ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114306301-70-01/F Helsinki, 27 July 2015

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

For [redacted] CAS No NS (EC No 468-710-7), 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 [redacted], CAS No NS (EC No 468-710-7), submitted by [redacted] (Registrant).
The scope of this compliance check decision is limited to the standard information requirements of Annex I of the REACH Regulation.

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 after the date (31 March 2015) when the draft decision was notified to the Registrant under Article 50(1) of the REACH Regulation.

The substance subject to the present decision was listed in the Community rolling action plan (CoRAP) for substance evaluation in 2012 by Germany as the evaluating MSCA, and decision-making is ongoing.

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 17 November 2014.

On 31 March 2015 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 04 May 2015 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 11 June 2015 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 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

   a) using the study or studies giving rise to the highest concern and re-assessment of related risks or providing a full justification for not using the study or studies giving rise to the highest concern shall be included as part of the technical dossier (Annex I, 1.1.4). The use of the study giving rise to highest concern and justification shall be in accordance with the ECHA Guidance on information requirements and chemical safety assessment Chapters R.7a and R.8; and
   b) using the assessment factors recommended by ECHA and re-assessment of related risks or providing a full justification for not using the recommended assessment factors in DNEL derivation (Annex I, Section 1.4.1.). The revised DNELs and justification shall be in accordance with the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8.

2. Revised exposure assessment for the inhalation route and risk characterisation for workers or a justification for why the use of an alternative percentile of the exposure data is considered appropriate (Art. 41.1(c) of the REACH Regulation and Annex I, Section 5.2.4 and 5.2.5.). Such exposure assessments shall be in accordance with the ECHA Guidance on information requirements and chemical safety assessment Chapter R.14.

B. Deadline for submitting the required information

Pursuant to Articles 41(4) and 22(2) of the REACH Regulation the Registrant shall submit to ECHA by **03 February 2016** an update of the registration dossier containing the information required by this decision.

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 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

   a) Using the study or studies giving rise to the highest concern and re-assessment of related risks or a full justification for not using the study or studies giving rise to the highest concern shall be included as part of the technical dossier (Annex I, 1.1.4). The use of the study giving rise to highest concern and justification shall be in accordance with the ECHA Guidance on information requirements and chemical safety assessment Chapters R.7a and R.8.

Annex I, 1.1.4 specifies "*If there are several studies addressing the same effect, then, having taken into account possible variables (e.g. conduct, adequacy, relevance of test species, quality of results, etc.), normally the study or studies giving rise to the highest concern shall be used to establish the DNELs and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment. If the study or studies giving rise to the highest concern are not used, then this shall be fully justified and included as part of the technical dossier, not only for the study being used but also for all studies demonstrating a higher concern than the study being used.*"

The registration dossier contains a number of repeated dose toxicity studies, including a 90-day study in rat (Test Guideline OECD 413), a 28-day study in rat (OECD 412), a 14 –day study in rat (OECD 412), a 14-day study in miniature swine (minipig) (containing a subset of investigations from OECD 412), a 28-day study in minipig (containing a subset of investigations from OECD 412), 7-day, 14-day and 28-day studies in rabbit (according to OECD 412), a two-generation reproduction toxicity test in rat (OECD 416), a prenatal developmental toxicity study in rat (OECD 414), a prenatal developmental toxicity study in rabbit (OECD 414), and some non-guideline studies on rat and mouse.

The Registrant has selected the NOAEC from the subchronic rat study (i.e. 50000 ppm) to derive the DNEL ([redacted] Section 5.11). The Registrant has not used the study giving rise to the highest concern (i.e. the 28-day study in rabbit with a NOAEC of 500ppm) and has provided a justification for the choice of study in Section 5.11.2. Summarising, the Registrant argues that the rabbit is an inappropriate model for assessing chemical related cardiac effects in humans, that rabbits and humans have significant cardiological differences, including critical structural and functional differences, that rabbits have unique biological features that are not found in other experimental animals in terms of the development of myocarditis, that there are hypotheses that may explain the toxicity of the registered substance in the rabbit heart, and that the minipig is accepted by regulatory authorities as a non-rodent surrogate for humans in the detection of cardiotoxicity and is generally accepted to be a sensitive and representative model for human cardiac responses (Swindle et al, 2011). In view of these considerations and the lack of cardiac effects of the registered substance on minipig heart (and in rat), the Registrant concludes that "*the effects observed in rabbits are not relevant for human risk assessment. As such, the appropriate endpoint for use in deriving the DNEL for HF)-1234yf is the 90-day inhalation toxicity study in the rat conducted under GLP following OECD guidelines.*"

