EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114288084-45-01/F Helsinki, 10 December 2014

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

For 4-hydroxy-4-methylpentan-2-one, CAS No 123-42-2 (EC No 204-626-7), 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 4-hydroxy-4-methylpentan-2-one, CAS No 123-42-2 (EC No 204-626-7), 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 tonnes per year. This decision does not take into account any updates submitted after 12 June 2014, 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 16 September 2013.

On 10 December 2013 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 24 January 2014 ECHA received comments from the Registrant on the draft decision.

On 6 February 2014 the Registrant updated his registration dossier with the submission number [redacted]

The ECHA Secretariat considered the Registrant's comments and update.

The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 12 June 2014 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, proposals for amendment to the draft decision were submitted.

On 18 July 2014 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 proposals for amendment received and amended the draft decision.

On 28 July 2014 ECHA referred the draft decision to the Member State Committee.

By 18 August 2014, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposals for amendment into account

The present decision relates solely to a compliance check requesting information in form of sub-chronic toxicity (90-day) and pre-natal developmental toxicity studies (Annex IX, 8.6.2 and Annex X, 8.7.2.), documentation for the recommended personal protective equipment (Annex I, 5.1.1. in conjunction with Annex II, 0.1.2. and 8.2.2.2(b)), and revised exposure assessment and risk characterisation for workers via dermal route or a justification why the efficiency values used for gloves are considered appropriate. The other compliance check requirement of two-generation reproductive toxicity study is addressed in a separate decision although all information requirements were initially addressed together in the same draft decision.

After discussion in the Member State Committee meeting on 16-18 September 2014, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 17 September 2015. 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)(vi) and/or (vii), 12(1)(e), 13 and Annex 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:

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats;

2. Pre-natal developmental toxicity study (Annex IX, 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)(c), 41(3), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

1. Documentation for the recommended personal protective equipment, i.e. gloves to be worn need to be specified clearly when handling the substance or mixture (Article 14(6), Annex I, 5.1.1., in conjunction with Annex II, 0.1.2. and 8.2.2.2.(b)(i))., including:
    a. The type of material and its thickness, and
    b. The typical or minimum breakthrough times of the glove material.

2. Revised exposure assessment and risk characterisation for workers via dermal route or a justification why the efficiency values used for gloves are considered appropriate (Art. 41.1(c) of the REACH Regulation and Annex I, Section 5.2.4 and 5.2.5.), as specified in section III.3.B.4. below.

Note for consideration by the Registrant:

The Registrant 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 sound scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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 Authorities of the Member States for possible enforcement.

C. Deadline for submitting the required information

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **17 June 2016**.

III. Statement of reasons

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

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.

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 Annex X of the REACH Regulation.

0. Read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "provided that the conditions set out in Annex XI are met". According to Annex XI, 1.5 there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

The Registrant has adapted the information requirements applying a read-across approach in accordance with the principles set out in Annex XI, Section 1.5(2). According to Annex XI, 1.5(2), the similarities may be based on the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals. According to the Registrant, the read-across hypothesis is based on rapid and extensive metabolism of methyl i-butyl ketone (MIBK) to diacetone alcohol, (DAA, 4-hydroxy-4-methylpentan-2-one, the registered substance), which is the major metabolite formed from MIBK exposures, and MIBK may thus be used as an appropriate surrogate for DAA.

To support the proposed read-across approach, the Registrant has provided five toxicokinetic studies conducted with the read-across substance MIBK. To further support the proposed read-across approach, the Registrant has provided repeated dose toxicity (14-week), carcinogenicity, pre-natal developmental toxicity and two-generation reproductive toxicity inhalation studies conducted with MIBK, and acute toxicity, skin and eye irritation, skin sensitization, mutagenicity, and an oral combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) and repeated dose toxicity (6-week) inhalation study conducted with DAA.

