SUBSTANCE EVALUATION REPORT

Substance Name: m-tolylidene diisocyanate
EC Number: 247-722-4
CAS Number: 26471-62-5

Submitting Member State Competent Authority:
Bureau for Chemical Substances
Dowborczykow 30/34
90-019 Lodz, Poland

Year of evaluation (as given in the CoRAP): 2012

VERSION NUMBER: 0.2 **DATE: November 2013**

Conclusions of the most recent evaluation step	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	X
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other: [*please specify*]	

The occupational exposure to TDI does not lead to unacceptable risk for workers if the appropriate risk management measures regarding process categories are used.

EXECUTIVE SUMMARY

Grounds for concern

Tolylidene diisocyanate – TDI (CAS No: 26471-62-5) has been proposed for substance evaluation based on Article 44 of the REACH Regulation.
TDI was included into the first CoRAP on account of the following reasons:

- as a respiratory and skin sensitizer,
- as a potential carcinogen and
- as a suspected PBT substance.

The concerns were also related to the wide dispersive use and high aggregated tonnage.
The aim of evaluation process was to clarify the initial concerns that the manufacture of TDI could pose a risk to human health or the environment.

Procedure

The evaluation was performed on the base of registration dossier (IUCLID file) and Chemical Safety Report (CSR) submitted by the registrants as a join registration dossier as well as on the other available information (data base and scientific publications).
All the available information was assessed regarding compliance to REACH requirements and reliability for evaluation of the main grounds of concern as well as other effects of TDI on human health and the environment.
For some scenarios the assessment of exposure was performed with the tool ECETOC Targeted Risk Assessment Programme. For the majority of scenarios the exposure assessment was evaluated taking into consideration the measurement data provided by the lead registrant. The data on environmental effects was verified by the evaluator using European Union System for the Evaluation of Substances (EUSES).
The results of the evaluation are documented in the present report.

Effects on human health

The evaluation of toxicity of TDI included all human health endpoints. A particular interest was directed to the main grounds of concern:

- inhalation and dermal exposure to TDI is thought to contribute to the development of asthma
- carcinogenic effect of transformation product of TDI – toluene-di-amine (TDA) cannot be excluded.

Effect on environment

The environmental health properties as well as environmental hazard assessment was evaluated. A potential PBT properties were particularly considered during this work.
The lead registrant provided explanation of our question regarding hydrolysis of TDI and potential for the release of TDA into the environment.

Worker exposure

Information on uses and occupational exposure to TDI was evaluated. The exposure scenarios for workers were checked with regard to operational condition and information about risk management measures.
The lead registrant provided detailed explanation on these scenarios which were prepared on the base of measurement data.

Consumer exposure

Consumer exposure was not assessed as not consumer uses have been registered for TDI.

Conclusions

Human health

Evaluation of existing information on TDI confirmed that TDI has a low toxicity after an oral administration and is not toxic via dermal route. However, TDI is very toxic by inhalation (vapours), what confirms the classification of TDI as Acute Tox.2 (Hazard statement H330, Fatal if inhaled).
Furthermore, weight of evidence of the summarized studies demonstrates a strong skin irritating reaction of TDI. Therefore the appropriate is the current legal classification of TDI as a strong skin irritant (Skin Irrit. 2, Hazard statement H315, Causes skin irritation). In case of eye irritation available studies show TDI also as severe eye irritant, what confirm the classification as irritating to eyes (Eye Irrit. 2, Hazard statement H319: Causes serious eye irritation).
The skin and respiratory sensitization properties of TDI are well documented in humans and animals. TDI plays an important role in development of asthma in workers occupationally exposed to this compound.
Recent studies suggest that skin exposure may play an import ant role in development of asthma. Studies in mice and rats have demonstrated that skin exposure to TDI could result in airways inflammation when followed by inhalation challenge (Redlich, 2010).
The relevant information on sensitizing properties of TDI provided by the registrant taken together with the extensive literature data indicate that classification as Skin Sens. 1 (Hazard statement H317, May cause an allergic skin reaction) and Resp. Sens. 1 (Hazard statement H334, May cause allergy or or asthma symptomsor breathing difficulties if inhaled) is appropriate.
The development of knowledge about TDI is currently directed into the other aspect of its toxicity – threshold level effect. Recent studies on animals demonstrate that it is possible to set a threshold for some isocyanates. In few inhalation studies NOAEC/LOAEC values for respiratory sensitisation were estimated. These values ranged between 0.11 ppm (Arts et al, 2008) and 0.02 ppm (Karol, 1983, Ban et al, 1994) for NOAEC and 0.02 ppm (Karol et al, 1980) and 1 ppm (Arts et al, 2008) for LOAEC.
According to present data by Schupp and Collins (2012) NOAEC for respiratory sensitization is in the range of 0.005 to 0.03 ppm, whereas LOAEC is about 0.02 to 0.04 ppm. These findings could be used during assessment of human effects although extrapolation from animal models to human health is difficult.
In case of repeated dose toxicity it was scientifically unjustified to conduct studies on dermal and oral toxicity and these routs of exposure are not relevant for assessment in contradiction to the
studies on inhalation exposure, because this is the most appropriate route for assessing occupational risk in humans. Effects from repeated exposure of animals to TDI are limited to effects on the respiratory tract caused by local irritation. Simultaneously, studies shows that nose is the targeted organ of the respiratory system. Thus, the assessment confirmed the legal classification of the substance as STOT Single Exp.3 (Hazard statement H335, May cause respiratory irritation).
In case of mutagenicity, available valid studies (in vivo studies) and the weight of scientific evidence supports the conclusion that TDI is not mutagenic or genotoxic. Studies show also that inhalation of TDI does not induce micronuclei formation or DNA damage. This confirm the legitimacy of classification TDI as not mutagenic according to provisions of directive 67/548/EEC and according to regulation (EC) No. 1272/2008.
Animal data indicate that TDI may be carcinogenic (Collins, 2002). Oral administration of TDI to rats and mice resulted in a dose-related increase of specific tumors. No treatment-related tumors was seen following inhalation exposure. The metabolic pathway plays an important role in induction of tumors. By oral exposure TDI undergoes hydrolysis to TDA which is known carcinogen. Following inhalation, TDI is absorbed in respiratory tract and converted into conjugates without transformation of TDA. Therefore the metabolism of TDI is particularly important regarding to the assessment of cancer risk.
The human carcinogenicity data revealed no association between occupational exposure to TDI and risk of cancer. Inhalation is the main route of human exposure therefore the concern about the possible development of tumors should not be relevant.
The conclusion of the above is that there is sufficient evidence for the carcinogenicity of TDI in experimental animals and inadequate evidence for the carcinogenicity of TDI in humans.
Thus, there can be confirmed the official classification of TDI as Carc.2 (Hazard statement H351, Suspected of causing cancer, route of exposure: oral).
Last assessed endpoint was reproductive toxicity. Available studies show no effects on fertility and developmental toxicity after exposure to TDI. No effects on any of the reproduction parameters were observed as well as no embryotoxicity or teratogenicity was found. Therefore it can be concluded that TDI is not toxic for reproduction.

The lead registrant submitted the appropriate data on the toxicological profile of TDI, particularly on critical effect of TDI – skin and respiratory sensitizing properties and potential for carcinogenicity. Moreover, the registrant as a member of the European Association for Diisocyanates and Polyols provided the scientific review containing the current statistical data on respiratory diseases in Europe as well as the plan for risk management options for TDI. All the information is appropriate for evaluation of TDI toxicity. There is no data gaps in the registration dossier or CSR regarding human health hazard assessment.

Therefore the concerns are clarified and no additional data is needed.

Environment

The information about environmental fate properties and ecotoxicity was evaluated on the base of submitted information. In some cases the data was waived. All of them were analyzed based on specific rules for adaptation set in column 2 of REACH Annexes VII-X and considered as acceptable.

Fate and behaviour in the environment

Toluene diisocyanates are synthetic organic compounds and are not known to naturally occur in the environment. The most releases reported are to the air, with no releases reported directly to water or land.
As a result of aqueous insolubility and inherent reactivity with water, it is not expected that significant concentrations of TDI would be found in water (or moist soil and sediment), and this has been seen to be the case. In fact, TDI has not been detected in any aquatic studies.
A computerized partitioning model proposed by Mackay indicated that toluene diisocyanates released into the environment will tend to partition into water and undergo rapid hydrolysis (half-life of 0.5 seconds - 3 days in water, depending on pH and water turbidity) leading predominantly to the formation of relatively inert polymeric ureas. Toluene diisocyanates would also be expected to undergo photolysis and hydroxy radical oxidation. Therefore, transport and occurrence would be limited to the immediate vicinity of effluents or spills, and the resulting polyureas would probably be resistant to further biodegradation.
In water, soil and sediment, and under conditions typical of the environment, it is expected that TDI's affinity to react with amines more strongly than with water, combined with its relative insolubility in water, would result in reactions that lead to the formation of a solid crust of polyureas, encasing unreacted TDI. Hydrolysis in the presence of water in these three media, acting as a catalyst for further reactions between the diisocyantes and amines, is expected to be the primary driver in the fate of TDI in the environment.
In most industrial situations, toluene diisocyanates are hydrolysed by water to give the corresponding polymeric ureas and carbon dioxide. However, when toluene diisocyanates come into contact with water without agitation, as in spills, a hard crystalline crust of polymeric ureas forms slowing down further degradation of the toluene diisocyanates, unless the crust is mechanically broken. The solid reaction products are insoluble and biologically inert. It was concluded that soft polyurethane foams prepared with toluene diisocyanate isomers are susceptible to chemical hydrolysis under extreme environmental conditions, and that under these circumstances, an accumulation of aromatic amines can occur, if their microbial degradation is impeded.

Based on the available data, the evaluation of hazards for non-human targets from environmental levels of TDI is not possible.

Evaluation of P, B and T Properties

The TDI compounds do not appear to persist in water, soil, or sediment, and in fact, their residence time in these media may be, in general, relatively quite short. However, given the reactive nature of these compounds, the degradation products from these reactions in the environment, namely polyureas and toluene diamines (TDA), were also examined. TDI compounds are considered transient in media where water is present (e.g. water, moist soils, sediment) with half-lives of under a minute noted. However, the reaction of an amine with isocyanate is faster than the hydrolysis reaction of water with isocyanate, which, in the case of a diisocyanate like TDI, leads primarily to reactions forming polyureas. Polyureas are generally considered to be inert, insoluble solids; albeit persistent for millennia.
Polyureas have been identified as polymers of low ecological concern, both because of their inert characteristics, and based on the expectation that they are not bioavailable, and thus unlikely to accumulate in organisms and food chains in the environment.
Besides polyureas, however, there is also the potential for TDAs ((2,4-toluene diisocamine (2,4-TDA) and 2,6-toluene diisoamine (2,6-TDA) to form as a by-product of the hydrolysis of TDI, although the formation of TDA is generally considered negligible relative to the formation of polyureas in aqueous media. The scenarios which resulted in a significant, albeit low, concentration of TDA in the water column would occur under what would normally be considered unnaturally high dispersion/agitation, and therefore, are not likely to occur in nature.
Nonetheless, appreciable TDA yields were noted with loadings less than 10 mg/L, therefore TDI under certain release scenarios could be viewed as a significant source of TDA to aquatic environments. As a result, it was deemed necessary to consider the persistence of TDA in its evaluation of TDI compounds. Studies provided

showed extensive biodegradation under various OECD test protocols. Based on the weight of evidence approach developed for categorization, these TDA substances would not meet the persistence criteria. As a result, it is believed that these TDA chemicals are not persistent based on experimental and modeled data.

The empirical and modeled data demonstrate that these TDI and TDA substances do not meet the persistence criteria.

It is expected that TDI isomers do not bioaccumulate because their tendency to hydrolyze rapidly makes their uptake and accumulation virtually impossible. The toluene diisocyanates were not categorized as bioaccumulative, and this decision was reaffirmed by the additional information provided by industry as well as additional literature searches performed.
The BCF models predicted a BCF in the range of BCF 151-1183 and a BAF of BAF 380. All of which indicates that these substances have a low potential for bioaccumulation in aquatic organisms. The predicted log Kow for these substances is approximately 3.74. However, it is worth noting that both the log Kow predictions, and the BCF models which depend them, likely overestimate the lipophilicity of these compounds because of the rapid reactivity and hydrolysis in water. The Kow model KOWWIN v1.67 while providing a prediction also notes in its output that that isocyanates hydrolyze and therefore the estimates are questionable. This rapid hydrolysis with water also limits the determination of log Kow experimentally, and as a result, reliable experimental log Kow's are not readily available in the literature. A log Kow of 3.4 was determined experimentally using OECD methods, however, it was of uncertain significance in terms of TDI's environmental fate and behaviour, again, because of TDI's reactivity in the aquatic environment. TDI is generally unavailable to aquatic organisms.
The transient existence of TDI in water also makes estimating bioaccumulation experimentally equally difficult.

Due to the rapid transformation of TDI into primarily inert polyureas, and in some cases TDA, bioaccumulation of TDI is not expected in organisms.

However, there was concern with the potential accumulation of some of products of hydrolysis. It was determined during categorization that the polyureas are a group of low concern polymers with no, or negligible, potential for bioaccumulation in organisms and food chains. There was, however, a concern over the formation of toluene diamines (TDA) as a result of the hydrolysis of TDI in certain situations, primarily rapid dispersion at low release concentrations; other scenarios tended to lead overwhelmingly towards the formation of inert polyureas as opposed to TDA. Regardless of the extent of TDA formation from the reaction of TDI in water, experiments investigating the bioaccumulation of 2,4-TDA found a BCF of <5 to <50. While these BCFs are based on nominal concentrations, and therefore likely underestimating the true BCF, they still provide a strong evidence that TDA compounds themselves are not bioaccumulative. In addition, Log Kow predictions for these compounds are predicted to be very low (log Kow 0.16) which indicates that these substances are not likely to accumulate in organisms in the environment.
Due to the anticipated transient existence of TDI in aqueous media, including moist soils, it is unlikely that ecological effects will be elicited by the parent TDI compounds. It is likely that test results for TDI in aquatic environments are actually testing the toxicity of the degradation products of TDI. Data on the ecological effects of TDI to sediment dwelling organisms are limited, but reactivity in this medium is expected to be similar to that observed in both the aquatic and moist soil environments. It is anticipated that TDI released to water will primarily form inert polyureas which have the potential to be deposited to sediment, forming an inert component of the sediment strata. While persistent, laboratory and field studies on these inert polyureas have indicated that in small quantities they pose virtually no potential for adverse impacts on the aquatic environment.
In the short term studies of TDI it is noted repeatedly that it is in fact the degradation products (hydrolysis) whose toxicity is being measured in the bioassays.

Based on the available information, TDI and its degradation products are expected to exhibit low to moderate acute toxicity to aquatic organisms.

Based on the available information, the TDI isomers do not persist in the environment and are not bioaccumulative. Information on concentrations of toluene diisocyanates in the aquatic environment has not been identified at this time. The information on potential impacts of TDI in other environmental compartments has not been identified either.

Ecotoxicology

Experimental ecotoxicological data for TDI and its degradation products indicate low to moderate toxicity to aquatic organisms. The current classification is Aquatic chronic 3 (Hazard statement H412, harmful to aquatic

life with long lasting aquatic environment).
The formation of toluene diamines (TDA) has taken place as a result of the hydrolysis of TDI in certain situations, primarily rapid dispersion at low release concentrations; other scenarios tended to lead overwhelmingly towards the formation of inert polyureas as opposed to TDA. Therefore the release concentrations of TDA depend on release scenario. It should also be noted that the scenarios which result in a significant, albeit low concentration of TDA in the water column would occur under what would normally be considered unnaturally high dispersion/agitation, and therefore, are not likely to occur in nature.
The conclusion is that all results of the study on short-term toxicity to fish should be related to the TDA. Assuming, that conditions of OECD 203 test reflect those in the natural environment, as a worst case scenario at least to some extent, the results can be valid to the same degree. The chemical risk assessment should be performed for TDA. The results can be related to TDI only indirectly, as to a parent compound.
For the same reason it appears appropriate to waiver the long-term fish toxicity studies. Besides, regarding the long-term toxicity study in fish, in terms of classification, TDA does not have physical and chemical properties that trigger the necessity for classification as dangerous (according to Directive 67/548/EEC or Directive 1999/45/EC) or to be assessed as PBT or vPvB (according to Annex XIII of Regulation (EC) 1907/2006). Known value of lowest LC_{50} for *Daphnia* sp. is 12.5 mg/L, experimental BCF from 5 to 50, and extensive biodegradation was found under various OECD test protocols. Therefore, and for reasons of animal welfare, long-term toxicity in fish is not provided.
The data on environmental toxicity for TDA compounds include as follows:
LC50 (96 h) 133 mg/L for freshwater fish *Oncorhynchous mykiss*
EC50 (48 h) 12.5 mg/L for freshwater invertebrates *Daphnia magna*
EC50 (96 h) 3230 mg/L for marine water invertebrate *Skeletonema costatum*
and
NOEC (21 d) 1.1 mg/L for freshwater invertebrates *Daphnia magna*

Based on the effect concentrations determined in the aquatic toxicity tests with TDA, it does not fulfill the T criteria. The L(E)C50 values for fish, invertebrates and algae are determined as > 0.1 mg/L and NOEC value for invertebrates > 0.01 mg/L, therefore TDA substances are indicated as not potentially T.

Worker exposure

During the assessment of exposure scenarios the evaluation was concentrated on the inhalation exposure as the main route of exposure.
The exposure scenarios as provided in CSR were reviewed with a focus on occupational conditions, risk management measures and risk characterization.
For process categories 7, 8a and 13 included in individual exposure scenarios, the generic exposure estimates were adapted from ECETOC TRA. In these PROCs some inconsistencies in calculation were found. According to ECETOC TRA, the efficiency of local exhaust ventilation should be 95% whereas in CSR it is 80%. These values should be updated in the registration dossier.
For all further PROCs reliable occupational hygiene measured data was chosen as the starting point for the risk assessment. The lead registrant submitted detailed calculation of some exemplary PROCs for which there was a possibility to exceed the RCR value.
In inhalation exposure one of the most important issue is vapour pressure of the substance which is determined by the temperature of process.
PROCs 1, 5 and 14 are supported for higher operational temperatures (55°C-110°C). For PROCs 5 and 14 the elevated temperature, and therefore justification for safe use, are covered by the measured data used. (Reliable measured data available for the entire temperature range of the process). Therefore an adaptation of the primary exposure estimates to higher vapor pressure at higher operational temperatures is not necessary.
The inhalation RCR calculated for PROC 15 in all relevant exposure scenarios (ES1, 2, 3, 4, 5, 6, 7, 8 industrial) seemed to be exceeded in all relevant exposure scenarios.
PROC15 (industrial) it is intended to describe the exposure of employees in analytical laboratories involved e.g. in routine analytical monitoring of an industrial production process. The amount of substance probed for analytical purposes is small (<1kg), though the purity may be up to 100% (in the best case). The daily exposure time is unlikely to be up to 8h, though it can not entirely exclude this in exemptional cases.
The registrant provided detailed calculation of this case as well as the other PROCs for which the measurement data was used instead of generic value from ECETOC TRA.

All the additional assessments are concluded as correct and no other explanation is required regarding occupational exposure to TDI.

Statement of reasons

Human health

The existing information on TDI is sufficient to conclude that exposure to TDI has been linked with the development of asthma in workers. This type of reaction can involve bronchial hyperresponsiveness, chest tightness and labored breathing.
In animal exposure studies, the respiratory tract was the target organ for TDI. The substance causes skin, eye and lung irritation, impairment of lung function and is a respiratory and skin sensitizer.
The classification of TDI as Acute Tox.2, Skin Irrit.2, Eye Irrit.2, Resp. Sens.1, Skin Sens.1 and STOT Single Exp.3 is considered appropriate.
Animal data indicate that TDI may be carcinogenic. IARC concluded that data were sufficient to show that TDI causes cancer in animals. WHO concluded that TDI should be treated as a potential human carcinogen.
Humans are not exposed to high levels of respiratory particles of TDI, concerns over the possible development of lung tumors should not be relevant. TDI is carcinogenic in animals following oral administration. No treatment-related tumor was observed in mice or rats following inhalation exposure. It is not clarified whether occupational exposure to such chemical is associated with an increased risk of cancer in humans. There is no known case of occupational cancer by TDI exposure (Nakashima et al, 2002).
On the base of available information the classification of TDI as Carc.2 is considered appropriate.

P, B and T Properties

Hydrolysis is the predominant process determining the overall environmental fate, transport and bioaccumulation potential of TDI.
The empirical and modeled data demonstrate that TDI and TDA substances do not meet the persistence criteria. It is expected that TDI isomers do not bioaccumulate because their tendency to hydrolyze rapidly makes their uptake and accumulation impossible
Based on the available information, TDI and its degradation products are expected to exhibit low to moderate acute toxicity to aquatic organisms (TDI is generally unavailable to aquatic organisms) and are indicated as not potentially T.

Occupational exposure

Because TDI represents an important health risk it is important to monitor the occupational exposure. The available data indicates a reduction of asthma cases induced by TDI. According to these data when the exposure limits are kept, risk of respiratory sensitization is properly controlled. The increase of analytical precision of the measurements of TDI in workplace, better practices in work places and development plans for risk management options caused a significant reduction of asthma cases.
The studies related to TDI exposure showed that in the early years of the industry, annual occupational asthma incidence was ~ 5-6% (both manufacturing and industry use). The reduction of TDI concentration below OEL led to decrease of asthma cases to less than 1% (Ott, 2002). Elimination of exposure to TDI is the primary preventive approach to eliminate occupational asthma. As it is not possible due to lack of alternatives, the second approach is to reduce the level of exposure by decrease of concentration or amount of the emitted substance or use of the best PPE or better ventilation. The best way is combination of different means. In several studies the respiratory protective devices intended to reduce exposure to isocyanates provided effective protection of workers. A study in a test chamber showed 99.4% protection when the respirators were used (Heederik et al, 2012). Use of respirators in industry significantly reduced cases of asthma. None of the workers using the full-face respirators developed asthma.
Another important issue is possibility to derive of a threshold for the elicitation of respiratory sensitization for TDI. In the review article by Schupp and Collins (2012) the authors concluded that there is a possibility to derive the threshold for respiratory sensitization.
The German Committee on Hazardous Substances (AGS, 2006) concluded that if TDI exposure concentrations are kept below 10 to 20 ppb (0.07 - 0.14mg/m^3), generally no new cases of asthma are observed. It is possible to conclude that where there is good control of exposures and compliance with current occupational exposure limits, then isocyanate asthma can be minimised. This is evidenced by the production site data where there is good training and surveillance and exposure control is rigorous.

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1. IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1. Name and other identifiers of the substance

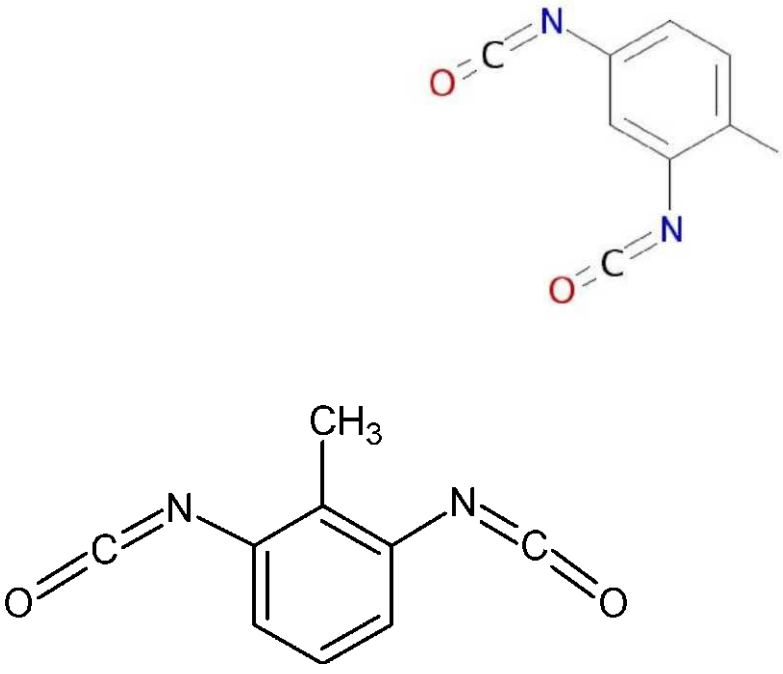
The substance **m-tolylidene diisocyanate** is a multi constituent substance (origin: organic) having the following characteristics and physical–chemical properties (see the IUCLID dataset for further details).

The following public name is used: m-tolylidene diisocyanate.

