ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki 30 March 2017

Addressee: [redacted]

Decision number: CCH-D-2114357257-44-01/F
Substance name: Oxirane, mono[(C12-14-alkyloxy)methyl] derivs.
EC number: 271-846-8
CAS number: 68609-97-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27.02.2015
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

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

1. **In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum with the registered substance; OR Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section 8.4., column 2; test method: EU B.58./OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach with the registered substance;**

2. **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;**

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

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

5. **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.**

You are required to submit the requested information in an updated registration dossier by **7 October 2020** except for the information requested under point 2 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier **6 April 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point 5 after **9 July 2018**, 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.

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

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

The scope of this compliance check decision is limited to Annex VII, Section 8.4.1., Annex VIII, Sections 8.4.2. and 8.4.3., Annex IX, Sections 8.4. and 8.6.2., and Annex X, Sections 8.7.2. and 8.7.3. of the REACH Regulation.

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, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

1. In vivo gene mutation assays (Annex IX, Section 8.4., column 2)

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

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The registration dossier contains an *in vitro* Ames study (OECD TG 471, 1997, reliability 1) which gave a positive result with strain TA 1535 with and without metabolic activation. In a second supporting Ames study (OECD TG 471, 1979, reliability 2), ambiguous results are reported for strains TA 100 (with metabolic activation), TA 98 (without metabolic activation) and TA 1535 (with metabolic activation). The positive results indicate that the substance is inducing gene mutations under the conditions of the test.

In addition two reported *in vitro* gene mutation studies (OECD TG 476, 1998, reliability 1 and OECD TG 476, 1979, reliability 2 respectively) on mammalian cells are both negative. However, according to the REACH legal requirements (Annex IX, section 8.4), these negative results do not rule out the positive result obtained in the Ames study.

The technical dossier also contains several *in vivo* studies: *in vivo* cytogenicity studies performed according to OECD TG 474 with the registered substance that show negative results (in one key and 2 supporting studies).

ECHA notes that the available *in vivo* studies, while negative, all address chromosome aberration and not gene mutation, *i.e.* the concern identified in the in vitro gene mutation assay in bacteria. Hence, ECHA concludes that the tests provided were not appropriate to follow-up a concern for gene mutations and that an appropriate *in vivo* genotoxicity study to follow up the concern for gene mutation is not available for the registered substance. Consequently there is currently an information gap and it is necessary to provide information for this endpoint.

According to the *ECHA Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.7.6.3, the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a positive *in vitro* result on gene mutation. Hence, ECHA considers that the TGR and the comet assay are suitable tests to follow up the concern on gene mutation for the substance subject to the decision.

In case you decide to perform a TGR assay according to the test method EU B.58/OECD TG 488, the test shall be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, and glandular stomach as rapidly proliferating tissue and site of direct contact. Male germ cells shall be collected at the same time as the other tissues (liver and glandular stomach), and stored up to 5 years (at or below -70°C). This duration is sufficient to allow the Registrant or ECHA, in accordance to Annex X, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells.

In case you decide to perform a comet assay according to the test method OECD TG 489, the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the substance, and probable different local absorption rates of the substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to sample both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

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 vivo mammalian alkaline comet assay (test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum,

OR

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach.

Notes for your consideration

You are reminded that according to Annex IX, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "*the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered*".

In case you decide to perform the comet assay, you may consider examining gonadal cells in addition to the other aforementioned tissues, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation."

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

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

a) Read-across

In the technical dossier you have provided a study record for a repeated dose toxicity study (90 days, according to OECD TG 411) via dermal route using the substance "C12-C13 alkyl glycidyl ether (AGE)" and in compliance with GLP ([redacted], 1997). However, this study does not provide the information required by Annex IX, Section 8.6.2., for the following reasons:

(i) although you claimed that the sub-chronic dermal toxicity study was conducted with the registered substance (Section 7.5.3. under "Test material") the information provided (section 7.5.3 under "Details on test material") indicate that the substance "Alkyl (C12-C13) glycidyl ether" (AGE) was used as the test material.

ECHA notes that the CAS RN of the substance AGE is 120547-52-6. ECHA notes the different (longer) chain lengths present in the registered substance (Oxirane, mono[(C12-14-alkyloxy)methyl] derivs.), and considers that you have used a different substance than the registered substance, and that you therefore appear to be applying an adaptation according to Annex XI, 1.5, Grouping of substances and read-across approach.

ECHA also notes that you did not provide any justification in the registration dossier regarding the read-across and how the registered substance "Oxirane, mono [(C12-14-alkyloxy) methyl] derivs" (CAS RN 68609-97-2) can be read across from "alkyl (C12-13) glycidyl ether" (CAS RN 120547-52-6).

