EUROPEAN CHEMICALS AGENCY

Helsinki, 14 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114348621-52-01/F
Substance name: 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, oligomers, allophanate type
EC number: 933-047-9
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 13.04.2015
Registered tonnage band: 100-1000T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Name(s) in the IUPAC nomenclature or other international chemical name(s) (Annex VI, Section 2.1.1.) of the registered substance;**
   - **Manufacturing process**
   - **Chemical name**
2. **Composition of the substance (Annex VI, Section 2.3.);**
3. **Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1; test method: EU C.7/OECD TG 111) of the registered substance;**
4. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD TG 421 or 422) in rats, oral route with the registered substance;**
5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route with the registered substance;**
6. **Soil simulation testing (Annex IX, Section 9.2.1.3; test method: Aerobic and anaerobic transformation in soil, EU C.23/OECD TG 307) at a temperature of 12 °C with the registered substance.** The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable shall be assessed. This can be done simultaneously during the same study;

7. **Sediment simulation testing (Annex IX, Section 9.2.1.4; test method: Aerobic and anaerobic transformation in aquatic sediment systems, EU C.24 / OECD TG 308) at a temperature of 12 °C with the registered substance.** The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable shall be assessed. This can be done simultaneously during the same study;

8. **Identification of degradation products (Annex IX, Section 9.2.3.);**

9. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5; test method: Daphnia magna reproduction test, EU C.20/OECD TG 211) with the registered substance;**

10. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

11. **Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD TG 305, [aqueous exposure/dietary exposure]) with the registered substance;**

12. **Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: revise the exposure assessment for all the exposure scenarios and revise the risk characterisation accordingly for the registered substance; and generate an exposure assessment for all the exposure scenarios and revise the risk characterisation accordingly for the degradation products as identified in Section 8.**

13. **Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for human health: provide a qualitative exposure assessment demonstrating the likelihood that effects are avoided (respiratory sensitising properties (inhalation)) for relevant exposure scenarios and detail the operational conditions and risk management measures.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **21 December 2018**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

In order to ensure that potential hazardous properties of the substance are not underestimated, the substance identification deficiencies must be resolved before identifying the test sample to be used for the testing requested in the present decision.

1. Name or other identifier of the substance (Annex VI, Section 2.1.);

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

The name and other identifiers are used to identify the substance in an unambiguous manner and are therefore essential parts of substance identification and the corner stone of all the REACH obligations.

ECHA notes that you identified the registered substance as of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB). The naming of UVCB substances shall consist of two parts: (1) the chemical name and (2) a detailed description of the manufacturing process, as indicated in chapter 4.3 of the 'Guidance for identification and naming of substances under REACH and CLP', referred thereafter as "the Guidance".

ECHA observes that you did not provide sufficient and appropriate information on the naming and description of the manufacturing process of the substance as required under Annex VI Section 2.1 of the REACH Regulation. This is explained under points (a) and (b) hereinafter.

(a) A detailed manufacturing process description to be submitted by the Registrant

The ratio of the starting materials and the process parameters information are necessary elements for the identification of the registered substance, because they determine the composition of the registered substance.

You state that "[redacted]

ECHA notes that the ratios of the starting materials and the relevant process parameters (e.g. temperature and pressure) used for the manufacturing of the registered substance have not been specified. More specifically the ratio of the different alcohols ([redacted]) is not clearly indicated in the manufacturing process. A detailed description of the different steps described as [redacted]" is also missing.

ECHA therefore concludes that the manufacturing process has not been provided to a sufficient level of detail for the identification of the registered UVCB substance. You are accordingly requested to clarify the identity of the registered UVCB substance. For this purpose, you shall provide the ratios of the starting materials and the relevant process parameters of the process used for the manufacturing of the substance registered.

Regarding how to report the identifiers of the UVCB substance, the following applies:
You shall include the information in the reference substance assigned in IUCLID section 1.1. Given the fact that the naming of a UVCB substance such as the registered substance consists of both the chemical name and the detailed description of the manufacturing process, you shall also ensure that the specific manufacturing process reported in IUCLID section 3.1 is also reported as an identifier in the description field in IUCLID section 1.1. Further technical details on how to report the identifiers of UVCB substances in IUCLID are available in paragraphs 2.1 of the Data Submission Manual 18 on the ECHA website.

(b) Information on the chemical name and numerical identifiers to be submitted by the Registrant

Regarding the chemical name to be assigned to the registered substance according to Annex VI section 2.1, the chemical name assigned to the registered substance must follow the naming conventions specified in the Guidance and be representative of the specific substance which is the subject of this registration, including its composition. In particular, the name must reflect the starting materials and the reaction that was involved in the manufacture of the substance. In particular, the naming of the starting materials used in the process and to be quoted in the name of the registered substance shall also follow the naming conventions specified in the Guidance. The description must be sufficiently detailed to allow ECHA to conclude on the numerical identifiers of the registered substance.

You provided a generic chemical name "*3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, oligomers, allophanate type*".

The information on the name provided in the registration dossier prevents ECHA from concluding on the appropriate and representative chemical identifiers for the registered substance. In particular, the presence of the different alcohols ([redacted]) used in the manufacturing process is not indicated in the name. Therefore, the provided chemical name cannot be considered appropriate at this stage based on the information provided in the dossier.

Hence you are requested to provide the chemical name of the registered substance, which unambiguously allows its identification, including the numerical identifiers, on the basis of the starting materials and the manufacturing process.

You shall note that the registration is currently linked to the list number 933-047-9 which refers to the chemical name "3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, oligomers, allophanate type". Should the substance intended to be covered by this registration refer to a different substance, you can however not remove or modify at this stage the list number for technical reasons, because the registration is linked to that number in REACH-IT. To ensure unambiguous identification of the registered substance and in case the name provided in the registration dossier is not appropriate, you shall indicate, in the "Remarks" field of the reference substance in IUCLID section 1.1, the following: "The list number 933-047-9 currently assigned does not specifically correspond to the registered substance. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons". You shall also specify, in the same "Remarks" field, any available and appropriate EC or List number for the substance.

You should note that ECHA has established a process, subject to certain conditions, enabling registrants to adapt the EC identifier of an existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

However, pending the resolution of all the incompliances highlighted in the present decision, the adaptation of the identifier can only be effective once ECHA is at least in a position to establish unambiguously the identity of the substance intended to be covered by you with this registration. Should the information submitted by you as a result of the present decision enable ECHA to identify the substance unambiguously, the process of adapting the identifier will be considered relevant. In that case, ECHA will inform you in due time as to when the identifier adaptation process shall be initiated.

In any case, you should note that the application of the process of adapting the identifier does not affect your obligation to fulfil the requirements specified in this decision.

You shall also ensure that appropriate and consistent identifiers are used throughout the registration whenever reference to the specific substance is made which is the subject of this registration.

2. Composition of the substance (Annex VI, Section 2.3.);

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the cornerstone of all the REACH obligations.

Annex VI, Section 2.3. of the REACH Regulation requires that each registration dossier contains sufficient information for establishing the composition of the registered substance and therefore its identity.

In that respect, according to chapter 4.3 of 'the Guidance', you shall note that for UVCB substances, such as the registered substance, the following applies:

- All constituents present in the substance with a concentration of ≥ 10 % shall be identified and reported individually,

- All known constituents and constituents relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually; and
- Unknown constituents shall be identified as far as possible by a generic description of their chemical nature.

For each constituent or group of constituents, the typical, minimum and maximum concentrations shall be specified.

ECHA notes that the registration does not contain sufficient information for establishing the composition of the registered substance and therefore its identity. More specifically, ECHA notes that one generic constituent ("[redacted] has been reported in a typical concentration of [redacted]%(w/w). This constituent is the sum of three GPC peaks ([redacted]) shown on the GPC analysis provided in the document "[redacted]" in IUCLID section 1.4. These three GPC peaks should be reported separately in the composition. Furthermore ECHA notes that a generic constituent ("[redacted]) has been reported in a typical concentration of [redacted]%(w/w). For this constituent, you provided a generic structural formula describing the different types of structures that may be obtained as a result of the reaction with the different alcohols. However it is not clear what the ratio of the different alcohols is in this constituent.