Table 1. Substance identity

EC number:	247-722-4
EC name:	m-tolylidene diisocyanate
CAS number (EC inventory):	26471-62-5
CAS name:	Benzene, 1,3-diisocyanatomethyl-
IUPAC name:	Reaction mass of 4-methyl-m-phenylene diisocyanate and 2-methyl-m-phenylene diisocyanate
Annex I index number:	615-006-00-4
Molecular formula:	C9H6N2O2
Molecular weight range:	174.1561

Structural formula:



1.2. Composition of the substance - Confidential

1.3. Physicochemical properties

Table 2. Physicochemical properties

Property	Description of key information	Value used for CSA / Discussion
Physical state		**Value used for CSA:** liquid at 20°C and 101.3 kPa
Melting / freezing point	The melting point of 80:20 TDI is 9.5°C and that of 65:35 TDI is 4°C.	A melting point of 9.5°C was established for the 80:20 mixture (2,4-TDI: 2,6-TDI), whereas the 65:35 mixture has a melting point of 4°C. Because of its presumably much higher volume, the value of the 80:20 mixture is used in the CSA.
Boiling point	A boiling range of 252°C to 254°C was determined for 80:20 TDI, and a range of 253°C to 255°C for 65:35 TDI.	A boiling point of about 253°C at 1013hPa was established for the 80:20 mixture (2,4-TDI: 2,6-TDI) and for the 65:35 mixture; this value is to be used in the CSA.
Relative density	At 20°C the relative density of 80:20 TDI and of 65:35 TDI was determined as 1.22.	A density of 1.22g/cm3 at 20°C was measured for the 80:20 as well as for the 65:35 mixture of 2,4-TDI: 2,6-TDI, and this value is to be used in the CSA.
Granulometry	not applicanle	The test does not need to be conducted as the substance is marketed or used in a non solid or granular form.
Vapour pressure	The vapour pressure of 80:20 TDI at 20°C was calculated as 0.015 hPa, and that of 65:35 TDI as 0.014 hPa.	At the low levels established, the EUA4 guideline recommends using the vapour pressure balance or the vapour saturation method. However, experience with pure 2,4 -TDI has shown, that the modified Watson method , using the measured boiling point, delivers almost the same value for vapour pressure. For the 80:20 mixture (2,4-TDI: 2,6-TDI), a vapour pressure of 0.015 hPa at 20°C was found, and the 65:35 mixture showed a vapour pressure of 0.014 hPa at 20°C.
Partition coefficient n-octanol/water (log value)	A log Pow value of 3.43 at 22°C was determined.	The use of a log Pow value for water-reactive substances is questionable. However, the analyte could be detected and a log Pow value was derived which may be used for the CSA, although it is only of theoretical value. One sharp peak indicated that both isomers show the log Pow of 3.43 at 22°C.
Water solubility	TDI is hydrolytically unstable. It can have only a transient existence in aqueous media. A water solubility value of 124 mg/l has been estimated (West et al, 2008) using a broadly accepted program, though a water solubility value for TDI is only a notional concept.	**Value used for CSA:** 124 mg/L at 25 °C TDI is rapidly hydrolysed in aqueous solution, with a half-life of under one minute (Yakabe et al., 1999). The product of hydrolysis of the isocyanate group is an amine, which itself reacts with another isocyanate group to yield a urea. This reaction of an amine with isocyanate is considerably faster than the reaction of water with the isocyanate (Yakabe et al, 1999). With TDI, a diisocyanate, this reaction leads to polyureas, which are inert, insoluble solids.

Property	Description of key information	Value used for CSA / Discussion
		However TDI is hydrophobic and poorly soluble in water (West et al., 2008), and such fast reaction is only achieved by vigorous agitation of the mixture. When the denser diisocyanate is less well dispersed into water, the reaction is heterogeneous (at the interface) and is slower. The reaction leads to the formation of a solid crust of polyureas encasing unreacted material. This crust restricts ingress of water and egress of amine, and thereby slows hydrolysis even further and enhances the amine reaction with isocyanate, leading to an even higher yield of polyureas.
Solubility in organic solvents / fat solubility	Not required by REACH annexes.	
Surface tension	not applicable	The test need not be conducted as, based on structure, surface activity is not expected or predicted, nor is it a desired property of the substance.
Flash point	The 80:20 mixture (2,4-TDI: 2,6-TDI) shows a flash point of 132°C, the 65:35 mixture has a flash point of 128°C.	The value of 128°C should be used for the CSA as a worst case approach.
Autoflammability / self-ignition temperature	No autoignition was observed up to 595°C at 1013hPa.	
Flammability	Non flammable. Based on the structural properties of the substance and the experience in handling, no pyrophoricity is expected.The substance does not liberate flammable gases on contact with water.	**Value used for CSA:** non flammable Based on the structural properties of the substance and the experience in handling, no pyrophoricity is expected. The substance does not liberate flammable gases on contact with water. The flammability is deducted from the flash- and boiling point.
Explosive properties	TDI was shown to have no explosive properties.	**Value used for CSA:** non explosive
Oxidising properties	not applicable	In accordance with column 2 of REACH Annex VII the oxidising properties study required in Section 7.13 need not be conducted if the substance is incapable of reacting exothermically with combustible materials on the basis of chemical structure.
Oxidation reduction potential	Not required by REACH annexes.	
Stability in organic solvents and identity of relevant degradation products	Not required; exempted by Annex 9. However the stability of the substance dissolved in some organic solvents has been studied. Dissolved in DMSO, TDI isomers are unstable with degradation half life being measured in minutes. The water content of the DMSO influences the rate of degradation. TDI isomers are relatively	

Property	Description of key information	Value used for CSA / Discussion
	stable for several hours in EGDE solvent.	
Storage stability and reactivity towards container material	Not required by REACH annexes.	
Stability: thermal, sunlight, metals	Not required by REACH annexes.	
Dissociation constant	not applicable	In accordance with column 2 of REACH Annex IX the dissociation constant study required in Section 7.16 does not need to be conducted as it is scientifically not possible to perform the test on this substance because of its hydrolytic properties.
Viscosity	2.221 mm²/s at 20° C	**Value used for CSA:** Viscosity at 20°C: 2.221 mm²/s (static)

Data waiving

The data on granulometry, surface tension, flammability and dissociation constant is waived. The registrant referred to the relevant annexes of REACH Regulation.

2. MANUFACTURE AND USES

Quantities 100,000 - 1,000,000 tonnes per annum

2.1. Manufacture

Commercial synthesis of TDI takes place in closed systems and involves three major stages:
1. Nitration of totuene to Dinitrotoluene (DNT)
2. Reduction of DNT to the corresponding Diaminotoluenes (TDA)
3. Phosgenation of TDA to Toluene diisocyanate, isomer mixture (TDI).

2.2. Identified uses

Uses by workers in industrial settings

#1: Manufacturing of TDI

Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 6c: Industrial use of monomers for manufacture of thermoplastics
ERC 1: Manufacture of substances

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 15: Use as laboratory reagent

#2: Manufacturing of other substances

Technical function of the substance during formulation: Intermediates, isocyanate component for polyurethanes

Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 3: Formulation in materials
ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates)

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)
PROC 15: Use as laboratory reagent

#3: Formulating, Repackaging and Distribution
Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 3: Formulation in materials

ERC 6c: Industrial use of monomers for manufacture of thermoplastics

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)
PROC 15: Use as laboratory reagent

#4: Flexible Foam Industrial Use

Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 3: Formulation in materials
ERC 6c: Industrial use of monomers for manufacture of thermoplastics

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation
PROC 15: Use as laboratory reagent
PROC 21: Low energy manipulation of substances bound in materials and/or articles

#5: Coating Industrial Use

Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 3: Formulation in materials
ERC 5: Industrial use resulting in inclusion into or onto a matrix
ERC 6c: Industrial use of monomers for manufacture of thermoplastics

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 7: Industrial spraying
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)
PROC 10: Roller application or brushing
PROC 13: Treatment of articles by dipping and pouring
PROC 15: Use as laboratory reagent

#6: Adhesives and Sealants Industrial Use

Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 3: Formulation in materials
ERC 5: Industrial use resulting in inclusion into or onto a matrix
ERC 6c: Industrial use of monomers for manufacture of thermoplastics

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 7: Industrial spraying
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)
PROC 10: Roller application or brushing
PROC 13: Treatment of articles by dipping and pouring
PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation
PROC 15: Use as laboratory reagent

#7: Elastomers, TPU, Polyamide, Polyimide and Synthetic Fibres Industrial Use

Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 3: Formulation in materials
ERC 6c: Industrial use of monomers for manufacture of thermoplastics

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)
PROC 15: Use as laboratory reagent

#8: Other Composite Material Industrial Use

Environmental release category (ERC):

ERC 2: Formulation of preparations
ERC 3: Formulation in materials
ERC 5: Industrial use resulting in inclusion into or onto a matrix
ERC 6c: Industrial use of monomers for manufacture of thermoplastics

Process category (PROC):

PROC 1: Use in closed process, no likelihood of exposure
PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)

PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities
PROC 13: Treatment of articles by dipping and pouring
PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation
PROC 15: Use as laboratory reagent

Uses by professional workers

#5: Coating Professional Use

Environmental release category (ERC):

ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix
ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix

Process category (PROC):

PROC 10: Roller application or brushing
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities

#6: Adhesives and Sealants Professional Use

Environmental release category (ERC):

ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix
ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix

Process category (PROC):

PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
PROC 10: Roller application or brushing

#8: Other Composite Material Professional Use

Environmental release category (ERC):

ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix
ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix

Process category (PROC):

PROC 2: Use in closed, continuous process with occasional controlled exposure
PROC 3: Use in closed batch process (synthesis or formulation)
PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact)
PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation

Uses advised against

Consumer uses are not supported for safety reasons

Summary

TDI is used by workers in industrial settings in the following processes:
Manufacturing of TDI,

Manufacturing of other substances,
Formulating, repackaging and distribution,
Flexible foam,
Coating,
Adhesives and sealants,
Eklastomers, TPU, polyamide, polyimide and synthetic fibres,
Other composite,

and by professional worker in the processes:
Coating,
Adhesives and sealants,
Other composite.

Consumer uses are not supported for safety reasons

3. CLASSIFICATION AND LABELLING

3.1. Classification and labelling according to CLP / GHS

Implementation: EU

Classification

TDI is not classified in respect of physicochemical properties

For health hazards TDI is classified as follows:

Table 3. Classification and labelling according to CLP / GHS for health hazards

Endpoint	Hazard category	Hazard statement	CSR section
Acute toxicity - inhalation:	Acute Tox. 2	H330: Fatal if inhaled.	5.2.3
Skin corrosion / irritation:	Skin Irrit. 2	H315: Causes skin irritation.	5.3.4 and 5.4.3
Serious damage / eye irritation:	Eye Irrit. 2	H319: Causes serious eye irritation.	5.3.4
Respiration sensitization:	Resp. Sens. 1	H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.	5.5.3
Skin sensitation:	Skin Sens. 1	H317: May cause an allergic skin reaction.	5.5.3
Carcinogenicity:	Carc. 2	H351: Suspected of causing cancer <state route of exposure if it is conclusively proven that no other routs of exposure cause the hazard>.	5.8.3
Specific target organ toxicity - single:	STOT Single Exp. 3	H335: May cause respiratory irritation.	5.2.3 and 5.3.4

Specific concentration limits:

Concentration (%)	Classification

Concentration (%)	Classification
>= 0.1	Resp. Sens. 1

For environmental hazards TDI is classified as follows:

Table 4. Classification and labelling according to CLP / GHS for environmental hazards

Hazards to the aquatic environment (long-term):	Aquatic Chronic 3	H412: Harmful to aquatic life with long lasting effects.		7.5

Table 5. Classification and labelling according to CLP / GHS for additional hazard classes

Additional hazard classes:	Aqautic Acute Cat. 3, H402

Labelling

Signal word: Danger

Hazard pictogram:

GHS06: skull and crossbones

GHS08: health hazard

GHS07: exclamation mark

Hazard statements:

H330: Fatal if inhaled.
H315: Causes skin irritation.
H319: Causes serious eye irritation.
H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335: May cause respiratory irritation.
H317: May cause an allergic skin reaction.
H412: Harmful to aquatic life with long lasting effects.

Precautionary statements:

P273: Avoid release to the environment.
P280: Wear protective gloves/protective clothing/eye protection/face protection.
P284: Wear respiratory protection.

P308+P313: IF exposed or concerned: Get medical advice/attention.
P403+P233: Store in a well-ventilated place. Keep container tightly closed.
P501: Dispose of contents/container to... (hazardous or special waste collection point)

3.2. Classification and labelling according to DSD / DPD

3.2.1. Classification and labelling in Annex I of Directive 67/548/EEC

Chemical name: m-tolylidene diisocyanate (toluene-diisocyanate)

Classification

TDI is not classified in respect of physicochemical properties

For health hazards TDI is classified as follows:

Table 6. Classification and labelling in Annex I of Directive 67/548/EEC for health hazards

Endpoint	Classification	CSR section
Acute toxicity:	T+; R26 Very toxic by inhalation.	5.2.3
Irritation / Corrosion:	Xi; R36/37/38 Irritating to eyes, respiratory system and skin.	5.3.4 and 5.4.3
Sensitisation:	R42/43 May cause sensitisation by inhalation and skin contact.	5.5.3
Carcinogenicity:	Carc. Cat. 3; R40 Limited evidence of a carcinogenic effect.	5.8.3

Table 7. Classification and labelling in Annex I of Directive 67/548/EEC for the environment

Endpoint	Classification	CSR section
Environment:	R52/53 Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.	7.5

Labelling

Indication of danger:

T+ - very toxic

R-phrases:

R40 - Limited evidence of a carcinogenic effect
R26 - Very toxic by inhalation
R36/37/38 - Irritating to eyes, respiratory system and skin
R42/43 - May cause sensitisation by inhalation and skin contact
R52/53 - Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment

S-phrases:

S1/2 - keep locked up and out of reach of children
S23 - do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by the manufacturer)
S36/37 - wear suitable protective clothing and gloves

S45 - in case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
S61 - avoid release to the environment. refer to special instructions/safety data sheets

Table 8. Specific concentration limits

Concentration (%)	Classification
>= 25.0	T+; R26 Very toxic by inhalation. Xi; R36/37/38 Irritating to eyes, respiratory system and skin. Carc. Cat. 3; R40 Limited evidence of a carcinogenic effect. R42/43 May cause sensitisation by inhalation and skin contact. R52/53 Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
>= 20.0 — < 25.0	T+; R26 Very toxic by inhalation. Xi; R36/37/38 Irritating to eyes, respiratory system and skin. Carc. Cat. 3; R40 Limited evidence of a carcinogenic effect. R42/43 May cause sensitisation by inhalation and skin contact.
>= 7.0 — < 20.0	T+; R26 Very toxic by inhalation. Carc. Cat. 3; R40 Limited evidence of a carcinogenic effect. R42/43 May cause sensitisation by inhalation and skin contact.
>= 1.0 — < 7.0	T; R23 Toxic by inhalation. Carc. Cat. 3; R40 Limited evidence of a carcinogenic effect. R42/43 May cause sensitisation by inhalation and skin contact.
>= 0.1 — < 1.0	Xn; R20 Harmful by inhalation. R42 May cause sensitisation by inhalation.

3.2.2. Self classification(s)

Not applicable.

3.2.3. Other classification(s)

Not applicable

4. ENVIRONMENTAL FATE PROPERTIES

4.1. Degradation

4.1.1. Abiotic degradation

4.1.1.1. Hydrolysis

The registrant submitted two key studies and four supporting studies on biodegradability of TDI. The key study of Kitano et al (1989) presented the more realistic environmental situation. According to this study a half-life of TDI was ca. 0.7 h. The key study results carried out under less realistic environmental conditions (Yakabe et al 1999) showed a shorter half-life (less than one minute).

Conlusion:
TDI is rapidly hydrolysed in aqueous solution, with a half-life of under one minute. The product of hydrolysis of the isocyanate group is an amine, which itself reacts with another isocyanate group to yield an urea. This reaction of an amine with isocyanate is considerably faster than the reaction of water with the isocyanate. With TDI, a diisocyanate, this reaction leads to polyureas, which are inert, insoluble solids.

Value used for CSA: Half-life for hydrolysis: 1 d at 300 K

4.1.1.2. Phototransformation/photolysis

4.1.1.2.1. Phototransformation in air

The registrant delivered a key study performed by Becker et al (1988), which confirmed oxidation by photogenerated hydroxyl radicals as the significant degradation mechanism for TDI. These results are in agreement with those of Holdren (1984) in predicting a relatively short lifetime for TDI following an emission of TDI to the atmosphere.
The QSAR predicted half-life value (Pemberton and Tury 2008) is comparable with the measured value of Becker et al (1988).

Conclusion:
A photoreactor study confirmed oxidation by photogenerated hydroxyl radicals as the significant degradation mechanism for TDI. In the atmosphere TDI has a half-life of ~ 2 days regarding the reaction with OH. The measured data are in accordance with the predicted QSAR data.

Value used for CSA:

Half-life in air: 2 d

4.1.1.2.2. Phototransformation in water

4.1.1.2.3. Phototransformation in soil

4.1.2. Biodegradation

4.1.2.1. Biodegradation in water

4.1.2.1.1. Screening tests

According to key study presented in the registration dossier (Caspers et al 1986), no bioderadation was observed under test condition performed in accordance with OECD Guideline 302C.

Conclusion:
TDI is rapidly hydrolysed in aqueous solution, with a half-life of under one minute. The product of hydrolysis of the isocyanate group is an amine, which itself reacts with another isocyanate group to yield an urea. This reaction of an amine with isocyanate is considerably faster than the reaction of water with the isocyanate and

leads to polyureas, which are inert, insoluble solids. In wet soil TDI is undergone of hydrolytic self-polymerisation and the reaction products are assumed to be non-biodegradable. The study results of Casper et al (1986) performed in accordance with OECD 302C method showed no degradation after 28 days.

4.1.2.1.2. Simulation tests (water and sediments)

Data waiving by the registrant is conclusive because TDI is poorly soluble in water and direct and indirect exposure of sediment is unlikely.

4.1.2.1.3. Summary and discussion of biodegradation in water and sediment

Please refer to point 4.1.3

4.1.2.2. Biodegradation in soil

According to the data no degradation of TDI in soil was observed after 4 month.

Conclusion:
TDI is rapidly hydrolysed in aqueous solution, with a half-life of under one minute. The product of hydrolysis of the isocyanate group is an amine, which itself reacts with another isocyanate group to yield an urea. This reaction of an amine with isocyanate is considerably faster than the reaction of water with the isocyanate and leads to polyureas, which are inert, insoluble solids. In wet soil TDI is undergone of hydrolytic self-polymerisation and the reaction products are assumed to be non-biodegradable. The laboratory and field study results of Martens and Domsh (1981) showed no degradation after 4 month. Since production is performed in closed systems, releases to soil and sediment are expected to be negligible

Discussion

According to Annex IX of REACH, for soil simulation testing, text column 2 says the study need not be conducted if direct or indirect exposure of soil is unlikely. TDI is known to polymerize to a polyurea in the presence of water (Yakabe et al., 1999). TDI is rapidly hydrolysed in aqueous solution with a half-life of under one minute. However, TDI is hydrophobic and poorly soluble in water and thus the heterogeneous reaction with water or soil is less rapid. The major product of such a reaction is insoluble polyurea.

In the production of TDI the formation of insoluble polyurea would cause abrasion problems and blockage of valves and pipes and therefore releases of TDI to effluents are expected to be non-existent. Since production is performed in closed systems, releases to soil and sediment are also expected to be negligible (TDI producer's draft risk assessment report, December 2008, chapter 3.1.1). Furthermore, the EUSES (2.0) program has been used to calculate PEC values based on measured emission data provided by TDI producers and processors, including polyurethane producers (ibid., chapter 3.1.5.3). Calculated PEC values were 1 x 10-9 mg/l for water, 5x10-10 mg/kg for sediment and ranged from 3.2 x 10-9 to 6.9 x 10-8 mg/kg for soils/grassland. The corresponding PEC/PNEC ratios would be extremely small and less than 1.

Taking into account the scientific and exposure arguments, it appears appropriate to waiver the long-term fish/plant/soil and sediment toxicity studies.

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

Direct or indirect exposure of soil is unlikely.

4.1.3. Summary and discussion of degradation

Evaluation of the abiotic degradation data has shown that TDI is rapidly hydrolysed in aqueous environment. The estimated half-life was under 1 minute. The major product of this reaction is insoluble polyurea. Phototransformation in air revealed that the oxidation by generating of hydroxyl radicals is the significant degeneration mechanism for TDI.

Evaluation of biodegradation data has shown that TDI is not readily biodegradable in water. The insoluble urea, a major product of the reaction of TDI in aqueous environment could cause abrasion problems and blockage of

valves and pipes and therefore releases of TDI to effluents are expected to be non-existent. Release to soil and sediment is negligible as the production is performed in closed system. Furthermore, the EUSES (2.0) calculated PEC values were 1 x 10-9 mg/l for water, 5x10-10 mg/kg for sediment and ranged from 3.2 x 10-9 to 6.9 x 10-8 mg/kg for soils/grassland. The corresponding PEC/PNEC ratios would be extremely small and less than 1. Therefore data waving by the registrant is correctly justified.
The laboratory and field study results of Martens and Domsh (1981) showed no degradation of TDI in soil after 4 month. Since production is performed in closed systems, releases to soil and sediment are expected to be negligible

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

- TDI is not readily biodegradable.
- Direct or indirect exposure of sediment is unlikely.
- Direct or indirect exposure of soil is unlikely.

4.2. Environmental distribution

4.2.1. Adsorption/desorption

In accordance with Annex XI of REACH the study is waived. Hydrolysis in the presence of water is expected to be the primary driver in the fate of TDI in the environment. As a result of aqueous insolubility and inherent reactivity with water, it is not expected that significant concentrations of TDI would be found in water, soil and sediment, and this has been seen to be the case. In fact, TDI has not been detected in any aquatic studies.
According to these arguments the waiving of adsorption study is conclusive.

4.2.2. Volatilisation

No information was provided by the registrant.
On the base of vapour pressure of 80:20 TDI at 20 ^{0}C calculated as 0.015 hPa TDI is considered as volatile organic compound.

4.2.3. Distribution modelling

No information on the expected distribution in the environment was provided by the registrant.
A computerized partitioning model proposed by Mackay (1991) indicated that toluene diisocyanates released into the environment will tend to partition into water and undergo rapid hydrolysis (half-life of 0.5 seconds - 3 days in water, depending on pH and water turbidity) leading predominantly to the formation of relatively inert polymeric ureas which are biologically and chemically inert.

4.2.4. Summary and discussion of environmental distribution

Toluene diisocyanates are synthetic organic compounds and are not known to naturally occur in the environment. The most releases reported are to the air, with no releases reported directly to water or land. As a result of aqueous insolubility and inherent reactivity with water, it is not expected that significant concentrations of TDI would be found in water**,** soil and sediment. TDI reacts with water and produces chemically inert and insoluble polymeric urea. Reaction of TDI-vapour with water vapour does not take place in the gaseous phase.

4.3. Bioaccumulation

4.3.1. Aquatic bioaccumulation

In accordance with the REACH Annex XI the bioaccumulation study was waived. TDI is generally unavailable to aquatic organisms. Data waiving by the registrant is conclusive.

4.3.2. Terrestrial bioaccumulation

No information was provided by the registrant. Direct or indirect exposure of soil is unlikely.

4.3.3. Summary and discussion of bioaccumulation

The predicted log Kow for these substances is approximately 3.74. However, it is worth noting that both the log Kow predictions, and the BCF models which depend them, likely overestimate the lipophilicity of these compounds because of the rapid reactivity and hydrolysis in water. The Kow model KOWWIN v1.67 while providing a prediction also notes in its output that that isocyanates hydrolyze and therefore the estimates are questionable. This rapid hydrolysis with water also limits the determination of log Kow experimentally, and as a result, reliable experimental log Kow's are not readily available in the literature. A log Kow of 3.4 was determined experimentally using OECD methods, however, it was of uncertain significance in terms of TDI's environmental fate and behaviour, again, because of TDI's reactivity in the aquatic environment. The above indicates that TDI has a low potential for bioaccumulation in aquatic organisms. Since production is performed in closed system release to soil is expected to be negligible.

4.4. Secondary poisoning

Based on the available information the bioaccumulation potential cannot be judged (see CSR chapter 7.5.3 "Hazard assessment conclusion for secondary poisoning").

5. HUMAN HEALTH HAZARD ASSESSMENT

The evaluation oft he toxicity of TDI has been based on data presented by the registrants (aggregated IUCLID, CSR).

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

5.1.1. Non-human information

Oral administration:

Absorbtion:

Orally administered [14C]-2,4-TDI or [14C]-2,6-TDI is not very well absorbed. There was a consistent finding that when rats were gavaged with high doses of 2,4-TDI, much of the isocyanate polymerised in the stomach and was excreted in the faeces (Jeffcoat, 1988, 1985; Stolz et al., 1987). Hence proportional bioavailability increased with decreasing dose: e. g. 3.5% of the applied radioactivity was recovered in urine after gavage with 700 mg/kg, 6.3% after 70 mg/kg and 16% after 7 mg/kg 2,4-TDI (Jeffcoat, 1988). A similar proportional excretion pattern was described for the isomer mixture (23% of 6 mg/kg and 16% of 60 mg/kg, Stolz et al., 1987) or 2,6-TDI (12% of 59 mg/kg and 5% of 900 mg/kg bw dose, Jeffcoat, 1985).These findings are consistent with the view that under the acidic conditions in the stomach TDI will hydrolyze to TDA which, in the presence of excess TDI, will react with it to form insoluble polyureas. Without the isocyanate as a reaction partner the TDA will be absorbed. The similarity of the urinary excretion kinetics and metabolite profiles for both orally administered TDI and TDA support this concept. Although the use of corn oil as the dosing vehicle and the stated degradation of the TDI in that vehicle to unidentified products rather compromises the data generated.

