Decision number: CCH-D-0000004262-82-05/F Helsinki, 22 August 2014

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

For propylene carbonate, CAS No 108-32-7 (EC No 203-572-1), 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 propylene carbonate, CAS No 108-32-7 (EC No 203-572-1), 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 6 March 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 14 June 2013.

On 22 October 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 21 November 2013 ECHA received comments from the Registrant agreeing on the information required under Section II.A.1 (Name in the IUPAC nomenclature) and II.C.5 (Revised exposure assessment for dermal route), while for Section II.C.4 (Revised DNELs for workers and for the general population), Section II.B 2 (Pre-natal developmental toxicity study) and 3 (Two-generation reproductive toxicity study) the Registrant provided comments which are addressed in the Statement of Reasons (Section III).

The ECHA Secretariat considered the Registrant's comments. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 6 March 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 10 April 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 did not amend the draft decision.

The present decision relates solely to a compliance check examination for name in the IUPAC nomenclature (Annex VI, 2.1.1), pre-natal developmental toxicity study in rabbits by oral route (Annex X, 8.7.2), revised DNELs for workers and for the general population (Annex I, 1.4.1 of the REACH Regulation), revised exposure assessment for dermal route (Annex I, section 5.2.4). The other compliance check requirement of the two-generation reproductive toxicity study is addressed in a separate decision although all endpoints were initially addressed together in the same draft decision.

On 22 April 2014 ECHA referred the draft decision to the Member State Committee.

By 12 May 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).

A unanimous agreement of the Member State Committee on the draft decision was reached on 26 May 2014 in a written procedure launched on 15 May 2014. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

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

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

1. Name in the IUPAC nomenclature or other international chemical name (Annex VI, 2.1.1.).

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

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

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

C. 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:

3. Revised DNELs for workers and for the general population using the recommended assessment factors by ECHA
   or
   A full justification for not using the recommended assessment factors in DNEL derivation (Annex I, 1.4.1 of the REACH Regulation);

4. A revised exposure assessment for dermal route (Annex I, section 5.2.4).

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 **31 August 2015**.

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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

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 related to the identity of the substance

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

1. Name in the IUPAC nomenclature or other international chemical name(s) (Annex VI, 2.1.1.)

"Name in the IUPAC nomenclature or other international chemical name(s)" is an information requirement as laid down in Annex VI, Section 2.1.1. of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant provided in the IUPAC name field of IUCLID Sections 1.1 and 1.2 the name "2-(carboxyoxy)-1-methylethyl carbonate" to identify the registered substance. This IUPAC name does not correspond to the IUPAC name of the registered substance which should be amended to "4-methyl-1,3-dioxolan-2-one".

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, the Registrant is requested to submit the information derived from the registered substance subject to the present decision: correct naming as specifically explained in the present decision. The Registrant shall ensure that the information is consistent throughout the dossier.

Regarding how to report the chemical name, the information shall be included in the IUPAC name field in IUCLID section 1.1 and 1.2.

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

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

2. 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. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

ECHA observes that the technical dossier contains data (key study) on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material. This study fulfils the standard information requirement for a pre-natal developmental toxicity study in a first species (Annex IX, 8.7.2.).

ECHA observes that the Registrant has neither provided any study record of a pre-natal developmental toxicity study in a second species in the dossier that would meet the information requirement of Annex X, Section 8.7.2. nor adapted this information requirement.

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.

The Registrant, in his comments submitted according to Article 51(1) of the REACH Regulation, expressed the intention to use a read across approach according to Annex XI section 1.5. in order to fulfil the standard information requirement of pre-natal developmental toxicity in a second species. The Registrant's approach is based on the rapid metabolism of an analogue substance, ethylene carbonate, to ethylene glycol and on the assumption that propylene carbonate will be quickly metabolised in a similar manner to propylene glycol. For this reason, the Registrant concludes that data on propylene glycol can be used to predict the pre-natal developmental toxicity (second species) of propylene carbonate. Existing data on the pre-natal developmental toxicity of propylene glycol in rat, mice, hamster and rabbit showed no effect up to the highest dose tested.

ECHA considers that, although the hypothesis contained in the read-across justification may be plausible, it is not supported by an adequate documentation. More specifically the scientific justification is not adequately substantiated with sufficient quantitative data and a reliable documentation is provided neither for the scientific rationale nor for the actual studies relied upon. Therefore, it does not fulfil the requirements of Annex XI, Section 1.5. for the following reasons:

- For the analogue substance ethylene carbonate 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 pre-natal developmental toxicity of ethylene carbonate from data available on ethylene glycol.
- There is no quantitative information provided on the half-life of the registered substance propylene carbonate and the blood levels of parent compound and metabolites at various time points to support the assumption of quick metabolism (e.g. data from a toxico-kinetic study).
- The pre-natal toxicity developmental toxicity studies on propylene glycol are not included in the registration dossier as robust study summaries that would allow assessing their reliability and verifying their findings.

