ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 19 December 2018

Substance name: Dicyclohexyl phthalate
EC number: 201-545-9
CAS number: 84-61-7
Date of latest submission(s) considered: 19 February 2018
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)[1] of Dicyclohexyl phthalate (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:

- Fish sexual development test according to OECD test guideline 234 using either Japanese Medaka (*Oryzias latipes*) or Zebrafish (*Danio rerio*), as further specified in Appendix 1.

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 **26 June 2020**.

In addition to the robust study summary, you shall submit the full study report by the same deadline.

The deadline takes into account the time that you may need to agree on which of the registrant(s) will perform the required test (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 on behalf of all registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

[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.

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 Leena Ylä-Mononen, Director of Evaluation

[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.

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on Dicyclohexyl phthalate (DCHP) 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 non-mammalian species in the follow up process.

1. **Fish sexual development test (FSDT) (OECD TG 234)**using either Japanese Medaka (*Oryzias latipes*) or Zebrafish (*Danio rerio*).

The concern(s) identified

The concern is related to the potential for environmental endocrine disruption in non-mammalian (fish) species. The potential of the substance to have endocrine disrupting properties in fish needs to be clarified in order to determine whether it poses a risk to the environment.

Exposure from DCHP to the environment can be expected from all life cycle stages. DCHP is used in the formulation of plastisol (sealant compounds and textile printing), and as plasticizer in the formulation of PVC compounds and rubber. It is also used as a phlegmatiser and dispersion agent in the formulation of organic peroxides. DCHP has wide dispersive both professional and consumer uses and is a component of several products e.g. adhesives and sealants, coating products, fillers, putties, plasters, modelling clay, finger paints, non-metal-surface treatment products, inks and toners, polishes and waxes, polymers and textile treatment products and dyes. DCHP can also be found in products with material based on: plastic (e.g. food packaging and storage, toys, mobile phones) and fabrics, textiles and apparel (e.g. clothing, mattress, curtains or carpets, textile toys) (Annex XV report DCHP, 2016). According to the estimations in the Chemical Safety Report the total yearly releases to the environment from all life cycle stages is approximately 1200 tpa. Little environmental monitoring data are available, but DCHP has been detected in e.g. household dust (Gevao et al., 2012; Guo and Kannan, 2011; Rakkestad et al., 2007), indoor air (Otake et al., 2004), municipal sewage treatment effluent (Nakada et al., 2004; Berset JD, Etter-Holzer R, 2001), and soil (Liu et al., 2010).

Why new information is needed

DCHP has been shown to adversely affect the endocrine system of mammals primarily through in vivo findings on reduced fetal testosterone production. These findings are further substantiated by mechanistic findings of inhibitory effects on enzymes in the steroidogenic biosynthesis pathway. The spectrum of effects observed in rats include increased areola mammae retention, decreased anogenital distance, prolonged preputial separation, genital malformations associated with small testis, signs of reduced sperm quality, atrophic tubules in prostate, prostatic intraepithelial neoplasia and testicular changes including tubular atrophy. DCHP has therefore been identified as a substance having endocrine disrupting properties whose effects to human health give rise to an

equivalent level of concern according to Article 57(f) of REACH (European Commission, 2018).

The endocrine effects of DCHP in rodents are similar to those observed for other phthalates identified as SVHC substances due to their endocrine mediated effects in mammals such as e.g. Bis(2-ethylhexyl) phthalate (DEHP), Dibutyl phthalate (DPB) and Benzyl butyl phathalate (BBP) for which the adverse effects also are considered to be primarily related to effects on steroidogenesis (MSC opinion DEHP, 2014; MSC opinion DBP, 2014; MSC opinion BBP, 2014).

