EUROPEAN CHEMICALS AGENCY

Helsinki, 06 July 2016

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate, CAS No 15625-89-5 (EC No 239-701-3)

Addressees: Registrant(s)[1] of 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate

This decision is addressed to the Registrant(s) of the above substance with active registrations pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided as an Annex to this decision.

Based on an evaluation by ANSES as the Competent Authority of France (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 07 May 2015, i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(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.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of France has initiated substance evaluation for 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate, CAS No 15625-89-5 (EC No 239-701-3) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/Sensitiser; Exposure/Wide dispersive use, exposure of workers, high RCR, 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of France was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding carcinogenicity, genotoxicity and environment.

The evaluating MSCA considered that further information was required to clarify the following concerns: genotoxicity and environment. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 24 March 2015.

On 07 May 2015 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrant(s) commenting phase

By 15 June 2015, ECHA received comments from the Registrant(s). Late comments were also received on 14 July 2015. The evaluating MSCA considered the comments received from the Registrant(s). These comments did not lead the evaluating MSCA to modify its requirement. However, some clarifications were added in order to clarify the decision.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 21 January 2016 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 26 February 2016 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

Referral to Member State Committee

On 7 March 2016 ECHA referred the draft decision to the Member State Committee.

By 29 March 2016, in accordance to Article 52(2) and Article 51(5), the Registrant(s) provided comments on the proposal(s) for amendment.

It should be noted that further to compliance check of the lead registration dossier additional information has been requested by ECHA in a decision issued on 16 December 2014 (Decision number: CCH-D-2114289316-41-01/F) while the decision-making for requesting a two-generation reproductive toxicity study or an extended one generation reproductive toxicity study has been referred to the Commission. The lead registration dossier has been updated on 22 December 2015 to comply with the ECHA decision CCH-D-2114289316-41-01/F. It was not possible for the evaluating MSCA to consider this update at this late stage of the decision making process of the present draft decision. The update has therefore not been evaluated in details but it has been consulted by the evaluating MSCA to confirm that new elements do not impact the need for the information required in this decision.

After discussion in the Member State Committee meeting on 26 – 29 April 2016, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 29 April 2016. ECHA took the decision pursuant to Article 52(2) and Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods (in accordance with Article 13(3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. *In vivo* Mammalian Alkaline Comet assay in mice (test method: OECD 489) analysing bone marrow and liver, *via* parenteral route using injection techniques appropriate for irritating substances;
2. Detailed description and justifications for each contributing scenarios and revision of spraying scenarios with appropriate models;
3. Fish, Acute Toxicity Test (test method: OECD 203);
4. Evaluation of bioaccumulation potential:
   - Refinement estimation of log Kow based on appropriate determination of CMC and solubility of TMPTA in octanol;
   - If refined log Kow ≥3, update of secondary poisoning risk assessment based on QSAR evaluation of the bioaccumulation potential with appropriate justification and documentation that the approach is valid for TMPTA;
   - If not technically possible to refine the log Kow, or if risk of secondary poisoning is identified further to risk assessment update, Bioaccumulation in Fish: Aqueous and Dietary Exposure (OECD TG 305).

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **13 October 2017** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report.

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

III. Statement of reasons

1. *In vivo* Mammalian Alkaline Comet assay in mice (OECD TG 489) analysing bone marrow and liver, *via* parenteral route using injection techniques appropriate for irritating substances

The available information showed clastogenic effects *in vitro*. The *in vivo* micronucleus assays do not enable the evaluating MSCA to convincingly dismiss the *in vitro* concern. Furthermore, carcinogenic effects were observed. Based on the available data, no conclusion can be set on the mechanism of carcinogenicity (genotoxic or not). Therefore, the evaluating MSCA judged that more information is required in order to state on genotoxic classification and risk characterisation linked to carcinogenicity potential of the substance.

Discussion on the requirement

Genotoxicity potential of TMPTA has been assessed in *in vitro* and *in vivo* assays.

