ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Helsinki, 03 January 2018

Substance name: 2,3-epoxypropyl o-tolyl ether
EC number: 218-645-3
CAS number: 2210-79-9
Date of latest submission(s) considered[1]: April 2017
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressee(s): Registrant(s)[2] of 2,3-epoxypropyl o-tolyl ether

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of the REACH Regulation (Regulation (EC) No 1907/2006), you are requested to submit the following information on the registered substance 2,3-epoxypropyl o-tolyl ether, abbreviated EPOTE in the following.

1. Human health endpoint Skin Sensitisation:

Local Lymph Node Assay (OECD TG 429). Dosing must be done using a freshly prepared test solution with an appropriate vehicle.

2. Human health endpoint Mutagenicity:

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice. Dosing shall be done by oral gavage daily in a freshly prepared test solution using an appropriate vehicle for 28 days. Germ cells from vas deferens/cauda epididymis shall be sampled 49 days after end of exposure and analysed. Glandular stomach, duodenum, bone marrow and liver shall be sampled 3 days after end of exposure and frozen and kept for a minimum of 5 years at or below -70 degrees Celsius.

OR

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice. Dosing shall be done by oral gavage daily in a freshly prepared test solution using an appropriate vehicle for 28 days. Germ cells from seminiferous tubules, and liver shall be sampled 28 days after end of exposure and

[1] This decision is based on the registration dossier(s) at the end of the 12-month evaluation period

[2] The terms registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

ECHA
EUROPEAN CHEMICALS AGENCY

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

analysed. Bone marrow, glandular stomach and duodenum shall be sampled 28 days after end of exposure and frozen and kept for a minimum of 5 years at or below -70 degrees Celsius.

3. CSR - Exposure-related requests:

a) Justification of the Registrant(s)' statement of no relevance for consumer exposure;

b) Combined exposure for humans due to high worker Risk Characterisation Ratios (RCRs) shall be described in more details. Either a reiteration of the developed exposure scenarios with higher tier exposure models is provided taking the results into account in the risk assessment, or further risk management measures are proposed and implemented.

You have to provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the chemical safety report by **03 October 2019**. The evaluating MSCA must have access to the full study reports for the skin sensitisation and mutagenicity requests including all relevant details of the studies, ensuring that a clear conclusion regarding the result of the studies can be drawn by the evaluating MSCA.

The deadline takes into account the time that you may need to agree on which of the Registrant(s) will perform the required tests.

The reasons of this decision and any further test specifications are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

Who performs the testing?

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all registrant(s) within 90 days. Instructions on how to do this 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 a suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals

Authorised[3] by Leena Ylä-Mononen, Director of Evaluation

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

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on 2,3-epoxypropyl o-tolyl ether (EPOTE) and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health.

EPOTE was initially selected for substance evaluation under CoRAP based on a concern for mutagenicity. During the substance evaluation process additional concerns for skin sensitisation, carcinogenicity and exposure of consumers and workers were identified.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested to clarify the concern for skin sensitisation, carcinogenicity, mutagenicity and exposure of consumers and workers.

Note on the identity of the substance evaluated under the present substance evaluation:

EPOTE is a mono-constituent substance; only one composition has been reported in the registration dossier. However, lack of clarity of the reported substance identity (degree of purity as well as identity of impurities) has been addressed in a compliance check by ECHA. The identified concerns addressed in this draft decision do not appear to be related to impurities. Therefore, the compliance check on the substance identity on the registered substance does not influence the present decision.

Several concerns for human health (skin sensitisation, mutagenicity, carcinogenicity, possible use of a too low reference dose for risk characterisation and potential underestimation of exposure of workers and consumers) were identified in the substance evaluation leading to a potential high risk for human health, including via non-threshold effect for the concerns of mutagenicity and carcinogenicity. Due to the severe nature of the concerns it was decided to proceed with substance evaluation in parallel to the compliance check evaluation targeting substance identity, in order to clarify the concerns identified without undue delay.

1. **Human health endpoint Skin Sensitisation:**

The concern(s) identified

Animal studies

A Guinea pig maximisation test was performed in 1989 according to OECD TG 406 (version 1981) with GLP compliance. However, the test substance was only identified by trade name (not chemical name or CAS Number). No information regarding composition and purity was available in the study report.

The induction was done in two stages: First, intradermal injections in the neck region were performed and secondly, closed patch occlusive epicutaneous exposure over the injection sites were performed one week later.

Induction stage 1: Three pairs of intradermal injections (of 0.1 ml per injection) were made at the same time into the neck (shaved) as follows: Adjuvant/saline mixture 1:1

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

(v/v), test substance in sesame oil (w/v) and the test substance in the adjuvant saline mixture (w/v). The dose level used was 3%.

Induction stage 2: The Epidermal induction phase was conducted one week later with the test substance (Vaseline was used as the vehicle(w/w)) applied on filter paper to the neck of the animals (patch 2x4 -cm; approx. 0.4 g paste/patch; occluded administration for 48 hours). The dose level used was 10%.

Challenge phase: Two weeks after the epidermal induction application. Animals were tested on the flank with the test substance in Vaseline (w/w) and the vehicle alone (patch 2x2 cm; approx. 0.2 g paste per patch; occluded administration for 24 hours). The dose level used was 3%. The challenge reactions were graded after 24 hours and 48 hours according to the Draize scoring scale.

The control group was treated with adjuvant and the vehicle during the induction periods. During the challenge period the group was treated with the vehicle and with the test substance to serve as irritation controls.

20/20 of the tested animals (100%) demonstrated positive dermal reactions when compared with the control group (0/20 positive dermal reactions).

The test substance is an extreme skin sensitizer under the conditions of this study.

The evaluating MSCA has evaluated this study as reliable with restrictions, Klimisch 2.

Another Guinea pig maximisation test was performed in 1991 according to OECD TG 406 (version 1981) with GLP compliance. The test substance was described as o-cresyl-glycidyl-ether (identical to 2,3-epoxypropyl o-tolyl ether) (purity 98.9%, no further information on the chemical identity of impurities was available). The highest non-irritating test article concentration used for the challenge phase was 1%. 10 male and 10 female guinea pigs were used in the test group and 5 male and 5 female guinea pigs in the control group.

Induction stage 1: Three pairs of intradermal injections (of 0.1 ml per injection) were made at the same time into the back: Freund’s complete adjuvant 1:1 with bi-distilled water, test article, diluted to 5 % with oleum arachides, and the test substance (dose 5%) emulsified in a 1:1 mixture of Freund’s complete adjuvant: oleum arachides.

Induction stage 2: The Epidermal Induction was conducted one week after the intradermal injections: A patch of filter paper was saturated with the test substance (10% in Vaseline) and placed over the injection sites of the test animals. The patches were left in place for approximately 48 hours.

Challenge phase: Two weeks after the epidermal induction application. Animals were tested on the flank with the test substance in Vaseline (w/w) and the vehicle alone (patch 2x2 cm; approx. 0.2 g paste per patch; occluded administration for 24 hours). The dose level used was 1%. The challenge reactions were graded after 24 hours (16 positive of 20 animals (80%)) and 48 hours (14 positive of 20 animals (70%)) according to the Draize scoring scale. In the negative control group no positive reactions were observed (0/10).

The test substance is considered a "Strong" dermal sensitizer under the conditions of the study.

The evaluating MSCA has evaluated this study as reliable with restrictions, Klimisch 2.

ECHA
EUROPEAN CHEMICALS AGENCY

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

A non-guideline study similar to the Guinea pig maximisation test was performed in 1976. The test substance was defined by trade name only (not identified by chemical name or CAS Number and no information was available about purity and chemical identity of impurities).

10 male and 10 female guinea pigs were tested in each group. For the positive control group a total of 10 animals were tested.

Induction phase: Volumes of 0.1 ml of the test substance (0.1%t) in saline without adjuvant were injected intradermally on three days. During the second and third week of induction the test substance was mixed with adjuvant in a 1: 1 ratio. A total of 6 sensitizing doses of 0.1 mL were injected intracutaneously into the skin of the neck on Monday, Wednesday and Friday.

Challenge phase: Two weeks after the last sensitizing treatment with the adjuvant mixture. 0.1 mL of the test substance (0.1%t) in saline without adjuvant was injected intradermally on the previously untreated flank. The reaction sites were evaluated 24 hours after the challenge by skin-fold thickness determined with a skin—fold gauge : length and height of erythema was recorded and compared to the length, width and height of erythema that occurred after the first week of induction. In the test group 3 animals out of 20 elicited an erythematous reaction. No erythematous reactions were observed in the negative control group. Dermal reaction scores according to the Magnusson and Kligman scale criteria were not recorded in this study.