In your comments, you argued that "the *"alkyl (C12 - 13) glycidyl ether" (CAS RN 120547-52-6)* [the analogue substance] *was considered to be representative of the alkyl glycidyl ether subcategory from the US EPA's test rule for glycidol and its derivatives"*, and that *"this agreed category also included the [registered] substance Oxirane, mono [(C12-14-alkyloxy) methyl] derivs" (CAS RN 68609-97-2)"*.

In addition, you stated that "*In this context, the US EPA and certain alkyl glycidyl ether manufacturers negotiated an Enforceable Consent Agreement (ECA) (Docket: OPPTS-42185, FR, March 22, 1996) wherein these companies agreed to perform certain health effects tests using alkyl (C12-C13) glycidyl ether (CAS # 120547-52-6) for which a REACH registration has also been submitted."* You further added that, "*In light of this agreement with the HPV program, the US EPA assessment, and structural similarities, when and where data are lacking for the substance, the registrant believes that the use of data from the following group (listed below) of surrogate/similar chemicals is scientifically justified and also should be encouraged to minimize, as well as optimize, animal usage."*

ECHA therefore understands that the basis of your read-across justification is that there has been an agreed approach on read-across with the US EPA, and that there is structural similarity.

ECHA considers that an agreement with the US EPA *per se* does not meet the requirements of Annex XI, Section 1.5. You are required under REACH to provide the necessary documentation to justify a read-across approach, such as a category justification and a data matrix. This information is lacking in the dossier and was not provided in your comments to the draft decision.

You argued that "*structural similarities*" are a basis for the read-across, stating that "*the chemical category, glycidyls, was defined [...] as all substances with the general formula: R-O-$CH_2CH(O)CH_2$, where R is a hydrogen atom or any alkyl, aryl or acyl group, and R is unrestricted as to the number and type of substituents it may carry."* Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that structural similarity *per se* is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties.

Hence, further elements are needed such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health properties that does not underestimate risks.

Such information have not been provided in your registration dossier. The information you submitted in your comments to the draft decision, suggest that similarity cannot be confirmed since the properties listed in Table 1, do not demonstrate that "different compounds have the same type of effect(s)" (e.g. biodegradability, irritation).

Therefore, in the absence of a justification for the read-across and of relevant information, ECHA considers that the requirement of Annex XI, Section 1.5, that "*Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach)*", has not been met.

ECHA finally considers that you have failed to meet the requirement of Annex XI, Section 1.5 that adequate and reliable documentation of the applied method shall be provided. Indeed, insufficient information has been provided in order to enable ECHA to assess your read-across justification.

(ii) You have provided a study with dosing by the dermal route. However, ECHA considers that this fails to meet the requirements of Annex IX, Section 8.6.2, because the dermal route is neither an appropriate route, nor is it the most appropriate route of administration, having regard to the likely route of human exposure.

b) Appropriate route

With respect to whether the dermal route is appropriate, ECHA notes that according to Annex IX, Section 8.6.2, column 2:

"*Testing by the dermal route is appropriate if:*

(1) skin contact in production and/or use is likely; and
(2) the physicochemical properties suggest a significant rate of absorption through the skin; and
(3) one of the following conditions is met: (i) toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test, or (ii) systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies, or (iii) in vitro *tests indicate significant dermal absorption, or (iv) significant dermal toxicity or dermal penetration is recognised for structurally-related substances.*"

You indicated the significant routes of human exposure as being the dermal and inhalation routes (IUCLID Section 3.7.3.; "General exposure potential"). In your comments to the draft decision you stated that the "*dermal route was selected as the most likely route for occupational exposure, given the low volatility of the [AGEs] and the unlikelihood of oral ingestion of any appreciative amounts*" and also that "*dermal exposure is highly unlikely*" and "*under no circumstances does the registrant envisage oral or inhalation exposure at high concentrations ever taking place.*"

However, from the information provided in the dossier, the three cumulative conditions of Annex IX, Section 8.7.2., column 2 for showing that the dermal route is appropriate are not met.

First, ECHA accepts that skin contact may occur during formulation and/ or industrial/ professional) use, as indicated by the following process categories (PROCs):

- Industrial formulation: 4, 8b and 9
- Industrial use: 7, 10 and 13
- Professional use: 4, 5, 10 and 13

Therefore, condition (1) of Annex IX, Section 8.7.2., column 2 is met. Similarly where exposure arises, inhalation or oral routes cannot be excluded, e.g if the substance is released from the end-use product (which is as inclusion into a matrix) or during roller application/ brushing (PROC 10).

