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EUROPEAN CHEMICALS AGENCY

Helsinki, 14 September 2020

Addressees
Registrants of tris(2-ethylhexyl) benzene-1,2,4- tricarboxylate listed in the last Appendix of this decision (registrant(s)[1])

Decision/annotation number
[For the final decision] Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: tris(2-ethylhexyl) benzene-1,2,4- tricarboxylate
EC number: 222-020-0
CAS number: 3319-31-1

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(3) of Regulation (EC) No 1907/2006 (REACH), ECHA requests you to submit the following information on tris(2-ethylhexyl) benzene-1,2,4- tricarboxylate (abbreviation: TOTM):

Environment

Request 1: Fish sexual development test (FSDT); test method: OECD TG 234; with Japanese medaka (*Oryzias latipes*) or zebrafish (*Danio rerio*), including gonadal histopathology. The study must be performed using 5 test concentrations, and if the test species is Japanese medaka, genetic sex must also be determined. A carrier solvent already validated in fish tests must be used.

Deadline to submit the requested information

Appendix 1: Section B.1 provides further details of how the deadline was derived.

You have to provide an update of the registration dossier(s) containing the requested information, including a robust study summary and, where relevant, an update of the chemical safety report by the deadline indicated below.

In addition to the robust study summary, you must submit the full study report by the same deadline, by attaching it to the relevant endpoint study record in IUCLID.

The information required must be generated and provided by **20 June 2022**.
A summary of the testing strategy and deadlines is provided in Appendix 1, Section B.1.

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

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Appendices

The reasons of this decision and any further test specifications of the requirements 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 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[2] by Christel Schilliger-Musset, Director of Hazard Assessment

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

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Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on tris(2-ethylhexyl) benzene-1,2,4- tricarboxylate (TOTM) 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 the environment.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in another decision to clarify the concern, according to Article 46(3) of REACH.

A.1 The potential risk for the environment

The identification of a potential risk is based on a combination of exposure and hazard information.

According to information in the registration dossier(s) the Substance is used for the manufacture of a wide range of products and articles e.g. lubricants, plasticizer for PVC, washing and cleaning products, coatings and inks, plant protection products, fertilizers, cosmetics, fuels, solvents. Significant exposure to the environment cannot be excluded based on the covered uses and high tonnages manufactured and applied.

As TOTM has been identified as a potential substitute for several phthalates (see for example Annex XV reports for dibutylphthalate/benzylbutylphthalate), TOTM tonnages and exposure are still expected to increase.

Based on information in the registration dossier(s), information from published literature and publically available model data as well as data derived using publically available modelling tools as detailed below, there is a concern that the Substance may be an endocrine disruptor (ED) for the environment according to the World Health Organisation/International Programme on Chemical Safety working definition (WHO/IPCS, 2002) and that the Substance exerts non-endocrine related long-term toxicity to fish.

Based on this exposure and hazard information there is a potential risk for the environment. As the available information is not sufficient to conclude on potential ED properties and chronic fish toxicity, further information is needed as explained below.

A.2 The possible risk management measures for the environment

If the obtained data from the request are sufficient to confirm the suspected ED properties as defined in the World Health Organisation/International Programme on Chemical Safety working definition (WHO/IPCS, 2002) the evaluating MSCA will assess the need for further regulatory risk management in the form of identification as a substance of very high concern (SVHC) under Article 57(f) of REACH.

The results of the request will, amongst other relevant and available information, also be used by the evaluating MSCA to assess whether the Substance should be classified as Aquatic Chronic as defined in the CLP Regulation (EC) No 1272/2008.

If the obtained data from the request are sufficient to confirm the suspected risk to the environment, the evaluating MSCA will also assess the need for further regulatory risk management, such as restriction under REACH.

All this would lead to stricter risk management measures than those currently in place.

A.3 Explanation of the testing strategy for the environment

A test is requested, which is capable to confirm the concern for endocrine disruption as it provides information on the mode of action as well as on population relevant adverse effects. At the same time the test also provides information on long-term fish toxicity. Thus, both concerns are addressed in one test. The evaluating MSCA will review the information submitted by you and evaluate if further information should be requested.

In addition, the eMSCA will assess whether further information would still need to be requested in a follow up decision to clarify the PBT/vPvB concern.

