4,4'-methylenedicyclohexyl diisocyanate

EC Number: 225-863-2

CAS Number: 5124-30-1

IUPAC name: 1-isocyanato-4-[(4-isocyanatocyclohexyl)methyl]cyclohexane

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 4,4'-methylenedicyclohexyl 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 4,4'-methylenedicyclohexyl diisocyanate.

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1. PHYSICAL AND CHEMICAL PROPERTIES

Molecular Weight: 262.35 g/mol

Molecular formula: $C_{15}H_{22}N_2O_2$

Appearance/physical state/colour: Colourless to light-yellow liquid

Melting / freezing point: No melting point was found between - 150 °C and + 50 °C. A glass transition was observed at - 74 °C. This reflects the fact that the test substance is a complex mixture of isomers that hardly find common crystalline structure upon cooling. Under favourable conditions, i.e. after slow cooling to - 60 °C followed by slow heating, an indication of melting could be observed at approx. 20 °C

Boiling point: Decomposition above 300°C at normal pressure, approx. 155 -160 °C at 0.67 hPa.

Relative density: 1.07 at 25 °C

Vapour pressure: $1.22*10^{-05}$ hPa at 20 °C

Water solubility: Hydrolytically unstable (half-life 1.97 hours).

Partition coefficient n-octanol/water (log value): 6.11(estimated) Test cannot be performed, as the substance decomposes in water within a few hours (half-time 1.97 hours)

Flash point: 200 °C at 1013 hPa

Self-ignition temperature: 225 °C at 1013 hPa

Stability in organic solvents: In protic solvents like alcohols, isocyanates react rapidly. Stablility is expected with non-protic solvents like toluene, acetone, dioxane etc. Isocyanates form urethanes in alcohol. The concentration of 4,4'-methylenedicyclohexyl diisocyanate in an acetonitrile solution without addition of water was stable over at least 6 hours at room temperature.

Viscosity: approx. 12.7 mPa*s at 55 °C

2. ENVIRONMENTAL FATE PROPERTIES

The main conclusions in this chapter have been prepared in accordance with the draft SIDS initial assessment report OECD (2005).

2.1. Hydrolysis

Discussion

If released to the environment, 4,4'-methylenedicyclohexyl diisocyanate will be rapidly degraded by hydrolysis.

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

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly. A half-life of approximately 2 hours was determined experimentally (Bayer AG, 1999).

In this GLP study, 1 g/l 4,4'-methylenedicyclohexyl diisocyanate dissolved in an acetonitrile/water-mixture was investigated at 23 °C. The decrease of NCO-content was observed in this solution during the study period. For this purpose the concentration of 4,4'-methylenedicyclohexyl diisocyanate was determined by means of capillary gas chromatography using flame ionisation detection at periodical time intervals.

A preliminary test according to the OECD TG 111 was carried out with 4,4'-methylenedicyclohexyl diisocyanate to determine the resulting products from the reaction with water. A solution of 2.64 g/l was incubated in demineralised, unbuffered water at 50°C during 5 days under continuous stirring (Bayer Industry Services, 2004).

In the aqueous phase the three isomers (cis,cis; cis,trans; trans,trans) of methylene bis(4-cyclohexyldiamine) (CAS 1761-71-3) were identified with GC- and HPLC-MS. Additionally, the HPLC-analysis showed to a minor extent traces of a trimeric diamine compound; this was bound by urea-groups. Insoluble droplets obtained during hydrolysis testing adhered to the glass wall. They were analysed with IR spectroscopy and were found to

contain urea components (polymeric urea) and encapsulated traces of isocyanate-groups. As no differences in the reaction products received in the hydrolysis of the test substances at pH 4, 7 and 9 were expected, no test have been performed at these pH values (Bayer Industry Services 2004).

2.2. Phototransformation in air

Discussion

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

There are no experimental data on the stability of 4,4'-methylenedicyclohexyl diisocyanate in the atmosphere. A half-life of about 15 hours is estimated due to reaction with photochemically produced hydroxyl radicals, considering a mean OH concentration of 0.5 x 10^6 OH radicals/cm³ as a 24 h-average (Currenta, 2009a). However, the AOPWIN program used for this estimate does not take into account that 4,4'-methylene- dicyclohexyl diisocyanate is sensitive to hydrolysis e.g. in aerosols with aquatic phases.

The photodegradation of the hydrolysis product of 4,4'-methylenedicyclohexyl diisocyanate was estimated with AOPWIN v. 1.92. The atmospheric oxidation rate constant of the hydrolysis product of 4,4'-methylenedicyclohexyl diisocyanate (CAS:1761 -71 -3) is 117 * $10^{-12}$$cm^3$/(molecule *s) and its atmospheric half-life is about 3 hrs at a mean OH concentration of 0.5 x 10^6 OH radicals/cm³ (Currenta, 2009b).

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:

In a GLP-study which was conducted according to Directive 92/69/EEC C.4-D (Manometric Respirometry Test), the biodegradation of 4,4'-methylenedicyclohexyl diisocyanate was investigated with a test substance concentration of 100 mg/l. Within the test period of 28 days, a degradation of 0 % was determined (Bayer AG, 2000a).

In a GLP-study which was conducted according to OECD TG 301F, the biodegradation of 4,4'-methylenedicyclohexyl diisocyanate was tested at an initial concentration of 12 mg/l. Within the test period of 28 days, a degradation of 0 % was observed (Bayer AG, 1992).

Discussion (simulation testing)

Not applicable.

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

According to Reach Annex XI section 1, a study is scientifically unjustified. A biodegradation test should provide data on biodegradation under specified environmentally relevant conditions. The study Bayer (1992) which is performed as a ready test is considered as similar to an inherent study as the relation amount of bacteria / test substance was higher. As no biodegradation (0%) was observed in a study on ready biodegradability 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. No additional information would be obtained through that test.

2.3.2. Biodegradation in soil

Discussion

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

According to Reach Annex XI section 1, a study is scientifically unjustified. A biodegradation test should provide data on biodegradation under specified environmentally relevant conditions. The study Bayer (1992) which is performed as a ready test is considered as similar to an inherent study as the relation amount of bacteria / test

substance was higher. As no biodegradation (0%) was observed in a study on ready biodegradability is not expected that significant degradation would occur in a soil degradation test. The test substance is considered as non-biodegradable in the soil compartment. Moreover, biodegradation is irrelevant as primary degradation step because immediate hydrolysis takes place. No additional information would be obtained through that test.