Excretion:

Urine is the predominant route of excretion of absorbed radioactivity and half of the [14C]-2,4-TDI derived total radioactivity which was recovered in urine was excreted in 7 hr ($t_{1/2}$ = 7.5 hr, Timchalk et al.,1992). Excretion of radioactivity from urine was most rapid 0-6 hr, decreasing rapidly by 24 hr (Stolz et al., 1987). Results from i. m. applications suggest, that also bilary excretion plays a major role in the overall excretion of absorbed radioactivity (39% of applied radioactivity, Saclay, 1976).

Distribution:

In rats the largest part of a [14C]-2,4-TDI dose was recovered in the GI tract and excretory organs, including the stomach, caecum, large intestine and bladder (Jeffcoat, 1988). Following oral application of [14C]-2,6-TDI (Jeffcoat, 1985) or [14C]-2,4-TDI/2,6-TDI-isomer mixture (Stolz et al., 1987), [14C]-tissue concentrations were highest in blood, liver, kidney and stomach. Total recovery in tissue did not exceed 1% of the doses recovered at 4hr after dosing.

Metabolism:

Metabolite profiles from orally administered TDI, including the identification of free TDA, were not dissimilar to those for orally administered TDA.

Oral dosage with 2,4-TDI yielded qualitatively similar metabolic profiles in urine to those following i. v. dosing of 2,4-TDA (Timchalk et al.,1992). Six metabolic products from TDI metabolism co-chromatographed with those from 2,4-TDA. Less than 10% were 2,4-bis(acetylamino) toluene and 80% of the radioactivity was associated with 5 other peaks with identical chromatographic retention times as the metabolites of 2,4-TDA (Jeffcoat, 1988). Differences were described when comparing the metabolic profiles of 2,4-TDA with 2,6-TDA. More than half of the 2,6-TDA derived material in urine was 2,6-bis(acetylamino) toluene (Jeffcoat, 1985).

Following [14C]-2,4-TDI oral dosing, approximately 65% of the quantitated urinary metabolites existed as acid-labile conjugates. Monoacetyl, diacetyl and free TDA were detected (Timchalk et al.,1992). Analysis of plasma showed the majority of the radioactivity present to be in the high molecular weight fraction (> 10 kDa) and associated with a range of high molecular weight components. The majority of the radioactivity present in the low molecular weight fraction was tentatively identified as TDA.

Inhalation exposure:

Absorbtion:

Acute inhalative administration of TDI as a vapor resulted in an almost complete absorbtion in rats (Timchalk et al., 1992 for 2,4-TDI; Stoltz et al., 1987 for the mixture). The major part of radioactivity was absorbed via the lungs while only a minor part was orally absorbed due to respiratory clearance. A proportional relationship between exposure and blood concentration was observed in rats (Kennedy, 1994) and guinea pigs (Kennedy, 1989).

Excretion:

The main proportion of the inhaled dose was excreted in the feces (>50%), resembling substance transported into the GI-tract via bilary excretion (Timchalk et al., 1992 for 2,4-TDI; Stoltz et al., 1987 for the mixture). The second greater proportion of excretion is via urine (20-24%) with a t1/2 of 20h, which is considerably higher than that for orally dosed TDI/TDA. No radioactivity was excreted via the expired air. In five days 86% of the dose was eliminated, and 8% was found in bile during the first 52 hours, with activity peaking between 6 and 9 hr. Faecal excretion (63.1% within 120 h) was greater than urinary excretion (23.4% within 120 h; Saclay, 1976).

Distribution:

Following a vapour exposure to mixed [14C]-TDI isomers (84% 2,4-, 16% 2,6-TDI) blood elimination of [14C] was biphasic and 90% of the radioactivity in plasma was associated with proteins. [14C] was distributed relatively uniformly throughout the body with a predominance for the stomach, small intestine, kidneys, lungs and thyroid (Saclay, 1976). In guinea pigs exposed to [14C]-2,4-TDI vapours, tissues showing highest levels of activity were trachea and lungs. Small amounts were found in kidney, liver, and heart (Kennedy et al., 1989). Similar findings were reported for the rat (Kennedy et al., 1994). Immediately after exposure of rats to [14C]-2,4-TDI the majority of radioactivity was detected in the carcass (74.5%), 48 h later the radioactivity in the carcass had declined to 10%, while 16.6% was found in the GI content. The total radioactivity in the carcass and tissues was approximately 34% 48 h after exposure (Timchalk et al.,1992; 1994). Slightly higher recoveries in the carcass (18% 96h after single application) were reported for the mixture (Stoltz et al., 1987).

Metabolism:

The urinary metabolite profiles between oral and inhalation exposure differed substantially, reflecting the different conditions on both application routes. In the lung (pH approx. 7), TDI-vapor conjugates with proteins, whereas in the stomach (pH below 2) protein binding is reduced and hydrolysis and formation of polyurea is facilitated.

Accordingly, even at a high inhalation exposure level of 2ppm [14C]-2,4-TDI for 4h, Timchalk et al. (1992; 1994) did not detect any free TDA in the urine. In rats orally exposed to 60 mg/kg bw [14C]-2,4-TDI small amounts of free TDA were detected (2.08 µg Eq/g urine). Furthermore, different ratios and absolute values of the mono- and di-acetylated derivates were determined in this study. Only very low total amounts of acetylated derivatives were detected following inhalation exposure (0.26 µg Eq/g urine) compared to the oral route (13.26 µg Eq/g urine). These acetylated derivatives are most likely not liberating free TDA. Even though, the low amount of acetylated derivatives detected following inhalation exposure guarantees that TDA would not be available in toxicologically relevant concentrations. Approximately 90% of the quantified urinary metabolites from inhaled 2,4-TDI existed as acid-labile conjugates, contrasting with only 65% for orally administered TDI (Timchalk et al., 1992).

When rats were exposed for 4 hours to [14C]-2,4-TDI vapours the majority of the label associated with the blood (74-87%) was recovered in the plasma. Plasma profiles showed that 97-100% of this radioactivity existed in the form of biomolecular conjugates. In contrast to oral dosing binding was predominantely associated with a single component of 70kDa, most likely representing albumin (Kennedy, 1994). The majority of the radioactivity present in the low molecular weight fraction was not identifiable as TDA but was spread across a number of unidentified components. The authors concluded that conjugation was the predominant reaction and that free TDA was not a primary in vivo reaction product following inhalation of 2,4-TDI vapour.

Further studies found polar and less polar metabolites following exposure to mixed TDI-isomers. Slightly less polar metabolites were recovered in urine, faeces and tissues with no apparent difference in distribution of polar and non-polar products due to dose (Stoltz et al., 1987). The most abundant derivative accounted for 25-30% of

14C in urine (Saclay, 1976).

Dermal administration:

When applied in a mixture on to skin, both 2,4 - and 2,6 -TDI disappeared, with either about 16% or 3% respectively, remaining after 8 hours (Gamer 2007). Both Administration of 2,4 -TDI to the skin of rats for eight hours resulted in less than 1% of the applied dose reaching the systemic circulation. The absorption of 2,4-TDI was 0.27%, 0.50% and 0.90% after exposure periods of 0.5, 1 and 8 hours, respectively. Highest tissue concentrations of radioactivity were found in blood cells and plasma (OECD427; Fabian and Landsiedel, 2008).

Following occlusive dermal application of 0.2%, 1% and 5% TDI (80:20 2,4-: 2,6-isomers) to rats, the amount of hydrolysed urinary TDA correlates linearly with the amount of TDI applied, suggesting that the absorption is dose-dependent (Yeh et al., 2008). Excretion of hydrolysed TDA followed a first order kinetic and the apparent half lives were about 20 and 23 hours for the 2,4- and 2,6-TDI isomers respectively, increasing by an increase of dose. Although exposures were to 2,4- and 2,6-TDI isomers in 80:20 ratio, urinary hydrolysed amine isomer recoveries were essentially close to unity (1:1), which was attributed to the greater reactivity of the 2,4-TDI isomer forming polymers which were not absorbed.

The urinary elimination half life following dermal and inhalation administration is similar at about 20 hours, and markedly different from that following oral administration (3-5 hours), indicating a similarity in disposition and metabolism between inhalation and dermal exposure routes.

Other routes:

Following a single intramuscular injection of [14C]-TDI (84% 2,4-, 16% 2,6-TDI) total urinary excretion after 360 h was 53%, faecal 39%, expired air was negligible, and the remaining activity in the carcass was 4% (Saclay, 1976).

In vitro metabolism:

According to an in vitro binding-study with blood proteins, 2,4-TDI binds preferentially to the N-terminal amino acids of globin (valine and lysine to a minor extend) and albumin (lysine and to a minor extent aspartic acid) (Mraz et al., 1997). N-terminal lysine adducts are the most abundant 2,4-TDI adducts. By this binding ureid adduct are being formed which can be converted to and determined as specific hydantoins.

In the presence of N-acetyl-L-cystein under aquaeous conditions, 2,4-TDI is predominantely forming (AcCys) -conjugates and insoluble urea with amino end groups. Free TDA/TDI is not detectable. The amount of conjugates being formed is increasíng with an excess of AcCys. With an excess of isocyanate insoluble urea is the predominant reaction product. Due to the hydrophobicity of TDI these reaction products are forming small droplets or solid perticles with an insoluble layer of urea at the surface and occluded TDI prevented from diffusion and therefore from further reaction (Morman, 2002).

5.1.2. Human information

No relevant human information is available.
The study of Rosenberg and Savolainen (1986) indicated the linear relationship between TDA concentration in urine following hydrolysis and the dose of TDI in people occupationally exposed to TDI. It was assumed that formed TDA undergone further conjugation and excretion. The quantitative data on excretion in urine was considered as insufficient.

5.1.3. Summary and discussion of toxicokinetics

TDI may be absorbed into the body by inhalation, ingestion and through the skin. The most important of human exposure to TDI are inhalation or dermal contact. TDI is almost completely absorbed after inhalation exposure, whereas following dermal or oral administration is not very well absorbed.
The metabolism of TDI is route-dependent. After oral administration TDI is hydrolysed to polyureas or TDA which is absorbed and metabolized. The studies revealed linear relationship between TDA and the level of TDI absorbed. Following inhalation exposure no TDA was detected in urine.
It has been postulated that after inhalation exposure TDI will conjugate or react with biological molecules in the lung which then enter the systemic circulation. Absorbtion as a glutathione conjugate may be a possible pathway.
No free TDA has been detected in urine of humans exposed to atmospheric TDI. It has been supposed that TDA

is excreted in the form of conjugates.

While a precise relationship between inhalation exposure and biomarker is not established, it is clear that urinary excretion reflects very recent exposures to TDI, while blood biomarkers may reflect exposures over the proceeding few weeks.
TDI is excreted in urine and faeces when it is injected intramuscularly.

5.2. Acute toxicity

5.2.1. Non-human information

5.2.1.1. Acute toxicity: oral

Several tests assessing the oral toxicity of TDI in rats or mice of both sexes are available. The acute oral LD_{50} value in rats (both genders) was greater than 2000 mg/kg/bw. Clinical observation included hypoactivity and reduced pain response. At necropsy, white crystalline material was found in the stomach and dark red lungs were observed. Overall, tests assessing the acute oral toxicity of TDI provide consistent evidence of low toxicity after an oral administration.

5.2.1.2. Acute toxicity: inhalation

Two reliable studies for the assessment of the inhalation toxicity of TDI are available. Animals dying on study or killed at the end of exposure revealed some hemorrhages or edema of the lungs. Overall, these results show that TDI is very toxic by inhalation.

5.2.1.3. Acute toxicity: dermal

The acute dermal LD_{50} value in rabbits (both genders) was greater than 9400 mg/kg/bw. Skin irritation was noted at all dose levels (2500 to 9400 mg/kg b. w.), at a moderate-to-marked degree. This result shows that TDI is not acutely toxic via the dermal route.

5.2.1.4. Acute toxicity: other routes

Not relevant for assessment

5.2.2. Human information

No relevant human information is available.
The acute effect of TDI in humans is irritation of eyes and mucous membranes of respiratory tract (Johnstone 1957).

5.2.3. Summary and discussion of acute toxicity

The data submitted by registrant are suitable for evaluation of acute toxicity of TDI.
Fort he endpoint acute oral toxicity four studies are submitted. Two oft hem was declared by the registrants as key study and two others as supporting studies. TDI is of low acute oral toxicity. In the key studies (NTP, 1986 and Woolrich, 1982) performed according to OECD Guideline 401, the estimated LD_{50} was 4130 mg/kg/bw and 5110 in rats males and females respectively and 4130 mg/kg bw in mouse males.
According to the supporting studies (Wazeter et al, 1964 and Ministry of Health, Labour & Welfare, Japan, 2001), the otained LD_{50} values did not result in classification regarding acute oral toxicity.
Fort the endpoint acute inhalation toxicity one key study (Doe and Horpool, 1980) and one supporting (MacKay, 1992) study are submitted. The estimated LC_{50} value is between 0.46 mg/l and 0.1 – 0.14 mg/l (for rats females and males respectively). On the base of classification criteria TDI warranted classification as very toxic by inhalation according to DSD and Acute Tox. 2 according to CLP.
Fort the endpoint acute dermal toxicity one key study is presented by the registrant. TDI is of low acute dermal toxicity. In the study of Wazeter et al (1964) and Woolrich (1982) performed according to method equivalent to OECD Guideline 402, the estimated LD_{50} was >9400 mg/kg bw in rabbit's males and females

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

Acute toxicity:

Oral: LD50 > 2000 mg/kg for rats or mice (following or equivalent to OECD TG 401)

Dermal: LD50 > 2000 mg/kg for rabbits (equivalent to OECD TG 402)

Inhalation: LC50 = 0.48 mg/l/1 hr for rats (equivalent to OECD TG 403)

Justification for classification or non classification

Official EU classification according to Directive 67/548/EEC is T+; R26, Very toxic by inhalation, and by EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008), Acute tox 2, fatal if inhaled.

Acute toxicity (oral): not classified (2,4/ 2,6 TDI (80/20), LD_{50} oral rat and mouse > 2000 mg/kg bw)

Acute toxicity (dermal): not classified (TDI unspecified isomers, LD_{50} dermal rabbit > 2000 mg/kg bw)

Acute toxicity (inhalation vapour): Category 2, fatal if inhaled (2,4/ 2,6 TDI (80/20), LC50, 1 hr, rat, 0.47 mg/l (66 ppm) (Doe and Horspool, 1980))

5.3. Irritation

5.3.1. Skin

5.3.1.1. Non-human information

There are several skin irritation studies, all showing evidence of strong irritation of various severity.

In a skin irritation study by Knapp and Baker (1974) severe edema and mild erythema was described. Both effects were not fully reversible after 7 days. The reliability of this assay is limited by the demonstrated inconsistencies in reporting and study conduction at the Industrial Bio-Test Laboratories within the time frame of the study performance.

A strong skin irritation, including persistent erythema, sclerema and edematous swelling were observed following in the study by Suberg (1984). Histopathology revealed damage of the epidermis ulcerating into the outer part of the dermis.

Suberg (1984) applied 0.5 ml of a TDI-isomer mixture for 1 or 4h on both flanks of 6 rabbits. One flank was covered occlusively, the other semiocclusively. Macroscopical readings were performed for up to 13 days and on days 6, 13 and 28 two animals were sacrificed for histopathology, respectively. Macroscopically, persistent erythema, sclerema, edematous swelling indicative for a strong skin irritation were seen following 4h of semiocclusive application. Erythema was not fully reversible within the observation period. Additionally slightly brownish discolorations and desquamation were described. Histopathology revealed damage of the epidermis ulcerating into the outer part of the dermis. The extend of this full thickness necrosis on the application area was not described in detail. Furthermore an intense and almost complete reepitheliation 13 to 28 days after removal of the test substance was described. An increased hair growth was detected on most of the regenerated skin area, which is not indicative for a scar-tissue. Alopecia is a key characteristic of scar tissue and by this of irreversible tissue damage.

In the following irritation assays exposure times were way longer than 4h required by the OECD guideline. These studies are therefore summarized for completeness:

In a skin irritation assay with a 24h exposure period moderate, reversible erytema and edema were reported. At intact skin areas necrosis of various severity was described. Histopathology revealed epidermal atrophy and cellular infiltration of the dermis 3-10 days following removal of the test substance (Duprat, 1976). A bioassay in rats demonstrates that with long exposure periods (8h) and high application volumes (100µl), no macroscopical signs of necrosis occurred (Gamer, 2007, see7.1.2). This may be partly due to the lower sensitivity of rat skin compared to rabbit skin. Though, histopathological examination revealed multifocal to coalescing epidermal full thickness necrosis. The assay was performed with the single isomers (2,4- and 2,6-TDI) but no significant differences in skin response was described.

Only mild irritation was observed on guinea pig skin exposed to an unknown amount of mixed TDI for an unknown exposure period (Peschl, 1970).

5.3.1.2. Human information

No relevant human information is available.

5.3.2. Eye

5.3.2.1. Non-human information

The eye irritation potential was determined by installation of sample of TDI mixed isomers into the conjunctival sac of rabbits. The test material was irritating to the eyes causing moderate-severe corneal opacity, severe irritation of the conjunctivae, purulent discharge and depilatory effects. Irritation was more persistent in the unwashed group with corneal opacity persisting in 2 rabbits until day 30. These results show that TDI is a severe eye irritant (Wazeter et al 1964).

5.3.2.2. Human information

No relevant human information is available.
Sittig (1981) and Woolrich (1982) noted lacrimation and inflammation of eyes following exposure to TDI.

5.3.3. Respiratory tract

5.3.3.1. Non-human information

Acute and chronic inhalation studies in rodents revealed signs of respiratory irritation like wheezing and gasping (acute) and rhinitis (chronic (Doe and Horsepool, 1980 and Owen, 1980).

5.3.3.2. Human information

No relevant human information is available.
Henschler et al (1962), Sittig (1981) and Woolrich (1982) described symptoms of respiratory tract irritation in people exposed to TDI at concentration of 0.1 – 3.9 ppm. The most common were: nose discharge, dyspnea, cough and inflammation of lungs.

5.3.4. Summary and discussion of irritation

The data submitted for registration to the endpoint skin irritation and serious eye damage/eye irritation are suitable for evaluation.
To evaluate the skin irritation of TDI two studies on rabbits (Knapp & Baker, 1974 and Suberg et al, 1984) and one on guinea pigs (Peschel ,1970) are presented. The last one is not taken into consideration as it does not give sufficient data (Klimisch score 4).
The weight of evidence of the summarized studies is demonstrating a strong skin irritating reaction of TDI. By definition skin corrosion is an irreversible damage to the skin. It should be a visible necrosis through the epidermis into the dermis, following the application of a test substance for up to 4h. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. A final evaluation and assessment of skin corrosion of TDI according to these criteria is not possible due to significant deficiencies in study performance or reporting of most studies. In non of the presented studies a strong discoloration was reported after exposure of rabbits, under guideline conditions (4h, 50µl). At the most a slightly brownish discoloration was reported by Suberg. Full thickness necrosis was identified by means of histopathology but the extend and severity (punctual or extensive) could not be unequivocally dissolved from the study report. Following a 8h exposure on rat skin (100µl), the extend of the full thickness necrosis identified by histopathology was described as multifocal to coalescing, though not planar. Finally, it can not be resolved to which extend chemical reaction of TDI to the skin surface is contributing to the observed effects.
Due to the described uncertainties a conclusive evaluation of the indications of skin corrosion according to the described legal guidance is not possible. Therefore the current legal classification in Annex I to Directive 67/548 as a strong skin irritant (R38, CLP Skin irrit. 2) seems to be appropriate.
To evaluate eye irritation of TDI two studies are presented (Watzer et al, 1964 and Woolrich, 1982). The results oft he studies indicate a serious eye irritating properties of TDI.
The current classification as irritating to eyes (R36, CLP Eye irrit. 2) seems to be appropriate.
The registrant submitted one study related to irritation of respiratory tract (Schiotsuka, 1987). TDI causes symptoms of respiratory irritation as wheezig, gasping and rhinitis.

The current classification as irritating to respiratory tract (R37, CLP STOT SE 3) seems to be appropriate.

The following information is taken into account for any hazard / risk assessment:
Skin irritation: irritating in rabbits (OECD TG 404)
Eye irritation: irritating in rabbits (Draize test)
Respiratory irritation: weight of evidence from acute and repeated dose inhalation studies in rodents.

Value used for CSA:
Skin irritation / corrosion: Adverse effect observed (irritating)
Eye irritation / corrosion: Adverse effect observed (irritating)
Respiratory irritation / corrosion: Adverse effect observed (irritating)

Justification for classification or non classification

Official EU classification according to Directive 67/548/EEC is Xi; R36/37/38, Irritating to eye, respiratory system and skin, and by EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008), is Eye irritation 2, Skin irritation 2, Causes serious eye irritation, causes skin irritation.

Skin irritation/ corrosion: Category 2, causes skin irritation

Eye irritation/corrosion: Category 2, causes serious eye irritation

5.4. Corrosivity

5.4.1. Non-human information
See Section 5.3

5.4.2. Human information
See Section 5.3

5.4.3. Summary and discussion of corrosion
See Section 5.3

5.5. Sensitisation

5.5.1. Skin

5.5.1.1. Non-human information

The senstising properties of TDI was investigated in LLNA, MEST and Buehler test. According to key study (Hilton et al, 1995) as well as to supporting studies (Woolhise et al, 1998, Zissu et al, 1998, Thorne et al 1987 and Karol et al, 1981) TDI is a strong sensitizer to the skin.

5.5.1.2. Human information

The exposure - related observations on skin sensitisation in humans revealed allergic reactions like palpable erythema, papules, oedematous and vesicless (Kanerva et al.,1999).

5.5.2. Respiratory system

5.5.2.1. Non-human information

TDI-dose dependent decrease in respiratory rate was observed following inhalation exposure in guinea pigs (Karol, 1983).
They bradypnoea and a laboured/irregular breathing pattern and breathing sounds at higher concentrations was observed in guinea pigs following inhalation exposure to TDI. The animals sensitized by a single, brief, high-level exposure appeared to be mildly more responsive to TDI challenge than those in the other groups. The guinea pigs receiving the id and the inhalation exposure, showed a longer, more intense response to TDI-GPSA, than those which received only the injection. Tissue sections from TDI exposed animals showed the presence of

epithelial disruption, pulmonary inflammation and activation of the lung associated lymph nodes (LALN). Inflammation was characterised by infiltration of eosinophils and polymorphonuclear leucocytes. Histological analysis of the lungs, and LALN, revealed an association of the influx of polymorphonuclear and eosinophilic granulocytes, and the TDI level at induction. The guinea pigs exposed to the polyisocyanate resin had IgG1 antibodies to both TDI-GPSA and resin-GPSA; apparently cross-reactivity (Pauluhn and Mohr, 1998).

5.5.2.2. Human information

Specific IgG binding to diisocyanate-human serum albumin (HSA) has been proposed as an indicator of diisocyanate exposure. According to study by Bernstein et al. (2006), specific and nonspecific IgG binding to HDI-HSA and TDI-HSA were detected in individuals without known exposure to isocyanates.

5.5.3. Summary and discussion of sensitisation

Skin sensitization

Animal data provide clear evidence of skin sensitisation due to TDI. The senstising properties of TDI was investigated in LLNA, MEST and Buehler test. According to key study (Hilton et al, 1995) as well as to supporting studies (Woolhise et al, 1998, Zissu et al, 1998, Thorne et al 1987 and Karol et al, 1981) TDI is a strong sensitizer to the skin.
Human experience finds that skin sensitization is rarely reported because of reduction of the risk of sensitization using extra protective measures as gloves and efficient ventilation. The sensitizing properties of TDI was investigated using human patch test in 360 individuals occupationally exposed to TDI. The allergic reaction was observed in 0.8% of the tested workers.
It can be assumed that in the industrial production sector only skilled workers will handle the substance and that protective gloves will routinely be worn so that the real skin exposure at these sites is considered to be very low.

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

Animal data provide clear evidence of skin and respiratory sensitisation due to TDI. Human experience provide clear evidence of respiratory sensitisation, however skin sensitization is rarely reported. Because of the risk of sensitisation at the workplace extra protective measures are demanded in the chemical industry as routine including use of protective gloves and efficient ventilation.

Value used for CSA: Adverse effect observed: sensitizing

Respiratory sensitization

The registrant submitted three studies on respiratory sensitization of TDI in laboratory animals (Pauluhn and Mohr, 1998, Botham et al, 1988 an Karol, 1983) and one study performed in 11 volunteers (Bernstein et al, 2006). It is well documented that TDI exposure can lead to work-related asthma. Typically, the inhalation exposure to high concentration of TDI can result in high incidences of asthma whereas fewer cases of asthma is associated with lower TDI exposure (U.S. EPA, 2011). Clinical studies (with humans) suggest that total dose may be more important than concentration in eliciting TDI-induced asthma (Vandenplas et al., 1993), while animal studies with guinea pigs do not support that view (Karol, 1983). At the present time, it is not possible to define reliable exposure-response relationships with regard to the risk of sensitisation for TDI (or indeed for any other known respiratory sensitiser). In rats the short high level exposure to diisocyanate is more effective in inducing respiratory sensitivity than longer exposure (Pauluhn and Poole, 2011). These results may suggest a threshold for induction. On the other hand, most workers who develop diisocyanate asthma have experienced long periods of exposure (U.S. EPA, 2011).
Animal data support the hypothesis that respiratory hypersensitivity may be induced by skin contact and this possibility has not been excluded in studies involving humans. It is likely that any significant skin exposure to TDI will involve a concomitant respiratory exposure, and discrimination of the contribution of the different exposure routes is unlikely to be resolved in humans.