The evaluating MSCA has evaluated this study as not reliable, Klimisch 3.

<u>Human studies</u>

The sensitising properties of EPOTE have been assessed in the report 'Ranking of components of epoxy resin systems on the basis of their sensitizing potency' from the German Forschungs- und Beratungsinstitut Gefahrstoffe (FOBIG). The report from 2012 (737 pages) is a thorough evaluation of the use, experimental and human data on the sensitising capacity of epoxy chemicals. Contact allergy against o-cresyl glycidyl ether has been described in studies of occupational exposure, usually with simultaneous reaction to phenylglycidyl ether:

In one study patch testing was performed in the years 1984 to 1988 on a total of 140 patients suspected of occupational skin disease. Of these, 8 responded positively (5.7%) to a concentration of 0.25% o-cresylglycidyl ether. Details about cross-reactions, of individual exposures or of the clinical relevance of the reactions in the patients with a positive response to o-cresylglycidyl ether are only available for one of the eight patients (Jolanki *et al*., 1990, reviewed in FOBIG 2012).

In 1997, Kanerva *et al*. published the results of patch tests (no further details) with 50 substances from a plastic and glue test series from patients where the majority were suspected of occupational dermatoses. For EPOTE, 3 out of 146 patients (2.1%) showed allergic reactions to a concentration of 0.25% o-cresylglycidyl ether. Details from the study (including details on the extent of pre-challenge exposure to EPOTE) were not available (Kanerva *et al*., 1997b, reviewed in FOBIG 2012).

A study by Tarvainen reported results of a plastic and glue test series, conducted on patients in a dermatologic clinic in the years 1985 to 1992. Only one of 343 patients, had a positive reaction to o-cresylglycidyl ether (0.25%). However, the clinical relevance of this reaction could not be established. No detailed information on the type and extent,

duration / frequency of pre-challenge exposure to EPOTE was available (Tarvainen 1995, reviewed in FOBIG 2012).

In 1996 Angelini *et al*. reported a case of contact dermatitis to o-cresyl glycidyl ether in patch tested marble workers. 10 out of 22 workers handling a bi-component resin, (produced by a reaction between bisphenol A and epichlorohydrin, at a 75% concentration in cresyl glycidyl ether) developed direct contact dermatitis and contact dermatitis by exposure to vapour mainly on hands and eyelids within 20 days to 2 months of exposure. No information on the amount of EPOTE in the bi-component resin was available. When patch tested the 10 symptomatic subjects were all positive to o-cresyl glycidyl ether (0.25%) and 4 of them also to epoxy resin. Phenyl glycidyl ether also yielded positive responses (in 7/10 cases). According to Angelini *et. al* the direct contact allergy by EPOTE vapour was due to the high vapour pressure of EPOTE and was accelerated because the bi-component resin was applied manually on hot marble slabs.

Conclusion of the FOBIG report: In the report EPOTE is categorised as having a high sensitizing potency ("HS").

Discussion of skin sensitising studies:
EPOTE has a harmonised classification as a skin sensitiser (Skin Sens 1) according to CLP. It is self-classified as Skin Sens 1 and Skin Sens 1B. EPOTE also has a harmonised classification according to CLP as irritant to the skin (Skin irrit 2).

Two reliable Guinea pig maximisation tests have been performed according to OECD TG 406. The results of these studies show that EPOTE is a skin sensitizer category 1 according to CLP. However, it is not possible to assess the sensitising potency (subcategorize either 1A or 1B) of EPOTE based on the data from these two studies because the intradermal doses used in the induction phase was >1% in both studies. It can thus not be ruled out that a high sensitisation response could also have been achieved if lower induction doses had been used.

The study from 1976, which was similar to the Guinea pig maximisation test, was not conducted according to any internationally accepted guideline. The induction was done by intradermal and intracuteneous injection instead of intradermal and epi-dermal application. It is not possible to assess whether a second induction using epidermal exposure instead of subcutaneous injection would have intensified or reduced the skin sensitizing effect of the tested substance. The challenge dose used (0.1%) in the test was very low and may not have been sufficient to elicit a response. According to the current guideline (version 1992) "The concentration used for the challenge exposure should be the highest non-irritant dose". The substance ID of the tested substance was not well described and there is no information on the purity of the substance. The parameters used to assess a positive dermal reaction was measured as height, width and length of the erythematous reaction and not scored according to the grading scale described in test guideline 406. The Magnuson and Kligman grading scale used in the TG 406 does not include precise size measurement, but does include the 'intensity' of the erythema, which this study does not. Due to the reasons stated above, this study is not considered reliable by the evaluating MSCA and is assigned a Klimisch score of 3.

Studies in humans suggest that EPOTE is a strong skin sensitizer (FOBIG report). In the four available patch test studies with patients exposed to o-cresyl glycidyl ether via their working environment positive patch test frequencies in selected workers (i.e. with known

exposure or dermatitis) were in the range 0.3-100%. In three out of four studies the positive patch test frequencies exceeded 1.0% indicating a high frequency of skin sensitisation according to the guidance on the application of the CLP criteria (ECHA 2015[4], table 3.4.2-b). In order to assess the skin sensitising potency of a substance based on human data the information on both exposure and sensitisation needs to be clear. There is, however, no information about the clinical relevance of the observations or of relevant exposure conditions for the patients tested. Due to the lack of information on the occupational pre-challenge exposure to EPOTE (extent, duration/frequency or exposure route) the human data do not allow a thorough assessment of the sensitising potency of EPOTE as the occurrence of skin sensitisation in humans needs to be seen in conjunction with the level of exposure in order to make a decision on correct sub-categorisation (ECHA 2015). Furthermore the number of published cases is relatively low (22 reported positive cases). According to the guidance on the application of the CLP criteria a high number (>100) of published cases is considered evidence of a high frequency of sensitisation.

While the human studies do confirm the concern for a strong sensitizing potency of EPOTE they are not on their own considered sufficient for a potency assessment according to the CLP criteria and guidance.

In order to assess whether EPOTE is a strong skin sensitizer and to correctly sub-categorise the substance as either subcategory 1A or 1B additional information is required as the design of the available animal studies (high intradermal induction doses >1%) and the shortcomings of the human data do not allow potency assessment according to CLP.

Currently the Local Lymph Node Assay OECD TG 429 (LLNA) is considered the most appropriate method to assess the potency of skin sensitisers. The LLNA (OECD 429) has significant advantages in respect to animal welfare (the principles of the 3Rs) and entails less distress for test animals as compared with the GPMT or Buehler test (OECD 406).

Why new information is needed

It is not possible to establish the skin sensitising potency of EPOTE based on the current data. A correct sub-categorization for skin sensitization will significantly influence hazard classification and hazard labelling (including concentration limits for the classification of mixtures containing the substance) and thus risk management measures for EPOTE. In order to appropriately manage the risk for workers and consumers exposed to the registered substances against skin sensitization reliable information on the skin sensitization potency is needed in order to sub-categorize the substance correctly. Hence a new in vivo study, the LLNA according to OECD 429 is needed.

What is the possible regulatory outcome

It is necessary to clarify the concern on whether EPOTE should be classified as a strong skin sensitiser in sub-category 1A, as this will trigger further risk management for consumers and workers. Further, labelling with H317 ("May cause an allergic skin reaction") will be triggered for mixtures containing EPOTE in concentrations ≥ 0.1%, or lower, should attribution of a specific concentration limit apply, and labelling with

[4] ECHA 2015: Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.1. June 2015

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

EUH208 ("Contains <name of sensitising substance>"may produce an allergic reaction") will be triggered at 1/10 of the concentration limit for classification of skin sensitisers according to the CLP Regulation.

Considerations on the test method and testing strategy

The Local Lymph Node Assay is according to REACH Annex VII the preferred test to investigate the potency of skin sensitisers. A result from the Local Lymph Node Assay of EC3 value ≤ 2 % is sufficient for a sub-categorisation in category 1A, which will trigger risk management for consumers and workers. Both OECD 406 and 429 allow assessment of the potency of skin sensitizers according to the CLP Guidance provided that the induction doses and the associated response give adequate information about the potency. Older OECD 406 studies often provide information that can be used to classify a skin sensitizer in at least sub-category 1B but cannot be used to rule out a sub-category 1A classification. Based on animal welfare considerations as well as the applicability of the available test methods for potency assessment an LLNA in accordance with OECD TG 429 is warranted.