Although negative results were obtained for point mutations in Ames tests and in an *in vitro* Mammalian cells mutation assay (HPRT assay in CHO cells), positive effects were found in mouse lymphoma assays (MLA) and in mammalian cell chromosomal aberration assays in CHO cells and in human lymphocytes.

Three MLA assays were available. In the first study ([redacted], 1979[3]), the results were not consistent between the three experiments: increased mutant frequency was observed in all experiments without metabolic activation, but without any dose-relationship in the third experiment; in the presence of metabolic activation, increase in mutant frequency was only observed in a context of severe cytotoxicity. In a second study (Cameron, 1991[4]), increased mutant frequency was reported only in the absence of metabolic activation at concentration leading to cytotoxicity (RTG comprised from 14.5% to 5%). In these two studies, the size of colonies was not reported to discriminate gene mutation and chromosomal aberration. In the last MLA study (Dearfield, 1989[5]) performed without metabolic activation, a dose dependent increase in mutant frequency was obtained at doses showing about 50% cytotoxicity or more. Colony sizing indicated that TMPTA almost exclusively induced small colonies, suggesting a clastogenic mechanism.

In CHO cells exposed to TMPTA without metabolic activation, chromosome aberrations were increased at concentrations associated with 72% to 13% survival (Moore, 1989[6]).

In a more recent and well performed *in vitro* mammalian cell chromosomal aberration study in human lymphocytes ([redacted], 2005[7]), statistically significant and concentration-related increases in the frequency of cells with structural chromosomal aberrations were noted without and with metabolic activation.

Therefore, results from *in vitro* studies showed that TMPTA may induce chromosome aberrations.

Two *in vivo* micronucleus (MN) studies were available.

[redacted].

[4] Cameron TP et al. (1991). Genotoxicity of Multifunctional Acrylates in the Salmonella/Mammalian-Microsome Assay and Mouse Lymphoma TK+/- Assay. Environmental and Molecular Mutagenesis 17:264-271.
[5] Dearfield KL (1989). Analysis of the genotixicity of nine acrylate/methacrylate compounds in L5178Y mouse lymphoma cells. Mutagenesis Vol. 4, No. 5, pp.381-393.
[6] Moore MM et al. (1989). Differential mutant quantitation at the mouse lymphoma tk and CHO hgprt loci. Mutagenesis vol. 4 no 5 pp.394-403.
[7] [redacted]

The first study was performed by the NTP after dermal exposure of B6C3F or Tg.AC hemizygous mice for 14 weeks or 6 months, respectively (NTP, 2005[8]). No increase in the frequency of micronucleated NCEs was observed. Although PCE/NCE ratio was unaltered after 3 month exposure, a decrease in the percentage of circulating NCEs among total erythrocytes was noted at the highest dose in both sexes. However, this study does not follow the appropriate guideline and no positive control was included to validate the protocol. Therefore, this study is judged inadequate to dismiss the positive results observed *in vitro*.

The second study was performed according to OECD 474. Swiss Ico:OF1 mice received a single oral dose of TMPTA in corn oil of up to 1750 mg/kg for males and up to 2000 mg/kg for females ([redacted], 2006[9]). Mean values of micronucleated cells (MPE) as well as the PCE/NCE ratios in the treated groups were equivalent to those of the control group for both harvest times. However, this negative result is questionable since there is no adequate evidence of target tissue (bone marrow) exposure: even if clinical signs (piloerection) and mortality of unknown cause were observed in males, pathological examination was not performed and no effect was observed in females. In this study, PCE/NCE ratio was not altered and plasma levels of the test substance were not investigated. Finally, no other toxicokinetics data was available in mice after oral exposure to estimate the systemic bioavailability and the distribution profile of TMPTA. In conclusion, since it is not clear if the substance has reached the bone marrow or not, the concern for clastogenicity potential remains.

In summary, clastogenic concern observed *in vitro* cannot be ruled out on the basis of the available *in vivo* studies. In this context, a concern is identified and needs to be clarified in order to conclude if a classification is required or not for this substance.

