3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer, isocyanurate type (IPDI homopolymer)

EC Number: **500-125-5**

CAS Number: **53380-05-0**

IUPAC name: **3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer, isocyanurate type**

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 homopolymer, isocyanurate type (IPDI homopolymer) 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 homopoly-mer, isocyanurate type.

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1. PHYSICAL AND CHEMICAL PROPERTIES

Molucular weight range: >= 222.29 g/mol

Molecular formula: residual $C_{12}H_{18}N_2O_2$, otherwise $C_{36}H_{54}N_6O_6$ (trimer) and higher species

Appearance/physical state/colour: Transparent to white solid (pellets)

Melting / freezing point: The melting temperature of isophorone diisocyanate homopolymer was determined by differential scanning calorimetry. The melting temperature is 73.5 °C (976 hPa). Additional studies show that this is not a melting point but an enthalpy relaxation because the substance is not crystalline.

Boiling point: No boiling point was found prior to decomposition (beginning at approx. 347 °C; 993.2 hPa). Therefore, a boiling point could not be determined.

Relative density: 1.1467 g/cm^3 at 20 °C

Vapour pressure: 1.9*10^{-09} Pa at 20 °C. (Indications of decomposition at the highest temperatures were observed.)

Water solubility: The substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours).

Partition coefficient n-octanol/water (log value): The following properties of the substance make the study technically not feasible:
(1) The water solubility is very low.

(2) The substance reacts with water (half-life < 12 hours at room temperature).

(3) Appropriate analytical methods are not available. The fact that the substance is a mixture increases the analytical difficulties.

Flash point: The substance is a solid melting above 60 °C. Therefore, the study is technically not feasible.

Flammability: 3-Isocyanatomethyl-3,5,5-trimethylcyclo-hexylisocyanate homopolymer is not highly flammable according to the definition in the Council Regulation (EC) No 440/2008, method A.10.

Explosive properties: As 3-isocyanatomethyl-3,5,5-trimethylcyclo-hexylisocyanate homopolymer was neither shock sensitive nor thermally or friction sensitive, according to the criteria of the EC test method A.14 of Council Regulation (EC) No 440/2008 it is not representing an explosive hazard and has not to be considered to present a danger of explosion.

Self-ignition temperature: The substance is a solid with a melting point ≤ 160 °C. Therefore, a test is not required.

Oxidising properties: Based on the chemical structure, the substance is incapable of reacting exothermically with combustible materials.

Stability in organic solvents: The stability of the substance in aprotic organic solvents is not considered to be critical.

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: The substance is a solid. Viscosity can only be measured for liquids.

2. ENVIRONMENTAL FATE PROPERTIES

General discussion of environmental fate and pathways:

Regarding the environmental fate and pathways there are only few data available. The substance has a high reactivity towards OH radicals in the atmosphere and hydrolyses rapidly, but it is not readily biodegradable in aqueous systems. As no biodegradation (0%) was observed in a study on ready biodegradability, it is not expected that a significant degradation would occur in a simulation 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. Due to the rapid hydrolysis, the determination of bioaccumulation in aquatic systems is not possible.

Furthermore it is not necessary to determine the adsorption/desorption potential since the substance hydrolyses rapidly. Under the test conditions required for covering this endpoint, the primary degradation product will react further. Therefore its adsorption / desorption also 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.

2.1. Hydrolysis

Discussion

According to experience with the substance itself as well as with diisocyanates and similar polyisocyanates, 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 oligomer predominantly polyurea molecules are formed. They are insoluble in water and thereby have a negligible mobility (including accumulation potential) in the environment.

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

The hydrolysis as a function of pH of 3-isocyanatomethyl-3,5,5-trimethylcyclo-hexylisocyanate homopolymer was determined by AQura (2010) based on the OECD guideline 111 (2004) and EU test method C.7 (2008) with modifications at room temperature (22.1 – 23.0 °C) and using the isophorone diisocyanate trimer as a representative of the whole test item.

Test series	pH	co-solvent concentration	Kobs [h-1]	t½ [h]
1	4	30 % acetonitrile in water	0.6556	1.06
2	7	30 % acetonitrile in water	0.1783	3.89
3	9	30 % acetonitrile in water	1.3128	0.53
4	7	15 % acetonitrile in water	0.0904	7.66
5	7	7.5 % acetonitrile in water	0.1916	3.62

The hydrolysis half-life was always clearly below 12 hours. Both acidic and basic media appear to accelerate the hydrolysis. No simple relationship between the rate of hydrolysis and the concentration of the organic co-solvent acetonitrile could be observed.

2.2. Phototransformation in air

Discussion

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

The QSAR calculated rate constant for the OH sensitized photodegradation of isophorone diisocyanate

cyclotrimer is approximately 4.02E-11 cm3/(molecule * s). At 500,000 OH radicals / cm3 (approximate 24-hour mean in cental Europe), this corresponds to a half-life of 9.6 hours. Higher oligomers have more reactive functions and therefore a lower half-life will be calculated.

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:

A "Manometric Respirometry Test" was conducted by Bayer Industry Services GmbH (2007) in accordance with EU-Method C.4-D and OECD TG 301 F in order to assess the ready biodegradability of the test item. A suspension of the test item was inoculated and incubated for 28 d under aerobic conditions. During this period, degradation was followed by BOD determinations. After 28 days, 0.0% degradation was observed. Therefore, the test item is considered to be "not readily biodegradable".

Discussion (simulation testing)

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

As no biodegradation (0%) was observed in a study on ready biodegradability it is not expected that a significant degradation would occur in a simulation 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.

2.3.2. Biodegradation in soil

Discussion

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

As no biodegradation (0%) was observed in a study on ready biodegradability is not expected that significant degradation would occur in a soil biodegradation 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 QSAR calculated rate constant for the OH sensitized photodegradation of isophorone diisocyanate cyclotrimer is approximately 4.02E-11 cm3/(molecule * s). At 500,000 OH radicals / cm3 (approximate 24-hour mean in central Europe), this corresponds to a half-life of 9.6 hours. Higher oligomers have more reactive functions and therefore a lower half-life will be calculated.