The following information is taken into account for any hazard / risk assessment:
TDI is also a potential respiratory sensitiser in animals and humans. Animal studies have shown that some responses relating to respiratory sensitisation can be induced by skin contact with TDI, but it is unclear how this might apply to induction of asthma in humans. The quantitative relationships between exposure (concentration, duration, rate of exposure, route of exposure) and incidence of sensitisation have not been established.

Value used for CSA: Adverse effect observed: sensitising

Justification for classification or non classification

Official EU classification according to Directive 67/548/EEC is R 42/43, May cause sensitisation by inhalation, by skin contact, and by EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008), Respiratory sensitiser 1, skin sensitiser 1. May cause allergy or asthma symptoms or breathing difficulties if inhaled, may cause an allergic skin reaction

5.6. Repeated dose toxicity

5.6.1. Non-human information

5.6.1.1. Repeated dose toxicity: oral

Data waiving

Information requirement: Repeated dose toxicity after oral administration

Reason: study scientifically unjustified

Justification: According to the REACh regulation Annex VII and IX a repeated dose study does not need to be conducted in case " a substance undergoes immediate disintegration and there are sufficient data on the cleavage product". TDI is highly reactive against traces of water (t 1/2 < 1 h). Oral contamination is therefore resulting in very rapid degradation to a variety of breakdown and polymerization products including 2,4-TDA and 2,6-TDA salts under the acidic conditions in the stomach. Therefore oral exposure against TDI itself is highly unlikely and the conductance of further repeated dose studies scientifically unjustified.

5.6.1.2. Repeated dose toxicity: inhalation

The repeated exposure of rats and mice (both genders) to TDI (6 hours per day, 5 days per week, 104-113 weeks) resulted in NOAEC ~ 0.05 ppm and LOAEC ~ 0.05-0.15 ppm. (key studies: Owen, 1980, 1984, 1986 and Loeser, 1983).
According to supporting studies on rats (6 hours per day, 5 days per week, 15-22 esposures) the LOAEL/NOAEL was ranged between 0.1-0.3 ppm (Henck et al. 1976, 1976a, 1976b, Bennett et al. 1980, Kociba et al. 1979).

5.6.1.3. Repeated dose toxicity: dermal

Data waiving

Information requirement: Repeated dose toxicity after dermal administration

Reason: study scientifically unjustified

Justification: Strong skin irritation is the leading acute effect of dermal exposure to TDI. No signs of systemic toxicity were observed in the irritation studies and in systemic oral/inhalation studies. Given the low bioavailability of TDI via the skin (<1%, Fabian & Landsiedel, 2007), the absence of systemic effects on the most relevant route of exposure (inhalation) and the strong irritating potency of TDI, the conductance of any type of repeated dose studies on the dermal route is scientifically unjustified.

5.6.1.4. Repeated dose toxicity: other routes

This information is not available

5.6.2. Human information

In workers occupationally exposed to TDI rhinitis of respiratory tract and hyperreactivity of bronchi were observed (Adams, 1975, Porter et al, 1975).

5.6.3. Summary and discussion of repeated dose toxicity

Discussion

Inhalation exposure is the most appropriate route for assessing occupational risk in humans. Effects from repeated exposure of animals to TDI are limited to effects on the respiratory tract caused by local irritation.

The most relevant evaluation of repeated dose toxicity comes from a 2-year chronic toxicity and carcinogenicity study with TDI in rats and mice (Owen, 1980, 1986; Loeser, 1983). The animals were whole body exposed to 0, 0.05 and 0.15 ppm of TDI (80/20) vapour for 6 hours/day, 5 days/week. In both species, body weight gain was reduced at 0.15 ppm over the first 12 weeks that persisted but did not worsen over the remaining period of the study. In rats, rhinitis was observed in males at 0.15 ppm and in females beginning at 0.05 ppm, generally characterized by squamous metaplasia/hyperplasia of the respiratory mucosa, with and without exudate in the lumen, and leucocyte infiltration in the lamina propria. This finding is considered to be due to local irritation of the anterior nasal cavity. In mice, histopathology revealed marked inflammatory processes in trachea, larynx, bronchi, lungs and predominantly in nasal turbinates (chronic and necrotic rhinitis) of male and female animals beginning at 0.05 ppm. Therefore, the LOAEC for rats and mice is 0.05 ppm (0.362 mg/m3) after long-term inhalation of TDI vapour.

The findings of the key study were supported by subchronic studies in various strains and species (Henck, 1976).30 day whole body exposure of SD- and Fischer-rats, hamsters and mice to vapors of 0.1 and 0.3 ppm resulted in repiratory irritation (LOAEL 0.1 ppm) but no signs of systemic toxicity.

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

Inhalation exposure is the most appropriate route for assessing occupational risk in humans. Effects from repeated exposure of animals to TDI are limited to effects on the respiratory tract caused by local irritation, no signs of systemic toxicity were observed.

The oral and dermal route of exposure are not relevant for assessment.

Value used for CSA (inhalation - systemic effects):

(LOAEC: 0.362 mg/m³)

Target organs: respiratory tract

Justification for classification or non classification

According to Directive 67/548/EEC and the CLP-Regulation (EC) 1272/2008, no classification for systemic toxicity following repeated exposures is appropriate. Due to local irritation of the respiratory tract, the R37 is appropriate according to Directive 67/548/EEC or STOT Cat. 3 according to CLP-Regulation (EC) 1272/2008.

5.7. Mutagenicity

5.7.1. Non-human information

5.7.1.1. In vitro data

The results of key study by Seel et al (1999) indicate: positivity or negativity dependent on solvent for S. typhimurium TA 1535, TA 1537, TA 98 and TA 100with and without metabolic activation; cytotoxicity: no, but tested up to precipitating concentrations (OECD Guideline 471 Bacterial Reverse Mutation Assay). Test results of supporting study (JETOC 1996) showed positive results with and without metabolic activation (OECD Guideline 473 In vitro Mammalian Chromosome Aberration Test). According to data in NTP Report (2011), TDI is mutagenic for microorganisms but not for mammals in both in vitro and in vivo studies.

Data waiving

Information requirement: In vitro genotoxicity
Reason: study scientifically unjustified
Justification: According to Annex VIII of REACH Text Column 2 in vitro cytogenetics does not need to be conducted since there are adequate data from an in vivo cytogenetics test.

Information requirement: In vitro genotoxicity
Reason: study technically not feasible

Justification: Data waiver is claimed according to Annex XI, Section 2. which includes unstable substances. In vitro cell studies using diisocyanates including MDI varieties, are not feasible
due to rapid degradation of the diisocyanate during solvation and in the test system. This degradation does not equate to in vivo exposure.

5.7.1.2. In vivo data

The results of genotoxicity studies in vivo were negative (MacKay 1992b, Loeser 1983b, Owen 1980, 1986b, Benford and Riley 1988, Zeiger 2005 and Zeiger and Woolhiser 2007).

5.7.2. Human information

No relevant human information is available

5.7.3. Summary and discussion of mutagenicity

Discussion

As aromatic diisocyanates are virtually insoluble in water, an organic solvent is required to ensure homogeneous dispersion in in vitro genotoxicity assays. Dimethylsulphoxide (DMSO) has been used routinely as the vehicle of choice for such assays. The validity of using DMSO as a solvent was queried by Gahlman et al (1993) * when it was found that there was a chemical conversion of TDI to TDA in the solvent which could explain a number of positive responses recorded in some in vitro genotoxicity assays. A detailed evaluation of the stability of TDI in dimethylsulphoxide (DMSO) by Seel et al (1999) showed there is a rapid breakdown of TDI in DMSO with less than 60% of the initial amount remaining after 15 minutes. A HPLC examination of the breakdown products showed TDA was first detected at 15 minutes rising to 8% after 30 minutes. The authors concluded that in traditional bacterial mutation assays with Salmonella typhimurium using DMSO as the solvent conversion of TDI to ureas, polyureas and TDA would be complete within minutes and the TDI would not have been tested. To determine if the positive results seen in in vitro genotoxicity assays when TDI was dissolved in DMSO was in fact a consequence of the chemical break down of TDI to TDA Seel et al (1999) undertook a series of mutagenic investigations using dry ethyleneglycol dimethylether (EGDE) as the organic solvent as investigations indicated TDI was stable in this solvent with 98 to 99% of original TDI remaining after 1 hour and more than 85% after 4 hours with no detectable formation of TDA. The studies with Salmonella typhimurium showed quite clearly the absence of any mutagenic response when TDI was dissolved in EGDE. Based on such evaluation the authors concluded that positive results seen in vitro genotoxicity studies undertaken using solvents such as DMSO must be treated with caution as such effects are very well be an artifact of the testing conditions caused by the breakdown of TDI to TDA which is known to produce mutations in Salmonella typhimurium. Based on these observations the use of results from in vitro tests in aqueous cell systems are problematic because of interaction with the test system components. These studies are considered to be invalid, and not useful for determining the genotoxic potential of TDI. For this reason mammalian cell gene mutation assays in vitro are not feasible and assessment relies on the in vivo studies.

A number of in vivo genotoxicity studies have been carried out with TDI. A slight increase in numbers of micronucleated erythrocytes was measured in a non-GLP micronucleus assay in rats exposed to TDI via inhalation (Owen, 1980, Loeser 1983). As the increase was not significant, occurred at only one dose level and because of the probably hyperthermia caused by the treatment the result was not considered to be biologically significant. Negative results were obtained with mice in the same study using similar exposures. Negative results have also been seen in a well conducted micronucleus assay in mice using inhalation route of exposure (Mackay, 1992) and an unscheduled DNA synthesis assay examining effects in liver and lungs in rats after acute and sub-acute inhalation exposures to TDI (Benford and Riley, 1988). Commercial grade TDI was also inactive in inducing sister chromatid exchanges and micronuclei in lung cells after intratracheal instillation in rats (Whong et al, 1991, cited in Zeiger 2005). Studies examining DNA adduct formation have produced mixed results and are inconclusive as to their relevance to human exposures.

Overall the data on genotoxicity show:

•Weight of scientific evidence supports the conclusion that TDI is not mutagenic or genotoxic

•As TDI is unstable in solvents such as DMSO and rapidly degrades to TDA results from the majority of in vitro genotoxicity test results are unsuitable for assessing the genotoxic potential of TDI.

•Inhalation of TDI does not induce micronuclei formation or DNA damage as measured by unscheduled DNA synthesis

•Supplemental investigations of DNA binding have proven inconclusive as data were, in the main, obtained with non-validated methodologies and the results are difficult to interpret

* Gahlmann R, Herbold A, Ruckes A, Seel K. Tests on the stability of aromatic diisocyanates in dimethylsulphoxide (DMSO): toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI) in the Ames test, Zbl Arbeitsmed 43 (1993), 34 -38.

Justification for classification or non classification

Not classified as mutagenic according to Directive 67/548/EEC and Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008).

5.8. Carcinogenicity

5.8.1. Non-human information

5.8.1.1. Carcinogenicity: oral

Animal data indicate that TDI may be carcinogenic. Oral exposure to TDI caused tumors at several different tissue sites in rats and mice. Administration of TDI by stomach tube caused liver tumors, benign mammary gland tumors and benign tumors of pancreas (NTP Report, 2011)

5.8.1.2. Carcinogenicity: inhalation

Experimental inhalation studies on rats and mice revealed no neoplsatic effects in both species (Owen 1980, 1984, 1986a, Loeser 1983a and Mueller 2008). The exposed animals showed only lesions involving the nose, nasal epithelial atrophy and inflammation of the nasal mucosa (mice and rats) and in mice lesions in the lower airways (interstitial pneumonia, bronchitis and inflammation of the bronchi). The observed changes depended on the concentration of TDI.

5.8.1.3. Carcinogenicity: dermal

Relevant information is not available.

5.8.1.4. Carcinogenicity: other routes

Relevant information is not available.

5.8.2. Human information

There is no epidemiological data on carcinogenic potential of TDI for human. Sorahan and Nichols (2002) and Collins (2009) have not confirmed the link between isocyanate exposure and risk of lung cancer.

5.8.3. Summary and discussion of carcinogenicity

Discussion

TDI administered by gavage induced a dose-related increase in the incidence of subcutaneous fibromas and fibrosarcomas (combined) in male rats, together with an increase in the incidence of pancreatic acinar-cell adenomas in male rats and of pancreatic islet-cell adenomas, neoplastic nodules of the liver and mammary gland fibroadenomas in female rats. In female mice, dose-related increases in the combined incidence of haemangiomas and haemangiosarcomas and of hepatocellular adenomas were observed after gavage administration.
No treatment-related tumour was observed after exposure of mice or rats to commercial toluene diisocyanates by inhalation, although the results of the study with rats have not been reported fully (IARC, 1986).

The most relevant assessment of carcinogenicity in animals comes from a 2-year chronic inhalation toxicity and carcinogenicity study with TDI in rats and mice (Owen, 1980 + 1986; Loeser, 1983). The animals were whole body exposed to 0, 0.05 and 0.15 ppm of TDI (80/20) vapour for 6 hours/day, 5 days/week. No evidence of any

increase in treatment-related tumors in either species was observed. An MTD was achieved in rats and mice as characterized by decreased body weights and moderate to severe rhinitis. Therefore, the NOAEC for carcinogenicity after long-term inhalation of TDI vapour is 0.15 ppm (1.086 mg/m3) for both species.

In contrast, an increase in the number of tumors in various organs was observed in rats and mice after oral long-term administration of TDI over 2 years (NTP, 1986; Dieter et al., 1990). Doses of 0, 30 and 60 mg/kg bw/day (male rats), 0, 60 and 120 mg/kg bw/day (female rats and mice) or 0, 120 and 240 mg/kg bw/day (male mice) were applied. In rats increased tumor incidences were seen in subcutaneous tissue and in the pancreas (both sexes). In addition, female rats showed nodular changes in the liver and mammary gland tumors. In female mice the incidences of hemangiomas, hemangiosarcomas and adenomas of the liver were increased. No increased incidence of compound-related tumors was observed in the male mouse.

The results of the studies using oral administration are compromised by severe deficiencies in test substance handling that led to the fact that the sample administered also contained other unidentified breakdown and reaction products of TDI, possibly including TDA. Hydrolysis of TDI to form the genotoxic and animal carcinogen TDA is the most plausible explanation for the observed tumors following oral administration of TDI. Therefore, these studies are considered "invalid" by Klimisch criteria. In addition the addition of TDI directly into the acidic environment of the stomach, bypassing the oral cavity, is an unrealistic exposure scenario which leads to generation of the diamine which would not occur in normal handling and use.

In people no association between the risk of cancer and occupational exposure to isocyanates has been found.

Overall Assessment:

1. Valid animal inhalation studies showed no carcinogenic effect from TDI exposure.

2. An oral chronic exposure study with TDI is considered invalid due to mishandling of test material and the inappropriate exposure route.

3. Human studies show no evidence of carcinogenic hazard. (see 7.10.2, summary in 7.10.2a, Collins 2009)

4. Based on these evidence there is a strong case that TDI should not be classified as a carcinogen.

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

Inhalation exposure is the most appropriate route for assessing occupational risk in humans. Effects from chronic exposure of animals to TDI are limited to effects on the respiratory tract caused by local irritation, no signs of tumor formation or systemic toxicity were observed.

The oral and dermal route of exposure are not relevant for assessment (see repeated dose toxicity).

Value used for CSA (route: inhalation):

NOAEC: 1.086 mg/m³

Justification for classification or non classification

Official EU classification according to Directive 67/548/EEC is Carc Cat 3; R40. Limited evidence of a carcinogenic effect, and by EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008), Carc.2. Suspected of causing cancer.

5.9. Toxicity for reproduction

5.9.1. Effects on fertility

5.9.1.1. Non-human information

The results of two-generation study performed according to OECD Guideline 416 indicate no impact on fertility (Tyl and Neeper-Bradley 1989).

5.9.1.2. Human information

No relevant human information is available.

5.9.2. Developmental toxicity

5.9.2.1. Non-human information

Following inhalation exposure TDI caused increased incidence of poorly ossified cervical centrum 5 (Tyl 1988).

5.9.2.2. Human information

No relevant human information is available.

5.9.3. Summary and discussion of reproductive toxicity

Effects on fertility

The toxicity on fertility of TDI was investigated in a two generation study in rats (Tyl et al. 1989). The study was performed in accordance to the OECD 416 guildeline under GLP. Vapor atmospheres of 0.02, 0.08 or0.3 ppm did not effect any of the reproduction parameters which were evaluated. The only signs of toxicity were transient irritations of the upper respiratory tract. Therefore, under the conditions of this study, there was no evidence of effects on reproduction at the highest exposures tested which was 0.3ppm.

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

No effects on fertility in a 2-Gen study. (OECD-guideline 416, GLP).

Developmental toxicity

Developmental toxicity of TDI was investigated by exposing mated female rats to TDI vapors of 0.02, 0.1, 0.5 ppm (Tyl et al., 1988). The study was performed in accordance to the OECD guildeline 414 under GLP.
No embryotoxicity or teratogenicity was observed at any exposure concentration employed. Exposure to toluene diisocyanate vapour by inhalation during organogenesis in rats resulted primary in irritation of the respiratory tract at the highest tested dose level (0.5 ppm). Most likely secondary to this irritation maternal toxicity and minimal fetotoxicity were observed (decreased food consumtion and bw).

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

No effects on development in a developmental toxicity study. (OECD-guideline 414, GLP).

Justification for classification or non classification

Not classified as toxic to reproduction according to Directive 67/548/EEC and Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008.

5.10. Other effects

5.10.1. Non-human information

No relevant human information is available.

5.10.1.1. Neurotoxicity

No relevant human information is available.

5.10.1.2. Immunotoxicity

No relevant human information is available.

5.10.1.3. Specific investigations: other studies

No information is available

5.10.2. Human information

No information is available

5.10.3. Summary and discussion of other effects

5.11. Derivation of DNEL(s) and other hazard conclusions

5.11.1. Overview of typical dose descriptors for all endpoints

Acute toxicity oral (rats, mice): LD50 > 2000 mg/kg
Acute toxicity dermal (rabbits): LD50 > 2000 mg/kg
Acute toxicity inhalation (rats): LC50 = 0.48 mg/l
Irritation /Corrosivity-skin: irritating
Irritation /Corrosivity-eye: irritating
Irritation /Corrosivity-respiratory tract: irritating
Sensitisation skin: sensitising
Sensitisation respiratory tract: sensitising
Repeated dose toxicity: sub-acute / sub-chronic / chronic-inhalation: LOAEC: 0.362 mg/m^3 Target organs: respiratory: nose
Carcinogenicity inhalation: NOAEC: 1.086 mg/ m^3

5.11.2. Selection of the DNEL(s) or other hazard conclusion for critical health effects

Table 9. Hazard conclusions for workers

Route	Type of effect	Hazard conclusion	Most sensitive endpoint
Inhalation	Systemic effects - Long-term	DNEL (Derived No Effect Level): 0.035 mg/m³	irritation (respiratory tract)
Inhalation	Systemic effects - Acute	DNEL (Derived No Effect Level): 0.14 mg/m³	irritation (respiratory tract)
Inhalation	Local effects - Long-term	DNEL (Derived No Effect Level): 0.035 mg/m³	irritation (respiratory tract)
Inhalation	Local effects - Acute	DNEL (Derived No Effect Level): 0.14 mg/m³	irritation (respiratory tract)

Discussion

Inhalation exposure is the most relevant route for assessing occupational risk in humans. Effects from repeated exposure of animals to TDI are limited to effects on the respiratory tract caused by local irritation. In a 2-year chronic toxicity and carcinogenicity study with vapour exposure of 2,4/2,6-TDI (80:20) to rats and mice a LOAEC of 0.36 mg/m3 (0.05 ppm) was determined for both species based on histopathological effects in the upper and lower respiratory tract (Owen, 1980 + 1986; Loeser, 1983). Neither indications of systemic toxicity nor evidence of a carcinogenic potential were found in rats and mice. Tests assessing the mutagenic potential of TDI in vitro and in vivo provide no convincing or consistent evidence of mutagenic or genotoxic activity.

According to the ECHA Guidance on information requirements and chemical safety assessment - chapter R.8 (May 2008) a national occupational exposure limit (OEL) was used as a surrogate for a DNEL. The German Committee on Hazardous Substances (Ausschuss für Gefahrstoffe - AGS) derived an OEL (Arbeitsplatzgrenzwert - AGW) for 2,4- and 2,6 -TDI which were substantiated in respective criteria documents (published in German on the website of the Federal Institute for Occupational Safety and Health (BAuA) - www. baua. de). According to the German Hazardous Substances Ordinance (Gefahrstoffverordnung) an AGW is a time-weighted average concentration in the workplace air, referring to a given period of time. The AGW states the concentration of a substance below which acute or chronic adverse health effects are generally not

expected. AGWs are thus based exclusively on available occupational medical experience and toxicological findings.

For 2,4- and 2,6-TDI the AGS established an OEL of 0.035 mg/m3 (0.005 ppm) referring to an 8-hour exposure period. This OEL is used as a surrogate DNEL for long-term exposure. A ceiling limit value of 0.14 mg/m3 (0.02 ppm) was given for both isomers. This ceiling limit is used as a surrogate DNEL for short-term exposure. The justification of the OELs was based on an TDI evaluation of the German MAK Commission (DFG, 1999) * and published in criteria documents for 2,4- and 2,6-TDI (issue: January 2006) with the following statements:

From an occupational-medical point of view, the most important effects of TDI are those on the respiratory tract. The local irritant effects can cause symptoms to the eyes and airways. High concentrations cause a reduction in the respiration rate and dyspnea. TDI is a respiratory sensitizer and can cause isocyanate asthma in the form of an obstructive respiratory disease, and unspecific bronchial hyperreactivity and, in rare cases, allergic alveolitis. Unlike its oral and dermal toxicity, the acute inhalation toxicity of TDI is high. Repeated long-term exposure to TDI may cause deterioration of lung function. Also in animal experiments damage in the upper and lower airways was observed after repeated inhalation (DFG, 1999). Bronchial asthma is a known syndrome, triggered by diisocyanates like TDI. The induction of sensitization depends on the concentration/dose and the individual (Diller, 1990). No DNEL for respiratory sensitization is calculated as there is no validated method. Human experience shows clearly that if the exposure concentrations of TDI are kept below 0.01 to 0.02 ppm, generally no new cases of TDI asthma are observed (Porter et al., 1975; Karol 1981; Olsen et al., 1989). The impairment of lung function by long-term exposure to TDI has been investigated in several studies. It can be deduced from these data that with observance of an 8-hour average value at the workplace of 0.005 ppm and limitation of exposure peaks to 0.02 ppm no significant deterioration in lung function is to be expected (DFG, 1999). Since the OEL for TDI was based on human data no additional assessment factors are required. Interindividual variability was taken into account by a large number of TDI exposed workers.

The German OELs for 2,4- and 2,6-TDI are in agreement with the threshold limit values (TLV-TWA: 0.036 mg/m3; TLV-STEL: 0.14 mg/m3) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2004). A plausibility check of the above mentioned national OELs revealed that the DNELs derived from animal data using assessment factors according to ECHA Guidance R.8 are in the same order of magnitude.

For TDI no repeated dose dermal toxicity studies are available. Skin penetration of TDI is considered to be low. Administration of 2,4 -TDI to the skin of rats for 8 hours resulted in less than 1 % of the applied dose reaching the systemic circulation (Fabian and Landsiedel, 2008). As mentioned above exposure to TDI via the air does not lead to systemic toxicity, therefore taking into consideration the low dermal penetration, systemic toxicity is covered by the respective DNELs for inhalation exposure and a DNEL for systemic toxicity (short-term and long-term) after dermal contact is not required. Regarding local effects the irritation potential (strongly irritative to corrosive) as well as the sensitization potential needs to be considered in the selection of the respective risk management tools at the workplaces.

No DNEL for skin sensitization is calculated as the relationship between skin dose and response is not clear. There is no validated method of DNEL calculation for skin sensitization. According to the potency categorisation approach TDI is classified as a moderate to strong skin sensitizer (Category 1) based on a guinea pig maximization test (GPMT: 5 % induction conc., ≥ 47 % incidence of sensitization; Duprat et al., 1976) and a Buehler test (5 % induction conc., 90 % incidence of sensitization; Zissu et al., 1998), respectively.

