Committee for Risk Assessment (RAC)

Request by the Executive Director of ECHA under Art. 77(3)(c) of REACH

Opinion on the feasibility of finding thresholds of effect for human health and the environment with bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP) in the context of applications for authorisation and review reports

ECHA/RAC/ A77-O-0000007035-80-01/F

RAC's opinion (adopted 26 November 2021)

26 November 2021
ECHA/RAC/ A77-O-0000007035-80-01/F

OPINION

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), the Committee for Risk Assessment (RAC) has adopted its opinion on the request to examine the feasibility of finding a threshold in the context of applications for authorisation and review reports in the cases of bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP).

I. PROCESS FOR ADOPTION OF THE OPINION

On 11 November 2021[1], the Executive Director of ECHA requested RAC and SEAC to review by 31 December 2021 to examine the feasibility of finding a threshold in the context of applications for authorisation and review reports in the cases of bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP).

Rapporteur, appointed by RAC: **Betty Hakkert**

In accordance with the mandate from the Executive Director of ECHA, the rapporteur developed the opinion, summarising the justifications for the feasibility of finding a threshold in the context of applications for authorisation and review reports in the cases of bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP).

The RAC opinion was adopted **by consensus** on **26 November 2021**.

[1] https://echa.europa.eu/documents/10162/17090/RAC_mandate_Art77_DEHP_DBP-DNEL_PNEC.pdf/7bfb1496-83dc-a3f1-a9ce-572e90b570fd?t=1637244009301

II. OPINION OF RAC

1. HUMAN HEALTH (DEHP and DBP)

1.1. Are the RAC (2013)[2] reference DNELs, sufficiently protective as they are, i.e. have the effects related to endocrine mode(s) of action already been sufficiently addressed?

RAC cannot provide a firm conclusion whether the current DNELs are protective enough. However, RAC has previously stated that the DNELs for reproductive toxicity may not be sufficiently protective for other effects of the phthalates (e.g. on the immune system, the metabolic system and neurological development) that possibly are more sensitive (RAC 2017).

1.2. If not, could these RAC (2013) reference DNELs be used to derive safer levels by the use of, e.g., appropriate assessment factors to cover remaining uncertainty?

To be able to assess whether DNELs for effects related to endocrine mode(s) of action (ED MoA) can be derived and, if so, which appropriate assessment factors may cover remaining uncertainty RAC would need at least an up-to-date literature review and an in-depth assessment of effects related to the endocrine modes of action. Such an assessment is not available to RAC and therefore the Committee is not able to state whether the RAC (2013) reference DNELs may be used to derive safer levels by the use of, e.g., appropriate assessment factors to cover remaining uncertainty.

1.3. If the current DNELs are seen as insufficiently protective and cannot be readily adjusted, then what data would be needed to derive appropriate DNELs to cover the endocrine disruptive properties of the two substances?

and

1.4. With the current state of knowledge, is a non-threshold approach the best option for RAC to evaluate the applications and review reports?

Based on the information available to RAC it is not possible to say whether the current DNELs based on reproductive effects are sufficiently protective to cover endocrine disruptive properties of the two substances.

RAC is not able to say which data would be needed to derive DNELs for endocrine disruptive properties. This would require an extensive new literature review and an in-depth assessment of the strength of the evidence for all relevant effects, their human relevance, and the possible endocrine mode(s) of action. Such an assessment is not available to RAC. Due to the uncertainty listed above and also noted in a report of 2016 by the European Commission[3] related endocrine disrupting properties in general, RAC proposes that an applicant may choose to assume that DEHP and DBP are non-threshold substances for the purposes of an application for authorisation for pragmatic reasons.