The tests on hydrolysis indicate a rapid decomposition of the test substance in water (half-life < 12 hours at 20 - 25 °C and relevant pH values).

Biotic degradation

A "Manometric Respirometry Test" was conducted by Bayer Industry Services GmbH (2007) in accordance with EU-Method C.4-D and OECD TG 301 F in order to assess the ready biodegradability of the test substance. A suspension of the test item was inoculated and incubated for 28 d under aerobic conditions. During this period,

degradation was followed by BOD determinations. After 28 days, 0.0% degradation was observed. Therefore, the test item is considered to be "Not Readily Biodegradable".

As no biodegradation (0%) was observed in a study on ready biodegradability it is not expected that a significant degradation would occur in a simulation test. The test substance is considered as non-biodegradable in surface water and sediment compartment. However, biodegradation is irrelevant as primary degradation step 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 VIII, 9.3.1, column 2 as well as REACH Annex IX, 9.3.3, 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

Environmental distribution considerations for isophorone diisocyanate homopolymer 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:

Hydrolysis inhibits establishing a steady concentration in the aqueous phase. Therefore a study is technically not feasible.

2.4.3. Summary and discussion of environmental distribution

Releases into the environment may occur during production of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer, during formulation, and during use of the substance or its formulations as an intermediate or as a crosslinker in various applications.

Distribution modelling is not possible because due to rapid hydrolysis the water solubility as a key input datum cannot be measured. Henry’s Law constant and adsorption / desorption behaviour also cannot be determined because of hydrolysis. It is expected that immobile polymers will be formed upon entry into the environment as soon as the substance reaches the hydrosphere or other wet compartments. Environmental distribution of the substance itself is inhibited by its rapid hydrolysis, and environmental distribution of the hydrolysis products is inhibited by their negligible vapour pressure and water solubility.

2.5. Bioaccumulation

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

Aquatic bioaccumulation

According to experience with the substance itself as well as with similar polyisocyanates, 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 oligomer predominantly polyurea molecules are formed. They are insoluble in water and they 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.

Terrestrial bioaccumulation

There are no data on terrestrial bioaccumulation available.

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 PNECoral 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 IPDI homopolymer.

3. ENVIRONMENTAL HAZARD ASSESSMENT

3.1. Aquatic compartment (including sediment)

3.1.1. Toxicity test results

3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer hydrolyses upon contact with water. The diisocyanate groups of the substance react by forming amines and CO_2. The amines formed may react further with unreacted diisocyanate groups of 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer resulting in oligo- and subsequently polyurea components. Test substance solutions of 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexyl isocyanate homopolymer 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. No effects were observed in any of the tested species (Daphnia, algae, fish) up the limit of the water solubility. The lowest endpoint was derived for fish (LC_{50}, 96 h, Cyprinus carpio was >1.5 mg/L).

3.1.2. Short-term toxicity to fish

Discussion

There is only one valid test available for the short term toxicity to fish.

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

Cyprinus carpio were exposed to isophorone diisocyanate homopolymer in a limit test for a period of 96 hours. The study was conducted according to EU Method C.1. No mortality was observed at the highest soluble loading. Thus the LC_{50} (96 hours) was determined as >1.5 mg/L (highest measured concentration) indicating that the substance has no acute toxic effects on fish at concentrations up to the water solubility limit.

3.1.3. Long-term toxicity to fish

Data waiving

Reason: study technically not feasible

Justification: According to Annex XI, 2 of Reach Regulation 1907/2006, both the study on the parent substance and the hydrolysis product can be waived because the studies are technically not feasible due to rapid hydrolysis (parent substance) and analytical/technical limitations (hydrolysis product).

Discussion

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

According to REACH Annex XI, 2 of the REACH Regulation 1907/2006 the study can be waived, because the study is technically not feasible (due to rapid hydrolysis and low water solubility).

3.1.4. Short-term toxicity to aquatic invertebrates

Discussion

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 at static conditions according to OECD 202 and EU method C.2 for a period of 48 hours. No effects were observed up to the limit of water solubility (3.36 mg DOC/L). Thus the EC_{50} (48 hours) was determined as >3.36 mg DOC/L (mean DOC corrected for control) indicating that the substance has no acute toxic effects on aquatic invertebrates at concentrations up to the limit of water solubility.

3.1.5. Long-term toxicity to aquatic invertebrates

Data waiving

Reason: study technically not feasible

Justification: According to Annex XI, 2 of Reach Regulation 1907/2006, both the study on the parent substance and the hydrolysis product can be waived because the studies are technically not feasible due to rapid hydrolysis (parent substance) and analytical/technical limitations (hydrolysis product).

Discussion

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

According to REACH Annex XI, 2 of the REACH Regulation 1907/2006 the study can be waived, because the study is technically not feasible (due to rapid hydrolysis and low water solubility).

3.1.6. Algae and aquatic plants

Discussion

Effects on algae / cyanobacteria

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

The green alga Scenedesmus subspicatus was exposed to isophorone diisocyanate homopolymer in a limit test for a period of 72 hours. The study was conducted according to OECD TGD 201 and EU Method C.1. No effects on biomass and growth rate were observed up to the limit of water solubility. Thus the EC_{50} values (72 hours) based on cell numbers and growth rate were determined as >3.1 mg DOC/L (saturated solution) indicating that the substance has no acute toxic effects on algae at concentrations up to the water solubility limit.

3.1.7. Sediment organisms

Data waiving

Reason: other justification

Justification: The results of the chemical safety assessment do not indicate the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms (compare column 2, Annex X of the REACH regulation). There is no indication that there is a relevant route of exposure regarding sediment. 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, homopolymer hydrolyses rapidly upon contact with water. The amines formed react further with unreacted diisocyanate groups of IPDI homopolymer resulting in oligo- and subsequently polyurea components. Polyurea is known to be inert and is probably due to its molecular size not bioavailable. Thus significant exposure of the sediment compartment is not expected.