However, according to ECHA Guidance Chapter R.7a: Endpoint specific guidance (version 3.0[1]), R.7.5.4.1, p.285, "*Studies on the most sensitive animal species should be selected as the significant ones, unless toxicokinetic and toxicodynamic data show that this species is less relevant for human risk assessment.*" The Registrant has not provided toxicokinetic or toxicodynamic data on the substance that show that the rabbit is less relevant for human risk assessment. The Registrant has demonstrated that there are similarities in the toxicokinetics of the substance between rabbit, mouse, rat and human (IUCLID section 5.1; Toxicology and Applied Pharmacology 244 (2010) 247–253), but has not demonstrated this for the minipig. In respect of toxicodynamics, while the Registrant has argued in general (but not in a substance-specific matter) that the minipig is a better model for cardiac toxicity than rabbit, the Registrant has provided no basis for considering even at a general level that the minipig is a better model for the substance-induced muscle toxicity or sudden death seen in repeated-dose / reproductive toxicity studies performed on the rabbit with the registered substance.

ECHA considers that non-substance-specific argument that one species (minipig) is better than another (rabbit) as a model for human risk assessment is an insufficient basis in itself for excluding data from rabbit, unless it is possible to show that data from rabbit is wholly irrelevant for human risk assessment. ECHA considers it has not been demonstrated that data from rabbit is irrelevant for human risk assessment. Moreover, ECHA considers that this argument cannot be regarded as a substance-specific toxicokinetic or toxicodynamic argument when it generically addresses a single target organ affected by a particular compound.

ECHA notes the Registrant's statements that the "*the rabbit is an inappropriate for model for assessing chemical related cardiac effects in humans*", and "*the cumulative data would suggest that the pig is a more relevant model than the rabbit for assessing the cardiotoxicity of HFO-1234yf in humans*" reflect inconsistent evaluations of the relevance of the rabbit; specifically, the minipig being "a more relevant model" is a distinct issue from the rabbit being "an inappropriate model" for human. ECHA notes the statement from the independent expert [redacted], "*Therefore, the available data suggests that the pig might be a better model in which to assess the toxicity of an inhalant and thus findings in the pig and the rat may be more relevant for understanding the potential effects in humans. However, it is important to understand that the only model that can definitively assess the risk of toxicity of any drug, chemical or infectious agent is the human model.*" The expert does not exclude the possibility that the rabbit behaves similarly to the human, i.e. that it is an appropriate model in this case. In summary, ECHA considers that the statement that the rabbit is not an appropriate model for assessing chemical related cardiac effects in human is not adequately justified by the underlying material, and that the Registrant has not demonstrated with toxicokinetic and toxicodynamic data that the rabbit is less relevant for human risk assessment.

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, 1.1.4 because the study or studies giving rise to the highest concern was not used to establish the DNELs in accordance with ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7 and R.8. or are not fully justified. Consequently it is necessary to revise the DNELs or to provide a full justification why the rabbit is less relevant for human risk assessment.

[1] http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf

The Registrant is given two options: The Registrant shall revise the DNELs for workers by using the study or studies giving rise to the highest concern, in accordance with ECHA Guidance, that are appropriate in this case. Subsequently, the Registrant shall re-assess related risks.

In the alternative, the Registrant shall, in accordance with Annex I, 1.1.4, provide a full justification for not using the study or studies giving rise to the highest concern to derive the DNELs for workers provided in the chemical safety report by specifying how they have addressed the issue that studies on the most sensitive animal species should be selected as the significant ones, unless toxicokinetic and toxicodynamic data show that this species is less relevant for human risk assessment.

In his comments according to Article 50(1), the Registrant agreed to revise the workers DNEL according the applicable ECHA Guidance on Information Requirements and Chemical Safety Assessment. The Registrant indicated that the revised information will be included in a registration dossier update and submitted to the ECHA by the latest 31 August 2015.

The Registrant is reminded that this decision does not take into account any updates submitted after 31 March 2015. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit in the chemical safety report either of the following information: Revised DNELs for workers using the study or studies giving rise to the highest concern, as recommended by ECHA, and re-assessment of related risks or a full justification for not using the study or studies giving rise to the highest concern shall be included as part of the technical dossier (Annex I, 1.1.4). The use of the study giving rise to highest concern and justification shall be in accordance with ECHA guidance.