ECHA has analysed the dossier update in light of the requirements of Annex XI, 1.5. Based on the information provided it can be concluded that:

(i) According to the Registrant, the read-across is based on "rapid and extensive metabolism of MIBK to DAA". However, an oral metabolism study in rats shows that the maximum plasma concentration of DAA was reached only nine hours after MIBK administration and MIBK was detectable until 12 hours after the dosing. An inhalation study in rats shows that one hour after the last dosing, the plasma concentrations of DAA were 100%, 75% and 50% of the MIBK concentrations after administration of 200, 400 and 600 ppm MIBK, respectively, and after oral administration of 150, 300 and 600 mg/kg bw/day MIBK 21%, 56% and 83% of the MIBK concentration, respectively. Therefore, the metabolism cannot be considered rapid and extensive in a sense that systemic exposure to MIBK can be deemed insignificant compared to systemic exposure to DAA. The Registrant has explained that exposure to "*DAA is significantly higher than the C_{max} of MIBK for 9 hours*" but he has not explained how the relatively slow metabolism may impact the toxicity of DAA when it is formed from MIBK.

(ii) The toxicokinetic assessment provided by the Registrant further indicates that DAA is readily absorbed via oral, dermal and inhalation routes. MIBK absorbs rapidly (C_{max} in 0.25 hours) and based on the quite similar physicochemical properties of DAA and MIBK, it can be expected that absorption of DAA is also rapid. However, the metabolism of MIBK to DAA is relatively slow as stated above, and thus it is possible that the rate by which DAA reaches systemic circulation, distribution and elimination is different if it is given as a parent substance. There is thus an uncertainty on how this may impact the overall effect of DAA when administered as a parent substance and when it is formed via metabolism, which the Registrant has not considered.

(iii) A toxicokinetic study in rats demonstrates that toxicokinetic behaviour of MIBK is different when it is administered orally or via inhalation. For example, after inhalation exposure of MIBK, MIBC, another metabolite, is detectable in plasma, liver and lungs (34% - 49% of MIBK concentration) one hour after the last dosing, whereas it was not detected after oral exposure in this study. The Registrant states that the majority of the internal exposure is to DAA in both oral and inhalation studies with MIBK. However, he has not addressed the difference in the MIBK metabolism after oral and inhalation administration.

(iv) The Registrant has used the $AUC_{0\text{-}12hour}$ value ('Area Under the Curve' value) of 80% for DAA based on the administration of MIBK to estimate the systemic exposure and toxicity of DAA. The Registrant has not provided an AUC value for DAA based on DAA administration, which would have provided a more accurate comparison of the bioavailability of the two substances. A toxicokinetic study in mice shows that the plasma concentrations of DAA are considerably lower after MIBK administration compared to DAA administration: MIBK (5 mmol/kg bw) and DAA (2.5 mmol/kg bw) were given as a single i.p. injection to mice. Plasma DAA concentrations were approximately 40, 40, 90 and 60 µg/ml after MIBK administration, and 450, 300, 150 and 150 µg/ml after DAA administration at 15, 30, 60 and 90 minutes, respectively. Therefore, it can be concluded that the systemic exposure of DAA is significantly higher when it is given as a parent substance (even at 50% lower dose than MIBK) than when is formed via metabolism after MIBK administration. The Registrant has taken into account the 80 % AUC value in the estimation of exposure and toxicity of DAA. However, in his estimation he has not taken into account the differences observed in the mouse study.

(v) According to the ECHA Guidance document on information requirements and chemical safety assessment (Chapter 6 – QSARs and Grouping of chemicals - section R.6.2.2.1), "*read-across of the PNEC or DNEL itself from the source to target chemical is not recommended. When deriving a DNEL or PNEC based on an endpoint which has been read-across, it is important to ensure that the read-across is sound and that the target chemical is unlikely to be more potent than the source chemical. In cases where there are multiple source chemicals, and consequently a range of possible values for read-across, the use of the most conservative (lowest) value may be sufficient to account for the uncertainty in the read-across*". The Guidance further states that "*An assessment factor on the quality of the whole database should, if justified, be applied to compensate for the potential remaining uncertainties in the derived DMEL. Special consideration should be given to the situation that alternative data are used, e.g. use of (Q)SAR, read across or chemical categories or the use of subchronic studies for deriving some surrogate dose descriptor.*" However, the Registrant has not taken into account the uncertainties described in sections i – iv above either by using the most conservative NOAEL values, e.g. NOAEC (1041 mg/m^3) from the repeated dose (6-week) inhalation study conducted with the

registered substance or by applying an additional assessment factor to cover the uncertainty when deriving DNEL values using the MIBK data. Instead he has used a MIBK OEL value of 83 mg/m3 for systemic dermal and inhalation DNEL derivation.