Abiotic degradation

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water. A half-life for 4,4'-methylenedicyclohexyl diisocyanate of approximately 2 hours was determined experimentally. Main hydrolysis product – beside a majority of oligomeric and polymeric ureas - is methylene bis(4-cyclohexylamine). Due to the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate, equilibrium partitioning of the substance between environmental compartments is unlikely. Consequently, a calculation of the Henry's Law Constant and of the distribution between the environmental compartments according to the Mackay fugacity model level 1 is not suitable.

4,4'-Methylenedicyclohexyl diisocyanate degrades relatively rapidly in the atmosphere by reaction with hydroxyl radicals (half-life, 15 hrs), and may also undergo hydrolysis. The photochemically induced half life of the hydrolysis product methylene bis(4-cyclohexyldiamine) is 3hours. Both half-lives correspond to an OH concentration of 0.5×10^6 OH radicals/cm³, which is a typical 24 hour-mean in Central Europe.

Biotic degradation

Based on the available experimental biodegradation test result for 4,4'-methylenedicyclohexyl diisocyanate, the substance is classified as not readily biodegradable.

2.4. Environmental distribution

2.4.1. Adsorption/desorption

Discussion

Adsorption properties of substances are an essential input to environmental exposure assessment as the main compartments to which the substances are partitioned are identified and then tests strategies may be adapted to the behaviour of these substances. However, adsorption may be of minor importance for compounds with specific chemical properties and can be considered as not relevant for the assessment of the environmental behaviour.

According to REACH Regulation, Annex VIII adsorption / desorption studies can be waived, if one of the following circumstances applies:

– based on the physicochemical properties the substance can be expected to have a low potential for adsorption (e. g. the substance has a low octanol water partition coefficient); or

– the substance and its relevant degradation products decompose rapidly.

Methods for adsorption/desorption tests:

The adsorption of a substance to sewage sludge, sediment and/or soil can be measured using several methods.

In the OECD 106 "batch equilibrium method" adsorption coefficients are determined on various soils as a function of soil characteristics (e. g. organic carbon content). The use of a range of actual soils allows to predict realistic conditions. However, as a direct measurement of the adsorption, this method requires a quantitative analytical method for the substance, reliable over the range of the test concentrations.

The other commonly used adsorption method is an HPLC method referred as the "OECD 121 guideline". It is an indirect estimation method based on the calibration of HPLC retention times for reference substances. In contrast to the OECD 106 method, the HPLC method does not require a quantitative analytical method. It is also independent from any choice of soils that might impair the results. However, the reference substances should be selected with known adsorption coefficients encompassing the expected value of the test chemical. In addition, the detection method does not guarantee that the parent substance or its degradation products are all detected implying some uncertainty on the results.

Instability of 4,4’-methylenedicyclohexyl diisocyanate:

Whatever method may have been chosen they all require the test substance to be sufficiently stable during the experiment. It may not apply to substances and relevant degradation products that decompose rapidly. Therefore, among others, information on the water solubility, the octanol/water partition coefficient and the stability of the substance is useful.

In water, 4,4'-methylenedicyclohexyl diisocyanate hydrolyses with a half-life of approximately 2 h (Bayer AG, 1999). The behaviour of 4,4’-methylenedicyclohexyl diisocyanate in soil will be affected by humidity due to its rapid hydrolysis. Therefore, an experimental study with 4,4’-methylenedicyclohexyl diisocyanate is scientifically unjustified.

The hydrolysis product is a complex mixture of water-insoluble oligomeric and polymeric ureas and of compounds derived from the corresponding diamine, where the isocyanate groups have been transformed to amino or urethane groups.

The diamine was considered in order to get an estimate on the adsorption behaviour of the hydrolysed product. For both, the unreacted diisocyanate as well as for the corresponding diamine, calculated values with three estimation methods are presented. For the polymers, no surrogate structure can be identified. However, negligible mobility and therefore insignificant adsorption is expected.

It is therefore concluded that adsorption of 4,4’-methylenedicyclohexyl diisocyanate to soil is unlikely to occur. The hydrolysis product methylene bis(4-cyclohexyl diamine) has only a small to medium tendency for adsorption.

Hydrolysis tests have been conducted and concluded rapid hydrolysis (half life <2h):

The 12 hours hydrolytical half-life value is considered as a threshold value below which this qualitative screening information is sufficient to evaluate the behaviour of the substance and its partition in the main compartments without conducting a full adsorption/desorption test (ECHA 2008: Guidance on information requirements and chemical safety assessment; chapter R.7. a: Endpoints specific guidance;4,4’-methylenedicyclohexyl diisocyanate is unlikely to adsorb to sediment, sludge or soil due to rapid hydrolysis processes which will prevail over adsorption mechanisms. Both components can be considered as unstable with a hydrolysis half life far below 12 hours (see above). Therefore adsorption/desorption tests cannot be performed without extended adaptations or deviations to the OECD standardised methods.

Conclusions

Due to the instability of 4,4’-methylenedicyclohexyl diisocyanate, none of the OECD 106 or OECD 121 method seems to be relevant as the rapid hydrolysis of the components (half lives below 12 hours) will prevent them from adsorption to soil, sludge or sediments. Experimental determination of adsorption / desorption of 4,4’-methylenedicyclohexyl diisocyanate is not feasible. Instead of an experimental study QSAR predictions on adsorption/desorption are available and summarised.

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

There are no experimental data on the geoaccumulation potential of 4,4’-methylenedicyclohexyl diisocyanate, because the substance hydrolyses rapidly in aqueous environment. The distribution of 4,4’-methylenedicyclohexyl diisocyanate between the organic phase of soil or sediments and the pore water was calculated using EPI-Suite software and two other QSARs.

