ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 1 August 2016

Addressee: [redacted]

Decision number: CCH-D-2114340872-49-01/F
Substance name: 2-dimethylaminoethanol
EC number: 203-542-8
CAS number: 108-01-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18.01.2012
Registered tonnage band: 1000 tonnes or more per year

DECISION ON A COMPLIANCE CHECK

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

1. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3; test method: OECD TG 476 or OECD TG 490 with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2; test method: EU B.31/OECD TG 414) in rabbits, oral route with the registered substance;**

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **At least ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

4. **Identification of DNELs and risk characterisation (Annex I, Sections 1.4. and 6.): derive acute and long-term DNELs for workers for inhalation and dermal route and systemic and local effects using the assessment factors according to ECHA Guidance R.8 for DNEL derivation and revise the risk characterisation accordingly.**

5. **Revised human health exposure assessment and risk characterisation for the workers (Annex I, section 5. and 6.).**

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

You are required to submit the requested information in an updated registration dossier by **8 August 2019**. **You shall also update the chemical safety report, where relevant.** The timeline has been set to allow for sequential testing.

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

Appeal

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

Authorised[1] by Guilhem De Seze, Head of Unit, Evaluation E1

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

Appendix 1: Reasons

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

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

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained. ECHA notes that the registration dossier contains negative results for Annex VII, Section 8.4.1.and Annex VIII, Section 8.4.2.. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a gene mutation test in mammalian cells from the year 1997, no GLP (a publication) with an assigned reliability score of 2. However, this study does not provide the information required by Annex VIII, Section 8.4.3., because the top dose only reaches 80% or 60% survival, while according to the OECD test guideline 476, it should "*result in approximately 10-20 % (but not less than 10%) relative survival*".

Since the test was conducted, significant changes have been made to the OECD test guideline 476 and this means that the study provided does not meet the current guidelines because the top dose used did not result in 10-20% relative survival as required in the updated OECD TG 476, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

In your comments to the draft decision you agreed to submit the requested study.

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

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to present decision: in vitro mammalian gene mutation test (test method: OECD TG 476[1] or OECD TG 490[2]).

[1] Only the OECD TG is mentioned since it has recently been updated while the corresponding EU test method has not yet been updated.
[2] Only the OECD TG is mentioned since it has recently been adopted while the corresponding EU test method has not yet been published.

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

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

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).
The technical dossier contains information on a pre-natal developmental toxicity study in rats by the inhalation route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

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

The test in the first species was carried out by using a rodent species rats. According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you propose to adapt the standard information requirement for pre-natal developmental toxicity study, second species (rabbit), by applying a read-across adaptation according to REACH Annex XI, 1.5. You propose to use the data from source substances DEA (Diethanolamine, CAS 111-42-2), MDEA (Methyldiethanolamine (CAS 105-59-9), MMEA (monomethyl-ethanolamine, CAS 109-83-1), and TEA (triethanolamine, CAS 102-71-6).

ECHA understands that your hypothesis is based on the structural similarity of the substances (*"a common structural "ethanolamine" moiety"*) and common mode of action, i.e. *"effects on choline homeostasis and metabolism"*. You claim that the impact on choline homeostasis is assumed to be due to functional amino alcohol group which is common to the registered and source substances. Therefore, the structural differences between the substances *"do not influence the read-across validity"*.

To support the read-across hypothesis you refer to

a. experimental data (publications) which demonstrate that the registered and source substances impair the choline homeostasis *in vivo* and *in vitro*. (ECHA notes that no studies on MDEA has been included),
b. similar systemic toxicity (target organs liver and kidney),
c. unpublished data on choline measurements and phospholipid composition with MDEA,

TEA, and MEA, and data on metabolomics, which will be provided in the update, and

d. self-classification of the registered substance as STOT RE Cat. 2, which is in line with the classification of DEA and MMEA.