You are accordingly requested to clarify the identity of the different constituents.

ECHA notes that in the event you cover different grades of the registered substance in the present registration dossier, you shall report separately the compositional information of each grade. This means that if the substance covered by the present registration has two (or more) different compositions, then these must be presented separately. ECHA highlights that failure to report separately the compositional information of each grade of a substance may result in one or more grades not being covered by this registration.

Regarding how to report the composition in IUCLID, the following applies:

You shall indicate each composition of the registered substance in IUCLID section 1.2.

For each constituent required to be reported individually, the IUPAC name, CAS name and CAS number (if available), molecular and structural formula, as well as the minimum, maximum and typical concentration, shall be reported in the appropriate fields in IUCLID.

For the other constituents to be reported under a generic description, a generic chemical name describing the group of constituents, generic molecular and generic structural information (if applicable), as well as the minimum, maximum and typical concentration, shall be reported in the appropriate fields in IUCLID.
Further technical details on how to report the composition of UVCB substances in IUCLID are available in paragraphs 2.1 and 2.2.2 of the Data Submission Manual – Part 18: How to report the substance identity in IUCLID 5 for registration under REACH (version: 2.0, July 2012) on the ECHA website. Information on how to report several compositions in IUCLID is specified in paragraph 2.3, Q&A8 of that manual.

You shall ensure that the reported composition is consistent with the description of the process used for the manufacturing of the registered substance, including the identity of the starting materials used. You shall also ensure that the composition is verifiable and therefore supported by a description of the analytical methods for the identification and quantification of the constituents required to be reported, as required under Annex VI, Section 2.3.7.

PROPERTIES OF THE SUBSTANCE

0. Weight of evidence, grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration dossier, you have adapted the standard information requirement for, inter alia,

- reproductive toxicity (namely screening test for reproductive/developmental toxicity, Annex VIII, Section 8.7.1.),
- pre-natal developmental toxicity, (Annex IX, Section 8.7.2.),

by providing a read-across adaptation according to the rules set out in REACH Annex XI, Section 1.5.

Furthermore, in the comments you provided on the draft decision of 8 January 2016, you have submitted a document (see section 0.1.2, document n) in which you clarified that for repeated dose inhalation, read across is applied, while for reproductive toxicity, a weight of evidence adaptation according to the rules set out in REACH Annex XI, Section 1.2. is applied.

The following analysis presents your justification for your proposed weight of evidence adaptation, as well as the grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and a property-specific context.

0.1 Description and support of the weight of evidence- and grouping and read-across approach proposed by the Registrant

0.1.1 Information you provided in the IUCLID dossier

ECHA observes that you have included, in IUCLID Section 7.8, the following documents to justify the category approach for aliphatic isocyanates:

a) "[redacted]".

This document lists the following substances as group members (short names as specified in the document): "IPDI oligomers, isocyanurate type" (EC No 931-312-3), "IPDI" (EC No 223-861-6), "HDI" (EC No 212-485-8), "HDI oligomers, uretdione type" (EC No 931-288-4), "HDI oligomers, isocyanurate type" (EC No 931-274-8), "HDI oligomers, iminooxadiazindione type" (EC No 931-297-3), "HDI oligomers, biuret type" (EC No 939-340-8) and "H12MDI" (EC No 225-863-2). You also indicated that this document is a continuation of the argumentation of the

b) "[redacted]. That report provides an argumentation for waiving further testing on reproductive toxicity for the aliphatic monomers and their polyisocyanates as listed below: "HDI" (EC No 212-485-8), "IPDI" (EC No 223-861-6), "H12MDI" (EC No 225-863-2), "HDI homopolymer – trimer type" (EC No 931-274-8), "HDI homopolymer – biuret type" (EC No 939-340-8) and "IPDI homopolymer – trimer type" (EC No 931-312-3).

c) Moreover, you have provided the following document to justify the appropriateness of the group extension of the category to cover also the registered substance "IPDI oligomers, allophanate type": "[redacted]".

ECHA observes that in the IUCLID dossier, in order to support the read-across, you have provided the following study summaries for the endpoint "fertility":

d) screening study (OECD TG 422) by inhalation with the analogue substance hexamethylene diisocyanate (HDI) (CAS no 822-06-0; Astroff 2000a);
e) screening study (OECD TG 422) by inhalation with the analogue substance 4,4´-methylenedicyclohexyl diisocyanate (H12MDI) (CAS no 5124-30-1; [redacted]

For the endpoint "developmental toxicity" you have provided the following study summaries:

f) pre-natal developmental toxicity study (OECD TG 414) by inhalation with the analogue substance isophorondiisocyanate (IPDI) (CAS no 4098-71-9; [redacted]);
g) pre-natal developmental toxicity study (OECD TG 414) by inhalation with the analogue substance 1,6-hexamethylene diisocyanate (HDI) (CAS no 822-06-0; Astroff 2000b);
h) pre-natal developmental toxicity study (OECD TG 414) by inhalation with the analogue substance 4,4´-methylenedicyclohexyl diisocyanate (H12MDI) (CAS no 5124-30-1; [redacted]);
i) screening study (OECD TG 421) by inhalation with the analogue substance 4,4´-methylenedicyclohexyl diisocyanate (H12MDI) (CAS no 5124-30-1; [redacted]);
j) screening study (OECD TG 422) by inhalation with the analogue substance hexamethylene diisocyanate (HDI) (CAS no 822-06-0; Astroff 2000a).

You have provided the following arguments in the read-across justification document ([redacted]) to justify the read-across hypothesis:

k) *"The structural similarity within the group is primarily based on the fact that all of these substances share a common functional group (NCO-group; -N=C=O) and, attributed to this, a common Mode of Action (port of entry irritant toxicity, no systemic toxicity). The available data for the group members unanimously confirm the common toxicological profile as it was shown in the justification by a comprehensive comparative evaluation."*

l) *"3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate oligomers, allophanate type (short name: IPDI oligomers, allophanate type; CAS no 53880-05-0, ECHA list no 933-047-9) is also a structurally similar aliphatic isocyanate, that should also belong to the above listed. It is not implicitly covered by the applicability domain; therefore this document was elaborated to give proof for the appropriateness of the group extension."*

While these arguments are included in the read-across justification document a) ([redacted]):

m) *"the available data on developmental toxicity, obtained from relevant representatives of the group, gives no indication for any specific developmental toxicity for the aliphatic isocyanates. Fetal development is affected only at levels that causes clear maternal toxicity and thus considered as secondary effect. Thus further testing on vertebrate animals for that endpoint should be omitted. Read across, according to REACH Annex XI, 1.5., to IPDI oligomers, isocyanurate type reveals that the substance is not a developmental toxicant."*

0.1.2 Information you provided in the comments on the draft decision

In your comments submitted to ECHA on 15 February 2016 in response to the draft decision, you submitted the following document ([redacted]):

n) [redacted]".

Within this document you indicated the following: *"For IPDI oligomers, allophanate type sufficient weight of evidence information is available with respect to reproductive toxicity (fertility and developmental toxicity). Further testing on vertebrate animals for that property shall be omitted for the substance.*

The arguments for the weight of evidence approach in short rely on:

1. *Experimental evidence, based on studies on reproductive toxicity/fertility and developmental toxicity from representatives of the upper end of potency (i.e. more toxic) that confirm the absence of a primary potential on reproductive toxicity (studies available for HDI, IPDI and a further monomeric diisocyanate 4,4'-Methylenedicyclohexyl diisocyanate; H12MDI, CAS 5124-30-1).*

It was shown in the available studies on reproductive toxicity/fertility and developmental toxicity that there is no evidence of a primary reproductive toxicity potential of the diisocyanate monomers after inhalation exposure (only secondary effects, e.g. secondary developmental toxicity caused by maternal toxicity were observed).