Moreover, the ability of a substance to induce genotoxicity is an indicator of potential carcinogenicity. In the case of TMPTA, dermal carcinogenicity studies were available and showed increase of some tumors in rats and mice (NTP, 2012[10]). In male rats, increase of malignant mesothelioma from tunica vaginalis was reported. Since this type of tumour is a common lesion observed in senescent animals and is generally considered related to Leydig tumour, the extrapolation of this effect to humans is questionable. In female mice, the increase of rare liver tumors and uterine polyps is considered biologically relevant. Moreover, increased incidences and multiplicity of skin papillomas are reported in a 6 month study performed with a genetically modified strain of mouse dermally exposed to TMPTA (NTP, 2005). Based on these results, ECHA considers that TMPTA has a carcinogenic potential. Carcinogenic chemicals have conventionally been divided into two categories according to the presumed mode of action: genotoxic or non-genotoxic. However, the mode of action cannot be identified based on the current genotoxicity dataset. In this context, new robust *in vivo* genotoxicity data is needed to know if a DNEL or a DMEL should be derived for the risk characterisation.

It is necessary to provide this toxicological information in order to clarify the clastogenic concern and to perform an adequate risk assessment for carcinogenicity. Without this requested information, it will be not possible to verify if there remains an uncontrolled risk for workers and general population.

Therefore, a new Comet assay *in vivo* (OECD 489) in mice is required.

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[8] NTP (2005). NTP Report of the toxicology studies of trimethylolpropane triacrylate (Technical grade) in F344/N rats, B6C3F Mice and genetically modified (FVB tg. AC hemizygous) mice. published NTP report. Testing laboratory: Battelle Columbus Laboratories. Report no.: NTP GMM 003. Study number: NIH Publication No. 06-4450.

[9] [redacted]

[10] NTP (2012). NTP Technical report on the toxicology and carcinogenesis studies of trimethylolpropane triacrylate (technical grade) (CAS No. 15625-89-5) in F344/N rats and B6C3F1 /N mice (dermal studies). U.S. Department of health and human services. Testing laboratory: Southern Research Institute. Report no.: NTP TR576. Study number: NIH Publication No. 13 - 5918.

Mouse is considered an appropriate species since carcinogenic effects were reported in this species.

The limitation of the current available *in vivo* micronucleus study is the lack of evidence that the substance was reaching the target organ; however sufficient exposure of the bone marrow must be ensured to conclude properly on this endpoint. In this context, investigation of levels of the test substance in plasma or in bone marrow is required in the new study and must demonstrate that exposure of the bone marrow occurred. Another option is to perform the study by a parenteral route. In the initial draft decision, intraperitoneal route was proposed as a possible alternative, without any requirement of dosage of the substance in the blood. However, the Registrant(s) consider this route not appropriate for TMPTA due to its physico-chemical and irritating properties. Instead, they proposed to perform this test by intravenous route. This route of administration can be considered adequate if specific precautions are taken to allow the administration of sufficiently high concentrations and to take into account the irritating properties of TMPTA. In particular, administration volume and dosing rate (slow rate of injection) need to be carefully selected[11] in order to minimise local reaction and to achieve sufficiently high dosages. These precautions need to be documented in the update of the registration dossier.

Considering that the main target organ for carcinogenicity is the liver, it is required to investigate DNA damage in the liver in addition to bone marrow in the Comet assay.

The evaluating MSCA initially considered the request to perform a new micronucleus study, which was agreed by the Registrant(s). However, considering the need to investigate liver and as suggested in the proposals for amendments received, the Comet assay is considered to be a more appropriate alternative with a guideline validated in liver tissues.

In reaction to the proposals for amendments the Registrant(s) considered that the possibility to perform a Comet assay was not relevant because it is performed when there is an alert for gene mutations. In the case of TMPTA, no gene mutations are expected based on *in vitro* data. ECHA agrees with the Registrant(s) that the *in vitro* database for TMPTA mainly raises a concern for clastogenicity and chromosomal aberrations. However, the Comet assay recognises primary DNA damage that would lead to both gene mutations and/or chromosome aberrations as stated in ECHA's guidance on information requirements and chemical safety assessment (R7a, version 4.1) and the Comet assay is therefore considered appropriate.

