Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked

EC Number: 617-779-3

CAS Number: 85940-94-9

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 Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked 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 Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked.

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1. PHYSICAL AND CHEMICAL PROPERTIES

Molecular weight range: Not applicable (UVCB substance)

Molecular formula: Not applicable (UVCB substance)

Appearance/physical state/colour: liquid /viscous/ not reported

Melting / freezing point : No melting/freezing point is available. A glass transition was observed at -3 °C.

Boiling point: The study does not need to be conducted as the registered substance undergoes thermal decomposition before boiling.

Relative density: 1.141 g/cm3 at 20°C

Vapour pressure: 1 x 10-3 Pa at 20°C.

Water solubility: 2.8 mg/L at 20°C (slightly soluble in water)

Partition coefficient n-octanol/water (log value): 1.6

Flash point: 144°C

Flammability: not flammable

Explosive properties: non explosive

Self-ignition temperature: -

Oxidising properties: no

Stability in organic solvents: stable

Dissociation constant: -

Viscosity: 4960 (+/- 248) mPa.s at 20°C and 823 (+/- 41) mPa.s at 40°C.

Thermal stability: the substance exhibits thermal decomposition at heating temperature above 90°C.

2. ENVIRONMENTAL FATE PROPERTIES

General discussion of environmental fate and pathways:

Justification for the non-equivalence of the test material to the submission substance identity

HDI trimer MEKO blocked is always produced and marketed as dissolved in solvent. Thus, the substance is reasonably expected to be handled and used in a form of a mixture of the registered substance in the solvent. The environment is anticipated to be exposed rather to the mixture than to the pure substance. Thus, the testing strategy was designed to take this route of exposure into account and it has been concluded that testing the mixture was more relevant than testing the registered substance as such.

To conclude, environmental fate studies were performed on the mixture and as a consequence for endpoint study records, the test material is not ticked when requesting if equivalent to submission substance identity.

Summary of available data

Considering the type of substance (UVCB) and according to manufactures experience, the registered substance is to be considered as difficult to analyse. In addition, the test material (being the mixture of the registered substance in the solvent) exhibits low water solubility (less than 100 mg/L). The test material has to be considered as a difficult mixture to be tested particularly for achieving exposure concentration and preparing representative media.

In a hydrolysis study (OECD TG 111), a half-life of 139 d for pH 7 at 25 °C in water was calculated for the registered substance (HDI Trimer MEKO-blocked) from experimental data obtained at 50, 65 and 80°C. Considering the nature of the substance (UVCB), it was not possible to identify the hydrolysis product. Therefore, the registered substance is to be considered as stable to hydrolysis based on the available half-life.

In a standard screening biodegradation test (manometric respirometry method), the percentage of biodegradation of test material was determined at 3, 4, 7 and 9% based on BOD after 6, 12, 20 and 28 days of exposure, respectively. Thus, the test material does not meet the readily biodegradable criterion. Therefore, the registered substance has to be considered as not readily biodegradable.

The adsorption coefficient (Koc) of the registered substance (HDI Trimer MEKO-blocked) was determined by High Performance Liquid Chromatography (HPLC). The experiment was conducted in accordance with the OECD Guideline 121 and in compliance with the OECD-GLP standard. A key value of log Koc values has been determined to 3.0. Therefore the registered substance is to be considered of low mobility.

2.1. Hydrolysis

Discussion

The test material was insoluble in water (far from 100 mg/L). Thus, test material meets the definition of poorly water soluble substances and has to be considered as a "difficult substance to test" according to OECD Guidance No 23 (2000) on aquatic toxicity testing of difficult substances and mixtures. A hydrolysis study has been performed according to OECD TG 111. The results of Tier 1 (50°C) indicated that HDI Trimer MEKO-blocked was unstable to hydrolysis. Tier 2 testing was performed at three pH and three temperatures (higher ones for pH 7 and 9). HDI Trimer MEKO-blocked exhibits an estimated half-life of 139 d for pH 7 at 25 °C (calculated from experimental data at 50, 65 and 80 °C).

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

The registered substance exhibits an estimated half-life of 139 d for pH 7 at 25°C (calculated from experimental data at 50, 65 and 80°C) and has to be considered as stable to hydrolysis

Value used for CSA: Hydrolysis rate constant: 139 d at 25 °C

2.2. Phototransformation in air

The studies on phototransformation in air are summarised in the following table:

Overview of studies on phototransformation in air

Method	Results	Remarks	Reference
Calculated with AOP Program v1.92 of EPI-Suite softwar PHOTOCHEMICAL REACTION WITH OH RADICALS - Concentration of OH radicals: 1.5 x 10^6 OH Radicals/cm3 - OH Time frame: 12 h - Computer programme: Aopwin Program (v1.92)	Half-life (DT50): 0.148 d (12-hr day; 1.5E6 OH/cm3) Degradation rate constant: ca. 7.24856 E-11 cm3/molecule/sec for reaction with: OH radicals	2 (reliable with restrictions) key study (Q)SAR **Test material (IUPAC name): Hexamethylene diisocyanate, oligomerisation product, blocked with 2-butanone oxime**	Perstorp (2010)

2.3 Biodegradation

2.3.1. Biodegradation in water

Discussion (screening testing)

In a manometric test conducted according to Directive 79/831/EEC (Annex V, Part C), the test material was found to be not readily biodegradable (after 28 days 9% of the test material has been degraded) (Bayer, 1991).

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

The mixture of the registered substance in the solvent does not fulfil the readily biodegradable criterion. Therefore, the registered substance has to be considered as not readily biodegradable.

Discussion (simulation testing)

Discussion not performed since simulation testing are not necessary.

2.3.2. Biodegradation in soil

Data waiving

Reason: other justification

Justification: In accordance with Column 2 of REACH Annex IX, the soil simulation testing does not need to be conducted as the chemical safety assessment according to Annex I indicates that this is not necessary.

2.3.3. Summary and discussion of degradation

Abiotic degradation

The registered substance is a complex substance (UVCB) which exhibits low water solubility. No significant hydrolysis is expected in aquatic compartment since a half-life of 139 d has been determined for pH 7 at 25 °C in OECD TG 111 study.

Considering its low vapour pressure and its high molecular weight, the registered substance is not expected to disseminate significantly to atmosphere. The prediction of its half-life (0.148 d) in atmosphere indicates that it will not persist in atmosphere.

Biotic degradation

The registered substance is determined to be not readily biodegradable.

2.4. Environmental distribution

2.4.1. Adsorption/desorption

Discussion

The Adsorption Coefficient (Koc) of the registered substance (HDI Trimer MEKO-blocked) was determined by High Performance Liquid Chromatography (Königer, 2009). The experiment was conducted in accordance with the OECD Guideline 121 and in compliance with the OECD-GLP standard. Two main peaks were identified in the chromatogram and two values of Log Koc were thus determined (first peak: Log Koc = 3.0, last peak: Log Koc = 6.6). However for the purpose of the chemical safety assessment a single value need to be derived. The value of 3.0 as Log Koc being compliant with a Log Kow value of 1.6, this value is determined as the key information for the chemical safety assessment.

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

A key value of Log Koc = 3.0 has been determined for the registered substance

Value used for CSA:

Koc at 20°C: 1000

2.4.2. Volatilisation

No data available.

2.5. Bioaccumulation

Aquatic bioaccumulation

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

Considering the Log Pow (1.6), the registered substance exhibits a low potential for bioaccumulation. Therefore, no key value and information are available for chemical safety assessment.

2.6. 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: The registered substance does not exhibit any potential for bioaccumulation based on a Log Kow of 1.6 and no data is available at present. Therefore, the PNEC oral is waived based on these assumptions.

Justification for PNEC oral derivation: The registered substance does not exhibit any potential for bioaccumulation based on a Log Kow of 1.6 and no data is available at present. Therefore, the PNEC oral is waived based on these assumptions.

Interpretation of the available data with regard to the potential to bio-accumulate in the food chain:

This assessment is not required for the registered substance since available date does not indicate a bioaccumulation potential.

3. ENVIRONMENTAL HAZARD ASSESSMENT

3.1. Aquatic compartment (including sediment)

3.1.1. Toxicity test results

Justification for the non-equivalence of the test material to the submission substance identity:

HDI trimer MEKO blocked is always produced and marketed as dissolved in solvent. Thus, the substance is reasonably expected to be handled and used in a form of a mixture of the registered substance in the solvent. The environment is anticipated to be exposed rather to the mixture than to the pure substance. Thus, the testing strategy was designed to take this route of exposureinto account and
it has been concluded that testing the mixture was more relevant than testing the registered substance as such.