2. *The conclusion is drawn that the absence of a primary potential on reproductive toxicity after repeated inhalation is also valid for the less toxic polyisocyanates, that also elicit toxicity via the same Mode of Action, i.e. the port of entry irritant toxicity, but with a lower degree. No systemic effects were observed in none of the acute or repeated inhalation studies for any of the aliphatic polyisocyanate or monomeric diisocyanate. Moreover, no indication for systemic toxicity is observed in any of the experimental studies, except a positive skin sensitization potential, which is evident for all of the substances, and which of course indicates some systemic availability , even if low.*
3. *There is in principle remaining uncertainty for the assessment of hazard for reproductive toxicity, since the maximum exposure concentrations in inhalation studies were limited by the irritant potency of the substances. Studies with repeated oral exposure could use, with respect to the maximum tolerated dose, much higher doses. On the other hand, acute oral toxicity studies of IPDI oligomers, allophanate type and of other polyisocyanates reveal no test-substance related effects at all, except for IPDI oligomers, isocyanurate type, which led to non-specific clinical signs at doses from 10000 mg/kg onwards when administered as a solution in xylol/ethyl acetate (2/1). Concluding, at least from the acute oral studies of the polyisocyanates there is no indication for a hazard following oral exposure.*
4. *Very recently the registrant has accepted the request expressed in the ECHA draft decision of 8th January 2016 for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD TG 421 or 422) in rats, oral route with the registered substance. This study is expected to further clarify if there is a hazard for reproductive toxicity after oral intake in the case of IPDI oligomers, allophanate type. The "allophanate"-species constitutes an even more complex UVCB compared to the other polyisocyanate and the database is less comprehensive. Therefore in this case such a study is regarded as valuable to further substantiate the read across and is expected to become a further building block in the weight of evidence approach for the hazard identification."*

In your comments submitted to ECHA on 15 February 2016 in response to the draft decision, you have furthermore agreed to conduct a combined repeated dose toxicity and screening for reproductive/developmental toxicity study (OECD TG 422) by the oral route in rats, to investigate the systemic availability of the registered substance after oral dosing.

0.2 ECHA analysis of the weight of evidence approach and grouping and read-across approach, in light of the requirements of Annex XI, 1.2 and 1.5.

With regard to the proposed adaptations ECHA has the following observations:

0.2.1 Analysis of the information you provided in the IUCLID dossier on read-across

ECHA acknowledges the information you have provided within the comments on the draft decision regarding grouping and read-across approach. ECHA notes that, for reproductive toxicity, you are applying a weight of evidence approach. However, since most information you provide is based on read-across and category information, ECHA considers that those adaptations also need to be evaluated.

(i) substance characterisation of source and target substances

The substance characterisation of the registered substance and of the source substances need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by differences in the composition and/or by the presence of impurities. It is important that the chemical structures and purity profiles of all substances are well defined to support the read-across hypothesis. In the ECHA practical guide 6 "How to report on Read-Across" it is recommended to follow the Guidance on identification and naming of substances under REACH and CLP (version 1.3, February 2014) for the substance characterisation of the source and target substances. This ensures that the identity of the source and target substances and their purity profile allows an assessment of the suitability of the substances for read-across purposes.

Neverthless, ECHA observes that you did not provide sufficient and appropriate information on the chemical name and manufacturing process of the registered substance (see Appendix 1, section 1 of this decision) and that it is necessary to clarify the identity of the different constituents and to provide the missing compositional information of the registered substance (see Appendix 1, section 2 of this decision). Additionally ECHA notes that there is unclarity on the chemical structure of the registered substance as it might consist of allophante, isocyanurate, uretdione groups or other structure as stated in the read-across justification document c) ([redacted]): "*The resulting substance is a mixture of components, each of which has several structural isomers and consists predominantly of allophanate and isocyanurate structures though it is known that uretdione- or other structures may occur in minor amounts.*"

ECHA concludes that the substance characterisation of the target substance is insufficient for read-across purposes. Since the composition, chemical name and manufacturing process of the target UVCB substance (the registered substance) is not described in sufficient detail, ECHA cannot verify that there is an adequate basis for predicting the properties of the registered substance from the proposed source substances.

In addition to the deficiencies of the description of the identitiy of the substance, the proposed read-across approach has further deficiencies as described below under (ii), (iii) and (iv).

(ii) Structural similarity and differences among the individual substances and scientific explanation on why and how these structural features allow predictions

a. Category approach

Document a) ([redacted]) describes a category of aliphatic isocyanates. The registered substance is not a member of this category as described in that document. Document b) ([redacted]) also does not address the registered substance. Hence, ECHA did not analyse in detail any potential short-coming of these justification documents (developed for other purposes than the registration dossier under consideration here) but focuses only on those aspects in them which are relevant to document c).
Document c) provides a justification for an extension of the category described in a) to include the registered substance "3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate oligomers, allophanate type". The document n) which you provided with the comments on the draft decision ([redacted]) provides a justification for a category including the registered substance "3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate oligomers, allophanate type". ECHA therefore analysed whether this extension is scientifically sound and subsequently whether the proposed analogue read-across adaptation is acceptable.

Extension of the proposed category (documents a, c and n) to the registered substance

ECHA acknowledges that the members of this proposed category share a common functional group (isocyanate-group, NCO). The number of isocyanate groups present in each individual member varies considerably ranging from two NCO groups in the monomers to higher numbers in the oligomers. In more detail, the proposed category consist of three monomeric diisocyanates (IPDI, HDI, H12MDI) and of different oligomers (HDI and IPDI oligomers), which are UVCBs and contain a range of different core structures (isocyanurate, uretdione, imino-oxa-diazin-dione, biuret). However, the variability among the category members in terms of chemical structures, cross-linking groups (isocyanurate, uretdione, imino-oxa-diazin-dione, biuret) and composition is not addressed in detail. Some information on the composition of the monomeric diisocyanates and oligomers is provided in Annex II of justification documents a) and c) in terms of weight % of oligomeric content. Nevertheless, the compositional information are in some cases not detailed enough to conclude on the substances' composition. ECHA observes that the presence and number of the different core structures is not addressed beside your claim that "*no toxic effect is anticipated from the aliphatic backbone of the molecules of the species that is yield from the NCO-conversion*" (document a). Instead, document n) demonstrates some differences between HDI oligomers allophanate type and HDI oligomers isocyanurate type, regarding BALF analysis and clinical signs, indicating differences in the toxicological profile. ECHA notes, however, that the NOAECs and LOAECs are very similar.

Documents c) ([redacted]) and n) [redacted] explain why you consider that also the registered substance is a member of this proposed category, specifying that the registered substance possesses a variability in the composition and in the chemical structure which is not yet clarified (see Appendix 1, section 1 and 2 of this decision). The registered substance is a UVCB type of substance and its constituent are IPDI oligomers (n >2) of allophanate and isocyanurate type (and also other core structures) containing different types of structures as a results of the reaction with different alcohols ([redacted]). The contribution of the different structures and of the different alcohols towards a potential reactivity of the registered substance in biological systems is not addressed.