Notes for consideration by the Registrant

The revised DNELs requested under section II.A.1.b and exposure assessment requested under section II.A.2 shall be taken into account when assessing the related risks.

b) Using the assessment factors recommended by ECHA and re-assessment of related risks or a full justification for not using the recommended assessment factors in DNEL derivation (Annex I, Section 1.4.1.). The revised DNELs and justification shall be in accordance with the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8.

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 [2] provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

The Registrant has provided an updated CSR ([redacted]), which uses a point of departure for the DNEL derivation which ECHA considers is not based on the study giving rise to highest concern (see Section III.A.1.a above). ECHA has examined the DNEL derivation which ECHA considers is based on the study giving rise to the highest concern (the 28-day study in rabbits), which is present in a second CSR file present in the dossier ([redacted]).

ECHA considers that the Registrant has not taken into account, in accordance with ECHA Guidance, the uncertainty arising from (a) inter-species differences (b) intra-species differences and (c) exposure duration. ECHA notes the Guidance Chapter R.8 states at R.8.4.3 "*when the available data do not allow the derivation of substance-specific or analogue-specific assessment factors, default assessment factors should be applied.*"

(a) Inter-species differences. In Table 30, under "AF Other interspecies differences", the Registrant states "*Per REACH guidance R.8.4.3.1, a factor of 1 is supported based on the following. (1) Measurement of the blood: air partition coefficient demonstrates the rabbit will adsorb twice the dose of humans. (2) Humans also have a lower metabolic rate compared to rabbits. (3) The DNEL is being derived based on data from the most sensitive species (rabbit)*".

ECHA notes the Guidance (CHAPTER R.8 - DOSE [CONCENTRATION]-RESPONSE REGARDING HUMAN HEALTH), R.8.4.3.1 provides: "*Data from animal studies are the typical starting points for risk characterisations and thus differences in sensitivity between experimental animals and humans need to be addressed, with the default assumption that humans are more sensitive than experimental animals.*" "*If no substance-specific data are available, the standard procedure for threshold effects would be, as a default, to correct for differences in metabolic rate (allometric scaling) and to apply an additional factor of 2.5 for other interspecies differences, i.e. toxicokinetic differences not related to metabolic rate (small part) and toxicodynamic differences (larger part). In case substance-specific information shows specific susceptibility differences between species, which are not related to differences in basal metabolic rate, the additional factor of 2.5 for 'remaining differences' should be modified accordingly.*"

ECHA considers that the registrant's arguments (1) and (2) refer to the allometric component, and are already accounted for under the Registrant's consideration for "Interspecies(allometric scaling)"; and that the allometric considerations do not apply to toxicokinetic differences not related to metabolic rate (small part) and toxicodynamic differences (larger part). The Registrant's third argument is that the rabbit is more sensitive than rat/mini-pig, but this is not substance-specific information to modify the additional factor of 2.5. For many chemicals with tests in multiple species, there will be a most sensitive species, and so this is not a substance-specific circumstance, and the presence of a most sensitive species is not per se a demonstration that humans are not more sensitive than experimental animals, and hence the Registrant has not justified that a factor of less than 2.5 for other interspecies differences is warranted. The Registrant does not demonstrate for interspecies differences which are not related to differences in basal metabolic rate, that there is substance-specific information which shows the relative susceptibility

[2] Link to ECHA guidance document R.8 is: http://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf

between experimental species and human, and hence the Registrant's justification is not in accordance with ECHA guidance.

(b) Intra-species differences. In Table 30, under the "Intraspecies" heading, the Registrant states "*Per REACH guidance R.8.4.3.1 an assessment factor of 3 was applied based on the facts that HFO-1234yf can be considered as poorly adsorbed, poorly metabolized, rapidly eliminated from the body and should show minimal intraspecies differences in toxicological properties.*"

ECHA notes that the Guidance provides that "*For workers, as standard procedure for threshold effects a default assessment factor of 5 is to be used, based on the fact that this sub population does not cover the very young, the very old, and the very ill.*" ECHA considers that the Registrant has not applied the default factor, and that the Registrant's justification does not provide substance-specific quantification of intraspecies variability in human. There is no indication that there is low variation in toxicologically-relevant absorption, metabolism and excretion in humans, leading to low-variation in human response to the chemical.