4,4’-methylenedicyclohexyl diisocyanate should be regarded as a substance with very high geoaccumulation properties with a Koc-value in the range between 4.3*1004 and 3.8*1005. The calculated Koc values indicate that of 4,4’-methylenedicyclohexyl diisocyanate may strongly adsorb to soil but due to its rapid hydrolysis any emission to the terrestrial compartment would be affected by humidity.

It is therefore concluded that geoaccumulation of 4,4’-methylenedicyclohexyl diisocyanate is unlikely to occur. The hydrolysis product has only a small to medium tendency for geoaccumulation (log Koc <3).

2.4.2. Volatilisation

Discussion

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

The calculation of the Henry's Law Constant is not suitable due to the hydrolysing properties of 4,4'-methylenedicyclohexyl diisocyanate.

However, for the later derivation of PNECsediment and PNECsoil (chapter 7.1, 7.2) a Henry's Law Constant of 6.9 Pa*m³/mol at a temperature of 25 °C was calculated with HENRYWIN v. 1.30 on the basis of the bond contribution method (Currenta, 2009a).

2.4.3. Summary and discussion of environmental distribution

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water. Hydrolysis product -, beside oligomeric and polymeric ureas - is methylene bis(4-cyclohexylamine). In water, a hydrolysis half-life for 4,4'-methylenedicyclohexyl diisocyanate of approximately 2 hours was determined experimentally. Due to the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate, equilibrium partitioning of the substance between environmental compartments is unlikely. Consequently, a calculation of the Henry's Law Constant and of the distribution between the environmental compartments according to the Mackay fugacity model level 1 is not suitable.

2.5. Bioaccumulation

Aquatic bioaccumulation

4,4'-Methylenedicyclohexyl diisocyanate is characterized by a BCF of 10186 being calculated with BCFWIN v. 2.17 (Currenta, 2009a). However, the direct and indirect exposure of aquatic organisms is unlikely because 4,4'-methylenedicyclohexyl diisocyanate hydrolysis rapidly in water within 2 hours (half-life 1.97 hours).

The hydrolysis product of 4,4'-methylenedicyclohexyl diisocyanate with a calculated bioconcentration factor of 7.3 does not have a high bioaccumulation potential (Currenta, 2009b).

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

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water with a half life of approximately 2 hours. Therefore a risk estimation regarding the bioaccumulation potential of 4,4'methylenedicyclohexyl diisocyanate on the basis of a log Kow or a BCF, determined by QSAR, is misleading. A calculated theoretical log Kow or BCF value reflects the undissociated and unreacted molecule without influence of water.

However, the substance is not persistent in water due to the rapid hydrolysis. Therefore it is not bio-available. Possible hydrolysis products are less lipophilic. On the basis of these information it can be expected that relevant bioaccumulation of 4,4'-methylenedicyclohexyl diisocyanate does not occur.

Terrestrial bioaccumulation

Not applicable.

Secondary poisoning

Because of the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate in water, it is not expected that this substance will bioconcentrate in aquatic organisms, or bioaccumulate in the food chain. No information on BCFs and food chain bioaccumulation could be found for 4,4'-methylenedicyclohexyl diisocyanate in the available literature; however, a BCF of approximately 7 was calculated for the hydrolysis product 4,4'-methylenedicyclohexyl diamine (CAS number 1761-71-3) which indicates a very low bioaccumulation potential. For this reason, there is no risk for secondary poisoning. It is not required to carry out a risk characterisation for secondary poisoning.

3. ENVIRONMENTAL HAZARD ASSESSMENT

The main conclusions in this chapter have been prepared in accordance with the draft SIDS initial assessment report OECD (2005).

3.1. Aquatic compartment (including sediment)

3.1.1. Toxicity test results

The inherent property of 4,4'-methylenedicyclohexyl diisocyanate is to hydrolyse in an aquatic environment. In the following the toxicity of 4,4'-methylenedicyclohexyl diisocyanate was tested . Due to the rapid hydrolysis the assessment basically focuses on the hydrolysis products. (mainly the soluble hydrolysis product methylene bis(4-cyclohexyldiamine)) Tests were conducted according to the GLP requirements and specially laid down test conditions.

Before the actual start of each ecotoxicity study (Danio rerio (formerly Brachydanio rerio), Daphnia magna and Scenedesmus subspicatus) pre-treatments were performed with 4,4'-methylenedicyclohexyl diisocyanate according to the recommendation mentioned in the "OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures" in order to accelerate test substance solution. For that purpose the solutions of the test substance were prepared at a nominal concentration that was 5-fold higher than the maximum water solubility reported for 4,4'-methylenedicyclohexyl diisocyanate in preliminary tests. The solutions were treated in water with ultra-turrax 60 s/8000 rpm, afterwards stirred for 24 hours on a magnetic stirrer and finally filtered. Because of the short half-life of 4,4'-methylenedicyclohexyl diisocyanate, testing with the degradation products is required and has been conducted as seen in this test. Filtration removed additional insoluble hydrolysis products. Substance concentrations (mainly the soluble hydrolysis product methylene bis(4-cyclohexyldiamine)) were determined as TOC and back-calculated to the parent compound.

3.1.2. Short-term toxicity to fish

Discussion

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

Acute toxicity to fish (Danio rerio) has been investigated in a limit test under static conditions according to Directive 92/69/EEC, C.1. A concentration of 30 mg/l 4,4'-methylenedicyclohexyl diisocyanate was pretreated before start as described above. A 96 h-LC50 of > 8.1 mg/l was observed (Bayer AG, 2000b). At this concentration level 10 % mortality was detected, however, in a range finding test no mortality occurred at the highest concentration tested of 6 mg/l (nominal).

3.1.3. Long-term toxicity to fish

Data waiving

Reason: other justification

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

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

Discussion

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

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

For the risk characterisation of the aquatic compartment, a PNEC has been derived on the basis of three acute aquatic toxicity data. According to the CSA, the risk characterisation yields a PEC/PNEC ratio smaller than 1.

Further test are not necessary as the risk is sufficiently described based on the already available data.

3.1.4. 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:

With the invertebrate Daphnia magna one acute static limit test in accordance with Directive 92/69/EEC, C.2, is available. For a test period of 48 hours an EC50 value of > 8.3 mg/l was determined. At this concentration no mortality was observed (Bayer AG, 2000c).

