Helsinki,14 December 2016

Decision number: CCH-D-2114348608-40-01/F

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer, isocyanurate type, (List No 931-312-3), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for 3-Isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate homopolymer, isocyanurate type, (List No 931-312-3), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates submitted after 21 July 2016, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 23 January 2014.

On 13 May 2014, ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 18 June 2014, ECHA received comments from the Registrant on the draft decision, concerning the information requirements of Annex IX and X, Sections 9.4.2, 9.4.4, 9.4.6, 8.7.2 and 8.7.3. The compliance check request to submit information to meet the information requirement for Annex X, Section 8.7.3 was removed from the draft decision due to the legislative amendment of this provision by virtue of Commission Regulation (EU) 2015/282 of 20 February 2015. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning this information requirement. ECHA may, in accordance with Article 41 of the REACH Regulation, initiate a further compliance check of the registration dossier with respect to this information requirement.

On 5 September 2014, the Registrant updated his registration dossier with the submission number [redacted].

On 13 May 2016, the Registrant updated his registration with the submission number [redacted]

The ECHA Secretariat did consider the Registrant's further comments and updates. On the basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 21 July 2016, ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposal(s) for amendment to the draft decision were submitted.

On 26 August 2016, ECHA notified the Registrant of the proposal(s) for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal(s) for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal(s) for amendment received and amended the draft decision.

On 5 September 2016, ECHA referred the draft decision to the Member State Committee.

By 26 September 2016, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 25–27 October 2016, a unanimous agreement of the Member State Committee on the draft decision was reached on 26 October 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annexes IX and X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route.

B. Information related to chemical safety assessment and chemical safety report

Pursuant to Articles 41(1), 41(3), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

1. Revised DNELs for workers and derivation of DNELs for the general population and re-assessment of related risks or a full justification for not using the recommendations of ECHA guidance in DNEL derivation (Annex I, 1.4.1.), as specified in section III.C.1 below;
2. Revised environmental exposure assessment and risk characterisation (Annex I, sections 5 and 6 of the REACH Regulation), as specified in section III.C.2 below.

C. Deadline for submitting the required information

Pursuant to Articles 41(4) and 22(2) of the REACH Regulation the Registrant shall submit the information required by this decision in the form of an updated registration to ECHA by **21 December 2017.**

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

A "pre-natal developmental toxicity study" 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.

Weight of evidence 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, the Registrant has adapted the standard information requirement for pre-natal developmental toxicity, Annex IX, Section 8.7.2., by applying a weight of evidence and read-across adaptation according to the rules set out in REACH Annex XI, Section 1.2 and 1.5.

The following analysis presents the justification for the 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.

Information provided by the Registrant

ECHA observes that in the IUCLID dossier the Registrant has provided the following study summaries for the endpoint "developmental toxicity":

a. pre-natal developmental toxicity study (OECD TG 414) by inhalation with the analogue substance isophorondiisocyanate (IPDI) (CAS no 4098-71-9; [redacted] 2004);
b. pre-natal developmental toxicity study (OECD TG 414) by inhalation with the analogue substance 1,6-hexamethylene diisocyanate (HDI) (CAS no 822-06-0; [redacted] 2000b);
c. 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] 2004);
d. screening study (OECD TG 421) by inhalation with the analogue substance 4,4´-methylenedicyclohexyl diisocyanate (H12MDI) (CAS no 5124-30-1; [redacted] 2004);
e. screening study (OECD TG 422) by inhalation with the analogue substance hexamethylene diisocyanate (HDI) (CAS no 822-06-0; [redacted] 2000a).

The Registrant has further provided the following justification document attached to IUCLID section 13:"[redacted]"

The Registrant has provided the following arguments to support the weight of evidence and read-across approach for developmental toxicity:

1. *"The only reactive functional group in the molecule, the isocyanate group (NCO-group; -N=C=O; common functional group), is responsible for the toxicological mode of action (MoA) of the substances.*
2. *No toxic effect is anticipated from the aliphatic backbone of the molecules or the species that is yield from the NCO-conversion.*
3. *The MoA is characterised by the local irritant effect at the first site of contact/port-of-entry (e.g. respiratory tract, skin, eyes) and is, moreover, the common MoA for other aliphatic monomeric and homopolymeric isocyanates.*
4. *This defines the applicability domain of substances that should belong to the group: aliphatic monomeric and homopolymeric isocyanates without any other functional groups.*[...]
5. *None of the* [available] *studies give indications for systemic availability of the substances for any of the aliphatic isocyanates and by that confirms the primary port-of-entry toxicity mode of action."*
6. "Fully reliable developmental toxicity studies on rats according to OECD TG 414 are available for three of the aliphatic isocyanates." "*Accordingly, reproductive toxicity data exists for two examples of the most severe as well as for one example of the less toxic aliphatic isocyanates, thus allowing a reliable estimation of the other members of the group.*"

