Helsinki, 11 February 2019

Substance name: Triphenyl phosphate
EC number: 204-112-2
CAS number: 115-86-6
Date of latest submission(s) considered[1]: 05 May 2017
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressee(s): Registrant(s)[2] of Triphenyl phosphate (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

Based on Article 46(1) of the REACH Regulation (Regulation (EC) No 1907/2006), ECHA requests you to submit the following information on the registered substance:

1. Fish Sexual Development Test, test method OECD 234, using Zebrafish (*Danio rerio*) and 5 test concentrations

   You have to provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the chemical safety report by **18 August 2020.**

The deadline 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).

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/ies on behalf of all registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

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

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

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has a suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals

Authorised[3] by Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on triphenyl phosphate (TPhP) 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 to clarify the concern for endocrine disruption in the environment in the follow up process.

ECHA has requested a study, which will address endocrine disruption.

1. Fish Sexual Development Test, test method OECD 234, using Zebrafish (*Danio rerio*) and 5 test concentrations

The concern(s) identified

A reduction in fecundity in female fish resulting from exposure to TPhP is observed in two endocrine disrupter (ED) screening studies (X Liu et al, 2013 and Japanese Ministry of Environment, 2012) which are level 3 tests according to the Conceptual Framework (CF) outlined in the revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption (OECD, 2018). Other data from these and further studies indicate changes in vitellogenin and sex hormone levels in fish. Together these effects provide a potential concern for environmental endocrine disruption and further information is required to investigate this.

Why new information is needed

There are four *in vivo* studies relevant to the assessment of endocrine disruption in fish due to TPhP, which are summarised below.

X Liu et al. (2012) performed a non-GLP 14-d test with adult Zebrafish *Danio rerio* and three test concentrations using semi-static exposure. This was not performed to a standard test guideline, and there was no chemical analysis. No mortality occurred, and sub-acute effects were not mentioned in the paper. At the highest nominal test concentration (1 mg/L) estrogen levels were statistically significantly elevated in both male and female fish compared to controls. At the same concentration, 11-ketotestosterone and testosterone levels were statistically significantly decreased in male fish, but no effects on these hormones occurred in females.

X Liu et al. (2013) performed a non-GLP 21-d test with adult *Danio rerio* and three test concentrations using semi-static exposure. This was similar to an OECD TG 229 study (Fish Short Term Reproduction Assay). There was very limited chemical analysis, with fresh and expired solutions measured over one 48-h renewal period (this indicated that for the nominal test concentration of 1 mg/L, the measured concentration at 0 and 48-h were 0.89 and 0.38 mg/L, representing a 57% loss, whereas measured concentrations for the 0.2 and 0.04 mg/L nominal test concentrations were 0.14 and 0.03 mg/L at 0-h and below the limit of detection at 48-h). No mortality occurred, and no effects on fish growth, gonadosomatic index (GSI) and heptasomatic index (HSI) were observed at any concentration. At the highest nominal test concentration (1 mg/L) a statistically significant increase in estrogen levels were observed in female fish, with a statistically significant decrease in 11-ketotestosterone and testosterone levels. In male fish, no

effects were observed for 11-ketotestosterone and testosterone. Estrogen levels in males were statistically significantly elevated at the middle concentration (nominal 0.2 mg/L) but not 1 mg/L. A statistically significant increase in vitellogenin levels occurred in both male fish (1 mg/L) and female fish (0.2 and 1 mg/L). Fecundity in female fish was reduced at 0.2 mg/L (from part-way through the test) and 1 mg/L (throughout the test).