A suitable vehicle shall be used in the study and the choice of vehicle must be justified (e.g. see Gamer et al. 2008 for inspiration). Analyses of the homogeneity and stability of the test solutions/formulations shall be performed. This shall be documented in the study report. To ensure a maximal exposure to unreacted EPOTE, preparations of test formulations shall be freshly made daily in the new study because EPOTE is reactive and may polymerize in solutions.

Based on your comments, the request for freshly made test preparations have been changed so that dosing shall take place no later than 2 hours after dose formulation preparation providing that stability can be demonstrated for this time period. The duration of dosing shall not exceed the stability period of the test article in the vehicle before administration of each dosage.

The evaluating MSCA must have access to the full study report from the requested study including all relevant details of the study. Access to such detailed test report information is in the experience of the evaluating MSCA often needed to ensure that a clear conclusion regarding the result of the study can be drawn.

Consideration of alternative approaches

The currently available and validated *in vitro* tests are not validated for reliable assessment of the potency of skin sensitizers with regard to differentiation between categories 1A and 1B. For substances for which a strong sensitisation potency is suspected information from *in vivo* studies and/or adequate human data are thus needed to correctly asses the potency.

Conclusion

Therefore, based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, you are required to carry out the following study using the main constituent of the registered substance (2,3-epoxypropyl o-tolyl ether (EPOTE)).

Local Lymph Node Assay, dermal route (OECD TG 429). Dosing must be done using a freshly prepared test solution with an appropriate vehicle. The choice of vehicle must be justified. The evaluating MSCA must have access to the full study report including all

relevant details of the study, ensuring that a clear conclusion regarding the result of the study can be drawn by the evaluating MSCA.

ECHA notes that in your comments you agree to perform the requested study.

2. Human health endpoint Mutagenicity:

The concern(s) identified

In silico predicitions for genotoxicity and cancer:

Predictions for EPOTE were made in the Danish (Q)SAR database (http://qsardb.food.dtu.dk/database/index.html): EPOTE was within the applicability domain and yielded a positive result in a battery of models (CASE Ultra, Leadscope and SciQSAR) for the Ames test in S. typhimurium; base-pair Ames Mutagens; chromosome aberrations in Chinese hamster ovary (CHO) cells; mutations in Thymidine Kinase Locus in Mouse Lymphoma cells, mutations in HGPRT Locus in Chinese Hamster ovary cells and Syrian Hamster Embryo (SHE) cell transformation.

In vivo predictions in the same battery of models was within the applicability domain and yielded positive results in sister chromatid exchange and in the Comet assay. The micronucleus test was inconclusive and out of domain.

Predictions were also made for EPOTE in a commercial MultiCASE CASE Ultra FDA cancer suite consisting of seven models for cancer in male rat, female rat, male mouse, female mouse, rats, mice and rodents, respectively. EPOTE yielded positive QSAR predictions within the applicability domain of all of the 7 carcinogenicity models.

In vitro:

Gene mutations in bacteria and yeast:

According to the registration dossier EPOTE was tested for gene mutations in bacteria and yeast in a study report from 1978. The test material was not identified by chemical name or CAS Number in the study report and no details on purity or chemical identity of impurities were given. The test was conducted prior to the adoption of the OECD 471 Bacterial Reverse Mutation Test guideline and was done according to the principles of Ames *et al*. (1975) and McCann *et al*. (1975), the test was not performed according to GLP.

The test material was tested in the *salmonella* strains TA 1535, TA1537, TA1538, TA98, TA100 and in *Saccharomyces cerevisiae* D4. Concentrations of approximately 0.001, 0.01, 0.11, 1.1 and 5.45 ug/plate were tested (vehicle DMSO) with and without metabolic activation (liver S9 preparations from Aroclor 1254-induced male, Sprague-Dawley rats).

Positive concentration-related results were obtained with the test substance in base-pair substitution strains TA1535 and TA100 without rat liver S9 metabolic activation. In tester strain TA100 a 6.7-fold increase was obtained at the 1.1 ug/plate dose level

without metabolic activation and for tester strain TA1535 a 19.8-fold increase was obtained for TA1535 without S9 metabolic activation at the 1.1 ug/plate dose level. With metabolic activation a 8.8-fold increase was observed in the TA1535 strain at a concentration of 1.1 ug/plate. The test material was toxic at 5.45 ug/plate.
Study details are well described except for the identity of the tested substance. Only 4 of the 5 strains which are required by the current version of the OECD 471 Bacterial Reverse Mutation Test guideline were tested. The 5th strain either: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 was not included. These strains, which are suitable for identifying crosslinking mutagens were introduced into OECD 471, when it was revised in 1997. The evaluating MSCA has evaluated this study as reliable with restrictions, Klimisch 2.

In another study from 1986 EPOTE was tested in the Ames test (OECD TG 471) in the *Salmonella* strains TA98,TA100,TA1535,TA1537 and TA97 with and without metabolic activation (liver S9 preparations from Aroclor 1254-induced male, Sprague-Dawley rats and Syrian hamsters). The substance was not tested in *E. coli* strains/TA102. The study was conducted according to the standard U.S. National Toxicology Program study protocol with GLP compliance. No information on the purity of the test substance or chemical identity of impurities was available in the study. Concentrations of 0, 3.3, 10, 33, 100 and 333 ug/plate were used (vehicle DMSO). The substance caused reproducible gene mutations in TA100 and TA1535 with a dose-related increase without metabolic activation. In tester strain TA100 a 6.2-fold increase was obtained at the 100 ug/plate dose level without metabolic activation and for tester strain TA1535 a 14.4-fold increase was obtained at the highest dose level (333 ug/plate without metabolic activation). Only 4 of the 5 strains which are required by the current version of the guideline were tested (*E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 was not included. These strains, which are suitable for identifying crosslinking mutagens were introduced into OECD TG 471, when it was revised in 1997. Positive results for gene mutations were obtained in base-pair substitution strains TA100 and TA1535 without metabolic activation.

The evaluating MSCA has evaluated this study as reliable with restrictions, Klimisch 2.

Gene mutations in mammalian cells

No studies assessing gene mutations in mammalian cells are reported in the dossier.

Chromosomal aberrations *in vitro*

No chromosomal aberration studies *in vitro* are reported in the dossier.

Induction of DNA damage/repair *in vitro*

An *in vitro* assay investigating unscheduled DNA synthesis (DNA excision repair assessed by amount of incorporated 3H-thymidine) in human lymphocytes was conducted in 1977. The test material was identified as o-cresyl glycidyl ether; no details on purity or chemical identity of impurities were given. The study was not conducted according to any international guidelines. Concentrations of test solution (in DMSO) were 10, 100 and 1000 ug/mL. Treatment was for 4.5 hours in triplicate cultures of 1.4 million lymphocytes. At both 10 and 100 ug/mL of the test substance there was a statistically significant ($p < 0.05$) increase of incorporated 3H-thymidine. At 100 ug/mL the increase

was approximately 1.5-fold of the mean value of the untreated control. At 1000 ug/mL obvious cytotoxicity was observed as well as a marked reduction in unscheduled DNA synthesis.

The evaluating MSCA has evaluated this study as reliable with restrictions, Klimisch 2.

Summary for *in vitro* genotoxicity:

EPOTE has been tested positive for gene mutations *in vitro* (*Ames* TA 100 (without metabolic activation) and TA 1535 (with and without metabolic activation) and for genotoxicity *in vitro* in human lymphocytes (unscheduled DNA synthesis).

Consequently, there is a concern for mutagenicity (gene mutations).

In vivo:

Gene mutations *in vivo*:

Transgenic rodent mutagenicity assay (2000):

In 2000 a Transgenic Rodent Mutation Assay was conducted in MutaMouse™, whose DNA bearing cells each contain a transgenic lambda vector with the bacterial lacZ gene. The study was conducted prior to the adoption of the OECD 488 test guideline and according to the following publications: Ashby and Tinwell (1994), and Dean and Mylir (1994). The study was conducted according to GLP.

The test material was o-cresyl glycidyl ether (Purity >99%). Dosing preparations were made on each day of treatments by diluting o-cresyl glycidyl ether in acetone to give the maximum required dosing solution concentration at a dose volume of 2 mL/kg. The test article preparations were protected from light and used within 2¾ hours of initial formulation. Vehicle control was acetone, at a dose volume of 2 mL/kg. The positive control used was Benzo[a]pyrene, which was administered at 0.25 mg/kg/day as a solution in acetone (dose volume of 1 mL/kg). Animals were dosed by dermal application to a shaved area of the skin on the back. Applications were made rapidly, and when the administration volume had been applied. Evaporation to dryness was permitted. The study report does not state the size of the shaved area of skin.