7. *"Regarding H12MDI and HDI also the data of the reproductive screening studies (OECD TG 421 and 422, respectively) were taken into account for the assessment of developmental toxicity. All study outcomes correlate well with the results of the corresponding repeated dose studies with respect to MoA and threshold of effects"*
8. *"It can be seen from the dataset (see table 6) that teratogenicity is not observed up to the highest dose for any of the substances. Moreover, no findings indicative for any specific developmental toxicity were observed. Fetal development is affected only at levels that causes clear maternal toxicity and thus considered as secondary effect."*
9. *"Therefore, the conclusion can be drawn that data uniformly show that toxicity for aliphatic isocyanates is limited to the port-of-entry; any other manifestations of toxicity occur only as secondary effect, e.g. secondary effects on the development. Since the port-of-entry effect is a local effect, and is therefore independent of the basal metabolic rate, it should be noted that this conclusion is valid independent of animal species. Based on read-across and taking into account the principle mode of action no potential for developmental toxicity was seen for the substance. It is not expected that further studies on developmental toxicity would reveal new insights for the hazard and risk assessment and therefore they should be omitted in case of IPDI oligomers, isocyanurate type. This conclusion is also based on animal welfare considerations taking into consideration the aim to balance the value of additional information gained with the need to avoid animal testing whenever possible."*

The Registrant concludes that *"Summarizing, 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."*

ECHA analysis of the proposed adaptation

With regard to the proposed adaptations ECHA has first evaluated the provided information with respect to grouping and read-across and then with respect to weight of evidence. ECHA has the following observations:

(i) Substance characterisation of source and target substances

The substance characterisation of the source/target substance(s) need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 *"How to use alternatives to animal testing"* (section 4.4. *substance characterisation)* it is recommended that *"UVCB substances should also be clearly characterised"* (version 1.3, February 2014). This ensures that the identity of the source/target substance(s) and their impurity profile allow an assessment of the suitability of the substances for read-across purposes. Specifically, there is ambiguity on the chemical composition of the registered substance; the entries for constituents "[redacted]" in section 1.2 of the dossier cover a variety of possible isomers. No analytical information regarding specific identification of isomers or the variation in the concentration of these isomers has been provided.

ECHA concludes that the current information does not allow a side-by-side comparison of the constituents and the composition between the source and target substances. Consequently it is not possible to establish a basis for the prediction of the properties of the registered substance.

In the Registrant's comments to one Member State Competent Authority's proposal for amendment, the Registrant has provided their detailed intentions to change the registration dossier. Furthermore, the Registrant provided the attachments

a) "[redacted]" and

b) "[redacted]."

ECHA considers that the Registrant's intentions on updating the registration dossier and document a) are outside the scope of the proposal for amendment of one Member State Competent Authority, and will be assessed in the updated registration dossier in the follow up stage.

ECHA considers that the Registrant's document b) is within the scope of the proposal for amendment. ECHA further notes that document b) provides an overview of the theoretical composition of the registered substance, which explains that testing is unsuitable due to the large number of hypothetical isomers. There is no information reported on the relative abundance of the different (groups of) constituents. Supporting (experimental) characterisation data has not been included. ECHA considers that the initial conclusion – rejection of read across- remains unchanged. In light of the complexity of this substance, the requested studies should be performed with the registered substance.

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

Grouping approach

The document [redacted] provided by the Registrant describes a group of aliphatic isocyanates and provides a justification for the group approach. ECHA therefore analysed whether the proposed grouping approach is acceptable.