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[2] DEHP: https://echa.europa.eu/documents/10162/1564405/rac_24_dnel_dehp_comments_en.pdf/e0506f6b-35f7-433e-99da-35464a26e2df?t=1441812802854
DBP: https://echa.europa.eu/documents/10162/1564405/rac_24_dnel_dbp_comments_en.pdf/44ab77fd-d6fa-4d73-b0ed-9317fd6c0422?t=1441812804827

[3] https://ec.europa.eu/transparency/regdoc/rep/1/2016/EN/COM-2016-814-F1-EN-MAIN-PART-1.PDF

Nevertheless, should an applicant choose to derive DNELs for the endocrine disrupting properties for human health for DEHP or DBP, RAC will evaluate these on a case-by-case basis. In such a case, an applicant or authorisation holder should review all relevant data, all relevant effects, and all endocrine mode of actions relevant the human health that are known or reasonably foreseeable.

2. ENVIRONMENT (DEHP)

2.1. Are the data provided in ECHA (2014) sufficient to derive PNECs for water, sediment and soil?

RAC is of the opinion that on the basis of the EU RAR (2008), supplemented by MSC (2014)[4], no thresholds can be identified relevant for either the aquatic (represented in this case by mainly fish and Daphnia) or the terrestrial environment (little or no information). Furthermore, extrapolation from rodent data, even if robust to such complex environmental compartments is not considered realistic.

2.2. If not, are the data indicative of a possibility to find a threshold? What kind of data would be needed for that?
With the current state of knowledge, is a non-threshold approach the best option for RAC to evaluate the applications and review reports?

Applicants for authorisation of DEHP are advised by RAC to take a non-threshold approach in their review reports where the environmental properties of DEHP are concerned. This could involve a detailed description of the operational conditions and risk management measures in place to minimise releases.

RAC noted that further studies on the endocrine disrupting properties of DEHP may well have been carried out since MSC concluded its work in 2014 (ECHA, 2014). Bearing in mind remarks on the likelihood of representative thresholds being found which are protective of relevant environmental compartments and diverse flora and fauna, even a new and thorough review of more recent studies might not solve the threshold problem.

[4] MSC Support Document:
https://echa.europa.eu/documents/10162/fa429d23-21e7-4764-b223-6c8c98f8a01c

III. OPINION JUSTIFICATION

The substances bis(2-ethylhexyl) phthalate (DEHP), benzyl butyl phthalate (BBP), dibutyl phthalate (DBP) and diisobutyl phthalate (DIBP) are listed in entries 4 to 7 of Annex XIV to Regulation (EC) No 1907/2006 due to their reprotoxic properties. DEHP has been identified as having endocrine disruptive properties to the environment in 2014[5]. In 2017, all four substances have further been identified as having endocrine disrupting properties to human health[6].

The Commission proposal to amend Annex XIV to REACH Regulation to include the above mentioned endocrine disrupting properties has been adopted on 23 November 2021[7]. This update results, on one hand, in authorisation requirements becoming applicable to some uses that have so far not been subject to it. On the other hand, there are several existing authorisations on DEHP and DBP and the Commission may need to determine whether there is a need to launch a review due to the new endocrine disruptive properties, pursuant to Article 61(2) of REACH. In light of the above, the Commission submitted a request[8] to the Committee for Risk Assessment (RAC) to draw up an opinion on the following issues:

> *"1. For* endocrine disruptive *properties for human health of DEHP, BBP, DIBP and DBP: whether a DNEL or reference dose-response curve can be derived. In the affirmative, please also derive this new reference DNEL or dose-response curve.*
>
> *2. For* endocrine disruptive *properties for the environment of DEHP: whether a reference PNEC or a concentration-ecosystem effect curve could be derived for those properties. In the affirmative, please also derive this reference PNEC or reference concentration-ecosystem effect curve".*

ECHA has derived thresholds and dose-response functions for substances on Annex XIV of REACH, only where it was expecting Applications for Authorisation to be submitted to ECHA for the continuing use of SVHC. No authorisation applications or review reports have been received by ECHA for BBP and DIBP to date, nor are any expected. Thus, BBP and DIBP have been excluded from the analysis below.