A.4 Request 1: The concerns identified

Endocrine disruption

ER ToxCast model prediction

TOTM is positive in the ER ToxCast model prediction of the Endocrine Disruption Screening Program for the 21st Century Dashboard (EDSP 21 dashboard, US EPA), with a score of 0.12 (activity for receptor area under the curve) for agonistic activity. From 16 tests used in this model for estrogen receptor (ER) agonistic activity 13 tests are positive. For every step in the cascade of this model tests were positive:

- Cellfree biochemical radioligand ER binding assays (2 of 3 tests positive for TOTM):
    - A1 NVS_NR_bER: bovine uterus: inactive
    - A2 NVS_NR_hER human: AC_{50}: 19.6 (flag: "less than 50% efficacy")
    - A3 NVS_NR_mER mouse: AC_{50}: 12.4
- Protein complementation assays that measure formation of ER dimers and test for activity against ERα and ERβ, each measured at two time points in human kidney cell line HEK293T (5 of 6 tests positive for TOTM);
    - A4 OT_ER_ERaERa_0480: AC_{50}: 44.9 (flag "less than 50% efficacy; only highest conc above baseline")
    - A5 OT_ER_ERaERa_1440: inactive
    - A6 OT_ER_ERaERb_0480: AC_{50}: 34.8
    - A7 OT_ER_ERaERb_1440: AC_{50}: 42.9
    - A8 OT_ER_ERbERb_0480: AC_{50}: 47.1

- A9 OT_ER_ERbERb_1440: AC_{50}: 46.9

- Assay measuring interaction of mature transcription factor with DNA at two time points in human cervix cell line HeLa (2 of 2 tests positive for TOTM):
  - A10 OT_ERa_EREGFP_0120: AC_{50}: 56.6
  - A11 OT_ERa_EREGFP_0480: AC_{50}: 70.8
- Reporter gene assays measuring RNA transcript levels in human liver cell line HepG2 (2 of 2 tests positive for TOTM):
  - A12 ATG_ERa_TRANS_up: AC_{50}: 24.6
  - A13 ATG_ERE_CIS_up: AC_{50}: 44.2
- Assays measuring reporter protein levels in human kidney cell line HEK293T (1 of 2 tests positive for TOTM):
  - A14 Tox21_ERa_BLA_Agonist_ratio: inactive
  - A15 TOX21_ERa_LUC_VM7_Agonist: AC_{50}: 35.1
- ER-sensitive cell proliferation assay in human breast cell line T47D (1 of 1 test positive for TOTM)
  - ACEA_ER_80hr: AC_{50}: 21.5

No cytotoxicity is observed for TOTM in any of the performed ToxCast cytotoxicity assays.

These multiple *in vitro* assays provide comprehensive pathway coverage for the biology of the ER signalling pathway (Browne et al., 2015). US EPA is accepting ToxCast ER model for 1812 chemicals also as alternative for an uterotrophic assay in their Endocrine disruptor screening program (US EPA ToxCast Screening Library) and in the ECHA/EFSA Guidance for ED assessment in biocides and plant protection products regulations (ECHA & EFSA, 2018) information from this model is treated as equally informative as a uterotrophic assay, which is Level 3 information according to the OECD ED Conceptual Framework (OECD CF; OECD, 2018).

With a score of 0.12[3] TOTM is in the same range as several already identified endocrine disruptors under REACH (4-nonylphenol, linear, 0.1; 4-octylphenol, 0.118; 4-heptylphenol, 0.113; p-tert-butylphenol, 0.16).

Other *in vitro* data

- Estrogenic activity for TOTM on ERα and ERβ was reported in a transactivation assay (ter Veld et al., 2006).

[3] https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID9026265#bioactivity-toxcast-models

- In a competitive binding assay no affinity of TOTM for ERα was observed (Ohashi et al., 2005).

- In a hybrid-yeast system no estrogenic activity was seen (Ogawa et al, 2006).

The negative findings in some of the *in vitro* studies (e.g binding studies) do not lessen the overall amount of evidence for estrogen agonistic activity of TOTM. The results of the hybrid yeast assay are considered unreliable because it is prone to false-negatives due to limitations with the method "*such as problems with materials that have fungicidal activity or inhibit cell proliferation, solubility, permeability or transport issues across the cell wall*" (cited in OECD, 2018). TOTM is considered to be prone to provide false negative results as water solubility of TOTM is low with 3.06 µg/L (according to OECD TG 105; registration dossier(s), study report, 2012a).