The results of a local lymph node assay with TDI (LLNA: calculated EC3 value of 0.02 %; Hilton et al., 1995) were not considered for the potency categorisation on skin sensitization since this testis also sensitive against respiratory sensitizers(De Jong et al., 2009) **anddoes not allow differentiation of antigen-specific immune responses from non-specific inflammatory reactions (McGarry, 2007) ***.
For strong skin irritants like TDI the test may therefore be false positive (Independent Scientific Peer Review Panel Report, ICCVAM, 2008) ****. or overpredictive, as shown by pretreatment with SDS (van Och, 2000).

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

Details:

The following DNELs / DMELs were not derived:

- Dermal exposure: Strong skin irritation is the leading acute effect of dermal exposure to TDI. No signs of systemic toxicity were observed in irritation studies and in systemic oral/inhalation studies. Given the low bioavailability of TDI via the skin (Fabian & Landsiedel, 2007), the derivation of DNELs for dermal exposure would therefore be misleading. In accordance to the ECHA Guidance on information requirements and chemical safety assessment - chapter R.8 (May 2008) a qualitative approach was applied or the assessment and control of risks due to skin irritation and sensitization (see above).

- Oral exposure: In principle ingestion is not an anticipated route of exposure in an industrial setting, since general workplace hygiene yield to avoid any oral ingestion. Particularly for TDI the low occupational exposure limits applied prohibit from any oral ingestion at the workplace. Accidental contamination from traces is furthermore unlikely, since TDI is highly reactive against traces of water (t 1/2 < 1 h) and therefore would result in rapid polymerisation.

- Systemic effects – inhalation exposure: From an occupational-medical point of view, local irritation to the eyes and upper airways are the most important effects of TDI (DFG, 1999) *. Following single or repeated inhalation exposure/s to irritating concentrations of TDI, neither from human experience nor in animal studies, signs of systemic toxicity were reported. In this context, protection from irritation is protecting from any kind of potential systemic toxicity.

Acute/short-term exposure – systemic effects – dermal DNEL

Not quantifiable; see above

Acute/short-term exposure – systemic effects – inhalation DNEL

Not quantifiable; see above

Acute/short-term exposure – local effects – dermal DNEL

Not quantifiable; see above

Acute/short-term exposure – local effects – inhalation DNEL

MAK-ceiling limit value 0.14mg/m3 (for details see rational)

Long-term exposure – systemic effects – dermal DNEL

Not quantifiable; see above

Long-term exposure – systemic effects – inhalation DNEL

Not quantifiable; see above

Long-term exposure – local effects – dermal DNEL

Not quantifiable; see above

Long-term exposure – local effects – inhalation DNEL

MAK-value 0.035 mg/kg bw(for details see rational)
* Greim H (2003) Toluene diisocyanate. In: Occupational Toxicants: Critical Data Evaluation for MAK Values and Classification of Carcinogens, Vol.20, 291 -338, Wiley-VCH. (ISBN: 3 -527 -27797 -8).
**De Jong WH, Arts JHE, De Klerk A, Schijf MA, Ezendam J, Kuper CF, Van Loveren H (2009): Contact and respiratory sensitizers can be identified by cytokine profiles following inhalation exposure, Toxicology 261: 103 -111
***McGarry HF (2007): The murine local lymph node assay: Regulatory and potency considerations under REACh. Toxicology 238: 71 -89
****http: //iccvam. niehs. nih. gov/docs/immunotox_docs/LLNAPRPRept2008. pdf

Consumer exposure to 2,4- and 2,6 -TDI is as yet unidentified.

6. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICOCHEMICAL PROPERTIES

6.1. Explosivity

TDI was shown to have no explosive properties (Fisk and Langner 1995a, b).

Classification according to GHS

Name: m-tolylidene diisocyanate

Reason for no classification: conclusive but not sufficient for classification

Classification according to DSD / DPD

6.2. Flammability

TDI was shown to have no explosive properties (ReachCentrum 2010).

Flammability

Based on the structural properties of the substance and the experience in handling, no pyrophoricity is expected. The substance does not liberate flammable gases on contact with water. The flammability is deducted from the flash- and boiling point.

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

Non flammable. Based on the structural properties of the substance and the experience in handling, no pyrophoricity is expected. The substance does not liberate flammable gases on contact with water.

Flash point

The value of 128°C should be used for the CSA as a worst case approach.

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

The 80:20 mixture (2,4-TDI: 2,6-TDI) shows a flash point of 132°C, the 65:35 mixture has a flash point of 128°C.

Classification according to GHS

Name: m-tolylidene diisocyanate

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

6.3. Oxidising potential

In accordance with column 2 of REACH Annex VII the oxidising properties study required in Section 7.13 need not be conducted if the substance is incapable of reacting exothermically with combustible materials on the basis of chemical structure.
The following information is taken into account for any hazard / risk assessment:
not applicable

Classification according to GHS

Name: m-tolylidene diisocyanate

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

7. ENVIRONMENTAL HAZARD ASSESSMENT

7.1. Aquatic compartment (including sediment)

PNECaqua (freshwater)

Given the reactivity of TDI with water it is probably more suitable to use data obtained from only acute toxicity studies to derive a PNECaqua value.

For Klimisch 2 studies only, the following test results were used for the PNECaqua value.

Fish (Tadokoro et al, 1997): 96h LC50 133mg/l

Daphnia (Tadokoro et al, 1997): 48h EC50 12.5mg/L

Algae (Tadokoro et al, 1997): 96h EC50 3230mg/l

A PNECaqua (freshwater) of 0.0125 mg/l may be derived using the EC50 of 12.5mg/l, obtained with the most sensitive species, and an assessment factor of 1000.

PNECaqua (marine water)

As daphnia are the most sensitive species the EC50 of 12.5 mg/l may be used to derive the PNECaqua (marine water).

7.1.1. Fish

7.1.1.1. Short-term toxicity to fish

Several tests assessing the acute toxicity of TDI in fish are available (Tadokoro et al, 1997a, b, Caspers et al 1986, Rhone-Poulenc 1977). According to the key study by Tadokoro et al (1997a) the acute LC_{50} (96h) was 133 mg/L.

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

Key study: Tadokoro 1997 (1)-(3), all of comparable quality. The 24h pre-test mixing of TDI into culture medium by magnetic stirring seems to be an acceptable compromise between "static" addition on the requirements of the OECD guidance document on difficult substances in aquatic toxicity testing.

Discussion

Results obtained in the short-term studies indicate that TDI does have low toxicity to a variety of fish. None of the authors of the studies attempted the determination of TDI at the end of the test period and it is highly probable that TDI disappeared from the media soon after addition to the water and any measured toxic effects were due to the presence of hydrolysis products. It should be noted that when TDA was formed, and measured, in several of the above studies, levels of only 4-16mg/l were detected. These levels are at least ten times lower than the 96h LC50 values of TDA (219-1420 mg/l) for fish other than Pagrus major. Caspers et al (1986) reported a markedly increased toxicity to fish (Brachydanio rerio) when TDI was dispersed into the experimental medium by high speed shearing, going from a lowest LC100 value of 250mg/l to an LC100 of 40-50 mg/l. This effect could have been caused by an increased yield of TDA in the medium, however these data should be considered as irrelevant as such a dispersion method does not reflect situations which might occur in the environment.

Taking this into account, data generated by Tadokoro et al (1997) are regarded as most relevant for the assessment of the acute toxicity of TDI to fish.

Value used for CSA:

LC50 for freshwater fish: 133 mg/L

7.1.1.2. Long-term toxicity to fish

Data waiving

Information requirement: Long-term toxicity testing on fish

Reason: other justification

Justification: According to Annex IX of REACH Column 2 states that longer term testing shall be proposed if the chemical safety report according to Annex I indicates a need.

TDI is rapidly hydrolysed in aqueous solution with a half-life of under one minute. TDI is hydrophobic and poorly soluble in water and thus the heterogeneous reaction with water or soil is less rapid. The major product of such a reaction is insoluble polyurea. In the production of TDI the formation of insoluble polyurea would cause abrasion problems and blockage of valves and pipes and therefore releases of TDI to effluents are expected to be non-existent. Since production is performed in closed systems, releases to soil and sediment are also expected to be negligible (TDI producer's draft risk assessment report, December 2008, chapter 3.1.1). Furthermore, the EUSES (2.0) program has been used to calculate PEC values based on measured emission data provided by TDI producers and processors, including polyurethane producers (ibid., chapter 3.1.5.3).

Calculated PEC values were 1 x 10-9 mg/l for water, 5x10-10 mg/kg for sediment and ranged from 3.2 x 10-9 to 6.9 x 10-8 mg/kg for soils/grassland. The corresponding PEC/PNEC ratios would be extremely small and less than 1. Taking into account the scientific and exposure arguments, it appears appropriate to waiver the long-term fish/plant/soil and sediment toxicity studies.

Discussion

Many details concerning the experimental set-up are lacking and there was no analytical monitoring performed. The latter is important as it can not be excluded that the water contained an unrealistic high concentration of TDA, depending on the mode of "stirring" of TDI into the water.

The chronic toxicity of the TDI hydrolysis product, TDA, was established in an OECD 212 study (III ref 11453) with an LOAEC of 10 mg/L (behaviour: odd swimming) and a NOAEC of 3.16 mg/l. The results of Yakabe et al, 1999 (see section 5.1.2 Hydrolysis) indicate that the hydrolysis of 10mg TDI/l may lead to the formation of about 4mg TDA/l. Therefore, the findings with TDI may be attributable to TDA. However, water is a carefully avoided reactant to TDI and is carefully controlled in all processes of TDI production and use. Vigorous stirring of TDI into water has no practical relevance. As a result of this and due to the poor quality of the chronic fish study, the value generated for the chronic fish toxicity of TDI should not be used for the Chemical Safety Assessment.
In the short term studies of TDI it is noted repeatedly that it is in fact the degradation products (hydrolysis) whose toxicity is being measured in the bioassays. Toluene diisocyanates react with water to form polyureas, carbon dioxide gas, and small amounts of diaminotoluenes (TDA), depending on the amount of water present and physico-chemical conditions of releasing substance into water. The formation of toluene diamines (TDA) has taken place as a result of the hydrolysis of TDI in certain situations, primarily rapid dispersion at low release concentrations; other scenarios tended to lead overwhelmingly towards the formation of inert polyureas as opposed to TDA. Therefore the release concentrations of TDA depend on release scenario. It should also be noted that the scenarios which result in a significant, albeit low, concentration of TDA in the water column would occur under what would normally be considered unnaturally high dispersion/agitation, and therefore, are not likely to occur in nature.

The conclusion is that all results of the study on short-term toxicity to fish should be related to the TDA. Assuming, that conditions of OECD 203 test reflect those in the natural environment, as a worst case scenario at least to some extent, the results can be valid to the same degree. The chemical risk assessment should be performed for TDA. The results can be related to TDI only indirectly, as to a parent compound.

The result LC_{50} (96 h) 15400 mg/L for freshwater fish *Oncorhynchous mykiss* (Klimish 2) is accepted as reasonable for TDA.

For the same reason it appears appropriate to waiver the long-term fish toxicity studies. Besides, regarding the long-term toxicity study in fish, in terms of classification, TDA does not posses physical and chemical properties that trigger the necessity for classification as dangerous (according to Directive 67/548/EEC or Directive 1999/45/EC) or to be assessed as PBT or vPvB (according to Annex XIII of Regulation (EC) 1907/2006). Known value of lowest LC_{50} for *Daphnia* sp. is 12.5 mg/L, experimental BCF from 5 to 50, and

extensive biodegradation was found under various OECD test protocols. Therefore, and for reasons of animal welfare, long-term toxicity in fish is not provided.

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

According to Annex IX of REACH Column 2 states that longer term testing shall be proposed if the chemical safety report according to Annex I

indicates a need.

7.1.2. Aquatic invertebrates

7.1.2.1. Short-term toxicity to aquatic invertebrates

According to the study on *Daphnia magna* the acute EC_{50} is ranged between 12.5 mg/L (48h) – 750 mg/L (24h) (Tadokoro et al 1997a/ Caspers et al 1986, Rhone-Poulenc 1977). For marine invertebrate *Mysidopsis bahia (new name: Americamysis bahia)*EC_{50} is 18.3 mg/L.

Discussion

The short-term results show that TDI has low to moderate acute toxicity to freshwater and marine invertebrates. It is highly probable that TDI disappeared from the media soon after addition to water and it is likely that any measured toxic effects were due to the presence of hydrolysis products. In the above studies, where TDA was formed and measured, it should be noted that the concentration levels at the endpoint (5-10 mg/l) are similar to the 24h and 48h LC50 values reported for TDA with invertebrates. Due to the quality of the study and relevance of the organism, the EC50 value of 12.5 mg/L detected for Daphnia magna by Tadokoro et al (1997) is regarded as being the most relevant data point for assessing the acute toxicity of TDI against aquatic invertebrates.
Taking into consideration all explanations under the point 7.1.1.1. the result EC_{50} (48 h) 12.5 mg/L for freshwater invertebrates *Daphnia magna* (Klimish 2) and EC_{50} (48 h) 18.3 mg/L for marine water invertebrate *Mysidopsis bahia* (Klimish 2) are accepted as reasonable for TDA.

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

Acute toxicity against aquatic invertebrates Key study: Tadokoro 1997, daphnia magna (more frequently used than Mysidopsis bahia, better comparability with other chemicals).

Value used for CSA:

EC50/LC50 for freshwater invertebrates: 12.5 mg/L

EC50/LC50 for marine water invertebrates: 18.3 mg/L

7.1.2.2. Long-term toxicity to aquatic invertebrates

NOEC values for long-term toxicity to aquatic invertebrates (*Daphnia magna*) were 1.1 mg/L and >= 0.5 mg/L for static and semi-static test respectively. LOEC values were: 2.2 mg/L and >= 0.5 mg/L for static and semi-static test respectively (Cerbelaud et al 1997 and Caspers et al 1986).

Discussion

In the long-term studies the 21d NOEC values are quite low. It would appear that the result obtained with TDI (NOEC 1.1 mg/l) is probably due to the toxicity of TDA. The concentration of TDA was measured throughout the study and found to be 0.39 mg/l at the end point. This concentration is consistent with the 21d NOEC (reproduction) value of 0.282 mg/l found for TDA with Daphnia magna.
TDA does not posses physical and chemical properties that trigger the necessity for classification as dangerous (according to Directive 67/548/EEC or Directive 1999/45/EC or to be assessed as PBT or vPvB (according to Annex XIII of Regulation (EC) 1907/2006). Known value of lowest LC_{50} for *Daphnia* sp. is 12.5 mg/L, experimental BCF from 5 to 50, and extensive biodegradation was found under various OECD test protocols. Therefore, the long-term toxicity test to aquatic invertebrates can be waivered. However, the study has been accomplished: resulting NOEC (21 d) 1.1 mg/L for freshwater invertebrates *Daphnia magna* got Klimish 1 and is accepted as reasonable for TDA. It is therefore beneficial to use this value for PNEC calculation (Technical

Guidance Document for Preparing Chemical Safety Assessment, (2007) (Chapter R.10, Table R.10-4 for freshwater and R.10-5 for saltwater). Therefore, this value should be taken into account for the derivation of PNEC.

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

Chronic toxicity against aquatic invertebrates Key study: Cerbelaud 1997 because of GLP.

7.1.3. Algae and aquatic plants

In the growth inhibition test on algae EC_{50} (96h) was 3230 mg/L and 4300 mg/L for *Skeletonema costatum* and *Chlorella vulgaris* respectively.

Data waiving

Information requirement: Growth inhibition study with aquatic plants other than algae

Reason: other justification

Justification: Not required by REACH annexes.

Discussion

Effects on algae / cyanobacteria

The results indicate that TDI has low toxicity to freshwater and marine algae. As an indication of any potential indirect hazard due to TDA formation, the 72h EC_{50} (growth rate) for TDA vs Scenedesmus subspicatus was 126 mg/l.

Taking into consideration all explanations under the point 7.1.1.1. the result EC_{50} (96 h) 4300 mg/L for freshwater algae *Chlorella vulgaris* (Klimish 2) and EC_{50} (96 h) 3230 mg/L for marine water invertebrate *Skeletonema costatum* (Klimish 2) are accepted as reasonable for TDA.

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

The two key Tadokoro studies appear to be of similar quality. They provide 96h EC50 values of 4,300mg/l and 3,230mg/l for freshwater and marine water algae species respectively.

Value used for CSA:

EC50/LC50 for freshwater algae: 4300 mg/L

EC50/LC50 for marine water algae: 3230 mg/L

7.1.4. Toxicity to aquatic micro-organisms

In the activated sludge, respiration inhibition test EC_{50} (3h and 10d) was ~ 100 mg/L (Caspers et al 1986 and Fujiwara 1981b).

Discussion

The 3 hour EC50 value of >100 mg/l may be used to determine a PNECstp for TDI of >1 mg/l.

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

Key study: Caspers 1986, as it reflects OECD 209.

Value used for CSA:

EC50/LC50 for aquatic micro-organisms: 100 mg/L

7.1.5. Sediment organisms

Data waiving

Information requirement: Effects on sediment organisms

Reason: exposure considerations

Justification: According to Annex X, Column 2, states that longer term testing shall be proposed if the chemical safety report according to Annex I indicates a need.
TDI is rapidly hydrolysed in aqueous solution with a half-life of under one minute. TDI is hydrophobic and poorly soluble in water and thus the heterogeneous reaction with water or soil is less rapid. The major product of such a reaction is insoluble polyurea. In the production of TDI the formation of insoluble polyurea would cause abrasion problems and blockage of valves and pipes and therefore releases of TDI to effluents are expected to be non-existent. Since production is performed in closed systems, releases to soil and sediment are also expected to be negligible (TDI producer's draft risk assessment report, December 2008, chapter 3.1.1). Furthermore, the EUSES (2.0) program has been used to calculate PEC values based on measured emission data provided by TDI producers and processors, including polyurethane producers (ibid.,
chapter 3.1.5.3). Calculated PEC values were 1 x 10-9 mg/l for water, 5x10-10 mg/kg for sediment and ranged from 3.2 x 10-9 to 6.9 x 10-8 mg/kg for soils/grassland. The corresponding PEC/PNEC ratios would be extremely small and less than 1. Taking into account the scientific and exposure arguments, it appears appropriate to waiver the long-term fish/plant/soil and sediment toxicity studies.

TDA does not possess physical and chemical properties that trigger the necessity for classification as dangerous (according to Directive 67/548/EEC or Directive 1999/45/EC or to be assessed as PBT or vPvB (according to Annex XIII of Regulation (EC) 1907/2006), therefore the Chemical Safety Report does not indicate the need for chronic toxicity assessment. Therefore, the toxicity to sediment organisms can be waivered.

7.1.6. Other aquatic organisms

This information is not available

7.2. Terrestrial compartment

In the TNO 1992 studies, no toxic effect of TDI was observed on the terrestrial organisms (earthworms, lettuce and oats) tested. However, it must be noted that in the tests performed, TDI was in contact with water (in moist soils) and so it is likely that the concentrations of TDI actually bioavailable were much lower than the nominal concentrations (loadings). As with aquatic systems, any ecotoxicity is probably due to soluble reaction products. As an indication of the potential indirect hazard due to TDA formation, in parallel studies EC50 values for both Avena sativa and Lactuca sativa of between 320 and 1000 mg/kg dry weight soil (highest level tested) were found.

7.2.1. Toxicity to soil macro-organisms

The NOEC (14d) based on mortality/ weight increase for *Eisenia fetida* (annelids) was >= 1000 mg/kg soil dw (van der Hoeven et al 1992a).

Data waiving

Information requirement: Toxicity to terrestrial arthropods
Reason: exposure considerations
Justification: According to Annex X, Column 2, states that longer term testing shall be proposed if the chemical safety report according to Annex I indicates a need.
TDI is rapidly hydrolysed in aqueous solution with a half-life of under one minute. TDI is hydrophobic and poorly soluble in water and thus the heterogeneous reaction with water or soil is less rapid. The major product of such a reaction is insoluble polyurea. In the production of TDI the formation of insoluble polyurea would cause abrasion problems and blockage of valves and pipes and therefore releases of TDI to effluents are expected to be non-existent. Since production is performed in closed systems, releases to soil and sediment are also expected to be negligible (TDI producer's draft risk assessment report, December 2008, chapter 3.1.1).

Furthermore, the EUSES (2.0) program has been used to calculate PEC values based on measured emission data provided by TDI producers and processors, including polyurethane producers (chapter 3.1.5.3). Calculated PEC values were 1 x 10-9 mg/l for water, 5x10-10 mg/kg for sediment and ranged from 3.2 x 10-9 to 6.9 x 10-8 mg/kg for soils/grassland. The corresponding PEC/PNEC ratios would be extremely small and less than 1. Taking into account the scientific and exposure arguments, it appears appropriate to waiver the long-term fish/plant/soil and sediment toxicity studies.

Discussion of effects on soil macro-organisms except arthropods

In the TNO (1992) study, no toxic effect of TDI was observed on the soil macroorganism (*Eisenia fetida*). However, it must be noted that in the tests performed, TDI was in contact with water (in moist soils) and so it is likely that the concentrations of TDI actually bioavailable were much lower than the nominal concentrations (loadings). As with aquatic systems, any ecotoxicity is probably due to soluble reaction products.

Results from long-term tests are not available and therefore the LC_{50} value of >1000mg TDI/kg soil (d. w.), obtained in this study, should be used together with an assessment factor of 1000 in order to derive a PNEC value.

7.2.2. Toxicity to terrestrial plants

NOEC/ EC_{50} value (14 - 17d) based on seedling emergence/ growth/ survival in *Lactuca sativa* (Dicotyledonae) and *Avena sativa* (Monocotyledonae) was >= 1000 mg/kg soil dw.

Discussion

In the TNO (1992) study, no toxic effect of TDI was observed on the terrestrial plants Avena sativa and Lactuca sativa. However, it must be noted that in the tests performed, TDI was in contact with water (in moist soils) and so it is likely that the concentrations of TDI actually bioavailable were much lower than the nominal concentrations (loadings). As with aquatic systems, any ecotoxicity is probably due to soluble reaction products. As an indication of the potential indirect hazard due to TDA formation, in parallel studies EC_{50} values for both Avena sativa and Lactuca sativa of between 320 and 1000 mg/kg dry weight soil (highest level tested) were found.

Results from long-term tests are not available and therefore the LC_{50} value of >1000mg TDI/kg soil (d. w.), obtained in this study, should be used together with an assessment factor of 1000 in order to derive a PNEC value.

7.2.3. Toxicity to soil micro-organisms

Data waiving

Information requirement: Effects on soil micro-organisms
Reason: exposure considerations
Justification: According to Annex IX, text Column 2 states that effects on soil microorganisms need not be performed if there is no direct or indirect exposure to the substance.
TDI is rapidly hydrolysed in aqueous solution with a half-life of under one minute. TDI is hydrophobic and poorly soluble in water and thus the heterogeneous reaction with water or soil is less rapid. The major product of such a reaction is insoluble polyurea. In the production of TDI the formation of insoluble polyurea would cause abrasion problems and blockage of valves and pipes and therefore releases of TDI to effluents are expected to be non-existent. Since production is performed in closed systems, releases to soil and sediment are also expected to be negligible (TDI producer's draft risk assessment report, December 2008, chapter 3.1.1). Furthermore, the EUSES (2.0) program has been used to calculate PEC values based on measured emission data provided by TDI producers and processors, including polyurethane producers (ibid., chapter 3.1.5.3).
Calculated PEC values were 1 x 10-9 mg/l for water, 5x10-10 mg/kg for sediment and ranged from 3.2 x 10-9 to 6.9 x 10-8 mg/kg for soils/grassland. The corresponding PEC/PNEC ratios would be extremely small and less than 1. Taking into account the scientific and exposure arguments, it appears appropriate to waiver the long-term fish/plant/soil and sediment toxicity studies.

7.2.4. Toxicity to other terrestrial organisms

This information is not available

7.3. Atmospheric compartment

This information is not available

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

7.4.1. Toxicity to birds

Data waiving

Information requirement: Toxicity to birds

Reason: other justification

Justification: In accordance with column 2 of REACH Annex X, the study on birds does not need to be conducted as sufficient reliable data are available from the mammalian dataset.

Discussion

According to Annex X, Column 2 says that long term toxicity to birds needs to be considered in the balance of the existing mammalian data. Oral TDI to rats showed the LD50 to be in excess of 2,000 mg/kg body weight. Ingested TDI forms mainly inert polyureas. There is no reason to suppose that TDI will show high oral toxicity to birds.

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

There are no reliable data on effects of oral TDI to birds. Data from experimental animals show TDI to be of low oral toxicity (Section 7.2).

7.4.2. Toxicity to mammals

Data waiving

Information requirement: Effects on other above-ground organisms / mammals

Reason: other justification

Justification: Not required by REACH annexes.

7.5. PNEC derivation and other hazard conclusions

Table 10. Hazard assessment conclusion for the environment

Compartment	Hazard conclusion	Remarks/Justification
Freshwater	PNEC aqua (freshwater): 0.0125 mg/L	Assessment factor: 1000 Extrapolation method: assessment factor Given the reactivity of TDI with water it is probably more suitable to use data obtained from only acute toxicity studies to derive a PNECaqua value. Results from such studies indicate that daphnia are the most sensitive of the three trophic levels of the base-set (fish, daphnia and algae). A PNECaqua value of 0.0125 mg/l may be obtained from the 48h EC50 of 12.5 mg/l and an assessment factor of 1000.