The opinion of RAC on the substances DEHP and DBP considers the context of the discussion threshold vs non-threshold for endocrine disrupting substances in the authorisation process under REACH in a report of 2016 by the European Commission[9]. The scientific background to the discussion on thresholds and the related uncertainties was summarised in the report. The paper

[5] On 11 December 2014 the MSC reached a unanimous agreement on the identification of DEHP as having endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which give rise to an equivalent level of concern according to Article 57(f) of Regulation (EC) No 1907/2006. Accordingly ECHA amended the DEHP entry in the candidate list on 17 December 2014. Available at: http://echa.europa.eu/role-of-the-member-state-committee-in-the-authorisation-process/svhc-opinions-of-the-member-state-committee

[6] Commission Implementing Decision (EU) 2017/1210 of 4 July 2017 on the identification of bis(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), benzyl butyl phthalate (BBP) and diisobutyl phthalate (DIBP) as substances of very high concern according to Article 57(f) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council

[7] https://eur-lex.europa.eu/search.html?scope=EURLEX&text=Regulation+EU+2021%2F2045&lang=en&type=quick&qid=1637742710104

[8] "Request to ECHA's Executive Director to request RAC to deliver, in accordance with Art. 77(3)(c) of REACH, an opinion on reference DNEL/PNEC values or dose-response curves considering updated properties of DEHP, BBP, DIBP and DBP", ARES(2021)4821562 – 27/07/21

[9] https://ec.europa.eu/transparency/regdoc/rep/1/2016/EN/COM-2016-814-F1-EN-MAIN-PART-1.PDF

concludes that the existence, or not, of a threshold for an endocrine disrupting substance will need to be justified on a case-by-case basis and that this is the responsibility of the applicant.

1. HUMAN HEALTH (DEHP and DBP)

1.1. Are the RAC (2013)[10] reference DNELs, sufficiently protective as they are, i.e. have the effects related to endocrine mode(s) of action already been sufficiently addressed?

Reference DNELs for DEHP and DBP were derived in 2013 for reproductive toxicity and thus pre-date RAC's opinion of 2017[11] on the restriction proposal from ECHA and Denmark on these phthalates as well as the opinion of EFSA on several phthalates (EFSA 2019)[12].
RAC (2017) stated in the opinion on the restriction proposal on phthalates that the Commission is considering to identify the four phthalates as substances of equivalent concern (SVHC) under Article 57(f) of REACH and that this raises additional uncertainties regarding the appropriateness of the derived DNELs. RAC (2017) further noted that the DNELs based on reproductive effects may not be sufficiently protective for other effects of the phthalates (e.g. on the immune system, the metabolic system and neurological development) that possibly are more sensitive. Yet, RAC (2017) acknowledged that these other effects cannot be dealt with in a quantitative way in risk assessment, due to the lack of robust dose response data. In view of that, RAC (2017) saw the approach[13] taken by the above Dossier Submitter as a pragmatic way forward, since risks were already identified for the traditional, apical endpoints (i.e., the proposed DNELs were already sufficient to justify the restriction proposal).[14]
EFSA (2019) derived a TDI for the phthalates DBP, BBP, DEHP, DINP and DIDP (individually and collectively). This TDI was a temporary TDI due to the observed uncertainties[15]. One of the main uncertainties identified was the lack of a sufficient evaluation of toxicity endpoints other than reproduction, i.e. neurodevelopment, immune and/or metabolic system, that could be more sensitive[16]. EFSA (2019) considered that this could lead to an underestimation of the risk based