Discussion

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

The results of the chemical safety assessment do not indicate the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms (compare column 2, Annex X of the REACH regulation). There is no indication that there is a relevant route of exposure regarding sediment. 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, homopolymer hydrolyses rapidly upon contact with water. The amines formed react further with unreacted diisocyanate groups of IPDI homopolymer resulting in oligo- and subsequently polyurea components. Polyurea is known to be inert and is probably due to its molecular size not bioavailable. Thus significant exposure of the sediment compartment is not expected.

3.1.8. Predicted No Effect Concentration (PNEC)

3.1.8.1. PNEC water

PNEC (mg/L)	Value	Assessment factor	Remarks/Justification
PNEC aqua (freshwater)	0.0015	1000	Extrapolation method: assessment factor The lowest endpoint derived from three aquatic tests covering three trophic levels was found for the acute fish test with Cyprinus carpio. The derived endpoint is LC_{50} >1.5 mg/L (saturated solution). No effects have been determined up to the level of water solubility. For this reason, the PNEC aqua should read as > 0.0015 mg/l.
PNEC aqua (marine water)	0.00015	10000	For the marine compartment no tests are available. For PNEC derivation, short-term toxicity results from three species representing three trophic levels (fish, Daphnia and algae) for the freshwater compartment are taken into account. The lowest concentration level was 1.5 mg/l for the fish species Cyprinus carpio: 96 h-LC_{50} > 1.5 mg/l (Infracor GmbH, 2000). No effects have been observed at the saturated concentration. For this reason, the PNEC aqua marine should read as > 0.00015 mg/l.
PNEC aqua (intermittent releases)	0.015	100	Extrapolation method: assessment factor Short-term toxicity results are available from three species representing three trophic levels (fish, Daphnia and algae). The default assessment factor of 100 is applied using the lowest available effect concentration, which was obtained for fish (Infracor GmbH, 2000). No effects were observed. For this reason, the PNEC intermittent release should be read as > 0.015 mg/l.

3.1.8.2. PNEC sediment

PNEC (mg/kg d.w.)	Value	Assessment factor	Remarks/Justification
PNEC sediment (freshwater)	No exposure of sediment expected		There are no test results available with sediment dwelling organisms. The partition equilibrium method (EPM) cannot be applied to this substance because no reliable input parameter can be calculated (e.g. Koc). Hence a determination of the PNEC sediment (freshwater) is not possible. However, due to rapid hydrolysis sediment exposure is unlikely to occur.
PNEC sediment (marine water)	No exposure of sediment expected		There are no test results available with sediment dwelling organisms. The partition equilibrium method (EPM) cannot be applied to this substance because no reliable input parameter can be calculated (e.g. Koc). Hence a determination of the PNEC sediment (marine water) is not possible. However, due to rapid hydrolysis exposure of marine sediment is unlikely to occur.

3.2. Terrestrial compartment

3.2.1. Toxicity to soil macro-organisms

Data waiving

Information requirement: Toxicity to soil macro-organisms except arthropods

Reason: other justification

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

Reason: other justification

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.

Discussion of effects on soil macro-organisms except arthropods

The following information is taken into account for effects on soil macro-organisms except arthropods for the derivation of PNEC:

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.

Discussion of effects on soil arthropods

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

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

Reason: other justification

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.

Discussion

The following information is taken into account for toxicity on terrestrial plants for the derivation of PNEC:

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

Reason: other justification

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.

Discussion

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

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	Value	Assessment factor	Remarks/Justification
PNEC soil (mg/kg d.w.)	No exposure of soil expected		There are no test results available with soil organisms. A determination of the PNEC soil is not possible. The partition equilibrium method (EPM) cannot be applied to this substance because no reliable input parameter can be calculated (e.g. Koc). Hence a determination of the PNEC soil is not possible. However, 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.

3.3. Atmospheric compartment

Direct data on biotic and abiotic effects of 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer in the atmospheric compartment are not available. There are no reliable methods for the assessment of biotic effects of substances in the air. On the other hand it is not indicated that 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer causes abiotic effects in the 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:

An activated sludge respiration inhibition test was conducted by Bayer Industry Services (2007) according to OECD 209 and EU Method C.11. The oxygen content was measured at three concentrations (100, 1000 and 10000 mg/L) over a period of 3 hours. The 3h-EC_{50} was found to be >10000 mg/L indicating that the test substance does not pose a significant risk to bacteria populations colonising sewage sludge.

3.4.2. PNEC for sewage treatment plant

PNEC (mg/L)	Value	Assessment factor	Remarks/Justification
PNEC STP	100	100	Extrapolation method: assessment factor The EC_{50} value of an activated sludge test was available (EC_{50}: >10000 mg/L). According to the TGD an assessment factor of 100 is applied.

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

3.5.1. Toxicity to birds

Data waiving

Information requirement: Toxicity to birds

Reason: exposure considerations

Justification: The risk for secondary poisoning is considered to be low 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 IPDI homopolymer.

3.5.2. Toxicity to mammals

There are no data on mammals available.

3.5.3. PNECoral (secondary poisoning)

PNEC (mg/kg food)	Value	Assessment factor	Remarks/Justification
PNEC oral	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 PNECoral 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 IPDI homopolymer.

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

Environmental classification justification

Directive 67/548/ECC

Based on the available ecotoxictiy data (fish, Daphnia, alga) IPDI oligomers and their hydrolysis products are not environmentally classified as dangerous according to Directive 67/548/EEC. No acute toxicity was recorded for any trophic level when testing saturated solutions. Based on available Environmental Fate data the classification "R53 May cause long-term adverse effects in the aquatic environment" may be considered. This classification (R53) applies to non-readily biodegradable substances with a very low water solubility (<1 mg/l) and accounts for the bioaccumulation and biomagnification potential that may arise from persistent substances. However, this classification is not considered appropriate for the present substance for the following reasons:

- The registered substance is not found to be readily biodegradable, but exhibits a dissipation time in water less than the cut-off value of 12 h and is therefore considered as hydrolytically unstable.