Range-finding study:

A range-finding study was conducted using groups of three male Muta™ mice each, which were dosed with 500, 1000 and 2000 mg/kg/day (dose volume 2mL/kg). The two highest dose groups displayed clinical signs of toxicity including swelling of the abdomen, closing of the eyes, opaque eyes, piloerection, lethargy and swollen hind limbs. Animals at all three dose groups displayed signs of significant irritation at the dermal site of administration, including reddening of the dosing site, eschar formation and lightening of the skin. For the two highest doses the irritation of skin was considered to be so severe that it compromised the endpoint of skin assessment, this along with the serious systemic effects for the two highest doses resulted in 500 mg/kg/day being considered as the maximum tolerated dose and this dose was used in the main experiment.

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Animals in the lowest dose group (500 mg/kg/day) were dosed once daily for five consecutive days with the test article via dermal application. However, due to the severity of the observed clinical signs, animals in the highest two dose groups (1000 and 2000 mg/kg/day) were dosed once daily for only four consecutive days. One animal in the 1000 mg/kg/day dose group was killed in extremis.

Main study:

Five male Muta™ mice were tested per group. Only one dose group (500 mg/kg/day) was tested. The animals were dosed dermally with EPOTE in acetone once per day on each of 5 consecutive days and sacrificed on Day 12 or 33 (7 and 28 days of mutation expression time respectively). A dose volume of 2 mL/kg of body weight was used. Tissues tested were skin, bone marrow and liver. The positive control used was benzo[a]pyrene (B[a]P) at 0.25 mg/kg for five consecutive days, at a dose volume of 1 mL/kg/day by dermal application for all tissues sampled. The positive control group was sacrificed on day 12.

Mutation frequencies (MF) were calculated when plaque forming units (pfu) for each tissue exceeded 200,000 for the majority of samples. When it was not possible to achieve 200,000 pfu, calculations were conducted for the highest number of pfu available (>120,000 pfu). For one animal in the bone marrow 500 mg/kg/day treatment group (sampled on day 33) it was not possible to recover any mutation data, due to extremely low pfu titres. Consequently, this test group consisted of only 4 animals instead of 5. Statistical analyses were performed using analysis of variance (ANOVA).

Results:
Treatment at 500 mg/kg/day resulted in some increases in mutation frequencies that were statistically significant when using ANOVA on both rank-transformed and untransformed data. Mutation frequencies for bone marrow and liver tissues from EPOTE treated animals sacrificed on day 12 both gave rise to MF values that were elevated in comparison to the concurrent vehicle controls. Because of the positive result in bone marrow additional pfu's were collected from the control group and test group sacrificed at day 12. This additional packaging and plating was done to reduce any artefactual variability. The positive result was unchanged after increasing the number of pfu's. The mean bone marrow MF of 64.9 x 10^{-6} (SD 24.3x10^{-6}) at 500 mg/Kg , was statistically significantly different ($p < 0.01$) from the concurrent vehicle control MF mean value of 38.5 x 10^{-6} (SD 4.8x10^{-6}) for bone marrow for un-transformed ($P<0.05$) and rank-transformed data ($P<0.01$).

The mean mutation frequency for liver tissue for the 500 mg/kg/day (sacrificed at day 12) group was 65.9 x 10^{-}6 (SD 15.2 x 10^{-6}). This result was statistically significantly elevated ($p < 0.05$) from the concurrent vehicle control MF mean value of 52.1 x 10^{-6} (SD 9.2 x10^{-6}) for the liver from animals sacrificed at day 12 when un-transformed data were analysed. When data was rank-transformed the increased mutation frequency in the test group was no longer statistically significant. Negative historic control data are available in the study report for bone marrow 47.9 x 10^{-6} (SD 23 x10^{-6}) (N=16) and liver 74.4 x 10^{-6} (SD 24.8 x10^{-6}) (N=24). Mutation frequency in skin samples was not elevated due to treatment.

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Discussion of the results of the Transgenic rodent mutagenicity assay:

For liver the observed mean value of mutation frequency at day 12 (65.9 x 10-6 (SD 15.2 x 10-6)) was higher than the concurrent control value (52.1 x 10-6 (SD 9.2 x10-6)). This result was statistically significant in the ANOVA assay when un-transformed data were analysed, but no longer statistically significant when data were transformed. However, the 1.26 increase in mutation frequency gives indications of a positive effect in the liver.

In bone marrow the study yielded a statistically significant positive result at day 12 for both un-transformed and rank-transformed when compared to the concurrent control.

The mean bone marrow MF of 64.9 x 10^{-6} for the treatment group is also higher than the mean MF for historical negative controls (47.9 x 10^{-6}), but may not be statistically significant due to the large standard deviation (48%) for the claimed historical control.

The historical controls are presented in the study report as mean values, standard deviations and number of trials with an unsubstantiated claim that they are unbiased. No further information e.g. on the age of the historical control animals, duration of exposure or sampling time/mutation manifestation time is provided in the report; all of which could have influenced the mutation rate. According to the study report the historical controls have been collected up to March 1998. There is no information provided on when the first studies were included in the historical control database. The lack of detail makes the interpretation of the historical controls very difficult and therefore conclusions in this regard uncertain.

This study is a pre-guideline study in Muta mouse and it has some limitations when compared to the OECD TG 488.

Mutations are rare events and for this reason sufficient statistical power is important in order to observe an effect. Because the experimental unit is the animal and not the number of pfu's, the statistical power in the 28 days group was low according to the OECD 488 guideline even if the number of pfu's from the remaining 4 animals were increased. Because mutations accumulate with each consecutive treatment, a repeated-dose regime for a period of 28 days is recommended in order for the test to have sufficient sensitivity. The duration of administration in this study (only 5 days) was much shorter than according to the OECD 488 test guideline and may have contributed to low sensitivity of the test: In a given tissue both germ cells and somatic cells can be a target for chemically induced mutations. Because of the different turn-over rates of somatic cells in various tissues the maximum mutation frequency for acute/short exposures differs between tissues. For some substances/tissues the mutant frequency can decline substantially in the time between exposure and sampling (Heddle et al 2013). For this reason the current guideline requests that exposure should be continuous for 28 days in order to maintain a high level of mutations throughout the manifestation period for mutations.

The systemic exposure to EPOTE in the conducted muta mouse study may also have been lower than expected: EPOTE has a boiling point of 260 +/- 0.29 °C and a calculated vapor pressure of 5.773 (Pa) according to the EPI Suite QSAR program. *In vitro* studies of dermal absorption of EPOTE into viable skin explants have also shown that EPOTE is a relatively volatile substance (Boogaard *et al*., 2000). In this study only 13-22% of the

applied amount of EPOTE was recovered after the end of the experiment. This was allegedly due to evaporation of EPOTE from the surface of the dissected skin samples. Furthermore, in Angelini *et al.* (1996), which investigated occupational dermatitis the authors concluded that workers were exposed to EPOTE vapour due to the volatility of EPOTE.

During the application of the dermal dose in the current transgenic study EPOTE was allowed to evaporate from the skin after application. It is unknown how much of the applied dose evaporated instead of being absorbed systemically. The systemic level of EPOTE was not measured in this study and it is likely that the systemic exposure was lower than expected. Furthermore, in a toxicokinetic study from 2000 it was shown that only ~22 % of the applied dose penetrated the skin in mice (for rats and human skin samples it was even less).

Hence, there are uncertainties in respect to the actual extent of systemic exposure, which caused a statistically significant increase in gene mutations in bone marrow and indications of an increase in mutation frequency in the liver as well.

Conclusion of the Transgenic rodent mutagenicity assay:

This pre-guideline transgenic mouse study was not very sensitive due to the following reasons: The volatility of the test substance combined with the application method and the choice of exposure route (based on toxicokinetic studies dermal absorption is not very high). This makes it uncertain how much of the applied dose was made systemically available. Furthermore, the duration of exposure in this study was insufficient and may have made the study insensitive.

Even so, the transgenic mouse study yielded a positive result in bone marrow (distant tissue) for the treatment group at day 12. Moreover, there are indications of an increase in mutation frequency in the liver as well (day 12).

The evaluating MSCA has evaluated this study as reliable with restrictions, Klimisch 2.