To conclude, ecotoxicological studies were performed on the mixture and as a consequence for endpoint study records, the test material is ticked as 'no' when requesting if equivalent to submission substance identity.

Available ecotoxicological information:

Four study reports record experimental results on ecotoxicological properties of the registered substance in the solvent. Among them, three references deal with aquatic organisms, the other one with microorganisms. An overview of the ecotoxicological dataset is provided in the table below.

Section	Guideline	Species	Basis for effect	Endpoint	Effect concentration (mg/L)	Reference
Short-term toxicity to fish	Similar to OECD 203	*Danio rerio*	Mortality	96h-LC50	141.4 (nom.)	Bayer, 1988
Short-term toxicity to aquatic invertebrates	OECD 202	*Daphnia magna*	Mobility	48h-EC50	> 1.61 (meas. Initial)	Weyers, 2007
Toxicity to aquatic algae	OECD 201	*Desmodesmus subspicatus*	Growth rate and biomass	72h-EC50	> 8.1 (nom.)	Weyers, 2007
Toxicity to microorganisms	OECD 209	Not identified	Respiration	3h-EC50	> 10000 (nom.)	Bayer, 1988

Conclusion

Based on the available results, the registered substance does not exhibit acute toxicity effects at its solubility limit to the three trophic levels and the microorganisms.

3.1.2. Short-term toxicity to fish

Discussion

An experimental study (Bayer, 1988) reported results of acute toxicity of the registered substance in the solvent to *Danio rerio*. The study was conducted according to the german guideline "UBA- Verfahrensvorschlag: Letale Wirkung beim Zebrabärbling (Brachydanio rerio), Stand Mai 1984 C1" which is comparable with the OECD guideline 203 (Bayer AG, 1988).

With increasing concentrations of Desmodur BL 3175 the test medium became more milky and cloudy. At all concentrations the test substance formed oily droplets on the surface of the test medium “water". These observations indicate that the tests were performed in concentration above the water solubility. Results are expressed in terms of nominal concentrations.

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

Under the conditions of the test, the registered substance in the solvent is not harmful to Danio rerio at its limit of water solubility.

Value used for CSA:

LC50 for freshwater fish: 141.4 mg/L

3.1.3. Long-term toxicity to fish

Data waiving

Reason: other justification

Justification: In accordance with Column 2 of REACH Annex IX, the long-term aquatic toxicity to fish study does not need to be conducted as the chemical safety assessment according to Annex I indicates that this is not necessary

3.1.4. Short-term toxicity to aquatic invertebrates

Discussion

Solubility and stability of HDI Trimer MEKO-blocked in water

The test material was insoluble in water (far from 100 mg/L). Thus, test material meets the definition of poorly water soluble mixture and has to be considered as a "difficult mixture to test" according to OECD Guidance No 23 (2000) on aquatic toxicity testing of difficult substances and mixtures.

Nevertheless, the registered substance (HDI Trimer MEKO-blocked) with a half-life of 139 d (for pH 7 and 25 °C, calculated from experimental data at 50, 65 and 80 °C), is stable in water for short-term testing.

Study design of Daphnia ecotoxicity testing on HDI Trimer MEKO-blocked (Weyers, 2007)

Test solutions were prepared by direct addition of test material to dilution water (nominal concentration = 100 mg/L), then treated with an ultra turrax for 30 sec at 8000 rpm and afterwards stirred for 24 h on a magnetic stirrer. Undissolved particles were removed by filtration using an aseptic filter of pore size 0.2 µm. The limit concentration of the test item was determined by HPLC resulting in initial concentration of 1.612 mg/L.

The preparation of the test solutions met recommendations from OECD Guidance No 23 (2000):

i. solution concentration higher than theoretical water solubility limit to achieve the maximum dissolved substance **ii.** separation of undissolved test substance from the test solution **iii.** direct addition to water and use of mixing techniques such as shaking and stirring

Results of Daphnia ecotoxicity (Weyers, 2007)

No immobilisation was recorded during the test. No perturbation of test medium was reported. The dissolved oxygen concentration has been more than 3 mg/L at the end of the test.

Conclusion
Results are expressed as % of initial concentrations. Recovery rates correspond to 2.35 % and 2.48 % of nominal values at 24 and 48 h, respectively.

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

The key study carried according to OECD Guideline provides a 48h-EC0 value above 1.61 mg/L (meas. Initial).

3.1.5. Long-term toxicity to aquatic invertebrates

Data waiving

Reason: other justification

Justification: In accordance with Column 2 of REACH Annex IX, the long-term aquatic toxicity to invertebrates study does not need to be conducted as the chemical safety assessment according to Annex I indicates that this is not necessary.

3.1.6. Algae and aquatic plants

Discussion

Effects on algae / cyanobacteria

Solubility and stability of HDI Trimer MEKO-blocked in water

The test material was insoluble in water (far from 100 mg/L). Thus, test material meets the definition of poorly water soluble mixture and has to be considered as a "difficult mixture to test" according to OECD Guidance No 23 (2000) on aquatic toxicity testing of difficult substances and mixtures.

Nevertheless, the registered substance (HDI Trimer MEKO-blocked) with a half-life of 139 d (for pH 7 and 25 °C, calculated from experimental data at 50, 65 and 80 °C), is stable in water for short-term testing.

Study design of Algae ecotoxicity testing on HDI Trimer MEKO-blocked (Weyers, 2007)

Test solutions were prepared by direct addition in water using ultra turrax, magnetic stirrer and filter as auxiliaries. Nominal test concentrations were 4.0 and 8.1 mg/L.

The study design included analytical determination of concentration. The preparation of the test solutions met recommendations from OECD Guidance No 23 (2000):

i. solution concentration higher than theoretical water solubility limit to achieve the maximum dissolved substance **ii.** separation of undissolved test substance from the test solution **iii.** direct addition to water and use of mixing techniques such as shaking and stirring

Results of Algae ecotoxicity (Weyers, 2007)

According to OECD Guidance No 23, the effect concentration should be determined and expressed relative to the geometric mean of the measured concentrations. However, in this study the observed recovery of the registered substance was variable. This variability might be explained by difficulties in preparing media leading more to a dispersion of test material rather than solution of test item. As a result, EC50 values are based on nominal test concentration.

Conclusion

The registered substance (HDI Trimer MEKO-blocked) is not harmful to Desmodesmus subspicatus at the limit of water solubility.

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

The key study carried according to OECD Guideline provides a 72h-EC50 value above 8.1 mg/L (nom.). Therefore, the registered substance (HDI Trimer MEKO-blocked) is not considered as harmful to Desmodesmus subspicatus at the limit of water solubility.

3.1.7. Sediment organisms

Data waiving

Reason: exposure considerations

Justification: In accordance with Column 2 of REACH Annex IX, the toxicity to sediment organisms study does not need to be conducted as the chemical safety assessment according to Annex I indicates that this is not necessary.

3.1.8. Calculation of Predicted No Effect Concentration (PNEC)

3.1.8.1. PNEC water

PNEC	Assessment factor	Remarks/Justification
PNEC aqua (freshwater): > 1.61 µg/L	1000	Extrapolation method: assessment factor The registered substance is slightly soluble in water and does not exhibit acute toxicity effects to the three trophic levels at its solubility limit. Thus, a true PNECaqua (freshwater) cannot be derived; instead an indicative of the lower limit of possible values for PNECaqua (freshwater) can be derived. Using this conservative approach, an assessment factor of 1,000 is applied to the lowest test concentration that did not induce acute toxicity effects. This leads to a PNECaqua (freshwater) of > 1.61 µg/L.
PNEC aqua (marine water): > 0.161 µg/L	10000	Extrapolation method: assessment factor The registered substance is slightly soluble in water and does not exhibit at its solubility limit acute toxicity effects to the three trophic levels. Thus, a true PNECaqua (marine waters) cannot be derived; instead an indicative of the lower limit of possible values for PNECaqua (marine waters) can be derived. Using this conservative approach, an assessment factor of 10,000 is applied to the lowest test concentration that did not induce acute toxicity effects. This leads to a PNECaqua (marine waters) of > 0.161 µg/L.
PNEC aqua (intermittent releases): > 16.1 µg/L	100	Extrapolation method: assessment factor The registered substance is slightly soluble in water and does not exhibit at its solubility limit acute toxicity effects to the three trophic levels. Thus, a true PNECaqua (intermittent releases) cannot be derived; instead an indicative of the lower limit of possible values for PNECaqua (intermittent releases) can be derived. Using this conservative approach, an assessment factor of 100 is applied to the lowest test concentration that did not induce acute toxicity effects. This leads to a PNECaqua (intermittent releases) of > 16.1 µg/L.

