EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114290256-46-01/F Helsinki, 18 December 2014

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

**For Ethylene Carbonate, CAS No 96-49-1 (EC No 202-510-0), 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 ethylene carbonate, CAS No 96-49-1 (EC No 202-510-0), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates submitted after 24 July 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 23 May 2013.

On 18 November 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted]

On 17 December ECHA received comments from the Registrant on the draft decision.

On 14 February 2014 the Registrant updated his registration dossier (submission number [redacted]).

The ECHA Secretariat considered the Registrant's comments and update. On basis of this information, Section II was amended by removing requests for which the required information was provided in the update. The Statement of Reasons (Section III) was changed accordingly. The information contained in the comments and update on the *in vitro* gene mutation study in bacteria, the sub-chronic toxicity study (90-day), the pre-natal developmental toxicity study, the two-generation reproductive toxicity study, the growth inhibition study aquatic plants, the short-term toxicity testing on fish, and the DNEL derivation is reflected in the Statement of Reasons (Section III) whereas no amendments to the respective "Information Required" (Section II) were made.

On 24 July 2014 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposals for amendment to the draft decision were submitted.

On 29 August 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and amended the draft decision.

The present decision relates solely to a compliance check requesting information in form of an in vitro gene mutation study in bacteria (Annex VII, 8.4.1.), sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.), pre-natal developmental toxicity study (Annex X, 8.7.2.), growth inhibition study on aquatic plants (Annex VII, 9.1.2.), short-term toxicity testing on fish (Annex VIII, 9.1.3.), revised DNELs for workers and for the general population and deriving a DNEL long-term local inhalation for workers (Annex I, 1.4.1.), documentation for the recommended personal protective equipment (Annex I, 5.1.1., Annex II, 0.1.2. and 8.2.2.2.(b)(i)), revised exposure assessment and risk characterisation for workers via dermal route (Annex I, Section 5.2.4 and 5.2.5.), revised consumer exposure assessment and risk characterisation (Annex I, Sections 5. and 6). The other information requirement for two-generation reproductive toxicity study (Annex X, Section 8.7.3) is addressed in a separate decision although all requirements were initially addressed together in the same draft decision.

On 8 September 2014 ECHA referred the draft decision to the Member State Committee.

By 29 September 2014 in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 28-29 October 2014, a unanimous agreement of the Member State Committee on the draft decision relating to the *in vitro* gene mutation study in bacteria, sub-chronic toxicity study (90-day), oral route, pre-natal developmental toxicity study, growth inhibition study on aquatic plants, short-term toxicity testing on fish, revised DNELs for workers and for the general population and deriving a DNEL long-term local inhalation for workers, documentation for the recommended personal protective equipment, revised exposure assessment and risk characterisation for workers via dermal route, revised consumer exposure assessment and risk characterisation as modified at the meeting was reached on 29 October 2014.

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

II. Information required

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

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

1. In vitro gene mutation study in bacteria (Annex VII, 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. /OECD 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102, as specified in section III.B.1 below;
2. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats;
3. Pre-natal developmental toxicity study (Annex X, 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route;
4. Growth inhibition study aquatic plants (Annex VII, 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD 201);
5. Short-term toxicity testing on fish (Annex VIII, 9.1.3.; test method: Fish, acute toxicity test, EU C.1./OECD 203).

Note for consideration by the Registrant:

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

Failure to comply with the 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 the Member States.

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

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

1. Revised DNELs for workers and for the general population using the recommended assessment factors by ECHA and deriving a DNEL long-term local inhalation for workers
   or
   A full justification for not using the recommended assessment factors in DNEL derivation and a qualitative assessment of local inhalation effects (Annex I, 1.4.1. of the REACH Regulation), as specified in section III.B.1;

2. Documentation for the recommended personal protective equipment, i.e. gloves to be worn when handling the substance need to be specified clearly (Article 14(6), Annex I, 5.1.1.)

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

4. Revised consumer exposure assessment and risk characterisation:
   a. Taking into account the consumers' activities and the duration and frequency of their exposure (Annex I, Sections 5 and 6).
   b. Using the fraction released to air recommended by ECHA Guidance R.15 (Annex I, Section 5.2.4) or a full justification for not using the recommended values in the consumer exposure estimates.