Furthermore, estrogenic activity is not contradicted by the competitive binding assay (Ohashi et al., 2005) because there are multiple other ways a substance may interact with the estrogen receptor signalling pathway and result in transcriptional activation; which *de facto* happened in the transactivation assays (ter Veld et al., 2006 and the ToxCast dataset). Moreover, two of the three binding assays from the ToxCast ER model were positive.

Other model data

The CERAPP Potency Level models[4] as well as the Danish (Q)SAR Database[5] provide no indications for activity regarding the estrogen modality.

Although the outcome of these models was negative, there is still a concern as the ER ToxCast model prediction, which is based on *in vitro* tests, is positive for TOTM.

In conclusion, there is sufficient mechanistic evidence (OECD CF Level 2 and Level 3) to support a conclusion that the Substance has endocrine activity in the estrogen modality for ER agonism.

In vivo data

No aquatic vertebrate data measuring ED related endpoints are available.

In a sediment-water Chironomid toxicity test using spiked sediment following draft OECD TG 218 TOTM did not exert any effects on growth or reproduction (registration dossier(s), study report, 2001). The No Observed Effect Concentration (NOEC) was 740 mg/kg dry weight (number of emerged adults, time to emergence, and sex ratio). The test is listed at Level 4 of OECD CF. However, insect growth and reproduction is regulated by other than vertebrate type steroid hormones (ecdysteroids and juvenile hormones) and the negative result in the chironomid test is not considered to rule out the potential ER agonism of TOTM.

In some of the rodent studies provided in the registration dossier(s) there are a number

[4] https://comptox.epa.gov/dashboard/dsstoxdb/results?search=3319-31-1#bioactivity-toxcast-models
[5] http://qsar.food.dtu.dk

of effects observed, which according to the OECD GD 150 (OECD 2018) can be considered to be mediated by the estrogen-, androgen- or steroidogenesis- (EAS) endocrine modalities. These include effects on epididymis weight/histopathology, seminal vesicle weight/histopathology, sperm morphology, testis weight/histopathology and retention of nipples/areolae (sexually dimorphic structures in rodents).

In an OECD TG 421 study (registration dossier(s), study report, 1998a) statistically significant effects on spermatogenesis demonstrated by histopathological examination of the seminiferous tubules and not statistically significant vacuolation of the Sertoli cells were observed. Histopathological observations on testes showed a slight decrease in spermatocytes and sperm cells in 2 of 12 animals in the mid dose group (300 mg/kg/day), and decreases in all 12 animals in the high dose group (1000 mg/kg/day): These were slight in 11 animals and secondary grade (moderate) in 1 animal. In stages I to VI, low numbers of sperm cells (round and elongated) were found in the mid dose group (300 mg/kg/day), and low numbers of spermatocytes and sperm cells (round and elongated) were found in the high dose group (1000 mg/kg/day). In stages VII to VIII low numbers of sperm cells (round) and a low value for sperm cell (round) Sertoli cell ratio were found in the high dose group. In stages IX to XI low numbers of sperm cells (elongated) and a low value for sperm cell (elongated) Sertoli cells ratio were found in the high dose group. In stages XII to XIV low numbers of spermatocytes, sperm cells (elongated), and a low value for the sperm cell (elongated) Sertoli cells ratio were found in the high dose group.

In a study comparable to OECD TG 414 (registration dossier(s), study report, 2002) retention of areolae in males was reported for the high dose group (1050 mg/kg/day) at post-natal day (PND) 13, which was no longer present at PND 18. In addition, increases of absolute and relative seminal vesicles weight in all dose groups as well as an increase of epididymides weight in the high dose group were observed.

A study according to OECD 408 in rat using dietary exposure was also conducted (registration dossier(s), study report, 2012b). In this study some slight effects on blood biochemistry parameters and organ weights (liver) as well as slight changes in motor activity were seen, but no effects were noted during evaluation of staging of the spermatogenic cycle. However, no data on total sperm counts are available in the study report. In addition, it is noted that in contrast to the above mentioned developmental study (similar to OECD 414) and OECD 421 studies, which were conducted via gavage, the OECD 408 study was a dietary study. The bolus exposure resulting from gavage dosing can lead to different results than dietary exposure, due to differences in toxicokinetics.

Based on the available information it is concluded that the OECD CF Level 3 information cited above supported with effects from mammalian studies indicate that the substance is likely to have estrogenic activity *in vivo*.