ECHA observes that you described the registered substance in the justification document c) ([redacted]) as: " *...prepolymerised aliphatic polyisocyanate compound...". ... manufactured by addition of alcohols... the resulting substance is a mixture of components, each of which has several structural isomers and consists predominantly of allophanate and isocyanurate structures though it is known that uretdione- or other structures, may occur in minor amounts.*[...] *The structural formulas indicate that IPDI oligomers, allophanate type is composed of approx.* [redacted]*% of IPDI oligomers, isocyanurate type, which is a member of the group so far.*" The claim that [redacted]% of the registered substance are IPDI oligomers, isocyanurate type which is identified as a member of the category described in a) emphasizes that [redacted]% of the registered substance is different from that category member and is not a convincing and satisfactory argument to extend the proposed category to the registered substance. In document n) ([redacted]) you further specify "*The figure shows the idealised mono allophanate formed by the reaction of an urethane with further IPDI (approx.* [redacted]*% from GPC) and the idealised isocyanurate formed by cyclotrimerisation of IPDI (approx.* [redacted]*% from GPC). The remaining* [redacted]*% are higher homologues of allophanates, isocyanurates and mixed allophanate-isocyanurate structures as well (a refined description of the composition is in progress)."*

The structural and compositional differences between the proposed category members as described in documents a) and n) and the registered substance are insufficiently substantiated at present. Therefore, ECHA understands that your claimed extended category is solely based on assumed similar properties deriving from the presence of isocyanate groups. Your claim is that the NCO group is causing local irritation at the port of entry as the dominant toxic effect. However, it is not explained what potency impact the differences in chemical structures and composition described above may have on this property and on other potential adverse effects.

b. Read across from analogue substances

Despite the rejection of the proposed category approach, ECHA has also assessed the predictions based on read-across from your indicated analogous substances to the registered substance (see d) – j) above). You propose to predict the toxicological properties of the registered substance, a UVCB type of substance, from the results obtained with monoconstituent diisocyanate monomers. As explained above, the UVCB composition is not characterised in sufficient detail for read across purposes and is also not compliant with Annex VI of REACH. Moreover, on the basis of the information available in the registration dossier, ECHA notes that the compositional information of the registered substance as provided in IUCLID section 1.2. indicate the presence of constituents whose structures differ from that of the mono-constituent diisocyanate monomers:

- [redacted]% w/w typical concentration ([redacted]% w/w concentration range) of [redacted];
- [redacted]% w/w typical concentration ([redacted]% w/w concentration range) of [redacted];
- [redacted]% w/w typical concentration ([redacted]% w/w concentration range) of [redacted];
- [redacted]% w/w typical concentration ([redacted]% concentration range) of [redacted]

Furthermore, you further state that "*No toxic effect is anticipated from the aliphatic backbone of the molecule or the species that is yield from the NCO-conversion, even in the case of allophanatisation. The available studies for IPDI oligomers, allophanate type, confirm the toxicological similarity, since they give evidence for a MoA characterised by the local irritant effect at the first site of contact/port-of-entry (e.g. respiratory tract, skin, eyes) due to the isocyanate reactivity, which is the common MoA for the other aliphatic monomeric and homopolymeric isocyanates.*", and in document n) [redacted] "*Nevertheless, the only reactive functional group in the molecule is the NCO-group (= common functional group). This group solely seemed to be responsible for the toxicological Mode of Action (MoA).*"

ECHA notes that the argument that the toxicity is solely determined by the local effects caused by the –N=C=O group is not sufficiently substantiated. ECHA acknowledges that the substances share a common functional isocyanate group which is linked to a proposed common mode of action (port of entry irritant toxicity). Such a common mode of action is plausible but does not exclude that other modes of action exist as well. The analogue substances tested for reproductive toxicity were all diisocyanate monomers (HDI, IPDI and H12MDI) while the registered substance is a UVCB type of substance (isocyanate oligomer). The presence of core structures (allophanate, isocyanurates and others) in the target substance (as compared to the monomers) is not supported with experimental evidence, nor are the possible different structures addressed that may be obtained as a result of the reaction with different alcohols. Furthermore the differences among the three diisocyanate monomers in terms of purity profile and/or chemical structures are not addressed either.

In the present case, additional complications for the attempted predictions arise from the fact that exposure to the registered substance results in a combined exposure of the experimental system to all constituents of this substance simultaneously. In contrast, exposure to the mono-constituent substances results in exposure to only that substance (plus its impurities) in the same study type. There are no considerations currently in the dossier which address possible combination effects of the individual constituents of the registered substance. There is no evidence provided which would support an assumption that such combination effects are negligible in this case. The proposed predictions, therefore, appear to be not reliable.

ECHA concludes that you have neither addressed nor described nor substantiated with supporting evidence to a sufficient extent the obvious structural and compositional differences between the source substances and the target substance and did not explain why those differences would not lead to differences in the mode of action and in the toxicity profile of target and source substances. The provided explanation is not considered as valid to establish the link between the structural and chemical similarity and the prediction.

(iii) Information in data matrices to support a similar or regular pattern as a result of structural similarity

You state that "*The toxicological database for inhaled aliphatic diisocyanate monomers and their polyisocyanates demonstrates consistently that toxicity is associated only with the portal of entry (respiratory tract), any other manifestations of toxicity are secondary to this*"

ECHA notes that from the absence of reproductive or any other systemic toxic effects in inhalation studies performed with aliphatic diisocyanate monomers it cannot be concluded that no reproductive toxicity is to be expected with the registered substance. The exposure concentrations via inhalation are limited by the irritant properties of the diisocyante monomers. If higher exposure concentrations would have been possible without causing suffering for the test animals, systemic uptake and subsequent toxic effects cannot be excluded. As evidence, ECHA notes that the registered substance is an aliphatic oligomeric isocyanate being about 10-times less irritating than the monomeric diisocyanates for which studies on reproductive toxicity have been provided. With oligomeric aliphatic isocyanates no study on reproductive toxicity was provided. Hence, due to the less irritating potency, higher exposure concentrations are possible and potential reproductive effects of the registered substance might occur. Since appropriate toxicokinetic information is not available for the registered substance to further clarify such possibility, aliphatic monomeric and oligomeric isocyanates might not have a similar pattern of reproductive toxicity.

ECHA concludes that the presented evidence in the data matrix does not allow predictions from monomeric diisocyanates to the registered substance regarding a similar or regular pattern of systemic toxicity as a result of structural similarity.

(iv) Qualitative and quantitative exposure of the test organism to source and target substances and to their hydrolysis/metabolic transformation products.

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances". One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the comparison of absorption, distribution, metabolism and elimination of source and target substances to allow assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

ECHA notes that no toxicokinetic data has been provided for the analogue substances nor for the registered substance. Consequently, it is not possible to conclude whether there are differences in the toxicokinetic behaviour, in particular in the uptake, distribution or metabolic fate/(bio)transformation of the substances and how these differences may influence the toxicity profile of the registered and analogue substances.

Information on the reactivity of isocyanates in water is provided in the justification documents a) and n) ([redacted]) where it is reported that "isocyanates hydrolyse readily in water to yield carbamic acid as an unstable intermediate, which decarboxylates to produce carbon dioxide and the corresponding amine. The amine then immediately reacts with remaining isocyanate groups to form oligo- and polyureas." Nevertheless, there is no assessment of the potential hydrolysis/transformation of the various oligomers (in terms of their cross-linking groups ad more in general of their chemical structures) in physiological matrices (respiratory tract, digestive tract, blood) and the subsequent potential effects caused by hydrolysis/metabolic transformation products. Neither is there any scientific data substantiating that your above claim of rapid hydrolysis of the isocyanate group and consequent formation of oligo- and polyureas is not influenced (reaction time and degree) by structural and compositional differences between the monomers and the different oligomers.

ECHA concludes that due to lacking information, the systemic exposure to the analogue substances and their hydrolysis/metabolic transformation products cannot be compared to the systemic exposure caused by the constituents of the registered substance and its hydrolysis/metabolic transformation products. Therefore, it is not possible to verify that systemic uptake and distribution of constituents of the registered substance does not occur. Consequently, it is also not possible to conclude that similar properties are indeed to be expected when test organisms are exposed to the analogue substances and to the registered substance in reproductive toxicity studies. Therefore, there is not an adequate basis for predicting the properties of the registered from the data of the analogue substances.