**C. Deadline for submitting the required information**

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **2 January 2017**. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

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

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

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

Before checking the dossier for compliance to each of the information requirements, ECHA first considered the scientific validity of the proposed read-across approach that the Registrants applied in adaptation to general information requirements as set out in Annexes VII to X of the REACH Regulation.

0. Consideration of the read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), "provided that the conditions set out in Annex XI are met".

According to Annex XI, 1.5. there needs to be structural similarity among the substances within a group or a category such that the relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation.

To fulfill the standard information requirements for ethylene carbonate with respect to the endpoints repeated dose oral toxicity, growth inhibition study on aquatic plants and short-term toxicity testing on fish, the Registrant proposed a read-across approach based on the analogue substance ethylene glycol.

For the standard information requirements of repeated dose oral toxicity the Registrant has provided a read-across justification under the relevant section of this endpoint in chapter 5 of the chemical safety report (CSR). For the standard information requirements growth inhibition study on aquatic plants and short-term toxicity testing on fish the Registrant did not provide any further read-across justification.

ECHA's compliance check aims at ensuring that the information provided by the Registrant fulfils the relevant information requirements. To this end, it is necessary to consider whether the information provided by the Registrant is appropriate and guarantees the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, as long as equivalent results to the prescribed information are provided on health and environmental hazards.

In the present case, ECHA considers that the read-across approach proposed by the Registrant does not give sufficient guarantees that equivalent results to the prescribed information will be provided on the health hazards. More specifically, Section 1.5. of Annex XI of the REACH Regulation sets out the conditions to be met by alternative methods so that equivalent results to the prescribed test may be obtained. The read-across justification provided by the Registrant does not fulfil those conditions in relation to the documentation provided. In particular, it does not enable the toxicological properties of the registered substance ethylene carbonate to be predicted from data for the ethylene glycol for the reasons outlined below.

It is a requirement of Annex XI, Section 1.5., that "adequate and reliable documentation of the applied method shall be provided." In the present case, ECHA notes that the documentation submitted is inadequate.

The table in section R.6.2.6.1 "Reporting Format for the analogue approach" of ECHA's Guidance on information requirements and chemical safety assessment, R.6 (May 2008), sets out aspects which must be addressed to justify a read-across hypothesis. In the dossier provided by the Registrant, the following issues were not addressed to a sufficient extent:

**Analogue approach justification.** The guidance highlights the following: "Based on available experimental data, including basic physico-chemical properties, summarise how these results verify that the read-across is justified. The data should also show that functional groups not common to source and target chemicals do not affect the anticipated toxicity. The available experimental results in the data matrix [...] should support the justification for the read-across."

Based on the initial dossier (submission number [redacted]), ECHA made the following observations:

For the standard information requirements of repeated dose oral toxicity, in order to justify the structural similarity between the analogue substance ethylene glycol and the registered substance ethylene carbonate, the Registrant states that "*Toxicokinetics demonstrated the rapid metabolisation of ethylene carbonate to ethylene glycol (CAS 107-21-1) (Hanley, 1989). Sufficient data are available on the repeated dose toxicity of ethylene glycol, which is demonstrated to be more toxic than its precursor. The key study for this endpoint is a chronic study in which male Wistar rats are exposed to ethylene glycol via the diet for a period of 12 months (Corley et al, 2008).*"

ECHA notes that the Registrant has supported the argument of rapid metabolisation with a toxicokinetic study in rats showing a half-life of 0.25 hours for Ethylene carbonate.

Nevertheless ECHA notes that the Registrant has not provided any justification why a half-life of 0.25 hours would exclude any toxic effects of non-metabolised ethylene carbonate and thus would allow predicting the repeated dose toxicity of ethylene carbonate from data available on ethylene glycol.

For the standard information requirements growth inhibition study on aquatic plants and short-term toxicity testing on fish the Registrant did not provide any further read-across justification. ECHA assumes that the Registrant is using the read-across approach on the basis of results of the above-mentioned toxicokinetic study conducted in blood. The Guidance on information requirements and chemical safety assessment, R.7b on p.78-79 indicates that "where degradation is rapid (e.g. half-life <1 hour), the available test data will frequently define the hazard of the degradation products since it will be these that have been tested. These data may be used to classify the parent substance in the normal way." ECHA notes that in the US EPA HPV (Riddick, J.A., Bunger, W.B. Sakano, T.K., Techniques of Chemistry 4th ed., volume II, Organic Solvents. New York, NY: John Wiley and Sons, Inc., 1985, p. 989) it is reported that the registered substance is: "stable in water at 100 °C; degrades rapidly at 125 °C in presence of alkalies." This information introduces uncertainty on whether the substance rapidly hydrolyses under environmentally relevant conditions and whether aquatic toxicity tests with ethylene glycol can be used to predict the hazard of the registered substance and whether results of these tests can be further used in the chemical safety assessment (CSA). It should be noted that the toxicokinetic study (which resulted in the calculated half-life of 0.25 h) was performed in blood and not in environmentally relevant aquatic systems.