Based on the justification provided (and data on DMEA provided in the registration dossier), ECHA notes that ethanolamines seem to impact the choline homeostasis. However, you have not explained if the substances impair the choline homeostasis in a similar way and if, consequently, the toxicity profile (especially regarding fertility and pre-natal developmental toxicity) of these substances is similar. Therefore, due to lack of experimental data on the impact of the substances on choline homeostasis, i.e. how the substances affect the choline homeostasis (do they affect choline's metabolism, activity, synthesis, incorporation in phospholipids, etc..) and whether this also affects the neural phospholipids/neural membrane composition (a, c) and detailed comparison of the structural (dis)similarities, this cannot be verified. You propose to classify the registered substance as STOT RE Cat. 2 (d), which suggests that you consider that the registered substance and source substances DEA and MMEA have similar target organ toxicity. However, without experimental data on the source substances comparison of the toxicity profile cannot be made and similar systemic toxicity (b), cannot be verified.

ECHA notes that it is not clear which substance is intended to be used as a source substance. You refer to multiple source substances in your comments and data which may be relevant for fulfilling the information requirement for a second pre-natal developmental toxicity study appears to be available for DEA (Diethanolamine, CAS 111-42-2), MDEA (Methyldiethanolamine (CAS 105-59-9), MMEA (monomethyl-ethanolamine, CAS 109-83-1), and TEA (triethanolamine, CAS 102-71-6). While you have formulated a read-across hypothesis, ECHA points out that no information on how the properties of the substance subject to this decision will be predicted from the existing information on these source substances is provided.

ECHA notes that the preliminary read-across justification described above is provided in your comments. You indicated your intention to provide a detailed read-across justification, including new data in the dossier update. The updated dossier and the read-across approach will be re-assessed for compliance after expiry of the deadline in the decision. Therefore, ECHA's observations presented above are only preliminary observations established on the basis of the information provided by you in your comments. These observations cannot be considered as ECHA's definitive opinion on this read-across approach.

As indicated in the draft decision, the testing requested in the (draft) decision can be adapted according to the rules outlined in Annexes VI to X and/ or according to the general rules contained in Annex XI of the REACH Regulation. Should you decide to adapt the testing requested in the (draft) decision according to the provisions of Annex XI, section 1.5 of the REACH Regulation, you are encouraged to make use of the information provided in the ECHA Guidance on information requirement and chemical safety assessment Chapter R.6. and to evaluate the robustness of their updated read-across approach using the ECHA Read-Across Assessment Framework.

As outlined above, ECHA considers that the read-across approach, as presented by you in your comments, does not comply with the requirements of A. XI section 1.5. Therefore, the information gap addressed in the draft decision still exists and the ECHA Secretariat has not amended the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species, rabbits, by the oral route.

3. Extended one-generation reproductive toxicity study

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

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have sought to adapt this information requirement. While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2.

In the technical dossier you have provided study records for a modified developmental toxicity screening study (oral route, prenatal and postnatal part, key study), a developmental toxicity study (inhalation route, similar to OECD TG 414, supporting study), and an oral study in pregnant rats examining the effect(s) of the registered substance on lung phospholipid and surfactant of new-born rats ("one-generation study", supporting study), and an oral study in pregnant rats examining the effect(s) of the registered substance on neonatal brain cholinergic and phospholipid profile ("one-generation study", supporting study). In addition, in your adaptation you refer to the results from two subchronic toxicity studies via inhalation route.

You have provided the following justification for the adaptation: "*In the 13-week repeated dose toxicity inhalation study (Klonne et al., 1987) there were no effects on gonads or any organ examined gross and histologically. In the GLP sub-chronic inhalation repeated dose toxicity study performed with a substance related to DMAE (2-(Diethylamino)ethanol (DEEA), EXXON, 1990) the most common gross pathological findings were ano-genital staining, ovarian cysts and distended uteri. These observations are not an evidence of reproductive toxicity hazard, because they were considered not to be treatment related (occurred in all four groups, inclusive control group) and the only adverse effects in this study were lesions of respiratory tract. In the Modified Developmental Toxicity Screening Test (BASF SE, ...) post-implantation losses occured in the range of strong ulcera in the stomach. In the developmental OECD 414 study (Leung et al., 1996) there were also no effects of treatment on gonads or on any gestational parameters, including pre- and post implantation loss or sex ratio. Gestation and parturition of pregnant rats fed with a choline deficient diet supplemented with 1% DMAE proceeded normally (Katyal and Lombardi, 1978, Zahniser et al., 1978). Litters of equal size were delivered. Further, no signs of maternal toxicity were noted (Zahniser et al., 1978). Based on findings of these studies, a*

testing of DMAE for effects on reproductive performance or fertility will not deliver additional information and considered to be superfluous."