- Upon contact with water the diisocyanate groups of IPDI trimer react by forming amines and CO2. The amines formed react further with unreacted diisocyanate groups of IPDI homopolymer resulting in oligo- and subsequently polyurea components. Polyurea is known to be inert and is probably due to its molecular size not bioavailable. The parent substance has an average molecular weight of 893 g / mol (residual monomers are negligible). According to ECHA guidance on information requirements a molecular weight higher than 700 g/Mol indicates that the BCF is below 5000 L/kg. It can be concluded from the structural formulae that the formed polyurea has a molecular weight amounting to multiples of that of the initial oligomers. Polyurea is therefore considered as less bioaccumulative compared to the parent substance.

- Moreover, a modelled Log Kow of 14.58 for the unhydrolysed parent substance indicates that the aquatic BCF is probably lower than 2000 L/kg (although this criterion should be treated with caution). Considering the above mentioned criteria the potential for bioaccumulation is regarded as minor for both the parent substance and the formed hydrolysis products.

GHS (Regulation 1272/2008/EEC)
Based on the available acute aquatic toxicity data and the arguments given above the substance is not classified.

4. HUMAN HEALTH HAZARD ASSESSMENT

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

3 -Isocyanatomethyl-3,5,5-trimethyl-cyclohexyl isocyanate homopolymer (IPDI homopolymer) (CAS-Nr. 53880-05-0); Information/Assumptions regarding toxicokinetics

The following remarks on the toxicokinetics of IPDI homopolymer are based on physiochemical properties of the compound and on toxicological data. Experimental toxicokinetic studies were not performed.

IPDI homopolymer is a odourless solid (pellets) with a very low vapour pressure ($1.3 * 10^{-11}$ hPa at 20 °C, AQura, 2010) under normal ambient conditions.

In water the substance hydrolyses rapidly with a half-live of clearly below 12 hours (23 °C) at different pH values. Because of the hydrolyzation potential and a very low water solubility experimental data such as pKa or log Kow can not be obtained for IPDI homolpolymer. The octanol-water partition coefficient of the test substance was calculated using a well established QSAR method at log Kow approx. 14.48 (Evonik, 2009).

Due to the low vapour pressure inhalation exposure via vapour is not to be expected. Wherever aerosolization occurs exposure is possible. There are no indications of systematic toxicity and systemic availability after inhalative exposure of the aerosol. No organ lesions other than respiratory tract could be found, and the clinical signs could all be related to respiratory distress and were seen as a consequence of the irritant properties of the substance (BayerAG, 1996; Pauluhn, 2003; Ma-Hock et al., 2009). These effects most probably are related to the chemical nature of the isocyanate-groups of IPDI homopolymer.

Regarding oral absorption at least partial hydrolysis is assumed to occur in the gastro-intestinal tract. In fact, oral toxicity was very low with an LD_{50} (rat) of > 14000 mg/kg bw (IBR, 1976). No systemic signs could be observed.

Dermal absorption of IPDI homopolymer could not be excluded based on a calculated log Kow that shows a high lipophility (approx. 14.48; Evonik, 2009). In fact, no signs of systemic toxicity were observed in an acute dermal irritation/corrosion study (LPT, 2005). Nevertheless, the test substance has shown skin sensitizing properties in a guinea pig maximization test (Notox B. V., 2004), thus indicating that a dermal uptake, even though small, can occur. Deducing from that IPDI homopolymer has the property to react with nucleophilic groups of proteins or peptides and form hapten-protein complexes or conjugate-antigens.

No data are available regarding the excretion of absorbed IPDI homopolymer.

Based on the results of several in vitro genotoxicity tests (DeVogel, 2007; Schulz and Hellwig, 2007; Harlan, 2009 and Herbold, 2002; all performed with and without metabolic activation) it is concluded that DNA-reactive metabolites of IPDI homopolymer will not be generated in mammals in the course of hepatic biotransformation.

4.2. Acute toxicity

3 -Isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is of low oral and inhalative acute toxicity with an oral LD_{50} (rat) of > 14000 mg/kg bw (IBR, Bio-Research, 1976) and an inhalative LC_{50} (rat, aerosol, 4 hrs) of > 5010 mg/m^3 (OECD 403: Bayer AG, 1996). No mortalities were observed. Clinical signs after oral administration like ataxia, abnormalities in posture and piloerection were observed beginning 10 min after dosing and lasting 24 hours. After inhalative administration the aerosolized test substance (dust) proved to have no significant acute inhalation toxicity to rats (secondary nonspecific signs like motility reduced, ungroomed hair-coat, piloerection were observed). The clinical observation demonstrate that the dust acts as mild respiratory tract irritant (bradypnea, laboured breathing pattern, serous discharge from nose, hypothermia).

Assessment of the acute inhalation toxicity data from another study with rats (Pauluhn, Bayer AG, 2003) also indicates that the exposure of respirable aerosols of 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) causes irritation of the respiraton tract as indicated by biochemical and

cytological parameters in BALF, increased weights of lung and concentration dependent increased incidence of macroscopic alterations of the respiratory tract. At the very high exposure level of 462.5 mg/m^3 clinical evidence existed that the aerosol elicited both a lower as well as an upper tract irritation potential whereas at 153.4 mg/m^3 clinical evidence of respiratory tract irritation was minimal or absent. The data generated show unequivocally that the concentration of respirable particulates required for the elicitation of irritant-related pulmonary response is in the range of 153.4 mg/m^3. With respect to pulmonary irritation **50 mg/m^3** is considered to be the non-irritant threshold concentration **(NOAEC).**

In consideration of risk management measures inhalation is the most probably route of exposure. Dermal exposure has to be avoided because of sensitizing properties.

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

3 -Isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is of low oral and inhalative acute toxicity with an oral LD_{50} (rat) of > 14000 mg/kg bw (IBR, Bio-Research, 1976) and an inhalative LC_{50} (rat, aerosol, 4 hrs) of > 5010 mg/m^3 (Bayer AG, 1996).