**Data matrix.** The Guidance R.6 highlights the following: "Provide a matrix of data (endpoints *vs.* target and source chemicals) [...]. In each cell in the Data Matrix, the study result type should be indicated in the first line, *e.g.*: experimental result, experimental study planned, read-across from supporting substance (structural analogue or surrogate), (Q)SAR. If experimental results are available, the key study results should be shown in the Data Matrix." As already pointed out above the Registrant states that "*ethylene glycol, (...) is demonstrated to be more toxic than its precursor. The key study for this endpoint is a chronic study in which male Wistar rats are exposed to ethylene glycol via the diet for a period of 12 months (Corley et al, 2008).*" However, the Registrant has not supported the argument of ethylene glycol being more toxic than ethylene carbonate with any data matrix or other comparison of toxicological or eco-toxicological properties of these two substances.

In his comments according to Article 50(1) the Registrant addressed the read across approach. In a subsequent update of the registration dossier (submission number [redacted]), the Registrant included a revised read-across justification document in IUCLID Section 13. The information submitted in the update is analysed by ECHA as follows:

For the toxicological endpoints, ECHA understands that the read-across hypothesis is based on a common metabolic pathway. The Registrant claims that following absorption the substance is rapidly metabolised to the proposed analogue substance ethylene glycol. This claim is supported by the toxicokinetics information provided by the Registrant.

Based on the information provided, although ECHA understands the generic rationale of the proposed read-across justification, it is noted however that the Registrant has not addressed the below-mentioned crucial aspects of the approach and therefore at this stage has not sufficiently demonstrated that the read-across approach can be accepted pursuant to Annex XI, Section 1.5 and that it would allow predicting the toxicological properties of the registered substance from data available on the proposed analogue substance, ethylene glycol. ECHA concludes that the Registrant has not provided sufficient endpoint specific

information to support the read-across approach for higher tier endpoints. More specifically, the documentation and justification is not satisfactory with regard to the following aspects:

i. Based on the toxicokinetics information, ethylene carbonate is detectable 60 minutes ($T_{1/2}$=15 min) after administration; ECHA notes that administration of ethylene carbonate through diet or drinking water may result in systemic exposure of the parent substance despite rapid metabolism. In ECHAs view, the Registrant has not fully justified as to why the parent substance (*i.e.* ethylene carbonate) would not cause adverse toxic effects;

ii. The Registrant argues that both ethylene carbonate and ethylene glycol have a similar toxicological profile; ECHA highlights that any adaptations to the standard information requirements are endpoint specific. Moreover, ECHA notes that the Registrant has not explained why similar acute toxicity, skin irritating/sensitizing properties and mutagenicity and different eye irritating properties allow accurate prediction of the hazard properties for sub-chronic toxicity and pre-natal developmental toxicity;

iii. Specifically for repeated dose toxicity; the comparison between the sub-chronic/chronic toxicity studies on ethylene glycol and the chronic toxicity study on ethylene carbonate do not support the read-across approach as the reliability of the the studies with the registered substance cannot be established (all considered to be of reliability 4 (not assignable) by the Registrant). In addition, the robust study summary provided for the analogue substance is insufficient for an independent evaluation of the results. Therefore, ECHA concludes that a similar toxicological profile has not been established be established.

iv. Specifically for pre-natal developmental toxicity, the Registrant has provided for the first species a PNDT study in rats on the ethylene carbonate with no effect levels (NOELs) of 1500 mg/kg/day and 750 mg/kg/day for maternal and developmental toxicity, respectively. For pre-natal developmental toxicity, second species the Registrant included a PNDT study in rabbits on ethylene glycol with no adverse effect levels (NOAELs) of 1000 mg/kg/day and 2000 mg/kg/day for maternal and developmental toxicity, respectively. In addition, the Registrant claims that "*The developmental toxicity of ethylene glycol has been intensively examined in a variety of species.*" ECHA notes that, apart from the rat and rabbit studies mentioned above, this statement is not supported by data in the technical dossier. Furthermore, the Registrant has not explained as to why this statement supports the read-across. Therefore, ECHA concludes that the Registrant has not provided any new information that would allow a comparison of the potential for developmental toxicity between source and target substance. Additionally, the Registrant's states that "*it is unlikely that the performance of a developmental toxicity study in a second species (rabbits) with ethylene carbonate will yield teratogenic effects or give any new information to a revised assessment of human hazard.*" However, ECHA underlines that the justification supporting this argument is relying on a read-across approach which is not adequately justified.