ECHA has assessed the weight of evidence of each lines of evidence separately and together and the conclusions of this assessment are reported below.

ECHA notes that the sub-chronic toxicity studies may provide relevant information on histopathological changes of reproductive organs but do not provide information on functional fertility (e.g. mating, fertility, gestation, parturition, lactation).

In the modified developmental screening test reduced viability of pups (postimplantation losses and low neonatal viability) was observed at the dose level causing also ulcera in the stomach of dams, indicating that the substance may cause adverse effects related to pup viability. ECHA notes that the modified developmental screening test as well as the prenatal developmental toxicity study via inhalation provide information on early postnatal period and on maintenance of pregnancy but they provide only limited information on sexual function and fertility.

In addition, the "one-generation" studies with choline deficient diet supplemented with the registered substance provide also only limited information on sexual function and fertility, namely information on maintenance of pregnancy and information on early postnatal period and, thus, the impact of the registered substance on e.g. mating and implantation is not examined.

Taken together, only limited information on sexual function and fertility has been provided. In particular, information on functional fertility (e.g. mating and fertility indices (including implantation), precopulatory period, sperm parameters, oestrous cycle) and late postnatal period including sexual maturation and histopathological integrity of the reproductive organs at adulthood for the generation exposed *in utero* is not available.

In addition, the criteria of Annex X, section 8.7.3., column 2 are met for inclusion of cohorts 2A and 2B (developmental neurotoxicity) and information for those properties is not provided.

Furthermore, you refer to several studies conducted with analogue substances under the chapter "Justification for classification or non-classification" in your CSR. ECHA notes that the results with analogue substances show effects on fertility. However, you have not made a read across argumentation and used this information in your conclusions. You propose not to classify the registered substance because the additional research can be considered for classification or non-classification decision and the research work planned will allow a final evaluation and hazard assessment of the observed findings. However, your dossier has not been updated with the results of the planned research work.

Taking into consideration the weight of each of the lines of evidence provided, ECHA considers that the overall weight of evidence is not sufficient to conclude that the registered substance has or has not a particular dangerous property in relation to the endpoint under consideration. Therefore, the general rules for adaptation of Annex XI, Section 1.2. are not met and your adaptation of the information requirement cannot be accepted.

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

extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 4.0, July 2015).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

It is recommended that results from a range-finding study (or range finding studies) for the extended one-generation reproductive toxicity study are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that existing information on the registered substance itself derived from available *in vivo* study (Zahniser et al., 1978) shows that choline and acetylcholine levels were increased and DMAE was detected in the brains of pups from DMAE-supplemented dams. In addition, based on the information provided in the dossier, DMAE is an inhibitor of choline uptake and choline kinase. Based on an *in vitro* mouse embryo study, inhibition of choline uptake (by DMAE) and/or metabolism during neurulation results in increased cell death and craniofacial and neural tube defects (Fisher et al., 2002). The authors conclude that abnormal choline uptake or metabolism during gestation has the potential to affect the developing embryo or foetus.
In addition, according to the CSR, human data on the registered substance and its derivatives indicate that DMAE as a potential precursor of a neurotransmitter (acetylcholine) may cause mental stimulation at low doses, larger doses producing insomnia, muscle tenseness and spontaneous muscle twitches
([redacted]). All these findings raise a particular concern for effects on neural development leading to developmental neurotoxicity.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified information in humans, *in vivo* study and from an *in vitro* study on the registered substance itself.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, July 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route. To avoid extensive irritation of the stomach, dietary route seems to be the most appropriate to evaluate the intrinsic properties of the registered substance.

In your comments to the draft decision you propose to adapt the standard information requirement for extended one-generation reproductive toxicity study by applying a read-across adaptation according to REACH Annex XI, 1.5. The Registrant proposes to use the data from source substances DEA (Diethanolamine, CAS 111-42-2) and MDEA (Methyldiethanolamine (CAS 105-59-9).

Your hypothesis, supporting data and ECHA's preliminary observations: see above.

In addition, you state that EOGRTS study is currently ongoing with DEA and a two-generation reproductive toxicity study with MEA may also be provided to support the read-across approach. An OECD 422 study with DEA will be submitted, and an OECD 422 (with additional choline-related parameters) will be conducted with the registered substance.