Compartment	Hazard conclusion	Remarks/Justification
Marine water	PNEC aqua (marine water): 0.00125 mg/L	Assessment factor: 10000 Extrapolation method: assessment factor The hydrolytic behaviour of TDI in freshwater and marine water is very similar (Yakabe et al., 1999). Furthermore the toxicity of TDI to both freshwater and marine water organisms is expected to be similar. The PNECaqua (marine water) may therefore be derived from the same acute toxicity result of 12.5mg/l for freshwater.
Intermittent releases to water	PNEC aqua (intermittent releases): 0.125 mg/L	Assessment factor: 100 Data, obtained from only acute toxicity studies, are used to derive a PNECaqua(intermittent releases) value. Results from such studies indicate that daphnia are the most sensitive of the three trophic levels of the base-set (fish, daphnia and algae). A PNECaqua(intermittent releases) value of 0.125 mg/l may be obtained from the 48h EC50 of 12.5 mg/l and an assessment factor of 100.
Sediments (freshwater)		As TDI is a reactant with water, access of water to TDI and vice versa is strictly controlled. Furthermore, TDI polymerizes in the presence of water and thus exposure of TDI to sediment is highly likely to be negligible. Therefore a PNECsediment cannot be determined experimentally for TDI. Using the Equilibrium Partitioning Method does not appear appropriate given the hydrolytic instabilty of TDI.
Sediments (marine water)		
Sewage treatment plant	PNEC STP: 1 mg/L	Assessment factor: 100 Extrapolation method: assessment factor A PNECstp of >1 mg/l may be derived from the EC50 value of >100 mg/l and an assessment factor of 100.
Soil	PNEC soil: 1 mg/kg soil dw	Assessment factor: 1000 Extrapolation method: assessment factor A PNECsoil of >1 mg/kg soil (d.w.) may be derived from the lowest EC50 value of >1000 mg TDI/kg soil (d.w.) and an assessment factor of 1000.
Air		
Secondary poisoning		Data from experimental animals show TDI to be of low oral toxicity (Section 7.2).

Environmental classification justification

GHS Environmental Hazards

II Hazardous to the aquatic environment (acute) - Category 3: Harmful to aquatic life (Daphnia magna 48h EC50 = 12.5 mg/l)

II Hazardous to the aquatic environment (chronic) - Not classified (Daphnia magna 21d NOEL = 1.1mg/l)

EU

Official EU classification according to Directive 67/548/EEC and EU Classification, Labelling and Packaging of Substances and Mixtures (CLP) Regulation (EC) No. 1272/2008), is R52-53. Harmful to aquatic organisms

– may cause long term adverse effects in the aquatic environment.

8. PBT AND vPvB ASSESSMENT

8.1. Assessment of PBT/vPvB Properties

8.1.1. PBT/vPvB criteria and justification

8.1.2. Summary and overall conclusions on PBT or vPvB properties

Overall conclusion:

Based on experimental results, 2,4-TDI is identified as *not potential* PBT and *not* vPvB. Further testing in the scope of the final PBT assessment is not considered to be required.

8.1.2. PBT/vPvB criteria and justification

Under REACH substances fulfilling the PBT/vPvB criteria are Substances of Very High Concern (SVHC) and are subject to authorisation (Title VII of the REACH Regulation).
The PBT and vPvB assessment is one of the elements of a Chemical Safety Assessment (CSA). The objective of the PBT and vPvB assessment will be to determine if a substance fulfils the criteria for the identification of PBT and vPvB substances given in Annex XIII and if so, to characterise the potential emission of the substance.

A PBT/vPvB assessment basically consists of two subsequent steps, which shall be clearly identified as such in Part C of the Chemical Safety Report (Annex I, section 7):
Identification of PBT/vPvB substances, by comparison with the criteria
Evaluation of the sources and most important routes of emission to the marine ecosystem. In order to take to most effective measures to reduce the emission of PBT/vPvB substances to the marine environment (emission characterisation)

When a substance is identified being a PBT or vPvB, the CSA shall also consider an exposure assessment (Annex I, section 5) and a risk characterisation (Annex I, section 6)
The result of the PBT assessment shall also be summarised in the Safety Data Sheet (SDS) under heading 12.

Substances recognised as PBT or vPvB require the production of an Annex XV dossier to propose that the substance should be identified as a PBT or a vPvB substance. If agreed, the substance is then added to the pool of substances to be prioritised for inclusion in Annex XIV after which it will be subject to authorisation.

As a minimum the data specified in Annex VII should be available, i.e. data comprising:
1. Degradation (ready biodegradability and/or hydrolysis)
2. Bioaccumulation (octanol/water coefficient, log Kow), and
3. Toxicity (human and aquatic toxicity)

A PBT assessment is preferably based on experimental data on the substance for biodegradation, bioaccumulation and aquatic toxicity. The identification of fulfilment of the PBT/vPvB criteria is done in a stepwise approach, which is outlined below.

Persistence (P) criterion
As a first screening the substance is assessed to determine its ready and inherently biodegradability; when the substance is ready or inherently biodegradable the substance can be considered as non-persistent according to the Reach Guidance R.11 (2007) and as a consequence is neither a PBT nor a vPvB substance. When a substance does not fulfil the criteria for ready biodegradability it is considered as being *potentially* persistent.
When the substance also fulfils the criteria for B and T, further testing is needed. In order to be able to assess whether a substance is a PBT/vPvB substance, it is required that its degradability has been studied in a simulation test where half-life in water, sediment and/or soil is determined under environmentally relevant conditions. This half-life is then compared with the persistent criteria of Annex XIII (i.e. a substance fulfils the P(vP) criterion of $T_{1/2}$ >40 (60) days). Careful consideration will need to be given to the formation of stable degradation products. Degradation products >10% of the concentration of the parent substance should be identified.

Table 11. Criteria for the identification of P and vP

Type of data	Criterion	Screening assignment	Definitive assignment
Ready biodegradability	Yes No	P or vP	Not P
Inherently biodegradability	Yes No	P or vP	Not P
BIOWIN model	Not predicted ready biodegradable	P or vP	-
Biodegradability simulation tests:			
Half-life, marine water	> 60 d	-	P or vP
Half-life freshwater (incl. estuaries)	>40 d >60 d	-	P vP
Half-life, marine sediment	> 180 d	-	vP
Half-life freshwater sediment (incl.	> 120 d	-	P
estuaries)	> 180 d	-	vP

Results
A ready biodegradation test with TDI is not available. In an inherent biodegradation test (non-GLP, guideline OECD 302C), on the other hand, no biodegradation was found after 28 days based on oxygen consumption (Caspers, 1986).

However, in a hydrolysis study (non-GLP, no guideline followed) it was found that TDI mixed isomers is highly unstable in water. With loadings of 1,000 mg/l added to vigoursly stirred water, the half-life was about 0.7 hours. The product of hydrolysis of the isocyanate group is an amine, which itself reacts with another isocyanate group to yield a urea. This reaction of an amine with isocyanate is considerably faster than the reaction of water with the isocyanate (Yakabe, 1999). Other transformation products are therefore not assessed. Results indicate that 2,4-TDI, at low loadings, has a half-life time of <1 minute (at 20°C) when dispersed by vigourous agitation (Yakabe, 1999).

Table 12. Results of the hydrolysis study (Yakabe, 1999)

TDI (mg/l)	Half-life (h)	TDA yield (mg/l)
10	<0.5	4.3
100	<0.5	13
1000	ca. 0.7	16.1
10,000	ca. 1.6	27.5

Conclusion for the P criterion
The results from the inherently biodegradation test indicate that TDI is not biodegradable.

However, significant and substantial abiotic degradation by means of hydrolysis has been confirmed for both TDI substances. TDI is rapidly hydrolysed in aqueous solution, with a half-life of less than one minute (Yakabe, 1999). The hydrolysis transformation product (TDA) has been assessed. The half-life obtained for TDI is much lower than the P(vP) criterion of $t_{1/2}$ > 40 (60) days. Therefore, TDI is not considered to be persistent in the environment and is identified as *not potentially* P.

Bioaccumulation (B) criterion
A substance has a potential to bioaccumulate if it is readily accessible for uptake by organisms, and is only slowly metabolised or excreted. How bioaccumulating a substance is, is indicated by the bioaccumulation factor (BAF), which is obtained by relating the concentration in the organisms at equilibrium to the concentration in the surrounding environment and in food. BAF is often replaced in practice by bioconcentration factor (BCF), where the concentration in the organisms is only related to the concentration in the surrounding environment, which is experimentally easier to determine.
In principle, the assessment of the bioaccumulation in context of the PBT/vPvB assessment has to be based on measured bioconcentration factors in aquatic organisms; freshwater or marine. Table 13 lists the criteria for the identification of B and vB substances.

Table 13. Criteria for the identification of B and vB

Type of data	Criterion	Screening assignment	Definitive assignment
Bioaccumulative potential	Log KOW < 4.5	Not B	-
	Log KOW > 4.5	B	-
	Log KOW > 5.0	vB	-
Bioconcentration factor, BCF	> 2,000	-	B
	> 5,000	-	vB

When the B or vB criterion is fulfilled in combination with the P criterion one should assess whether the substance also fulfil the criteria for T. When the vB criterion is fulfilled in combination with the vP criterion the substance is classified as a vPvB substance and an Annex XV dossier has to be produced. Therewith an emission characterization shall be conducted compromising the relevant parts of exposure assessment as described in REACH, Annex I (Section 5). When the B criteria are not met, the substance is not categorised as a PBT substance and as a consequence an Annex XV dossier need not to be produced based on PBT or vPvB criteria.

Results

The log K_{OW} of TDI mixed isomers is 3.43, tested according to OECD 117 (Yakabe, 2000). The fact that only one sharp peak was observed in the chromatogram indicates that the two isomers present in the 80/20 TDI have very similar log Pow values.

Conclusion for the B criterion

In the absence of a measured BCF value TDI is classified as not potentially bioaccumulating based on the experimental log Kow of 3.43 and is therefore identified as *not potentially* B.

Toxicity (T) criterion

For persistent and bioaccumulative substances, long-term exposure can be anticipated and expected to cover the whole life-time of an organism and even multiple generations. The toxicity of a substance should, in principle, be assessed on the basis of chronic or long-term ecotoxicity data, ideally covering the reproductive stages. Table 14 lists the criteria for the identification of T substances.

Table 14. Criteria for the identification of T

Type of data	Criterion	Screening assignment	Definitive assignment
Chronic aquatic toxicity	NOEC < 0.01 mg/L	-	T
Chronic avian toxicity	NOEC < 30 mg/kg food	-	T
Mutagenicity	Mutagenic cat. 1 or 2	-	T
Reproductive toxicity	Toxic for reproduction cat. 1, 2 or 3	-	T
Repeated dose toxicity	Carcinogenic cat. 1 or 2	-	T
Evidence for chronic toxicity	Classifications: T, R48; Xn, R48 or R64 (Directive 67/548/EEC)	-	T
Acute aquatic toxicity	LC50 or EC50 > 0.1 mg/L LC50 or EC50 < 0.1 mg/L LC50 or EC50 < 0.01 mg/L	Poss. Not T T -	- - T

If the substance is classified as mutagenic (cat. 3), carcinogenic (cat. 3) or if there is substantiated evidence that the substance has other long-term adverse effects (e.g. endocrine disrupting effects), an assessment must be made on a case-by-case basis to decide whether the substance fulfils the T criterion.

Where data on chronic effects are lacking to assess whether a substance is a PBT substance, results from acute toxicity studies can be used to determine whether a substance is potentially toxic, provided that the screening criteria for P and B are fulfilled. Mammalian toxicity data must also be considered in the selection due to the fact that toxic effects on top predators, including man, may occur though long term exposure via the food-chain.

Where experimental data on chronic effects are lacking to assess whether a substance is a PBT substance, results from acute toxicity studies can be used to determine whether a substance is potentially toxic, provided that the screening criteria for P and B are fulfilled.

Results
The experimental data on acute or chronic toxicity for both TDI substances are summarised in Table 15 and 16, respectively. Information has been taken from the IUCLID5 files. The results from aquatic toxicity studies with TDI mixed isomers were taken as read-across to 2,4-TDI. The assessment of the T criterion is based on the $L(E)C_{50}$ values for acute toxicity and the NOECs for chronic toxicity. The lowest effect concentration in short-term toxicity studies is the 48-h EC50 of 12.5 mg/l in *Daphnia magna* (Tadokoro et al., 1997). The 21-d NOEC is 1.1 mg/l in *Daphnia magna* (Cerbelaud et al., 1997). No data is available for chronic toxicity to fish and algae.

Table 15. Acute toxicity to fish, invertebrates and algae

	Mixed isomers TDI
Fish 96-h LC50	133 mg/l in *Oncorhynchus mykiss*
Invertebrates 48-h EC50	12.5 mg/l in *Daphnia magna* 18.3 mg/l in *Mysidopsis bahia*
Algae 96-h EC50	3,230 mg/l in *Skeletonema costatum*

Table 16. Chronic toxicity to fish, invertebrates and algae

	Mixed isomers TDI
Fish	No data
Invertebrates 21-d NOEC	1.1 mg/l in *Daphnia magna*
Algae	No data

Conclusion for the T criterion
Both TDI substances are not classified as carcinogenic, mutagenic and reprotoxic according to Annex I of 67/548/EEC. Based on the effect concentrations determined in the aquatic toxicity tests with TDI, TDI does not fulfil the T criteria. The $L(E)C_{50}$ value for fish, Daphnia and algae are determined as > 0.1 mg/L and the NOEC value > 0.01 mg/l, therefore both TDI substances are indicated as not potentially T.

8.2. EMMISSION CHARACTERISATION

This section is not required for non PBT/vPvB substances.

9. EXPOSURE ASSESSMENT

9.0.1 Introduction and uses

Based on the uses reported in the document: "ISOPA communication in the supply chain on Aromatic Diisocyanates (MDI & TDI) & Polyols", the following Exposure Scenarios are taken into account by the registrant:

a. Section 9.1 Manufacturing of TDI
b. Section 9.2 Manufacturing of other substances
c. Section 9.3 Formulating, Repackaging & Distribution
d. Section 9.4 Flexible Foam: Industrial Use
e. Section 9.5. Coatings: Industrial & Professional use
f. Section 9.6 Adhesives & Sealants: Industrial & Professional Use
g. Section 9.7 Elastomers, TPU, Polyamide, Polyimide & Synthetic Fibres Industrial Use
h. Section 9.8 Other Composite Material: Industrial and Professional Use
i. Section 9.9 Overall exposure (combined for all relevant emission/release sources)

No Exposure Scenarios (ES) have been developed for the possible exposure to residual monomer due to the use of TDI-based polymers (in articles) by workers or consumers. When monomers have been used to produce polymers and the polymers are fully cured, the life cycle of the monomers has ended. A polymer made from TDI is considered fully cured when it is no longer sticky and warm when touched, when it has cured for 24 hours or more or when chemical analysis shows that there is less than 0.1% of monomer in the polymer. Any residual monomer is not a component of the polymer product (which is an article in itself), but a contamination.

Furthermore, the residual monomer levels in cured polymers made from TDI are very low (< 0.1%). By analogy to Article 14(2), which states that no ES need to be made for preparations containing < 0.1% of a substance, it was concluded that also no ES would need to be made for (possible exposure due to exposure to) articles containing < 0.1% of a substance.

Exposure due to the handling of not fully cured polymers has been accounted for in the ES for the production of the polymers.

The following information has been used for the exposure assessments:

Table 17. Relevant substance information used in the exposure assessment

Substance	*TDI mixed isomers*
CAS number	26471-62-5
EC-number	247-722-4
Molecular weight range	174.17
Physical state	Liquid
Melting point	9.5 °C
Boiling point	253 °C
(Relative) density	1.22 g/cm^3 at 20 °C
Vapour pressure at 20 °C	1.5 Pa
Partition coefficient at 22 °C	3.43
Water solubility at 25 °C	124 mg/l

9.0.2. Quantitative worker exposure assessment
9.0.2.1 Worker inhalation exposure

For the majority of PROCs, worker inhalation exposure estimates are based on occupational hygiene measured data. However, to facilitate the reading of this information , the condensed description of it is given below.

For the exposure assessment and risk characterization, described in chapter 9 and 10 of the CSR, the 90-percentile of the exposure distribution was used. For some uses further iteration, for instance prescribing the use of RPE, was needed, which was done based on the same key values. The table below depicts the key values without a correction for the use of RPE.

Table 18. Overall results of the tier 2 worker inhalation exposure assessment of TDI

PROC	*Description / industry sector*	*LEV*	*Inhalation key values (mg/m^3) 90-%ile*	*Source reference value used*
1	Manufacture general	Yes	0.0121	Value from PROC2 measured in formulating
2	Formulating	Yes	0.0121	Value from PROC2 measured in formulating
3	Closed molding	Yes	0.0300	Value from PROC 3 measured for closed molding
4	Open molding	Yes	0.0322	Value from PROC 4 open molding
5	Open mixing	Yes	0.4410	Read-across from CASE to Flexible foam
8b	Transfer	Yes	0.0192	Value from PROC 8b Open or Partially substance collection and transfer, e.g. as waste
9	Dedicated filling line	Yes	0.0148	Value from PROC 9 dedicated filling line
10	Rolling / brushing -small scale (up to 10 m^2)	Yes	0.0334	Value from PROC 10 rolling and brushing general
10	Rolling / brushing -large scale scale (> 500 m^2)	No[a)]	0.0349	Estimated values based on multi head space method and calculations using mixed room equations
14	Read-across from worst-case open molding to rebonding	Yes	0.9180	Value from PROC 14 open molding
15	Laboratory	Yes	0.0046	Value from PROC 15 laboratory work
21	Flexible foam -read-across from open molding	Yes	0.0397	Value from PROC21 PU article treatment

In the scope of the CSA for TDI, process categories (PROCs) were identified where not sufficient data for fulfilling the REACH guidance requirements for a statistical analysis of exposure (i. e. at least 6-12 data points per PROC, personal sampling) were available. The following way ahead was chosen:

1. If personal data are too limited in number, but additional stationary data are available, the latter are taken into account provided that they are generated by the same analytical method as the personal data, and if the location of sampling is representative for personal exposure (proven either by pictures of the workplace or statement of technician).
2. If the first approach is not viable, data gaps for a PROC are filled up by read across from PROCs which by definition are deemed to pose higher personal exposures.
3. If steps 1. and 2 are not viable, the Chemical Safety Report (CSR) shall state that there are not enough (or no) data points for the evaluation of personal worker inhalation exposure. For the time being, the risk characterization ratio (RCR) will be based on calculated exposure using ECETOC TRA V2. The following phrase is then included:

"Personal exposure data are not available, or do not fulfil the requirements of chapter R.14.4.4 of the Guidance on information requirements and chemical safety assessment. Therefore, the RCR is based on calculated exposure using ECETOC TRA V2. As all inhalation exposure models are slightly conservative in their exposure estimate l Risk Management Measures might be needed to demonstrate safe use that are more stringent than those applied in the actual workplace. In those cases we recommend the downstream user to perform their own occupational hygiene measurement to

demonstrate safe use of TDI or TDI containing mixtures. With submission of the dossier, the registrant is requested to inform the ECHA what RMMs are taken to improve the situation".

The measured data available for PROC 10, is considered relevant only for relatively small scale application. Therefore, these data were expanded with the results of experiments in a chamber test and calculations used to assess worst case TDI inhalation exposure in CASE applications at large scale use and to assess the relevant RMM needed.

For the following PROCs exposure estimates for inhalation exposure were made using ECETOC TRA v2:

PROC7, PROC 8a and PROC 13.

PROCs 1, 5 and 14 may be carried out at elevated temperatures in the range of 55 ºC to 110 ºC. This has been taken into account in the follwing manner:

- For PROCs 5 and 14 the elevated temperature, and therefore justification for safe use, are covered by the measured data used.
- For PROC 1 elevated temperatures are not covered by the measured data. Therefore calculations were with ECETOC TRA V2 using a high fugacity class. For PROC 1 ECETOC TRA V2 an inhalation exposure estimate of 0.01 ppm independent of fugacity class for industrial use. As ECETOC TRA v2 does not show an increase in inhalation exposure for PROC 1 at elevated temperatures, it is assumed that the use of worst case value from PROC 2 of 0.0121 mg/m^3 for PROC 1 at elevated temperatures is justified.

Short term worker inhalation exposure was assessed by multiplying the long term inhalation exposure with a factor two. This is in line with the defaults assumption in Reach Guidance R.16 and is therefore a default assumption and does not need to be clarified as ECHA knows this is a conservative assumption.

A brief set of general rules for use of the key values per PROC data for contributing scenarios in the ES is as follows:

- As much as possible specific data sets have been used for each combination of ES and contributing scenario (PROC)
- When no specific data set was available, where possible a more general data set for the PROC (irrespective of ES) was used
- When no data set was available for a PROC (e.g. for PROC1) a value was used from a PROC considered to be similar, but leading to more worst case emissions; in the case of PROC1 the general values from PROC2 were used.

The availability of measured data has determined the choice of operational conditions and risk management measures. Operational conditions and risk management measures at the situations covered by the measured data per contributing scenario have been reported in the ES. In some cases therefore risk management measures may have been mentioned that may not be fully necessary to achieve control of risk for TDI for the specific contributing scenario. This may also lead to a situation where more stringent risk management measures have been described for contributing scenarios with an expected lower emission of TDI.

General assumptions:

- The exposure estimates can be modified by additional risk management measures:
- Use of LEV (if estimates based on measurements without LEV): reduction by 90%
- Use of appropriate RPE: reduction by 90% (PROC 21) or a factor 1000 for organic vapour filters (PROCs 5, 7, 8a, 13 and 14). The reduction factor for TM 3 is based on the scientific paper of Dharmarajan et al, 1987.

Evaluation

Only occupational hygiene measured data are provided by the registrant in the CSR for inhalation exposure to TDI for PROC 2, 3, 4, 5, 8b, 9, 10, 14, 15 and 21, as the starting point (primary inhalation key value) for the Risk Assessment.

For PROC 1 measured data are not available but registrant applied a worst-case approach using inhalation exposure estimate per available measures data for PROC 2, because the activities under PROC2 are more worst case than the activities under PROC1.

For PROC 7, 8a, 13 exposure estimates for inhalation exposure were made using ECETOC TRA v2.

The measured data available for PROC 10, is considered relevant only for relatively small scale application. Therefore, these data were expanded with the results of experiments in a chamber test and calculations used to

assess worst case TDI inhalation exposure in CASE applications at large scale use and to assess the relevant RMM needed).

Registrant established following risk management measures.

For PROCs for which occupational hygiene measured data is available an efficiency of 90% is anticipated as a general assumption for LEV. When ECETOC TRA exposure estimates were applied as starting point (PROCs 7, 8a and 13) the LEV efficiencies implemented in ECETOC TRA were used.

Use of appropriate RPE: reduction by 90% - respirator confirming to EN140 with Type A-2 filter or better - (PROC 21); or a factor 1000 for organic vapour filters – full face respirator TM3 confirming to EN147 with type A-2 filter or better - (PROCs 5, 7, 8a, 13 and 14).

Conclusion

The measured data are well documented and plausible. Assumptions, calculations and estimations of inhalation exposure done by the registrant are appropriate.

9.0.2.2. Dermal exposure

Worker dermal exposure has been estimated by registrant using ECETOC TRA V2. In the calculations the following key assumption were used:

- The effect of protective gloves (90% reduction, default) was taken into account by multiplying the resulting value by 0.1. This effect was added to all estimates because the qualitative risk characterisation for skin sensitizers requires the use of protective gloves.
- The use of TDI in concentrations in products up to 100%. With the exception of PROC7 and PROC10 up to 60%, PROC14 in concentrations in products up to 85% and PROC21 up to 1%
- No short term dermal exposure was calculated as the substance is not classified for acute effects apart from local irritation.
- For dermal exposure the effect of LEV in ECETOC TRAv2 is not taken into account
- There will be no skin exposure to hot liquids, due to the direct severe burning of the skin at contact with hot liquids (> 70 °C)

Estimated intensity of exposure based on the quantitative exposure assessment in is expressed in mg/cm^2 by multiplying the dermal exposure estimates from the relevant contributing scenario with the body weight (70 kg) and dividing by skin area (potentially) exposed (820 cm^2; two hands).

Gloves considered as PPE by the registrant follow to default 90% (in ECETOC TRAv2) of effectiveness reduction of dermal exposure and are appropriate RMM.

Registrant applied appropriate assumptions for calculation of worker dermal exposure

9.0.3 Consumer exposure

Consumer exposure was not assessed as consumer use of TDI is not supported.

9.0.4 Environmental emission assessment using EUSES

Production and use volumes used in the environmental emission assessment were taken from the TDI producer's risk assessment: Environment (III, 2008). As the latest information from all producers was present for 2004, it is assumed that the expected volumes in 2009 can be calculated with an increase in volume every year from 2004 with 5%. This results in a TDI production of 480 kton and a pre-polymer production of 32 kton in 2009. The production of TDI and pre-polymers are added, since most production of pre-polymers takes place in TDI manufacturing sites with the same emission control systems. This results in a total production volume of 512 kton in 2009.

For the environmental emission assessment the substance properties of 2,4-TDI have been used.

