ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000004225-80-03/F Helsinki, 28 November 2014

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

For isoprene, CAS No 78-79-5 (EC No 201-143-3), 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 isoprene, CAS No 78-79-5 (EC No 201-143-3), 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 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 12 August 2013.

On 25 October 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.

On 22 November 2013 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

A. Information in the technical dossier related to the identity of the substance

Pursuant to Articles 41(1), 41(3), 10(a)(ii) and Annex VI, Section 2 of the REACH Regulation the Registrant shall submit the following information for the registered substance subject to the present decision:

1. Spectral data (Annex VI, 2.3.5), as further specified under section III.A.1. below;
2. Description of the analytical methods or the appropriate bibliographical references for the identification of the substance (Annex VI, 2.3.7.), as further specified under section III.A.2. below.

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

Pursuant to Articles 41(1)(c), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report (CSR) and in section 6 of the technical registration dossier (IUCLID):

3. Revised predicted no effect concentrations (PNECs) for freshwater and marine water as specified in the Statement of reasons (section III).

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 **4 June 2015**.

III. Statement of reasons

A. Information in the technical dossier related to the identity of the substance

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

1. Spectral data (Annex VI, 2.3.5.)

"Spectral data" is a standard information requirement as laid down in Annex VI, Section 2.3.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA observes that the registration does not contain Ultra-Violet (UV) and Infra-Red (IR) spectral data as required according to Annex VI Section 2.3.5. of the REACH Regulation to support the identity of the registered substance. ECHA points out that the UV and IR spectra are a formal information requirement under Annex VI section 2.3.5. ECHA regards this required information scientifically relevant for the registered substance for the following reasons:

- The substance absorbs in the UV range due to the presence of chromophores in the composition. A UV spectrum representing the absorption of these constituents in the UV range can therefore be recorded;
- The IR spectrum displays characteristic vibration bands of covalent bonds in molecules present in the substance, including characteristic vibration bands from the chemical functionalities expected to be present in the composition.

The Registrant commented on the draft decision stating that "*UV and IR test technique has not been applied, because it will not provide additional information beyond the other testing methods which have been utilized*". The Registrant considers that "*GC and NMR have sufficiently characterised the substance*". However, the Registrant also notes that "*in the meantime more guidance and explanation through webinars from ECHA became available. According this we understand that the requirement is rigid and a full set of spectral data is required as is appropriate for the substance in question.*"

Consequently, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the UV and IR spectral data for the registered substance in order to confirm the identity of the substance subject to the present decision.

As for the reporting of the spectral data in the registration dossier, the information should be included in IUCLID section 1.4.

The Registrant shall ensure that the description of the analytical methods used for the recording of the UV and IR spectra are specified in the dossier, in line with the requirements under Annex VI Section 2.3.7.

2. Description of the analytical methods or the appropriate bibliographical references for the identification of the substance (Annex VI, 2.3.7.).

"Description of the analytical methods or the appropriate bibliographical references for the identification of the substance" is a standard information requirement as laid down in Annex VI, Section 2.3.7. 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.

ECHA observes that the Registrant did not provide sufficient description of the analytical methods used for the identification and quantification of the registered substance, as requested according to Annex VI Section 2.3.7.

More specifically, the Registrant provided a copy of a 1H-NMR (Nuclear Magnetic Resonance) spectrum measured for the registered substance. However, the description for the NMR method was not provided, furthermore, the spectrum did not include integration of the peaks. This information is required to assess the NMR spectrum and to verify the identity of the substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the missing information on the description of the 1H-NMR method or the appropriate bibliographical references for the identification of the substance subject to the present decision. The Registrant is also requested to provide the integration of the 1H-NMR spectrum. The method description shall be sufficient for the method to be reproduced. As for the reporting of the above data in the registration dossier, the information should be included in IUCLID section 1.4.

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

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance for the purpose of registration within the applicable tonnage band of 1000 tonnes or more per year in accordance with Article 6 and 11(1) of the REACH Regulation, does not comply with the requirements of Articles 10(b), and 14 and Annex I thereof. Consequently, the Registrant is requested to submit the information mentioned in section II.B above that is needed to bring the registration into compliance with the relevant information requirements.