3.1.8.2. PNEC sediment

PNEC	Assessment factor	Remarks/Justification
PNEC sediment (freshwater): > 0.167 mg/kg sediment dw		Extrapolation method: partition coefficient In the absence of sediment ecotoxicological data, the PNECsediment (freshwater) is calculated using the equilibrium partitioning method using a Ksusp-water of 25.9 m3.m-3 and RHOsusp of 1150 kg.m-3. As

PNEC	Assessment factor	Remarks/Justification
		the calculation uses the PNECaqua, the calculated PNECsediment (freshwater) is to be considered as a conservative value. This value is used as a screening approach for the risk assessment for sediment compartment. This leads to a PNECsediment (freshwater) of > 0.0363 mg kgwwt-1 (or > 0.167 mg kgdwt-1) (calculated with EUSES 2.1).
PNEC sediment (marine water): > 0.0167 mg/kg sediment dw		Extrapolation method: partition coefficient In the absence of sediment ecotoxicological data, the PNECsediment (marine water) is calculated using the equilibrium partitioning method using a Ksusp-water of 25.9 m3.m-3 and RHOsusp of 1150 kg.m-3. As the calculation uses the PNECaqua (freshwater), the calculated PNECsediment (marine water) is to be considered as a conservative value. This value is used as a screening approach for the risk assessment for sediment compartment. This leads to a PNECsediment (marine waters) of > 3.63 x 10-3 mg kgwwt-1 (or > 0.0167 mg kgdwt-1) (calculated with EUSES 2.1).

3.2. Terrestrial compartment

3.2.1. Toxicity to soil macro-organisms

Data waiving

Information requirement: Toxicity to soil macro-organisms except arthropods

Reason: exposure considerations

Justification: In accordance with Column 2 of REACH Annex IX, the study does not need to be conducted because both direct and indirect exposure of soil to the substance are not expected. In addition, the chemical safety assessment indicates that further testing is not necessary.

Information requirement: Toxicity to terrestrial arthropods

Reason: exposure considerations

Justification: In accordance with Column 2 of REACH Annex IX, the study does not need to be conducted because both direct and indirect exposure of soil to the substance are not expected. In addition, the chemical safety assessment indicates that further testing is not necessary.

3.2.2. Toxicity to terrestrial plants

Data waiving

Reason: exposure considerations

Justification: In accordance with Column 2 of REACH Annex IX, the study does not need to be conducted because both direct and indirect exposure of soil to the substance are not expected. In addition, the chemical safety assessment indicates that further testing is not necessary.

3.2.3. Toxicity to soil micro-organisms

Data waiving

Reason: exposure considerations

Justification: In accordance with Column 2 of REACH Annex IX, the study does not need to be conducted

because both direct and indirect exposure of soil to the substance are not expected. In addition, the chemical safety assessment indicates that further testing is not necessary.

3.2.4. Calculation of Predicted No Effect Concentration (PNEC soil)

PNEC	Assessment factor	Remarks/Justification
PNEC soil: > 0.0324 mg/kg soil dw		Extrapolation method: partition coefficient In the absence of soil ecotoxicological data, the PNECsoil is calculated using the equilibrium partitioning method using a Ksusp-water of 30.2 m3.m-3 and RHOsusp of 1700 kg.m-3. As the calculation uses the PNECaqua (freshwater), the calculated PNECsoil is to be considered as a conservative value. This value is used as a screening approach for the risk assessment for soil compartment. This leads to a PNECsoil of > 0.0286 mg kgwwt-1 (or > 0.0324 mg kgdwt-1) (calculated with EUSES 2.1)

3.3. Atmospheric compartment

No data are available on potential effects of the registered substance in the atmospheric compartment.

3.4. Microbiological activity in sewage treatment systems

3.4.1. Toxicity to aquatic micro-organisms

Discussion

An experimental study (Bayer, 1988) reported results of acute toxicity of HDI Trimer MELO-blocked to bacteria from activated sludge. The study was performed according to OECD Guideline No 209.

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

Under the conditions of the test, Desmodur 3175 had no inhibitory effect on the respiration of microorganisms from sewage sludge.

3h EC50 for respiration, activated sludge > 10000 mg/L.

3.4.2. PNEC for sewage treatment plant

Value	Assessment factor	Remarks/Justification
PNEC STP: > 100 mg/L	100	Extrapolation method: assessment factor A respiration inhibition test performed according to OECD Guideline No 209 is available. A 3h-EC50 was found to be higher than 10,000 mg/L. Therefore, an assessment factor of 100 is applied on the value 10,000 mg/L. This leads to a PNECstp of > 100 mg/L

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

3.5.1. Toxicity to birds

Data waiving

Information requirement: Toxicity to birds

Reason: exposure considerations

Justification: In accordance with Point 1 of Reach Annex XI, there is no need for testing toxicity to birds.

3.5.2. Toxicity to mammals

3.5.3. Calculation of PNECoral (secondary poisoning)

PNEC	Assessment factor	Remarks/Justification
No potential for bioaccumulation		The registered substance does not exhibit any potential for bioaccumulation based on a Log Kow of 1.6 and no data is available at present. Therefore, the PNEC oral is waived based on these assumptions.

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

Environmental classification justification

Data elements

The registered substance is a poorly water soluble substance. A Log Kow of 1.6 is determined for the registered substance and is an indication of low potential for bioaccumulation which can be used as a BCF data are lacking.

As explained in relevant sections, the ecotoxicological studies were performed on the mixture of the registered substance in the solvent.

The aquatic toxicity dataset is provided here after: Fish: 96h-LC50 = 141.4 mg/L; Aquatic Invertebrates: 48h-EC50 > 1.61 mg/L; Algae: 72h-EC50 > 8.1 mg/L. Therefore, acute toxicity is recorded at levels higher than water solubility limit.

The test material was found to degrade up to 9% after 28 days in a screening biodegradation test. The registered substance is thus considered as not readily biodegradable. The hydrolysis study performed on the test material record a half-life of 139 d at pH 7 and 25°C in water and allows concluding that the registered substance does not exhibit any potential for rapid degradation in water.

Reasoning

No hazard classification is requested for the registered substance considering the low potential for acute aquatic toxicity and the low potential for bioaccumulation.

General discussion

Justification for the non-equivalence of the test material to the submission substance identity:

HDI trimer MEKO blocked is always produced and marketed as dissolved in solvent. Thus, the substance is reasonably expected to be handled and used in a form of a mixture of the registered substance in the solvent.

The environment is anticipated to be exposed rather to the mixture than to the pure substance. Thus, the testing strategy was designed to take this route of exposure into account and it has been concluded that testing the mixture was more relevant than testing the registered substance as such.

To conclude, ecotoxicological studies were performed on the mixture and as a consequence for endpoint study records, the test material is not ticked when requesting if equivalent to submission substance identity.

4. HUMAN HEALTH HAZARD ASSESSMENT

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

Basic Toxicokinetics

The following remarks on the toxicokinetics of HDI Trimer MEKO-blocked are based on physico-chemical properties of the compound and on toxicological data. Experimental toxicokinetic studies were not performed.

HDI Trimer MEKO-blocked is a viscous liquid at 20 °C and 1013 hPa with a low vapor pressure (1.10 -3 Pa at 20 °C and 4.10 -3 at 40 °C). Due to the low vapor pressure, inhalation exposure via vapour is not to be expected. Nevertheless, wherever aerosolization occurs, exposure is possible. There are no indications of systemic toxicity and systemic availability after inhalation exposure of the aerosol (L. Ma Hock, 2010). No organ lesions could be found outside the respiratory tract and these histopathological findings were seen as a consequence of the irritant properties of the substance.

The test substance is not stable at hydrolysis at ph=4, therefore it could be hydrolysed and may release HDI Trimer and MEKO or analogs.