Concern on non-endocrine related long-term toxicity to fish

Quantitative structure activity relationship (QSAR) models predict high chronic toxicity for fish: According to Ecological Structure Activity Relationships (ECOSAR) Predictive Model (ECOSAR V1.11)[6] the predicted Chronic Values (ChV: geometric mean of NOEC and the lowest observed effect concentration (LOEC)) are 489 ng/L for ECOSAR class "Esters"

[6] https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model

and 345 ng/L for ECOSAR class "Neutral Organic SAR". With a log Kow of 8.0 (measured at 25°C according to OECD TG 123; registration dossier(s), study report, 2012c) the substance is within the applicability domain of this prediction model. The predicted long-term toxicity for the other trophic levels is also high but lower than for fish (Green algae: 7 µg/L for ECOSAR class "Esters" and 12 µg/L for ECOSAR class "Neutral Organic SAR" - both values flagged that the chemical may not be soluble enough to measure the predicted effect; Daphnid: 3 µg/L for ECOSAR class "Esters" and 827 ng/L for ECOSAR class "Neutral Organic SAR").
No experimental long-term data are available for fish.

In a semi-static OECD TG 203 limit test with *Oryzias latipes* an LC_{50} (96h) >100 mg/L was reported. In the dose and control group 1 of 10 fish was found dead, respectively (registration dossier(s), study report, 1998b). In an OECD TG 204 study (Fish, Prolonged Toxicity Test: 14-day study, flow-through) with *Oryzias latipes* a NOEC > 75 mg/L was reported (registration dossier(s), study report, 1998c).

In the acute tests with algae and daphnia no effects were observed up to the highest concentrations tested (100 mg/L and 180 mg/L respectively; registration dossier(s), study report, 1998d and e). In an OECD TG 211 study with only 2 concentrations tested a NOEC of 55.6 mg/L and a LOEC of 100 mg/L based on cumulative number of juveniles produced per adult were determined (registration dossier(s), study report, 1998f).

Summary of concerns

In summary, an ED concern for the environment is identified based on the results of the *in vitro* assays, model data equivalent to OECD CF Level 3 data and EAS mediated effects in mammalian studies. Moreover, due to QSAR predicting high long-term toxicity to fish there is a concern for chronic non-endocrine related fish toxicity.

A.5 Request 1: Why new information is needed

Taking into account the above findings concerning endocrine activity and non-endocrine related long-term fish toxicity as well as the wide dispersive use of the substance, further information is needed.

The literature shows that there are multiple potential sources of environmental exposure to the Substance. High tonnages of the Substance are manufactured and used in the EU (substance as manufactured, as component of products or articles) (for more details see Appendix 1: Reasons, A.1 The potential risk for the environment).

A.6 Request 1: Considerations on the test method

A Fish Sexual Development Test (OECD TG 234) is an *in vivo* assay listed at OECD CF Level 4 providing apical information on endocrine and non-endocrine mediated effects. The study must be performed with Japanese medaka (*Oryzias latipes*) or zebrafish (*Danio rerio*)with 5 test concentrations in order to provide a reliable NOEC/ECx to be used for further risk management considerations.

As the water solubility is rather low with 3.06 µg/L, a carrier solvent already validated in fish tests must be used. In addition, you are required to consider the practical aspects of the OECD Guidance Document 23 on Aqueous-Phase Aquatic Toxicity Testing of Difficult

Test Chemicals for the conduction of this test (OECD, 2019).

Furthermore gonad histopathology must be examined to enhance the sensitivity and the statistical power of the test. If the test species is Japanese medaka, genetic sex must also be determined.

You must submit the full study report of the required information in your dossier(s) update. Indeed, a complete rational and access to all available information (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) are needed to fully assess the provided information and to clarify efficiently the concerns.

A.7 Request 1: Alternative approaches and proportionality of the request

An alternative option, which provides more comprehensive information on endocrine disruption and non-endocrine-related toxicity to fish is the Medaka Extended One Generation Reproduction Test (MEOGRTS, OECD TG 240). This OECD CF Level 5 test uses considerably more fish than the FSDT and is thus not the least onerous option in terms of the use of vertebrate animals.

Also a Fish Short Term Reproduction Assay (OECD TG 229) would have been an alternative option. However the purpose of the requested study is not only to elucidate the *in vivo* mode of action in fish but also to elucidate potential endocrine adverse effects as well as possible non-endocrine related toxicity.

