EUROPEAN CHEMICALS AGENCY

Helsinki, 9 April 2018

Addressee: [redacted]

Decision number: CCH-D-2114394628-32-01/F
Substance name: Diallyl 2,2'-oxydiethyl dicarbonate
EC number: 205-528-7
CAS number: 142-22-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30/09/2010
Registered tonnage band: Over 1000

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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

2. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the study requested under 2. has negative results;**

4. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **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;**

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

6. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance.**

7. **Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: revise estimation of the local exposure and revise the**

risk characterisation accordingly

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 to the REACH Regulation. 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 adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by ***18 October 2021*** except for the information requested under point *1* for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by ***16 April 2019***. You may only commence the extended one-generation reproductive toxicity study as requested under point *4* after ***16 July 2019***, unless an indication to the contrary is communicated to you by ECHA before that date. 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 and advice and further observations are provided in Appendix 3.

Appeal

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, has to 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/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

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.

You have sought to adapt this information requirement with the following justification for the adaptation:

"*There was no sign of toxicity at the highest dose level in the Combined Repeat Dose Toxicity with the Reproduction/Developmental Toxicity Screening Test (OECD 422) by the route of exposure considered most appropriate (= dermal). The oral exposure level can be assessed by extrapolation procedure from the valid data of the dermal study. Hence, an oral long-term testing is superfluous (aspects of animal welfare).*"

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 1.1 governing "use of existing data".

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422). However, this study does not provide the information required by Annex IX, Section 8.6.2. and does not comply with Annex XI, Section 1.1, because exposure duration is less than 90 days. You have also provided three repeated dose 14-day-exposure supporting studies. However, as mentioned above none of the provided studies fulfils the information requirements for this endpoint.

Therefore, your adaptation of the information requirement is rejected.

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 has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration.

More specifically, the substance is a liquid of low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. You consider in your waiving that the route of exposure considered most appropriate is the dermal route. However, ECHA notes the following:

- There is no justification for testing via dermal route and there are no apparent substance specific properties (the substance has a low volatility, water soluble liquid with a LogKow of 1.543) or special uses that would justify the use of dermal route over the oral.
- You argue in the waiver that "*There was no sign of toxicity at the highest dose level in the Combined Repeat Dose Toxicity with the Reproduction/Developmental Toxicity Screening Test (OECD 422) by the route of exposure considered most appropriate (= dermal).* " The highest dose in the dermal screening study showing no toxicity was 1030 mg/kg/day. However, in an oral acute study a single dose of 800 mg/kg bw/d caused death in all the tested animals within 3 days and severe clinical effects ([redacted] 1981). The LD 50 for the oral route was 515 mg/kg bw/d. The substance seems to be more toxic via oral than dermal route and it is self-classified as Acute Tox 4 oral.
- There are different effects observed in the oral acute study (inactivity, lethargy, bodies cool to touch, ataxia, glassy eyes, lacrimation, eyes half shut, salivation, convultions, congestion of gastric mucosa or gastric healed perforation with chronic organized peritonitis, localized thickened area in the forestomaeh, generalized visceral congestion, hemorrhage of hindstomach and/or mottled liver, or stomach mottled dark red) compared to the dermal acute studies (anorexia, adipsia, decreased defecation, intraperitoneal fluid red, spleen mottled light, exterior surface of stomach reddened and interior hemorrhagic, vaginal area congested, irregular, pale, yellow foci noted over the liver).
- The rat species used in the dermal studies does not seems to be the most appropriate testing system for the dermal route as outlined also in the dossier in the dose range finding studies for the repeated dose ([redacted] 1980b): "*In view of the relatively minor effects observed in this and an earlier range finder with diallyl diglycol carbonate applied dermally to rats at maximal dose levels, it is suggested that an alternate species be considered for future studies. The rabbit is a specie with a thinner and perhaps more permeable skin for this test material.*"

In your comments on the draft decision, while you acknowledged that there is a formal information gap for this endpoint, you considered that the dermal route is the most relevant route of administration '*on the basis of the identified uses, the lack of consumer uses and the use of good occupational hygiene practice*'.

ECHA notes that exposure-based arguments are not valid for hazard characterization and that the reasons for testing via the oral route are already explained in the draft decision. Indeed, according to the criteria listed in Annex IX Section 8.6.2. Column 2 of the REACH Regulation, testing via the dermal route may be appropriate. However, the most appropriate route is still considered to be the oral route in order to reach appropriate systemic exposure, mainly because the extent of systemic exposure via the dermal route is currently not known as all the provided toxicokinetic information were obtained following intramuscular injection. Therefore, taking into account the above arguments and your comments, ECHA considers that the oral route is the most appropriate. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 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, you are 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 TG 408) in rats.

2. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

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 recognised by the Commission or ECHA.

Other tests 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 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 TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: *S. typhimurium* TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). This includes 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.

