers for effects on respiratory tract (see Appendix R. 8 -9 of TGD). Furthermore chapter R.8.4.3.1 of the TDG states that in general the assessment factor for local (concentration-dependent) effects is very scarce and no attempt has therefore been made to refine the default intraspecies factors already used for systemic effects. So TGD proposes to use the same assessment factor (5 in case of workers sub-population) for local as well as for systemic effects as generic step but justified deviations are possible.

In general the assessment factor should cover intraspecies differences which are a result of biological factors such as genetic polymorphism affecting e. g. toxicokinetic/metabolism, age, gender, health status and nutritional status as well as environmental influences as described in TGD. Regarding Isophorone diisocyanate the mechanism of toxicity at the port of entry is still a mechanical destruction of membranes because of the corrosive effects of the substance. Metabolic activities are not involved in this mechanism. Hence intraspecies differences should not be related to metabolic differences between the individuals und thus these differences could be caused only by non-metabolic differences. The workers sub-population is more homogeneous than other populations also for non-metabolic effects like e. g. good health status, restricted age range, good nutrition status.

So as a conclusion the remaining relevant differences between individuals which should be represented by the intraspecies assessment factor are non-metabolic differences and most of these non-metabolic differences should be rather small due to the homogeneousness of the workers sub-population. Furthermore in general for the workers sub-population metabolic differences should contribute much more to such a intraspecies assessment factor than non-metabilic differences, but the local toxic effect of the substance Isophorone diisocyanate is not related to metabolic mechanisms, because it is a simple destruction of membranes due to corrosivity of the substance. Therefore a reduced assessent factor of 3 for remaining intraspecies differences within the workers sub-population provides sufficient protection. The possibility to reduce the default assessment factor is in line with the statement of the TGD that default assessment factors represent a fall back position rather than the starting point (see R.8.4.3).

[4]The assessment factor suggested by the ECHA TGD for exposure duration from subchronic to chronic should be 2, but extrapolation factors for differences in duration of exposure are not always needed. In the depicted case

no systemic effects were observed, and the observed local effects lead to LOAECs and NOAECs that does not give evidence for a major time-dependent change of the response threshold for comparison: $NOAEC_{subacute}$= 0.24 mg/m^3 (Bayer AG, 2003) versus $NOAEC_{subchronic}$ = 0.27 mg/m^3 (Pauluhn, 2008)

and $LOAEC_{subacute}$= 1.05mg/m^3 (Bayer AG, 2003) versus $LOAEC_{subchronic}$ = 1.1 mg/m^3 (Pauluhn, 2008)

On this basis it is not expected that a longer duration of the study would change the outcome and an AF of 1 is warranted.

[5]When the starting point for the DNEL delineation is a NOAEC, the default assessment factor, as a standard procedure, is 1.

[6]The default assessment factor to be applied for good/standard quality of the database, taking into account completeness, consistency and the standard information requirements, is 1.

Therefore the overall AF (assessment factor) is 3.

$DNEL_{long-term}$ for workers for inhalation route – local effects = (NOAEC corr.): (Overall AF)

$DNEL_{long-term}$ for workers for inhalation route – local effects = 0.0453 mg/m^3

This derived long term DNEL for workers for inhalation route (local effects) is in line with the German Occupational Limit Value (= Arbeitsplatzgrenzwert (AGW) =0.046 mg/m^3) as listed in Technical Rule for Hazardous Substances (TRGS) No. 900 (Joint Ministerial Gazette (GMBI) 2010 Nr. 5-6 S. 111 (04.02.2010).

According to the TRGS No. 900 the AGW multiplied by an exceeding factor results in a 15 minutes average value. The exceeding factor(Überschreitungsfaktor), which is set per default 1 when the deviation of the limit value is governed by local effects or by the respiratory sensitization potential of the substance (could be adjusted to max. 8 on a case by case decision). For Isophorone diisocyanate an exceeding factor of 1 is applied, since the most prominent effect of the substance is the portal-of-entry dependent local irritation both for the acute and for the long-term toxicity, leading to the 15 minutes average value or

$DNEL_{acute}$for workers for inhalation route – local effects of 0.0453 mg/m^3.

This procedure is in accordance to ECHA Guidance, Chapter R.8., Appendix R. 8-8, Box 6and is in line with the German15 minutes average value. (=0.046 mg/m^3). In addition a ceiling limit value of 0.092 mg/m^3 is stated (using an exceeding factor of 2) which may be exceeded at no time (Joint Ministerial Gazette (GMBl) 2010 Nr. 5-6 S. 111 (04.02.2010).

In animal studies as well as in occupational health reports a dermal sensitization potential was shown for isophorone diisocyanate. According to the potency categorisation approach isophorone diisocyanate is classified as a moderate skin sensitizer based on a Guinea Pig Maximization Test (10 % induction conc., 85 % incidence of sensitization; Hüls/IBR, 1983).

At present 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. Althrough some of the results of the following studies are ambiginous and still under discussion this hypothesis will be supported by further investigations (Plitnick 2005, De Jong et al. 2009, Arts et al. 2008, Farraj et al. 2007, Selgrade et al. 2006) leading to the conclusion that Isophorone diisocyanate appears to have some potential to induce respiratory hypersensitivity.
Because there are currently no available methods to determine thresholds and DNELs for respiratory sensitizers, therefore a quantitative risk assessment for this endpoint is not possible. Substances with R42/Cat. 1 for respiratory sensitization have to be allocated to the high hazard category (ECHA Guidance on information requirements and chemical safety assessment – Part E: Risk characterisation (May 2008)). Since there is evidence from both human and animal studies, that effective sensitization of the respiratory tract can result from dermal contact with a chemical respiratory allergen, the delineation of a DNEL for skin sensitization is not indicated.