3. Revised predicted no effect concentrations (PNECs) for freshwater and marine water

According to section 3.3.1 of Annex I of the REACH Regulation the PNEC for each environmental sphere shall be established based on the available information.

The Registrant has derived the PNEC aquatic organisms using a non-validated (Q)SAR approach, although measured acute toxicity data for the registered substance have been included in the dossier:

"Although measured acute toxicity data are available for fish, invertebrates and algae, the HC5 QSAR equation (Di Toro et al., 2000a, 2000b; McGrath and Di Toro, 2004; McGrath and Di Toro, 2009; Redmann et al., 2009) was selected to calculate the PNEC. This model calculates an HC5 and covers aquatic organisms. The range of organisms (47 species) used in the training set are known and include plants, invertebrates and fish, both freshwater and marine."

The Registrant has not justified the reasons for selecting the proposed model and in particular why the model is expected to produce a more adequate PNEC derivation than the measured data for this mono constituent substance. It should be noted that the PNECs derived from the measured data following the ECHA guidance recommendations (Chapter R.10) would produce PNEC values well below those proposed by the Registrant. The proposed PNEC value is even higher than the value potentially derived from the chronic QSAR estimations for the registered substance proposed by the Registrant. In addition, the Registrant proposed the use of an assessment factor of 1 on a non-validated QSAR approach without presenting an assessment of the characteristics of the model and the uncertainties associated to the proposed approach.

The Registrant commented the draft decision stating that the *"reasons for selecting the proposed model and in particular why the model is expected to produce a more adequate PNEC derivation"* were already justified in the submitted dossier.

The reasons are listed as follows:

- The QSAR is validated in line with the issued Guidance. A QMRF, which details how the model has been developed and the associated supporting literature was produced and accompanied the registrations. The QMRF details all the OECD principles and explains how the Hazard Concentration (HC5) is covered by these principles. These include 1) The definition of the endpoint 2) The defined algorithm 3) The Applicability Domain 5) The internal validation conducted, 6) The external validation process and finally 7) The mechanistic interpretation.

- The theory underpinning the Target Lipid Model (TLM) is that the concentration of a substance in a lipid that is responsible for the onset of a non-polar narcosis effect is the same when expressed on a molar basis for a range of taxonomic groups e.g. fish, invertebrates and algae. Consequently the toxic potency of a substance depends upon its capacity to achieve the threshold concentration within an organism. There are a number of variables that determine this capacity, key of which are the solubility of the substance in water and lipid and its molecular size. In an application of the theory, DiToro et al. (2000a, b) have published a non-polar narcosis-based QSAR for predicting the aqueous concentration of a hydrocarbon substance that induces a specified level of biological effect. The QSAR relates biological effect to the log Kow of the substance. Log Kow is a function of the solubility of a substance in water and lipid (octanol) but is limited by molecular size because large molecules cannot pass through biological membranes.

- The TLM and associated QSARs provide a theoretical basis for predicting the ecotoxicity of a substance. McGrath et al. (2004) have also utilised statistical theory developed by a number of workers to define an acute species sensitivity distribution for narcotic chemicals. A relationship has been established enabling the concentration of a hydrocarbon substance to be determined that will affect a specified proportion of the species present in a community. By setting the proportion to a notional low level (e.g. 5%), a hazard concentration (HCx where x is the proportion that might be affected i.e. 5%) is obtained. The HCx has similarities with a hazard concentration derived by applying statistical extrapolation procedures described in the ECHA Guidance to a set of test substance data. It can also be considered analogous to, and used for risk assessment in the same way as, a PNEC derived by applying an Assessment Factor (AF) specified in the TGD to a lowest acute EC50 or LC50 value in a data set.

- Based on the EPIWEB data produced at the time of registration, the PNEC would have been 0.127 mg/l. As these data are derived from QSAR for which the data is wider than hydrocarbons, it is probable that a QSAR based on hydrocarbons ought to be more accurate.