(v) Summary

ECHA considers that structural similarity alone is not sufficient for predicting toxicological properties. It has to be justified why such prediction is possible in view of the unclarities in the substance characterisation, chemical structures and purity profiles of the target substance. ECHA notes that in view of the issues listed above it has not been demonstrated that the analogue substances have the same properties or follow a similar pattern with regard to studies on screening for reproductive toxicity and pre-natal developmental toxicity. ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

0.2.2 Analysis of the information you provided in the comments on the draft decision on weight of evidence

ECHA has evaluated your weight of evidence information according to REACH Annex XI, Section 1.2., and assessed whether you have provided *"sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the substance has or has not a particular dangerous property"* with respect to the information requirement of Annex VIII, Section 8.7.1 and Annex IX, Section 8.7.2. for the registered substance.

0.2.2.1 ECHA acknowledges that in the mentioned reproductive/fertility and developmental toxicity studies performed by inhalation with the listed monomeric diisocyanates, no specific reproductive toxic effects were reported. However, ECHA notes that all three source substances are diisocyanate monomers, which exhibit a tenfold or higher potency of local pulmonary irritation as compared to the registered substance. Furthermore, ECHA notes that the absence of (systemic) effects on reproductive organs in these studies does not allow to predict on the absence of effects by the registered substance, because the higher potency of respiratory irritation limits the maximum dose that could be tolerated by the test animals, as compared with the registered substance.

0.2.2.2 ECHA acknowledges that no systemic effects were observed in acute and repeated dose inhalation toxicity studies with polyisocyanates. However, ECHA notes that the argument of a lack of systemic availability is based on the absence of systemic effects in repeated-dose toxicity studies. This argument does not account for the possibility that systemic exposure may be devoid of effects on the endpoints typically investigated in repeated-dose toxicity studies, while, at the same time, it may cause reproductive toxic effects, which are not covered by the repeated-dose toxicity study.

0.2.2.3 ECHA acknowledges your statement that uncertainty remains for the hazard assessment regarding reproductive toxicity of the registered substance, also with regard to the administration by inhalation (see also above, 0.2.2.1). Please refer to section 5, as this comment is addressed under the specific endpoint.

0.2.2.4 ECHA acknowledges your acceptance of the testing request.

ECHA concludes that, for the reasons set out above, the evidence you provided to adapt the standard information requirement for a reproductive toxicity screening study (REACH Annex VIII, 8.7.1) and a pre-natal developmental toxicity study (REACH Annex IX, 8.7.2) based on Annex XI, Section 1.2. is not sufficient to conclude that the registered substance does not have hazardous properties with regard to sexual function, fertility, and developmental toxicity. Therefore, your adaptation of the information requirement is rejected.

0.3 Conclusion on the weight of evidence and read-across approach

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints screening for reproductive/ developmental toxicity and pre-natal developmental toxicity in the technical dossier based on the proposed weight of evidence and read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.2 and 1.5. Therefore, ECHA rejects those adaptations in the technical dossier that are based on Annex XI, 1.2 and 1.5.

3. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Hydrolysis as a function of pH" is a standard information requirement as laid down in Annex VIII, Section 9.2.2.1 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The technical dossier contains data for this standard information requirement, containing two experimental studies. The first study provides information on hydrolysis at pH value 5,5 only. According to the test guidelines EU C.7 and OECD TG 111 "*The hydrolysis test should be performed at pH values of 4, 7 and 9*". As the information reported in the technical dossier do not contain information of hydrolysis in all three pH values prescribed by the method, the reported study is not adequate to fulfil the standard information requirement.

The second study provides limited information on hydrolysis, where the amount of solvent used was 70% w/w. According to the test guidelines EU C.7 and OECD TG the recommended amount of solvent should not exceed 1% w/w. Moreover, the test was only run for 24 hrs instead of 5 days.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

In your comments according to Article 50(1) you stated that "*The Registrant agrees to the need for further information on the hydrolysis behaviour* [...]". ECHA notes your intention to deviate from the standard OECD test protocol and to use an analogue substance. Such deviations from the OECD test guideline need to be adequately justified. ECHA cannot assess the proposed deviation(s) without knowing the identity of the substance(s) to be tested.

In any event, ECHA reminds you that any adaptation with an analogue substance needs to be justified in accordance with Annex XI, section 1.5. Your comments do not contain any such justification.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Hydrolysis as a function of pH (test method: EU C.7/OECD TG 111).

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided study records for an OECD 422 screening study by the inhalation route with the analogue substances hexamethylene diisocyanate (CAS no 822-06-0) and OECD 421 screening study by the inhalation route with the analogue substance 4,4´-methylenedicyclohexyl diisocyanate (CAS no 5124-30-1). Hence, you have sought to adapt this information requirement according to Annex XI, Section 1.5. and Section 1.2. of the REACH Regulation.

However, as explained above in the section '*Grouping of substances and read-across approach'* of this decision, your adaptation of the information requirement is rejected.

ECHA notes that your adaptation for reproductive toxicity studies is also based on "*weight of evidence conclusions (REACH Annex XI, Section 1.2.) based on mechanistic toxicity data*". ECHA notes that you provided a weight of evidence justification to adapt the sub-chronic toxicity study (90-days). However, you did not provide any scientific argumentation justifying the adaptation of the reproductive toxicity studies based on weight of evidence. Hence, ECHA considers that the information provided does not provide sufficient weight of evidence leading to the assumption or conclusion that the registered substance has no dangerous property with regard to reproductive toxicity. Hence, ECHA concludes that you have failed to the meet the requirement of Annex XI, Section 1.2.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421 and 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

With respect to the route of administration, ECHA considers that the oral route is the most appropriate route of administration as explained below in section 5 of this Appendix. Therefore, ECHA concludes that testing should be performed by the oral route.

In your comments according to Article 50(1) you stated that "*the registrant agrees to conduct a Screening for reproductive/developmental toxicity according to OECD TG 422 in rats, oral route with the registered substance*".

ECHA acknowledges your proposal for a step-wise approach to firstly conduct a combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test (OECD TG 422) in rats, oral route and secondly, on the outcome of that study, to consider the need of a pre-natal developmental toxicity study (OECD TG 414), oral route in a first species.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) in rats by the oral route *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

5. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in the first species

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

A "pre-natal developmental toxicity study" (test method B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided study records for pre-natal developmental toxicity studies according to OECD TG 414 by the inhalation route with the analogue substances isophorondiisocyanat (IPDI) (CAS no 4098-71-9), 1,6-hexamethylene diisocyanate (HDI) (CAS no 822-06-0) and 4,4´-methylenedicyclohexyl diisocyanate (CAS no 5124-30-1). Hence, you have sought to adapt this information requirement according to Annex XI, Section 1.5. and Section 1.2. of the REACH Regulation.

However, as explained above in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement is rejected.

Furthermore, you indicated that your adaptation for reproductive toxicity studies is also based on "*weight of evidence conclusions (REACH Annex XI, Section 1.2.) based on mechanistic toxicity data*". As justified above in section 4 of this Appendix, ECHA concludes that you have failed to the meet the requirement of Annex XI, Section 1.2.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Furthermore, in your comments according to Article 50(1) you proposed a stepwise approach to testing, making the testing of the pre-natal developmental toxicity study (OECD TG 414) dependent on the outcome of the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422). However, ECHA reminds you that a "combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test" (OECD TG 422) does not provide the information required by Annex IX, Section 8.7.2, because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations. Therefore, an OECD TG 422 screening study cannot be used to adapt for an OECD TG 414 pre-natal developmental toxicity information requirement. However, you may adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

With respect to the route of administration, ECHA notes that all studies provided with the analogue substance were performed by the inhalation route. ECHA also notes the justification for the inhalation route "*if additional studies on developmental toxicity are judged to be necessary such new studies should take into account the relevant route of exposure. This is for the specific substance the inhalation route, since inhalation exposure might occur during handling and use. In contrast, oral exposure is not expected to occur. In addition, the toxicological profile of the substance is dominated by the local reactivity at the respiratory tract. Systemic availability after oral exposure is not known. Under such circumstances route to route extrapolation is scientifically questionable and therefore the oral route should be avoided. Also dose finding for any additional study will benefit from the already available database on repeated dose toxicity, which is by the inhalation route.*" Furthermore, as mentioned in section 0.2.2.3, ECHA acknowledges your statement in your comments according to Article 50(1) that uncertainty remains for the hazard assessment regarding reproductive toxicity of the registered substance, also with regard to the administration by inhalation.