(vi) For the sub-chronic toxicity (90-day) endpoint, the Registrant has submitted an oral OECD 422 screening study and a repeated dose (6-week) inhalation study conducted with DAA, and a repeated dose (14-week) and carcinogenicity studies conducted with the read-across substance MIBK via inhalation. From the registration dossier of MIBK, ECHA is aware of an oral sub-chronic toxicity (90-day) study conducted with MIBK, which however, has not been submitted to support the hypothesis. The results indicate that when given orally, DAA is more potent than MIBK which is in line with the results of the toxicokinetic studies that indicate lower internal dose of DAA after MIBK administration than suggested by the Registrant. The NOAECs and LOAECs of DAA and MIBK were at similar levels when the substances were given via inhalation indicating a quite similar toxicological profile. However, due to shorter exposure period of the DAA study (6 weeks) and relatively slow metabolism of MIBK to DAA a definite conclusion about the toxicity profiles of the two substances cannot be made. The uncertainties regarding the metabolism and differences in toxicity potencies have not been taken into account by the Registrant resulting in underestimation of hazard of the registered substance.

(vii) For the pre-natal developmental toxicity and two-generation reproductive toxicity endpoints the Registrant has submitted an oral OECD 422 screening study conducted with DAA, and pre-natal developmental toxicity and two-generation reproductive toxicity studies conducted with MIBK via inhalation. An oral screening study indicates that DAA might have adverse effects on fertility (decreased fertilisation rate, number of implantations and implantation rate at the highest dose). Although maternal toxicity (CNS, mild-moderate liver, kidney and adrenal effects) was observed at the same dose level as fertility effects it is not possible to conclude if the effects were secondary to maternal toxicity. No reproductive adverse effects were noted in an inhalation two-generation reproductive toxicity study with MIBK up to the highest dose of 8219 mg/m3. In the pre-natal developmental toxicity study with MIBK, decreased pup weight and delayed skeletal ossification were observed only at highest dose 12292 mg/m3. The results indicate different developmental and fertility toxicity profile of DAA and MIBK. In addition, as stated above in section (iii), route-to route extrapolation cannot be made due to different oral and inhalation toxicokinetic behaviour of MIBK.

Based on the data submitted, ECHA considers that the Registrant has not provided sufficient evidence to demonstrate that the metabolism of the source substance MIBK to the registered substance DAA is rapid and extensive enough and thus the criteria of Annex XI, 1.5 (2) are not met.

ECHA concludes that the read-across approach cannot be accepted for the sub-chronic toxicity (90-day) endpoint as the uncertainties discussed above in paragraphs (i) – (vi) have not been taken into account by the Registrant. Therefore, the Registrant is not able to predict relevant properties of the registered substance by using the results of the read-across substance without underestimating the hazards and thus the information submitted is not adequate for the purpose of classification and labelling and/or risk assessment.

ECHA further concludes that the read-across approach is not acceptable for the pre-natal developmental toxicity endpoint as there is uncertainty regarding the route-to-route extrapolation due to different oral and inhalation toxicokinetic behaviour of MIBK and because the underlining toxicological information (an oral OECD 422 screening study conducted with DAA, and pre-natal developmental toxicity and two-generation reproductive toxicity studies conducted with MIBK via inhalation) does not support the hypothesis. Therefore, the Registrant is not able to predict the relevant properties of the registered substance by using the results of the read-across substance. Further, the results of the read-across substance cannot be considered adequate for the purpose of classification and labelling and/or risk assessment.