X Liu et al. (2016) performed a non-GLP 120-d test with *Danio rerio* covering development from embryos through to adult fish. It used three test concentrations with semi-static exposure. This was not performed to a standard test guideline. There was very limited chemical analysis, with fresh and expired solution measured over one 48-h renewal period (this indicated that for the nominal test concentration of 0.5 mg/L, the measured concentration at 48-h was 0.011 mg/L, which is approximately 2% of the starting nominal concentration, whereas measured concentrations for the nominal 0.005 and 0.050 mg/L treatments were below the limit of detection). No mortality occurred. No effects on female fish growth were observed, but male fish growth was affected at 0.05 mg/L and 0.5 mg/L. Female GSI was affected at 0.005 and 0.50 mg/L but not 0.05 mg/L. Male GSI was unchanged in the test. The paper states that there was no significant difference in sex ratio amongst the treatment groups including the controls (the actual ratio is not specified). A statistically significant elevation in estrogen levels occurred in female fish at 0.005 and 0.50 mg/L but not 0.05 mg/L, and only at the lowest concentration in male fish (0.005 mg/L). A statistically significantly decrease in 11-ketotestosterone levels was seen in both male (at all concentrations) and female fish (at 0.50 mg/L only). Testosterone was not measured.

In January 2018 ECHA was provided with an English summary translation of a study performed by the Japanese regulatory authorities as part of the Japanese EXTEND 2010 endocrine disruption programme (Japanese Ministry of Environment, 2012). The Japanese authorities have also provided some additional information to allow ECHA to validate the test. The study was a 21-d OECD TG 229 test with adult Japanese Medaka *Oryzias latipes* using four concentrations. Test concentrations were measured (arithmetic mean of weekly measured concentrations), with flow-through exposure conditions. No significant mortality occurred. No effects on male fish growth were observed, but female fish growth was affected at the highest measured test concentration (0.045 mg/L). HSI was affected in male fish at the three highest test concentrations (0.007, 0.017 and 0.045 mg/L, measured) but female fish were unaffected. GSI was unchanged in both male and female fish. Vitellogenin levels were unchanged in male fish at all concentrations, but a statistically significant reduction occurred in female fish (at 0.007 mg/L and above). Fecundity in female fish (number of eggs and number of fertile eggs) was reduced at the highest test concentration (0.045 mg/L, measured). The secondary sexual characteristics in male fish were unaffected at all concentrations. The study concluded that TPhP was not estrogenic, however the decrease in female vitellogenin meant that an *in vitro* anti-estrogenic assay should be performed. The Japanese authorities have confirmed that no mortality occurred in the controls, and that oxygen saturation and temperature were within the test guideline stipulations. Specific fecundity data prior to the start of the test have not been provided, but the Japanese authorities state that the best tanks were selected (for the test); test concentration information is not sufficiently detailed to confirm that measured concentrations were maintained within +/-20 %, but the test was flow-through which makes significant (measured) concentration decline less likely. The number of replicates exceeded the test guideline requirements. The Japanese authorities have also said the test results were reviewed by an expert committee on the assessment of endocrine disrupting effects in Japan – which ECHA consider as providing quality assurance.

Overall, the evidence indicates that the validity criteria were generally met, even though full details are not available for every criterion. It is also clear that a non-EU authority is satisfied with the test.

Overall, a clear effect on fecundity is observed in two OECD CF level 3 studies (X Liu et al. (2013): NOEC = 0.04 mg/L, LOEC = 0.2 mg/L; Japanese Ministry of Environment (2012): NOEC = 0.017 mg/L, LOEC = 0.045 mg/L). However, in relation to a potential specific endocrine mode of action, the findings of the different X Liu et al. studies (estrogenic) are different to those of the Japanese regulatory study (not estrogenic, but potentially anti-estrogenic). There were also varying concentration-responses for some other endpoints, for example estrogen levels in male and female fish in X Liu et al. (2016). The estrogen levels in male fish in X Liu et al. (2013) also did not fully align with the vitellogenin changes in that test. These latter observations are less supportive of an estrogenic mode of action. It is possible that the apical effect (and other perturbations such as for sex hormones) are observed at concentrations where they are a secondary effect caused by other modes of toxicity. This is because there is evidence from other data, both in the REACH registration and published in the literature, that cardiotoxicity, neurotoxicity and liver toxicity as well as malformations and hemorrhagic areas might be caused by TPhP at similar concentrations. To briefly summarise these data:

- Acute fish toxicity data provided in your registration dossier indicate the 96-LC50 is around 0.3 mg/L in a range of species (but not *Danio rerio*). More recent data published by Du et al. (2015 and 2016) indicated a 96-h LC50 of around 1 and 1.5 mg/L for adult and embryo *Danio rerio*, respectively, based on nominal concentrations.