Chromosomal aberrations:

Micronucleus assay (1977):

A pre-guideline micronucleus assay with the test material identified as O-cresyl-Glycidyl ether (no information on purity or chemical identity of impurities available). Ten female mice of the B6D2F1 strain were exposed by oral gavage at 125 mg/Kg/day for 5 days. The positive control (triethylmelanine) was i.p. injected at 0.5 mg/kg. All animals were sacrificed 4 hours after the last treatment. The details for this study are limited. No information on how many cells were scored per animal is available. Furthermore, no information on changes in PCE/NCE ratio or other indications or other data demonstrating that the bone marrow was exposed under the conditions of this study are available. The test substance did not induce an increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow micronuclei under the conditions of this study.

The evaluating MSCA has evaluated this study as unreliable, Klimisch 3.

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Micronucleus assay (1991):

An OECD TG 474 guideline micronucleus assay according to GLP was conducted with the test material identified as O-cresyl-Glycidyl ether (95.3%, no information on chemical identity of impurities is available). Groups of 5 male and 5 female mice of the albino BKW strain were exposed by oral gavage to a single dose of 2000 mg/kg bodyweight. The test material was freshly prepared in a suspension with arachis oil B.P. Groups of ten animals were killed after 24, 48 or 72 hours. The positive control was treated with cyclophosphamide (50 mg/kg bodyweight) and killed 24 hours after treatment. 1000 PCE cells and 1000 NCE cells were scored per animal. The test substance did not induce evidence of chromosome damage in the bone marrow of treated mice under the conditions of the study. The test substance did not induce evidence of cytotoxicity to the bone marrow. There was no significant change in the NCE/PCE ratio in any of the test material treatment groups when compared to their concurrent vehicle control groups or other indications or other data demonstrating that the bone marrow was exposed under the conditions of this study are available.

The evaluating MSCA has evaluated this study reliable with restrictions, Klimisch 2.

Germ cell mutations:

Dominant lethal assay (1977)

This study was performed before the first OECD test guideline 478 was adopted in 1984 according to the principles in Green *et al.* 1975. Mice of the B6D2F1 strain were used for the study. Male mice were 8-10 weeks old at the beginning of the study and females were 8—10-weeks old when mated. 10 male mice and 60 female mice were used per group. Male mice had proven fertility.

24 hours prior to treatment 15-20% of the surface area in the dorsal area of the male mice were clipped by electric shears and remaining hairs were chemically depilated (Neet,Whitehall Labs, Inc.) so that no hair remained to interfere with absorption of the test substance. Chemical depilation was only used as needed following the initial removal of hair and did not exceed one dipilation per week. According to the study report male mice were exposed to 1.5 g/kg body weight undiluted EPOTE by dermal exposure 3 times a week for a minimum of 8 weeks. The positive control used was Triethylenemelamine (TEM), which was prepared freshly in 0.9% saline and injected once via I.P. at 0.2 mg/kg body weight. Negative controls were sham treated. Following the treatment period 3 untreated nulliparous females were randomly caged per treated male for one week. At the end of the first week the females were replaced with three other untreated virgin females for the duration of the second week.

Female animals were sacrificed 13-14 days from the presumed mating time without being checked for vaginal plugs. At autopsy females were scored for pregnancy, total number of implants and fetal deaths. Statistical comparison between treatment groups and controls were done by analysis of variance. According to the study report the dose was selected based on a range finding study. No further information is available in the study report.

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Results:
There were no changes in the total number of fetal deaths per pregnancy between the control group and the treated group. When implants per pregnancy where compared between the control group (8.28) and the treated group 2 weeks post treatment (6.97) a statistically significant reduction was observed (P<0.05). Furthermore, when the treated group was compared to the control group a statistically significant reduction (P< 0.03) was observed in the pregnancy rate of the treated group (week one 75.8%; week 2 63.6%) when compared to the control group (week one 73.4%; week 2 83.5%).

Discussion:
The study lacks a detailed description and only one high dose group was tested. A statistically significant decrease in the number of implants, which could be due to preimplantation loss, and in the pregnancy rate of the treated group was observed. No effects were seen in the number of fetal deaths.

Conclusion:
There was an indication of a potential effect of EPOTE on pregnancy rate and number of implants. Induction of dominant lethal mutations after exposure to test material indicates that the test material has affected the germ cells of the test animal. Dominant lethal mutations are believed to be primarily due to structural or numerical chromosome aberrations even though a mechanism of gene mutation cannot be fully ruled out. However, it is also possible that the induced effect is non-genotoxic.

The evaluating MSCA has evaluated this study as reliable with restrictions, Klimisch 2.

Discussion and Summary for *in vivo* mutagenicity:

A reliable *in vivo* mammalian erythrocyte micronucleus test (OECD 474) performed with a high dose (2000 mg/kg bodyweight) showed no micronucleus induction by EPOTE in bone marrow. However, evidence of bone marrow exposure by the test substance has not been shown in the study report. Indeed, no decrease in the ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) (PCE/NCE ratio) has been observed in the treated animals compared to control animals during the evaluation of the micronucleus test. Furthermore, no plasma or blood analysis to check for the presence of the substance has been performed. In addition, no toxicokinetics data are available in the registration dossier to demonstrate bone marrow exposure. Consequently, a concern for chromosomal aberrations *in vivo* cannot be ruled out.

However, a mutagenic effect in bone marrow was observed in the pre-guideline TGR study conducted via dermal exposure in 2000: EPOTE induced gene mutations in the distant tissue of the bone marrow in the pre-guideline transgenic rodent assay of low sensitivity. In this study indications of an effect in liver were also observed. This shows that EPOTE may cause gene mutations in distant tissues.

Furthermore, a decrease in pregnancy rate and the number of implants per pregnancy were observed in the dominant lethal assay. This indicates that exposure to EPOTE affected the germ cells of the test animal; this effect may have been caused by chromosomal aberrations or gene mutations. However, an alternative non-genotoxic effect cannot be ruled out.

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Why new information is needed

Taking into account the high tonnage (1,000-10,000 T/year), the many uses of EPOTE, as well as the potential for consumer exposure to articles/materials/mixtures with residual unreacted EPOTE monomers (see Section 3. CSR - Exposure-related requests for details) a risk for human health cannot be excluded.

EPOTE has been shown to induce gene mutations in the distant tissue of the bone marrow in a pre-guideline transgenic rodent assay of low sensitivity. Furthermore, an effect was seen in pregnancy rate and number of implants in the dominant lethal assay, which may have been caused by chromosomal aberrations or gene mutations. The available genotoxicity data is unable to address the remaining concerns about the potential of EPOTE and/or its reactive metabolites to induce heritable gene mutations in germ cells. Moreover, because there is a strong correlation between *in vivo* mutagenicity and carcinogenicity based on the data there is a clear concern that EPOTE may be a genotoxic carcinogen. This is supported by positive QSAR predictions within the applicability domain of all of the 7 carcinogenicity models from the Danish (Q)SAR database (http://qsardb.food.dtu.dk/database/index.html): Predictions were made for EPOTE in a commercial MultiCASE CASE Ultra FDA cancer suite consisting of seven models for cancer in male rat, female rat, male mouse, female mouse, rats, mice and rodents, respectively. All gave a positive prediction. No carcinogenicity studies have been performed for EPOTE.

These concerns for germ cell mutagenicity and carcinogenicity are heightened by the fact that many exposure scenarios for EPOTE show very high RCRs for single worker exposures (RCRs in the range of 0.9 – 0.998). Reports on skin sensitization in workers also corroborate the potential for exposure to this potential genotoxic carcinogen in an occupational setting. This in combination with exposures of the general population with RCRs >0.002 would lead to an unacceptable exposure. In addition to this, there is a potential for consumer exposure to articles/materials/mixtures with residual unreacted EPOTE monomers.

What is the possible regulatory outcome

At present EPOTE has a harmonised classification for mutagenicity as Muta 2 according to the CLP Regulation. This classification, which was adopted before the results of the dermal TGR study (from 2000) were available, is based on the positive results in vitro (Ames TA 100 and TA 1535, UDS in human lymphocytes) and in vivo (dominant lethal assay). The TC C&L Follow-up III meeting in Arona in 2006, recommended that EPOTE should be declassified from Muta 3 (old legislation classification equivalent to Muta 2 under CLP). This seems to be based partly on the result of the dermal TGR study from 2000, which the TC C&L evaluated as not being sufficient for classification. Details on the evaluation of the studies by the TC C&L are unavailable. The recommendation to declassify EPOTE was never legally implemented.

Based on all available data there is a concern that EPOTE and/or its metabolites is carcinogenic and/or mutagenic in germ cells. If this is the case, there are currently not appropriate regulatory measures in place to ensure safe use. It is noted that a harmonised Carc. 1B classification or a harmonised Muta Cat. 1B classification, if adopted, in accordance with the CLP Regulation would elicit various downstream risk management measures according to existing EU legislation. This would limit the

exposure to EPOTE and would also make it possible for a Member State to propose to include EPOTE on the Candidate List of REACH as an initial step in the Authorisation procedures of REACH.