You have provided data from two Ames test ([redacted] 1980; [redacted] 1981) performed following a method similar to OECD TG 471 but not according to GLP with an assigned reliability score of 2 and 3, respectively. Both tests used five different strains of *S. typhimurium* TA 1535, TA 1537, TA 15378, TA 98 and TA 100 but they did not include tests with strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

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

Moreover, it is noted that the outcome of these two studies is not clearly described: while the authors of the studies describe the outcome as positive (in TA 98 or in TA1535, respectively), your conclusion/interpretation is that these studies are 'ambiguous'. The results obtained raise uncertainty regarding the assessment of the potential of the registered substance to induce gene mutation in bacteria.

In your comments to the draft decision, you proposed to fill this information gap by providing an analysis using the *in silico* tool 'OECD QSAR Toolbox Version 4.1'. The grouping method you used was the mechanistic profiler 'DNA binding by OECD'. You performed a subcategorization according to 'DNA alerts for Ames by OASIS' and structural features ('organic functional groups' and 'chemical elements'). Your approach returned a 'negative' prediction for genotoxicity towards *E. coli* WP2 uvrA, WP2 uvrA pKM101 and *S. typhimurium* TA 1535, TA 1537, TA 97, TA 97A, TA 98, TA 100 and TA 102. ECHA reviewed your information and considers that the provided documentation is incomplete (e.g. analogues are not specified and the data matrix is not attached). In addition, in your approach, you only used mechanistic profilers showing no alerts, hence not assessing the registered substance against possible 'positive' analogues. This is not a valid basis to form a robust category, which was also confirmed when the described workflow was repeated, and the analogues selected by your grouping approach were found to show low structural similarity.

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 bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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 does not contain appropriate study records for Annex VII, Section 8.4.1 information requirements. Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the

registered substance to meet this information requirement provided that the studies requested under request 2 (Ames test) have negative results.

You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

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.

In your comments on the draft decision, you agreed to conduct an in vitro mammalian cell gene mutation test (test method: OECD TG 476 or OECD TG 490).

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: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under request 2 has negative results.

4. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with 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. Further detailed guidance on study design and triggers is provided in in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 5.0, December 2016).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

- *The information provided*

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) and waived the extended one generation with the following justification:

> *"In accordance with column 1 of REACH Annex IX, the two-generation reproductive toxicity study does not need to be conducted, if the 28-day or 90-day study does not*

indicate adverse effects on reproductive organs or tissues. Due to the low observed toxicity of the substance on the target organs (based on the repro-screening study (OECD 422)), the testing is superfluous (aspects of animal welfare)."

However, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. Furthermore, ECHA notes that this is an Annex X dossier and at this tonnage band an extended one generation study is mandatory. Therefore, your adaptation of the information requirement is rejected.

Hence, 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.

- *The specifications for the study design*

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 5.0, December 2016).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

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* Chapter R.7a, Section R.7.6 (version 5.0, December 2016).

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.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted 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.

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 5.0, December 2016) Chapter R.7a, Section 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 on the draft decision, while you acknowledged that there is a formal information gap for this endpoint, you considered that the dermal route is the most relevant route of administration '*on the basis of the identified uses, the lack of consumer uses and the use of good occupational hygiene practice*'.

However, as explained previously under section 1, ECHA considers that the most appropriate route is still the oral route. In addition, an important aspect in establishing the most appropriate route of exposure for the reproductive studies is that the route of administration should result in sufficiently high systemic exposure for hazard identification and classification. Based on the information you provided, there is no evidence that the dermal route leads to a sufficiently high systemic exposure for hazard identification.

- 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:

- 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.

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request *1*) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by ***16 April 2019***. If, on the basis of this

update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by ***16 July 2019*** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study.

If you do not receive a communication from ECHA by ***16 July 2019***, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision ***18 October 2021***.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 5.0, December 2016)*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design 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.

5. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) 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 rabbits by the dermal 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.

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

In your comments on the draft decision, while you acknowledged that there is a formal information gap for this endpoint, you considered that the dermal route is the most relevant route of administration '*on the basis of the identified uses, the lack of consumer uses and the use of good occupational hygiene practice*'.

However, as explained previously under sections 1 and 4, 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 5.0, December 2016) Chapter R.7a, Section 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.

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 rat by the oral route.

6. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance.

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet 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 IX, Section 9.1., column 2. You provided the following justification for the adaptation *:*

'In Annex IX of Regulation (EC) No 1907/2006, it is laid down that chronic tests shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of the substance reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, and for reasons of animal welfare a chronic test on fish is not provided'.

ECHA points out that long-term toxicity testing on fish is a standard information requirement at the current tonnage level, as described above.

In addition, ECHA considers that long-term toxicity studies on aquatic organisms are warranted in the present case as the outcomes of the chemical safety assessment, in its present form, does not demonstrate that the risks towards the aquatic compartments are adequately controlled (RCR > 1 as further explained in request 7 below).

Therefore, your adaptation of the information requirement cannot be accepted and information on long-term toxicity to aquatic organisms needs to be provided.