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

C. 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.

3. Revised DNELs for workers and for the general population using the recommended assessment factors by ECHA or a full justification for not using the recommended assessment factors in DNEL derivation (Annex I, 1.4.1. of the REACH Regulation)

Annex I, 1.4.1. of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:

- 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.

The ECHA "Guidance on information requirements and chemical safety assessment" (Volume 8, R8) provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

The assessment factors (AF) applied by the Registrant and the default assessment factors recommended in the ECHA Guidance are given in detail in Annex I attached to this decision.

ECHA observes that the Registrant has not followed recommendations of the above mentioned ECHA's Guidance and has not provided a full justification for the derivation of DNELs as requested in 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 as well as for systemic long term DNEL for oral route for the general population the default AF of 2.5 for remaining interspecies differences has not been applied. ECHA notes also that when deriving the above-mentioned DNELs an AF for duration of exposure of 1 has been applied. 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. ECHA notes that severe maternal toxic effects, including mortality, were observed in that pre-natal developmental toxicity study.

Thus the Registrant shall revise his DNELs by applying the recommended assessment factors apropriate in this case.

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 chemical safety report 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.

The Registrant, in his comments, submitted according to Article 51(1) of the REACH Regulation, indicated his willingness to amend the DNEL derivation, as regards the use of an AF of 2.5 for the remaining interspecies difference. While, concerning the AF accounting for the duration of exposure, the Registrant indicated that the absence of systemic toxicity recorded during a 90-day repeated dose toxicity study, up to doses of 5000 mg/kg/d (=NOAEL), was an indication that prolongation of treatment does not increase toxicity. Moreover, the Registrant considered the effects observed in dams treated during an OECD 414 pre-natal developmental study would allow concluding that gestation rather than time seems to sensitize to propylene carbonate-induced toxicity (five dams treated with 5000 m/kg/d died while effects on body weight and food consumption were the only effects observed in mid- and high dose dams surviving treatment). Therefore, since pregnancy is

covered by the intraspecies factor of 5 for workers and 10 for the general population, and the factor for remaining interspecies differences of 2.5 will be included, the Registrant is of the opinion that an additional factor accounting for duration of exposure does not need to be applied.

ECHA acknowledges the Registrant's willingness to amend the DNEL derivation, as regards the use of an AF of 2.5 for remaining interspecies difference. However, ECHA disagrees, firstly, that absence of systemic toxicity in a 90-day study would allow concluding that prolongation of exposure would not increase toxicity. This could only be concluded if comparisons between 28-day study and 90-day study findings or between two pre-natal developmental toxicity studies with different exposure durations were available which is not the case. Secondly, ECHA notes that although adverse effects were observed only above the limit dose in the pre-natal developmental toxicity study, the findings were severe (fatality) and the Registrant did not address the severity of effects observed with any justification or any additional assessment factor according to Annex R.8-12 of ECHA guidance. The observed effects on survival may be the result of sub-lethal adverse effects that already occur at lower dose levels and that would have been observed if the standard endpoints of a repeated dose toxicity test were investigated. The number of endpoints investigated in the dams of a pre-natal developmental toxicity study is limited compared to the number investigated in a repeated dose toxicity study. Thirdly, ECHA notes that neither allometric scaling nor default intraspecies AFs account for differences in duration of exposure. Therefore taking into account that the NOAEL used in DNEL derivation for long-term systemic effects was taken from a pre-natal developmental toxicity study and that the duration of pregnancy in rats is longer than the duration of exposure in that study, an assessment factor for duration of exposure (higher than 1) should be applied. The default assessment factor for extrapolation from subacute to chronic should be applied unless a case-specific full justification is given that an AF other than the default AF meets all the conditions set in Annex I section 1.4.1. and bullets a) to c) therein, more specifically duration of exposure, severity of effect and sensitivity of the human sub-population to which the information on exposure applies.

Based on the above, the Registrant shall revise his DNELs and reassess related risks. The results of the studies requested under section II.B. shall be taken into account when revising the DNELs. If DNELs are not revised, this shall be fully justified. The chemical safety report shall be amended accordingly.