Justification for classification or non classification

Based on the results of the acute oral and inhalation studies and according to the criteria of EC Directive 67/548/EEC and EC Regulation 1272/2008 3-isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) has a very low acute toxicity if swallowed or inhaled. Therefore, the test substance must not be classified.

4.3. Irritation

3 -Isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is not irritating to skin of rabbits (OECD 404: LPT, 2005). In a second study, IPDI homopolymer, tested approx. 70% in solvent (1-Methoxypropylacetate-2/Xylol (1:1)), showed slightly skin irritating effects in rabbits (OECD 404: LPT, 2002), which do not meet the criteria to be classified as "irritating to skin".

The test substance (tested approx. 70 % in solvent, 1-Methoxypropylacetate-2/Xylol (1:1)) showed slightly eye irritating effects in rabbits (OECD 405: LPT, 2002; IBR, 1977), which also do not meet citeria to be classified as "irritating to eyes".

The repeated dose study (OECD 413: Ma-Hock et al, 2009) as well as the acute inhalation studies (OECD 403: Bayer AG, 1996; OECD 403: Pauluhn, 2003) indicate that 3 -isocyanatomethyl-3,5,5 –trimethylcyclo-hexylisocyanate homopolymer (IPDI homopolymer) causes irritation of the respiratory tract.

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

3 -Isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is not irritating to skin (LPT, 2005). In further studies, the test substance, tested approx. 70% in solvent (1-Methoxypropylacetate-2/Xylol (1:1)), is slightly irritating to eyes and to skin of rabbits (LPT, 2002; IBR, 1977), which do not meet criteria to be classified. The acute inhalation studies (see " Acute toxicity: inhalation") as well as the repeated dose study (see "Repeated dose toxicity: inhalation") do indicate that 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) causes irritation of the respiratory tract.

Justification for classification or non classification

According to criteria of EC Directive 67/548/EEC and EC Regulation 1272/2008 3 -isocyanatomethyl-3,5,5-trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is not irritating to skin and eyes.

Based on the assessment of two animals studies (acute and repeated inhalation) 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is an respiratory irritant.

4.4. Sensitisation

Skin sensitisation

The skin sensitization properties of 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer, tested as a 70% solution in Solvesso 100) were conducted in a **guinea pig maximization test** according to OECD 406 in compliance with Good Laboratory Practice regulations (Notox B. V., 2004). The test substance was administered at a concentration of 50 % intradermally (in corn oil) and 100 % epidermally to 10 female guinea pigs. Sensitisation was observed in 8 of 10 animals in the first challenge phase using a challenge concentration of 50 % test substance. In the second challenge phase with test substance concentration of 50 % six of ten animals were positive. Based on these results and according to the OECD Classification System, IPDI homopolymer should be classified as contact sensitizer.

A **modified LLNA** (IMDS; OECD TG 429) was performed on 6 female NMRI mice per dose group using test item (IPDI homopolymer, tested as a 70% solution in 1-Methoxypropylacetate-2/Xylol (1:1)) in concentrations of 0% (vehicle control), 3%, 10% and 30%.

There was no increase compared to control animals regarding weight of the draining lymph nodes in all dose groups. Compared to vehicle treated animals the cell counts exceeded the "positive levels" defined for this assay in all dose groups, but only in the lowest group the increase was statistically significant. A slight significant increase compared to vehicle treated animals regarding ear swelling was detected in the highest dose group. No increase was determined for the ear weights in any dose group.

Under the conditions of this study the test item IPDI homopolymer has a slight irritating and a sensitizing potential in mice after dermal application.

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

3 -Isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is skin sensitizing in a guinea pig maximization test (Notox B. V., 2004) and a LLNA (Vohr_2003).

Respiratory sensitisation

A lung sensitization study with 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer)

was performed in accordance with the exposure criteria defined in OECD TG 403 using female guinea pigs (Bayer AG, 1996). A standard approach was used that included three intradermal injections (one per day, 5%, 50 µl in acetone). In order to investigate wether the test substance has any potential to induce specific or non-specific airway hyperreactivity an additional group of female guinea pigs was induced by using a 5 x 3 hours inhalation (147 mg/m^3) sensitization protocol followed by inhalation challenge with the hapten, acetylchloline and conjugate by inhalation.

Under the conditions of this study no conclusive immediate-onset responses were observed nor was there any indirect evidence of a lung sensitizing potential, i. e. eosinophilia of airways or production of specific antibody. Therefore, this study does not provide any evidence that IPDI-homopolymer is a respiratory sensitizer.

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

Under the condition of the animal study (Bayer AG, 1996) the test item 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) does not induce respiratory sensitization in guinea pigs.

Justification for classification or non classification

According to the criteria of EC Directive 67/548/EEC and EC Regulation 1272/2008 3-isocyanatomethyl-3,3,5 -trimethylcyclohexyl- isocyanate homopolymer (IPDI homopolymer) is classified as sensitizing to skin. A animal study does not provide any evidence that IPDI homopolymer is a respiratory sensitizer and no respective data are available for humans, therefore the test substance must not be classified.

4.5. Repeated dose toxicity

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

Because inhalation is the most likely route of human exposure, a 90 days repeated dose **inhalation** study (0,3, 15, 75 mg/m^3;

6 hours/day on five days/week for 13 weeks; OECD TG 413, Ma-Hock, BMS, 2009) with 3-isocyanatomethyl-3,5,5 -trimethyl- cyclohexyl-isocyanate homopolymer (IPDI homopolymer) was conducted.

The exposure of rats to the test substance caused concentration dependent pulmonary irritation as indicated by biochemical and cytological parameters in BALF, increased weights of lung and corresponding histological findings of the lung and the mediastinal lymph nodes. Overall, at the high concentration of 75.0 mg/m^3 several effects were not reversible within 4 weeks recovery period due to the expected low lung clearance rate for poorly soluble particles. No substance-related clinical signs of toxicity were observed.