- The use of an AF of 1 is justified as follows:

  Database: The database used for this model has been developed initially by Di Toro et al. (2000) and Di Toro and McGrath (2000), then further enhanced by McGrath et al. (2004, 2005) and McGrath and DiToro, (2009) and Redman et al. (2007, 2011) and CONCAWE (2011). The database comprises of reviewed acute and chronic toxicity information covering 85 species.

  Diversity and representation of taxonomic groups: The full database used for the model (including water, sediment and soil) contains critical body burdens for a large number of taxonomic groups (covering 85 species). The acute-to-chronic ratio (ACR) used for evaluating chronic toxicity and the chronic data using in the validation work cover all of the taxonomic groups (TG) and in some cases have several (>10) entries for a given TG.

Knowledge of presumed mode of action: The model is based on the assumption that all the chemicals for which the model is valid, and upon which the model is based, act as type I narcotics. It is based on the hypothesis that target lipid is the site of toxic action within the organism, that octanol is the appropriate surrogate, and that target lipid has the same physical–chemical properties in all organisms. The TLM is used to derive the predicted-no-effect concentrations (PNECs) using the hazardous concentration to 5% species (HC5) statistical extrapolation procedure.

Statistical uncertainties: The uncertainty associated with the critical acute and chronic aqueous concentrations, results from the uncertainty in the variables in equations used in the model. In the references cited a full description is available as to how this variability was characterised. The method is basically an adaption of the HC5 methodology for computing the hazard concentration at which 5% of species are affected and is consistent with references and recommendations in the Guidance. Comparisons between field and mesocosm studies: Direct comparisons of the HC5 to mesocosm and field tests have not been performed at this stage, but literature is being gathered and more information will be forthcoming. However, the EPA sediment quality guidelines for PAH mixtures (EPA 2003) are based on TLM and support the use of the HC5 in field applications.

ECHA acknowledges the comments of the Registrant but notes that by employing (Q)SARs the Registrant has to meet the respective requirements in order to replace the available test data.

Annex XI, section 1.3. sets out the conditions which must be fulfilled in order for the results of (Q)SARs to be acceptable as a replacement for experimental studies:

- Results are derived from a (Q)SAR model whose scientific validity has been established,
- The substance falls within the applicability domain of the (Q)SAR model,
- Results are adequate for the purpose of classification and labelling and/or risk assessment, and
- Adequate and reliable documentation of the applied method is provided.

ECHA considers that the results from the application of the Target Lipid Model (TLM) fail to meet the first condition above as the scientific validity of this model has not been sufficiently established. Consequently, the TLM is not suitable for classification and labelling and/or risk assessment. The TLM in in its current form is not considered as scientifically valid for the following reasons[1]:

1. the insufficient number of taxonomic groups used in the acute and chronic Species sensitivity distributions (SSDs),
2. shortcomings in the acute-to-chronic ratio (ACR) derivation,
3. shortcomings in the HC5 derivation: the assumption of a normal distribution, which is not met for log CTLBB (critical target lipid body burden) and log ACR (acute to chronic ratio) and the assumption of independent parameters, which is not met for the combination of CTLBB and the universal slope for narcosis,
4. omission of phototoxicity effects of PAHs,
5. underestimation of chronic toxicity when compared with data from experimental studies.

[1] Emiel Rorije, Eric M.J. Verbruggen & Joop A. de Knecht. Service Request on a critical review of the environmental and physicochemical methodologies commonly employed in the environmental risk assessment of petroleum substances in the context of REACH registrations (05 August 2012, Version 4).
http://echa.europa.eu/documents/10162/13628/review_environmental_physicochemical_methodol_en.pdf

Consequently ECHA considers that there is an inconsistency between the available experimental data not used in the PNEC derivation and the reported PNECs derived from the TLM model and that the PNECs in the registration dossier for freshwater and marine water are not valid. ECHA considers the methodology described in the ECHA guidance documents for the derivation of PNEC values from measured data to be fully applicable to this mono-constituent substance. The Registrant has deviated from this approach using a non-validated method without justifying the deviations and without using the information available on the registered substance for substantiating his approach.

ECHA considers that these deviations are not acceptable and therefore requests the Registrant to derive a PNEC from the available information on the registered substance according to the methodology described in the ECHA guidance document.

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.

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