[10] DEHP: https://echa.europa.eu/documents/10162/1564405/rac_24_dnel_dehp_comments_en.pdf/e0506f6b-35f7-433e-99da-35464a26e2df?t=1441812802854
DBP: https://echa.europa.eu/documents/10162/1564405/rac_24_dnel_dbp_comments_en.pdf/44ab77fd-d6fa-4d73-b0ed-9317fd6c0422?t=1441812804827
[11] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e1806e7a36
[12] https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2019.5838
[13] The approach includes addressing the uncertainties related to the DNELs, the impact of the endocrine disrupter status and the potential for effects on other, possibly more sensitive endpoints in the uncertainty analysis and, as far as possible, in the socio-economic analysis (SEA).
[14] RAC (2017) furthermore stated: *"According to current policy, substances having endocrine disrupting properties do not have a threshold, except when it can be demonstrated that a threshold exists. The existence of a threshold has not yet been assessed and documented for the four phthalates under consideration. Although there would be consequences for the PoDs and DNELs if there is no threshold, RAC is of the opinion that in this specific case the proposed PoDs and DNELs, which are based on traditional, apical endpoints, are already sufficient to substantiate the restriction. Therefore, an assessment to determine whether or not a threshold exists appears not to be necessary for the current restriction proposal. RAC proposes to take the possible consequences for the PoDs and DNELs into account in the uncertainty analysis. Further, the SEA should, where possible, address the endocrine-related effects."*
[15] Regarding uncertainties EFSA (2019) stated: "A qualitative approach was chosen for the uncertainty analysis. In addition to several other sources of uncertainty, for the hazard identification and characterisation, the main impacts on risk assessment were attributed to the following issues: - Due to the limited time for the completion of the evaluation and the large amount of new evidence available since the EFSA AFC Panel's assessments of DBP, BBP, DEHP, DINP and DIDP in 2005, the CEP Panel considered it unfeasible to perform a comprehensive review of all the new data on these phthalates. In agreement with ECHA's assessment of 2017, the Panel concluded that effects not sufficiently investigated in this opinion, in particular potential effects on neurodevelopment, the immune and/or the metabolic systems for DBP, BBP and DEHP, could be more sensitive endpoints compared to their reproductive toxicity. The possibility of endpoints more sensitive than liver toxicity may also be true for DINP and DIDP.[…]. "
[16] Furthermore, it is stated: "The Panel highlights that other possible effects (as pointed out by the 2017 ECHA RAC assessment) e.g. on the immune and metabolic systems and/or on neurodevelopment, have not been sufficiently investigated and this is taken into account in the uncertainty analysis and in the recommendations of this opinion.".

on the currently proposed group approach focusing on the reproductive effects. RAC notes that EFSA (2019) did not discuss the potential relationships between these effects and endocrine disruption.
RAC cannot therefore provide a firm conclusion whether the current DNELs are protective enough. However, RAC has previously stated that the DNELs for reproductive toxicity may not be sufficiently protective for other effects of the phthalates (e.g. on the immune system, the metabolic system and neurological development) that possibly are more sensitive (RAC 2017).

1.2. If not, could these RAC (2013) reference DNELs be used to derive safer levels by the use of, e.g., appropriate assessment factors to cover remaining uncertainty?

Endocrine disruptors may exert effects through multiple modes of action, and equally, a single mode of action may lead to multiple adverse effects that do not necessarily all belong to a single endpoint such as reproductive toxicity. The scope of an assessment of endocrine disrupting properties for human health in applications for authorisation is not necessarily limited to the evidence that formed the basis for the identification as SVHC for endocrine disruptive properties.[17]

The mode of action of DEHP and DBP was identified to be anti-androgenic in the MSC Support Document for the identification as SVHC for endocrine disrupting properties for human health and the environment[18], more specifically through reduced foetal testosterone. However, there are reports of effects on the immune system, changes in germ cell differentiation (multinucleated germ cells), effects on metabolism, neurodevelopmental effects, delayed puberty onset, and effects on female reproduction (RAC 2017 and EFSA 2019).
To be able to assess whether DNELs for effects related to endocrine mode(s) of action can be derived and, if so, which appropriate assessment factors may cover remaining uncertainty RAC would need at least the following:

- an up-to-date literature review
- followed by an in-depth assessment of
    - the strength of the evidence for all effects of these substances potentially related to endocrine disruptive properties, as well as their human relevance
    - the possible endocrine mode(s) of action
    - a gap analysis of the information needed
    - selection of an appropriate point of departure for DNEL setting
    - careful characterisation of the underlying uncertainties
    - an evaluation of the appropriateness of the use of an assessment factor for endocrine disruptive properties
    - if applicable, justification of the size of a possible assessment factor to cover remaining uncertainty.

Such an assessment is not available to RAC and therefore RAC is not able to say whether the RAC (2013) reference DNELs may be used to derive safer levels by the use of, e.g., appropriate assessment factors to cover remaining uncertainty.

[17] Other evidence may have been available to the submitting Member State but may not have been considered necessary to include in order to demonstrate the endocrine disrupting properties of the substance. Alternatively, over the course of time, new information may become available in support of other endocrine modes of action that lead to adverse effects. Thus, it can be argued that all evidence relevant to endocrine disrupting properties would need to be assessed when attempting to derive threshold values or dose-response relationships for endocrine disrupting substances
[18] https://echa.europa.eu/documents/10162/3f5d91bc-0a63-04f8-8f62-ccc9c8265e7d

1.3. If the current DNELs are seen as insufficiently protective and cannot be readily adjusted, then what data would be needed to derive appropriate DNELs to cover the endocrine disruptive properties of the two substances?

and

1.4. With the current state of knowledge, is a non-threshold approach the best option for RAC to evaluate the applications and review reports?

The documents available to RAC (MSC Support Document 2014, restriction proposal on phthalates, EFSA (2019), registration dossiers on DEHP and DBP[19]) do not provide the necessary basis to conclude whether the available toxicity data for DEHP and DBP will be sufficient to demonstrate a threshold for the endocrine disrupting properties for human health or which data would need to be generated to reduce uncertainties. This would require an extensive new literature review and an in-depth assessment of the strength of the evidence for all relevant effects, their human relevance, and the possible endocrine mode(s) of action.

As noted before, such an assessment is not available to RAC and therefore RAC is not able to conclude whether the RAC (2013) reference DNELs may be used to derive safer levels. Due to the uncertainty listed above and also noted in a report of 2016 by the European Commission[20] related endocrine disrupting properties in general, RAC proposes that an applicant may choose to assume that DEHP and DBP are non-threshold substances for the purposes of an application for authorisation for pragmatic reasons.

Nevertheless, should an applicant choose to derive DNELs for the endocrine disrupting properties for human health for DEHP or DBP, RAC will evaluate these on a case-by-case basis. In such a case, an applicant or authorisation holder should review all relevant data, all relevant effects, and all endocrine mode of actions relevant the human health that are known or reasonably foreseeable.

2. ENVIRONMENT (DEHP only)

2.1. Introduction

The main reviews available are the EU RAR (2008) and the MSC Support Document for identification of DEHP as SVHC (ECHA 2014)[21] which provide some details on the endocrine disruptive properties of DEHP for the environment. The latter report reviewed the literature from 2008 to 2013/14. The Registration dossier[22] for DEHP relies heavily on the EU RAR (2008), e.g. the most recent long-term fish study reported is from 2010.