DEHP has also been identified as an SVHC due to its endocrine disrupting properties for the environment. DEHP acts as a weak estrogen and/or anti-androgen changing the sex ratio of fish, inducing ovo-testis, decreasing reproductive output in combination with vitellogenin induction as well as decreasing male reproductive output (MSC Support Document DEHP, 2014). Also for DBP several in vivo fish studies report estrogen or anti-androgenic effects in fish such as decrease vitellogenin in female fish, skewed phenotypic sex ratio towards females and effects on steroidogenesis (Bhatia et al., 2013, Jarmołowicz et al., 2013, Tollefsen et al., 2002).

The similar endocrine mediated effects of e.g DEHP, DBP and DCHP in rodents raise a concern that DCHP may have also similar endocrine disrupting properties in fish as DEHP. A study by Urushitani et al. (2003) on estrogen receptor (ER) binding using a ERα clone derived from mummichog (*Fundulus heteroclitus*) where DCHP and DEHP both showed weak, but similar, receptor binding affinities, gives some support to such an assumption. Furthermore, as highlighted below, the information available on endocrine disrupting (ED) relevant effects of DCHP in fish, although limited, points in the same direction.

Only two studies on DCHP have been identified in which endocrine relevant parameters were investigated, both of which were conducted by the Japanese Ministry of the Environment (MoE)(2002) and have been briefly summarised in Dang et al. (2011):

I. A 21-day fish screening assay on Japanese Medaka (*Oryzias latipes*) similar to the OECD 230 21-day fish assay (OECD conceptual framework level 3) did not indicate endocrine effects as no vitellogenin induction in male fish was identified. The test was performed with solvent control, control and five exposure groups of 17.9, 38.2, 87.2, 188 and 388 µg/L (average measured concentrations).

II. A fish partial Life-Cycle Test with similarities to the OECD 234 FSDT test (OECD conceptual framework level 4) using Japanese Medaka. The test substance used was DCHP with a purity of 99.8% and DMSO was used as solvent. The test was conducted with 60 fish (four replicates with 15 fish) in each exposure group consisting of control, solvent control, 0.429, 1.41, 4.39, 13.3 and 35.8 µg DCHP/L (average measured concentrations).

    No statistically significant effects were recorded on hatchability, time to hatching, mortality and hepatosomatic index. The sex ratio was significantly skewed towards more males at the test concentration of 1.41 µg/L, but not at any other test concentration. A statistically significant increase in vitellogenin in the liver of male fish was observed at the test concentration of 4.39 µg/L, but not at any other exposure concentration. The lack of dose response for these effects makes them difficult to interpret. More importantly, a statistically significant increase in the gonadosomatic index was observed for males in the highest exposure group

(35.8 µg/L). In addition, one of ten fish in the highest exposure group (35.8 µg/L) developed testis-ova, an intersex condition characterized by both testicular and ovarian tissue in the gonad. The medaka is completely dioecious in nature and emergence of testicular eggs in medaka is only known to be caused by exposure to estrogen agonist or anti-androgenic substances. The finding of testis-ova in one fish is however, not considered sufficiently robust to make a firm conclusion. Based on a proposal for amendment (PfA), it is further noted that the study was performed far below the water solubility of DCHP (ca. 1 mg/l). Given that no effects were seen in an acute toxicity study with Japanese medaka up to the highest concentration of 2 mg/l, higher test concentrations could have been used in this study and it cannot be excluded that more pronounced effects would be observed at higher concentrations.

To conclude: the available data on rodents shows that DCHP is an endocrine disruptor in rodents. DCHP acts via the same mode of action as other phthalates identified as endocrine disruptors, e.g. DEHP. DEHP is identified as an endocrine disruptor also for the environment (fish) with an estrogenic/antiadrogenic mode of action. It is considered plausible that DCHP could act in the same way. A receptor binding study with ERα clone derived from mummichog (*Fundulus heteroclitus)* where DEHP and DCHP had similar receptor binding affinities supports such an assumption. In a partial Life Cycle study with DCHP on Japanese medaka endocrine mediated effects such as induction of vitellogenin, increased gonadosomatic index and testis-ova were seen further indicating that DCHP may have an estrogenic/antiandrogenic mode of action. However, statistically significant vitellogenin induction was observed only at one test concentration. Some of the effects (changed gonadosomatic index and testis-ova) were observed only at the highest tested concentration (35.8 µg/l). This study indicates endocrine disrupting effects, but it cannot be used to draw firm conclusion on endocrine disrupting properties for fish because the tested concentrations were too low. Further studies are therefore needed to judge whether or not DCHP is an endocrine disruptor also in fish.

