EUROPEAN CHEMICALS AGENCY

Helsinki, 13 November 2017

Addressee: [redacted]

Decision number: CCH-D-2114373450-54-01/F
Substance name: 2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-methyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate
EC number: 260-828-5
CAS number: 57583-34-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05.01.2015
Registered tonnage band: 100-1000 (submission number [redacted] with latest tonnage band)

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 vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the study requested under 1. has a negative result;**

3. **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;**

4. **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;**

5. **Extended one-generation reproductive toxicity study (Annex IX, 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;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity); and**
   - **Cohort 3 (Developmental immunotoxicity).**

You are required to submit the requested information in an updated registration dossier by ***20 May 2021*** except for the information requested under point *3* for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **20 November 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point *5* after **20 February 2019**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to IX 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.

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 Claudio Carlon, Head of Unit, Evaluation E2

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

Appendix 1: Reasons

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

In the registration, you have adapted the standard information requirements for the following endpoints relevant for the current decision making:

i. *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.);
ii. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);
iii. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.); and
iv. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5 whereby you predict the properties of the substance subject to this decision from data on the claimed analogue substance monomethyltin chloride (MMTC) (EC no. 213-608-8).

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

According to Annex XI, 1.5(2), the similarities may be based on "*the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals*".

According to the information provided in IUCLID section 7.1, under Toxicokinetics, and in the CSR, under the section on "Basic Toxicokinetics" (p. 36), ECHA understands that your read-across hypothesis is based on the rapid and complete hydrolysis of the registered substance into the source substance, MMTC and hence it can be used as an appropriate surrogate for the registered substance.

In the technical dossier you provide various studies with MMTC to fulfill the specific endpoints for the registered substance. You also provide the following justification: "*This read-across is justified because oral exposure to MMT(EHTG) places it in the gastro-intestinal tract where, based on this study, it is hydrolyzed to MMTC as the initial metabolic action. Therefore, MMTC studies can be used to fulfill the REACH requirements for MMT(EHTG) related to exposure via the oral route, in particular the mammalian toxicology endpoints of repeated dose, reproduction, developmental, and in vivo toxicity.*"

ECHA has evaluated the information and documentation provided in the registration dossier in light of the requirements of Annex XI, Section 1.5 of the REACH Regulation. Based on the information provided it can be concluded that:

(i) The registered substance may indeed undergo rapid degradation by hydrolysis. The thioester ligand may be rapidly displaced to form MMTC hydroxide, which eventually precipitates as an oxide. ECHA notes that this analysis cannot be interpreted simply, since extended incubation leads to lower levels of hydrolysis, e.g. 78% after four hours. Hence it is not possible to conclude that there is only systemic exposure to the monomethyl tin chloride, and hence the read-across to monomethyl tin chloride does not provide a basis for predicting the properties of the registered substance. Additionally, the displaced thioester ligand, EHTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid (mercaptoacetic acid EC no. 200-677-4) and 2-ethylhexan-1-ol (2-EH EC no. 203-234-3). Both of these substances are classified as toxic substances. In addition, 2-EH can be further metabolised to 2-ethylhexanoic acid (EC no. 205-743-6) which is classified as Repr. 2, H316d (Suspected of damaging the unborn child). This shows that it cannot be assumed that "*MMTC is the only methyltin toxophore from oral exposure*". In addition, it cannot be concluded that MMTC is the only metabolite that is going to be "*more readily available in the GI tract than MMT(EHTG)*" since the solubility of thioglycolic acid in water is similar to that of MMTC (1×10^5 g/L[2]). ECHA notes that the proposed read-across to monomethyl tin chloride does not provide a way of predicting the properties of these other hydrolysis products.