[9] The Registration dossier https://ec.europa.eu/transparency/regdoc/rep/1/2016/EN/COM-2016-814-F1-EN-MAIN-PART-1.PDF

[21] MSC Support Document: https://echa.europa.eu/documents/10162/fa429d23-21e7-4764-b223-6c8c98f8a01c Candidate List of substances of very high concern for Authorisation – DEHP, all MSC documents: https://echa.europa.eu/candidate-list-table/-/dislist/details/0b0236e1807d8dc8

[22] The registrant states that "*In summary, there is no reliable long-term study indicating adverse effects at or below the "apparent" water solubility of DEHP or when administrated via food. Therefore, it is not considered suitable to specify a chronic NOEC for fish exposed via water or food.*"

The conclusion of ECHA (2014) on identifying DEHP as an endocrine disruptor was based on a combination of studies, predominately with rodents and other mammals and to a lesser extent, aquatic organisms. This is in conformity with the agreement of the European Commission's Endocrine Disrupters Expert Advisory group that "*In relation to ecotoxicology, data on all species, including mammalian data generated to assess human toxicity, are generally considered relevant for the assessment of effects on ecosystems*". However, this approach of combining all relevant data, while well justified for the purpose of SVHC identification, does not make the identification of appropriate and representative effect thresholds any simpler; this is particularly true for the aquatic and terrestrial environments.

2.2. Wildlife

According to ECHA (2014), DEHP has been shown to adversely affect the endocrine system of mammals primarily through *in vivo* findings on reduced foetal testosterone. These findings are further substantiated by mechanistic data, also *in vivo*, of down-regulation of genes in the steroidogenic biosynthesis pathway. The spectrum of effects observed in male rats include increased incidence of nipple retention and genital malformations, decreased anogenital distance, reduced number of spermatocytes and testicular changes including multinucleated gonocytes, tubular atrophy and Leydig cell hyperplasia of which almost all are considered adverse (OECD 2008). In relation to the environment, adverse effects concerning development and reproduction are generally regarded as endpoints of particular relevance because such effects are likely to manifest themselves at the population level. The effects observed in rats are of particular concern for mammalian wildlife species with a natural low reproductive output (including endangered species) as negative effects on reproduction has an even higher potential for causing long term negative effect at the population level for such taxa. Even if a threshold could be identified for a key event in the mode of action pathway for such effects in rats, the representativeness (level of protection) afforded to wildlife is unknown.

2.3. Fish and amphibians

The EU RAR (2008) concluded that it was not possible to definitively conclude whether DEHP is an endocrine disrupter in fish (and amphibians) based on the studies reviewed. ECHA (2014) reviewed a further 8 long-term fish studies dating from 2010 to 2014, coming to a different conclusion.
Many of the fish studies considered by both of the above reviews suffer from dosing at concentrations well above the solubility limit of DEHP in water. Out of a very variable dataset on water solubility, the EU RAR (2008) selected a non-colloidal solubility of 3 µg/l and this is critical in assessing the quality and outcome of the relevant studies. ECHA (2014) concluded with regard to non-mammalian vertebrates that: "*adverse effects caused by DEHP have also been identified in non-mammalian wildlife where change of the sex ratio or induction of ovo-testes in male fish have been observed in some studies and in addition decrease of the reproductive output was observed in other fish studies……. Looking at the studies overall, they considered that it is biologically highly plausible that the adverse effects on the phenotypic sex and reproductive output in both male and female fish are induced by an estrogenic mode of action (Norrgren et al., 1999; Norman et al., 2007; Carnevali., et al 2010; Corradetti et al 2013)*".

The above four studies are summarised in Annex 1, Table 1. The first two studies were dosed via the food and/or by injection and are difficult to interpret in terms of any threshold. The latter two studies have quite a robust triplicate design using 30 fish per replicate and dosed DEHP in water using ethanol as a vehicle at concentrations of 0.02, 0.2, 2, 20 and 40 µg/L and 0.02 and

0.2µg/L respectively. They provide a LOEC for embryo production and spermatogenesis respectively of 0.02µg/L (nominal). However, the frequency of replacement of the semi-static media is not reported and no analytical confirmation of the dose levels was carried out. Considerable effects are seen at even this lowest nominal concentration in both studies and as a result no dose response is visible among the reproductive endpoints which could provide information on a threshold.

No further amphibian studies were identified by ECHA (2014).