In his comment on the proposals for amendments, the Registrant indicated his agreement with the proposal of the MSCA which suggested that the read-across is sufficiently justified. ECHA acknowledge that there is an extensive toxicological database available for ethylene glycol. However, most of this information is currently not included in the technical dossier of the registered substance. In order to justify the read-across approach, all information relevant for hazard and risk assessment should be included in the technical dossier of the registered substance. Additionally, the Registrant would need to justify as to why this information is sufficient for the purpose of adaptation of each standard information requirement.

For eco-toxicological endpoints, the Registrant included in the updated registration dossier an improved read-across justification for the standard information requirements of a growth inhibition study on aquatic plants and short-term toxicity testing on fish. In this justification the Registrant concluded that "*based on the fact of the probable formation of the degradation product, ethylene glycol, in the standard test media and the low acute aquatic invertebrate toxicity of both substances, a read-across from ethylene glycol to ethylene carbonate for both endpoints of growth inhibition in aquatic plants and short-term toxicity testing in fish are deemed valid*". ECHA notes, as already explained above, that the Registrant's hypothesis of rapid hydrolysis, i.e. half-life <1 hour, and transformation into ethylene glycol is not substantiated by any experimental data under environmentally relevant conditions. ECHA considers that the justification of the read-across for growth inhibition study on aquatic plants and short-term toxicity testing on fish provided by the Registrant is not acceptable.

Based on the above, the proposed read-across approach does not satisfy requirements of Annex XI, section 1.5., and consequently does not allow predicting the toxicological and eco-toxicological properties of the registered substance ethylene carbonate from the data available for the analogue substance ethylene glycol. Therefore the information on the analogue substance is not appropriate to fulfil the information requirements of the substance subject to the present decision.

1. *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.)

An "*in vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or ECHA as being appropriate.

Other test methods may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2. of Annex XI provides that existing data on human health properties from experiments not carried out according to good laboratory practice (GLP) or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD 471 test guideline (updated 1997) at least five strains of bacteria should be used. These should include four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

The Registrant has provided four Bacterial Reverse Mutation Assays with and without methabolic activation according to OECD 471 test guideline conducted with the registered substance in 1980-1996 with an assigned reliability score of either 2 or 3. The tests used four different strains of S. typhimurium (TA 1535, TA 1537, TA 98 and TA 100). However, since those tests were conducted, significant changes have been made to OECD guideline 471 and this means that the study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI.

ECHA concludes that a test using E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 has not been submitted by the Registrant and that the test using one of these is required to conclude on in vitro gene mutation in bacteria.

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

In his comments according to Article 50(1) the Registrant agreed to perform the requested study.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14/OECD 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

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

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier the Registrant has provided a study record for a Chronic Toxicity Study (OECD 452) conducted with the analogue substance Ethylene glycol. As already explained in subsection A.0 "Consideration of the read-across approach" (above), the justification of the read-across approach does not meet the general rules for adaptation of Annex XI, 1.5.

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

ECHA notes that the registered substance is a liquid with a low vapour pressure, used also in spray application, but in a diluted form. In light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD 408) in rats.

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

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).

There is information available on this endpoint only for a pre-natal developmental toxicity study in a first species for the registered substance in the technical dossier. However, there is no information available for a pre-natal developmental toxicity study in a second species and the Registrant has not provided an adaptation argument (this observation was made by ECHA on the original submission number, [redacted], upon which the draft decision sent to the Registrant was based). Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.
The test in the first species was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rabbit as a second species to be used.

In his comments according to Article 50(1) and in the dossier update ([redacted]), the Registrant proposes to address the information requirement for a pre-natal developmental toxicity study in a second species with a read-across approach and an argument that a developmental toxicity study in a second species with ethylene carbonate would not provide any new information to a revised assessment of human hazard. Those arguments are addressed in Section III.A.0. above.