ECHA notes that your strategy to provide OECD 422 studies with DEA and the registered substance (to be conducted) may provide valuable support to the read-across approach.

ECHA notes that it is not clear which substance is intended to be used as a source substance. You refer to multiple source substances in your comments and data which may be relevant for fulfilling the information requirement for a second pre-natal developmental toxicity study appears to be available for Diethanolamine (DEA, CAS 111-42-2) and for Methyldiethanolamine (MDEA, CAS 105-59-9). While you have formulated a read-across hypothesis, ECHA points out that no information on how the properties of the substance subject to this decision will be predicted from the existing information on these source substances is provided.

ECHA notes that the preliminary read-across justification described above is provided in your comments. You indicated your intention to provide a detailed read-across justification, including new data in the dossier update. The updated dossier and the read-across approach will be re-assessed for compliance after expiry of the deadline in the decision. Therefore, ECHA's observations presented above are only preliminary observations established on the basis of the information provided by you in your comments. These observations cannot be considered as ECHA's definitive opinion on this read-across approach.

As indicated in the draft decision, the testing requested in the (draft) decision can be adapted according to the rules outlined in Annexes VI to X and/ or according to the general rules contained in Annex XI of the REACH Regulation. Should you decide to adapt the testing requested in the (draft) decision according to the provisions of Annex XI, section 1.5 of the REACH Regulation, you are encouraged to make use of the information provided in the ECHA Guidance on information requirement and chemical safety assessment Chapter R.6. and to evaluate the robustness of your updated read-across approach using the ECHA Read-Across Assessment Framework.

As outlined above, ECHA considers that the read-across approach, as presented by you in your comments, does not comply with the requirements of Annex XI section 1.5. Therefore, the information gap addressed in the draft decision still exists and the ECHA Secretariat has not amended the request.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56/ OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohorts 2A and 2B (Developmental neurotoxicity).

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA guidance. You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

4. Identification of DNEL(s) and risk characterisation (Annex I, Sections 1.4. and 6.)

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

Annex I, Section 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.

A full justification shall be given specifying, inter alia, the choice of the information used, the routes of exposure (oral, dermal, inhalation) and the duration and frequency of exposure to the substance for which the DNEL is valid.

The ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8 (version 2.1, November 2012) states that "when an EU IOEL exists the registrant may, under conditions as described below, use the IOEL in place of developing a DNEL. Alternatively the registrant should, in accordance with the requirements of REACH, derive a DNEL following the steps outlined in the hazard assessment section of REACH Annex I." More specifically, it is stated that "a registrant is allowed to use an IOEL as a DNEL for the same exposure route and duration". Further, it also states that "when the registrant is using a substance in a way that leads to other exposure routes or exposure durations than the exposure route and duration on which the IOEL is based (typically derived for inhalation exposure over 8 hours per working day (TWA) and/or short term exposures, typically of 15 minutes duration (STEL)) or if other human populations are exposed, the relevant DNELs should be derived. For example, in the case when the use may lead to dermal or oral exposure of the population at large or vulnerable sub-populations, DNELs to cover these situations will be required."

According to Appendix R. 8-13 of the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8, the use of national OEL in place of developing a

DNEL requires an evaluation of both approaches applied for setting the national OEL and for deriving DNEL taking into account any potential differences that may impact the calculated values.

You have used the UK national OEL values of 7.4 mg/m3 (8-h TWA) and 22 mg/m3 (short term limit value) as a DNEL long-term, inhalation (local and systemic effects) and DNEL acute, inhalation (local and systemic effects), respectively. You have derived DNELs and compared them with these OELs and concluded that the OEL provides an equal or more conservative approach to risk characterisation.