Consequently, the Registrant's justification does not address the intra-species variation and does not use the default factor, and hence the Registrant's justification is not consistent with ECHA guidance.

(c) Exposure duration. In Table 30, the Registrant states under Exposure duration, "*HFO-1234yf will be poorly adsorbed, undergo minimal metabolism, and be rapidly cleared from the body. It will not bioaccumulate. In addition, in this 28-day study, rabbits were exposed for 7 days/week not 5, subacute/chronic cardiac inflammation did not show progression with increased days of exposure as similar effects were noted in animals exposed for 7, 14 and 28 days of exposure and recovery was observed following 28 day recovery period. Biotransformation was very low. It was not altered by repeated exposure. Urinary metabolite profile was similar following acute exposure, 7day, 14 day, or 28 days of exposure For these reasons adjustment factor of 2 is considered adequate to account for exposure duration per REACH guidance R.8.4.3.1*".

ECHA notes that the Guidance provides: "*If only a sub-acute or sub-chronic toxicity study is available, the following default assessment factors are to be applied, as a standard procedure (Table R. 8-5)*:" "*However, substance-specific information is preferred and, if available, should be used to modify the default values, upwards or downwards. - A lower factor (minimum 1) may for instance be used if there is specific evidence that increasing exposure duration does not increase the incidence or severity of adverse effects. This applies to most local dermal effects. It is also relevant for certain local effects in the respiratory tract for which there is no substantial difference in N(L)OAECs following acute and subacute exposure by inhalation (the effects can thus be considered concentration- rather than dose-dependent.*"

ECHA considers that there is specific evidence that increasing exposure length causes increased severity of toxicity (compare the acute toxicity vs. 28 day exposure toxicity in rabbits). Moreover, within the 28-day rabbit study and prenatal developmental toxicity study, there is evidence that severity increases with time. For example, moderate myofiber necrosis is only seen at day 29, and not earlier timepoints, and this is consistent with clinical chemistry measurements of myotoxicity which progress with time. Substance-induced deaths did not occur within the first five days of exposure, again indicating a concern that toxicity becomes severe with increasing exposure time.

The Registrant states "*The acute nature of the skeletal muscle necrosis indicates suggests this is not a direct effect of the test substance exposure.*" ECHA notes that the skeletal muscle necrosis is dose-dependent and exposure-dependent, is supported by clinical chemistry measurements, and considers that the 'acute' nature of the lesion cannot exclude that this is a substance-dependent direct effect. Thus the Registrant's statement that there is no progression does not reflect the evidence that there is progression of toxicity with increased exposure time.

The Registrant argues that the time-course of lesion severity/incidence within this 28-day study is informative about the progression of lesions within a 90-day study, but ECHA considers that the information presented does not support a conclusion about the effects of a substance after a 90-day exposure. ECHA considers that the arguments about absorption, metabolism, clearance, bioaccumulation and biotransformation do not explain the mechanism of toxicity of the substance, and do not thereby, or otherwise, provide specific evidence that increasing exposure duration to longer than 28 days does not increase the incidence or severity of adverse effects.

Consequently, the Registrant's justification does not provide specific evidence that increasing exposure duration does not increase the incidence or severity of adverse effects and does not use the default factor, and hence the Registrant's justification is not consistent with ECHA guidance.

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. because the assessment factors used are not in accordance with ECHA *Guidance on information requirements and chemical safety assessment* Volume 8, Chapter R.8. or are not fully justified. Consequently it is necessary to revise the DNELs or to provide a full justification.

The Registrant is given two options: The Registrant shall revise the DNELs for workers by applying the assessment factors recommended by ECHA that are appropriate in this case. 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 DNELs derived for workers provided in the chemical safety report by specifying how the following has been taken into account:

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.

In his comments according to Article 50(1), the Registrant agreed to revise the workers DNEL according the applicable ECHA Guidance on Information Requirements and Chemical Safety Assessment. The Registrant indicated that the revised information will be included in a registration dossier update and submitted to the ECHA by the latest 31 August 2015.

The Registrant is reminded that this decision does not take into account any updates submitted after 31 March 2015. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit in the chemical safety report either of the following information: Revised DNELs for workers using the assessment factors recommended by ECHA and re-assessment of related risks *or* a full justification for not using the recommended assessment factors in DNEL derivation. The revised DNELs and justification shall be in accordance with ECHA guidance.