ECHA notes that it is also possible as an alternative to perform in mice and using parenteral route of exposure, a combined assay of *in vivo* mammalian erythrocyte micronucleus test in bone marrow and modified *in vivo* mammalian comet assay on liver and bone marrow. This would be an interesting option to have a more solid understanding on the genotoxic potential of TMPTA and perform a state-of-the-art assay.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide the following information: *In vivo* Mammalian Alkaline Comet assay in mice (OECD TG 489) analysing DNA damage in bone marrow and liver, via parenteral route using injection techniques appropriate for irritating substances or the alternative test proposed above.

[11] Diehl KH et al. (2001) A Good Practice Guide to the Administration of Substances and Removal of Blood, Including Routes and Volumes. J. Appl. Toxicol. 21, 15–23 (2001)

2. Detailed description and justifications for each contributing scenarios and revision of spraying scenarios with appropriate models

In order to clarify the exposure and the emission pathways, more information on the life cycle of the substance is needed. For each step of the life cycle, an exposure scenario must be proposed, detailed and justified using the identified relevant form(s) of the substance(s). Exposure scenarios have to be extensively and properly described and all considered parameters or deviations from default parameters have to be explained and justified in accordance with REACH guidance documents. The protection factors of each individual or collective risk mitigation measures must also be indicated. Furthermore, a brief description of the sequence of the activities/tasks at the industrial sites is also required to enable a better understanding of the practices. The description of activities and parameters is particularly important if Tier 2 models were used.

Furthermore, in case different exposure models were used for inhalation and dermal exposure, consistency of risk mitigation measures need to be checked between the different models.

Finally, exposure models must be chosen considering their relevance and limitation for some PROCs. For example, for PROC 7 and 10, ECETOC TRA only predicts vapour phase exposure and is not appropriate to evaluate exposure to spray aerosol. In this context, the inhalation exposure of TMPTA can be underestimated and other model must be considered.

Without these clarifications, a robust exposure assessment with refinements cannot be conducted. In this context, it is difficult to check the necessity and applicability of personal protective equipment (PPE) and risk management measures (RMM).

The Registrant(s) commented that a revised CSR and Risk Assessment was in progress and to be submitted. In this regards, it is specified that the following dossier update could not be considered by the evaluating MSCA at this late stage of the decision making process, therefore the request is kept in the decision.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide the following information: detailed description and justifications for all the parameters used for the exposure assessment and revision of spraying scenarios with appropriate models.

3. Fish, Acute Toxicity Test (OECD TG 203)

In the registration dossier, one acute toxicity test on fish *Leuciscus idus* ([redacted], 1988[12]) has been provided by the Registrant(s) and was used to determine a $PNEC_{aquatic}$ of 1.47 µg/L. This acute study on fish is not considered sufficiently reliable to be used for the $PNEC_{aquatic}$ determination for the reasons described below.

In this study, the results showed that no mortality occurred at the first four concentrations (0.1, 0.215, 0.464 and 1 mg/L) whereas 100% of fish died at the highest tested concentration of 2.15 mg/L. Then, the Registrant(s) accurately proposed the geometric mean between the highest concentration without effect and the lowest concentration with 100% effect to determine the LC_{50} of 1.47 mg/L. ECHA points out that this approach allows an approximation for the LC_{50}, as stated in the OECD 203.

12 [redacted]

However, it should be underlined that these results are not consistent with the results observed in the two range-finding studies where LC_{50} between 0.3 and 1 mg/L were detected. The LC_{50} might therefore be below 1 and there is a high uncertainty on the data provided. Besides these questionable toxicity results, no concentrations were measured in this static acute study performed on a surface-active substance and the toxic effect relates to the nominal concentration of TMPTA. Also, the study does not follow the good laboratory practices.

Tests on algae and daphnia were also available, however with some deficiencies. In these both studies, toxic effect endpoints are based on nominal concentrations since no analytical measurements were performed. The results gave an higher daphnia EC_{50} and algae E_rC_{50} than the fish LC_{50}. So fish is considered as the most sensitive species.