- The key (and lowest) value from the chronic fish toxicity dataset provided in your registration dossier is a 30-d EC10 of 0.037 mg/L, resulting from growth effects in an egg & sac fry test with Rainbow Trout *Oncorhynchus mykiss* (Sitthichaikasem, 1978). A partial life-cycle test using the same species detected no effects up to the highest concentration tested over the 90-d test (Mayer et al., 1981). The study was performed using 7 measured test concentrations between 0.00022 mg/L and 0.0014 mg/L and so the NOEC was an order of magnitude below the EC10 value of Sitthichaikasem (1978). The Mayer et al. (1981) test also did not include the exposure of the egg stage of the life-cycle as it commenced with fry.

- In a 7-d test using adult *Danio rerio*, Du et al. (2016) observed liver toxicity (based on histopathology) at nominal exposure concentrations of 0.05 and 0.30 mg/L. Cardiotoxicity in both *Danio rerio* and *Oryzias latipes* embryos has been recorded by several authors, for example Du et al. (2015) (pericardial edema in *Danio rerio* at nominal concentrations of 0.50 mg/L and above), McGee et al. (2013) (pericardial edema in *Danio rerio* at nominal concentrations of 0.03 mg/L and above) and Sun et al. (2016) (heart rate decrease in *Oryzias latipes* at nominal concentrations of 0.125 mg/L and above). Several authors claim neurotoxic effects occur in fish due to TPhP based on behavioural differences in exposed fish compared to control fish. Levels of the neurotransmitter acetylcholinesterase (AChE) decreased in *Oryzias latipes* in one test (96-h NOEC = 0.025 mg/L) (Sun et al, 2016). ECHA has not considered the significance of these neurotoxic effects in detail, but note that they are indicative of a further potential mode of toxic action.

In your evaluation of potential endocrine disrupting properties of TPhP provided in your registration dossier you argue that the effects in X Liu et al. (2013) and X Liu et al. (2016) are a result of unspecified toxicity, based on the results of acute fish toxicity in

your registration dossier. ECHA note that the acute toxicity of TPhP to *Danio rerio* appears to be around 1 mg/L, but fecundity was affected both at 1 mg/L and a lower concentration of 0.2 mg/L with no sub-acute effects noted in the test (all nominal concentrations). In *Oryzias latipes*, fecundity was affected at 0.045 mg/L, which is an order of magnitude below the available acute toxicity levels. As described above, ECHA agree that the apical effects could be secondary to other modes of toxicity, but at present the concentration at which these forms of toxicity occur over the long-term requires clarification. There is also a need to address the inconsistency in the effects reported in the academic literature, for example pericardial edema was not noted in the X Liu et al. (2016) study nor several other *Danio rerio* embryo studies. More importantly, for some of the ED tests using higher (nominal) concentration no lethality was observed despite the studies being performed at concentrations where it would be expected to occur. Growth and liver effects were, however, observed in female and male *Oryzias latipes*, respectively, in the Japanese Ministry of Environment (2012) study. Overall, more comprehensive data are needed before a robust conclusion can be drawn regarding the significance of other modes of toxicity.

The current long-term fish toxicity dataset in your registration dossier comprises several egg & sac fry tests, and a fish partial life-cycle study, which cover stages at and beyond fry but your dataset does not include any study specifically investigating endocrine disruption.

ECHA considers that performing an FSDT will address the endocrine concern resulting from the variety of endocrine effects seen in the Zebra fish tests performed by X Liu et al. (2012), (2013) and (2016), and the Medaka study of Japanese Ministry of Environment (2012). At the same time, possible non-endocrine-related toxicity will be accounted for in the FSDT.

What is the possible regulatory outcome?