ECHA notes that "*The applicability domain of the group and the read-across assessment was defined by expert judgement. The similarity is based on the fact that these substances share a common functional group (-NCO-group) and attributed to this, a common Mode of Action (port of entry irritant toxicity, no systemic effects)*". ECHA acknowledges that the members of this proposed group share a common functional group (isocyanate-group, NCO). However, 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 consists 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 the justification document 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 the claim that "*no toxic effect is anticipated from the aliphatic backbone of the molecules of the species that is yield from the NCO-conversion*". Instead, the document does demonstrate differences between HDI oligomers and IPDI oligomers, both of the isocyanurate type, indicating differences in the toxicological profile. ECHA notes that the NOAECs and LOAECs differ one order of magnitude (NOAEC = 3 mg/m^3 for HDI oligomers, isocyanurate type; NOAEC = 5 mg/m^3 for IPDI oligomers, isocyanurate type).

The structural and compositional differences between the proposed group members as described in the justification document and the registered substance are insufficiently substantiated at present. Therefore, ECHA understands that the group is solely based on assumed similar properties deriving from the presence of isocyanate groups. The 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.

ECHA concludes that there is no appropriate definition of the claimed group. The claim of structural similarity is only based on the presence of one functional group. The other structural and compositional differences and their potential impact remain largely unaddressed. The Registrant did not address the differences in core structures and side chains (e.g. R residue). Therefore, there is no adequate basis for predicting the properties of the registered substance from the proposed category members.

Read across from analogue substances

Despite the rejection of the proposed grouping approach, ECHA has also assessed the predictions based on read-across from the indicated analogous substances to the registered substance. The Registrant proposes 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. 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. indicates 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] % w/w concentration range) of [redacted]
- [redacted] % w/w typical concentration ([redacted] % concentration range) [redacted]

Furthermore, the Registrant further states that "*No toxic effect is anticipated from the aliphatic backbone of the molecules or the species that is yield from the NCO-conversion. The MoA is characterised by the local irritant effect at the first site of contact/port-of-entry (e.g. respiratory tract, skin, eyes) and is, moreover, the common MoA for other aliphatic monomeric and homopolymeric isocyanates.*"

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 in the target substance (as compared to the monomers) is insufficiently supported with experimental evidence. 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.

ECHA concludes that the Registrant has 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

The Registrant states that "*toxicity for aliphatic isocyanates is limited to the port-of-entry; any other manifestations of toxicity in reproductive toxicity studies occur only as secondary effect*"

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 document a) where it is reported that "isocyanates hydrolyse readily in water to yield carbamic acid as an unstable intermediate, which decarboxylates to produce carbondioxide 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 the 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 of the grouping and read-across approach

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 pre-natal developmental toxicity. ECHA concludes that the Registrant has 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).

(vi) Weight of evidence approach

ECHA has evaluated the weight of evidence information according to REACH Annex XI, Section 1.2., and assessed whether the Registrant has 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 IX, Section 8.7.2. for the registered substance.

ECHA acknowledges that in the mentioned developmental toxicity studies performed by inhalation with the listed monomeric diisocyanates which are of slightly different local toxiciy, no specific developmental toxic effects were reported. However, ECHA notes that the absence of developmental toxic (teratogenic) effects in the pre-natal developmental toxicity studies and in the mentioned reproductive screening studies do not allow to predict on the absence of developmental toxic effects by the registered substance, because the higher potency of respiratory irritation limits the maximum dose that could be tolerated by the test animals (MTD), as compared with registered substance. Furthermore, there are structural differences between the registered (UVCB) substance and the source substances (see read-across analysis above) which leads to the rejection of the proposed read-across.

ECHA concludes that the evidence provided to adapt the standard information requirement for 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 developmental toxicity. Therefore, the adaptation of the information requirement is rejected.

(vii) 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 endpoint 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, Section 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.

As explained above, the information available 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 method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

ECHA notes that in the comments on the draft decision, the Registrant has indicated that: "*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.*"

However, ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. In this Guidance document it is further noted that corrosive or highly irritating substances should be tested preferentially via the oral route. ECHA notes that the diisocyanate monomers for which developmental toxicity studies were provided, are either corrosive (IPDI, HDI) or severe irritating (H12MDI) to the skin. Hence, this information is less informative for hazard identification. ECHA notes that since systemic availability of the registered substance after oral administration is unknown, it cannot be concluded that route-to-route extrapolation is questionable and should be avoided. 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 414) in rats or rabbits by the oral route.

Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, Section 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if weight of evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that testing is necessary to fulfil this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, Section 8.7.2.

B. Information related to the chemical safety assessment and chemical safety report

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.

1. Revised DNELs for workers and derivation of DNELs for the general population and re-assessment of related risks or a full justification for not using the recommendations of ECHA guidance in DNEL derivation (Annex I, 1.4.1.).