Since fish is the most sensitive species of the three trophic levels tested with TMPTA and as no chronic data are available, this LC_{50} has been proposed by the Registrant(s) to determine the PNEC aquatic. Considering the deficiencies and uncertainties listed above and in contrast to the Registrant(s) opinion, the available acute toxicity study on fish can not be considered reliable to be used for the determination of the $PNEC_{aquatic}$. It should be underlined that the sediment and soil risk assessment will also depend on the aquatic PNEC value since the PNECs for the sediment and soil compartments will be derived using the equilibrium partitioning method. Then the environmental risk assessment strongly depends on this $PNEC_{aquatic}$ value. It is noted that in the recently updated registration dossier (see Section I), RCR are close to 1 for some uses (e.g. RCR = [redacted]). The LC_{50} obtained from the requested study may therefore result in the need to set risk management measures and/or refine environmental exposure assessment. Finally, the Registrant(s) proposes as a consensus to take 1.001 mg/L to derive the aquatic PNEC, based on the absence of effects observed at 1.0 mg/L. Nevertheless, ECHA disagrees with this proposal since a substance with an $LC_{50} \leq$ 1mg/L is classified H400, thus a reliable measure of the acute toxicity on fish is necessary to conclude on an unequivocal acute and chronic classification of TMPTA. Consequently, ECHA considers that the request of a new acute fish toxicity (AFT) test of TMPTA according OECD 203 is justified and is conform to the EU Directive on animal protection (Directive 86/609/EEC).

Following a proposal for amendment of the request, the possibility to adapt this information requirement using the additional option of performing a non-vertebrate animal test, such as the Zebra Fish Embryo Toxicity Test OECD TG 236 (ZFET test) was considered together with other adaptations from Annex XI of REACH. However, there are some uncertainties about the relative sensitivity of the ZFET compared to the AFT test.

In addition, considering that an AFT test with some limitations and inconsistencies in its results between the range-finding and the main study is already available, it is strongly prefered to perform a test using a similar test guideline in order to compare the results for the whole database. Using a different test guideline would provide additional uncertainties related to methodological differences in sensitivity. An AFT test will allow a more robust assessment for PNECs derivation and classification also considering that current results are close to the trigger for the acute classification. Therefore, alternatives to the AFT test are not considered relevant in this specific case.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide the following new study using the registered substance subject to this decision: Fish, Acute Toxicity Test, according to test method OECD 203 (1992). Special consideration should be taken to the surface active property of TMPTA, and exposure concentrations should be determined at multiple time points during the test in order to determine robust LC_{50} and PNEC values.

The Registrant(s) are reminded that depending on the revised related risks, long-term aquatic toxicity testing might be required.

The Registrant(s) are also reminded that, depending on the outcome of the AFT, the interim conclusion that fish is the most sensitive species may need to be reconsidered and acute tests on algae and/or aquatic invertebrates might be required at a later stage.

4. Evaluation of bioaccumulation potential:

- **Refinement estimation of log Kow based on appropriate determination of CMC and solubility of TMPTA in octanol;**
- **If refined log Kow ≥,3 update of secondary poisoning risk assessment based on QSAR evaluation of the bioaccumulation potential with appropriate justification and documentation that the approach is valid for TMPTA;**
- **If not technically possible to refine the log Kow, or if risk of secondary poisoning is identified further to risk assessment update, Bioaccumulation in Fish: Aqueous and Dietary Exposure (OECD TG 305)**

The Registrant(s) initially proposed a QSAR calculation of BCF from the Kow value. However, according to a key study included in the registration dossier in the course of the substance evaluation, it was established that TMPTA is a surface active substance (51 mN/m, [redacted], 2014a[13]). Then, the initial measured log Kow value available in the dossier was not reliable. A new log Kow ≥ 3.3 based on the individual solubilities ([redacted], 2014b[14]) was subsequently submitted by the Registrant(s) whithout any considerations of the critical micelle concentration (CMC). This new Log Kow is still questionable and therefore the uncertainty about the estimated BCF value still remains. The TMPTA has wide dispersive uses, high tonnage, and mammals exposure is expected as showed in the recently updated CSR (see Section I). It is currently not possible to assess the risk for secondary poisoning since neither reliable Kow nor BCF values are available. Consequently, reliable information about bioaccumulation potential are needed to remove uncertainties about the risk for secondary poisoning.