ECHA has requested the OECD TG 234 study to investigate the potential endocrine disrupting properties of the substance. Ultimately, if the obtained data are sufficient to confirm the suspected endocrine disruption properties according to the World Health Organisation/International Programme on Chemical Safety working definition, 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 and subsequent authorisation or restriction of the substance.

Considerations on the test method and testing strategy

You are requested to perform a Fish Sexual Development Test (FSDT, OECD 234). The test guideline offers both Medaka and Zebrafish, indicating no difference in sensitivity. However, in this case you are required to perform the test using Zebrafish. This is because ECHA considers that the endocrine mode of action is most apparent in the available data for Zebrafish, while the potentially resulting adverse effects has not been shown in an OECD CF level 4 test.

The test must be performed using 5 test concentrations. This is because, in this case, the test is used to investigate potential adverse effects, which based on the available dataset may occur over a broad range of concentrations, a significant number of studies only have nominal concentrations causing uncertainty in exact exposure levels where effects occurred.

The use of 5 test concentrations may also provide more precise NOEC/LOEC/EC10 values. If the results indicate that the substance would require identification as a substance of very high concern (SVHC) due to endocrine disrupting properties, a NOEC/EC10 would be important for risk management purposes.

The test concentrations shall be spaced according to the test guideline. You shall justify the exact concentration range chosen. However based on the concentrations at which effects were observed in the Japanese Ministry of Environment (2012) study, it is suggested that the concentration range includes one concentration below 0.01 mg/L.

You are recommended to include liver histopathology as this may help interpret the result of the test. At the end of the test, fish at each concentration should be randomly selected for liver histopathology. You should choose and justify the number of fish needed to provide a statistically robust measure for this endpoint. For further practical guidance, please consult OECD 240 Medaka Extended One Generation Reproduction Test (MEOGRTS), where liver histopathology is included as a measured parameter.

Furthermore you are encouraged to consider the measurement of sex steroid hormones in fish. This could help in identifying the mode of action if endocrine effects are seen in the study.

As part of the abnormal appearance observations to be performed during the requested study (paragraph 39 of the TG), you may also wish to consider evidence of cardiotoxicity based on observation of pericardial edema. This effect was observed by McGee et al. (2013) in Zebrafish embryos. This information may be useful in the interpretation of any developmental or growth effects occurring in this test.

Prior to conducting the test you should refer to the OECD Difficult Substances guidance (OECD Guidance Document 23), paying particular attention to advice for substances which degrade in the test system or are adsorptive.

Efforts shall be made to maintain test concentrations as close to the nominal concentrations as far as technically feasible throughout the experiment. You shall justify the exposure conditions used to achieve this, for example flow-through or semi-static. Flow-through is strongly preferred for this test.

<u>Consideration of alternative approaches</u>

An alternative option is to perform a MEOGRTS (OECD TG 240).

This OECD CF level 5 test includes fecundity and so would address that endpoint, but uses considerably more fish than the FSDT. In this case as mentioned above, Medaka is not the preferred species for investigating endocrine disruption. Therefore a MEOGRTS is clearly not the least onerous option in terms of vertebrate animals if the FSDT can also investigate whether endocrine disruption effects can occur.

The request for the FSDT is suitable and necessary to obtain information that will clarify whether there is a potential risk from endocrine disruption. More explicitly, of the available alternatives it is the least onerous way to obtain the necessary information. The possible alternative of a MEOGRTS provides a more comprehensive test but requires more animals. ECHA notes that there is no experimental study available at this stage that will generate the necessary information and avoid the need to test vertebrate animals.

Registrant's comments on the original Decision request and the Proposals for Amendment

In your comments you provide several reasons why you disagree that there is sufficient evidence to justify further vertebrate testing to address the environmental endocrine disruption concern.

You comment that the X Liu et al. series of studies do not follow a standard test guideline or GLP. ECHA agrees, although it is noted that X Liu et al. (2013) has a number of similarities to OECD TG 229. All data sources need to be reviewed and weighted appropriately to evaluate whether further data are needed to address a concern. In your report *Evaluation on potential endocrine disrupting properties of triphenyl phosphate*, you consider that X Liu et al. (2013) and X Liu et al. (2016) "may be attributed to OECD CF level 3" [of the revised OECD 150 guidance document, OECD 2018]. This suggests that you also acknowledge that the data need to be evaluated when assessing the need or not for further data regarding endocrine disruption.