However, the appropriateness of the inhalation route of administration used in the reproductive toxicity studies is disputed by ECHA, because the default route of administration for hazard identification in reproductive toxicity studies is the oral route (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2.). ECHA notes that the absence of systemic effects in oral acute toxicity studies does not allow predictions on the absence of systemic effects in oral repeated dose toxicity studies. While you have argued why the inhalation route would be an appropriate route, it has not been demonstrated why the (default) oral route would not be an appropriate route.

ECHA notes that hazard assessment for repeated dose toxicity and reproductive toxicity have different aims. Hazard assessment for repeated dose toxicity studies following the REACH Regulation is dependent on the route of human exposure. Consequently, DNELs have to be derived for all relevant routes of human exposure. For derivation of such DNELs route-specific information is preferred or even required in case route-to-route extrapolation is not possible. However, hazard assessment for reproductive toxicity is intended to identify the reproductive hazard of a substance and DNELs for reproductive toxicity (pre-natal developmental toxicity and fertility) are not derived for a specific route of human exposure but usually by the oral route as indicated by the respective test methods (OECD TG 421 or 422; EU B.31/OECD TG 414). Therefore, the criteria for the selection of the most appropriate route of administration for testing are different. This difference is reflected in the REACH Regulation: for repeated dose toxicity studies conditions are provided in column 2 of Annex VIII, Section 8.6.1 and Annex IX, Section 8.6.2 when testing by inhalation or dermal route are appropriate. However, such criteria are not listed for reproductive toxicity studies according to Section 8.7. of Annexes VIII, IX or X. Furthermore, ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, July 2015), Chapter R.7a, section R.7.6.2.3.2 specifies that "*The selection of the "most appropriate route of administration" focuses on identification of hazards (...) and depends on the most appropriate route for identification of the intrinsic properties of the substance for reproductive hazard.* [...] *It is to be noted that corrosive or highly irritating substances should be tested preferentially via the oral route, however it must be noted that in vivo testing with corrosive substances at concentration/dose levels causing corrosivity must be avoided (see REACH Annex VII-X preamble)".* Since the substance to be tested is a solid used in a solution in an organic solvent and no information was provided to demonstrate that the oral route would not be appropriate, ECHA concludes that testing should be performed by the oral route.

In your comments according to Article 50(1) you stated with respect to administration by inhalation that, "*Considering the dose-response no primary developmental toxicity is expected to occur at doses below the irritant threshold after inhalation exposure.*"

ECHA notes that your comment is an argument in favour of testing by the oral route, since oral dosing is limited by local irritant effects to a lesser extent than inhalation, and thus, subsequent systemic availability could be higher.

In your comments according to Article 50(1) you stated that, *"No repeated dose study by the oral route exists for IPDI oligomers, allophanate type or any other polyisocyanate. Nevertheless, it not expected that repeated oral exposure to IPDI oligomers, allophanate type will lead to systemic toxicity. This assumption is based on physico-chemical properties and on acute oral toxicity data. At first, the molecular weight of 518 g/mol for the smallest possible oligomer (approx. at 12 % in the substance) does not favour absorption of the substance. Due to the reactivity of the isocyanate groups the formation of higher oligomers is expected to occur in the stomach, especially at high doses, where the substance can react with itself (isocyanate groups can hydrolyse to the amine, which can then react with remaining isocyanate groups3); therefore, the molecular weight of the administered species is even expected to increase after oral exposure. It is not known if degradation processes in the gastro-intestinal tract can form more readily systemically available species. In fact, acute oral toxicity studies of the substance and of other polyisocyanates reveal no test-substance related effects at all, except one polyisocyanate tested as a solution in xylol/ethyl acetate (2/1), which led to non-specific clinical signs at doses from 10000 mg/kg onwards. From a plausibility viewpoint the core structures (allophanate, isocyanurate and others) are not expected to readily degrade down as at least the final materials obtained from the aliphatic polyisocyanates, which are coatings, have to have excellent resistance to chemicals, abrasion and weathering per se and have shown since decades to behave so."*

ECHA notes that you did not provide experimental evidence to support the claims made in the comment regarding the registered substance's fate in mammalian organisms, specifically the gastrointestinal tract. On the contrary, you confirm that no oral repeated dose toxicity studies exist with the registered substance, which could substantiate the claims. Hence, ECHA is unable to conclude on these predictions. Since no information was provided to demonstrate that the oral route would not be appropriate, ECHA still considers that the oral route is the most appropriate route of administration for identification of a pre-natal developmental hazard of the registered substance.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rats or rabbits) by the oral route.

6. Soil simulation testing (Annex IX, Section 9.2.1.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Soil simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.3. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement Annex XI, Section 1. You provided the following justification for the adaptation: *'According to chapter 1 of Reach Regulation Annex XI, performing of a test is scientifically unjustified. In tests for ready biodegradation as well as tests with adapted inoculum no signs for biodegradation were observed. Therefore, it is not expected that biodegradation will occur in a simulation test for soil.'*

ECHA observes that in the respective sections of the registration dossier you have concluded that the substance is not readily biodegradable and has a logarithmic value of octanol-water partitioning coefficient of 6.7 which indicates potential for high adsorption of the substance to soil. ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.2.1.3., column 2 or the general adaptation rules of Annex XI because your substance is not readily biodegradable.

Furthermore, based on the provided screening level information in the dossier the substance can be considered as potentially P or vP. There is also no information on the degradation products and their fate. In addition, information on relating endpoints, bioaccumulation and aquatic toxicity, is missing and has been requested in this decision. ECHA hence considers that at this stage the information in the CSA is not complete due to the data gaps addressed in this decision. On this basis, the CSA cannot be used to justify that there is no need to investigate further the degradation of the substance and its degradation products.

In conclusions, ECHA considers that the information is needed for the PBT/vPvB assessment and for the identification of the degradation products in relation to the PBT/vPvB assessment.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

As the registered substance is a UVCB, ECHA notes that the simulation test on degradation needs to be performed for each relevant group of homologous constituents, the constituents tested being the ones deemed to be relevant for the PBT/vPvB assessment.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) Aerobic and anaerobic transformation in soil (test method EU C.23. / OECD TG 307) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.3.

In your comments according to Article 50(1) you stated that "[...] *Depending on the actual outcome of the hydrolysis experiments* [...]*, the Registrant will consider performing of an experimental study or an adaptation of the standard testing regime.".* ECHA notes that currently, no valid adaptation has been provided. ECHA notes further that the compliance of this data requirement will be evaluated after your submission of new information in a future dossier update.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic and anaerobic transformation in soil (test method: EU C.23./OECD TG 307). The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable shall be assessed. This can be done simultaneously during the same study.

7. Sediment simulation testing (Annex IX, Section 9.2.1.4.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Sediment simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.4. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement Annex XI, Section 1. You provided the following justification for the adaptation: *'According to section 1 of Reach Regulation Annex XI, performing of a test is scientifically unjustified. In tests for ready biodegradation as well as tests with adapted inoculum no signs for biodegradation were observed. Therefore, it is not expected that biodegradation will occur in a simulation test for water and sediment.'*

ECHA observes that in the respective sections of the registration dossier you have concluded that the substance is not readily biodegradable and has a logarithmic value of octanol-water partitioning coefficient of 6.7 which indicates potential for high adsorption of the substance to sediment. ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.2.1.4., column 2 or the general adaptation rules of Annex XI because your substance is not readily biodegradable.