A harmonized Muta Cat. 1B classification, if adopted, would most likely result in implementation of sufficient risk management measures to ensure worker and consumer safety, and hence, the need to clarify the concern for carcinogenicity may not be necessary if EPOTE received a harmonised classification as Muta Cat. 1B. However, if it is concluded based on the requested information that EPOTE should maintain the Muta Cat. 2 classification, the need to address the remaining concern for carcinogenicity will be evaluated.

Considerations on the test method and testing strategy

The only suitable standard test method with which to assess gene mutations in germ cells is the OECD TG 488. The current version of the OECD TG 488 (from 2013) offers two major recommendations for male germ cell mutation analysis:

1. Analyses of spermatozoa from the cauda epididymis and/or vas deferens at two time points a) 3 days and b) a minimum of 49 days (mouse) after completion of dosing. The guideline acknowledges that the 28+3 sample does not sufficiently cover exposure of the spermatogonial or stem cell period. The addition of the later sample time (28+49) enable measurement of effects in spermatogonial stem cells

OR 2. Analyses of germ cells collected from the seminiferous tubules and spermatozoa from the cauda epididymis and/or vas deferens 3 days after completion of animal dosing. Sampling of these two types of germ cells provides some, but not complete coverage of cells exposed across the majority of phases of germ cell development, and may be useful for detecting some germ cell mutagens.

Consideration of the Registrant(s)' comments

You commented that an OECD Standard Protocol Submission Form (SPSF) project is currently active to revise the TG 488 and that the Germ Cells workgroup of the International Life Science Institutes/Health and Environmental Sciences Institute (ILSI/HESI) Genetic Toxicology Technical Committee (GTTC) has been working toward identifying a single time point that would allow the simultaneous assessment of mutagenicity in somatic tissues and germ cells and making recommendations about potential modifications to the current recommended protocol for germ cell testing in TG 488.

The GTTC workgroup have applied a mathematical model to quantify the exposure history of germ cells collected from seminiferous tubules. According to you the results of this work show that a 28+3 day exposure of these cells does not allow the measurement of effects in cells that were spermatogonial stem cells throughout the exposure because the majority (78%) of cells isolated from the seminiferous tubules are spermatids, which, according to you, the model shows would only have been exposed for an average of 1.3 days (range 0-5 days) as stem cells and 8.4 days (range 2 -11 days) as spermatogonia. Consequently, a negative result does not negate the possibility that the chemical is a germ cell mutagen. Collection of sperm from the cauda epididymis/vas

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

deferens in a 28+3d protocol for assessment of mutagenicity in germ cells is not useful according to you.

Furthermore, according to you, the model shows that if sampling is extended to 28 days (i.e. a dosing/sampling regimen of 28+28 days), germ cells isolated from the seminiferous tubules would contain spermatogonia and spermatocytes that received the majority of 28 days of exposure as stem cells or spermatogonia, whilst the majority population of spermatids would have been exposed for an average of 23 days as stem cell exposure and 4.2 days as spermatogonia.

Analysis of spermatozoa from the cauda epididymis and/or vas deferens isolated 49 days after completion of dosing ensures assessment of stem cells exposed over the entire dosing period. However, the advantage of looking at germ cells from seminiferous tubules after 28+28 days is that the mixed population of cells represents 28 days exposure during the stem cell and dividing spermatogonal stages of sperm development and also enables examination of somatic cells, without the use of additional animals.

Analysis of spermatozoa from the cauda epididymis and/or vas deferens isolated 49 days after completion of dosing ensures assessment of stem cells.

The initial request in the draft decision sent to you for comments was for 28 + 3 days of exposure with sampling and analysis of germ cells from vas deferens/cauda epididymis as well as sampling of glandular stomach, bone marrow and liver (to be frozen and kept for a minimum of 5 years). Combined with an additional sampling time and analysis of germ cells from vas deferens/cauda epididymis sampled 49 days after end of exposure.

You proposed that this request was changed to 28 days of dosing with sampling 28 days later of the requested somatic tissues (liver, bone marrow and glandular stomach) as well as germ cells from the seminiferous tubules.

Based on your argumentation and personal communication with a member of the GTTC work group, ECHA is of the opinion that there is scientific evidence that sampling at 28 + 3 days may give false negative results in germ cells because the most sensitive (mitotically active) cell populations may not be adequately exposed to the test material, see also (O'Brien et al 2016, Tox Sci 152:363-371). This is the case both for vas deferens/cauda epididymis samples (where all the cells are at the same developmental stage) and for samples from the seminiferous tubules (mixed cell population in different developmental stages).

The proposal to omit the sampling at 28 + 3 days of germ cells from vas deferens/cauda epididymis has therefore been accepted by ECHA.

However, the 28 + 3 day sampling time is currently the recommended sampling time for somatic tissues:

As stated in the TG 488 the sampling time is a critical variable determined by the period needed for mutations to be fixed. This period is tissue-specific and depends upon the turnover time of the cell population (see paragraph 30 of TG 488).

It is unknown to ECHA at this time if a sampling time of 28+28 days (which is currently only recommended in the TG 488 for slowly proliferating tissues) would be as sensitive as 28+3 days for measuring rapidly dividing tissues such as glandular stomach,

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

duodenum and bone marrow. It is our understanding that this question will be addressed by the GTTC group.

Proposals for amendment

A proposal for amendment (Pfa) was received from another MSCA, which argued that the 28 + 28 day testing strategy would be suitable for liver, but may not be sensitive enough for rapidly dividing tissues such as bone marrow, glandular stomach and duodenum and hence the MSCA proposed to not request testing of rapidly dividing tissues in the 28 + 28 days test design. The MSCA proposed to request only liver as a somatic tissue or to request an additional test with the 28+3 d setup for glandular stomach and duodenum.

Response to proposals for amendment

ECHA agrees with the other MSCA that the 28 + 28 day testing strategy is suitable for liver and that liver should be sampled and analysed at 28 + 28 days. The question of whether a sampling time of 28+28 days is as sensitive as 28+3 days for measuring rapidly dividing tissues is currently being addressed.

Therefore ECHA is of the opinion that if the 28 + 28 days test design is indeed equally sensitive as a 28 + 3 days test design for measuring rapidly dividing somatic tissues – or at least sufficiently sensitive to avoid false negative results - and if these tissues were not sampled, you would miss the opportunity to obtain the necessary amount of information from each animal in the requested test, which may ultimately reduce the number of animals needed in accordance with the 3R principles.

ECHA therefore requires you to sample and freeze bone marrow, glandular stomach and duodenum for potential future analysis (frozen samples have to be stored at least for the next 5 years at or below -70 degrees Celsius) depending on future scientific research results and taking into account the recommendations in the future revised version of the TG 488 guideline.

Registrant(s)' comments to proposals for amendment by other MSCAs

You noted that at the TC C&L Follow-up III meeting held in Arona on the 4-5 October 2006 it was recommended that EPOTE should be declassified from Muta 3 (old legislation classification equivalent to Muta 2 under CLP) and that this decision was based on all relevant and available genotoxicity data (including the dermal TGR study from 2000).

Secondly, you argued that a delay for the TGR study should be instituted until the proper TG can be finalized in order to minimize the number of animals for testing and to eliminate the need to perform multiple studies with various protocols and injecting doubt as to their conclusions.

Consideration of the Registrant(s)' comments of the PfAs

Your comment regarding the classification of EPOTE is not directly related to a PfA and should therefore be considered as outside the scope of commenting on PfAs.

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Nevertheless, ECHA considered the same data that was available to TC C&L in October 2006 and found a clear concern for gene mutations in somatic cells and germ cells. Even though the duration and extent of exposure made the study less sensitive than if it had been performed in accordance with the OECD TG 488, the pre-guideline dermal TGR study from 2000, which was discussed at the meeting in 2006 yielded a positive result in bone marrow for the treatment group at day 12 as well as indications of an increase in mutation frequency in the liver at day 12. ECHA further notes that at present EPOTE has a harmonised classification for mutagenicity as Muta 2 according to the CLP Regulation. The recommendation from the TC C&L meeting in October 2006 to declassify EPOTE was never legally implemented.