Dermal absorption of HDI Trimer MEKO-blocked is assumed to be low, due to its physico-chemical properties (slight water soluble and high molecular weight). Furthermore, no signs systemic toxicity were observed in an acute dermal toxicity study (Gillessen U., 2010). However, HDI Trimer MEKO-blocked showed skin sensitising properties (Kolb J., 1993), indicating that a dermal uptake, even though small, can occur and deducting from that the substance has the property to react with nucleophilic groups of proteins or peptides and form hapten-protein complexes or conjugate-antigens.

4.2. Acute toxicity

DESMODUR BL 3175 was tested for acute oral toxicity (Bomhard, 1991) according to the OECD 401 guideline in a limit test and in compliance with GLP. Groups of rats (5 by sex) were given a single oral dose of DESMODUR BL 3175 in propylene glycol at 2000 mg/kg bw.

As HDI Trimer MEKO blocked is present at a percentage of 75% in the preparation, the maximum dose tested for HDI Trimer MEKO blocked is therefore about 1500 mg/kg bw.

DESMODUR BL 3175 was tested for acute dermal toxicity (Gillessen, 2010) according to the OECD 402 guideline in a limit test and in compliance with GLP. Groups of rats (5 by sex) were applied with DEMSODUR BL 3175 SN (75% HDI Trimer MEKO blocked in 25% solvent naphta 100) at a concentration of 2667 mg/kg bw, which means at 2000 mg/kg bw of HDI Trimer MEKO blocked.

DESMODUR BL 3175 was tested for acute inhalation toxicity (Pauluhn,1990) according to the OECD 403 guideline in compliance with GLP. The assay was conducted in groups of rats (5 by sex) by inhalation route at concentrations of 0, 343, 543, 1573 and 2757 mg/m3 air of aerosol for 4 hours. The maximum technically concentration producible was 2757 mg/m3 of air.

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

HDI Trimer MEKO blocked is not classified according to an expert judgment as LD50 was found higher than 1500 mg/kg bw for acute oral toxicity without deaths and any signs of toxicity.

HDI Trimer MEKO blocked is not likely to be classified for acute dermal toxicity as LD50 is above 2000 mg/kg bw (LD50 above 2667 mg/kg bw for DESMODUR BL 3175).

HDI Trimer MEKO blocked is not classified for acute inhalation toxicity.

Value used for CSA:

LD50 (oral): 1500 mg/kg bw

LD50 (dermal): 2000 mg/kg bw

LC50 (inhalation): 2068 mg/m³ air

Justification for classification or non classification

Acute oral toxicity

LD50 is 2000 mg/kg bw for DESMODUR BL 3175 which corresponds to 1500 mg/kg bw considering HDI Trimer MEKO blocked. This dose was well-tolerated without mortalities, body weight changes or clinical signs of toxicity.

DESMODUR BL 3175 SN is not classified for acute oral toxicity according to the criteria of the CLP regulation (EC) N°(1272/2008) and the Annex VI to the Directive 67/548/EEC.

As no mortalities, no clinical signs, no unsual lesions occured and no toxic effects appeared at this tested concentration it is likely that the LD50 for HDI Trimer MEKO blocked is above 2000 mg/kg bw.

Therefore, according to an expert judgment, HDI Trimer MEKO blocked is not considered to be classified for acute oral toxicity.

Acute dermal toxicity

LD50>2667 mg/kg bw of DESMODUR BL 3175 SN.

No mortality, no clinical signs in male, no effect on body weight have been observed. Artial reddening, encrustration and formation of scale of the treatment area were observed in females.

DESMODUR BL 3175 SN is not classified for acute dermal toxicity according to the criteria of the CLP regulation (EC) N°(1272/2008) and the Annex VI to the Directive 67/548/EEC.

Therefore, according to an expert judgement, it is unlikely that HDI Trimer MEKO blocked would be considered to be classified for acute dermal toxicity.

Acute inhalation toxicity

LC50 is above 2,757 mg/L air of DESMODUR BL 3175 which corresponds to 2,068 mg/L air of HDI Trimer MEKO blocked.

This maximum technically producible concentration of 2,757 mg/L air was tolerated without deaths and signs of toxicity. The observed symptoms are seen in a causal context with the used solvent xylene.

DESMODUR BL 3175 SN is not classified for acute inhalation toxicity according to the criteria of the CLP regulation (EC) N°(1272/2008) and the Annex VI to the Directive 67/548/EEC.

Therefore according to expert judgment, it is unlikely that HDI Trimer MEKO blocked is classifed for acute inhalation toxicity.

4.3. Irritation

In a dermal irritation study with DESMODUR BL 3175, conducted according to OECD 404 guideline in compliance with GLP (Märtens, 1990), 3 healthy adult rabbits were exposed to 0.5 mL of DESMODUR BL 3175 to 6% of the dorso-lateral area of the trunk covered with a semi-occlusive dressing for 4 hours. Mean individual scores (within 24, 48 and 72 hours) were 2.0/2.0/2.0 for erythema and 0.0/0.0/0.0 for oedema. At the end of the observation period, the scores for erythema at Day 14 were 1.0/1.0/1.0, not completeley reversible.

In an eye irritation study conducted according to OECD 405 guideline in compliance with GLP (Märtens, 1990), 3 adult albino rabbits were instilled into the conjunctival sac with DESMODUR BL 3175. Mean individual scores were 0.0 for cornea, iris, conjunctivae and chemosis.

In a sensory irritation study in which the protocol is based on the ASTM method designed E981-84, 4 male mice per dose were exposed to aerosol of DESMODUR BL 3175 at 0, 335, 486, 821 and 1459 mg/m3 aerosol for 3 hours according to an exposure technique which met the requirements of the OECD 403 guideline. The RD50 was 1450 mg/m3. No mortality has been observed up to the highest dose. Slight bradypnea has been observed at the highest dose. No body weight and no indications of specific organ changes has been observed. The pulmonary function test showed that the preparation in aerosol induced a concentration-dependant decrease in the respiratory rate.

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

In a dermal irritation study with DESMODUR BL 3175, conducted according to OECD 404 guideline in compliance with GLP, mean individual scores

were 2.0/2.0/2.0 for erythema and 0.0/0.0/0.0 for oedema. At the end of the observation period, the scores for erythema at Day were

1.0/1.0/1.0, not completeley reversible.

In an eye irritation study conducted according to OECD 405 guideline in compliance with GLP, mean individual scores were 0.0 for cornea, iris,

conjunctivae and chemosis.

In a sensory irritation study in which the protocol is based on the ASTM method designed E981-84, the exposure technique met the requirements of

the OECD 403 guideline. The RD50 was 1450 mg/m3. No mortality has been observed up to highest dose.

Slight bradypnea has been observed at the highest dose. No body weight and no indications of specific organ changes observed. The pulmonary

function test showed that the preparation in aerosol induced a concentration-dependant decrease in the respiratory rate.

Value used for CSA:

Skin irritation / corrosion: irritating

Eye irritation: not irritating

Justification for classification or non classification

As signs of irritation were observed in a dermal irritation study with DESMODUR BL 3175 (75% of HDI Trimer MEKO blocked in 25% of solvent naphta 100) conducted according to OECD 404 guideline in compliance with GLP, DESMODUR BL 3175 is classified as irritating to the skin according to the Annex I of the CLP Regulation N° (1272/2008) and to the Annex VI of the Directive 67/548/EEC. Solvent naphta (64742 - 95 -6) was evaluated in the OECD/HPV programm; it was shown to induce slight to moderate skin irritation. Having 25% of the solvent in the preparation it is not likely it is the unique inducer of irritation. Therefore according to an expert judgment HDI Trimer MEKO blocked is likely classified as irritating to skin.

As no signs of irritation to eye were observed in an eye irritation study conducted according to OECD 405 guideline in compliance with GLP, DESMODUR BL 3175 (75% of HDI Trimer MEKO blocked in 25% of solvent naphta 100)

is not classified as irritating to eyes according to the Annex I of the CLP Regulation N° (1272/2008) and to the Annex VI of the Directive 67/548/EEC. Therefore, according to an expert judgment, considering that the scores are all over 0, the solvent is not classified for irritancy to eye and the preparation contains about 75% of test substance, HDI Trimer MEKO blocked is not likely to be classified as irritating to the eye.

A sensory irritation study with aerosol exposure (head/nose-only) of Desmodur BL 3175 revealed a 3-hour RD50 (50 % inhibition of respiration) of 1450 mg/m3 air in male mice. The examinations showed that an aerosol of Desmodur BL 3175 considered as respirable has a weak but toxicologically not relevant sensory irritation potency.