ECHA therefore concludes that the criteria of Annex XI, 1.5 are not met, and the read-across approach, as presented by the Registrant, cannot be accepted to meet the information requirements in question.

Notes for consideration by the Registrant:

In the comments to the draft decision and in the updated dossier the Registrant acknowledged the analysis of the shortcomings of the read-across adaptation. He provided a detailed justification and a testing plan (decision tree) to support the read-across approach, but these did however not yet resolve the above shortcomings. The Registrant indicated that he plans to provide additional toxicokinetic information to address the concerns raised by ECHA. In the decision tree the Registrant proposed different options in case the toxicokinetic study does not support the read-across approach:

- The toxicokinetic study will be performed with the registered substance, DAA, which will allow direct comparison of DAA and MIBK.
- If the results show that C_{max}, AUC and $T_{1/2}$ of DAA are lower or equal than MIBK data from MIBK can be used as they present the worst case scenario.
- If the study indicates that absorption of DAA is higher than MIBK, the Registrant will conduct toxicokinetic modelling for MIBK and DAA (oral and inhalation, single and repeated exposure).
- If the modelling results in insufficient information on inhalation toxicokinetic parameters, the read-across will be further substantiated to meet the criteria of Annex XI, 1.5.
- If the modelling does not provide sufficient information, an inhalation study with DAA will be conducted, followed by a new toxicokinetic modelling, and read-across will be substantiated to meet the criteria of Annex XI, 1.5.

The Registrant further states that "*depending on the outcome, any assessment factors will be taken into account if necessary, but the read across in itself will be able to be fully justified with the information generated as presented in the decision tree...*"

The Registrant states that the DNEL derivation and risk assessment will be addressed and updated, if needed, once the new information is available, and that the different toxicological profiles of DAA and MIBK will be addressed.

ECHA stresses that – as indicated in Section II above – the Registrant may under his own responsibility improve the adaptation, as he seems to propose in his comments. The Registrant may take the following observations of ECHA on his strategy into consideration:

- ECHA has analysed the more detailed justification and decision tree in light of the requirements of Annex XI, 1.5 and notes that the Registrant has based his read-across justification on a toxicokinetic study of DAA and different options based on the results of that study. ECHA notes that the Registrant intends to address the concerns raised by ECHA in paragraphs (i)-(vii) above, i.e. comparison of systemic exposure of DAA and MIBK (toxicokinetic parameters such as Cmax, AUC and T1/2), different toxicological profiles of DAA and MIBK, oral and inhalation toxicokinetic of MIBK, DNEL derivation and risk assessment. Further information on toxicokinetic profile of DAA might address some of the uncertainties mentioned in paragraphs (i)-(vii) above.

- The Registrant has to demonstrate that all issues in paragraphs (i)-(vii) above, in particular, the uncertainties regarding the rate and completeness of the metabolism, toxicokinetic behaviour of MIBK via oral and inhalation route (uncertainty regarding route-to route extrapolation due to different oral and inhalation toxicokinetic behaviour of MIBK), systemic exposure (rate at which it reaches systemic circulation, plasma concentration, distribution and elimination) of DAA after MIBK metabolism and after administration as parent substance, are adequately addressed.

- ECHA notes that as the read-across approach should be endpoint-specific the issues regarding the pre-natal developmental toxicity study discussed in paragraph (vii) above (different developmental and fertility toxicity profile of DAA and MIBK and route-to-route extrapolation) need to be addressed. It is at the Registrant's discretion to initiate any such investigations to acquire sufficient data to substantiate his read-across hypothesis.

- In case where the planned toxicokinetic test, the subsequent modelling/studies and new information would not confirm the read-across hypothesis relied upon by the Registrant, this outcome shall not alter the obligation of the Registrant to meet the standard information requirements. Should the read-across strategy be inadequate, it is the responsibility of the Registrant to submit reliable information or adaptations which is used in a way that does not underestimate the hazards of the registered substance in relation to relevant endpoints to fulfil the information requirements.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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.