3.1.5. Long-term toxicity to aquatic invertebrates

Data waiving

Reason: other justification

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

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

Discussion

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

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

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

3.1.6. 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:

Concerning the algal toxicity, a 72-hour test with Scenedesmus subspicatus was performed. According to Directive 92/69/EEC, C.3, the growth inhibition of the alga species was investigated with test substance concentrations in the range of 0.08 to 5 mg/l. The proceeding for preparation of the stock solution was in the same way as described above (7.1.1). A 72 h-ErC50 of > 5 mg/l was determined. As the test concentrations for the determination of the NOEC and LOEC were below the detection limit of the TOC determination (2 mg/l), the test results of the algal toxicity study refer to nominal concentrations. The arithmetic means of the TOC determination of the highest test concentration (5 mg/l) exhibited an expected recovery rate (90%) of the test substance based on organic C (Bayer AG, 2000d).

Effects on aquatic plants other than algae

The following information is taken into account for effects on aquatic plants other than algae for the derivation of PNEC: No data.

3.1.7. Sediment organisms

Data waiving

Information requirement: Sediment organisms

Reason: scientifically unjustified

Justification: According to section 1 of Reach Annex XI, performing of a test is scientifically unjustified. Reach guidance document R7b states that a log Kow should be used as a trigger value for assessing sediment toxicyty. For the substance, a log Kow of 6.11 was calculated. However, the substance hydrolyses rapidly to either oligomeric or polymeric ureas or to 4,4'-methylenebis(cyclohexylamine). The ureas are unsoluble in water and therefore not bioavailable. 4,4'-methylenebis(cyclohexylamine) has a log Kow of about 2 indicating that distributed mainly in the aquatic compartment and not absorbed to sediment.

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

3.1.8. Predicted No Effect Concentration (PNEC)

3.1.8.1. PNEC water

	Value	Assessment factor	Remarks/Justification
PNEC aqua - freshwater (mg/L)	>0.005	1000	No effects have been observed in the acute studies for fish, invertebrates and algae. The highest tested concentration level for the algae study (72 h-ErC_{50} > 5 mg/l, nominal) (Bayer AG, 2000d) was taken for PNEC derivation.
PNEC aqua - marine water (mg/L)	>0.0005	10000	No effects have been observed in the acute studies for fish, invertebrates and algae. The highest tested concentration level for the algae study (72 h-ErC_{50} > 5 mg/l, nominal) (Bayer AG, 2000d) was taken for PNEC derivation.
PNEC aqua - intermittent releases (mg/L)	>0.05	100	No effects have been observed in the acute studies for fish, invertebrates and algae. The highest tested concentration level for the algae study (72 h-ErC_{50} > 5 mg/l, nominal) (Bayer AG, 2000d) was taken for PNEC derivation.

3.1.8.2. PNEC sediment

	Value	Assessment factor	Remarks/Justification
PNEC sediment (mg/kg d.w.)	>21.75	See PNEC aqua	extrapolation method PNEC sediment on the basis of wet weight: >4.7 mg/kg. The PNEC sediment was derived on the basis of aquatic toxicity data (PNECaqua) applying the Equilibrium Partitioning Theory (EPT) as no data is available covering sediment organisms. To derive the PNECsediment on the basis of EPT, the Koc, the Henry's Law Constant as well as the PNECaqua are crucial. Following values have been used for 4,4'-methylene-dicyclohexyl diisocyanate: Koc**= 43471 (calc. acc. to the method of Sablijec) (Currenta, 2009a) HLC = 6.9 Pa*m^3/mole (calc. acc. to EPIWIN) (Currenta, 2009a) PNECaqua= >0.005 mg/L

			Due to dissociating properties, the adsorption/desorption behaviour, expressed as Koc, is characterized by a range rather than a single value. Describing processes in the sediment, lower values are linked to a lower sorption potential, what in turn means higher concentrations in the pore water. As effects towards sediment organisms are assumed to be caused by the fraction dissolved in the pore water, lower Koc values are synonymous with a higher exposure of sediment organisms and were thus used to calculate the PNECsediment. ** If released to the environment, 4,4'-methylenedicyclohexyl diisocyanate, will be rapidly degraded by hydrolysis. The hydrolysis product has only a small to medium tendency for adsorption. Therefore the lowest Koc-value of 4,4'-methylenedicyclohexyl diisocyanate was used for the derivation of PNEC-soil, which is even higher then the highest, calculated KOC-value of its hydrolysis product (Currenta, 2009b).

3.2. Terrestrial compartment

3.2.1. Toxicity to soil macro-organisms

Data waiving

Information requirement: Toxicity to soil macro-organisms

Reason: exposure considerations

Justification: According to section 3 of Reach Annex XI, these studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. A test towards soil macro-organisms is not proposed by the registrant as the chemical safety assessment indicates no need to further investigate the effects on terrestrial organisms.

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

Information requirement: Toxicity to terrestrial arthropods

Reason: exposure considerations

Justification: According to section 3 of Reach Annex XI, these studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. A test towards soil arthropods is not proposed by the registrant as the chemical safety assessment indicates no need to further investigate the effects on terrestrial organisms.

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

3.2.2. Toxicity to terrestrial plants

Data waiving

Information requirement: Toxicity to terrestrial plants

Reason: exposure considerations

Justification: According to section 3 of Reach Annex XI, these studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. A test towards terrestrial plants is not proposed by the registrant as the chemical safety assessment indicates no need to further investigate the effects on terrestrial organisms.

For the risk characterisation of the terrestrial compartment, a PNEC soil has been derived on the basis of the

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

3.2.3. Toxicity to soil micro-organisms

Data waiving

Reason: exposure considerations

Justification: According to section 3 of Reach Annex XI, these studies do not need to be conducted, if direct and indirect exposure of the soil compartment is unlikely. A test towards soil micro-organisms is not proposed by the registrant as the chemical safety assessment indicates no need to further investigate the effects on terrestrial organisms.