4.4. Sensitisation

Skin sensitisation

In a dermal sensitization study, performed according to the OECD 406 guideline (Maximization test of Magnusson and Kligman) (Daamen P. A. M., 1995) in compliance with GLP, 10 female guinea-pigs per dose were exposed to DESMODUR BL 3175 in propylene glycol. A preliminary test has been performed in order to select the concentrations for the main study. The highest concentration inducing skin irritation is 100% and the non-irritant highest concentrations is 50%. Therefore, the concentration used for induction is 100% and 50, 25 and 10% respectively for induction and challenges.

Nine, eight and seven animals showed skin reaction in response to the 50, 25 and 10% concentrations in the main study, respectively.

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

In a dermal sensitization study with DESMODUR BL 3175 in propylene glycol, performed according to the OECD 406 guideline, in compliance with GLP

dermal reactions were observed in more than 30% of the animals tested for the three concentrations challenged.

Thus DESMODUR BL 3175 is classified as sensitising to the skin according to the criteria of the Annex VI to the Directive 67/548/EC and to the

criteria of the Annex I to the CLP Regulation N° (1272/2008).

Value used for CSA: sensitising

Respiratory sensitisation

No data

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

No data

Justification for classification or non classification

As dermal reactions were seen during the three challenges in more than 30% of the animals (9/10 for 50%, 8/10 for 25 and 7/10 for 10% respectively test item formulation), in a dermal sensitization study performed according to guideline OECD 406 in compliance with GLP, DESMODUR BL 3175 (75% HDI Trimer MEKO blocked in 25% of solvent naphta 100) is classified as sensitising to the skin according to the criteria of the Annex VI to the Directive 67/548/EC and to the criteria of the Annex I to the CLP Regulation N° (1272/2008).

According to an expert judgment, HDI Trimer MEKO blocked is classified as a sensitiser to the skin by default as the solvent is not sensitising and as the preparation contains about 75% of test substance.

4.5. Repeated dose toxicity

Discussion

In a subchronic inhalation toxicity study (Ma. Hock L, 2010), performed according to the OECD guideline 413, in compliance with GLP, HDI Trimer MEKO-blocked in 77.3% of acetone was administered to 10 Wistar rats per sex and concentrations by nose-head exposure at concentrations 0, 5, 25 and 150 mg/m3. A recovery group has also been tested in order to see the reversibility of potential effects.

No mortality has been induced during the exposure period. All animals tolerated the treatment without clinical symptoms.

Histopathological changes are seen for the high and intermediate concentrations in a concentration manner in the respiratory tract (lungs and mediastinal lymph nodes). A secondary hematological response due to the irritation and inflammation of the respiratory tract is observed. At the high concentration these effects are not reversible comparing to the intermediate concentration.

There was no evidence of damage to any organs except the respiratory organs.

Value used for CSA (route: inhalation):

NOAEC: 5 mg/m³ (subchronic; rat

Target organs: respiratory: lung

Justification for classification or non classification

Regarding the significant toxic lesions observed in the respiratory tract confirmed at microscopic examination in the lungs and the mediastinal lymph nodes, regarding also the non-reversibility of effects in the lungs and mediastinal lymph nodes of the highest dose group within a 4-week recovery period and the significant histopathological effects observed in the mid-group dose (25 mg/m3) whereas no effects has been observed for the same group dose (30 mg/m3) in the 14 days inhalation study, it could be presumed that the test substance has the potential to be harmful to human following repeated exposure by inhalation route. As a consequence, HDI Trimer MEKO blocked is classified for repeated exposure by inhalation route as R48/20 accordingto the Annex VI of the Directive 67/548/EEC and as a STOT RE 2 according the Annex I and to the guidance values of the CLP regulation (EC) N°(1272/2008).

4.6. Mutagenicity

Discussion

In a mammalian cell gene assay performed according to the OECD guideline N° 476 in compliance with GLP (Herbold, 2007), Chinese Hamster lung fibroblasts were exposed to HDI Trimer MEKO blocked in Solventnaphta 100 at concentrations ranging from 12.5 to 400 µg/mL in the presence and absence of metabolic activation.

In an *in vitro* chromosome aberration test performed according to the OECD 473 in compliance with GLP (de Vogel, 2007), Chineses Hamster Ovary cells were exposed to HDI Trimer MEKO blocked in solventnaphta 100 within 2 tests. In the first chromosome aberration test, in both presence and absence of metabolic activation, the treatment harvesting time was 4/18 hours and the concentrations selected were 62.5, 125, 250, µg/mL and in the second chromosomal aberration test, in both presence of metabolic activation, the treatment harvesting time was 4/18 hours and the concentrations selected were 50, 200 and 300 µg/mL and in the absence of metabolic activation, the treatment harvesting time was 4/18 hours and the concentrations selected were 50, 200 and 300 µg/mL.

In a reverse gene mutation assay in bacteria performed according to the OECD 471 guideline, in compliance with GLP (Gahlmann, 1994),

S. Typhirium TA 1535, TA 1537, TA 98 and TA 100 were exposed to DESMODUR BL 3175 (HDI Trimer MEKO blocked in Solventnaphta 100) within 2 independant tests. The first test was conducted at 0, 8, 40, 200, 1000 and 5000 µg/plate for DESMODUR BL 3175. The second assay involved a 30-minute pre-incubation at 37°C using 0, 8, 40, 200, 1000 and 3000 µg/plate for DESMODUR BL3175.

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

In a mammalian cell gene assay performed according to the OECD guideline N° 476 in compliance with GLP, HDI Trimer MEKO blocked in

Solventnaphta 100 induced no biologically relevant increases in mutant frequencies at any concentrations in both presence and absence of metabolic activation.

In an in vitro chromosome aberration test performed according to the OECD 473 in compliance with GLP, HDI Trimer MEKO blocked in solventnaphta 100 did not induce statistically significant increase in the number of aberrant cells at any concentrations in both absence and presence of metabolic activation.

In a reverse gene mutation assay in bacteria performed according to the OECD 471 guideline, in compliance with GLP, DESMODUR BL 3175 (HDI Trimer MEKO blocked in Solventnaphta 100) did not induce increase of revertants in any strains at any concentrations, in both absence and presence of metabolic activation.

Value used for CSA: Genetic toxicity: negative

Justification for classification or non classification

In 3 *in vitro* genotoxicity studies, a mammalian cell gene assay in Chinese Hamster fibroblasts, an *in vitro* chromosome aberration test in Chinese Hamster Ovary cells and in a reverse gene mutation assay in bacteria, HDI Trimer MEKO blocked in Solvent naphta 100 showed neither significant nor relevant increase of mutant frequencies nor aberrant cells nor revertants.

Therefore, HDI Trimer MEKO blocked in Solventnaphta 100 is not classified for genetic toxicity according to the criteria of the Annex VI to the Directive 67/548/EC and CLP Regulation N°(1272/2008). As these tests have been performed either up to precipitation or cytoxicity with the preparation, HDI Trimer MEKO blocked is not considered to be mutagenic and claastogenic either.

4.7. Carcinogenicity

Data waiving

Reason: other justification

Justification: In 3 in vitro genotoxicity studies, a mammalian cell gene assay in Chinese Hamster fibroblasts, an in vitro chromosome aberration test in Chinese Hamster Ovary cells and in a reverse gene mutation assay in bacteria, HDI Trimer MEKO blocked in Solvent naphta 100 showed neither significant nor relevant increase of mutant frequencies nor aberrant cells nor revertants. Therefore the test substance is not considered to be genotoxic.

Moreover regarding the repeated-dose toxicity, no signs of carcinogenicity has been detected up to 90 days.

Moreover, as HDI Trimer MEKO-blocked is a skin irritant and a skin sensitizer, individual protection equipment are used and exposure is not expected.

Therefore no carcinogenicity is expected.

4.8. Toxicity for reproduction

4.8.1. Effects on fertility

Data waiving

Reason: other justification

Justification: No histopathological effects on the reproductive organs were observed in the 90-day dose repeated toxicity study. Hence, it is assumed that HDI

Trimer MEKO blocked has no toxicity for the reproduction including the fertility. Moreover, there was no evidence of significant absorption rate from any of the studies conducted with the test substance. Thus, effect on lactation and via lactation would not be expected to occur.