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

4. Growth inhibition study on aquatic plants (Annex VII, 9.1.2.)

"Growth inhibition study on aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has sought to fulfil the information requirements for Growth inhibition study on aquatic plants with two read-across studies conducted on the substance ethylene glycol. As already explained in subsection A.0 "Consideration of the read-across approach" (above), the justification of the read-across approach does not meet the general rules for adaptation of Annex XI, 1.5.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Alga, growth inhibition test (test method EU C.3./OECD 201).

5. Short-term toxicity testing on fish (Annex VIII, 9.1.3.)

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has sought to fulfil the information requirements for short-term toxicity on fish with a read-across study conducted on the analogue substance ethylene glycol. As already explained in subsection A.0 "Consideration of the read-across approach" (above), the justification of the read-across approach does not meet the general rules for adaptation of Annex XI, 1.5.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Fish, acute toxicity test (test method EU C.1./OECD 203).

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

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

1. Revised DNELs for workers and for the general population using the recommended assessment factors by ECHA and deriving a DNEL long-term local inhalation for workers or a full justification for not using the recommended assessment factors in DNEL derivation and a qualitative assessment of local inhalation effects (Annex I, 1.4.1. of the REACH Regulation), as further specified below

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, R.8 (version 2.1, November 2012) provides further details and specifically provides default factors which should be applied to derive derived no effect levels (DNELs) in the absence of substance specific information.

Based on the initial dossier (submission number [redacted]), ECHA made the following observations.

ECHA observes that the Registrant has not followed recommendations of ECHA's Guidance R.8 and has not provided a full justification for the derivation of DNELs in line with Annex I, 1.4.1. In particular, ECHA notes that for the systemic long term DNELs for inhalation route and dermal route both for workers and the general population the AF for duration of exposure is 1. The starting point for these DNELs is a prenatal developmental toxicity study which uses an exposure period corresponding to a sub-acute study and therefore the default AF of 6 should have been applied.

Furthermore, ECHA notes that the Registrant has not derived a DNEL for long-term local inhalation to demonstrate that in industrial or professional spray application the risk for respiratory tract is controlled. The Registrant justifies the omission of this DNEL with the argument that no local irritant effects were observed in the oral prenatal developmental toxicity study. ECHA considers this argument not valid as the gastrointestinal tract with its low pH is not as sensitive to local irritation as the respiratory tract. ECHA further observes that the substance is irritating to the eye indicating irritative potential. Therefore a risk characterisation is needed for long-term local inhalation effects either quantitatively based on a DNEL or qualitatively according to *Practical Guide 15 How to to undertake a qualitative human health assessment and document it in a chemical safety report*[1].

As explained above, the information provided on DNELs for the registered substance in the CSR 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. and the deviations are not fully justified. Furthermore a DNEL has not been derived for long-term local inhalation for workers. Consequently it is necessary to revise the DNELs or to provide a full justification.

As regards assessment factors, the Registrant is given two options: The Registrant shall revise the DNELs for workers and for the general population 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 current DNEL derivation for workers and for the general population provided in the CSR by specifying how the following has been taken into account:

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

As regards DNEL for long-term local inhalation for workers, the Registrant is given two options: The Registrant shall derive a DNEL according ECHA Guidance on information requirements and chemical safety assessment, R.8 (version 2.1, November 2012). In the alternative, the Registrant shall perform a qualitative assessment of local inhalation effects.

ECHA notes that in his comments according to Article 50(1) or REACH and in the updated dossier, the Registrant considered as new starting point for the DNEL derivation the NOAEL

[1] Link to ECHA Practical Guide 15 is: http://echa.europa.eu/documents/10162/13655/pg_15_qualitative-human_health_assessment_documenting_en.pdf

of 150 mg/kg/d from a repeated dose chronic toxicity study with ethylene glycol. The Registrant further corrected the NOAEL due to the different molecular weight of ethylene carbonate compared to ethylene glycol (88.06 vs 62.07 g/mol) and obtained as a starting point a NOAEL of 212.9 mg/kg/d for ethylene carbonate.