You comment that effects occur in the X Liu et al. series of studies at a concentration where TPhP causes acute toxicity in fish. ECHA's main concerns with accepting this argument using the present information are firstly the absence of any reported acute toxic effects in these studies; and secondly that the actual exposure concentrations in these studies (based on the very limited analytical data described above) appear to be much lower than the nominal values, and therefore below the acute effect level.

You note the contradictory (endocrine) mode of action proposed by X Liu et al. (2013) and by Japanese Ministry of Environment (2012). This is already discussed in the Decision. It must be remembered that there is a possibility that there is an endocrine mode of action – i.e. confirming either the screening findings of X Liu et al. or the findings of Japanese Ministry of Environment (2012). While ECHA considers that another non-ED mode of action may be possible, the difficulty is being able to reach clear conclusions without performing a test that evaluates ED effects in the same test. Although originally a FELS test was proposed, based on Proposals for Amendment (PfA), an FSDT is now required.

For the Japanese Ministry of Environment (2012) study, you note the absence of several details to be able to validate the test. These were received by the eMSCA after the original draft decision was sent. Key points have now been added to the Decision as well. ECHA acknowledges that a full test report is not available (either to you or to ECHA), but considers that this is a relevant and credible test, since it has been accepted by the Japanese regulatory authorities and has triggered additional investigations by them.

You mention considering the inconsistency in the gene expression results in the X Liu et al. (2016) study. ECHA acknowledges that there is variability across the concentrations for this aspect of the study. These details were not included in the Decision as currently there is no guidance about how these measurements should be made or interpreted (for example the level of change required to be biologically significant). For this study there are more unequivocal measurements such as hormone concentration changes, which are preferred for the Decision. You also commented that the concentration-response for estrogen level changes was inconsistent in the test. The variability was already recognised in the concluding remarks, but misrepresented earlier in the Decision, and this has now been amended.

Several PfAs were made to change the FELS test to an FSDT (OECD TG 234). The reasoning provided included the ability to measure effects resulting from endocrine disruption such as changes in vitellogenin concentrations and sex ratio, the ease in having both endocrine and non-endocrine mediated effects measured in the same study, which may help in interpreting the results, and in one case that the concentration at which acute fish toxicity occurred was significantly different to the level at which endocrine effects occurred.

Some of the proposals also suggested including other parameters in the test such as kidney histopathology and the measurement of steroid hormone concentrations as well as retaining the additional points for the FELS test (liver histopathology and preference to observe cardiotoxicity). A number of PfAs proposed that the FSDT should include 5 test concentrations, with the reasoning that the concentration range would allow better coverage of both endocrine and non-endocrine mediated effects in the test. One PfA suggested that the study should specifically be performed using *Danio rerio*. This was because of the perception that the available TPhP data for this species was more limited in connecting systematic and reproductive effects.

ECHA agrees that based on the justification provided in the PfAs and discussion at MSC 62, the FSDT is the appropriate test in this case. Therefore the initially proposed FELS test has been replaced, and the Decision has been modified accordingly.

In your comments on the PfAs, you disagreed with the proposals to perform an FSDT. You reiterated your view that the available data does not sufficiently substantiate the ED concern, and therefore justify requesting an FSDT. You consider that the ED data is inconsistent and contradictory. Instead, you indicated that a FELS test should be performed first, which you consider would allow a comparison of acute toxicity with effects reported in the available data.

You state that if an FSDT is requested, the decision needs to provide justification for any modifications to the test that are required (for example increased number of test concentrations or histopathological examinations) and also guidance for how these are measured. You accept that the liver histopathology in the originally requested test was justified.