2.4. Invertebrates

In the EU RAR (2008), 12 long term toxicity tests to invertebrates exposed via water (predominantly using *Daphnia magna*) were presented and it was concluded that no reproductive effects were seen below the level of systemic toxicity and that toxicity occurred at levels above DEHP water solubility. No further relevant long-term aquatic invertebrate studies were identified by ECHA (2014).

2.5. The example of NP and NPEO

RAC previously reviewed the endocrine disrupting properties of nonylphenol and its ethoxylates (NP, NPEO respectively) in the context of a restriction on imported textiles (RAC, 2015[23]). It revisited this opinion when considering Applications for Authorisation of the continued use of octyl and nonylphenol ethoxylates (OPEO and NPEO.

A comparison of both cases (DEHP and OP/NPEO) is warranted, as the types of studies and the level of detail in the respective databases is comparable. Having evaluated the available relevant fish and invertebrate studies for the aquatic and terrestrial compartments, RAC (2015) concluded the following for NP:

- *For traditional, apical endpoints, RAC concludes on a PNECaqua of 0.4 µg/L for NP. Based on all available NP-specific test data and information from several species of fish, amphibians, algae, crustaceans (daphnids, amphipods, copepods, mysids), insects, nematodes, mussels, snails, and echinoderms, this PNEC is considered to provide sufficient coverage of additional species diversity in the marine compartment.*
- *With a view to the endocrine disruptive properties of NP, RAC notes that it still appears difficult to precisely quantify the threshold for adverse endocrine disruptive effects of NP or to definitely exclude lower effect concentrations in taxonomic groups not yet covered by adequate testing protocols (the latter being a matter of principle that can apply to many other substances).*
- *Limited to fish, RAC efforts to further explore the evidence from available studies suggest that a PNEC lowered by about a factor of 5 (i.e. to 0.08 µg/L) might cover adverse endocrine disruptive effects. Even though there is currently no specific indication from any study with NP (presented in the dossier and during public consultation) that endocrine-mediated adverse effects occur at much lower concentrations than other apical effects in comparable test systems, RAC assesses the available evidence as insufficient to provide conclusive quantitative coverage of endocrine disruptive effects of NP for all taxonomic groups.*
- *In conclusion, RAC cannot offer any opinion about whether the proposed PNEC is*

[23] https://echa.europa.eu/documents/10162/4eba1b02-83b2-24e4-ee8d-9876c9239674

sufficiently protective of all relevant hazards posed by this substance.

- *As a pragmatic way forward for evaluating the present restriction proposal, RAC will use the 'traditional' PNECaqua of 0.4 µg/L to get an indication of the possible risks. If any risks are identified for traditional, apical endpoints of NP, then the risks addressing in addition the endocrine disruptive effects will in all likelihood be greater bearing in mind that the 'traditional' PNEC appears not to sufficiently cover the uncertainties identified (not only on the level of endocrine disruptive effects of NP, but also on the level of endocrine disruptive (and toxic) effects of NPEOs/NPECs (see next section) and on the combination effect of these substances with a similar mode of action).*

The question needs to be again posed (as did RAC 2015, see above) whether for endocrine disrupting chemicals, in particular industrial chemicals under REACH, we will ever have sufficient information to establish robust thresholds to protect key taxonomic groups of flora and fauna from endocrine disruption in relevant environmental compartments, recalling that there are many more groups of organisms that live exclusively in marine waters than in freshwater and that terrestrial diversity while patchy can be immense, e.g. for insects.

The case of NP illustrates this well. While relatively solid data on fish was available, sufficient to observe normal growth and a cessation of apical, mainly reproductive effects down to a LOAEL at 0.4µg/L, this was not the case for the invertebrates where test data was much less convincing, and it was even unclear what the most sensitive taxa might be – terrestrial data was largely absent.