What is the possible regulatory outcome

DCHP has been identified as a substance having endocrine disrupting properties whose effects to human health give rise to an equivalent level of concern according to Article 57(f) of REACH (European Commission, 2018).

In addition and in reply to a Proposal for Amendment (PfA) from a MSCA, it is further clarified that DCHP has a harmonised classification for reproductive toxicity category 1B and has been included in the candidate list also for this reason. As a consequence of the harmonised classification DCHP cannot be placed on the market, or used, as a substance, as a constituent of other substances, or, in mixtures at a concentration ≥0.3%, for supply to the general public (Annex XVII, entry 30 to REACH). However, according to the exposure estimations performed by you, only a minor part (<5%) of the environmental emissions result from consumer use of chemical products containing DCHP. The major sources of emissions to the environment appear to be manufacturing and industrial use of plastisol, manufacturing and industrial use of PVC, rubber and plastic articles, and professional use of organic peroxide. The consequences of the current classification for reproductive toxicity on the emissions to the environment are therefore expected to be limited.

If the required information confirms that DCHP is an endocrine disruptor for fish, this will trigger consideration to also identify it as a substance having endocrine disrupting properties whose effects to the environment give rise to an equivalent level of concern

according to Article 57(f) of REACH. If DCHP is included in Annex XIV of REACH this means that in addition to an assessment of the risk for human health, an assessment of risk for the environment would be added to the scope for authorisation, according to Article 62(4)(d) of REACH. Furthermore, if the substance would be identified as having endocrine disrupting properties for environment, the exemptions specified in Article 56(5) of REACH would not apply.

Considerations on the test method and testing strategy

The test shall be conducted according to OECD TG 234 (Fish Sexual Development Test). Potential endocrine-mediated (anti-) oestrogenic or androgenic effects shall be investigated by vitellogenin measurements and sex ratio determination, according to the recommendations in the test guideline. Sex determination shall be based on gonadal histopathology (according to OECD Guidance document No. 123). Staging of the gonads shall be examined because it enables detection of e.g. testis-ova which was the strongest indication from the available study on ED-effects in fish. If Japanese Medaka (*Oryzias latipes*) is chosen as test species, genetic sex determination shall be performed, as well as reporting of any change of the secondary sex characteristics as proposed in a PfA.

The study shall be conducted up to the limit of solubility of the substance in the test medium. A minimum of three test concentrations together with controls shall be used, as proposed in a PfA and prescribed in the test guideline. However, to increase the robustness of the study, the use of five test concentrations is recommended. Close attention should be paid to the analysis and reporting of actual measured concentrations of the substance. You shall also submit the full study report for the information requirement. Considering the complexity of the case, a complete rationale and access to all information available in the full study report (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) are needed. This will allow the evaluating MSCA to fully assess the provided information, including the statistical analysis, and to clarify the concern for endocrine disrupting properties. Depending on the results of this test, further testing according to Level 5 in the OECD Conceptual Framework may be required (e.g. a Medaka Extended One Generation Reproduction Test (OECD TG 240) or Full Fish Life-Cycle Test (USEPA OPPTS 850.1500)).