(ii) Furthermore, according to the recent toxicokinetics study by [redacted] (2015), for 2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate (DMT(EHTG), EC No. 260-829-0), during simulated gastric hydrolysis, the substance did not hydrolyse completely to form the alkyltin dichloride derivative (DMTC, EC no. 212-039-2), but rather into the metabolite DMT(Cl)(EHTG). It is not ruled out that, on the basis of the [redacted] (2015) study, the same may apply for the registered substance, which is an analogue substance to DMT(EHTG). For the registered substance the primary metabolite may not be MMTC but MMT(Cl)(EHTG), a metabolite which you have not considered in the read-across justification. Since both methyltin and dimethyltin substances are considered as substance categories, (as recognised by OECD at SIAM 23, 2006) the outcome of this new study by [redacted] (2015) on DMT(EHTG) should be followed by additional toxicokinetics' analysis of the registered substance.

(iii) As explained above, though the registered substance may undergo hydrolysis to MMTC "*as the initial metabolic action*", it cannot be concluded that MMTC is the "*sole organotin metabolite of MMT(EHTG) via oral exposure*". If the read-across hypothesis is to be viable further experimental evidence would be needed to show that there is no systemic exposure to anything other than monomethyl tin chloride.

Based on the data submitted, ECHA notes that the read-across approach is not considered to be acceptable since the registered substance metabolises to other metabolites which further metabolise into potentially toxic metabolites which have not been tested and accounted for in the justification for using the read-across approach with MMTC. Additionally, systemic exposure to the parent substance, or a non-MMTC metabolite, has not been excluded.

[2] WHO, 2006. Mono- and disubstituted methyltin, butyltin, and octyltin compounds, Concise International Chemical Assessment Document 73, p.7, retrieved from: http://www.inchem.org/documents/cicads/cicads/cicad73.pdf

In view of the reasons presented above, and considering all the registrant's arguments, ECHA considers that there is not a sufficient reliable basis whereby the human health effects may be predicted from the data of only one of the possible metabolites (MMTC) by interpolation to the registered substance, that is by read-across approach, as required by Annex XI, 1.5. As a consequence, the adaptation of the information requirement based on this read-across approach cannot be accepted.

In the technical dossier, the adaptation of the standard information requirements for the: *in vitro* cytogenicity and gene mutation; sub-chronic toxicity (90-day); and the pre-natal developmental toxicity endpoints, is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

You have sought to adapt this information requirement according to Annex VIII, Column 2 of the REACH Regulation, where the study does not need to be conducted "*if adequate data from an in vivo cytogenicity test are available*". Indeed, you provided an *in vivo* study ([redacted], 2003) according to OECD TG 474, with the alleged analogous substance monomethyltin chloride (MMTC) (EC no. 213-608-8). However, as explained in Appendix 1, Section 0 of the decision, the read-across justification of the analogous substance to the registered substance cannot be accepted, hence you have not provided such "*adequate data*" to fulfill the adaptation requirements, according to Annex VIII, column 2. Therefore, your adaptation of the information requirement is rejected.

ECHA also notes that the self-classification of the substance as Muta. 2 is also questionable since it is based on the study with the alleged analogous substance and not with the registered substance itself. Additional data with the registered substance is therefore required to determine the actual classification for mutagenicity.

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

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier does not contain an appropriate study record for this information requirement. Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under 1. has negative results.

You have sought to adapt this information requirement according to Annex VIII, Section 8.4.3., column 1. You provided the following justification for the adaptation: "*In accordance with column 1 of REACH Annex VIII, the gene mutation study does not need to be performed unless a negative result is obtained for Annex VII, Section 8.4.1 and Annex VIII, Section 8.4.2. As a positive result was obtained in an in vivo micronucleus study, the study does not need to be performed.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VIII, Section 8.4.3., column 1, as the *in vitro* gene mutation study in mammalian cells shall be conducted if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells (or in vitro micronucleus study) have negative results. Indeed, the study does not need to be conducted, if there is adequate data from a reliable *in vivo* mammalian gene mutation test available, according to Annex VIII, Section 8.4.2., column 2)

In the view of ECHA, the *in vivo* study mentioned in the adaptation ([redacted], 2003) cannot be considered for this endpoint, mainly because:

(i) The type of *in vivo* study available in the technical dossier is a micronucleus assay that investigates chromosome aberration and not gene mutation data, hence the data from an *in vivo* mammalian gene mutation test would be an adequate waiver for this endpoint; and
(ii) The *in vivo* study provided is with the claimed analogous substance, and as explained in Appendix 1, Section 0 of the decision, the read-across justification cannot be accepted.