ECHA notes that, apart from the information that the OEL that you have used is based on corrosivity, no information on the key study and methodology used to derive the national OEL is provided in the CSR. The ECHA Guidance on information requirements and chemical safety assessment Chapter R.8 provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information to fulfill the REACH obligations. ECHA points out that the assessment factors that you have used when deriving the DNELs are not in line with the default assessment factors presented in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8. Specifically, you have used in all your calculations, where applicable, an assessment factor (AF) of 3 to account for intraspecies differences for workers instead of the default AF of 5. For long-term systemic effects via the inhalation route the default AF for the remaining interspecies differences (factor 2.5) has not been used. No substance-specific justification has been provided for these deviations from the default values. ECHA observes that applying the standard AF specified in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8 would lead to a long-term systemic DNEL (inhalation) of 1.8 mg/m3; the use of this value for risk characterization is a more conservative approach than the currently preferred OEL of 7.4 mg/m3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the DNELs for workers should be revised using the AF recommended in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8 or a detailed justification on how the chosen approach meets the general requirements for DNEL derivation as described in Section 1.4 of Annex I should be provided. Further, an evaluation of the scientific background for setting the national OEL is needed in order to assess and compare the calculated DNELs with this value. Finally, a scientific justification for the selection of preferred value for risk assessment (i.e., the national OEL and/or a DNEL) should be provided.

5. Revised human health exposure assessment and risk characterisation for the worker (Annex I, section 5. and 6.)

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.

ECHA notes that you have classified the substance as Flam. Liquid 3 (H226), Acute Tox. 4 (H302, H312), Acute Tox. 3 (H331), Skin Corr. 1B (H314), Eye Damage 1 (H318) and STOT Single Exp. 3 (H335) and thus, fulfilling the criteria set out in Article 14(4) of the REACH Regulation to require an exposure assessment and risk characterisation in the chemical safety assessment.

Article 14(6) as well as Annex I, 0.3, 0.5, 5.1.1, 5.2.4. and 6.2.- 6.4. of the REACH Regulation require registrants to identify and apply appropriate measures to adequately control the risk identified in the 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. Annex I, 5.2.5. states that appropriate models can be used for the estimation of exposure levels.

ECHA notes that according to the information provided in the technical registration dossier and in the CSR, you have used the ECETOC TRA version 2 model for estimating exposure. However, you have modified several default values provided by the selected model, without providing any justification.
First, the outputs of the selected TRA model have been amended through applying a linear approach, taking account of concentration, to both inhalation and dermal exposure estimations. However, ECETOC Technical Report 93 states "*The inhalation modifiers (1; 0.6; 0.2; 0.1) are linked to concentration bands (>25%; 5-25%; 1-5%; <1%) and skewed based on potential differences in volatility of the components of the vapour phase of a mixture. As the dermal exposure will normally be to the bulk mixture, however, correction on the basis of actual (typical high-end) percentage in the mixture can be applied rather than resorting to bands.*" In other words, it may be justifiable within the context of the model, in some circumstances, to modify dermal exposures linearly through reference to concentration, but the model and associated guidance makes no such similar provision for inhalation exposures and the banding approach should be used. As a result, in several exposure scenarios, the inhalation exposure is under-predicted and risk characterisation ratios would need to be amended.

Second, in some scenarios the ECETOC TRA predictions of dermal exposure have been amended through the application of factors for the effectiveness of gloves. In ES 7, use as an additive in concrete and cement (professional), you have applied a factor for glove effectiveness of 98%. In comparison, ECETOC Technical Report 93, Appendix D suggests values for exposure reduction for gloves of up to 95%. Later versions of ECETOC guidance (Technical Report 114) suggest professional workers may obtain a maximum level of exposure reduction of 90%. ECETOC guidance states values above 90% are only likely to be encountered in an industrial setting.

Therefore, the linear approach for inhalation exposure and the above-mentioned assumptions in the CSR cannot support a conclusion that the risks are appropriately controlled and must, therefore, be rejected.

For some scenarios respiratory protective equipment has been specified as a required risk management measure. However the required effectiveness, and the equipment capable of delivering this level of performance, has not been included within the exposure scenario (for example ES 2: PROC 8a and 8b, and ES 6: PROC 7). This information is required to ensure safe use of the substance.

The Registrant proposes a qualitative assessment to demonstrate, for effects where it was not possible to determine a DNEL, the likelihood that effects are avoided when implementing the exposure scenario. This qualitative assessment would lead to a set of risk management measures that would form the basis for the quantitative assessment and would include provision for risk management measures to minimise exposure. In particular the CSR should refer to a consistent policy on glove management and not rely solely on the

outcome of the quantitative assessment. Although the quantitative assessment for professional users may use a conservative value to predict exposure (e.g 90% for professionals), the required risk management phrases may suggest a higher level of performance is required to manage qualitative risks effectively.