The lowest tested concentration of **2.9 mg/m^3** is the No Observed Adverse Effect Level (**NOAEC**) under the current test conditions.

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

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

A 14-day range finding inhalation study (5, 25, and 125 mg/m3; 6 hours/day, 5 days/week; OECD TG 412) with male Wistar rats indicates the respiratory tract to be the target organ. The exposure of rats to the test substance caused concentration dependent pulmonary irritation as indicated by biochemical and cytological parameters in BALF, the increased weights of lung and the histomorphology of the lungs. The lowest tested concentration of 5 mg/m3 is the NOAEC under the current test conditions.

The 90 day inhalation exposure to 3, 15, and 75 mg/m^3 IPDI homopolymer (male and female Wistar rats; OECD TG 413) did not lead to any substanc related clinical signs of toxicity. The exposure of rats to the test substance caused concentration dependent pulmonary irritation as indicated by biochemical and cytological parameters in BALF, increased weights of lung and corresponding histological findings of the lung and the mediastinal lymph nodes. The lowest tested concentration of 2.9 mg/m^3 is the No Observed Adverse Effect Level (NOAEC) under the current test conditions.

Target organs: respiratory: lung

Justification for classification or non classification

Regarding repeated dose toxicity the substance 3 -isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer (IPDI homopolymer) is not classified according to the criteria of EC Directive 67/548/EEC and EC Regulation 1272/2008.

4.6. Mutagenicity

3 -Isocyanatomethyl-3,5,5 -trimethyl- cyclohexyl-isocyanate homopolymer (IPDI homopolymer) did not induce gene mutations in bacteria (OECD TG 471; Harlan, Evonik Degussa GmbH, 2009) or in mammalian cells (OECD TG 476; Schulz and Hellwig, BASF, 2007) and demonstrate no potential to induce chromosome aberrations in Chinese Hamster Ovary cells in vitro (OECD TG 473; de Vogel, BASF, 2007) either with or without metabolic activation.

Results from genetic toxicity tests in vivo are not available.

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

All in vitro genotoxicity studies, 3-isocyanatomethyl-3,5,5 -trimethyl- cyclohexyl-isocyanate homopolymer (IPDI homopolymer) revealed clearly negative results. Therefore, it can be concluded that the test substance is not genotoxic in vitro.

Justification for classification or non classification

Because all in vitro genotoxicity studies revealed clearly negative results, it can be conluded that 3-isocyanatomethyl-3,5,5 -trimethyl- cyclohexyl-isocyanate homopolymer (IPDI homopolymer) is not genotoxic in vitro and therefore must not be classifed according to the criteria of EC Directive 67/548/EEC and EC Regulation 1272/2008.

4.7. Carcinogenicity

There are no data available.

4.8. Toxicity for reproduction

4.8.1. Effects on fertility

Data waiving

Reason: study scientifically unjustified

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-trimethylcyclohexylisocyanate homopolymer (isophorone diisocyanate homopolymer; IPDI homopolymer) 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 homopolymer, sub-chronic study shows toxicity confined to the respiratory tract. Fertility studies with the similar 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 homopolymer, 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 diisocyanates"" 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 homopolyme and additional toxicity testing is not necessary.

4.8.2. Developmental toxicity

Data waiving

Reason: study scientifically unjustified

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-trimethylcyclohexylisocyanate homopolymer (isophorone diisocyanate homopolymer; IPDI homopolymer) 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 developmental study is available for IPDI homopolymer, sub-chronic study shows toxicity confined to the respiratory tract. Hence the databases for other aliphatic diisocyanates (IPDI, H12MDI, HDI) 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 relation-ship applies to IPDI, H12MDI and HDI when tested in developmental studies in the rat and is considered to apply equally to IPDI homopolymer, i. e., if any effects were to be seen in a developmental 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 diisocyanates"" elaborating this data waiver is attached to this record. Using the weight of evidence, it is concluded that

developmental toxicity is not an endpoint of concern for IPDI homopolymer and additional toxicity testing is not necessary.

4.8.3. Summary and discussion of reproductive toxicity

Discussion

Effects on fertility

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-trimethyl-cyclohexyl isocyanate homopolymer (IPDI homopolymer). A data waiver is claimed.

Histopathological results of a subchronic 13 week inhalation study with IPDI homopolymer in female and male Wistar rats according to OECD Guideline 413 (Ma-Hock et al., BASF, 2009) showed no substance induced effects on the examined reproductive organs (testes/ovaries, epididymides/oviducts, uterus/vagina) at tested concentrations up to 75 mg/m^3.

Conclusion

The toxicological database for inhaled Isophorone Diisocyanate homopolymer (IPDI homopolymer) 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 homopolymer, subchronic and subacute (and acute) 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 homopolymer, 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 homopolymer 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:

No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-isocyanatomethyl-3,5,5-trimethyl-cyclohexyl isocyanate homopolymer (IPDI homopolymer). A data waiver is claimed.

Developmental toxicity

Studies in Animals

No studies have been performed to explicitly address the question of developmental toxicity in animals caused by 3-isocyanatomethyl-3,5,5-trimethyl-cyclohexyl isocyanate homopolymer (IPDI homopolymer). A data waiver is claimed.

Histopathological results of a subchronic 13 week inhalation study with IPDI homopolymer in female and male Wistar rats according to OECD Guideline 413 (Ma-Hock et al., BASF, 2009) showed no substance induced effects on the examined reproductive organs (testes/ovaries, epididymides/oviducts, uterus/vagina) at tested concentrations up to 75 mg/m3.

The developmental toxicity of the monomer 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (IPDI)

was investigated in a vapor inhalation study conducted according to OECD TG 414 (2001). Groups of 27 female Wistar rats were exposed to 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate via nose-only inhalation, 6 hours/day on gestation days 6 to 19 at target concentrations of 0.25, 1.0 or 4.0 mg/m^3(0.206, 0.929, 4.536 mg/m^{3}analytical).