Notes for consideration by the Registrant

The revised DNELs requested under section II.A.1.a and exposure assessment requested under section II.A.2 shall be taken into account when assessing the related risks. ECHA further notes that some of the deficiencies identified above in calculating the assessment factors may also apply to the second CSR dated 19 May 2014 provided by the Registrant. In the event that the Registrant, in response to the request under section II.A.1.a., can provide a valid justification why the rabbit is not the relevant species and therefore decides to rely upon the CSR of 19 May 2014, the Registrant is invited to take into account the considerations above in reviewing the assessment factors to derive the DNELs.

2. Revised exposure assessment for the inhalation route and risk characterisation for workers or a justification for why the use of an alternative percentile of the exposure data is considered appropriate (Art. 41.1(c) of the REACH Regulation and Annex I, Section 5.2.4 and 5.2.5.). Such exposure assessments shall be in accordance with the ECHA Guidance on information requirements and chemical safety assessment Chapter R.14.

Pursuant to Article 41.1(c) of the REACH Regulation ECHA may verify that any required Chemical Safety Assessment and Chemical Safety Report 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.

The Registrant in the CSR ([redacted]) uses exposure data for HFC-134a as a reference material for the exposure data to the registered substance (page number 65). The geometric mean concentration of analogue substance was used in Exposure Scenario 2 (CSR p78). However, the Guidance on information requirements and chemical safety assessment Chapter R.14: Occupational exposure estimation[3] sets out in R.14.4.5: "*It is recommended to select the 90th percentile of an exposure distribution reflecting the whole spectrum of conditions of use described in a particular exposure scenario.*

[3] http://echa.europa.eu/documents/10162/13632/information_requirements_r14_en.pdf

Under particular conditions other percentiles may appear applicable as well. A justification should be provided in the CSR.

It may for example be appropriate to use a 75th percentile if the measured data set represents only the worst case situation but is applied to characterise a broader range of conditions, and where the real percentage of exposures exceeding the selected value will be much lower than 25% (see Example R.14-1).

Another case for possible use of lower percentile could be a well defined, high quality data set referring to homogenous (narrow) exposure conditions, characterised by a risk characterisation ratio clearly below 1 and being fully representative for the OC and RMM described in the exposure scenario.
The 50th percentile or median of measured data is not recommended as the estimator for worker exposure in a chemical safety assessment."

As explained above, the information provided on the inhalation 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. For example the Registrant has used a geometric mean value for exposure estimation, rather than a 90th percentile value as recommended by the Guidance. It is not clear from the CSR what the relationship is between the quoted geometric mean values and the exposure distributions from which they are derived and why the selected value is appropriate for assessment puproses. It is also unclear how the quoted values relate to the specified sampling periods and how these correspond to typical operational conditions. Consequently, it is necessary to revise the exposure assessment in accordance with the guidance, using the 90th percentile of an exposure distribution, or to provide suitable justification for another value in accordance with the Guidance.

> 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 for the inhalation route and risk characterisation for workers or a justification for why the selected value arising from the exposure data is considered appropriate (Art. 41.1(c) of the REACH Regulation and Annex I, Section 5.2.4 and 5.2.5.). Such exposure assessments shall be in accordance with the ECHA Guidance on information requirements and chemical safety assessment Chapter R.14

Notes for consideration by the Registrant

The revised DNELs requested under section II.A.1.a and II.A.1.b shall be taken into account when assessing the related risks.

IV. Note for consideration by the Registrant

ECHA considers that there is concern arising from the toxicity of the registered substance to rabbits, and specifically as to whether the toxicity will become more severe/ potent after sub-chronic or chronic exposure, as compared to a 28-day exposure. As explained in section III.A.1.a above so far the Registrant has not sufficiently justified why the rabbit is less relevant for human assessment. The Registrant's derivation of a DNEL using Assessment Factors which ECHA considers inadequate, together with worker exposure estimates, may therefore lead to concerns for the safe use of the substance if humans show similar sensitivity to the substance as does the rabbit. As a result of information received from this decision, ECHA will consider whether there is a need for further information on sub-chronic toxicity to ensure safe use of the substance. ECHA notes that the Registrant is responsible for the safe use of the substance, and may consider proposing a test to clarify the sub-chronic toxicity of the substance in rabbit, if appropriate.

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 Ofelia Bercaru, Head of Unit Evaluation, E3

[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.