According to Annex I, 0.3., 0.5. and 5.1.1. the applied Risk Management Measures (RMM) have to be described in the CSR. The CSR needs to contain sufficient information to allow ECHA to gain assurance that the risks are adequately controlled and that appropriate risk management measures can be prescribed by actors in the supply chain. Accordingly, the supplier is required to describe the relevant RMM in detail in the Safety Data Sheet in order to minimise the exposure for workers handling the registered substance (e.g. the type of gloves to be worn, protection equipment for parts of the body other than the hand or respiratory protection 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 exposure in accordance with Annex II, section 8.2.2.2.(b)(i), (ii) and 8.2.2.2.(c) respectively). The information provided in the Safety Data Sheet (SDS) shall be consistent with information in the Chemical Safety Report (Annex II, section 0.1.2. of the REACH Regulation).

ECHA notes that specific detailed information on the recommended personal protective equipment is missing both from the CSR and from the information on safe use within the IUCLID dossier. In the CSR, you did not provide information on material, breakthrough time and thickness for gloves. Information on suitable glove materials was specified in Section 11 of IUCLID, the guidance on safe use.

It is also noted that you propose, in several exposure scenarios in the CSR, the need for "light weight barrier material" to provide full skin coverage. However this advice is not complete as, for instance, it is missing from ES 6, PROC 7, industrial spraying with a substance between [redacted]% concentration. Further, no information is given on the appropriate material or clothing that can provide the necessary level of protection. Typically protective clothing against chemicals used in sprays would need to meet the requirements of EN 14605:2005 - Protective clothing against liquid chemicals. Performance requirements for chemical protective clothing with spray-tight (Type 4) connections. Or for lower levels of challenge, EN 13034:2005 - Protective clothing against liquid chemicals. Chemical protective clothing offering limited protection against liquid chemicals (type 6 and type PB [6] equipment).

To ensure the safe use of a substance, Annex I Section 5.1.1 requires a description of the risk management measures to reduce or avoid direct and indirect exposure of humans. Gloves are reported in the CSR and IUCLID Section 11 as required personal protective equipment to prevent dermal exposure to the substance. Generally, gloves that are capable of preventing exposure to the skin for a pre-determined duration shall be specified. Typically, this information, as a minimum, has to specify the glove material (which is provided) and, depending on the exposure scenarios, may also need to include the breakthrough time and thickness of the glove material.

In your comments to the draft decision you agreed to update the CSR.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to provide a revised exposure assessment and risk characterisation for all identified uses and detailing the operational conditions and risk management measures to take account of the requirement for both qualitative and quantitative assessment. In particular, the exposure

estimates should apply the default exposure modifiers within the latest version of an appropriate model used (the Registrant may consider, under its own responsibility, using ECETOC TRA v3, which is the latest version of that model and provides a banded approach to modifying both inhalation and dermal exposure) or provide a detailed suitable and adequate justification for using non-default values for duration in the exposure estimation. The chemical safety report shall be amended accordingly.

Extension of the deadline

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 70 months (30 months + "*additional time period of 40 months*") months.

You sought to justify this request by conducting the OECD 422 study, "*feedback from the UK authorities*" regarding the new studies and validation of the OECD 443 study with DEA.

ECHA notes that the planned OECD 422 study may provide valuable information to support the read-across approach, and therefore, additional time can be granted to conduct the OECD 422 study with the registered substance. ECHA notes that the study duration of OECD 422 is 6 months and therefore, ECHA has only partially granted the request and set the deadline to 36 months.

Appendix 2: Procedural history

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

The compliance check was initiated on 13 October 2015.

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

ECHA took into account your comments and did not amend the requests.
ECHA took into account your comments and amended the deadline.

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

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

ECHA invited you to comment on the proposed amendment(s). Your comments on the proposed amendment(s) were taken into account by the Member State Committee and are reflected in the Reasons (Appendix 1).

ECHA referred the draft decision to the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-48 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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

3. In relation to the information required by the present decision, the sample of substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance composition manufactured or imported 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 tests 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 or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new tests 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 tests to be assessed.