Therefore, your adaptation of the information requirement is rejected.

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

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under 1. has negative results.

3. 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 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX 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.

You have not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing two study records for a sub-chronic study with the analogous substance: monomethyltin chloride (MMTC) (EC no 213-608-8) ([redacted], 2004; [redacted], 1978). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Moreover, the study by [redacted] (1978, conducted according to OECD TG 408 (non-GLP study) provided limited information on histopathology examinations, as according to the technical dossier, not all organs listed in OECD TG 408, (such as: brain, spinal cord, pituitary, thyroid, parathyroid, thymus, liver and adrenal glands) have been examined. ECHA considers that there is not adequate and reliable coverage of key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3). Hence, the conditions for adaptation of the information requirement of Annex IX, Section 8.6.2, by means of the "*use of existing data*", as set out in Annex XI, Section 1.1.2.(2) are not met.

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 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, based on the low vapour pressure and the high boiling point, inhalation exposure is unlikely to occur. Moreover, according to the information provided within the CSR "*the anticipated exposure via dermal and inhalation routes is negligible*." 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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

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.

4. 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 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX 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.
You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have sought to adapt this information requirement according to Annex XI, Section 1.2. of the REACH Regulation by providing a weight of evidence analysis with two study records for a developmental toxicity study on rats ([redacted] 2005; [redacted], 1982) and a study record for a "reproduction/ developmental toxicity screening test" (test method: OECD TG 421) ([redacted], 2004). These three study records have been conducted with the analogous substance, monomethyltin chloride (MMTC) (EC no. 213-608-8).

For the weight of evidence arguments, ECHA notes the following:

(i) The key study ([redacted] 2005; reliability 1) follows the EPA OPPTS 870.6300, while the other developmental toxicity study on rats ([redacted], 1982) does not follow any test guidelines and has an assigned reliability score of 2. Both studies are non-GLP compliant. The rational for reliability for both studies is mainly based on the read-across test result from the analogue substance MMTC to the registered substance MMT(EHTG). However, the read-across from the alleged analogue substance to the registered substance for the pre-natal developmental toxicity is not accepted, as explained above in Appendix 1, section 0 of this decision. In addition, ECHA notes that the study by [redacted], (1982) provides limited information in the study summary as there is no data on the maternal toxic effects and on the teratogenic effects, hence it deviates significantly from the requirements of OECD TG 414.

(ii) To provide further support to the weight of evidence analysis you have also provided a study record for a "reproduction / developmental toxicity screening test" ([redacted], 2004) (test method: OECD TG 421) with the analogue substance. However, this study does not provide the information required by Annex IX, Section 8.7.2., because (a) it does not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations, and (b) the read-across from the analogue substance cannot be accepted, as explained above in Appendix 1, section 0 of this decision.

(iii) ECHA further notes that you state that the weight of evidence analysis supports no classification for fertility effects. However, this substance has a harmonised classification of Repr. 2 (Hazard statement: H361: Suspected of damaging fertility or the unborn child). The developmental adverse effects of the other metabolites of the registered substance, which were not tested, seem to have different effects on the brain and the skeletal system and therefore either all metabolites or the registered substance should be tested in order to get the full toxicological profile of the registered substance.

ECHA thus considers that there is not sufficient weight of evidence from the totality of these sources of information that could lead to the reliable conclusion that the registered substance does not have developmental toxicity effects. Consequently, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. hence 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 assumption ECHA considers testing should be performed with rats or rabbits as a first species.

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 6.0, July 2017) 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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

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.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX 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 IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

In your comments, you accepted the requirement for an extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.). You also indicated that the production volumes have been reviewed, and in line with this, you submitted a dossier update reflecting a tonnage band of 100-1000 tonnes for the joint submission. ECHA notes that this change of tonnage is reflected below in the justification for the request for an extended one-generation reproductive toxicity study.