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

3.2.4.Predicted No Effect Concentration (PNEC soil)

	Value	Assessment factor	Remarks/Justification
PNEC soil (mg/kg.d.w.)	>4.3	See $PNEC_{aqua}$	PNEC sediment in mg/kg ww: 3.8. The PNEC sediment was derived on the basis of aquatic toxicity data applying the Equilibrium Partitioning Theory (EPT) as no data is available covering soil organisms. To derive the PNECsoil on the basis of EPT, the Koc, the Henry's Law Constant as well as the PNECaqua are crucial. Following values have been used for 4,4'-methylenedicyclohexyl diisocyanate: Koc**= 43471 (calc. acc. to the method of Sablijec) (Currenta, 2009a) HLC = 6.9 Pa*m³/mole (calc. acc. to EPIWIN) (Currenta, 2009a) PNECaqua= >0.005 mg/L Due to dissociating properties, the adsorption/desorption behaviour, expressed as Koc, is characterized by a range rather than a single value. Describing processes in the soil, lower values are linked to a lower sorption potential, what in turn means higher concentrations in the pore water. As effects towards sediment organisms are assumed to be caused by the fraction dissolved in the pore water, lower Koc values are synonymous with a higher exposure of sediment organisms and were thus used to calculate the PNECsoil. ** If released to the environment, 4,4'-methylenedicyclohexyl diisocyanate, will be rapidly degraded by hydrolysis. The hydrolysis product has only a small to medium tendency for adsorption. Therefore the lowest Koc-value of 4,4'-methylenedicyclohexyl diisocyanate was used for the derivation of PNEC-soil, which is even higher then the highest, calculated KOC-value of its hydrolysis product (Currenta, 2009b).

3.3. Atmospheric compartment

Direct data on biotic and abiotic effects of 4,4'-methylenedicyclohexyl 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, no indications suggest that 4,4'-methylenedicyclohexyl 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:

Regarding the toxicity to microorganisms, an oxygen consumption inhibition test according to Commission Directive 88/302/EEC, Part C (corresponds to the OECD TG 209) with activated sewage sludge during 3 hours was performed and an EC50 of 191 mg/l was determined (Bayer AG, 2000e). Before testing a pre-treatment was performed with the test substance according to the recommendation mentioned in the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures in order to accelerate the solution procedure. For that purpose 4,4'-methylenedicyclohexyl diisocyanate was treated in water by ultrasound for 3 - 4 hours and stirred overnight.

3.4.2. PNEC for sewage treatment plant

	Value	Assessment factor	Remarks/Justification
PNEC stp (mg/L)	1.91	100	The lowest acute tested concentration for activated sludge 3 h-EC 50 191 mg/l (Bayer AG, 2000e)

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: According to section 3 of Reach Annex XI, these studies do not need to be conducted if direct and indirect exposure of birds is unlikely. A test towards birds is not proposed by the registrant as the chemical safety assessment indicates no need to further investigate the effects on birds.

3.5.2. PNECoral (secondary poisoning)

	Value	Assessment factor	Remarks/Justification
PNEC oral (mg/kg food)			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 water, sediment of 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 of 4,4'-methylenedicyclohexyl diisocyanate.

3.6. Conclusion on the environmental classification and labelling

Classification and labelling according to aquatic toxicity data

Justification for classification or non classification

Three acute tests have been performed with fish, daphnia and algae. No effects have been observed up to the highest possible concentrations tested (algae: 5 mg/l, fish: 8.1 mg/l, daphnia 8.3 mg/l). Therefore, a classification related to risk phrases R50, 51, 52 can be ruled out.

Classification and labelling according to degradation and bioconcentration

Justification for classification or non classification

4,4´-Methylenedicyclohexyl diisocyanate is not readily biodegradable and has a log Kow of 6.11 (calculated). However, the substance hydrolysis rapidly with a half life of 2 hours. The hydrolysis product is - beside insoluble oligomeric and polymeric ureas - the corresponding 4,4´-Methylenedicyclohexyl diamine. The latter has a log Kow of 2.03 (measured). Therefore, a classification related to risk phrase R53 is not required.

4. HUMAN HEALTH HAZARD ASSESSMENT

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

4,4´-methylenedicyclohexyl diisocyanate (CAS-Nr. 5124-30-1); Information/Assumptions regarding toxicokinetics

The following remarks on the toxicokinetics of 4,4´-methylenedicyclohexyl diisocyanate are based on physicochemical properties of the compound and on toxicological data. Experimental toxicokinetic studies were not performed.

4,4´-Methylenedicyclohexyl diisocyanate is a colourless to light yellow liquid with a low vapour pressure (1.22 * 10^{-5}hPa at 20 °C, Bayer AG 1994) under normal ambient conditions.

Due to the low vapour pressure inhalation exposure via vapour is not to be expected. Wherever aerosolization occurs exposure is possible. Only the respiratory tract is concerned after acute and repeated inhalative aerosol exposure to rats (Pauluhn 1995 and 2008; Bernstein 1987). All clinical signs and histopathological findings in these studies could be related to the irritant properties of the substance, indicating certain reactivity due to the chemical nature of the isocyanate-groups of the molecule. There are no indications reported suggestive for an absorption or systemic availability of the substance or a metabolite. Nevertheless, absorption through the lung epithelium could not be neglected at all, e. g. after conjugation of 4,4´-methylenedicyclohexyl diisocyanate to lung fluid proteins.

Regarding oral absorption at least partial hydrolysis is assumed to occur in the gastro-intestinal tract. In fact oral toxicity was low with an LD50 (rat) of 18200 mg/kg bw (Sterner 1976). In this non-guideline study strong hyperemia for acute mortalities up to slight hyperemia for late mortalities was recorded as gross pathology observations, confirming the substance's irritating properties at the portal of entry. Other organs were reported to be unobtrusive, therefore no indications for systemic bioavailability could be concluded from the study.

Dermal absorption of 4,4´-methylenedicyclohexyl diisocyanate could not be excluded at all, since the calculated K_{ow} shows a high lipophilicity (6.11, Currenta 2009). In fact, systemic availability after dermal exposure could not be deduced from an acute study, where a low dermal toxicity was observed (LD50 (rat) > 7000 mg/kg bw, Mürmann 1985) and from acute dermal irritation/corrosion studies, where no signs of systemic toxicity were observed (Wakefield 1996, Krötlinger 1994). Nevertheless, 4,4´-methylenedicyclohexyl diisocyanate has shown skin sensitizing properties (Sterner 1983), thus indicating that a dermal uptake, even though small, can occur. Deducing from that the substance has the property to react with nucleophilic groups of proteins or peptides and form hapten-protein complexes or conjugate-antigens.