As explained fully in section (6) above, ECHA considers that with the current information gaps the CSA cannot be used to justify that there is no need to investigate further the degradation of the substance and its degradation products. ECHA notes further that the information requested here is needed for the PBT/vPvB assessment and for the identification of the degradation products in relation to the PBT/vPvB assessment.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

As the registered substance is a UVCB, ECHA notes that the simulation test on degradation needs to be performed for each relevant group of homologous constituents, the constituents tested being the ones deemed to be relevant for the PBT/vPvB assessment.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) Aerobic and anaerobic transformation in aquatic sediment systems (test method EU C.24. / OECD TG 308) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.4.

In your comments according to Article 50(1) you stated that "[...] *Depending on the actual outcome of the hydrolysis experiments* [...], *the Registrant will consider performing of an experimental study or an adaptation of the standard testing regime.".* ECHA notes that currently, no valid adaptation has been provided. ECHA notes further that the compliance of this data requirement will be evaluated after your submission of new information in a future dossier update.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic and anaerobic transformation in aquatic sediment systems (test method: EU C.24./OECD TG 308). The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable shall be assessed. This can be done simultaneously during the same study.

8. Identification of degradation products (Annex IX, Section 9.2.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Column 2 of Section 9.2.3. of Annex IX further states that the study does not need to be conducted if the substance is readily biodegradable.

You have not provided any information on identification of degradation products that would meet the information requirement of Annex IX, Section 9.2.3.

As explained fully in section (6) above, ECHA considers that with the current information gaps the CSA cannot be used to justify that there is no need to investigate further the degradation of the substance and its degradation products. ECHA notes further that the information requested here is needed for the PBT/vPvB assessment and for the identification of the degradation products in relation to the PBT/vPvB assessment.

As explained above, there is no information on this endpoint for the registered substance in the technical dossier. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding appropriate and suitable test method, the methods will have to be substance specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You may obtain this information from the simulation study also requested in this decision, or by some other measure. You will need to provide a scientifically valid justification for the chosen method.

In your comments according to Article 50(1) you stated that "*The Registrant agrees to the need for further information on the identification of degradation products* [...].".

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Identification of the degradation products using an appropriate and suitable test method, as explained above in this section.

Notes for your consideration for requests 6 - 8

Before conducting the above request 8, you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), Chapter R.7.b., Sections R.7.9.2.3 and R.7.9.4. These guidance documents explain that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section R.7.9.4. further states that when substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.

Before conducting the above requests, 6 – 7 you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Sections R.7.9.4 and R.7.9.6 (version 3.0, February 2016) and Chapter R.11, Section R.11.4.1.1 (version 2.0, November 2014) on PBT assessment to determine the sequence in which the simulation tests are to be conducted and the necessity to conduct all of them. The order in which the simulation biodegradation tests are performed needs to take into account the intrinsic properties of the registered substance and the identified use and release patterns which could significantly influence the environmental fate of the registered substance.

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when results of the requests 6 -8 detailed above are available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

9. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.
"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex IX, column 2. You provided the following justification for the adaptation: *'According to column 2 of Reach Annex VII-X, a long-term ecotox study should be proposed by the registrant if the chemical safety assessment indicates the need to further investigate the effects on those organisms. No PNEC has been derived on the basis of three acute aquatic toxicity data as no effects have been observed in any of the studies. For this reason, performing of a CSA for the environment does not give a need for performance of a chronic study.'*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2, because in the short-term toxicity studies on aquatic invertebrates it is claimed that the substance is poorly water soluble, which according to Annex VII, Section 9.1.1 columns 2 and 1 indicates the need to consider a long-term study instead of the short-term study.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

In your comments according to Article 50(1) you stated that "*Depending on the outcome of the hydrolysis experiments* [...]*, adaptation of the standard testing regime is considered to be justified.*". ECHA notes that currently, no valid adaptation has been provided. ECHA notes further that the compliance of this data requirement will be evaluated after your submission of new information in a future dossier update.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

Notes for your consideration

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4) if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

10. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement to Annex IX, column 2. You provided the following justification for the adaptation: *'According to column 2 of Reach Annex VII-X, a long-term ecotox study should be proposed by the registrant if the chemical safety assessment indicates the need to further investigate the effects on those organisms. No PNEC has been derived on the basis of three acute aquatic toxicity data as no effects have been observed in any of the studies. For this reason, performing of a CSA for the environment does not give a need for performance of a chronic study.'*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2, because in the short-term toxicity studies on fish it is claimed that the substance is poorly water soluble, which according to Annex VIII, Section 9.1.3 columns 2 and 1 indicates the need to consider a long-term study instead of the short-term study.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 2.0, November 2014) fish early-life stage toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

Regarding the long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, ECHA considers that the FELS toxicity test according to OECD TG 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b, Figure R.7.8-4). The test method OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance Chapter R7b, version 2.0, November 2014). For these reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as most appropriate and suitable.

In your comments according to Article 50(1) you stated that *"Depending on the outcome of the hydrolysis experiments* [...]*, adaptation of the standard testing regime is considered to be justified.".* ECHA notes that currently, no valid adaptation has been provided. ECHA notes further that the compliance of this data requirement will be evaluated after your submission of new information in a future dossier update.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Before conducting any of the tests mentioned above in points 9-10 you shall consult the ECHA *Guidance on information requirements and chemical safety assessment (version 2.0, November 2014)*, Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

11. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD 305).

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Bioaccumulation in aquatic species, preferably fish" is a standard information requirement as laid down in Annex IX, Section 9.3.2.of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Sections 1 and 2.

You provided the following justification for the adaptation: '*The substance has several isocyanate groups which are expected to hydrolyse rapidly. In pure water however, no sign of hydrolysis was observed. The obvious reason for that are the very low water solubility and the fact that undissolved particles of the substance are passivated on its surface yielding a thin layer of polymeric ureas. Due to the physical-chemical properties it is well known that isocyanate groups react with water or alcohols. For this reason a non-guideline experiment was performed where the substance was mixed with a solution of the substance in acetonitrile and with water. During this procedure a decrease of isocyanate functions and formation of undissolved polyureas has been observed. Based on this fact the substance hydrolyses rapidly and is therefore not able to bioaccumulate. As long as the substance is not P and not T, further investigations for the B criterion are unnecessary.*'

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.3.2., column 2 or general rule for adaptation of Annex XI; Section 1 and 2 because the substance is reported to have log Kow 6.7 that according to Annex IX 9.3.2 indicates the need to perform the bioaccumulation test. Additionally, due to data gaps in information requirements according to Annex VIII, Section 9.2.2.1 (Hydrolysis as a function of pH), Annex IX Sections 9.1.5 (Long-term toxicity testing on invertebrates), 9.1.6 (Long-term toxicity testing on fish), 9.2.1.3 (Soil simulation testing) and 9.2.1.4 (Sediment simulation testing), the claim in the adaptation '[...]*the substance is not P and not T* [...]' cannot be confirmed.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7c* (version 2.0, November 2014) bioaccumulation in fish: aqueous and dietary exposure (test method EU C.13. / OECD TG 305) is the preferred test to cover the standard information requirement of Annex IX, Section 9.3.2. ECHA Guidance defines further that results obtained from a test with aqueous exposure can be used directly for comparison with the B and vB criteria of Annex XIII of REACH Regulation and can be used for hazard classification and risk assessment. Comparing the results of a dietary study with the REACH Annex XIII B and vB criteria is more complex and has higher uncertainty. Therefore, the aqueous route of exposure is the preferred route and shall be used whenever technically feasible. If you decided to conduct the study using the dietary exposure route, you shall provide scientifically valid justification for your decision. Data obtained from a dietary study will also need to be used to estimate BCF values.