4.8.2. Developmental toxicity

Method	Results	Remarks	Reference
rat (Wistar) inhalation: aerosol (nose/head only) 5, 25 and 150 mg/m3 (nominal conc.) 5.5, 24.7 and 146.9 mg/m3 (analytical conc.)	NOAEC (maternal toxicity): >= 25 — < 150 mg/m³ air (nominal) (gross pathology and histopathology in the lungs: multiple granuloma at 150 mg/m3) NOEC (developmental toxicity): >= 150 mg/m³ air (nominal)	1 (reliable without restriction) key study experimental result **Test material (IUPAC name): Hexamethylene**	Schneider. S (2010)

Method	Results	Remarks	Reference
Exposure: From Gestational Day (GD) GD6 to GD19. (6 hours per day) OECD Guideline 414 (Prenatal Developmental Toxicity Study)		**diisocyanate, oligomerisation product, blocked with 2-butanone oxime**	

4.8.3. Summary and discussion of reproductive toxicity

Discussion

Effects on fertility

No histopathological effects on the reproductive organs were observed in the 90-day dose repeated toxicity study (Ma. Hock L., 2010). Hence, it is assumed that HDI Trimer MEKO blocked has no toxicity for the reproduction including the fertility. Moreover, there was no evidence of significant absorption rate from any of the studies conducted with the test substance. Thus, effect on lactation and via lactation would not be expected to occur.

Developmental toxicity

In a Prenatal Developmental toxicity study (Schneider S., 2010) performed according to the guideline OECD 414, in compliance with GLP, HDI Trimer MEKO-blocked (77.3% in acetone) was administered to 25 female Wistar rats per dose by inhalation at dose levels of 5, 25 and 150 mg/m3 from Day 6 to Day 19 of gestation (GD= Gestational Day). The control group, consisting of 25 females, was exposed to acetone in parallel. At terminal sacrifice on Day 20, 21 - 25 females per group had implantation sites.

The analyses of the atmospheres showed that the scheduled aerosol concentrations were met and the particule sizes of the aerosol in the inhalation atmosphere were within the respirable range.

There were no toxicologically relevant effects on the dams concerning mortality and clinical observations, food consumption, body weight and gross/net body weight gain up to and including a dose of 150 mg/m3. Test substance-related, overt signs of maternal toxicity were observed at the high dose of 150 mg/m3 where test susbtance-related histopathologic findings were observed in the lungs. One animal showed foci in the lung at macroscopical examination and seven animals of this test group revealed multiple granuloma in the lungs at microscopical examination. The animal with the macroscopic finding in the lung showed the most severe (grade 3) granuloma. These findings wre regarded to be treatment-related and adverse. Animals of the intermediate and low dose (25 and 5 mg/m3) were not affected.

There were no test substance-related effects on the dams concerning gestational parameters as well as uterine and placental weights up to and including a dose of 150 mg/m3. Terefore the NOAEC for maternal toxicity is 25 mg/m3 based on multiple granuloma in the lungs in the dams at 150 mg/m3.

Fetal examinations revealed no influence of the test substance on sex distribution of the fetuses and fetal body weight. HDI Trimer MEKO -blocked has no adverse effect on prenatal development of offspring at any of the dose levels tested. Therefore, the NOAEC for prenatal developmental toxcicity is 150 mg/m3. No adverse fetal findings of toxicity relevance were evident at any dose.

Value used for CSA (route: inhalation): NOAEC: 150 mg/m³

Justification for classification or non classification

As no histopathological effects on the reproductive organs were observed in the 90-day dose repeated toxicity study, it could be concluded that HDI Trimer MEKO-blocked is not classified for toxicity to reproduction.

As no adverse effects have been observed on prenatal development of offspring at any of the dose levels tested, HDI Trimer is not classified for prenatal developmental toxicity according to the criteria of the Annex VI to the Directive 67/548/EEC and the Annex I to the CLP Regulation (EC) N°(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					
Acute - systemic effects	Inhalation					
Acute - local effects	Dermal	No-threshold effect and/or no dose-response information available				A sensitization study was conducted according to the Guinea-Pig Maximisation Test and showed positive results. Considering that no dose response relationship was observed in this study, it is difficult to derive a threshold and to set a DNEL.
Acute - local effects	Inhalation	DNEL (Derived No Effect Level)	1.5 mg/m³	NOAEC: 4.5 mg/m³ (based on AF of 3)	repeated dose toxicity	The DNEL for acute local effects has been extrapolated from the long-term inhalation DNEL set up because no effects have been observed in the acute inhalation toxicity study.
Long-term - systemic effects	Dermal					
Long-term - systemic effects	Inhalation					According to the physico-chemical and toxicological properties, HDI Trimer MEKO blocked is not likely to be systemically absorbed at a significant rate. As determined in the long-term studies, only local effects were observed after HDI Trimer MEKO blocked exposure. Hence, extrapolation of the DNEL for systemic effects is not relevant.
Long-term - local effects	Dermal	No-threshold effect and/or no dose-response information available				A sensitization study was conducted according to the Guinea-Pig Maximisation Test and showed positive results. Considering that no dose response relationship was observed in this study, it is difficult to derive a threshold and to set a DNEL.

Exposure pattern	Route	Descriptor	DNEL / DMEL	(Corrected) Dose descriptor *)	Most sensitive endpoint	Justification
Long-term - local effects	Inhalation	DNEL (Derived No Effect Level)	0.502 mg/m³	NOAEC: 2.510 mg/m³ (based on AF of 5)	repeated dose toxicity	

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

Discussion

Justification for the non-equivalence of the test material to the submission substance identity

HDI Trimer MEKO blocked is always produced and marketed as dissolved in solvent. Thus, the substance is expected to be handled and used in a form of a mixture of the registered substance in the solvent. It was concluded that testing the mixture for acute effects (acute toxicity studies, eye and skin irritation and sensitization) was more relevant than testing the registered substance as workers would be exposed to the mixture rather than to the pure substance. However, for long-term effects (repeat dose and reproductive studies), it has been concluded to test the registered substance instead of the mixture considering that the route of exposure is the inhalation route and the solvent could present inhalation long-term toxicity properties.

To conclude as a consequence in the endpoint study records, when toxicological studies were performed on the mixture, the test material was not ticked when requesting if equivalent to submission substance identity.

Discussion: DNELs

HDI Trimer MEKO-blocked is classified as a skin sensitizer.

The derivation of DNEL is assessed for **workers** only and by inhalation and dermal routes.

According to the physico-chemical and toxicological properties, HDI Trimer MEKO blocked is unlikely to be systemically absorbed at a significant rate. As determined in the long-term studies, only local effects were observed after HDI Trimer MEKO blocked exposure. Hence, extrapolation of the DNEL for systemic effects is not relevant.

1. DNEL for acute exposure-local effects

1.1Dermal route

A sensitization study was conducted according to the Guinea-Pig Maximisation Test and showed positive results. Considering that no dose response relationship was observed in this study, it is difficult to derive a threshold and to set a DNEL. Hence, only qualitative assessment can be performed following the approach described in the dossier to define the risk management measures (RMMs) and operational conditions (OCs).

1.2Inhalation

Derivation of an acute inhalation DNEL by extrapolation from a long-term inhalation DNEL

Cf 2.2 DNEL for long-term inhalation exposure

The DNEL for acute toxicity could be set for a reference period of 15 min at 3 times the value (default value) of the long term DNEL.

Acute inhalation DNEL extrapolated = 0.502*3 = 1.50 mg/m^3

2. DNEL for long-term exposure-local effects

2.1 Dermal route

A sensitization study was conducted according to the Guinea-Pig Maximization Test and showed positive results. Considering that no dose response relationship was observed in this study, it is difficult to derive a threshold and to set a DNEL. Hence, only qualitative assessment can be performed following the approach described in the dossier to define the risk management measures (RMMs) and operational conditions (OCs).

2.2 Inhalation

The long-term DNEL inhalation exposure for local effects is derived from the repeated dose toxicity study by inhalation (90d) (L. Ma Hock, 2010)

In this long-term study, 3 concentrations have been tested: 5, 25 and 150 mg/m3.

At the clinical examination (mortality, clinical observation, BW, food consumption, rectal temperature, ophthalmology), no effect or changes has been observed.

At the clinical pathology, a statistically significant increase treatment related of absolute and relative weights has been observed in the lungs of both males and females at 150 mg/m3. The gross lesions have been observed in the mediastinal lymph nodes at 150 and 25 mg/m3.