Annex I, 1.4.1 of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:

a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
b) the nature and severity of the effect;
c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
d) and that the DNELs reflect the likely route(s), duration and frequency of exposure.

The ECHA *Guidance on information requirements and chemical safety assessment* Volume 8, Chapter R.8 (version 2.1, November 2012) provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

ECHA notes firstly that when deriving the long-term local DNEL for the inhalation route the Registrant has not used the remaining interspecies assessment factor (AF) of 2.5 recommended by ECHA guidance. He gives the following justification *"A factor 2.5 is suggested by the ECHA TGD for remaining interspecies differences, but justified deviations are possible. Rodents like the rat are in general more sensitive compared to humans as the rat`s ventilation frequency is higher. Therefore, as a general rule a factor of 1 for remaining interspecies differences provides sufficient protection."* ECHA notes that according to table R.8-6 of ECHA guidance a default remaining interspecies AF of 2.5 should be used for local effects on respiratory tract furthermore for local respiratory effects page 25 of the guidance states (emphasis added in underlined) *"Given that there could be significant quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms between humans and animals and when there is no data to inform on this uncertainty, it is prudent to assume that humans would be more sensitive than animals to effects on the respiratory tract. In such a situation, a chemical-specific remaining uncertainties factor or the default factor of 2.5 should be applied, as would be the case for systemic effects".* ECHA notes that the Registrant has not provided any substance specific arguments why the *"rats are more sensitive compared to humans* for respiratory irritation after inhalation exposure to the registered substance and why consequently an AF of 1 deviating from the default AF of 2.5 would be justified.

ECHA notes secondly that when deriving the long-term local DNEL for the inhalation route the Registrant has not used the default AF of 2 for the duration of exposure when extrapolating from sub-chronic to chronic exposure. He gives the following justification *"the assessment factor suggested by the ECHA TGD for exposure duration from subchronic to chronic should be 2, but extrapolation factors for differences in duration of exposure are not always needed. In the depicted case only local effects (no systemic effects) were observed, and the 14-days repeated dose toxicity inhalation pre-study ([redacted] 2009) leads to nearly the same result as the subchronic 90-days study ([redacted], 2009) (NOAEC 5 mg/m3 versus 2.7 mg/m3).*

Therefore it is not expected that a longer duration of the study would change the outcome and a AF of 1 is warranted". ECHA notes that the findings seen in the mid dose group of both 14-day (25 mg/m^3) and 90-day (15 mg/m^3) studies indicate severe irritation. These findings are reported quite similar in IUCLID and they occur at a lower dose in the 90-day study, therefore a time factor cannot be excluded and an AF should be applied.

ECHA notes thirdly that the Registrant has not derived DNELs for the general population. He gives the following justification *"The exposure of consumers to IPDI homopolymer is unlikely to occur via consumer products, because no consumer product is known to contain the substance. An exposure of consumers or general population via the environment is also unlikely to occur, because there are only low levels of exposure from environmental sources, and IPDI homopolymer released to the environment would rapidly be degraded by water and photooxidants. Therefore, DNELs for consumers or general population are not applicable as consumers are not involved in the industrial or professional use of IPDI homopolymer or of preparations containing this substance. Additionally, in view of low toxicity in experimental studies and lowlevels of exposure from environment sources, the risk to the general population appears to be minimal."* As specified in section III.C.2 below the assessment of environmental exposures is not adequate and consequently an absence of exposure of the general population via the environment is not demonstrated. Therefore, after revising the environmental exposure assessment, it is necessary to derive the DNELs and provide a transparent risk characterisation for the general population reflecting the likely routes of human exposure.

As explained above, the information provided on DNEL for the registered substance in the chemical safety report does not meet the general provisions for preparing a chemical safety report as described in Annex I, 1.4.1.