No maternal mortalities were reported. Treatment with 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate at the 4 mg/m^{3}exposure level affected the respiratory tract and the fur of the females and comprised bradypnea, labored breathing, breathing sounds, reddish encrusted nostrils, serous nasal discharge and rough fur. 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; for further details see chapter 7.8.2 of IUCLID 5 set of IPDI).

Conclusion

The toxicological database for inhaled Isophorone Diisocyanate homopolymer (IPDI homopolymer) 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 or developmental study is available for IPDI homopolymer, subchronic and subacute (and acute) studies all show toxicity confined to the respiratory tract. Hence the databases for other aliphatic diisocyanates (IPDI, H12MDI, HDI) 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 IPDI, H12MDI and HDI when tested in developmental toxicity studies in the rat and is considered to apply equally to IPDI homopolymer, i. e., if any effects were to be seen in a developmental 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 developmental toxicity is not an endpoint of concern for IPDI homopolymer 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:

No developmental toxicity/teratogenicity studies are available for 3-isocyanatomethyl-3,5,5-trimethyl-cyclohexyl isocyanate homopolymer (IPDI homopolymer). A data waiver is claimed.

Toxicity to reproduction: other studies

No further studies available

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 and EC Regulation 1272/2008.

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 (skin)	No DNEL derivation, because IPDI homopolymer is considered to be a skin sensitizer and no indications of systemic toxicity were found within the studies.
Acute - systemic effects	Inhalation					No DNEL derivation, because no indications of systemic toxicity were found within the studies.
Acute - local effects	Dermal				sensitisation (skin)	No DNEL derivation, because IPDI homopolymer is considered to be a skin sensitizer.
Acute - local effects	Inhalation	DNEL (Derived No Effect Level)	0.58 mg/m³		irritation (respiratory tract)	see below: “Derivation of corrected dose descriptors (correct starting point) and selection of assessment factors”
Long-term - systemic effects	Dermal					No DNEL derivation, because IPDI homopolymer is considered to be a skin sensitizer.
Long-term - systemic effects	Inhalation					No DNEL derivation, because no indications of systemic toxicity were found within the studies.
Long-term - local effects	Dermal				sensitisation (skin)	No DNEL derivation, because IPDI homopolymer is considered to be a skin sensitizer.
Long-term - local effects	Inhalation	DNEL (Derived No Effect Level)	0.29 mg/m³	NOAEC: 1.45 mg/m³ (based on AF of 5)	irritation (respiratory tract)	see below: “Derivation of corrected dose descriptors (correct starting point) and selection of assessment factors”

**) 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.*

Derivation of corrected dose descriptors (correct starting point) and selection of assessment factors:

[6]Conversion of an rat NOAEC $_{inhalatory; rep. dose}$ from 90 day rat inhalativ repeated dose toxicity study into an corrected NOAEC $_{inhalatory; rep. dose}$ (derived from figure R.8-2; Chapter R 8.4.2 of TGD "Chapter R.8: Characterisation of dose [concentration]-response for human health"):

For workers:
assumptions:
- 8h exposure/day
- Inhalation absorption rat = inhalation absorption human

corrected NOAEC $_{inhalatory; rep.dose}$ = rat NOAEC $_{inhalatory; rep. dose}$ * ((6 h/d) / (8 h/d)) * (6.7 m^3 (8h) / 10 m^3 (8h))

= 2.9 mg/m^3 * 0.75 * 0.67

= 1.46 mg/m^3

Selected assessment factors (according to Table R 8-6 of the TGD):

- Interspecies: factor for allometric scaling (local)	1*
- Interspecies: remaining differences (local)	1**
- Intraspecies (worker, local)	5***
- Exposure duration (local; subchronic to chronic)	1****
- Dose-response (local)	1*****
- Quality of the database (local; overall)	1******
overall Assessment Factor (overall AF)	**5**

* An allometric scaling factor is not applicable for local effects (see section R 8.4.3.1 of TGD), therefore AF 1 is chosen.
** 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.
*** For intraspecies variability, the default assessment factor for workers for local effects is 5.
**** 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 only local effects (no systemic effects) were observed, and the 14-days repeated dose toxicity inhalation pre-study (Ma-Hock, 2009) leads to nearly the same result as the subchronic 90-days study (Ma-Hock, 2009) (NOAEC 5 mg/m^3 versus 2.7 mg/m^3). Therefore it is not expected that a longer duration of the study would change the outcome and a AF of 1 is warranted
***** Starting point is a NOAEC. Thus standard assessment factor 1 is used as described in chapter R 8.4.3.1 of TGD
****** Because of good/standard quality of the database the standard assessment factor 1 is used as described in chapter R 8.4.3.1 of TGD

DNEL $_{long-term}$ for workers for inhalation route – local effects = NOAEC corr. / Overall AF

= 1.46 mg/m^3 / 5

= 0.29 mg/m^3

[7] A DNEL will be derived to quantify possible local irritation effects on respiratory tract after *short term* inhalation exposure (according to Chapter R.8, Appendix R. 8-8, Box 6 of the TGD

For workers:
According to the German rule for OELs (Technical Rule for Hazardous Substances 900, German Federal Ministry of Labour and Social Affairs, 2006/2009) for short-term ceiling concentrations an exposure limit could be established by multiplication to an exceeding factor (Überschreitungsfaktor), which is set per default 1 (could be adjusted to max. 8). For 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate an exceeding factor of 2 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 a short term ceiling limit or a

DNEL $_{acute}$ for workers for inhalation route – local effects of 0.58 mg/m³.

This procedure is in accordance to ECHA Guidance, Chapter R.8., Appendix R. 8-8, Box 6.

Discussion

Derivation of the corrected starting points, overall assessment factors and DNEL´s for workers, which are exposed via inhalation and via dermal contact, see tables in section 5.11.1 and 5.11.2 of the Chemical Safety Report.

For workers in industrial settings, which are exposed via inhalation, DNELs for acute and long-term inhalation effects of 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) have to be derived. In addition, the sensitization potential after skin contact to IPDI homopolymer has to be assessed.