Second, the physicochemical properties do not suggest a significant rate of absorption through the skin. You reported (Section 7.1.1) that: *"the test item may bind to carrier proteins in the circulatory system thereby facilitating systemic distribution. Once absorbed, the substance may potentially accumulate in adipose tissue due to the high log octanol/water partition coefficient value (log P_{ow} 6.0, [redacted], 2010)."* In addition, the ECHA Guidance, R.7c, which includes toxicokinetics and absorption, provides (p.173 and surrounding, Table R.7.12-3) that *"[...] substances with [...] Log P values between 1 and 4 favour dermal absorption (values between 2 and 3 are optimal) particularly if water solubility is high. Above 4, the rate of penetration may be limited by the rate of transfer between the stratum corneum and the epidermis, but uptake into the stratum corneum will be high. [...]"* ECHA notes that the registered substance, which has a log P_{ow} of 3.77, is only slightly soluble (0.5 mg/L) and that *"dose selection for repeat dose dermal studies was limited by dermal irritancy"* (as you indicated). No data were submitted to assess the toxicokinetic properties of the registered substance.

In your comments to the draft decision you have discussed and made references to papers by Boogaard, which deal with dermal penetration and metabolism of analogue substances of the registered substance. This empirical data does not address ECHA's view that "the physicochemical properties suggest that there is not a significant rate of absorption". Furthermore the data used in these papers do not specifically refer to the registered substance and as explained above no valid justification has been provided to read-across to this data.

For these reasons ECHA concludes that you have failed to establish that the physicochemical properties suggest that there is a significant rate of absorption through the skin, and that the information provided rather indicates a potential for the registered substance to accumulate leading to local irritancy. Therefore, the condition under point 2 under Annex IX, Section 8.6.2, column 2, for assessing the appropriateness of testing through the dermal route has not been met.

Third, ECHA further considers that none of the four conditions of point 3 under Annex IX, Section 8.6.2, column 2, are met.

(1) With respect to condition (i) of point 3 ("toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test") specifically, whilst there is evidence of local toxicity in the acute dermal toxicity test at lower doses than in the oral toxicity test, ECHA considers that there is no evidence of systemic toxicity in the dermal toxicity study, except as a result of local toxicity. Further in your comments to the draft decision, you indicated that acute oral and acute dermal LD_{50}s, *"technically [...] cannot necessarily be differentiated"*. ECHA therefore concludes that condition (i) is not met.

(2) For condition (ii), you have not provided any evidence for systemic effects and ECHA notes that the publications of Boogaard do not refer to the registered substance and as explained above no valid justification has been provided to read-across to other substances; you have neither provided other evidence of absorption in skin and/or eye irritation studies. Therefore, condition (ii) is not met.

(3) For condition (iii) ECHA notes that the publications of Boogaard do not refer to the registered substance and as explained above no valid justification has been provided to read-across to other substances; hence condition (iii) is not met because there is no information for the registered substance.

(4) For condition (iv) and demonstrating that there is "*significant [...] dermal penetration is recognised for structurally-related substances*", ECHA notes that you refer to publications of Boogaard where testing was performed on analogue substances. As the information is not in the registration dossier, and as your comment does not provide a clear exposition of the data, ECHA cannot ensure an independent assessment of this piece of information. Nonetheless, ECHA notes that for the structural analogue C12 GE, the percentage of the total applied dose that penetrated unchanged was reported as 0.23 and 0.21 % for mouse and rat skin, respectively. ECHA therefore considers that significant dermal penetration for structurally-related substances has not been demonstrated. Further, ECHA considers that more distant structural analogues have distinct physicochemical properties, and are not informative for the registered substance.

ECHA notes that it is necessary to satisfy points 1 to 3 of Annex IX, Section 8.6.2, column 2 requirements in order for the dermal route to be appropriate, and that, as demonstrated in the reasons set out above, both points 2 and 3 are not met. Therefore ECHA concludes that the dermal route is not appropriate.

c) Most appropriate route

However, even if the dermal route were to be appropriate, ECHA considers that the dermal route is not the most appropriate route of administration. There is no adequate evidence to show significant absorption of the registered substance by the dermal route and the physicochemical properties suggest it will have very limited absorption. This is supported by your statement that "*dose selection for repeat dose dermal studies was limited by dermal irritancy*". In addition ECHA notes that the registered substance has sensitising properties. Hence these considerations argue against the dermal route for evaluating the systemic hazard of the registered substance.