At histopathology, only l**ocal effects** have been observed in the respiratory tract.

Ø **Nasal cavity**: subepithelial lymphoid infiltrates in the septum of the nasal cavity

Ø **Trachea**: goblet cells and hyperplasia and inflammation of the respiratory epithelium and granuloma in the carina

Ø **Lungs**: granulomatus inflammation and lympho-reticular hyperplasia with development of granulomas in the BALT

Ø **Mediastinal lymph nodes**: lympho-reticular hyperplasia with development of multifocal granulomas

Moreover in hematology**,** an increase of neutrophil counts and total white blood cells is noticed, considered as a systemic effect in response to the inflammation and irritation of the respiratory tract after test substance exposure.

Table 1.2: Calculation of long-term DNEL by inhalation for local effects for HDI Trimer MEKO-blocked

Worker	**Local / Long-term DNEL / inhalation**	
Step a: determination of the critical dose		
Key study	Ma-Hock L., 90-day inhalation study in Wistar rats liquid aerosol	
Relevant dose descriptor	NOAEC = 5.00 mg/m^3	
Step b: Correct starting point– factor for uncertainties		
Differences in absorption depending on route of exposure (route-route extrapolation, human/animal)	**-** (local effects)	
Modification for exposure (experiment and human)	**6/8**	
Modification for respiratory volume	6.7/10	
Correct starting point = relevant dose descriptor / overall factor for uncertainties	**2.51 mg/m3**	
Step c: assessment factors		
Interspecies differences	**1**(local effects)	
- Differences in metabolic rate per b. w. (allometric scaling)	**1**(effects on respiratory tract)	

Worker	**Local / Long-term DNEL / inhalation**	
- Remaining differences		
Intraspecies differences	**5** (worker, local effects)	
Duration extrapolation (sub-acute/sub-chronic/chronic)	**1**(local effects on respiratory tract)	
Issues related to dose-response	**1**(DNEL is derived from a NOAEC)	
Quality of whole database	**1**	
Overall assessment factor	**5**	
DNEL calculation	**0.502 mg/m3**	

Justification for the interspecies (remaining differences) assessment factor

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.

DN(M)ELs for the general population

Exposure pattern	Route	Descriptor	DNEL / DMEL	(Corrected) Dose descriptor *)	Most sensitive endpoint	Justification
Acute - systemic effects	Dermal					
Acute - systemic effects	Inhalation					
Acute - systemic effects	Oral					
Acute - local effects	Dermal					
Acute - local effects	Inhalation					
Long-term - systemic effects	Dermal					
Long-term - systemic effects	Inhalation					
Long-term - systemic effects	Oral					
Long-term - local effects	Dermal					
Long-term - local effects	Inhalation					
**) The (corrected) dose descriptor starting points have been automatically calculated by multiplying the values of the fields "D(N)MEL" and "Assessment factor" provided in the Endpoint summary of IUCLID section 7. Toxicological information. It reflects the value after any corrections, e.g. route-to-route extrapolation. See column "Justification" for the rationale behind such modifications and the use of assessment factors.*						

Discussion

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

5. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

5.1. Explosivity

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

As the registered substance does not exhibit chemical moiety directly associated with explosivity and energy decomposition is below 500J/g, thus the information requirement on explosivity is waived. Therefore, the registered substance is considered as non explosive

Classification according to GHS

Name: Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked

State/form of the substance: liquid

Reason for no classification: conclusive but not sufficient for classification

Classification according to DSD / DPD

Classification status: 67/548/EEC self classification (Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked)

Reason for no classification: conclusive but not sufficient for classification

5.2. Flammability

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

The study on flammability property of the registered substance does not need to be conducted as the registered substance is a liquid for which flammable properties are assessed using the flashpoint. With reference to the flashpoint, the registered substance is not considered as flammable

Flash point

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

The registered substance which exhibits a flashpoint of 144°C is not considered as flammable.

Classification according to GHS

Name: Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked

State/form of the substance: liquid

Reason for no classification (Flammable gases): conclusive but not sufficient for classification

Reason for no classification (Flammable aerosols): conclusive but not sufficient for classification

Reason for no classification (Flammable liquids): conclusive but not sufficient for classification

Reason for no classification (Flammable solids): conclusive but not sufficient for classification

Classification according to DSD / DPD

Classification status: 67/548/EEC self classification (Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked)

Reason for no classification: conclusive but not sufficient for classification

5.3. Oxidising potential

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

The registered substance does not exhibit chemical groups associated with oxidising properties. Therefore, the registered substance is considered as not oxidising

Classification according to GHS

Name: Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked

State/form of the substance: liquid

Reason for no classification (Oxidising gases): conclusive but not sufficient for classification

Reason for no classification (Oxidising liquids): conclusive but not sufficient for classification

Reason for no classification (Oxidising solids): conclusive but not sufficient for classification

Classification according to DSD / DPD

Classification status: 67/548/EEC self classification (Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked)

Reason for no classification: conclusive but not sufficient for classification

6. PBT AND VPVB ASSESSMENT

6.1. Assessment of PBT/vPvB Properties

Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked is a UVCB substance.

All known constituents present at concentrations equal or higher than 10% are listed in Table below. IUPAC Names, typical concentration, concentration range and molecular weight are specified for each relevant constituent.

Constituent	Typical concentration (% w/w)	Concentration range (% w/w)	Molecular weight (g/Mol)
1,3,5-tris[6-[[[[(1-methylpropylidene)amino]oxy]carbonyl]amino]hexyl]-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	50.0	>= 40.0 — <= 75.0	765.9
HDI-Isocyanurate, 2-butanone oxime-blocked, n=5	20.0	>= 10.0 — <= 30.0	1189.4
HDI-Isocyanurate, 2-butanone oxime-blocked, n=7	10.0	>= 3.0 — <= 30.0	1611.9

The registered substance is always produced and marketed as dissolved in solvent. Thus, the substance is reasonably expected to be handled and used in a form of a mixture of the registered substance in the solvent. The environment is anticipated to be exposed to the mixture rather to the pure substance. Thus, the testing strategy was designed to take into account this route of exposure and it has been concluded that testing the mixture (named as *test material* here after) was more relevant than testing the registered substance as such.

6.1.1. Persistence assessment (P and vP)

In a standard screening biodegradation test (manometric respirometry method), the percentage of biodegradation of the mixture of the registered substance in the solvent (test material) was determined to 9% based on BOD after 28 days of exposure. Thus, the test material does not meet the readily biodegradable criterion. Therefore, the registered substance is considered as not readily biodegradable.

In a hydrolysis study (OECD TG 111), a half-life of 139 d in water (pH 7, at 25 °C) was calculated for the registered substance from experimental data obtained at 50, 65 and 80°C. Considering the nature of the substance (UVCB), it was not possible to identify the hydrolysis product. Therefore, hydrolysis is not a significant abiotic degradation pathway of the registered substance.

Among the available data, there is no evidence indicating non-persistence of the registered substance.

Studies on inherent biodegradation and test on simulation of biodegradation are not available for the registered substance. The available hydrolysis half-life has to be compared to persistence criteria of REACH Annex XIII. The hydrolysis half-life of the registered substance is higher than the *very persistence* criteria for waters (ie half-life of 60 days in marine, fresh- or estuarine water).

In a screening assessment of persistency, the registered substance meets the vP criterion based on a hydrolysis half-life (139 days).

6.1.2. Bioaccumulation assessment (B and vB)

An experimental Log Kow (Pow) of 1.6 (at 20°C) is determined for the registered substance. Based on a Log Kow below 3.0, no further testing is required for the bioaccumulation assessment of the registered substance. Thus, a fish BCF value for the registered substance is not available.

Considering that the Log Kow is below 4.5, the registered substance is to be considered as not B and not vB.

In addition, the relevant known constituents of the registered substance exhibit high molecular weight which are higher than 700 g/Mol (see Table 8.1). Therefore, based on a weight of evidence approach, the relevant known constituents may be considered as not B on the basis of these high molecular weights.

Among the available data, there is no evidence indicating bioaccumulation potential for both registered substance and relevant known constituents.

In a screening assessment of bioaccumulation, the registered substance does not meet the B or the vB criterion based on a Log Kow of 1.6.