Based on the results of several in vitro genotoxicity tests (Wirnitzer 2005, Herbold 2004 and 2007, all performed with and without metabolic activation) it is concluded that DNA-reactive metabolites of 4,4´-

methylenedicyclohexyl diisocyanate will most probably not be generated in mammals in the course of hepatic biotransformation.

4.2. Acute toxicity

Partly cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): 4,4´-Methylenedicyclohexyl diisocyanate is of low oral and dermal acute toxicity with an oral LD50 (rat) of 18200 mg/kg bw and a dermal LD50 > 7000 mg/kg bw for rat and > 10000 mg/kg bw for rabbit. "Toxic symptoms after oral administration included severe diarrhea, loss of appetite and increasing weakness." After dermal administration transiently inhibited body weight gain was observed at the end of the study. "Assessment of the acute inhalation toxicity data indicates that exposure to respirable aerosols of 4,4´-methylenedicyclohexyl diisocyanate confined predominantly to the respiratory tract. Clinical signs (salivation, bradypnea, stridor) indicated respiratory distress. A hemorrhagic lung edema was considered to be causative for mortality." Animal studies according to OECD TG 403 give LC50 (4 h, rat) of 330 - 434 mg/m³.

Justification for classification or non classification

Not classified for acute oral and dermal toxicity according to EU-Directive 67/548/EEC, Annex I. No classification required for acute oral and dermal toxicity according to Regulation (EC) No 1272/2008, Annex VI-1.

Classified for acute inhalation toxicity according to EU-Directive 67/548/EEC, Annex I: R 23, Toxic by inhalation.

Due to LC50 of 330 -434 mg/m³ classification required for acute inhalation toxicity according to Regulation (EC) No 1272/2008, Annex I: Cat.2; H330: Fatal if inhaled.

4.3. Irritation

Cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "4,4´-methylenedicyclohexyl diisocyanate is moderately to severe irritant to the skin of rabbits (OECD TG 404). Irritant effects were observed after instillation of 4,4´-methylenedicyclohexyl diisocyanate into the eyes of rabbits (OECD TG 405). The repeated dose studies indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract. "

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

Partly cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "Based on 'regulatory' acute toxicity studies (cf. section "Acute toxicity: inhalation") no conclusions can be drawn regarding the respiratory irritating properties of 4,4´-methylenedicyclohexyl diisocyanate. The same applies for the studies that determined the 4,4´-methylenedicyclohexyl diisocyanate concentration causing a 50 % decrease in respiratory rate (RD50) for mice" (cf. section "Acute toxicity: inhalation"). For aerosols the deposit pattern strongly depends on the generation of the test atmosphere and "irritation of the respiratory tract is apparently more dependent on the specific site receiving the highest fraction of the dose rather than the total airborne concentration. However, the repeated dose studies (see "Repeated dose toxicity: inhalation" and "Toxicity to reproduction") do indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract. "

Justification for classification or non classification

According to EU-Directive 67/548/EEC, Annex I, the test substance is classified as R36/37/38: Irritating to eyes, respiratory system and skin. According to Regulation (EC) No 1272/2008, Annex VI-1, classification is required as Cat. 2 for eye irritation (H319: Cause serious eye irritation), Cat. 2 for skin irritation (H315: Causes skin irritation) and STOT SE 3 for respiratory tract irritation (H335: May cause respiratory irritation).

4.4. Sensitisation

Skin sensitisation

Partly cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "Animal data are not uniform however they frequently provide evidence of a skin sensitizing potential of 4,4´-methylenedicyclohexyl diisocyanate." Human case reports have demonstrated skin effects usually attributable to occupational exposure to 4,4´-

methylenedicyclohexyl diisocyanate. Some of these cases were subsequently determined to be cases of dermal sensitization as confirmed by patch testing.

Respiratory sensitisation

Cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "Although no validated animal model is available to assess the potential for respiratory sensitization or asthma in humans, animal data support to some extent the hypothesis that respiratory hypersensitivity may be induced by 4,4´-methylenedicyclohexyl diisocyanate."

Justification for classification or non classification

According to EU-Directive 67/548/EEC, Annex I, the test substance is classified as R43: May cause sensitization by skin contact.

According to Regulation (EC) No 1272/2008, Annex VI-1, classification is required as skin sensitising Cat.1; H317: May cause an allergic skin reaction.

According to EU-Directive 67/548/EEC, Annex I, the test substance is classified as R42: May cause sensitization by inhalation.

According to Regulation (EC) No 1272/2008, Annex VI-1, classification is required as respiratory sensitising Cat.1; H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled. Reason: No human case reports indicating respiratory sensitisation potential for the substance are available, but animal data do predict respiratory tract sensitization.

4.5. Repeated dose toxicity

Partly cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure."

A subchronic (0.5, 3, 18 mg/m³; 6 hours/day on five days/week for 13 weeks; OECD TG 413) and a subacute (1, 6 and 36 mg/m³; 6 hours/day on five days/week for 4 weeks; OECD TG 412) inhalation study with rats "indicates the respiratory tract to be the target organ of respirable 4,4´-methylenedicyclohexyl diisocyanate aerosol." The reported NOAELs for effects governed by respiratory tract irritation (i. e. histopathological changes in nasal passages, larynx and bronchi) are 3 mg/m³ for the subchronic study and 1 mg/m³ for the subacute study (LOAELs: 18 mg/m³ and 6 mg/m³, respectively). "The results of the reproduction/developmental toxicity screening test (OECD TG 421) correspond to the results of the subacute study."

Justification for classification or non classification

No classification according to EU-Directive 67/548/EEG, Annex I. No classification required according to Regulation (EC) No 1272/2008, Annex VI-1. Reason: Classification as STOT repeated exposure is not justified, due to lack of cumulative toxicity.