Consequently the available repeated dose toxicity study (90 days) via dermal route does not fulfil the information requirements as the provisions of Annex IX, Section 8.6.2, column 1, for the use of the "most appropriate route of administration, having regard to the likely route of human exposure," have not been met. In your comments to the draft decision, you argued that "*following the permeation of dermal, repiratory, gastrointestinal surfaces, C_x glycidyl ethers are rapidly hydrolysed and converted from the parent to the diol with 86% metabolised for human [...] skin [...].*" ECHA fails to understand how the metabolisation rates indicated support your argument that oral route is not the most appropriate route.

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 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure (0.018 Pa at 20°C). In addition you indicated that the relevant routes of exposure to humans to be dermal and inhalation: *"whilst available repeated dose toxicity data was via the dermal route; there is no reason to presume that absorption via the skin is more favourable compared with the oral route. This is particularly of note when considering that dose selection for repeat dose dermal studies was limited by dermal irritancy."* Further ECHA considers that the oral route will likely have better absorption and dosing is less likely to be limited by dermal irritancy. This is further illustrated in the acute oral toxicity study you submitted where effects were observed. Thus the oral route is the most appropriate route, and the dermal route would not be most appropriate route.

Finally, the ECHA Guidance (October 2015 - Section R.7.5.4.1, page 325) notes *"that potential effects in certain target organs (e.g., the thyroid) following repeated exposure may not be observed within the span of the 28-day study. Attention is also drawn to the fact that the protocols for the oral 28-day and 90-day studies include additional parameters compared to those for the 28-day and 90-day dermal and inhalation protocols."*

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.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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

A "pre-natal developmental toxicity study" (test method EU B.31/ OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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 you have provided a study record for a developmental toxicity screening study (dermal route and on the registered substance), which protocol is claimed to be equivalent to the OECD TG 414 protocol.

However, this study was not performed according to OECD TG 414, and does not meet the requirement of Annex XI, Section 1.1.2 for adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3) of the REACH Regulation. Specifically, the eight animals per dose are not sufficient. Indeed, the OECD TG 414 states that *"Groups with fewer than 16 animals with implantation sites may be inappropriate."* ECHA therefore considers that eight animals per dose group is inadequate for coverage of the key parameters.

ECHA considers that the route of administration of the study you have provided is not appropriate for the following reasons:

(i) The OECD TG 414 guideline recommends that *"The test substance or vehicle is usually administered orally by intubation. If another route of administration is used, the tester should provide justification and reasoning for its selection, and appropriate modifications may be necessary"*. ECHA considers that you have not provided any justification for the choice of the route of administration.

(ii) Furthermore, ECHA considers that you have not met the column 1 requirement of Annex IX, Section 8.7.2 for a study by "the most appropriate route of administration, having regard to the likely route of human exposure." ECHA notes that the dose selection was limited by dermal irritancy (fissuring), and hence the measurement of systemic effects on pre-natal developmental toxicity is impeded. ECHA additionally considers that there is no appropriate evidence to show significant absorption of the registered substance by the dermal route and the physicochemical properties suggest it will have very limited absorption.

In your comments to the draft decision, you claimed that the prenatal developmental toxicity screening study in rats, which was provided in the dossier is adequate, by providing justification for the choice of dermal route. ECHA reiterates that the study otherwise fails to cover key parameters of the test guideline (specifically the number of animals per group). This study is therefore not acceptable.

In addition, ECHA has considered your arguments concerning the most appropriate route. ECHA remains of the view that there is no appropriate evidence to show significant absorption of the registered substance by the dermal route and the physicochemical properties suggest it will have very limited absorption (see ECHA's reasons set out in section 1 above). Additionally, ECHA notes that you have not addressed the considerations indicated in the initial draft decision on the dermal irritancy of the substance, and the limitation of dose by this route.

ECHA has evaluated the other arguments, as set out in request 2 above. After evaluation of the arguments against the column 1 test of Annex IX, Section 8.7.2 for the most appropriate route of administration, having regard to the likely route of human exposure, ECHA concludes that the dermal route is not the most appropriate route. Hence for both reasons, ECHA considers that the dermal route is strongly contra-indicated. By contrast, ECHA considers it highly likely that the oral route will show better absorption, and that it will not show the same limitations on dose caused by dermal irritation. Therefore the dermal route is not the most appropriate route of administration. As explained above, ECHA considers that the developmental toxicity screening study 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 the test method EU B.31 / OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption, ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA has evaluated the choice of route for the prenatal developmental toxicity study to be performed. For similar reasons as set out above (request 2), ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2.

Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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 first species (rat or rabbit) by the oral route.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The 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 does not contain information on a pre-natal developmental toxicity study with the registered substance.