9.0.5 Qualitative human exposure assessment

For the assessment of risks of hazards without a DNEL, for example skin and eye irritancy and skin sensitization, a qualitative exposure assessment is done. The qualitative exposure assessment is a two step process.

Both likelihood and/or frequency of exposure are assessed. When the likelihood/frequency is considered to be negligible or very low no further assessment of exposure is done. When the likelihood and/or frequency of exposure is considered to be more than very low the intensity of exposure is assessed, where possible using the quantitative exposure estimates.

Skin exposure

Likelihood/frequency of actual skin exposure of workers is assessed taking account of the use of protective gloves and suitable coveralls, which is assumed in general for TDI due to its sensitizing properties. The following relation between PROCs and likelihood/frequency of skin exposure are assumed if proper protective gloves and suitable coveralls are used:

- Very low likelihood/frequency of actual skin exposure: PROCs 1, 2, 3, 8b and 9 due to generally closed systems with limited potential of skin contact, PROC14 due to no or very limited manual handling, PROC 15 due to careful procedures in laboratories and PROC 21 due to TDI being bound in a matrix
- Low likelihood/frequency of actual skin exposure: all other PROCs

The use of proper protective gloves and suitable coveralls in all cases is assumed to lead to no more than low likelihood/frequency of actual skin exposure of the hands.

The intensity of actual local skin exposure is calculated from the dermal systemic exposure level as follows:

Intensity of actual local skin exposure (mg/cm^2) = intensity of dermal systemic exposure * 70 (body weight in kg) / skin area exposed (taken per PROC from ECETOC TRA in cm^2).

Ocular exposure

In conclusion:

- For PROCs 7 and 10 the use of suitable eye protection is in all cases prescribed.
- For other PROCs the use of goggles is prescribed when and where there is a likelihood of splashes, when the activities are done overhead or when workers need to be close to the source, e.g. for visual inspections.

Exposure to the eyes is assessed qualitatively, taking into account likelihood/frequency of exposure (between ‘very low’ and ‘high’) and intensity of exposure. Intensity of exposure is only taken into account when likelihood/frequency of exposure is considered to be more than ‘very low’.

For eye exposure two routes are important. Direct eye exposure occurs to substances in the air and indirect exposure via hand-eye contact. For both the likelihood/frequency is assessed. If the likelihood/frequency of eye exposure via a specific route is more than very low the intensity of eye exposure is also assessed.

It is assumed that eye exposure to vapour generally constitutes low intensity of exposure, unless vapour concentrations are high. Since vapour concentrations are low for TDI, eye exposure to vapour is low for all PROCs for TDI. Eye exposure to air including aerosols is considered to constitute at least medium intensity eye exposure if no specific RMM (such as goggles) are used. For the following PROCs, aerosol formation or splashing is considered to be likely: PROCs 7 and 10.

These PROCs are those for which in ECETOC TRA v2 even with very low vapour pressure the estimated exposure levels can be higher than 0.1 ppm, because of their emission processes. For these activities specific eye protection (e.g. goggles, full face masks or face shields), should always be used. For PROC10 (brushing and rolling), this requirement can be removed if the work is not done overhead and the distance between worker and activity is at least 1 meter.

For other PROCs the likelihood/frequency of aerosol formation and/or splashing is generally low. For these PROCs suitable eye protection only needs to be used if a specific situation exists in which eye exposure can be foreseen, e.g. when the specific characteristics of the task increase the likelihood of splashes, when the activities are done overhead or when workers need to be close to the source, e.g. for visual inspections.

If suitable eye protection is used the frequency/likelihood of eye exposure due to direct contact is very low. Likelihood/frequency of eye exposure due to hand-eye contact depends on the contamination of the hands and the likelihood/frequency of touching the eyes or the close proximity of the eyes with the hands. If protective

gloves are used, as is the case for TDI for all PROCs, the likelihood/frequency of contact of contaminated hands with the eyes is considered to be very low. Therefore, in all PROCs the likelihood/frequency of eye exposure due to hand-eye contact is considered to be very low.

9.0.6 Suitable skin and eye protection

Where necessary a reference is made to made to the use of suitable eye and skin protection.
Suitable personal breathing, eye and skin protection are:

Respiratory protection:
- Filter for organic gases with particle filter, at least A2P2 (EN 143 or 149)

Hand protection:
- Chemical resistant protective gloves (EN 374).
- Suitable materials also with prolonged, direct contact (recommended: protective index 6, corresponding > 480 minutes of permeation time according to EN 374):
    - nitrile rubber (NBR) - 0.4 mm coating thickness
    - butyl rubber (butyl) - 0.7 mm coating thickness
    - chloroprene rubber (CR) - 0.5 mm coating thickness.
    - Unsuitable materials:
    - polyvinylchloride (PVC) - 0.7 mm coating thickness

Eye protection:
- Safety glasses with side-shields (frame goggles) (e.g. EN 166)

9.0.7 Overall exposure (combined for all relevant emission/release sources)
9.0.7.1 Human health (combined for all exposure routes)

Combined exposure was not calculated over all scenarios.

9.0.8 Environmental emission assessment (combined for all emission/release routes)

It is not expected that a combination of emission sources would lead to an environmental risk as the risk characterisation ratios are far below one.

9.0.8.1 Environmental emission assessment - regional exposure concentrations
9.0.8.1.1 Environmental releases

The total regional release to the environment that is taken into account for the exposure estimation is listed in Table 19

Table 19. Summary of the releases to the environment

Compartments	Total release for regional exposure estimation (kg/d)	Justification
Waste water	70.1	EUSES calculation
Surface water	17.5	EUSES calculation
Air (direct + STP)	1,600	EUSES calculation
Soil (direct releases only)	0	Table R16.23 (Reach Guidance R.16, 2008)

9.0.8.1.2 Regional exposure concentrations in the environment

The regional Predicted Exposure Concentrations (PECs) in the environment are listed in Table 20.

Table 20. Regional concentrations in the environment

Compartments	*Predicted regional Exposure Concentrations*	*Measured regional exposure concentrations*	*Explanation / source of measured data*
Freshwater (mg/l)	$4.14x10^{-8}$		EUSES calculation
Marine water (mg/l)	$9.71x10^{-10}$		EUSES calculation
Agricultural soil (mg/kg)	$3.29x10^{-3}$		EUSES calculation
Natural soil (mg/kg)	$9.91x10^{-4}$		EUSES calculation
Industrial soil (mg/kg)	0.102		EUSES calculation
Air (mg/m^3)	$2.62x10^{-5}$		EUSES calculation

As TDI is a reactant with water, access of water to TDI and vice versa is strictly controlled. TDI rapidly hydrolyses when in contact with water (DT50 ranges from 0.5 to 30 min at ambient temperature [see Section 4]) and thus exposure of TDI to sediment is highly likely to be negligible. An exposure assessment for this compartment is therefore considered not to be relevant

9.0.8.1.3 Indirect exposure of humans via the environment (oral)

As TDI is a reactant with water, access of water to TDI and vice versa is strictly controlled. TDI rapidly hydrolyses when in contact with water (DT50 ranges from 0.5 to 30 min at ambient temperature [see Section 4]), forming high molecular weight, inert and insoluble polyureas, and therefore does not pose a risk to humans as a result of intake of food. A risk characterisation for this compartment is therefore considered not to be relevant.

10. RISK CHARACTERISATION RELATED TO COMBINED EXPOSURE

The risk characterisation of TDI has been conducted based on the PNECs and DNELs in the following tables. DNELs were not derived for the general population as consumer exposure to TDI mixed isomers is as yet unidentified.

Table 21. PNECs used in modeling

Compartments	PNEC
Freshwater (mg/l)	0.013
Marine water (mg/l)	$1.25x10^{-3}$
Freshwater sediment (mg/kg dw)	n.r.
Marine sediment (mg/kg dw)	n.r.
Soil (mg/kg dw)	> 1.0
STP (mg/l)	> 1.0

Table 22. DNELs for workers used in the risk assessment

Route	*DNEL*
Acute - systemic effects	
Dermal (mg/kg bw/day)	not quantifiable
Inhalation (mg/m^3)	0.14
Acute - local effects	
Dermal (mg/cm^2)	not quantifiable
Inhalation (mg/m^3)	0.14
Long-term - systemic effects	
Dermal (mg/kg bw/day)	not quantifiable
Inhalation (mg/m^3)	0.035
Long-term - local effects	
Dermal (mg/cm^2)	not quantifiable
Inhalation (mg/m^3)	0.035

10.1. Exposure Scenarios

10.1.1. Human health

10.1.1.1 Workers

A qualitative assessment of risk is done for hazards without DNEL.

Eye irritation

For risk of eye irritation the hazard is considered to be high since TDI is considered to be a severe eye irritant. The intensity of direct eye exposure is very low. The likelihood of exposure is at most very low due to the processes and the use of safety glasses. The risk for eye irritation is sufficiently controlled.

Skin irritation and skin sensitisation

The hazard of skin sensitisation is considered to be high, because TDI is a moderate to strong skin sensitizer. The likelihood/frequency of exposure is at most very low due to the processes and the use of protective gloves. It is considered that the risks of skin sensitisation are sufficiently controlled.

Inhalation exposure

For long and short-term exposure, RCR value are < 1. The risk resulting from inhalation exposure is sufficiently controlled.

10.1.1.2 Consumers

Not applicable

10.1.1.3 Indirect exposure of humans via the environment

As TDI is a reactant with water, access of water to TDI and vice versa is strictly controlled. TDI rapidly hydrolyses when in contact with water (DT50 ranges from 0.5 to 30 min at ambient temperature [see Section 4]), forming high molecular weight, inert and insoluble polyureas, and therefore does not pose a risk to humans as a result of intake of food. A risk characterisation for this compartment is therefore considered not to be relevant.

10.1.2 Environment

10.1.2.1 Aquatic compartment (including sediment)

A risk characterisation for aquatic compartment is controlled.

As TDI is a reactant with water, access of water to TDI and vice versa is strictly controlled. TDI rapidly hydrolyses when in contact with water (DT50 ranges from 0.5 to 30 min at ambient temperature [see Section 4]) and thus exposure of TDI to sediment is highly likely to be negligible. A risk characterisation for this compartment is therefore considered not to be relevant.

10.1.2.2. Terrestrial compartment

A risk characterisation for terrestrial compartment is controlled.

10.1.2.3. Atmospheric compartment

TDI has a low vapour pressure (2.1 Pa) in concordance with emissions of TDI to the atmosphere are also very low. Which is verified by the low calculated PEC for production of 0.0288 Lig/m^3. In the atmosphere TDI reacts with hydroxyl radicals and the calculated half-life is 2.55 days. It is not expected that TDI has an effect on global warming, ozone depletion in the stratosphere or ozone formation in the troposphere.

Furthermore, there are no indications or studies available that ambient air concentrations of TDI may cause direct adverse effects for plants or animal species. Because there are no tested data for the atmospheric compartment and the calculation of PNEC**atmospheric** is not possible, no quantitative characterization of risk as a PEC/PNEC comparison is possible. A risk characterisation for this compartment is therefore considered not to be relevant.

10.1.2.4 Microbiological activity in sewage treatment systems

Not relevant as no exposure to a sewage treatment plant is expected. The production of TDI is a dry process as TDI rapidly hydrolyses when in contact with water (DT_{50} ranges from 0.5 to 30 min at ambient temperature [see Section 4]). Therefore a risk characterisation is not necessary.

10.1.2.5 Exposure concentration relevant for the food chain (Secondary poisoning)

A risk characterisation through secondary poisoning is not necessary for TDI; because of its reactivity it has no potential to accumulate in living organisms, it is not classified as very toxic (T+), toxic (T) or harmful (Xn) via oral ingestion, according to mammalian toxicity data. Furthermore, as TDI rapidly hydrolyses when in contact with water (DT50 ranges from 0.5 to 30 min at ambient temperature [see Section 4]), secondary poisoning as a result of exposure via the environment is not anticipated for TDI itself. It is therefore anticipated to not pose a risk as a result of secondary poisoning via the aquatic food web.

Conclusion

Pursuant to Article 14(4a) of the REACH regulation, exposure assessment and risk characterisation is to be performed on the substance that fulfils the criteria for certain hazard classes or categories set out in Annex I of regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (the CLP regulation). General provisions for the assessment are laid down in Annex I of the REACH regulation.

Exposure to TDI at the workplace occurs mainly via inhalation of its vapours and/or via dermal contact with the liquid. Analysis of available data and all exposure scenarios submitted by registrant (see exposure information described in chapter 9) indicates that the risk associated with the use of TDI can be sufficiently controlled if appropriate risk management measures (RMM) are implemented and adequately communicated. With respect to the uses reported in the registration dossiers and the resulting exposures to TDI, quantitative risk characterisation was performed by comparing individually the inhalation exposure measured data and estimates for each exposure scenario (ES) with the respective inhalation DNELs (i.e., assessing initially the risk characterization ratios (RCR) inhalation pathway).

Specifically, the inhalation exposure estimates were compared to the long-term and short-term inhalation DNEL of 0.035 mg/m^3 and 0.14 mg/m^3, respectively.

For the worst-case activities like:

- mixing or blending in batch processes for formulation of preparations and articles (PROC 5),
- industrial spraying(PROC 7),
- transfer of substance or preparation (PROC 8a),
- treatment of articles by dipping and pouring (PROC 13)

risk can be sufficiently controlled only by wearing, as PPE, a full face respirator with reduction exposure factor 1000 durig handling of TDI,.

Worker dermal exposure has been estimated by registrant using ECETOC TRA V2.

Likelihood/frequency of actual skin exposure of workers is assessed taking into account the use of protective gloves and suitable coveralls, which is assumed in general for TDI due to its sensitizing properties. The following relation between PROCs and likelihood/frequency of skin exposure are assumed if proper protective gloves and suitable coveralls are used:

- very low likelihood/frequency of actual skin exposure: PROCs 1, 2, 3, 8b and 9 due to generally closed systems with limited potential of skin contact, PROC14 due to no or very limited manual handling, PROC 15 due to careful procedures in laboratories and PROC 21 due to TDI being bound in a matrix
- low likelihood/frequency of actual skin exposure: all other PROCs

The use of proper protective gloves and suitable coveralls in all cases is assumed to lead to no more than low likelihood/frequency of actual skin exposure of the hands.

The intensity of actual local skin exposure is calculated from the dermal systemic exposure level as follows:

Intensity of actual local skin exposure (mg/cm^2) = intensity of dermal systemic exposure * 70 (body weight in kg) / skin area exposed (taken per PROC from ECETOC TRA in cm^2).

The intensity of skin exposure is significantly low (0.2mg/cm^2). It is considered that the risk of skin sensitization is sufficiently controlled.

Production process of TDI is a dry process and TDI does not come into contact with water during production and based on above assumption the emission factor to waste water from production was set to 0. Therefore, predicted exposure concentrations (PEC) in sewage are 0.

PECs in aquatic and terrestrial compartment were estimated with EUSES tool for industrial and professional uses, separately. The comparison of PECs to the relevant PNECs leads to the conclusion that risk for the environment posed by TDI is controlled.

What is more, TDI hydrolyses rapidly in contact with water thus consequently exposure of sediment, sewage treatment plants to TDI is highly likely to be negligible.

REFERENCES

Abele L & Brochhagen F (1976). Reaction of TDI with water and with wet sand. Testing laboratory: Bayer AG. Report no.: III Report 10040. Owner company: International Isocyanate Institute. Study number: III project E-E-12. Report date: 1976-11-30.

Adams W.G.F. 1975. Long-term effects on the health of men engaged on the manufacture of toluene diisocyanate (TDI). Br. J. Ind. Med. 32, 72-78.

AGS (2006). Begründung zu 4-Methyl-m-phenylendiisocyanat in TRGS 900. Ausschuss für Gefahrstoffe, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA), Dortmund, Germany. Available from: http://www.baua.de/nn_5846/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/900/900-4-methyl-m-phenylendiisocyanat.pdf .

Arts, J. H., de Jong, W. H., van Triel, J. J., Schijf, M. A., de Klerk, A., van Loveren, H., and Kuper, C. F. (2008). The respiratory lymph node assay as a tool to study respiratory sensitizers. *Toxicol.Sci.*, 106, (2), Dec., 423-34.

Ban, M., Hettich, D., Goutet, M., and Bonnet, P. (1997). TDI inhalation in guinea-pigs involves migration of dendritic cells. *Toxicol.Lett.*, 93, 185-94.

Baur X (1995). Hypersensitivity pneumonitis (extrinsic allergic alveolitis) induced by isocyanates. J. Allergy Clin. Immunol. 95: 1004-10. Owner company: Research Institute for Occupational Medicine; (BGFA).

Becker KH, Bastian V & Klein T (1988). The reactions of OH radicals with TDI, TDA and MDA under simulated atmospheric conditions. J. Photochem. Photobiol. A 45: 195-205. Owner company: International Isocyanate Institute.

Benford DJ & Riley RA (1988). Mutagenicity study for the detection of unscheduled DNA synthesis ex-vivo in hepatocytes and lung following a single exposure of TDI to rats by inhalation. Testing laboratory: Bayer AG. Report no.: III Report 10547. Owner company: International Isocyanate Institute. Report date: 1988-12-09.

Bennett IP, Chart IS, Doe JE, Gore CW & Patton DSG (1980). Tolylene di-isocyanate three week inhalation toxicity in the rat. Testing laboratory: ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Report no.: III Report 10024. Owner company: International Isocyanate Institute. Study number: III project A7. Report date: 1980-02-02.

Bernstein DI & Jolly A (1999). Current diagnostic methods for diisocyanate induced occupational asthma. Am. J. Ind. Med. 36: 459-68. Owner company: International Isocyanate Institute. Study number: III project 142-AM-MTX.

Bernstein DI, Ott MG, Woolhiser M, Lummus Z & Graham C (2006). Evaluation of antibody binding to diisocyanate protein conjugates in a general population. Ann. Allergy Asthma Immunol. 97 Sept: 357-64. Owner company: International Isocyanate Institute. Study number: III project 233-AM-MTX.

Botham PA, Hext PM, Rattray NJ, Walsh ST & Woodcock DR (1988). Sensitisation of guinea pigs by inhalation exposure to low molecular weight chemicals. Toxicol. Lett. 41: 159-73. Testing laboratory: CTL. Owner company: Huntsman.

Brorson T, Skarping G & Sango C (1991). Biological monitoring of isocyanates and related amines. IV. 2,4- and 2,6-toluenediamine in hydrolysed plasma and urine after test-chamber exposure of humans to 2,4- and 2,6-toluene diisocyanate. Int. Arch. Occup. Environ. Health 63: 253-9.

CITI (1991). Summary report for the study on the fate of TDI in water. FE-E-63 project parts I, II and III. Testing laboratory: Chemicals Inspection and Testing Institute (CITI), Japan. Report no.: III Report 10912. Owner company: International Isocyanate Institute. Study number: III project FE-E-63. Report date: 1991-11-17.

Caspers N, Hamburger B, Kanne R & Klebert W (1986). Ecotoxicity of toluenediisocyanate (TDI), diphenylmethanediisocyanate (MDI), toluenediamine (TDA), and diphenylmethanediamine (MDA). Testing laboratory: Bayer AG. Report no.: III Report 10417. Owner company: International Isocyanate Institute. Study

number: III project E-CE-41. Report date: 1986-06-01.

Cerbelaud E, Saugues M, Cellier P & Argoud M (1997). Determination of the effect of TDI on the reproduction of Daphnia magna. Testing laboratory: Rhône-Poulenc Chimie. Report no.: III Report 11298. Owner company: International Isocyanate Institute. Study number: III project 152-EU-ENV. Report date: 1997-12-16.

Collins, M (2002). Toxicology of toluene diisocyanate. Appl. Occup. Environ. Hyg. 17, 846-855.

Collins, M (2009). An overview of the epidemiology on MDI and TDI. Owner company: International Isocyanate Institute. Report date: 2009-02-10.

Czuppon AB, Marczynski B & Baur X (1992). Detection of protein changes in serum of workers following inhalation exposure to toluene diisocyanate vapors. Toxicol. Ind. Health 8 (6): 407-13.

Diller WF (2002). Frequency and trends of occupational asthma due to toluene diisocyanate: a critical review. Appl. Occup. Environ. Hyg. 17 (12): 872-7. Owner company: Düsseldorf University.

Doe JE & Horspool GM (1980). Toluene diisocyanate: acute inhalation toxicity in the rat. Testing laboratory: ICI Central Toxicology Laboratory. Report no.: III Report 10142. Owner company: International Isocyanate Institute. Study number: III project E-A-7. Report date: 1980-02-02.

Fisk PR & Langner EJ (1995a). Tolylene-2,4/2,6-diisocyanate mixture (80:20-TDI): determination of physicochemical properties. Testing laboratory: Shell Research Ltd. Sittingbourne Research Centre. Report no.: III Report 11186. Owner company: International Isocyanate Institute. Study number: III project 111-EU-ENV. Report date: 1995-06-01.

Fisk PR & Langner EJ (1995b). Tolylene-2,4/2,6-diisocyanate mixture (65:35-TDI): determination of physicochemical properties. Testing laboratory: Shell Research Ltd. Sittingbourne Research Centre. Report no.: III Report 11221. Owner company: International Isocyanate Institute. Study number: III project 111-EU-ENV. Report date: 1995-11-01.

Fisk PR & Langner EJ (1995c). Tolylene-2,4/2,6-diisocyanate mixture (65:35-TDI): determination of physicochemical properties. Testing laboratory: Shell Research Ltd. Sittingbourne Research Centre. Report no.: III Report 11221. Owner company: International Isocyanate Institute. Study number: III project 111-EU-ENV. Report date: 1995-11-01.

Fisk PR & Langner EJ (1995d). Tolylene-2,4/2,6-diisocyanate mixture (80:20-TDI): determination of physiochemical properties. Testing laboratory: Shell Research Ltd. Sittingbourne Research Centre. Report no.: III Report 11186. Owner company: International Isocyanate Institute. Study number: III project 111-EU-ENV. Report date: 1995-06-01.

Fujiwara K (1980). Aquatic life study, Phase II, Step 1: biodegradation of TDI and MDI in the model river and marine water. Testing laboratory: Institute of Community Medicine, University of Tsukuba, Japan. Report no.: III Report 10234. Owner company: International Isocyanate Institute. Study number: III project FE-E-19-2-1. Report date: 1980-01-31.

Fujiwara K (1981a). Aquatic life study Phase II, Step 2. Accumulation of TDI, MDI, TDA and MDA in fish and their toxicity. Testing laboratory: Institute of Community Medicine, University of Tsukuba, Japan. Report no.: III Report 10019. Owner company: International Isocyanate Institute. Study number: III project FE-E-19-II-2. Report date: 1981-08-15.

Fujiwara K (1981b). Aquatic life study, Phase II, Step 2: accumulation of TDI, MDI, TDA and MDA in fish and their toxicity. Testing laboratory: University of Tsukuba, Japan. Report no.: III Report 10019. Owner company: International Isocyanate Institute. Study number: III project FE-E-19-II-2. Report date: 1981-08-15.

Gamer AO (2007). 2,4-TDI and 2,6-TDI dermal tolerance pilot study in rats. Testing laboratory: BASF Aktiengesellschaft, Experimental Toxicology and Ecology, D-67056 Ludwigshafen, Germany. Report no.: III Report 11532. Owner company: International Isocyanate Institute. Study number: III project 259-EU-MTX. Report date: 2007-01-29.

Greim H (2003). Toluene diisocyanate. In: Occupational Toxicants: Critical Data Evaluation for MAK Values and Classification of Carcinogens, Vol.20, 291-338, Wiley-VCH. (ISBN: 3-527-27797-8).

Heederik D., Henneberger P.K., Redlich C.A. Primary prevention: exposure reduction, skin exposure and respiratory protection. 2012. Eur. Resp. Rev. 21:124, 112-124.

Henck JW, Kociba RJ, Keyes DG & McKenna MJ (1976). A 30-day repeated inhalation toxicity study of TDI in laboratory animals. Testing laboratory: Dow Chemical Company. Report no.: III Report 10153. Owner company: International Isocyanate Institute. Study number: III project A-A-5. Report date: 1976-02-25.

Henck JW, Kociba RJ, Keyes DG & McKenna MJ (1976a). A 30-day repeated inhalation toxicity study of toluene diisocyanate (TDI) in laboratory animals. Testing laboratory: Dow Chemical Company. Report no.: III Report 10153. Owner company: International Isocyanate Institute. Report date: 1976-02-25.

Henck JW, Kociba RJ, Keyes DG & McKenna MJ (1976b). A 30-day repeated inhalation toxicity study of toluene diisocyanate (TDI) in laboratory animals. Testing laboratory: Dow Chemical Company, Midland, Michigan 48640, USA. Report no.: III Report 10153. Owner company: International Isocyanate Institute. Study number: III project A-A-5. Report date: 1976-02-25.

Henschler D., Assmann W., Meyer K.O. 1962. Toxicology of toluene diisocyanate. Arch. Toxicol. 19, 364-387.

Hilton J, Dearman RJ, Basketter DA & Kimber I (1995). Identification of chemical respiratory allergens dose-response relationships in the mouse IgE test. Toxicol. Methods 5 (1): 51-60. Testing laboratory: ICI CTL. Owner company: Huntsman.