4.6. Mutagenicity

Cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "4,4´-Methylenedicyclohexyl diisocyanate did not induce gene mutations in bacteria (OECD TG 471)" or in mammalian cells (OECD TG 476) "and demonstrated no potential to induce chromosome aberrations in Chinese hamster V79 cells mammalian cells in vitro (OECD TG 473) either with or without metabolic activation."

Justification for classification or non classification

No classification according to EU-Directive 67/548/EEG, Annex I. No classification required according to Regulation (EC) No 1272/2008, Annex VI-1.

4.7. Toxicity for reproduction

Effects on fertility

Cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "Data from an inhalative reproduction/developmental toxicity screening test according to OECD TG 421 with rats (1, 6 and 36 mg/m³) did not reveal substance related impairment of reproduction up to a 4,4´-methylenedicyclohexyl diisocyanate concentration of 6 mg/m³. A slightly reduced fertility index was observed at an exposure level (36 mg/m³) that was associated with parental toxicity. NOAELs were considered to be 1 mg/m³ in males and females for general toxicity. NOAEL for reproductive toxicity is 6 mg/m³. "

According to section 1.2 of Annex XI, a study according to OECD TG 416 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 4,4´-methylenedicyclohexyl diisocyanate demonstrates consistently that toxicity is associated only with the portal of entry (respiratory tract), any other manifestations of toxicity are secondary to this. A study according to OECD TG 421 and other repeated dose studies (OECD TG 413, 407) all show toxicity confined to the respiratory tract. No effects on reproductive parameters were observed. Hence the databases for other diisocyanates IPDI and 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. Especially for 4,4´-methylenedicyclohexyl diisocyanate any effects were to be seen in a fertility study, 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 elaborating this data waiver is attached to the record. Using the weight of evidence, it is concluded that reproductive toxicity is not an endpoint of concern for 4,4´-methylenedicyclohexyl diisocyanate and additional toxicity testing is not necessary.

Developmental toxicity

Cited from SIAR for SIAM20 (Paris, April 19 -22, 2005): "Pre-natal inhalation toxicity testing in rats (OECD TG 421) indicates the absence of selective toxicity to the development at levels up to 36 mg/m³. No findings indicate any specific developmental effects such as live birth index, viability index and apparent malformation. The reported NOAEL(developmental) for 4,4´-methylenedicyclohexyl diisocyanate in a developmental toxicity study according to OECD TG 414 (1, 6 and 36 mg/m³) is 6 mg/m³/day. At the 36 mg/m³ level that caused clear maternal respiratory tract toxicity (NOAEL(maternal) = 1 mg/m³) increased incidences of ventricular septal defects of the heart and slight dilation of lateral brain ventricles were observed, which lay marginally above the upper or within the normal range of scattering of the rat strain used respectively."

Justification for classification or non classification

No classification according to EU-Directive 67/548/EEC, Annex I. No classification required according to Regulation (EC) No 1272/2008, Annex VI-1. Reason: Impairment of reproduction/developmental toxicity is not observed at exposure levels without parental/maternal toxicity.

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

DN(M)ELs for workers

Exposure pattern	Route	Descriptor	DNEL / DMEL *)	Most sensitive endpoint
Acute - systemic effects	Dermal (mg/kg bw /day)			
Acute - systemic effects	Inhalation (mg/m³)			
Acute - local effects	Dermal (mg/kg bw /day)		not quantifiable	sensitisation (respiratory tract and skin)
Acute - local effects	Inhalation (mg/m³)		0.6	irritation (respiratory tract)
Long-term - systemic effects	Dermal (mg/kg bw /day)			
Long-term - systemic effects	Inhalation (mg/m³)			
Long-term - local effects	Dermal (mg/kg bw /day)		not quantifiable	sensitisation (respiratory tract and skin)
Long-term - local effects	Inhalation (mg/m³)		0.3	irritation (respiratory tract)

*) Unit as specified in column "Route"

Discussion

For workers in industrial settings, which are exposed via inhalation, DNELs for acute and long-term inhalation effects of 4,4'-methylenedicyclohexyl diisocyanate have to be derived. In addition, the sensitization potential after skin contact to 4,4'-methylenedicyclohexyl diisocyanate have to be assessed.

For repeated dose toxicity a subacute and a subchronic inhalation study with aerosol exposure of 4,4´-methylenedicyclohexyl diisocyanate to rats are available (Pauluhn, 2004 and 2008). The obtained LOAECs were 6 mg/m³ (subacute study) and 18 mg/m³ (subchronic study), respectively, for effects governed by respiratory tract irritation. No indications of systemic toxicity were found within the studies.

Histopathological changes in the respiratory tract were related to portal-of-entry, local irritant effects, i. e. squamous epithelial metaplasia and inflammatory changes in the larynx. For the subchronic study the NOAEC relating to these changes was set 3.0 mg/m³. The result of a reproduction/developmental toxicity screening test (NOAEC: 1 mg/m³/LOAEC: 6 mg/m³ for clinical signs as changes in breathing behavior and/or serous nasal discharge; NOAEC: 6 mg/m³ for reproduction/developmental toxicity; Eiben, 2004) is in line with the NOAEC of 3 mg/m³ based on the subchronic inhalation study. Therefore 3.0 mg/m³ was used as a starting point for the delineation of a DNEL $_{long\text{-}term}$.

Irritant properties of the substance are also reflected in studies investigating skin and eye irritation (Wakefield 1996, Krötlinger 1994).

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 = 3.0 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 = 1.508 mg/m³

According to ECHA Guidance, part B, 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 (workers)	5
[4]Differences in duration of exposure	1
[5]Dose-response relationship	1
[6]Quality of whole Database	1
Overall Assessment Factor	5

[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 for workers for local effects is 5.

[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 (Pauluhn 2004 and 2008, Eiben 2004; for comparison $NOAEC_{subacute}$ vs. $NOAEC_{subchronic}$ vs. $NOAEC_{general\ toxicity\ OECD\ TG\ 421\text{-}study}$ 1 : 3: 1 mg/m³; $LOAEC_{subacute}$ vs. $LOAEC_{subchronic}$ vs. $LOAEC_{general\ toxicity\ OECD\ TG\ 421\text{-}study}$ 6:18: 6 mg/m³).