ECHA acknowledges that there are differences and variability in the ED database. The requested FSDT will provide high quality information to allow an assessment of any ED mode of action and related ED adverse effects in fish and may allow a comparison between effect concentrations where any ED mediated effects occur relative to where any non-ED mediated effects may occur.

Therefore an FSDT is now requested. ECHA has provided justification for the request of 5 concentrations. Remaining observations such as liver histopathology and heart effects, and steroid sex hormone measurements are only recommended based on the reasons reported in the section “Considerations on the test method and testing strategy”.

Conclusion

Therefore, based on the substance evaluation and in accordance with Article 46(1) of the REACH Regulation, ECHA concludes that you are required to carry out the following study using the substance subject to this decision:

Fish Sexual Development Test, test method OECD 234, using Zebrafish (*Danio rerio*) and 5 test concentrations.

References

Du Z, Wang G, Gao S & Wang Z. 2015. Aryl organophosphate flame retardants induced cardiotoxicity during Zebrafish embryogenesis: By disturbing expression of the transcriptional regulators. Aquatic Toxicology Vol. 161, pp25–32.

Du Z, Zhang Y, Wang G, Peng J, Wang Z & Gao S. 2016. TPhP exposure disturbs carbohydrate metabolism, lipid metabolism, and the DNA damage repair system in Zebrafish liver. Sci. Rep, Vol. 6, No.11, pp1771−1778.

Japanese Ministry of Environment, 2012, not published.

Liu X, Ji K & Choi K. 2012. Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in Zebrafish. Aquatic Toxicology Vol. 114– 115, pp173– 181.

Liu X, Ji K, Jo A, Moon H-B & Choi K. 2013. Effects of TDCPP or TPhP on gene transcriptions and hormones of HPG axis, and their consequences on reproduction in adult Zebrafish (*Danio rerio*). Aquatic Toxicology Vol. 134– 135, pp104– 111.

Liu X, Jung D, Jo A, Ji K, Moon H-B, & Choi K. 2016. Long-term exposure to triphenylphosphate alters hormone balance and HPG, HPI, and HPT gene expression in Zebrafish (*Danio rerio*). Environmental Toxicology and Chemistry, Vol. 35, No. 9, pp 2288–2296.

Mayer, F.L., Adams, W.J., Finley, M.T., Michael, P.R., Mehrle, P.M. and Saeger, V.W., 1981. Phosphate ester hydraulic fluids: An aquatic environmental assessment of Pydrauls 50E and 115E. Aquatic Toxicology and Hazard Assessment: 4th Conference, ASTM STP 737, American Society for Testing and Materials, 103-123.

McGee SP, Konstantinov A, Stapleton HM, & Volz DC. 2013. Aryl phosphate esters within a major PentaBDE replacement product induce cardiotoxicity in developing Zebrafish embryos: potential role of the aryl hydrocarbon receptor. Toxicol. Sci. Vol. 133, pp144–156.

OECD (2018), *Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption*, OECD Series on Testing and Assessment, No. 150, OECD Publishing, Paris, https://doi.org/10.1787/9789264304741-en.

Sitthichaikasem, S., 1978. Some toxicological effects of phosphate esters on rainbow trout and bluegill. Iowa State University, Dissertation.

Sun L, Tan H, Peng T, Wang S, Xu W, Qian H, Jin Y & Fu Z. 2016. Developmental Neurotoxicity Of Organophosphate Flame Retardants In Early Life Stages Of Japanese Medaka (Oryzias latipes) Environmental Toxicology and Chemistry, Vol. 35, No. 12, pp 2931–2940.

Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to potential endocrine disruption (including wide dispersive use, consumer use, high aggregated tonnage) and environmental risk assessment, Triphenyl phosphate CAS No 115-86-6 (EC No 204-112-2) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2017. The updated CoRAP was published on the ECHA website on 21 March 2017. The competent authority of the United Kingdom (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

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

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 19 March 2018.

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 your comments, which were sent within the commenting period, into account and they are reflected in the reasons (Appendix 1).

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 a unanimous agreement on the draft decision during its MSC-62 meeting and ECHA took the decision according to Article 52(2) and 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 requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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

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