ECHA underlines that, as already explained above in section III.A.0, the justification for the read-across approach from ethylene glycol to ethylene carbonate does not fulfil requirements of Annex XI, section 1.5., and consequently does not allow predicting the toxicological properties of the registered substance ethylene carbonate from the data available for the analogue substance ethylene glycol. Consequently the information on the analogue substance is not appropriate to predict the DNELs of the substance subject to the present decision. For these reasons, the Registrant shall revise the DNELs for workers and for the general population using as starting point the lowest NOAEL obtained in toxicological studies with the registered substance and apply the assessment factors recommended by ECHA that are appropriate or provide a full justification for not using the recommended assessment factors. Subsequently, the Registrant shall re-assess related risks.

As regards the DNEL for long-term local inhalation for workers, ECHA observes that the Registrant made use of a local occupational exposure level of 26 mg/m3 derived by the MAK Commission for ethylene glycol for a daily eight hour exposure. The Registrant further corrected the local OEL due to the different molecular weight of ethylene carbonate in contrast to ethylene glycol (88.06 vs 62.07 g/mol) and obtained as local OEL for ethylene carbonate 36.9 mg/m3. However ECHA notes that Appendix 8-13 of the Guidance on information requirements and chemical safety assessment, R.8 (version 2.1, November 2012), does provide for the use of an OEL in place of developing a DNEL for the same substance and for the same exposure route, duration and population. Nevertheless ECHA notes that there is no provision in that Guidance that would allow the Registrant making use of an OEL of a proposed analogue substance (not fulfilling requirements of Annex XI, section 1.5.). ECHA further notes that the Registrants provided an updated exposure assessment including detailed information for each contributing scenario in terms of operational conditions and risk management measures. Nevertheless, a full description of the measures that need to be taken in the absence of a DNEL for local inhalation effects needs to be included in the qualitative risk assessment to ensure that exposures to the registered substance are managed effectively. As part of the qualitative assessment there needs to be a description of the management/supervision in place to check that the RMMs in place are being used correctly and operational conditions followed (Guidance on information requirements and chemical safety assessment Part E: Risk Characterisation, version 2.0, November 2012, Table E.3-1, page 32), as referenced from Practical Guide 15. Therefore ECHA considers that it is not demonstrated that the risk for the respiratory tract is sufficiently controlled.

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 and for the general population 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. In addition the Registrant is requested to submit in the CSR either of the following information: A DNEL long-term local inhalation for workers and re-assessment of related risks *or* a qualitative assessment of local inhalation effects.

*Notes for consideration by the Registrant*

The results of the studies requested under section II.A.1.-4. shall be taken into account when revising the DNELs.

2. Documentation for the recommended personal protective equipment, i.e. gloves to be worn when handling the substance need to be specified clearly (Article 14(6), Annex I, 5.1.1.)

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

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 shall be clearly specified based on the hazard of the substance or mixture and potential for contact and with regard to the amount and duration of dermal exposure in accordance with Annex II, section 8.2.2.2. (b)(i)). 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, the Registrant indicated the following for hand protection: *"wear chemical resistant gloves (EN374)in combination with intensive management supervision controls"*, while in IUCLID Section 11 has reported*: "hand protection: chemical resistant, impervious gloves complying with an approved standard should be worn at all times when handling chemical products if a risk assessment indicates this is necessary"*.

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 and, depending on the exposure scenarios, may also need to include the breakthrough time and thickness of the glove material.

Therefore, pursuant to Article 41(1)(c) the registrant is required to provide in the CSR a description of the gloves to be used when handling the pure substance. The information provided by the Registrant shall be sufficiently detailed to allow suppliers to fulfil their obligations specified under Annex II for the compilation of the safety data sheets.

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

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

ECHA notes that the Registrant has used RISKOFDERM to estimate exposure for a variety of worker exposure scenarios using efficiency for gloves of 98% and 99% (example scenarios 3.8, 5.8 and 6.8) to estimate the exposure via dermal route. However, ECHA notes that other models (e.g. ECETOC TR 114), with the risk management measure option included within them, limit modelled reductions to 95% for industrial users and 90% for professional users. In general, reduction factors of up to 95% are considered reasonable within quantitative exposure assessment. Higher factors would require a justification to provide assurance that the modelling used is indeed appropriate. In this particular case, ECHA notes that, additionally, 99% has no associated defining EsCom phrase to assist the user in how they may achieve this level of exposure reduction. It is also important to point out that reduction factors for gloves up to 95% would generate exposure levels when compared to the current DNELs that produce risk characterisation ratios above 1, therefore demonstrating that risks are not controlled.