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 5.

$$DNEL_{long\text{-}term}\ \text{for workers for inhalation route – local effects} = \frac{\text{NOAEC corr.}}{\text{Overall AF}}$$

$DNEL_{long\text{-}term}$ for workers for inhalation route – local effects = 0.302 mg/m³

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 of an occupational exposure limit (Arbeitsplatzgrenzwert) to an exceeding factor (Überschreitungsfaktor), which is set per default 1 (could be adjusted to max. 8). For 4,4´-methylenedicyclohexyl diisocyanate 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 0.6 mg/m³.

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

Although data were not uniform a dermal sensitization potential was shown for 4,4´-methylenedicyclohexyl diisocyanate. According to the potency categorisation approach 4,4´-methylenedicyclohexyl diisocyanate is classified as a moderate skin sensitizer based on a Guinea Pig Maximization Test (10 % induction conc., 100 % incidence of sensitization; Sterner, 1983). Non-validated animal testing data support to some extent the hypothesis that respiratory hypersensitivity may be induced by the substance (Pauluhn 1995, Selgrade 2006, Farraj 2007, Plitnick 2005). 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.

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 SIAM20 (Paris, April 19 -22, 2005): "4,4’-Methylenedicyclohexyl diisocyanate is exclusively used as an intermediate in chemical processes. A direct use of this substance is not known (Bayer MaterialScience AG, 2004). Consistently, there is no registration of a consumer product containing 4,4’-methylenedicyclohexyl diisocyanate in the Danish, Finnish, Swedish (SPIN, 2004), and Swiss Product Register (2004). 4,4’-Methylenedicyclohexyl diisocyanate is confidentially listed in the Norwegian Product Register (SPIN, 2004), but since the main use category is “non-dispersive use”, it is assumed that the confidential registration is also for industrial use only. The exposure of consumers to 4,4’-methylenedicyclohexyl diisocyanate is unlikely to occur via consumer products, because no consumer product is known to contain 4,4’-methylenedicyclohexyl diisocyanate (Bayer MaterialScience AG, 2004). An exposure of consumers to 4,4’-methylenedicyclohexyl diisocyanate via the environment is also unlikely to occur because there are virtually no emissions of 4,4’-methylenedicyclohexyl diisocyanate, and 4,4’-methylenedicyclohexyl diisocyanate released to environment would rapidly be degraded by photooxidants and water."

5. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

5.1. Explosiveness

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

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

5.2. Flammability

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

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

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

(c) Not a flammable solid: On approach of an ignition source, a short burning may be expected, however, due to the low melting point, a self-sustaining combustion without supply of further energy is to be excluded. Therefore, a classification as flammable solid can be ruled out. Further, due to the low melting point, self-heating behavior can be excluded.

Flash point

Reference:

Bayer AG, 1979

Guideline:

German standard method: DIN 51758

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

200 °C at 1013 hPa

5.3. Oxidising potential

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

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

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

6. PBT AND VPVB ASSESSMENT

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

PBT and vPvB criteria and the corresponding properties of 4,4'-methylenedicyclohexyl diisocyanate

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 2000a) but rapidly hydrolysing (Bayer AG 1999; Bayer Industry Services GmbH & Co. OHG 2004)	*Preliminary* yes
B	BCF > 2000	BCF > 5000	Not B not vB	no
T	Long-term NOEC for marine or freshwater organisms < 0.01 mg/l	Not applicable.	72h-NOEC 0.31 mg/l for algae (Bayer AG 2000d)	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

4,4'-methylenedicyclohexyl diisocyanate is not readily biodegradable with 0 % biodegradation in 28 days (Bayer AG, 2000a), and hence it might be classified as *preliminary* persistent according to screening criteria. However, hydrolysis studies show a half-life far below the PBT and vPvB threshold values.

6.1.2. Bioaccumulation Assessment

Measured bioconcentration factors (BCF) for 4,4'-methylenedicyclohexyl diisocyanate are not available. 4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water with a half life of approximately 2 hours. Therefore a risk estimation regarding the bioaccumulation potential of 4,4'-methylenedicyclohexyl diisocyanate on the basis of a log Kow or a BCF, determined by QSAR, is misleading. A calculated theoretical log Kow value of 6.11 reflects the unreacted molecule without influence of water. The substance is not persistent in water due to the rapid hydrolysis. Therefore it is not bio-available. Possible hydrolysis products are less lipophilic. On the basis of these information it can not be expected that bioaccumulation of 4,4'-methylenedicyclohexyl diisocyanate occurs.
Main hydrolysis products are oligomeric and polymeric ureas and 4,4'-methylenebis(cyclohexylamine). The ureas are unsoluble in water and therefore not bioavailable. 4,4'-methylenebis(cyclohexylamine) is also not bioaccumulative (EU PBT Working Group, 2003). With a measured log Kow (OECD 107) of 2.03, and a calculated log Kow value of 2.55 (CLOGP3 program) (EU PBT Working Group, 2003) and 3.26 (EPIWIN BCF Program (v2.15)) (European Commission, 2000), log BCF values of 0.863 (BCF = 7), 1.264 (BCF = 18), and 1.814 (BCF = 65) were calculated, respectively. Therefore the B and vB criteria are not fulfilled.

6.1.3. Toxicity Assessment

There is one aquatic toxicity test for algae available which counts as a chronic test. The NOEC was 0.31 mg/l (Bayer AG, 2000d). Furthermore, the substance is not classified as carcinogenic, mutagenic or toxic for reproduction or R48. For these reasons, the substance does not meet the T-criterion.

6.1.4. Summary and overall Conclusions on PBT or vPvB Properties

A substance only is identified as a PBT substance if it fulfils all criteria described above According to information summarized above, only the P criteria was preliminarily fulfilled and hence 4,4’-methylene-dicyclohexyl diisocyanate is not a PBT substance.

A substance only is identified as a vPvB substance if it fulfils both vPvB criteria described above.
The P criterion is preliminarily fulfilled, the B criterion is not fulfilled. Therefore, 4,4’-methylenedicyclohexyl diisocyanate is not a vPvB substance.

6.2. Emission Characterisation

It is concluded that 4,4’-methylenedicyclohexyl diisocyanate does not fulfil the PBT and vPvB criteria. An emission characterisation is therefore not required.

7. REFERENCES

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