In their comments to the draft decision, the Registrant(s) disagree that the substance TMPTA is a surfactant based on the previous *Technical Guidance Document in support of the Directive 98/8/EC concerning the placing of biocidal products on the market, Guidance on data requirements for active substances and biocidal product (2000)*. However, according to the EU Regulation 528/2012 and the updated guidance document, the threshold value for surfactant is 60 mN/m, then TMPTA has to be considered as a surface active substance. The Registrant(s) additionally disagree in their comments to perform a bioaccumulation study in fish and suggested as an alternative approach to perform a preliminary analysis of bioaccumulation potential with a CMC-refined Kow.

ECHA agrees with the Registrant(s) to consider the calculated log Kow ≥ 3 from the registration dossier as unreliable and that the CMC should be taken into account to estimate a more realistic Kow value for TMPTA. Although measured BCF values are preferred for surface active substances, the new approach suggested by the Registrant(s) to perform a preliminary analysis of bioaccumulation potential with a CMC-refined Kow could therefore be acceptable provided several issues are addressed and appropriately documented.

13 [redacted]
14 [redacted]

First, for the calculation of the new CMC-refined log Kow value, the determination of the CMC should be performed according to a standardized method (for example ISO 4311:1979) and clearly detailed. Furthermore, regarding the high solubility of TMPTA in octanol, this parameter will have a great influence on the Kow ratio, consequently the value of >900 g/L (reported in the final Log Kow study included in the registration dossier updated on 27 November 2014 ([redacted], 2014b[15])) is not precise enough and should also be refined.

In case of refined log Kow <3, it could be considered that TMPTA have no bioaccumulation potential and presents no potential risk for secondary poisoning. Therefore no further request is needed.

However, if the refined log Kow ≥3, the Registrant(s) have to update the secondary poisoning risk assessment based on the CMC-refined log Kow and BCF derived by an appropriate QSAR(s) prediction(s) of the bioaccumulation potential.

The Registrant(s) have to follow the recommendation of the Appendix R7.10-1 of Chapter R7.c of the ECHA guidance on information requirements and chemical safety assessment (version 2.0, November 2014) to choose the appropriate QSAR models. Registrant(s) are reminded that the QSAR prediction(s) needs to meet the conditions of Section 1.3. of Annex XI further explained in Practical guide 5[16].

In case a risk for secondary poisoning is identified, the OECD TG 305 test is required to have a more accurate BCF value for TMPTA to clarify the bioaccumulation potential of TMPTA and refine the risk assessment for secondary poisoning.

If it is not technically possible to refine the log Kow based on CMC determination and solubility in octanol, the Registrant(s) has to perform a Bioaccumulation test in fish (OECD TG 305).

A request for a Bioaccumulation test in fish will also be reconsidered by the evaluating MSCA in a further step of the Substance Evaluation if the QSAR evaluation of the bioaccumulation potential is considered not valid based on insufficient data or insufficient justification by the Registrant(s).

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide a refined log Kow value based on CMC determination. If the refined log Kow ≥3, the Registrant(s) are required to provide a BCF estimation based on QSAR with appropriate justification to validate the approach and to update the risk for secondary poisoning. If a risk is identified, the Registrant(s) are required to provide a Bioaccumulation test in Fish: Aqueous and Dietary Exposure, according to test method OECD 305 (2012) is required with taking particular attention of the surface active properties of TMPTA in its test design.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental studies, the sample of the substance to be used shall 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 tests subject to this decision and to document the necessary information on composition of the test material.

[15] [redacted]

[16] Practical guide 5 – How to use and report (Q)SARs. ECHA. March 2016

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. Finally, the tests must be shared by the Registrant(s).

V. Avoidance of unnecessary testing by data- and cost-sharing

In relation to the experimental studies the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to 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.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[17] by Leena Ylä-Mononen, Director of Evaluation

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

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