4. A revised exposure assessment for dermal route (Annex I, section 5.2.4.)

Pursuant to sections 0.6.2. and 0.6.3. of Annex I of the REACH Regulation the chemical safety assessment (CSA) performed by a Registrant shall include an exposure assessment according to section 5 of Annex I. 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 (workers, consumer and humans liable to exposure via the environment) for which exposure to the substance is known or reasonably foreseeable. Each relevant route of exposure (inhalation, oral, dermal and combined through all relevant routes and sources of exposure) shall be addressed. In addition, Annex I, section 5.2.5. of the REACH Regulation indicates that appropriate models can be used for the estimation of exposure levels.

ECHA notes that the Registrant has used ECETOC TRA version 2 to estimate exposure for a variety of worker and consumer exposure scenarios. More precisely the Registrant has used the local exhaust ventilation (LEV) exposure modifier even when inappropriate such as for estimating dermal exposure.

ECHA underlines that the Guidance on information requirements and chemical safety assessment, R.14 version 2.1 (section R.14.4.8, page 21) advises against the use of the LEV modifier for dermal exposure estimation.

ECHA notes that the calculated exposure estimates are likely to be unrealistically low and therefore the worker (industrial and professional users) exposure assessment for the dermal route needs to be revised. Taking into account the need to revise the calculated DNEL(s), the Registrant shall ensure that the calculated risk characterisation ratios will still be below 1, in order to demonstrate the safe use of the registered substance.

As explained above, the information provided on the dermal exposure estimates for the registered substance in the Chemical Safety Report are inappropriate and do not meet the requirements of Annex I, Section 5.2.4. and 5.2.5. Consequently it is necessary to revise the dermal exposure estimates.

Based on the above the Registrant shall revise the exposure assessment for dermal route and assess related risks. The revised DNELs requested under section II.C.1 shall be taken into account when assessing the related risks. The chemical safety assessment shall be amended accordingly.

D. 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 requested 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 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

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

In relation to the information required by the present decision, the sample of substance used for the new study 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 study 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 study 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 study to be assessed.

V. Information on right to appeal

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

[redacted]
Leena Ylä-Mononen
Director of Evaluation

Annex I.

Assessment factors (AF) applied by the Registrant:

For workers - systemic long term – inhalation route:
- interspecies: 1 (remaining differences between species non related to allometry)
- intraspecies: 5
- exposure duration: 1
  (overall AF: 5)

For workers - systemic long term – dermal route:
- interspecies: 4
- intraspecies: 5
- exposure duration: 1
- absorption difference dermal-oral: 1
  (overall AF: 20)

For workers - local long term – inhalation route:
- interspecies: 1 (remaining differences between species non related to allometry)
- intraspecies: 5
- exposure duration: 1
  (overall AF: 5)

For the general population - systemic long term – inhalation route:
- interspecies: 1 (remaining differences between species non related to allometry)
- intraspecies: 10
- exposure duration: 1
  (overall AF: 10)

For the general population - systemic long term – dermal route:
- interspecies: 4
- intraspecies: 10
- exposure duration: 1
- absorption difference dermal-oral: 1
  (overall AF: 40)

For the general population - systemic long term – oral route:
- interspecies: 4
- intraspecies: 10
- exposure duration: 1
  (overall AF: 40)

For the general population - local long term – inhalation route:
- interspecies: 1 (remaining differences between species non related to allometry)
- intraspecies: 10
- exposure duration: 1
  (overall AF: 10)

The default assessment factors recommended in the ECHA Guidance[1]:

For workers - systemic long term – inhalation route:
- interspecies: 2.5 (remaining differences between species)
- intraspecies: 5 (workers)
- exposure duration: 6 (sub-acute to chronic)
  (overall AF: 75)

For workers - systemic long term – dermal route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 5 (workers)
- exposure duration: 6 (sub-acute to chronic)
- absorption difference dermal-oral: 1
  (overall AF: 300)

For workers - local long term – inhalation route:
- interspecies: 1 (remaining differences between species, no respiratory effects)
- intraspecies: 5 (workers)
- exposure duration: 1 (no respiratory effects)
  (overall AF: 5)

For the general population - systemic long term – inhalation route:
- interspecies: 2.5 (remaining differences between species non related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 6 (sub-acute to chronic)
  (overall AF: 150)

For the general population - systemic long term – dermal route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 6 (subchronic to chronic)
- absorption difference dermal-oral: 1
  (overall AF: 600)

For the general population - systemic long term – oral route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 6 (subchronic to chronic)
  (overall AF: 600)

For the general population - local long term – inhalation route:
- interspecies: 1 (remaining differences between species, no respiratory effects)
- intraspecies: 10 (workers)
- exposure duration: 1 (no respiratory effects)
  (overall AF: 10)

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