The Registrant has not provided any study record of a sub-chronic toxicity study (90-day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

In the technical dossier the Registrant has provided study records for an oral "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422) and a repeated dose toxicity (6-week) inhalation study conducted with the registered substance. However, these studies do not provide the information required by Annex IX, Section 8.6.2., because the exposure duration on both studies is less than 90 days.

Furthermore, the Registrant has sought to adapt this information requirement and has provided study records for repeated dose toxicity (14-week) and carcinogenicity studies conducted with the read-across substance MIBK. The justification of the adaptation given by the Registrant is based on rapid and extensive metabolism of methyl i-butyl ketone (MIBK) to diacetone alcohol, (DAA, 4-hydroxy-4-methylpentan-2-one, the registered substance), which is the major metabolite formed from MIBK exposures.

However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, 1.5. as explained in Section III.0. 'Read-across approach' above. In particular, the uncertainties regarding the rate and completeness of the metabolism, toxicokinetic behaviour of MIBK via oral and inhalation route, systemic exposure (rate at which it reaches systemic circulation, plasma concentration, distribution and elimination) of DAA after MIBK metabolism and after administration as parent substance have not been taken into account thus resulting in underestimation of hazard of the registered substance. Therefore, the information provided is not adequate for the purpose of classification and labelling and/or risk assessment.

Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

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.

ECHA considers that testing by the oral route is most appropriate because a) of the physico-chemical properties of the substance, b) the information provided on the uses and human exposure, and c) as the Registrant has derived a DNEL for long-term local inhalation exposure and has thus covered the risk for respiratory irritation.

According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD 408) in rats.

2. Pre-natal developmental toxicity study (Annex IX, 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.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

In the technical dossier the Registrant has provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422). However, this study 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.

Furthermore, the Registrant has sought to adapt this information requirement and has provided study records for pre-natal developmental toxicity studies in rats and mice conducted with the read-across substance MIBK. The justification of the adaptation given by the Registrant is based on rapid and extensive metabolism of methyl i-butyl ketone (MIBK) to diacetone alcohol, (DAA, 4-hydroxy-4-methylpentan-2-one, the registered substance), which is the major metabolite formed from MIBK exposures.

However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, 1.5. as explained in Section III.0. 'Read-across approach' above. In particular, the results of the toxicological studies indicate different developmental and fertility toxicity profile of DAA and MIBK. In addition, as stated above in section (iii), there is an uncertainty in route-to route extrapolation due to different oral and inhalation toxicokinetic behaviour of MIBK. Therefore, the information provided is not adequate for the purpose of classification and labelling and/or risk assessment.

Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

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.

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, 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 fulfill 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, 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 (CSR) which shall document the chemical safety assessment (CSA) conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

1. Documentation that risks to workers are adequately controlled

Article 14(6) as well as Annex I, 0.1., 5.1.1., 5.2.4. and 6.2. of the REACH Regulation require registrants to identify and apply appropriate measures to adequately control the risks identified in a CSR. The exposure shall be estimated and risks shall be characterised in the CSR under the assumption that relevant risk management measures have been implemented.

Pursuant to Annex VI, section 5 and Annex II, section 0.1.2. of the REACH Regulation the information provided in the registration dossier shall be consistent with that in the Safety Data Sheet (SDS). The requirements of Safety Data Sheets are specified in Annex II of the REACH Regulation (amended by Commission Regulation (EU) No 453/2010).

According to Annex I, 0.3., 0.5. and 5.1.1. the applied Risk Management Measures (RMM) have to be indicated in the CSR. Annex II, section 8.2.2.2. (b)(i), requires the Registrant to describe the relevant RMM in detail (e.g. the type of gloves to be worn shall be clearly specified based on the hazard of the substance or mixture and potential for contact and with regard to the amount and duration of dermal exposure) in order to minimise the exposure for workers handling the registered substance. In particular, the following requirements for hand protection in order to avoid dermal exposure need to be provided consistently in the SDS and CSR:

- The type of material and its thickness,
- The typical or minimum breakthrough times of the glove material.

In the CSR, the Registrant indicated the following for hand protection: *Wear gloves tested to EN374.* The Registrant also provided additional good practice advice in those cases where it was determined use of gloves was not required to generate the predicted quantitative estimates of exposure below the DNEL.