6.1.3. Toxicity assessment (T)

The test material did not exhibit any toxicity effects to tested aquatic organisms at limit of solubility. The registered substance is not classified for aquatic toxicity, on the basis of data available on fish, Daphnia and algae. Therefore, based on short-term aquatic toxicity data, the registered substance is presumably not T.

The registered substance is not classified for long-term human health effects (CMR properties). The registered substance is classified Xn R48/20 (*Danger of serious damage to health by prolonged exposure through inhalation*) according to Directive 67/548 EEC. Thus, the registered substance meets definitively the T criterion based on the classification Xn R48/20.

The registered substance meets definitively the T criterion; therefore no further testing is necessary for the T assessment.

6.1.4. Summary and overall conclusions on PBT or vPvB properties

The registered substance meets the vP criterion based on its hydrolysis half-life (139 days). The registered substance does not meet the B and vB criteria based on a Log Kow of 1.6. The registered substance meets the T criterion based on the classification Xn R48/20.

The available data do not allow a direct comparison with all the criteria in REACH Annex XIII but nevertheless indicate that the registered substance would not have these properties and consequently the registered substance is not considered a PBT or vPvB substance.

In this case, the PBT/vPvB assessment stops at this point.

6.2. Emission Characterisation

The emission characterisation is not considered in the light of the substance is neither PBT of vPvB.

7. REFERENCES

Bayer AG (1988a). Letale Wirkung beim Zebrabärbling - Brachydanio rerio - LC0/LC 50/LC100 - 48 h bis 96 Stunden. Bayer AG, Building W 15, 51368 Leverkusen (Germany). Testing laboratory: Bayer AG, Institut für Umweltanalyse und Bewertungen. Report no.: 20 A/88. Owner company: Bayer MAterialScience AG. Report date: 1988-06-21.

Bayer AG (1988b). Prüfbericht 20 A/88. Bayer AG, Building W 15, 51368 Leverkusen (Gernany). Testing laboratory: Bayer AG, Institut für Umweltanalyse und Bewertungen. Report no.: 20 A/88. Owner company: Bayer MaterialScience AG. Report date: 1988-08-01.

Bayer AG (1991). Untersuchungen zum ökologischen Verhalten von Desmodur BL 3175. Bayer AG, Building W 15, 51368 Leverkusen (Germany). Testing laboratory: Bayer AG, Institut für Umweltanalyse und Bewertungen. Report no.: 225 A/91. Owner company: Bayer MaterialScience AG. Report date: 1991-07-25.

Bomhard (1991). Desmodur BL 3175 - Untersuchungen zur akuten oralen Toxizität an männlichen und weiblichen Wistar-Ratten. Testing laboratory: Bayer AG, Fachbereich Toxikologie, Wuppertal, Germany. Report no.: 20668. Owner company: Bayer MaterialScience AG. Study number: T8040257. Report date: 1991-09-26.

Feldhues E. (2007). Determination of the hydrolysis of HDI Trimer MEKO-blocked. Testing laboratory: Bayer Industry Services. Report no.: 2006/0121/02. Owner company: PERSTORP FRANCE & Bayer Material Science AG. Report date: 2007-09-24.

Gillessen U. (2010). Acute toxicity in the rat after dermal application. Testing laboratory: Bayer Schering Pharma AG. Report no.: AT05973. Owner company: BAYER MAterial Science AG and PERSTORP France, SAS. Study number: T6081584. Report date: 2010-07-06.

Herbold B (2007). HDI Trimer MEKO-blocked: V79/HPRT-test in vitro for the detection of induced forward mutations. Testing laboratory: Bayer Healthcare AG. Report no.: AT03926. Owner company: PERSTORP FRANCE & Bayer MaterialScience AG. Study number: T 0077187. Report date: 2007-07-11.

Kolb (1993). Untersuchungen auf hautsensiblisierende Wirkung bei Meerschweinchen (Buehler Test). Testing laboratory: Bayer AG, Fachbereich Toxikologie, Wuppertal, Germany. Report no.: 22463. Owner company: Bayer MaterialScience AG. Study number: T 3044122. Report date: 1993-08-23.

Königer A. (2009). Determination of the adsorption coefficient (Koc) by high performance liquid chromatography (HPLC) method of HDI Trimer MEKO-blocked. Testing laboratory: CURRENTA GmbH & Co/ OHG. Report no.: 2006/0121/07. Owner company: PERSTORP FRANCE & Bayer MaterialScience AG. Report date: 2009-02-23.

Ma-Hock L. (2010a). Subchronic 90-day inhalation study with recovery period in Wistar rats liquid aerosol. Testing laboratory: BASF SE. Report no.: 51I0356/06100. Owner company: Bayer Material Science AG and PERSTORP France SAS. Report date: 2010-05-27.

Ma-Hock L. (2010b). Subacute 14-day inhalation study in Wistar rats liquid aerosol exposure. Testing laboratory: BASF SE. Report no.: 99l0356/06050. Owner company: Bayer Material Science, Perstorp France. Report date: 2010-05-26.

Mekelburger, H-B (2010). Determination of physical-chemical properties of Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked. Testing laboratory: AQura. Report no.: AN-ASB 0514. Owner company: PERSTORP FRANCE & Bayer MaterialScience AG.

Märtins T. (1990). Study for skin and eye irritation/corrosion in rabbits according to OECD guideline N°. 404 and 405. Testing laboratory: Institute of Toxicology Agrochemicals, Bayer AG, Wuppertal. Report no.: 19359. Owner company: BAYER AG. Study number: T9033977. Report date: 1990-08-01.

P. A. M Daamen (1995). Assessment of contact hypersensitivity to Polyisocyanate-Resin, blocked NR. 94831484 in the albino guinea pig (Maximisation-test). Testing laboratory: NOTOX B. V. Report no.: 126337. Owner company: BAYER AG. Report date: 1995-06-20.

Pauluhn J (1990a). Desmodur BL 3175: Untersuchungen zur akuten Inhalationstoxizität nach OECD-Richtlinie No. 403. Testing laboratory: Bayer AG, Department of Toxicology, Wuppertal, Germany. Report no.: 19402. Owner company: Bayer MaterialScience AG. Study number: T 1033276. Report date: 1990-08-09.

Pauluhn J (1990b). Untersuchungen zum sensorischen Reizpotential an der Maus (RD50-Bestimmung). Testing laboratory: Bayer AG, Department of Toxicology, Wuppertal, Germany. Report no.: 18935. Owner company: Bayer MaterialScience AG. Study number: T 2033277. Report date: 1990-03-22.

Perstorp (2010). Photochemical reactions in the atmosphere Substance: Hexane, 1,6-diisocyanato-, homopolymer, Me Et ketone oxime-blocked. Testing laboratory: Company data. Report date: 2010-07-27.

R. Gahlmann (1994). Salmonella/Microsome Test (Plate incorporation and Preincubation Method). Testing laboratory: Institute of Toxicology, BAYER AG. Report no.: 22949. Owner company: BAYER AG. Study number: T 3039173. Report date: 1994-03-22.

Schneider. S (2010). Prentatl Developmental Toxicity Study in Wistar Rats Administration via inhalation. Testing laboratory: BASF SE. Report no.: 31R0356/06107. Owner company: Bayer MaterialScience and Perstorp France.

T. Märtins (1990). Study for kin and eye irritation/corrosion in rabbits according to OECD guideline N°404 abd 405. Testing laboratory: Institute of Toxicology Agrochemicals, Bayer AG, WUppertal. Report no.: 19359. Owner company: BAYER AG. Study number: T9033977. Report date: 1990-08-01.

Weyers A. (2007a). HDI Trimer MEKO-blocked Acute Daphnia Toxicity. Testing laboratory: Bayer Industry Services. Report no.: 2006/0121/04. Owner company: PERSTORP FRANCE & Bayer Material Science AG. Report date: 2007-02-14.

Weyers A. (2007b). HDI Trimer MEKO-blocked; Alga, growth inhibition test. Testing laboratory: Bayer Industry Services. Report no.: 2006/0121/03. Owner company: PERSTORP FRANCE & Bayer Material Science AG. Report date: 2007-09-19.

de Vogel N (2007). Chromosomal aberration test with HDI Trimer MEKO blocked in cultured Chinese Hamster Ovary (CHO). Testing laboratory: TNO. Report no.: V6802/19. Owner company: PERSTORP FRANCE & Bayer Material Science AG. Study number: 6802/19. Report date: 2007-01-0