Corrosive effect to the skin and irritant properties on eye and mucosa are also reflected in studies investigating effects on skin (Krötlinger 1994) and eye (Mobay Chemical 1987, Schreiber 1981). Qualitative assessment: Substance is considered to be corrosive to the skin and irritant to eyes and mucosa. No DNEL can be derived from the data of the studies because no dose response information is available.

The DNEL acute/long-term for inhalation for workers covers also reproductive toxicity, as the local effects at the respiratory tract are the most sensitive effects.

DN(M)ELs for the general population

Discussion

Cited from SIAR for SIAM 23 (Korea, October 17 -20, 2006): "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. ” Because Isophorone diisocyanate (3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate) is used only in industrial and professional applications there is no need to derive DNEL´s for consumers.

5. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

5.1. Explosivity

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

As 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl-isocyanate was neither shock sensitive nor thermally sensitive (AQura, 2009), according to the criteria of the EC test method A.14 it is not representing an explosive hazard and has not to be considered to present a danger of explosion.

5.2. Flammability

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

The test substance is a liquid. The EU method is not applicable for liquids.

Experimental experience, in particular from studies on flash point (chapter 4.11) and water solubility (chapter 4.8), shows that isophorone diisocyanate is neither pyrophoric nor flammable in contact with water. Upon hydrolysis carbon dioxide (mineral) and very unvolatile organic substances are formed.

Flash point

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

The flash point of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl-isocyanate was determined according to EU test method A.9 (2008) with the Pensky-Martens method (closed cup). The result was 150.5 °C at 1013 hPa.

5.3. Oxidising potential

Data waiving

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

Based on the chemical structure, the substance is incapable of reacting exothermically with combustible materials. The substance contains oxygen atoms (no halogen atoms), but the oxygen atoms are not bonded directly to nitrogen atoms or other oxygen atoms. Therefore, according to REACH Annex VII, 7.13, column 2 testing is not required.

6. PBT AND VPVB ASSESSMENT

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

PBT and vPvB criteria and the corresponding properties of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate

Criterion	PBT criteria	vPvB criteria	property	Criterion fulfilled?
P	Half-life in marine water > 60 d, or half-life in fresh- or estuarine water > 40 d, or half-life in marine sediment > 180 d, or half-life in fresh- or estuarine water sediment > 120 d, or half-life in soil > 120 d	Half-life in marine, fresh or estuarine water > 60 d, or Half-life in marine, fresh or estuarine sediment > 180 d, or half-life in soil > 180 d	Not readily biodegradable (Bayer AG 2000), but abiotic degradation; Half-life in fresh water < 12 hours. Half-life of hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine >120 d	yes (hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine)
B	BCF > 2000	BCF > 5000	Not B (based on QSAR calculations the BCF was estimated to be 910 for the parent substance and 3.16 for the main hydrolysis product) Not vB (based on QSAR calculations)	no
T	NOEC < 0.01 mg/L for marine or freshwater organisms	Not applicable.	72h-NOEC 4.4 mg/l for algae (Bayer AG 2000) Long-term NOEC (Daphnia reproduction) for hydrolysis product (3-aminomethyl-3,5,5-trimethylcyclohexylamine): 3.0 mg/L	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

3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is not readily biodegradable with 0 % biodegradation in 28 days (Bayer AG 2000). However, biodegradation is irrelevant as primary degradation step because immediate hydrolysis takes place. The hydrolysis products are polyurea components and 3-aminomethyl-3,5,5-trimethylcyclohexylamine. 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. 3-aminomethyl-3,5,5-trimethylcyclohexylamine was observed to be hydrolytically stable (half-life > 1 year) and insignificantly biodegradable (9 % within 28 days). Based on these considerations, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is classified as persistent until there are further data available that may allow other conclusions.

6.1.2. Bioaccumulation Assessment

Measured bioconcentration factors (BCF) for 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate are not available. The substance hydrolyses rapidly in the presence of water with a half life < 12 hours (Bayer AG 1999; Infracor GmbH 2000). QSAR calculations resulted in a BCF of 910, but it has to be noted, that due to rapid hydrolysis bioaccumulation processes of the parent substance are negligible. The BCF of the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine was estimated to be 3.16 (BCFWin v 2.14) indicating a low bioaccumulation potential. This is supported by a low log Pow (0.99). The other hydrolysis products (polyurea

components) are known to be inert insoluble materials with limited mobility. Hence their bioaccumulation potential is of minor relevance. Considering the mentioned criteria the potential for bioaccumulation is regarded as low for both the parent substance and the formed hydrolysis products.

6.1.3. Toxicity Assessment

There is one aquatic toxicity test on algae for the parent substance available which can be regarded as a chronic test. The NOEC was 4.4 mg/l (Bayer AG 2000). In a Daphnia reproduction test (21 days) with the hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine, the NOEC was estimated as 3.0 mg/L. The substance is not classified as carcinogenic, mutagenic or toxic for reproduction or R48. Hence the substance does not meet the T-criterion.

6.1.4. Summary and overall conclusions on PBT or vPvB properties

According to Annex XIII of the REACH regulation, a substance is classified as PBT substance, if all criteria described above are fulfilled. According to the available information only the P criterion is fulfilled. Hence the substance is provisionally classified as persistent until there are additional data available that may allow other conclusions. However, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is not classified as PBT substance.

A substance is classified as a vPvB substance, if both vPvB criteria described above are fulfilled. The vP criterion is fulfilled (hydrolysis product 3-aminomethyl-3,5,5-trimethylcyclohexylamine), the vB criterion is not fulfilled. Hence 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate is not classified as vPvB substance.

6.2. Emission Characterisation

It is concluded that 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate does not fulfil the PBT/vPvB criteria. An emission characterisation is therefore not required.

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