ECHA also acknowledges your note that for this substance there are no consumer or professional uses reported in the registration dossier.

a) The information requirement

ECHA considers that concerns in relation with reproductive toxicity are observed. More specifically, the GLP-compliant study by [redacted] (2004) which is a combination of OECD TGs 408 and 421, conducted with the structurally analogue substance MMTC (EC no. 213-608-8) shows increased post-implantation loss, decreased number of pups delivered, and increased pup mortality at the high dose (750 mg/kg bw/day). With this dose, maternal toxicity was reported as "*Mean body weight on PN 4 and mean body weight change PN 1-4 of the 750 mg/kg group was decreased, although not statistically significantly*". Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

MMTC is considered to be a substance structurally analogous to the registered substance because, according to the information provided in the dossier, the registered substance hydrolyses into MMTC in conditions which simulate gastric hydrolysis. As decomposition to MMTC is an intrinsic property of the registered substance being evaluated, information on MMTC is considered relevant for deciding if the criteria set out in Annex IX, Section 8.7.3. are met.

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement according to Annex VIII, Section 8.7.1., column 2. You provided the following justification for the adaptation "*In accordance with column 2 of REACH, a reproductive toxicity study does not need to be conducted if a pre-natal developmental toxicity study is available.*" However, ECHA notes that your adaptation is not valid since the registered substance is an Annex IX substance and the extended one-generation reproductive toxicity study is a standard information requirement if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. ECHA notes that the repeated dose study provided in the dossier ([redacted], 2004) indicates a concern in relation with reproductive toxicity, as specified above. 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 IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the required study

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 6.0, July 2017).

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 6.0, July 2017).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex IX. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information. These triggers include existing information on effects caused by substances structurally analogous to the registered substance, suggesting such effects or mechanisms/modes of action.

Notwithstanding the conclusion on the read-across from the analogue substance MMTC (EC no. 213-608-8) in section 0 above, ECHA notes that existing information on this structurally analogous substance to the registered substance, derived from available *in vivo* sub-chronic toxicity study (90-day), shows evidence of neurotoxicity and, thus, there is a particular concern for developmental neurotoxicity in terms of column 2 of 8.7.3., Annex IX. The 90-day study ([redacted], 2004) with the analogue substance MMTC (EC no. 213-608-8) shows some statistically significant neurobehavioral effects at the end of the study in the group of rats at the highest dose level. The brain weight was statistically reduced at the highest dose level, in both females and males. At microscopic examination, treatment-related histopathological changes were observed in the brain, mainly consisting of "*loss of perikarya of neuronal cells*".

According to the ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, Appendix R.7.6–2 (p. 529), *"changes in brain weight"* and *"(histo)pathological findings in brain"* are both findings that may indicate a particular concern justifying inclusion of the developmental neurotoxicty cohorts.

In your comments, you indicate that the inclusion of Cohorts 2A and 2B '*may be premature, given that the decisions for such testing are frequently predicated on the results of repeated-dose studies*'. You also refer to a testing proposal examination for the registered substance. ECHA notes that you have not submitted any testing proposals for the registered substance, but a sub-chronic toxicity study (90-day) and a pre-natal developmental toxicity study are requested as part of the current decision.
ECHA notes that you are required to conduct the sub-chronic toxicity study before the extended one-generation reproductive toxicity study, as stated above in section "*Information from studies to be conducted before the extended one-generation reproductive toxicity study*". Once you have submitted the results of the sub-chronic toxicity study, the study design of the EOGRTS will be reconsidered.

To support your request to reconsider the need of Cohorts 2A and 2B, you note that despite the clear neurotoxicity observed in adult rats, there was minimal to no developmental neurotoxicity observed in the studies provided.

ECHA notes that in the technical dossier, you have provided a developmental neurotoxicity study ([redacted]. 2005) conducted with the structurally analogous substance MMTC (EC 213-608-8), which studied the effects of monomethyltin following perinatal exposure. When brain weight and neuropathology were evaluated at PND 2, 12, 22 and as adults, the results showed "*a trend towards decreased brain weight in the high dose group. In addition, there was vacuolation of the neuropil in a focal area of the cerebral cortex of the adult offspring in all dose groups (1 -3 rats per treatment group).*" ECHA considers that these effects indicate a concern for developmental neurotoxicity.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the structurally analogous substance to the registered substance.