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 X, Section 8.7.2., column 2. As a justification you stated that *"As no developmental toxic effects were noted in a dermal developmental toxicity performed with rats and as no effects were noted in the reproductive organs in the 13-week repeated dose dermal toxicity, an additional developmental toxicity study on a second species in considered scientifically unjustified."*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7.2., column 2 because you have not submitted evidence to demonstrate that (i) the registered substance is unreactive, insoluble and not inhalable and (ii) there is no evidence of toxicity in 28-day repeated dose toxicity study, and (iii) that there is limited human exposure and no absorption.

In addition, as described in the previous section, ECHA considers that there is actually no acceptable pre-natal developmental toxicity study in a first species available, and that you therefore cannot rely on that study in order to waive the second species.

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.

According to the test method EU B.31 / OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

As indicated above (point 2) ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2.

Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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 (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation. The 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 the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

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

a) The information requirement

In the technical dossier you have provided a study record for two studies: preliminary developmental toxicity screen (EPA OTS 798.4420 guideline) and a 13-week repeated dose dermal toxicity study (OECD TG 411). However, these studies do not provide the information required by Annex X, Section 8.7.3. because they do 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. Therefore, your adaptation of the information requirement is rejected.

Also while you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2 (weight of evidence). You provided an EPA OTS 798.4420 guideline study and a OECD TG 411 study, both via dermal route, without any specific justification for the adaptation.

However, ECHA notes that your adaptation does not meet the general rules for adaptation of Annex XI, Section 1.2., because it is not possible to conclude based on the information provided whether the registered substance has or has not a hazardous property on sexual function and fertility. 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.

b) 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* R.7a, chapter R.7.6 (version 4.1, October 2015).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* R.7a, chapter R.7.6 (version 4.1, October 2015). Ten weeks exposure duration is supported also by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating (log P_{ow} 3.77 to > 6.0).

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 other (e.g. a repeated dose toxicity study) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

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

In your comments you proposed that, "*in the interest of animal welfare, a combined approach of testing is used to fulfil the requirements of the rat 90-day repeated dose and extended one-generation reproductive toxicity studies as described in Annex [...].*"

In summary, you proposed to perform the 90-day repeated dose toxicity study and the EOGRTS study in one joint study, which would include the following: "*(a) extending the pre-mating interval from 10 to 13 weeks; (b) collecting full hematology and clinical chemistry at the end of the extended pre-mating period; (c) conducting neurobehavioral functional testing at the end of the extended pre-mating period.*"

ECHA notes that your comments do not address ECHA's considerations that 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)*" and hence that the sub-chronic toxicity study is a critical step, relevant for the expansion of the study design of the extended one-generation reproductive toxicity (EOGRT) study.

ECHA acknowledges that the proposed study design would provide additional information on the neurotoxicity endpoint and equivalent information to the information required for an oral 90-day repeated dose toxicity study. However ECHA points out that triggers such as changes of organ weights or other immunotoxicity-related events would not be available in time for a decision to expand the EOGRTS study design.

ECHA highlights that the purpose of sequential testing is to allow an informed decision on the most appropriate study design for the EOGRT study based on effects observed in the repeated dose toxicity study performed before starting the reproductive toxicity study and therefore to address concerns (i.e. triggers) which may arise.

Even though the combination of the studies could result in the use of a reduced number of animals, there is also the possibility that a combined 90-day repeated dose toxicity/ EOGRT study would fail to identify all relevant triggers in time to expand the EOGRTS study design, and that the resulting study would fail to address the information requirements for the triggered studies. If the combined 90-day repeated dose toxicity/ EOGRT study design would fail to meet the information requirement because triggered studies were not included in the design, there would be the necessity to consider proposing a further EOGRT study which would include the necessary triggered cohorts. This second, and unnecessary, EOGRT study is avoidable through sequential testing of the 90-day and EOGRTS studies, as detailed in this draft decision.

ECHA emphasises that the need to trigger additional cohorts (to assess neurotoxicity or immunotoxicity) addresses a concern for human health, which may have substantial public health significance. Consequently, the reasons to want the triggered cohorts is to address these concerns relevant to the human population, while addressing the information on reproductive properties.

Hence ECHA concludes that the two studies cannot be combined in this case, as it is necessary to have sequential testing to ensure that the column 2 conditions of REACH Annex X are fulfilled.

Species and route selection

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

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

c) Outcome

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

- 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 (point 2) 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 **6 April 2018**. 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 **9 July 2018** (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 **9 July 2018**, 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 **7 October 2020**.

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 R.7a, chapter R.7.6 (version 4.1, October 2015)*).

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.

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 08 April 2016.

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 requests.

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

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

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

You provided comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-52 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2018.

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

3. 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 your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) 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 test(s) to be assessed.