The request for the FSDT is suitable, proportionate and necessary to obtain information that will clarify whether there is a potential risk from endocrine disruption or non-endocrine-related toxicity. More explicitly, of the available alternatives it is the least onerous way to obtain the necessary information. It is noted that there is no experimental study available at this stage that will generate the necessary information and avoid the need to test vertebrate animals.

A.8 Request 1: Consideration of your comments on the original draft decision

In your comments you mention discrepancies in the ER ToxCast model prediction and missing flags. The draft decision was amended accordingly. Nevertheless, this does not change the overall outcome of the ER ToxCast model prediction.

You note that positive findings of the ToxCast assays were only observed at concentrations 3 to 4 orders of magnitude above the water solubility of the Substance and recommend caution in interpreting the outcome. In reply it is stated that the data from the ToxCast assays consistently point towards TOTM exhibiting estrogenic activity. These indications come from a variety of assays based on different cell lines and read-outs that all focus on different parts of the estrogenic signalling cascade. These observations were all made in the absence of signs of cytotoxicity based on the viability assays that were included in the data set. The responses also appear to be specific to the ER pathway as the similar assays in the ToxCast data set – utilizing the same combinations of cell lines and read-outs - investigating the androgen receptor pathway do not show this activity. As all substances that are investigated in ToxCast also TOTM is tested up to a concentration of 10^{-4} M (nominal concentration). Indeed, the estrogenic activity is observed at relatively high concentrations and caution is always warranted in interpreting such results as the response

might be attributable to non-specific effects. Also, generally when substances are added at concentrations above their solubility this might lead to increased cytotoxicity. However, the overall picture is consistent here and the (in)solubility of the substance does not seem to interfere with the specificity of the response and no indications of cytotoxicity are observed in the viability controls.

You note ECHA's observation that in the ECHA/EFSA Guidance for ED assessment in biocides and plant protection products regulations (ECHA & EFSA, 2018), information from ToxCast model is treated as equally informative as an uterotrophic assay, which is Level 3 information according to the OECD CF (OECD, 2018) but observes that while positive ToxCast data are accepted in place of an uterotrophic assay, negative outcomes must still be confirmed by a Level 3 uterotrophic assay in order to support a conclusion on absence of EATS-related endocrine activity and that the ToxCast model is firmly described as a Level 2 assay. In reply to your observation it needs to be stated that although ECHA/EFSA guidance was specifically designed for biocides and pesticides to allow a conclusion on ED criteria, the guidance follows the general principles of the OECD CF.

In reply to your comment on not considered Level 1 information (CERAPP methodology and Danish (Q)SAR) of the OECD CF (OECD, 2018) as well as on not considered data regarding sediment dwelling invertebrates, this information has been included and considered for the ED assessment: Also taking into account these negative predictions, there is still a concern as the ER ToxCast model prediction, which is based on *in vitr*o tests, is positive for TOTM. As insect growth and reproduction is regulated by other than vertebrate type steroid hormones (ecdysteroids and juvenile hormones) the negative result in the chironomid test is not considered to rule out the potential ER agonism of TOTM.

Referring to the available OECD TG 408 and 421 studies you contend that dietary exposure can be argued to be more representative of the likely human/environmental exposures (continuous, low level) and that, therefore, the OECD TG 408 study would carry greater weight. In reply to this, ECHA considers it not justified to disregard the results of the gavage studies as less relevant. In ECHA's view gavage and dietary studies are equally relevant for the purpose of hazard identification. The relevance of bolus vs continuous exposure might be more relevant for risk assessment.

In your comment on the developmental toxicity study comparable to an OECD 414 study you correctly describe that areolae were retained in the top dose males on PND 13, but were absent on PND 18. Moreover, you consider the observed small but statistically significant increases of absolute and relative seminal vesicles weight and an increase of epididymides weight being of no biological significance.

In reply to this, ECHA notes that although the effects on areolae were transient they are still an indication of possible endocrine interference. Also the observed effects on the weight of hormone responsive tissues (seminal vesicles and epididymis) are considered an indication of possible endocrine interference regardless their biological relevance, which you questioned based on the minor extent of the effect.

You contend that the Fish Early Life Stage (FELS) toxicity test (OECD TG 210) is most suitable to clarify a concern on long-term toxicity to fish and that the FELS test would be another OECD CF Level 4 assay.

In reply to this ECHA notes that the OECD 210 test is not specifically studying any ED related endpoints.