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

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex IX. These triggers include existing information on effects caused by substances structurally analogous to the registered substance, suggesting such effects or mechanisms/modes of action.

Notwithstanding the conclusion on the read-across from the analogue substance MMTC (EC no. 213-608-8) in section 0 above, ECHA notes that existing information on this structurally analogous substance to the registered substance, derived from available *in vivo* sub-chronic toxicity study (90-day), shows evidence of immunotoxicity and, thus, there is a particular concern for developmental immunotoxicity in terms of column 2 of 8.7.3., Annex IX.

In the 90-day study ([redacted], 2004) with the analogue substance MMTC (EC no. 213-608-8) the following findings were noted:

(i) Significantly decreased organ weights of both the thymus and spleen, at the highest dose level; and
(ii) Treatment-related histopathological changes observed in the thymus accompanied by a decrease in the ratio of the cortex/medulla were considered to be "*toxicologically relevant.*"

In your comments, you indicate that the inclusion of Cohort 3 '*may be premature, given that the decisions for such testing are frequently predicated on the results of repeated-dose studies*'. You also refer to a testing proposal examination for the registered substance.

ECHA notes that you have not submitted any testing proposals for the registered substance, but a sub-chronic toxicity study (90-day) and a pre-natal developmental toxicity study are requested as part of the current decision. ECHA notes that you are required to conduct the sub-chronic toxicity study before the extended one-generation reproductive toxicity study, as stated above in section "*Information from studies to be conducted before the extended one-generation reproductive toxicity study*". Once you have submitted the results of the sub-chronic toxicity study, the study design of the EOGRTS will be reconsidered.

To support your request to reconsider the need of Cohort 3, you referred to "published studies which indicate that the effect of organotin substances on the thymus gland of rats is related to acute exposure, "this effect is reversible", and "could be unrelated to gestational exposure". As you did not provide any references, ECHA cannot evaluate these statements.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study on the structurally analogous substance to the registered substance.

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

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 6.0, July 2017) 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;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

Currently, the extension of Cohort 1B is not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request *3*) 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 **20 November 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 **20 February 2019** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **20 February 2019**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision **20 May 2021.**

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 6.0, July 2017)*).

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.

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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 draft decision was notified to you under Article 50(1) of the REACH Regulation. Exceptionally, following your comments on the draft decision indicating a tonnage band downgrade, ECHA has however taken into account the updated tonnage band (submission number: [redacted] and date: 22 March 2017). Based on the average production or import volumes for the three preceding calendar years, the tonnage band has been changed from more than 1000 tonnes per year (submission number: [redacted] from 5 January 2015) to 100-1000 tonnes per year (submission number: [redacted]).

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

The compliance check was initiated on 5 October 2016.

ECHA notified you of the draft decision on 30 November 2016 and invited you to provide comments.

ECHA took into account your comments and your information about tonnage band downgrade and amended the draft decision. This has resulted in the removal of the following decision request: pre-natal developmental toxicity study in a second species; and the amendment of the following decision request: extended one-generation reproductive toxicity study.

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

ECHA received proposal(s) for amendment and did not modify the draft decision.

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

ECHA referred the draft decision to the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-55 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 listed in the Community rolling action plan (CoRAP) for substance evaluation in 2015. The substance evaluation is suspended, pending the outcome of this compliance check.

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 requests in this decision, or to fulfil otherwise the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.
   In your general comments to the draft decision pursuant to Article 50(1) of the REACH Regulation, you stated that the test substance should be a pure substance for several reasons. ECHA notes that it is your responsibility to ensure that the tested substance is suitable for use by all members of the joint registrations. ECHA further stresses that as the registrants have chosen the approach to register the constituents of their multi-constituents substances separately, the registrants must ensure that the information generated is relevant for the actual substance manufactured and that proper hazard and risk assessment are done.