For repeated dose toxicity one subchronic inhalation study with dust exposure of IPDI homopolymer to rats is available (Ma-Hock, 2009). The obtained NOAEC and LOAEC were 2.9 mg/m^3 and 15 mg/m^3, respectively, for effects governed by respiratory tract irritation. No indications of systemic toxicity were found within this study.

Because no reproduction/developmental toxicity test is available, 2.9 mg/m^3 was used as a starting point for the delineation of a $DNEL_{long\text{-}term}$ for workers for inhalation route.

For acute dose toxicity two short term inhalation studies with aerosol exposure of IPDI homopolymer to rats are available (Bayer AG, 1996 and Pauluhn, 2003). In the first study an inhalative LC_{50} value of > 5010 mg/m^3 was obtained. No mortalities were observed. The clinical observation demonstrate that the dust acts as mild respiratory tract irritant. Assessment of the acute inhalation toxicity data from the second study with rats (single 6 hours inhalation exposure) also indicates that the exposure of respirable aerosols of IPDI homopolymer causes irritation of the respiratory tract. No indications of systemic toxicity were found within these two studies.

For the short-term ceiling concentration an exposure limit has been etablished by multiplication the long-term ceiling concentration to an exceeding factor (see above). For 3 -isocyanatomethyl-3,5,5 trimethylcyclohexyl-isocyanate homopolymer an exceeding factor of 2 is applied.

A dermal sensitization potential was shown for 3 -isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) in two skin sensitization studies (Vohr, 2003 and NOTOX, 2004). According to the potency categorisation approach (Appendix R.8-10 of TGD) IPDI homopolymer is classified as a moderate skin sensitizer based on the Guinea Pig Maximization Test (50 % induction conc., >= 60 % incidence of sensitisation; NOTOX B. V., 2004). In consideration of risk management measures inhalation is the most probably route of exposure. Dermal exposure has to be avoided because of sensitizing properties of IPDI homopolymer.

DN(M)ELs for the general population

Discussion

3 -Isocyanatomethyl-3,5,5 -trimethylcyclohexylisocyanate homopolymer (IPDI homopolymer) is exclusively used as intermediate in chemical processes (i. e. hardener for coating materials or adhesives for industrial and professional use). A direct use of this substance is not known. The exposure of consumers to IPDI homopolymer is unlikely to occur via consumer products, because no consumer product is known to contain the substance. An exposure of consumers or general population via the environment is also unlikely to occur, because there are only low levels of exposure from environmental sources, and IPDI homopolymer released to the environment would rapidly be degraded by water and photooxidants. Therefore, DNELs for consumers or general population are not applicable as consumers are not involved in the industrial or professional use of IPDI homopolymer or of preparations containing this substance. Additionally, in view of low toxicity in experimental studies and low levels of exposure from environment sources, the risk to the general population appears to be minimal.

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-trimethylcyclo-hexylisocyanate homopolymer was neither shock sensitive nor thermally or friction sensitive, according to the criteria of the EC test method A.14 of Council Regulation (EC) No 440/2008 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:

3-Isocyanatomethyl-3,5,5-trimethylcyclo-hexylisocyanate homopolymer is not highly flammable according to the definition in the Council Regulation (EC) No 440/2008, method A.10.

Flash point

Data waiving: see CSR section 1.3 Physico-chemical properties.

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

The substance is a solid melting above 60 °C (see chapter 4.2). EC method A.9 is not applicable to solids. Therefore the hazard of flammability is determined using EU method A.10.

5.3. Oxidising potential

Data waiving: see CSR section 1.3 Physico-chemical properties.

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.

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.

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 homopolymer

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 esturarine water > 60 d, or Half-life in marine, fresh or estuarine sediment > 180 d, or half-life in soil > 180 d	Not readily biodegradable (Weyers A 2007) Stable hydrolysis products that have to be considered as persistent (non-biodegradable, non-mobile)	yes (hydrolysis product)
B	BCF > 2000	BCF > 5000	Not B (based on molecular weight and modelled Log Kow) Not vB (based on molecular weight and modelled Log Kow	no
T	Long-term NOEC for marine or freshwater organisms < 0.01 mg/l	Not applicable.	72h-NOEC 3.1 mg/l for algae (Scheerbaum D 2002)	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 homopolymer is not readily biodegradable with 0 % biodegradation in 28 days (Weyers A 2007). However, biodegradation is irrelevant as primary degradation step because immediate hydrolysis takes place. The hydrolysis products are oligo- and subsequently polyurea components. Polyurea is known to be inert and is probably due to its molecular size not bioavailable. Moreover, polyurea is considered insoluble in water and is characterised by limited mobility. Based on these considerations, 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer 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 homopolymer are not available. 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer hydrolyses rapidly in the presence of water with a half life of approximately 2.7 hours. The parent substance has an average molecular weight of 893 g / mol. According to ECHA guidance on information requirements a molecular weight higher than 700 g/Mol indicates that the BCF is below 5000 L/kg. It can be concluded from the structural formulae that the formed polyurea (hydrolysis product) has a molecular weight amounting to multiples of that of the initial oligomers. Polyurea is therefore considered as less bioaccumulative compared to the parent substance. Moreover, a modelled Log Kow of 14.58 (SRC Kowwin v1.67 Computer Program, integrated in U.S. EPA's EPI program Vers. 3.20) for the unhydrolysed parent substance indicates that the aquatic BCF is probably lower than 2000 L/kg (although this criterion should be treated with caution). Considering the mentioned criteria the potential for bioaccumulation is regarded as minor for both the parent substance and the formed hydrolysis

products.

6.1.3. Toxicity Assessment

There is one aquatic toxicity test for algae available which can be regarded as a chronic test. The NOEC was 3.1 mg/l (Scheerbaum D 2002). Furthermore, 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 homopolymer is not classified as PBT substance.

A substance is classifed as a vPvB substance, if both vPvB criteria described above are fulfilled. The P criterion is fullfilled, the B criterion is not fulfilled. Hence 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer is not classified as vPvB substance.

6.2. Emission Characterisation

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

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