It is noted that the decision is addressing endocrine disruption in aquatic vertebrates as well as chronic fish toxicity: These concerns are addressed in the least onerous way via a request of an FSDT (OECD TG 234). Based on a fish test according to OECD TG 210 it is not possible to conclude on ED properties of TOTM in aquatic vertebrates.

You correctly state that with QSAR using experimentally determined values for log Kow and water solubility the predictions for chronic fish toxicity are: 489 ng/L for ECOSAR class "Esters" and 345 ng/L for ECOSAR class "Neutral Organic SAR". The draft decision was amended with the correct values. Nevertheless, also with these correct values high toxicity is predicted for fish and the concern is still valid.

You note that the structure of the Substance, a trimellitate, would be outside the ester family's domain (acetates, benzoates, dicarboxylic aliphatics, phthalates derived from aliphatic alcohols and phenol) and, as a result, the predictions may not be representative nor reliable. As TOTM is an ester and the moiety of the molecule contains the sub-structure of a phthalate it is deemed justified to consider the results for the ester domain. The estimates for neutral organic SARs instead as an alternative result in even lower chronic values (ChV) using the same input data.

A.9 Consideration of proposals for amendment and your comments

Two Member State Competent Authorities submitted proposals for amendments (PfAs) regarding the consideration that the Substance would not have P/vP properties based on the study provided by you. One MSCA concluded the Substance to meet the P/vP criteria based on this study and proposed to request a bioaccumulation study as the Substance reveals a potential for bioaccumulation. Another MSCA proposed to reconsider the P status of the Substance.

Based on these two PfAs, the ECHA removed the statement that the Substance does not meet the PBT/vPvB criteria. Under section A3 "Explanation of the testing strategy for the environment" further explanation on the possible need for further information to clarify the PBT/vPvB concern was added.

Considering another PfA, it was added that you are required to consider the practical aspects of the OECD Guidance Document 23 on Aqueous-Phase Aquatic Toxicity Testing of Difficult Test Chemicals (OECD, 2019) for the conduction of the requested study as the substance comprises a low water solubility.

In your comments on the PfAs related to the PBT/vPvB-concern, you have provided several reasons why you consider the Substance not to fulfill the PBT/vPvB criteria. Based on the submitted reasons, you regard the P/vP-concern to be not clarified yet. You argue that the Substance does not meet the B/vB criteria based on already available data. The eMSCA will consider your reasons and arguments when assessing whether further information would still need to be requested in a follow up decision to clarify the PBT/vPvB concern.

B.1 Consideration of the time needed to perform the requested studies

The deadline for provision of the requested data takes into account the time that you may need to agree on which of the registrant(s) will perform the required tests (3 months is allocated for this) and include the time required for developing an analytical method, conduct of the study according to the test guideline, preparation of the study report and reporting in IUCLID.

For the request, ECHA considers that 18 months is a sufficient time for conduct and reporting of the study.

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B. 2 References

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US EPA ToxCast Screening Library
https://comptox.epa.gov/dashboard/dsstoxdb/results?abbreviation=TOXCAST&search=3319-31-1

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after 4 July 2019 – one day before the end of the 12-month evaluation period 5 July 2019.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Environment/Suspected PBT, Exposure/ Wide dispersive use and high aggregated tonnage tris(2-ethylhexyl) benzene-1,2,4- tricarboxylate CAS No 3319-31-1 (EC No 222-020-0) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2012. The updated CoRAP was published on the ECHA website on 29 February 2012. The competent authority of Austria (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 46(1) of the REACH Regulation, a substance evaluation decision was issued on 22 May 2014 requesting further information on persistence (OECD TG 308). You submitted all the requested information on 5 July 2018. The evaluating MSCA carried out the evaluation of the information in your updated registration(s) and other relevant and available information. Further information may need to be requested in a follow up decision to clarify the PBT/vPvB concern.

In the course of the follow up evaluation, the evaluating MSCA identified additional concerns regarding endocrine disruption and non-endocrine related toxicity to fish.

The evaluating MSCA considered that further information was required to clarify the concern for endocrine disruption and non-endocrine related toxicity to fish. Therefore, it prepared a draft decision under Article 46(3) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 4 July 2019. 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 and the deadline were not 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).

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 an unanimous agreement on the draft decision in its MSC-70 written procedure and ECHA took the decision according to Article 52(2) and Article 51(6) 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 request(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 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 study 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.aspxF 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