Holdren M, Spicer C & Riggin R (1993). Fate of TDI, part II: vapour phase studies. Testing laboratory: Battelle Laboratories. Report no.: III Report 11047. Owner company: International Isocyanate Institute. Study number: III project NA-E-24-II. Report date: 1993-05-06.

Holdren MW, Spicer CW & Riggin RM (1984). Gas phase reaction of toluene diisocyanate with water vapor. Am. Ind. Hyg. Assoc. J. 45 (9): 626-33. Owner company: International Isocyanate Institute. Study number: III project NA-E-24-I.

International Isocyanate Institute Biochemistry Task Force (2003). Toxicity of TDI: evaluation with respect to cancer. III Report 11488, International Isocyanate Institute, December 2003. Report no.: III 11488. Owner company: III.

JETOC (1996). [Toluene diisocyanate: chromosome aberration test results]. In: Mutagenicity test data of existing chemical substances based on the Toxicity Investigation System of the Industrial Safety and Health Law, 11, 41-46, 512-5, Japan Chemical Industry Ecology-Toxicology and Information Center.

Jeffcoat AR, Feldman D, Maarr H, Tippin T & Sumrell B (1985a). Disposition of 2,6-toluene diisocyanate in Fischer 344 rats. Project report no.7 (Revised). Pharmacokinetics of xenobiotics. Testing laboratory: Research Triangle Institute. Report no.: Report RTI/2227/00-06P. Owner company: National Institute of Environmental Health Sciences. Study number: N01-ES-1-5007. Report date: 1985-07-01.

Jeffcoat AR, Feldman D, Maarr H, Tippin T & Sumrell B (1985b). Disposition of 2,6-toluene diisocyanate in Fischer 344 rats. Project report no.7 (Revised). Pharmacokinetics of xenobiotics. Testing laboratory: Research Triangle Institute. Report no.: Report RTI/2227/00-06P. Owner company: National Institute of Environmental Health Science. Study number: N01-ES-1-5007. Report date: 1985-07-01.

Johnstone R.T. (1957). Toluene-2,4-diisocyanate: clinical features. Ind. Med.Surg. 26, 33-34.

Kanerva L. et al. (1999). Patch-test Reactions to Plastic and Glue Allergens. Acta Derm Venereol, 79: 296-300. Testing laboratory: Section of Dermatology, Finnish Institute of Occupational Health.

Karol MH (1983). Concentration-dependent immunologic response to toluene diisocyanate (TDI) following inhalation exposure. Toxicol. Appl. Pharmacol. 68: 229-41.

Karol MH, Hauth BA, Riley EJ & Magreni CM (1981). Dermal contact with TDI produces respiratory tract hypersensitivity in guinea pigs. Toxicol. Appl. Pharmacol. 58: 221-230. Owner company: NIOSH, NIEHS, Mobay.

Kitano M, Ouchiyama N & Shimogawa Y (1989). Fate of TDI in water. Part 1: 2,4-TDI (T-100). Testing

laboratory: Chemicals Inspection and Testing Institute (CITI), Japan. Report no.: III Report 10691. Owner company: International Isocyanate Institute. Study number: III project FE-E-63. Report date: 1989-09-01.

Knapp R & Baker RG (1974). Primary skin irritation test with toluene diisocyanate in albino rabbits: report to BASF Wyandotte Corporation. Testing laboratory: Industrial Bio-Test Laboratories. Report no.: IBT No.601-05008. Owner company: BASF. Report date: 1974-05-07.

Kociba RJ, Keyes DG & Wolfe EL (1979). Histopathological observations in selected tissues of Syrian hamsters exposed by inhalation to vapors of TDI for 6 hours/day, 5 days/week for 4 weeks. Testing laboratory: Dow Chemical Company. Report no.: III Report 10100. Owner company: International Isocyanate Institute. Study number: III project NA-A-12. Report date: 1979-09-27.

Kääriä K, Hirvonen A, Norppa H, Piirilä P, Vainio H & Rosenberg C (2001). Exposure to 2,4- and 2,6-toluene diisocyanate (TDI) during production of flexible foam: determination of airborne TDI and urinary 2,4- and 2,6-toluenediamine (TDA). Analyst 126 (7): 1025-31.

Lind P, Dalene M, Lindstrom V, Grubb A & Skarping G (1997). Albumin adducts in plasma from workers exposed to toluene diisocyanate. Analyst 122 Feb: 151-4.

Lind P, Dalene M, Skarping G & Hagmar L (1996). Toxicokinetics of 2,4- and 2,6-toluenediamine in hydrolysed urine and plasma after occupational exposure to 2,4- and 2,6-toluene diisocyanate. Occup. Environ. Med. 53: 94-9.

Lind P, Dalene M, Tinnerberg H & Skarping G (1997). Biomarkers in hydrolysed urine, plasma and erythrocytes among workers exposed to thermal degradation products from toluene diisocyanate foam. Analyst 122 Jan: 51-6. Owner company: Swedish Work Environment Fund.

Loeser E (1983a). Long-term toxicity and carcinogenicity studies with 2,4/2,6-toluene diisocyanate (80/20) in rats and mice. Toxicol. Lett. 15: 71-81. Testing laboratory: Hazleton Laboratories Europe Ltd.

Loeser E (1983b). Long-term toxicity and carcinogenicity studies with 2,4/2,6-TDI (80/20) in rats and mice. Toxicol. Lett. 15: 71-81. Testing laboratory: Hazleton UK. Owner company: International Isocyanate Institute.

Loeser E (1983). Long-term toxicity and carcinogenicity studies with 2,4/2,6-toluene diisocyanate (80/20) in rats and mice. Toxicol. Lett. 15: 71-81. Testing laboratory: Hazleton Laboratories Europe Ltd.

MacKay JM (1992a). Toluene di-isocyanate: an evaluation in the mouse micronucleus test. Testing laboratory: ICI Central Toxicology. Report no.: III Report 10995. Owner company: International Isocyanate Institute. Study number: III project E-AB-65. Report date: 1992-10-13.

MacKay JM (1992b). Toluene di-isocyanate: an evaluation in the mouse micronucleus test. Testing laboratory: ICI Central Toxicology Laboratory. Report no.: III Report 10995. Owner company: International Isocyanate Institute. Study number: III project E-AB-65. Report date: 1992-10-13.

Maitre A, Berode M, Perdrix A, Romazini S & Savolainen H (1993). Biological monitoring of occupational exposure to toluene diisocyanate. Int. Arch. Occup. Environ. Health 65: 97-100.

Martens R & Domsch KH (1981a). Microbial degradation of polyurethane foams in different media. Testing laboratory: Institut für Bodenbiologie, Braunschweig, Germany. Report no.: III Report 10440. Owner company: International Isocyanate Institute. Study number: III project E-E-6.

Martens R & Domsch KH (1981b). Microbial degradation of polyurethane foams and isocyanate based polyureas in different media. Water, Air & Soil Pollut. 15: 503-509. Owner company: International Isocyanate Institute. Study number: III project E-E-6.

Martens R & Domsch KH (1981c). Microbial degradation of polyurethane foams in different media. Testing laboratory: Institut für Bodenbiologie, Braunschweig, Germany. Report no.: III Report 10440. Owner company: International Isocyanate Institute. Study number: III project E-E-6. Report date: 1981-01-01.

Martens R & Domsch KH (1981d). Microbial degradation of polyurethane foams and isocyanate based polyureas in different media. Water, Air & Soil Pollut. 15: 503-9. Owner company: International Isocyanate Institute. Study number: III project E-E-6.

Ministry of Health, Labour & Welfare, Japan (2001). Tolylene diisocyanate; CAS No. 26471-62-5; methyl-1,3-phenylene diisocyanate/toluene diisocyanate. Toxicity Testing Reports of Environmental Chemicals 8 (2): 1113-1117.

Müller K (2008). TDI inhalation study: tumour statistics review. Testing laboratory: BASF. Report no.: III Report 11544. Owner company: International Isocyanate Institute. Study number: III project 269-EU-REG. Report date: 2008-01-01.

Nakashima K., Takeshita T., Morimoto K. 2002. Review of the occupational exposure to isocyanates: mechanizm of action. Environ. Health Prevent. Med. 7, 1-6.

National Toxicology Program (1986). Toxicology and Carcinogenesis studies of commercial grade 2,4(80%) - and 2,6(20%) - toluene diisocyanate (CAS No. 26471-62-5) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 251, NIH Publication No. 86-2507, US Dept. of Health and Human Services, NC, USA.

Ott M.G. 2002. Occupational asthma, lung function decrement and toluene diisocyanate (TDI) exposure: a critical review of exposure-response relationship. 2002. Appl. Occup. Environ. Hyg. 17, 891-901.

Ott MG, Jolly AT, Burkert AL & Brown WE (2007). Issues in diisocyanate antibody testing. Crit. Rev. Toxicol. 37 (7): 567-85. Owner company: International Isocyanate Institute. Study number: III project 100 part 38.

Owen P (1980). The toxicity and carcinogenicity to rats of TDI vapour administered by inhalation for a period of 113 weeks. Testing laboratory: Hazleton Laboratories UK. Report no.: III Report 10210. Owner company: International Isocyanate Institute. Study number: III project A-A-1. Report date: 1980-10-01.

Owen PE (1980). The toxicity and carcinogenicity to rats of toluene diisocyanate vapour administered by inhalation for a period of 113 weeks. Testing laboratory: Hazleton Laboratories Europe Ltd. Otley Road, Harrogate HG3 1PY, UK. Report no.: III Report 10210. Owner company: International Isocyanate Institute. Study number: III project A-A-1. Report date: 1980-10-01.

Owen PE (1984). The toxicity and carcinogenicity to rats of toluene diisocyanate vapour administered by inhalation for a period of 113 weeks. Addendum Report Volume 1. Testing laboratory: Hazleton Laboratories Europe Ltd. Otley Road, Harrogate HG3 1PY, UK. Report no.: III Report 10233. Owner company: International Isocyanate Institute. Study number: III project A-A-1. Report date: 1984-03-01.

Owen PE (1986a). The toxicity and carcinogenicity of toluene diisocyanate vapour when administered to mice over a period of approximately two years. Volumes I and II. Testing laboratory: Hazleton Laboratories Europe Ltd. Otley Road, Harrogate HG3 1PY, UK. Report no.: III Report 10382. Owner company: International Isocyanate Institute. Study number: III project A-A-1. Report date: 1986-03-01.

Owen PE (1986b). The toxicity and carcinogenicity of TDI vapour when administered to mice over a period of approximately 2 years. Testing laboratory: Hazleton Laboratories UK Ltd. Report no.: III Report 10382. Owner company: International Isocyanate Institute. Study number: III project A-A-1. Report date: 1986-03-01.

Pauluhn J & Mohr U (1998). Assessment of respiratory hypersensitivity in guinea pigs sensitized to toluene diisocyanate: a comparison of sensitization protocols. Inhal. Toxicol. 10: 131-54.

Pauluhn J., Poole A. 2011. Brown Norway rats asthma model of diphenylmathane-4,4'-diisocyanate (MDI): determination of theelicitation threshold concentration of after inhalation sensitization. Toxicology 281, 15-24.

Pemberton D & Tury B (2008). Prediction of atmospheric half-lives for MDI, TDI, MDA and TDA using the AOPWIN™ model. GIL Report 2008/C. Owner company: International Isocyanate Institute. Report date: 2008-03-01.

Persson P, Dalene M, Skarping G, Adamsson M & Hagmar L (1993). Biological monitoring of occupational exposure to toluene diisocyanate: measurement of toluenediamine in hydrolysed urine and plasma by gas chromatography-mass spectrometry. Br. J. Ind. Med.50: 1111-8.

Peschel H. (1970). Skin changes by Isocyanates (Desmodur). Dermatologische Monatsschrift, Band 156, Heft 7, 691-697. Testing laboratory: Hautklinik Karl-Marx-Universität Leipzig.

Porter C., Higgins R.L., Scheel L.D. 1975. A retrospective study of clinical, physiologic and immunologic

changes in workers exposed to toluene diisocyanate. Am. Ind. Hyg. J. 36, 159-163.

ReachCentrum (2010). Phys/Chem. Testing on Lupranat T80A. ReachCentrum, Avenue E. van Nieuwenhuyse 6, B-1160 Brussels, Belgium. Testing laboratory: Chilworth Technology Limited, Process Safety Laboratories, Beta House, Southampton Science Park, Southampton, SO16 7NS, United Kingdom. Report no.: GLP103540BR1V1/10. Owner company: ReachCentrum. Study number: GLP103540BR1V1/10. Report date: 2010-03-16.

Redlich C.A. Skin exposure and asthma. Is there a connection? 2010. Proc. Am. Thorac. Soc. Vol. 7, 134-137.

Redlich CA & Karol MH (2002). Diisocyanate asthma: clinical aspects and immunopathogenesis. Int. Immunopharmacol. 2 (2/3): 213-24.

Rhone-Poulenc Chimie (1977). Biological action of TDI and MDI in water. Testing laboratory: Rhone-Poulenc Chimie. Water Research Laboratory. Report no.: III Report 10092. Owner company: International Isocyanate Institute. Study number: III project E-E-10. Report date: 1977-09-06.

Rhône-Poulenc Chimie (1977). Biological action of TDI and MDI in water. Testing laboratory: Rhône-Poulenc Chimie. Report no.: III Report 10092. Owner company: International Isocyanate Institute. Study number: III project E-E-10. Report date: 1977-09-06.

Rosenberg C & Savolainen H (1986). Determination of occupational exposure to toluene diisocyanate by biological monitoring. J. Chrom. 367: 385-92.

Saclay (1976). A study of the diffusion rate of TDI in rats contaminated via the respiratory system. Preliminary study. Testing laboratory: Laboratoire d'etudes du Metabolism des Medicaments, France. Report no.: III Report 10064. Owner company: International Isocyanate Institute. Study number: III project E-A-4. Report date: 1976-01-01.

Saclay (1977). Pharmacokinetics of TDI after inhalation exposure of rats to labelled TDI. Testing laboratory: Laboratoire d'etudes du Metabolism des Medicaments, France. Report no.: III Report 10035. Owner company: International Isocyanate Institute. Study number: III project E-A-4. Report date: 1977-07-01.

Sakai T, Morita Y, Kim Y & Tao YX (2002). LC-MS determination of urinary toxicokinetics in workers exposed to toluenediisocyanate. Toxicol. Lett. 134 (1-3): 259-64.

Sakai T, Morita Y, Roh J, Kim H & Kim Y (2005). Improvement in the GC-MS method for determining urinary toluene-diamine and its application to the biological monitoring of workers exposed to toluene-diisocyanate. Int. Arch. Occup. Environ. Health 78 (6): 459-66.

Schupp, T. and Collins, M. A. (2012). Toluene diisocyanate (TDI) airway effects and dose-responses in different animal models. *EXCLI J.*, 11, 24 Jul., 416-35.

Seel K, Walber U, Herbold B & Kopp R (1999). Chemical behavior of seven aromatic diisocyanates (toluenediisocyanates and diphenylmethanediisocyanates) under in vitro conditions in relationship to their results in the Salmonella/microsome test. Mutat. Res. 438 (2): 109-123. Owner company: Bayer AG.

Sennbro CJ, Lindh CH, Tinnerberg H, Gustavsson C, Littorin M, Welinder H & Jonsson BAG (2003). Development, validation and characterization of an analytical method for the quantification of hydrolysable urinary metabolites and plasma protein adducts of 2,4- and 2,6-toluene diisocyanate, 1,5-naphthalene diisocyanate and 4,4'-MDI. Biomarkers 8 (3-4): 204-17.

Sennbro CJ, Lindh CH, Tinnerberg H, Welinder H, Littorin M & Jönsson BAG (2004). Biological monitoring of exposure to toluene diisocyanate. Scand. J. Work Environ. Health 30 (5): 371-8.

Sennbro CJ, Littorin M, Tinnerberg H & Jonsson BA (2005). Upper reference limits for biomarkers of exposure to aromatic diisocyanates. Int. Arch. Occup. Environ. Health 78: 541-6.

Shiotsuka RN (1987). Sensory irritation of Mondur TD 80 in SD rats. Testing laboratory: Mobay Corporation, Stillwell, KS, USA. Report no.: 842. Owner company: Bayer Corp. Study number: 86-341-02. Report date: 1987-04-30.

Sittig M. 1981. Handbook of toxic and hazardous chemicals. New Jersey, Park Ridge, Noyes Publications 664-665.

Skarping G, Brorson T & Sango C (1991). Biological monitoring of isocyanates and related amines. III. Test chamber exposure of humans to toluene diisocyanate. Int. Arch. Occup. Environ. Health 63: 83-8.

Sorahan T & Nichols L (2002). Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry: updated findings, 1958-98. Occup. Environ. Med. 59 (11): 751-8. Owner company: International Isocyanate Institute. Study number: III project 162-EU-MTX.

Stoltz M, Czarnecki D, Litle L, Pallas F & El-hawari M (1987). Metabolism and disposition of 14C-labeled toluene diisocyanate (TDI) following oral and inhalation exposure: preliminary studies. Testing laboratory: Midwest Research Institute (MRI) Kansas City, USA. Report no.: III Report 10434. Owner company: International Isocyanate Institute. Study number: III project NA-AB-37. Report date: 1987-06-12.

Suberg H, Löser E & Kaliner G (1984). Toluylenediisocyanate (TDI): Assessment of primary irritating/corrosive effects on the rabbit skin (Untersuchungen zur primär reizenden/ätzenden Wirkung an der Kaninchenhaut). Testing laboratory: Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report no.: Bericht Nr: 12533. Owner company: Bayer Material Science AG. Report date: 1984-03-07.

Tadokoro H, Nozaka T, Hirata S & Tounai T (1997a). Ecotoxicities of TDI and TDA to fish, algae, and aquatic invertebrates. Testing laboratory: Chemicals Inspection and Testing Institute, Kurume Research Laboratories, Japan. Report no.: III Report 11217. Owner company: International Isocyanate Institute. Study number: III project FE-E-66. Report date: 1997-10-01.

Tadokoro H, Nozaka T, Hirata S & Tounai T (1997b). Ecotoxicities of TDI and TDA to fish, algae, and aquatic invertebrates. Testing laboratory: Chemicals Inspection and Testing Institute, Japan. Report no.: III Report 11217. Owner company: International Isocyanate Institute. Study number: III project FE-E-66. Report date: 1997-10-01.

Tarlo SM, Liss GM, Dias C & Banks DE (1997). Assessment of the relationship between isocyanate exposure levels and occupational asthma. Am. J. Ind. Med. 32: 517-21.

Thorne PS, Hillebrand JA, Lewis GR & Karol MH (1987). Contact sensitivity by diisocyanates: potencies and cross-reactivities. Toxicol. Appl. Pharmacol. 87: 155-165. Owner company: III and NIEHS.

Tinnerberg H, Dalene M & Skarping G (1997). Air and biological monitoring of toluene diisocyanate in a flexible foam plant. Am. Ind. Hyg. Assoc. J. 58 Mar: 229-35.

Tyl RW & Neeper-Bradley TL (1989). Two-generation reproduction study of inhaled toluene diisocyanate in CD (Sprague-Dawley) rats. Testing laboratory: Bushy Run Research Center, 4, Mellon Rd., Export, Pennsylvania 15632, USA. Report no.: III Report 10608. Owner company: International Isocyanates Institute. Study number: III project NA-AB-50. Report date: 1989-03-17.

Tyl RW (1988). Developmental toxicity study of inhaled toluene diisocyanate vapor in CD (Sprague-Dawley) rats. Testing laboratory: Bushy Run Research Center, R. D.4, Mellon Road, PA 15632, USA. Report no.: III Report 10548. Owner company: International Isocyanate Institute. Study number: III project NA-AB-50. Report date: 1988-12-06.

U.S. Environmental Protectin Agency, 2011. Toluene diisocyanate (TDI) and related compounds. Action Plan [RIN 2070-ZA14]

Vandenplas O., Malo J. L. Saetta M., Mapp C. E. and Fabbri L. M. 1993. Occupational asthma and extrinsic alveolitis due to isocyanates: current status and perspectives. Br. J. Ind. Med., 50:213-228.

Wazeter FX, Buller RH & Geil RG (1964). Toluene diisocyanate (TDI) and polymethylene polyphenylisocyanate (PAPI): acute dermal toxicity studies (LD50) in the albino rabbit. Testing laboratory: International Research and Development Corporation. Owner company: Dow Chemical Corporation. Report date: 1964-01-27.

Wazeter FX, Keller JG, Buller RH & Geil RG (1964a). Toluene diisocyanate (TDI) and polymethylene polyphenylisocyanate (PAPI): acute toxicity studies (LD50) in male albino rats. Testing laboratory:

International Research and Development Corporation. Owner company: Dow Chemical Company. Report date: 1964-03-12.

Wazeter FX, Keller JG, Buller RH & Geil RG (1964b). Toluene diisocyanate (TDI) and polymethylene polyphenylisocyanate (PAPI): eye irritation test in the albino rabbit. Testing laboratory: International Research and Development. Report no.: Report 100-012. Owner company: Dow Chemical Corporation. Report date: 1964-03-13.

Woolhiser MR, Hayes BB & Meade BJ (1998). A combined murine local lymph node and irritancy assay to predict sensitzation and irritancy potential of chemicals. Toxicol. Methods 8 (4): 245-256. Owner company: NIEHS.

Woolrich PF (1982). Toxicology, industrial hygiene and medical control of TDI, MDI and PMPPI. Am. Ind. Hyg. Assoc. J. 43 (2): 89-97.

Yakabe Y, Henderson KM, Thompson WC, Pemberton D, Tury B & Bailey RE (1999). Fate of methylenediphenyl diisocyanate and toluene diisocyanate in the aquatic environment. Environ. Sci. Technol., 33 (15): 2579-83. Owner company: International Isocyanate Institute.

Yakabe Y, Mori E & Tadokoro H (1994). A study of the fate of TDI in water. Effect of interfacial area under static condition. Testing laboratory: Chemicals Inspection and Testing Institute (CITI), Japan. Report no.: III Report 11121. Owner company: International Isocyanate Institute. Study number: III project FE-E-63-4. Report date: 1994-02-10.

Yeh H-J, Lin W-C, Shih T-S, Tsai P-J, Wang S-T & Chang H-Y (2008). Urinary excretion of toluene diisocyanates in rats following dermal exposure. J. Appl. Toxicol. 28 (2): 189-95. Owner company: National Cheng Kung University; Chia Nan University of Pharmacy and Science (+ 5 others).

Zeiger E & Woolhiser M (2007). The genetic toxicity of diisocyanates in humans and laboratory animals. Poster presented at Society of Toxicology (SOT) 46th Annual Meeting, Charlotte, NC, 25-29 Mar. Owner company: International Isocyanate Institute. Study number: III project 254-AM-MTX.

Zeiger E (2005). Evaluation of the genetic toxicity of methylenediphenyl diisocyanate (MDI) and toluene diisocyanate (TDI) in humans. Testing laboratory: Errol Zeiger Consulting, Chapel Hill, NC 27514, USA. Report no.: III Report 11516. Owner company: International Isocyanate Institute. Study number: III project 254-AM-MTX. Report date: 2005-08-25.

Zissu D, Binet S & Limasset J-C (1998). Cutaneous sensitization to some polyisocyanate prepolymers in guinea pigs. Contact Derm. 39: 248-251. Testing laboratory: INRS. Owner company: INRS.

van der Hoeven N, Roza P & Henzen L (1992a). Determination of the LC50 (14 days) of TDI, TDA, MDI, and MDA to the earthworm Eisenia fetida according to OECD guideline no. 207. Testing laboratory: TNO Institute of Environmental Sciences, Delft, Netherlands. Report no.: III Report 11025. Owner company: International Isocyanate Institute. Study number: III project E-CE-96. Report date: 1992-11-05.

van der Hoeven N, Roza P & Henzen L (1992b). Determination of the effect of TDI, TDA, MDI, and MDA on the emergence and growth of the plant species Avena sativa and Lactuca sativa according to OECD Guideline no.208. Testing laboratory: TNO Institute of Environmental Sciences, Schoemakerstraat 97, P. O. Box 6011, 2600 JA Delft, The Netherlands. Report no.: III Report 11024. Owner company: International Isocyanate Institute. Study number: III project E-CE-95. Report date: 1992-11-24.

van der Hoeven N, Roza P & Henzen L (1992c). Determination of the effect of TDI, TDA, MDI, and MDA on the emergence and growth of the plant species Avena sativa and Lactuca sativa according to OECD Guideline no.208. Testing laboratory: TNO Institute of Environmental Sciences, Delft, Netherlands. Report no.: III Report 11024. Owner company: International Isocyanate Institute. Study number: III project E-CE-95. Report date: 1992-11-24.

von Blumencron HO (1978a). Leaching of isocyanates from soil. Testing laboratory: BASF. Report no.: III Report 10452. Owner company: International Isocyanate Institute. Study number: III project E-E-21. Report date: 1978-10-23.

von Blumencron HO (1978b). Leaching of isocyanates from soil. Testing laboratory: BASF. Report no.: III

Report 10452. Owner company: International Isocyanate Institute. Study number: III project E-E-21. Report date: 1987-10-23.