ECHA notes that it is expected to take several years before the revision of the TG 488 is finalized and that during that time EPOTE will potentially be on the market without adequate risk management measures in place. It is therefore important to conclude on germ cell mutagenicity as soon as possible. ECHA accepted your proposal to change the testing strategy from the 28 + 3 days and 28 + 49 days to a single time point of 28 + 28 days based on the scientific argumentation brought forth by you and in order to reduce the number of animals needed.

Scientific research results are constantly developing and waiting for a revision of the TG will not ensure that new developments will not come to light that may need to be taken into account. Based on the current knowledge it seems likely that the 28 + 28 days time point will be as sensitive as the 28 + 49 days time point for germ cells. It is also possible that due to the faster cell cycle of spermatogonial cells compared to stem cells the 28 + 28 days sampling strategy will be more sensitive for germ cells than 28+ 49 days. Knowledge of the sensitivity of the 28 + 28 days time point for fast dividing somatic tissues is lacking at this time and ECHA therefore proposes to freeze these tissues in order to ensure that the information gathered per animal is maximised and to minimize the need for further testing.

However, if you are reluctant to perform the test strategy that you yourself proposed and ECHA accepted, the choice to perform the TGR study using the test strategy that was requested prior to the commenting round is made available to you. The original request has been amended by ECHA to omit the request for sampling at 28 + 3 days of germ cells from vas deferens/cauda epididymis based on the argumentation of the Registrant. It has been further amended to include sampling and freezing of duodenum, as proposed by another MSCA, which requested an additional test with the 28+3 d setup for glandular stomach and duodenum. You did not comment on the inclusion of this additional tissue.

You will therefore be given the choice between the original test strategy for somatic and germ cell tissues as recommended in the current version of OECD TG 488 (2013) of 28 + 3 for somatic cells and 28 + 49 days for germ cells with the modifications mentioned above (e.g. sampling at 28 + 3 days of germ cells from vas deferens/cauda epididymis is also currently recommended in the OECD TG 488 but has been omitted from the request).

OR

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

the test strategy proposed by you, with a single time point of 28 + 28 days for both somatic cells and germ cells.

As mentioned above the 28 + 28 day time point is recommended for slowly proliferating tissues. The liver has a much slower cell turnover than glandular stomach and bone marrow and the maximum mutation frequency occurs at much longer sampling times (see for example ENV/JM/MONO(2009)7).

Analysing germ cells from the seminiferous tubules at the 28+28 day time point will ensure that the germ cells have been exposed during the developmental stages of stem cell as well as during mitotically dividing spermatogonial stages.

Sampling sperm cells collected from the vas deferens/cauda epididymis after 49 (mouse)days assesses a population of cells which have been exposed as stem cells for the entire dosing period. ECHA is unsure which of these options would be the most sensitive for assessing germ cell mutagenicity.

It is the understanding of ECHA that the option of sampling seminiferous tubules at the 28+28 day time point and the option of sampling vas deferens/cauda epidydimis at 28 + 49 (mouse)day will both be included in the revised TG 488.

In summary, ECHA acknowledges the benefit of sampling both somatic and germ cell tissues at a single time point as this will reduce the number of animals needed. Therefore ECHA is not requesting that rapidly proliferating tissues such as bone marrow and glandular stomach should be tested at 28+3 days at this time in case the second option is chosen by you.

Based on the considerations above and taking your comments into account, ECHA concludes that the following testing strategy shall be requested as a second option:

ECHA accepts your proposal to request 28 days of dosing with sampling 28 days later of the requested somatic tissues (liver, glandular stomach and bone marrow) as well as of germ cells collected from the seminiferous tubules. Germ cells collected from the seminiferous tubules and liver shall be analysed. Bone marrow and glandular stomach shall be sampled 28 days after end of exposure and frozen and kept for a minimum of 5 years at or below -70 degrees Celsius. Duodenum (the additional tissue proposed by another MSCA) shall also be sampled 28 days after end of exposure and frozen and kept for a minimum of 5 years at or below -70 degrees Celsius.

If the germ cells from the seminiferous tubules and/or liver cells sampled at 28 + 28 days yield a negative result the evaluating MSCA will evaluate if this is sufficient to conclude on the mutagenic potential or if further studies should be requested in a subsequent decision. Such potential follow up studies could be the assays according to OECD TG 488 (i.e. to sample germ cells from the vas deferens/cauda epididymis at 28 + 49 days, if a negative result for germ cell mutagenicity is obtained in the first requested TGR test), and/or to analyse the frozen somatic tissues (bone marrow, duodenum and glandular stomach) sampled at 28 + 28 days, and/or to sample somatic tissues at 28+3 days (if a negative result for mutagenicity in somatic cells is obtained in the first requested TGR test). In this evaluation the evaluating MSCA will also take into account the recommendations in the revised version of the OECD TG 488 guideline (which is now under revision).

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Analyses of the homogeneity and stability of the test solutions/formulations shall be performed. This shall be documented in the study report. The duration of the gavage procedure for each group shall also be documented in the study. To ensure a maximal exposure to unreacted EPOTE, preparations of test formulations shall be freshly made daily in the new study because EPOTE is reactive and may polymerize in solutions. Based on your comments, the request for freshly made test preparations have been changed so that dosing shall take place no later than 2 hours providing that stability can be demonstrated for this time period. The duration of dosing shall not exceed the stability period of the test article in the vehicle.

ECHA considers that for mutagenicity testing the oral route is the most appropriate route of administration except for substances that are gases at room temperature. Hence ECHA concludes that testing should be performed by dissolving the registered substance in a suitable vehicle by the oral route (gavage).

In case of a negative result in germ cells the concerns for mutagenicity in somatic tissues and for carcinogenicity remain. Sampling of bone marrow is therefore requested as a distant tissue, which yielded a positive result, when exposed via the dermal route in the TGR study from 2000. Furthermore, sampling and analysis of the liver is requested as the primary site of xenobiotic metabolism, (and an often highly exposed tissue to both parent substance and metabolites). Glandular stomach and duodenum shall be sampled as first site of contact tissues after oral exposure. 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 mutagenicity at the site of contact in the gastro-intestinal tract. In the case that a follow up study may be needed (e.g. a cancer study) the choice regarding the most suitable exposure route for such a study (i.e. dermal or oral) depends amongst other things on the mutagenic response in the previously conducted dermal TGR compared with the response in the now requested oral TGR. The requested oral TGR assay shall be performed in the mouse because the dermal TGR was conducted in this species and because transgenic mouse models are more widely used than transgenic rat models.

<u>Consideration of alternative approaches</u>
The request for a TGR assay is suitable and necessary to obtain information that will allow clarifying whether there is a risk for germ cell mutagenicity. More explicitly, there is no equally suitable alternative way available of obtaining this information. ECHA notes that there is no experimental study available at this stage that will generate the necessary information and does not need to test on vertebrate animals.

Alternatively, the concern for carcinogenicity could be clarified first by performing a Carcinogenicity Study in rat, oral route by gavage; OECD 451. However, this study is very time consuming, expensive and uses a large number of animals.

A harmonised classification as Muta. 1B according to CLP will result in the same risk management measures as a harmonised Carc. 1B classification and it has therefore been decided in accordance with the 3R principles for more ethical use of laboratory animals to proceed with a request for an OECD TG 488 as specified above in the same species

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ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

(mouse) that tested positive in somatic cells before in a non-guideline and less sensitive study.

Conclusion

Therefore, based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, you are required to carry out the following study using the main constituent of the registered substance (2,3-epoxypropyl o-tolyl ether (EPOTE)).

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice. Dosing shall be done by oral gavage daily in a freshly prepared test solution using an appropriate vehicle for 28 days. Germ cells from vas deferens/cauda epididymis shall be sampled 49 days after end of exposure and analysed. Glandular stomach, duodenum, bone marrow and liver shall be sampled 3 days after end of exposure and frozen and kept for a minimum of 5 years at or below -70 degrees Celsius.

OR

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice. Dosing shall be done by oral gavage daily in a freshly prepared test solution using an appropriate vehicle for 28 days. Germ cells from seminiferous tubules and liver shall be sampled 28 days after end of exposure and analysed. Bone marrow, glandular stomach and duodenum shall be sampled 28 days after end of exposure and frozen and kept for a minimum of 5 years at or below -70 degrees Celsius.

The evaluating MSCA must have access to the full study report including all relevant details of the study, ensuring that a clear conclusion regarding the result of the study can be drawn by the evaluating MSCA.

3. CSR - Exposure-related requests:

a) Justification of the Registrant(s)' statement of no relevance for consumer exposure

Annex I, section 5 of the REACH Regulation requires the Registrant to generate exposure scenarios and exposure estimations for the registered substance. The exposure assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards. Each relevant route of human exposure (inhalation, oral, dermal and combined through all relevant routes and sources of exposure) shall be addressed (Section 5.2.4).