In your comments according to Article 50(1) you stated that "*Depending on the outcome of the hydrolysis experiments* [...]*, adaptation of the standard testing regime is considered to be justified.*". ECHA notes that currently, no valid adaptation has been provided. ECHA notes further that the compliance of this data requirement will be evaluated after your submission of new information in a future dossier update.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bioaccumulation in fish: aqueous or dietary bioaccumulation fish test (test method: OECD TG 305)

Notes for your consideration

Before conducting the above test you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R.11.4. and Figure R.11-4 on the PBT assessment for further information on the integrated testing strategy for the bioaccumulation assessment of the registered substance. You should revise the PBT assessment when information on bioaccumulation is available.

12. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

Annex I, Section 5 of the REACH Regulation requires the Registrant to generate exposure scenarios and exposure estimations for the registered substance. The exposure assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards.

Pursuant to section 5.1.1 of Annex I exposure scenarios shall be generated. An exposure scenario, where relevant, should include the risk management measures to reduce or avoid direct and indirect exposure of the different environmental compartments to the substance.

Pursuant to Annex I, section 5.2.1 of the REACH Regulation the exposure estimation entails three elements: emission estimation, assessment of chemical fate and pathways and estimation of exposure levels. Emission estimation shall be performed under the assumption that the risk management measures (RMMs) and operational conditions (OCs) described in the exposure scenario (ES) have been implemented.

Additionally, Annex I, Section 5.2.4 specifically states that an estimation of the exposure levels shall be performed for all human populations (workers, consumers and humans liable to exposure indirectly via the environment) and environmental spheres for which exposure to the substance is known or reasonably foreseeable. Each relevant route of human exposure (inhalation, oral, dermal and combined through all relevant routes and sources of exposure) shall be addressed. Such estimations shall take account of spatial and temporal variations in the exposure pattern. In particular, the exposure estimation shall take account of (among others): transformation and/or degradation products.

Annex I, Section 6 of the REACH Regulation requires the Registrant to characterise the risk for each exposure scenario and to consider the human population (exposed as workers, consumer or indirectly via the environment and if relevant a combination thereof) and the environmental spheres for which exposure to the substance is known or reasonable foreseeable, under the assumption that the risk management measures described under exposure scenario in Section 5 of the same Annex have been implemented. In addition, the overall environmental risk caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments.

ECHA observes that for exposure estimation for all identified uses/exposure scenarios you claim the absence of emissions to environment leading to zero concentrations as predicted in environmental compartments (water, soil, air).

To justify absence of emissions to water you claim in all the exposure scenarios that: '*Cleaning processes are not performed with water as the substance reacts rapidly forming insoluble oligomeric and polymeric ureas.*'
To justify absence of emissions to soil you claim in all the exposure scenarios that: '*No direct or indirect exposure to soil as no waste water is generated and indirect emission via vapour is not* expected.'
To justify absence of emissions to air you claim in all the exposure scenarios that: '*No release expected due to the low vapour pressure of the substance. Further the substance hydrolyses rapidly with the humidity of the air.*'

ECHA notes that information on provided OC's and/or RMM's in the dossier is not detailed enough to understand how these measures might be implemented on a user site addressing different scenarios of the use of the substance (e.g. when the substance is used outdoor in building and construction work in brushing and spraying applications where the aerosols might be formed). ECHA considers that you have not demonstrated that reported risk management measures are adequate and sufficient to avoid emissions to environment. ECHA notes that, for example, ECHA's Guidance and Practical Guide on Intermediates describes how strictly controlled conditions of the use, leading to negligible releases of a substance, might be presented/justified.

ECHA additionally notes, that you have not provided the estimation of the exposure levels for the possible transformation and/or degradation products.

If you maintain the risk management measures, the revision should consist of a clear and detailed justification of their adequacy, addressing different scenarios of the use of the substance, and demonstrating how the proposed environmental risk management measures noted are feasible for all the uses, e.g. by providing detailed description of the scenarios of use of the substance together with a detailed description of a set up of technical measures (effciencies of those to be provided) necessary to ensure zero releases to environment.

In your comments according to Article 50(1) you stated that "*In the Chemical Safety Report the Registrant has demonstrated for indoor uses that direct or indirect exposure to surface water, soil and air is zero due to specific RMMs* [and due to] *the chemical (e.g. hydrolytical) and physico-chemical nature (e.g. low vapour pressure). The Registrant accepts that for outdoor uses a better description of the use and the behavior of the substance as a reactive intermediate in coatings is needed..*".

ECHA notes, that there are no RMM's described in the CSR together with their efficiency to allow to conclude zero exposure to environment and that the data describing the physico-chemical nature of the substance is not complete. Therefore ECHA concludes that currently, no valid adaptation has been provided

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to revise the exposure assessment for all the exposure scenarios for the registered substance and generate an exposure assessment for all the exposure scenarios for the degradation products and revise the risk characterisation accordingly. The chemical safety report shall be amended accordingly.

13. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for human health

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

Further, Annex I, Section 6.5. of the REACH Regulation states that "*for those human effects and those environmental spheres for which it was not possible to determine a DNEL or a PNEC, a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out.*"

ECHA observes that the registered substance is classified on the basis of the residual IPDI content. If the IPDI concentration is [redacted] %, the registered substance is classified as acute toxicity 4 (inhalation), skin sensitiser 1B and STOT single exposure 3 (resp. tract), while in case the concentration of IPDI is [redacted]%/[redacted] % the registered substance has an additional classification as respiratory sensitiser 1. According to ECHA's Guidance on information requirements and chemical safety assessment, Chapter E, section E.3.4, pages 18 to 32, as well as ECHA Guidance R.8 Appendix R. 8-10 and 8-11, for endpoints such as irritation/corrosion, sensitisation, acute toxicity where no dose descriptor is available, a more qualitative assessment has to be chosen. This qualitative approach shall define risk management measures (RMMs) and operational conditions (OCs) to prevent exposure and adequately protect against local effects.

ECHA notes that you have conducted a qualitative assessment for the substance being a skin sensitiser category 1 and therefore falling within the moderate hazard band. The recommended RMMs and OCs appear to be adequate in preventing dermal contact and therefore in ensuring safe use of the registered substance. In addition these RMMs and OCs are in line with those recommended in ECHA's Guidance on information requirements and chemical safety assessment, Chapter E.

Nevertheless, ECHA observes that there is no qualitative assessment for the hazard represented by the classification of the registered substance as respiratory sensitiser 1. Such type of substances are allocated to the high hazard band on the basis that exposure to such substances should be strictly contained because they may cause serious health effects for which a dose threshold is not usually identifiable. Indeed, the effective prevention of respiratory sensitisation requires appropriate protection of both respiratory tract and skin.

ECHA observes that for exposure scenarios described by process categories (PROCs) 7 and 11 (industrial and non-industrial spraying, respectively), the RMMs and OCs you recommended to protect against the risk arising from the respiratory sensitising properties are adequate, nevertheless those RMMs/OCs which have to be applied to ensure safe use against the respiratory sensitising properties are not addressed through a proper qualitative assessment in all exposure scenarios throughout the CSR.

In your comments according to Article 50(1) you stated that "*The classification for respiratory sensitising properties (inhalation) was derived by application of the mixture rules according to GHS. Thus a content of residual 3- isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate (IPDI, CAS 4098-71-9) of [redacted]% results in the hazard category Resp. Sens. 1, H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled. An evaluation of the manufacturing process has proven that the specification for the content of residual IPDI can be lowered to [redacted]%. Hence no classification for respiratory sensitising properties is required.*"

ECHA notes that this could be a valid reason for not performing the exposure assessment and risk characterisation. However, this comment has not been reflected in the registration dossier. The compliance of this data requirement will be evaluated after your submission of this information in a future dossier update.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to provide a qualitative exposure assessment demonstrating the likelihood that effects for respiratory sensitisation are avoided for all identified uses and exposure scenarios and to detail the operational conditions and risk management measures and revise the risk characterisation accordingly.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 16 November 2015.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the requests. In your comments you agreed to requests 1 and 2.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment(s).

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-50 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.