In his comments according to Article 50(1) the Registrant stated that *"After a final decision from ECHA the registrants will provide a full and substance specific justification for adaption of the assessment factors (AFs) and subsequently for the DNEL derived for workers for the long-term inhalation (local effects) provided in the original CSA. After a final decision from ECHA the registrants will also provide a full justification why no significant exposure to the general population would occur."*

Therefore, pursuant to Article 41(1)(c) and (3) of the REACH Regulation, the Registrant is requested to submit in the chemical safety report revised DNELs for workers and derive DNELs for the general population and re-assessment of related risks or a full justification for not using the recommendations of ECHA guidance in DNEL derivation, as specified below:

- As regards DNEL for workers for the long-term inhalation local effects the Registrant is given two options: The Registrant shall revise the DNEL by applying the assessment factors recommended by ECHA as explained above. Subsequently, the Registrant shall re-assess related risks. In the alternative, the Registrant shall, in accordance with Annex I, 1.4.1, provide a full justification for the DNEL derived workers for the long-term inhalation local effects provided in the chemical safety report by specifying how the following has been taken into account:
  - the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
  - the nature and severity of the effect;
  - the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
  - and that the DNELs reflect the likely route(s), duration and frequency of exposure.

- As regards DNELs for the general population the Registrant is given two options: The Registrant shall derive the DNELs for general population according ECHA Guidance on information requirements and chemical safety assessment, R.8 (version 2.1, November 2012) reflecting the likely routes of human exposure. Subsequently, the Registrant shall re-assess related risks. In the alternative, the Registrant shall provide a full justification why no significant exposure to the general population would occur.

Notes for consideration by the Registrant

The results of the studies requested under section II.B. shall be taken into account when revising the DNELs.

2. Revised environmental exposure assessment and risk characterisation (Annex I, sections 5 and 6 of the REACH Regulation)

According to Article 14(4) of the REACH Regulation, if the substance fulfils the criteria for any of the hazard classes of Annex I to Regulation (EC) No 1272/2008 listed in Article 14(4) of the REACH Regulation or is assessed to be a PBT or vPvB, the chemical safety assessment (CSA) shall include an exposure assessment and risk characterisation. The exposure assessment shall be carried out according to section 5 of Annex I and shall include exposure scenarios and exposure estimations for the registered substance. 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. According to the Article 41 (1)(c) of the REACH Regulation the ECHA may examine any registration in order to verify that the proposed risk management measures are adequate.

ECHA notes that the Registrant has classified the substance for hazard classes H317 and H335 (sensitising to skin and may cause respiratory irritation) and thus, fulfilling the criteria set out in Article 14(4) of the REACH Regulation to require an exposure assessment and risk characterisation in the chemical safety assessment.

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. Guidance on information requirements and chemical safety assessment, Chapter R.16 (ECHA, October 2012) further specifies that "*professional use may include the use of substances as such or in mixtures, in order to deliver services to business or private customers. This may include sophisticated equipment and specialised, trained personnel.*"

ECHA observes that for exposure estimation for all identified uses/exposure scenarios the Registrant claims absence of emissions to environment leading to zero concentrations as predicted in environmental compartments. ECHA underlines that for the use under professional settings the Registrant claims also following environmental risk management measures: "*all waste gases from professional end use are transferred to a combustion unit or to an activated carbon filter*" and "*sealing of all relevant soil surfaces in the facility*". ECHA notes that information provided 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 as a process regulator in brushing and spraying applications).

ECHA considers that the Registrant has not demonstrated that these risk management measures are feasible for the use under professional settings. Therefore, ECHA concludes that releases, at least to air and soil, from uses under professional settings can be expected and consequently, exposure estimation for Exposure scenario 4 (professional end use) provided in the Chemical Safety Report (CSR) is not reliable.

In his comments according to Article 50(1) the Registrant stated that *"The registrants consider direct/indirect exposure of soil unlikely even for the use under professional settings"* and that *"Details and data on transformation pathways, toxicological profile of degradation/transformation products, etc. will be presented and discussed in the dossier update. The exposure assessment including risk management measures will be refined and updated in order to demonstrate that the risk management measures are adequate for use under professional settings. This will be carried out following the final decision."*

Therefore, pursuant to Article 41(1) and 41(3) of the REACH Regulation the Registrant is requested to provide a revised Exposure scenario 4. The Registrant can provide in the Exposure scenario 4 an exposure assessment based on demonstrated adequate environmental risk management measures, and release factors supported by those risk management measures. If the Registrant maintains 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 uses under professional settings, e.g. by providing detailed description of the scenarios of use of the substance under professional setting together with a detailed description of a set up of technical measures (efficiencies of those to be provided) necessary to ensure zero releases to environment. The chemical safety report shall be amended accordingly.

C. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation/extended one-generation reproductive toxicity study (Annex X, 8.7.3) and studies on terrestrial toxicity (Annex IX, 9.4.2, 9.4.4., 9.4.6). As those requests are not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant

covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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.