According to REACH Annex I (0.3) "The chemical safety assessment of a manufacturer shall address the manufacture of a substance and all the identified uses. The chemical safety assessment shall consider the use of the substance on its own (including any major impurities and additives), in a preparation and in an article, as defined by the identified uses. The assessment shall consider all stages of the life-cycle of the

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

substance resulting from the manufacture and identified uses."

Concerns identified:
Concern is raised in situations where consumers are at risk of being exposed to residual EPOTE monomers. This is furthermore important, when the concerns for carcinogenicity and/or germ cell mutagenicity are taken into consideration together with the other serious effects of the substance; (e.g. harmonized CLP classifications for Skin Irrit. 2; Skins Sens. 1; Muta.2).

You state that consumers are not exposed to EPOTE, but in spite of the fact that EPOTE is a highly reactive substance, data in literature have been found with information that may indicate a risk for consumer exposure. According to information provided by you and the literature, EPOTE is found to be an ingredient in e.g. modeling clay, plasters, building materials. For further information, see below.

Review of existing information:
According to you, EPOTE is used in a vast number of sectors, industrial as well as professional e.g. :

- building & construction work
- manufacture of: chemicals, plastic products, fabricated metal products, electrical, electronic and optical equipment, machinery and vehicles, rubber products and mineral products (e.g. plasters, cement).

Furthermore, according to you EPOTE is used in the following products:

- adhesives and sealants,
- coating products and fillers, putties, plasters, modelling clay , used in relation to joint less floors indoors.

A search in the *SPIN-database* shows (http://195.215.202.233/DotNetNuke/default.aspx with data from 2014) that EPOTE is to be found in*:*

Paints, lacquers and varnishes:	Finland – 18.6 Tonnes p.a.; Sweden – 1 Tonnes p.a. Denmark, data confidential
Construction materials:	Sweden – 1 Tonnes p.a. Denmark, data confidential

According to *ECHA Substance information (Info card, latest update 17/12-16),* EPOTE is manufactured and/or imported in the European Economic Area in 1 000 – 10.000 tonnes per year. It is used in the following products: adhesives and sealants, coating products and fillers, putties, plasters, modelling clay.

EPOTE is used in the following areas: building & construction work. It is used for the manufacture of chemicals, plastic products, machinery and vehicles, fabricated metal products and electrical, electronic and optical equipment.

Release to the environment of this substance is likely to occur from industrial use, in the production of articles and formulation of mixtures. Other release to the environment of

this substance is likely to occur from indoor use (e.g. machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners) and outdoor use.

This substance can be found in complex articles, with no release intended: machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines).

These findings indicate a need for further information, as the origin of release of EPOTE (either from the manufacture, formulation of products and articles or from articles as an unreacted residual monomer) into the environment is not known. If in spite of its reactivity EPOTE is still found as a monomer in the surroundings, this may be due to the fact that excess of the monomer is used in the production of intermediates, articles or as a result of releases from migration in/release from articles / materials with residual unreacted EPOTE monomer to which both the environment and the general population/consumers may be exposed.

ECHA has no data indicating whether residual unreacted EPOTE monomer occurs in mixtures (chemical products) and articles, and if so in which mixtures/ articles or to which extent this occur amongst marketed mixtures and articles and finally in which concentrations.

Conclusion:

ECHA cannot conclude that workers and consumers are not exposed to unreacted EPOTE via consumer products and hence that there are no risk from exposure to EPOTE. This fact is of utmost importance, having the already known serious effects of the substance in mind (e.g. Skin Irrit. 2; Skins Sens. 1; Muta.2) as well as the concerns for skin sensitisation and in particular carcinogenicity and germ cell mutagenicity. There are many exposure scenarios developed you showing high RCRs for single worker exposures (RCRs in the range of 0.9 – 0.998) for different working scenarios (industrial and professional). This is a particular concern when these working scenarios are combined with scenarios where workers, already exposed at work, also are exposed to unreacted EPOTE monomer in their private life via release from mixtures (chemical products), materials and articles available to consumers or the general population.

If you have results from testing chemical products (articles/materials/polymers) according to OECD Guidelines 118/119 (EU A.18/A.19*) these should be used as documentation. Otherwise testing according to these guidelines is requested on the final material/mixture leaving the factory/ies to justify that consumers are not exposed to EPOTE, i.e. that there are no residual monomers in mixtures/materials/articles available to consumers. This information is essential in order for the evaluating MSCA to be able to conclude that consumers are not exposed to the EPOTE monomer from such materials.

*OECD 118/EU A.18 – Determining of the Number-Average Molecular Weight and the Molecular Weight Distribution of Polymers using Gel Permeation Chromatography.
OECD 119/EU A.19 - Determining of the Low Molecular Weight Content of a Polymer using Gel Permeation Chromatography

b) Combined exposure for humans due to high worker RCRs shall be described

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

in more details; Either a reiteration of the developed exposure scenarios with higher Tier exposure models is requested taking the results into account in the risk assessment, or further RMMs should be proposed and implemented

Many exposure scenarios developed by you show high RCRs for single worker exposures (RCRs in the range of 0.9 – 0.998) for different working scenarios (industrial and professional). You recommend that performance of multiple tasks involving exposure to the compound in the same work shift should not be conducted without ensuring that the total exposure for all tasks performed will not exceed the DNELs for the substance. However, this may constitute a risk to a worker when these working scenarios are also combined with other scenarios where workers already exposed at work are also exposed in private via e.g. mixtures/materials/ articles available to consumers or via environmental compartments as general population. The margin in relation to whether a risk occurs is very small referring to the many high RCRs from single working processes described in the CSRs.

You have estimated risks related to exposures of the general population with RCRs > 0.002 (*) in addition to the estimated RCRs for workers, but not including potential consumer exposures, further information is needed in order to be able to document overall safe use.

(*) SPERCs from: The European Council of the Paint, Printing Ink and Artists' Colours Industry (CEPE); European Federation for Construction Chemicals (EFCC); European Solvents Industry Platform (ESVOC); Association of the European Adhesive & Sealant Industry (FEICA)

Overall conclusion: You have stated that the development of overall exposure scenarios (combined for all exposure routes) for humans is not relevant. A more detailed description is requested on how you have estimated combined routes in relation to the combination of working scenarios and relevant scenarios for the consumers /general population, taking into account the potential exposure to unreacted EPOTE monomer by release from mixtures/ materials and articles where EPOTE was involved in the manufacture or processing/formulation.

Either a reiteration of the developed exposure scenarios with higher tier exposure models is requested taking the results into account in the risk assessment, or further risk management measures (RMMs) should be proposed and implemented.

You have stated in your comments that presently 2,3-epoxypropyl o-tolyl ether is only used in industrial flooring and the manufacture of water-based hardeners for waterborne epoxy systems. These uses of EPOTE, including calculated RCRs, will be further evaluated in an updated CSR.

Why new information is needed

High RCRs for combined exposures (inhalation and skin) for a number of single working scenarios (RCRs in the range of 0.9 – 0.998) have been estimated. Furthermore, you have estimated risks related to exposures of the general population with RCRs > 0.002. No consumer scenarios have been considered. Further information is needed for ECHA and the evaluating MSCA to be able to conclude that humans are not at risk.

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

What is the possible regulatory outcome

Further RMMs in order to reduce worker exposures to EPOTE.

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All other references are available in the registration dossier(s).

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to mutagenicity, 2,3-epoxypropyl o-tolyl ether CAS No 2210-79-9 (EC No 218-645-3) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2016. The updated CoRAP was published on the ECHA website on 22 March 2016. The competent authority of Denmark (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding skin sensitisation, carcinogenicity and exposure of consumers and workers.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 16 March 2017.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation as described below.

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

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took the comments from you, which were sent within the commenting period, into account and they are reflected in the reasons (Appendix 1). The request(s) were amended.

Proposals for amendment by other MSCAs and ECHA and referral to the Member State Committee

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposal(s) for amendment to the draft decision and modified the draft decision. They are reflected in the reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

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

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-57 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

ECHA Draft Decision communicated pursuant to Article 52(1) of the REACH Regulation

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

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

3. In relation to the required experimental study/ies, the sample of the substance to be used ('test material') has to have a composition that is within the specifications of the substance composition that are given by all registrant(s). It is the responsibility of all the registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on the composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who will carry out the study on behalf of the other registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

   Further advice can be found at
http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the registrants to perform the stud(y/ies) on behalf of all of them.