Consideration of alternative approaches

As indicated in one PfA, one approach would be to undertake testing first using a Level 3 test in the OECD conceptual framework (OECD, 2012), 21-day Fish Screening Assay (OECD TG 230) or a Fish Short Term Reproduction Assay (OECD TG 229). However, if positive results related to endocrine disruption were seen in these alternative tests then the Fish Sexual Development Test would still be required and this would not be in the interests of animal welfare. A further Level 3 test would not investigate the range of mechanistic and apical endpoints of a Level 4 test, nor show how these are linked. Therefore, further testing at this Level is not justified, as the concern would remain.

A Medaka Extended One Generation Reproduction Test (OECD TG 240) or a Full Fish Life-Cycle Test (USEPA OPPTS 850.1500) have been considered as alternatives to the requested FSDT-study. These studies, level 5 in the OECD conceptual framework (OECD, 2012), have the advantage of also including endpoints related to reproduction. Therefore, they may provide more conclusive information than a FSDT-test. These test methods are however, more time consuming, require more animals and are more

expensive.

Therefore, ECHA considers that a FSDT-test is at this stage the least onerous way to obtain information necessary for the clarification of the concern. After obtaining the requested information the evaluating MSCA will consider in the follow-up evaluation whether further testing (e.g. testing according to Level 5 in the OECD Conceptual Framework) would be needed.

Consideration of your comments on the PfAs

In your comments on the PfAs from the MSCAs and ECHA you express that you agree with the PfA proposing to withdraw the request for a Fish sexual development test on the basis that DCHP has a harmonised classification as reprotoxic category 1B, and is included in the Candidate List as an SVHC for this reason and due to concerns about human endocrine disruption. You argue that the environmental exposure would be already reduced because of the restriction of uses deriving from the inclusion of the substance in the Candidate List. Requesting a FSDT would therefore in your view not be justified. However, as you acknowledge the concerns on the potential ED effects on the environment, you instead propose to build an expert judgment report, based on similar substances, instead of running the FSDT.

It should be noted that the listing of the substance on the Candidate list as an SVHC does not automatically lead to banning of the uses of the substance. Furthermore, as also explained under "What is the possible regulatory outcome" above, the existing restriction of the substance in consumer products due to its classification as Reprotoxic. 1B does not eliminate environmental exposure. In addition, the information on similar phthalates confirmed the ED concern for the registered substance, but were not considered sufficient to confirm that DCHP itself would elicit the same effects in fish. Therefore, the requested experimental information on DCHP is considered necessary to verify the ED effects.

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 registered substance subject to this decision:

A Fish Sexual Development Test conducted on the registered substance according to OECD test guideline 234 using either Japanese Medaka (*Oryzias latipes*) or Zebrafish (*Danio rerio*), as specified above.

References

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Opinion of the Member State Committee on the identification of benzyl butyl phthalate (BBP) as a substance of very high concern according to Articles 57 and 59 of Regulation (EC) 1907/2006, MSC, 11 December 2014

Opinion of the Member State Committee on the identification of bis(2-ethylhexyl)phthalate (DEHP) as a substance of very high concern according to Articles 57 and 59 of Regulation (EC) 1907/2006, MSC, 11 December 2014

Opinion of the Member State Committee on the identification of dibutyl phthalate (DBP) as a substance of very high concern according to Articles 57 and 59 of Regulation (EC) 1907/2006, MSC, 11 December 2014

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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 endocrine disrupting properties for the environment Dicyclohexyl phthalate CAS No 84-61-7 (EC No 201-545-9) 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 Sweden (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 above mentioned 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 21 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 did not receive any comments from you by the end of the commenting period.

Proposals for amendment by other MSCAs and ECHA and referral to 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 proposals for amendment to the draft decision regarding the fish sexual development test. They are reflected in the Reasons (Appendix 1).

ECHA referred the draft decision to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s). Any comments on the proposal(s) for amendment were taken into account by the Member State Committee and are reflected in the Reasons (Appendix 1).

MSC agreement seeking stage

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-62 written procedure and ECHA took the decision according to 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 requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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

   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.