As explained above, the information provided on the dermal exposure estimates for the registered substance in the chemical safety report does not meet the requirements for preparing a chemical safety report as described in Annex I. In particular, the Registrant has not included in the CSR any case specific justification (e.g. related to the substance or the specific recommended or implemented personal protection measures or based on relevant biomonitoring data) for deviating from the recommended efficiency factor. Consequently, it is necessary to revise the dermal exposure estimates or to provide a justification supporting the higher efficiency values used for gloves (98% and 99%).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit in the chemical safety report the following information: revised exposure assessment and risk characterisation for workers via dermal route using the pre-defined values for gloves efficiency stated above or a justification explaining why in this specific case using higher efficiency values for gloves (98% and 99%) is considered appropriate.

4. Revised consumer exposure assessment and risk characterisation:
    a. Taking into account consumers' activities and the duration and frequency of their exposure (Annex I, Sections 5 and 6)

According to Annex I, Section 5.2.4 of the REACH Regulation the estimation of exposure shall take into account duration and frequency according to operational conditions. According to Annex I, Section 6.3 the risk characterization consists of a comparison of the exposure of each human population known to be or likely to be exposed with the appropriate DNEL.

ECHA notes that the Registrant reported a frequency of exposure for consumers of 2 days/year and, in his consumer exposure calculations, has used a function within the exposure tool to average out exposure over a year, in order to compare the resulting average "long-term systemic exposure" to a corresponding DNEL and achieve risk characterisation ratios below 1. However, as noted in the REACH Guidance on information requirements and chemical safety assessment, (ECHA (November 2012); Chapter R.8:

Characterisation of dose [concentration]-response for human health, p.8): 'The actual daily dose is independent of the exposure frequency. This means that if for a certain scenario, worker or consumer exposure is for instance only for a number of days per year, the exposure value is the actual dose on the exposure days, and not the daily dose averaged out (and thus divided!) over the whole year.' Therefore, the long term exposure to be compared to the DNEL long term is not the exposure level calculated by averaging exposure events over the year, but the actual daily exposure. The annual averaging factor appears to have been used for a number of the exposure scenarios reported within the CSR.

Therefore pursuant to Article 14(4) and Annex I, Sections 5 and 6 of the REACH Regulation, the Registrant is requested to provide in the CSR revised consumer exposure estimations, i.e. actual daily doses and risk characterisations for exposures to take account of the duration and frequency of exposure resulting from the registered substance within consumer products.

b. Using the fraction released to air recommended by ECHA Guidance R.15 (Annex I, Section 5.2.4) or a full justification for not using the recommended values in the consumer exposure estimates.

Annex I, 5.2.4 of the REACH Regulation requires that the exposure estimation shall take account matrix dependent release/migration of the substance. In the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.15, the vapour pressure bands and the related percentage of compound released to air are listed just as they are implemented in the ECETOC TRA tool.

The Registrant has identified a consumer use of ethylene carbonate (waterborne latex wall paints (PC 9a)) and has used for consumer exposure estimates the calculation model of ECETOC TRA. In the chemical safety report the vapour pressure is described to be 1 Pa. For the vapour pressure range between 0.1 and 1 Pa a fraction released to air of 0.01 g/g is recommended by the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.15, Table R.15-5, as described in the ECETOC TRA tool. However, ECHA notes that the Registrant used in the consumer exposure estimations a fraction release factor of 0.0001 g/g, which is 100-fold lower than the recommended factor. ECHA underlines that the Registrant has indicated, in the relevant consumer contributing scenarios, the following justification for the fraction released to air: *"99.99 %. Fraction release to air = 0.0001 g/g. Since vapour pressure of ethylene carbonate is low (VP = 1 Pa). It is expected that a limited fraction of the substance will be released to air"*. Nevertheless, ECHA underlines that the low vapour pressure of 1 Pa is already considered in the banding approach of 0.1 g/g in the ECETOC TRA model, in accordance with the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.15.

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: revision of the consumer exposure assessment and risk characterizations using the fraction released to air as recommended by the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.15, and reassessment of related risks or a full justification for not using the recommended fraction released to air in the consumer exposure estimates.

**C. Deadline for submitting the information**

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also included a two-generation

reproductive toxicity study (Annex X, 8.7.3.). As this endpoint is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

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

In addition, it is important to ensure that the particular sample of substance tested in the new studies is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

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

V. Information on right to appeal

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

[redacted]
Leena Ylä-Mononen
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