Based on Section R.7.8.5.3. of ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017), long-term toxicity data on fish should be preferred over long-term toxicity data on invertebrates "*if there is compelling evidence to suggest that the invertebrate value is likely to be at least a factor of about 10 less sensitive than algae or fish there are no further requirements for invertebrate testing*". ECHA notes that the short-term LC50 for fish reported in your dossier is about 30 times lower than the lowest short-term EC50 reported for aquatic invertebrates, suggesting that fish is substantially more sensitive than aquatic invertebrates. Therefore, ECHA considers that long-term toxicity should be investigated on fish.

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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment , Chapter R7b,* version 4.0, June 2017).

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

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: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

7. Exposure assessment and risk characterisation (Annex I, Sections 5. and 6.) for environment: revise estimation of the local exposure and revise the risk characterisation accordingly

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

According to Article 14(4) of the REACH Regulation, the CSA must include the additional steps of exposure assessment and risk characterisation if the substance fulfils the criteria for any classifications set out in Annex I to Regulation (EC) No 1272/2008 and listed in Article 14(4).

Your registered substance fulfils the criteria for classification as Aquatic Acute 1 (Hazard statement: H400: Very toxic to aquatic life) set out in Annex I to Regulation (EC) No 1272/2008, triggering the need to perform a CSA.

According to Section 5.0 of Annex I of the REACH Regulation, the objective of the exposure assessment shall be to make a quantitative or qualitative estimate of the dose/concentration of the substance to which humans and the environment are or may be exposed. Pursuant to Annex I, section 5.1.1 of the REACH Regulation, if the initial assumptions lead to a risk characterisation indicating that risks to human health and the environment are not adequately controlled, then it is necessary to carry out an iterative process with amendment of one or a number of factors in hazard or exposure assessment with the aim to demonstrate adequate control of the risks.

Section 6.1 of Annex I provides that risk characterisation must be carried out for each exposure scenario. The risk characterisation shall consider the environmental spheres for which exposure to the substance is known or reasonably foreseeable, under the assumption that the risk management measures described in the exposure scenarios have been implemented (Section 6.2).

ECHA *Guidance on information requirements and chemical safety assessment Part E: Risk characterisation* (version 3.0, May 2016) explains that adequate control of risk for a substance is demonstrated when the outcome of both the hazard assessment and exposure assessment are robust and where risk characterisation ratio (RCRs) for all exposures (for all compartments, routes, populations and durations) related to all exposure scenarios and all end-points are below one.

In the CSR, you state that "[redacted]".

Based on the information you provided, ECHA considers that releases of the substance into the environment cannot be ruled out for the reasons described in the following paragraphs.

ECHA notes that the CSR includes RCR estimates that are well above '1' for most environmental compartments (e.g. RCR for local freshwater for manufacture is quoted as [redacted]). You state that "*ECETOC TRA allows only Tier 1 environmental assessments based on extremely conservative, unrealistic default assumptions*", yet you did not provide refined predicted environmental concentrations (PECs). You did provide a qualitative assessment including a description of the waste water treatment plant (WWTP) at the manufacturing facility. However, insufficient justification were provided to demonstrate adequate control of the risks. You have explicitly indicated that emissions to waste water

are possible. However, no information on the actual amount released to waste water is provided. You have mentioned that waste water is processed in a waste water treatment plant (WWTP) and you provided a list of the physico-chemical and biological treatments applied. However, no evidence of the actual removal of the registered substance is given.

In particular, ECHA notes that the registered substance has a limited potential for adsorption and is not especially volatile: it is not expected to adsorb to a large extent to the sludge or to be evaporated. Therefore, the effectiveness of the physico-chemical treatments you have reported is deemed to be limited.

ECHA further notes that the registered substance is readily biodegradable, but also that the RCR for the sewage treatment plant (STP) microorganisms indicates a risk in exposure scenario 1 (manufacture of the substance). If releases of the registered substance to the waste water exceed the toxic level for degrading microorganisms in the STP, then the biological treatments are likely to be impaired.

ECHA therefore considers that your assessment currently does not demonstrate an adequate control of the risks.

According to Section E.4.6 of ECHA *Guidance on Information Requirements and Chemical Safety Assessment Part E* (Version 3.0 May 2016), iterations of the CSA may involve the following options: (i) improve hazard information, (ii) improve exposure information and/or consider to introduce sufficient RMMs and (iii) conclude that it is not possible to demonstrate control of risk, and provide the necessary documentation that uses are advised against. As described above, the CSR currently reports RCRs that are well above '1'. ECHA considers that improving the exposure information is the first step to adress these concerns.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to revise the estimation of the local exposure and revise the risk characterization accordingly. The revised risk characterization will also need to consider the new hazard information generated in accordance with request 6.

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 26 July 2017.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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 otherwise fulfil 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 the 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 compositions 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 the 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 grades registered to enable the relevance of the tests to be assessed.