In section 11 of the technical registration dossier in the part for Exposure controls/personal protection, the following is stated:

Hand Protection: Intermittent contact: PVC, nitrile rubber, Impervious butyl rubber gloves according to permeation index EN 374: 1 (time elapsed > 10 mins). Prolonged contact: Neoprene gloves.

To ensure the safe use of a substance it is essential to have detailed guidance on risk management measures, e.g. personal protective equipment. Although the gloves are reported in the CSR and IUCLID section 11 as required personal protective equipment to prevent dermal exposure to the substance and the material type of gloves to be worn is specified, thickness and typical or minimum breakthrough time when handling the substance is not.

It is recognised that many exposure scenarios for the registered substance will result in exposure to a mixture of chemicals and the appropriate advice on the specific glove requirements for these undefined situations will be within the safety data sheets relating to product formulations. The selection of glove will be determined by the most relevant components of those mixtures and further specification of this information is not required within the CSR or section 11 of IUCLID.

Therefore, pursuant to Article 41(1)(c) and 41(3) of the REACH Regulation the Registrant is requested to provide for the substance documentation for the recommended material type, its thickness and the typical or minimum breakthrough time for the glove type recommended, with regard to the amount and duration of dermal exposure.

Notes for consideration by the Registrant:

Regarding how to report the gloves specifications, the information should be included both in section 11 of the technical IUCLID dossier (Guidance on Safe Use) which is the disseminated part of the dossier and in the CSR where the appropriate measures to adequately control the risk are to be reported.

It is the responsibility of the Registrant to ensure consistency of the information within the CSR, and between the CSR, IUCLID section 11 and the safety data sheet.

2. Revised exposure assessment and risk characterisation for workers via dermal route or a justification why the efficiency values used for gloves are considered appropriate (Art. 41.1(c) of the REACH Regulation and Annex I, Section 5.2.4 and 5.2.5.).

Pursuant to Article 41.1(c) of the REACH Regulation ECHA may verify that any required Chemical Safety Assessment (CSA) and Chemical Safety Report (CSR) comply with the requirements of Annex I and that the proposed risk management measures are adequate.

A chemical exposure assessment performed by a Registrant shall include an exposure assessment according to section 5 of Annex I of the REACH Regulation. Annex I, section 5.2.4 of the REACH Regulation, requires the Registrant to perform an estimation of the exposure levels for all human populations and each relevant route of exposure shall be addressed. Further, the estimation of exposure shall take account of implemented or recommended risk management, including the degree of containment. In addition, Annex I, section 5.2.5 of the REACH Regulation indicates that appropriate models can be used for the estimation of exposure levels.

ECHA notes that the Registrant has used ECETOC TRA to estimate exposure for a variety of worker exposure scenarios using efficiency for gloves of 98% to estimate the exposure via dermal route. However, ECHA notes that according to the guidance for the model used (ECETOC TR 114) the maximum pre-defined values are 95% for industrial users and 90% for professional users. The registrant has not included in the CSR any case specific justification (e.g. related to the substance or the specific recommended or implemented personal protection measures or based on relevant biomonitoring data) for deviating from the recommended efficiency factor in using ECETOC TRA.

As explained above, the information provided on the dermal exposure estimates for the registered substance in the chemical safety report does not meet the requirements for preparing a chemical safety report as described in Annex I. Consequently, it is necessary to revise the dermal exposure estimates or to provide a justification explaining why in this specific case using higher efficiency values for gloves (98%) is considered appropriate.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit in the chemical safety report the following information: revised exposure assessment and risk characterisation for workers via dermal route using the pre-defined values for gloves efficiency stated above or a justification explaining why in this specific case using higher efficiency values for gloves (98%) is considered adequate.

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 addressed another study (two-generation reproductive toxicity study, Annex X, Section 8.7.3). As this study is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 18 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

ECHA stresses that the information submitted by other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation

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://echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]
Leena Ylä-Mononen
Director of Evaluation