Even if the NP dataset would have been sufficient to derive a PNEC for water, data for sediment and soil were very limited. An equilibrium partitioning method had been proposed by some applicants for authorisation of NPnEO, to be used to convert the $PNEC_{water}$ to $PNEC_{soil}$ and $PNEC_{sediment}$. RAC noted that use of such methods for endocrine disruptors has not been researched, evaluated or broadly discussed in the scientific community.

2.6. Conclusion

On the basis of the EU RAR (2008), supplemented by MSC (2014), no threshold can be identified relevant for either the aquatic (represented in this case by mainly fish and Daphnia) or the terrestrial environment (little or no information). Furthermore, extrapolation from rodent data, even if robust to such complex environmental compartments is not considered realistic.

Applicants for authorisation or authorisation holders of DEHP are advised to take a non-threshold approach in their applications or review reports where the environmental properties of DEHP are concerned. This could involve a detailed description of the operational conditions and risk management measures in place to minimise releases.

It is noted that further studies on the endocrine disrupting properties of DEHP may well have been carried out since MSC concluded its work in 2014 (ECHA, 2014). The timeframe of the current request from the Commission ruled out the preparation of a fresh review. The likelihood of establishing representative thresholds which are protective of relevant environmental compartments and diverse flora and fauna is very low, and even a new and thorough review of more recent studies might not solve the threshold problem.

Annex 1

Table 1. Summaries of fish studies referred to in the MSC SVHC support document as supportive of endocrine disruption. Italicised conclusions are from the original papers.

Species	**Vehicle**	**Exp. period**	**Endpoint**	**Effect conc. mg/L)**		**Comment**	**Reference and estimated reliability score (Klimisch)**
Atlantic salmon, (Salmo salar)	In food	4 weeks	Sex ratio and liver somatic index	NOEC LOEC	300 1,500 (in food)	Test conc.: 300 and 1500 mg/kg food (nominal concentrations) 2-4 Injections of 160 mg/kg DEHP during 17 days caused no vitellogenin induction in juvenile salmon (7.5 g). The result is not reliable because of an unvalidated method.	Norrgren et. al (1999) (Score 2) 7
Atlantic salmon, (Salmo salar)	In food	4 weeks	Intersex (ovotestis)	NOEC LOEC	800 1,500 (in food)	Test conc.: 400, 800 and 1500 mg/kg food. The EU RAR (2008) used a NOEC of 160 mg/kg for ovotestis by dividing 800 with 5 to normalize the dry food used, to food with normal water content	Norman et al (2007) (Score 2)
Female zebrafish *(Danio rerio)*	ethanol	3 weeks semi-static [Control, EE2 positive control, 0.02, 0.2, 2, 20, 40	Reduction of total embryos; plasm vitellogenin; various biomarkers controlling reproduction	LOEC	0.02µg/L	*"The results of this study, both in vivo and in vitro, clearly demonstrate that all doses of DEHP strongly impair oocyte maturation and*	Carnevali[24] et al. (2010)

[24] Carnevali O, Tosti L, Speciale C, Peng C, Zhu Y, Maradonna F. 2010. DEHP Impairs Zebrafish Reproduction by Affecting Critical Factors in Oogenesis. PLOS One Vol. 5 Issue 4.

		µg/L DEHP in triplicate with 30 fish per replicate]				*ovulation by influencing the expression of factors involved in these processes".*	
Male zebrafish *(Danio rerio)*	ethanol	3 weeks semi-static [Control, EE2 positive control, 0.02, 0.2 µg/L DEHP in triplicate with 30 fish per replicate]	Inhibition of spermatogenesis, form morphometric gonadal analyses	LOEC	0.02µg/L	DEHP impaired reproduction in zebrafish by inducing a mitotic arrest during spermatogenesis, increasing DNA fragmentation in sperm cells and markedly reducing embryo production (up to 90%) at 0.2 µg/l,…. relatively short term exposure below the water solubility level of DEHP is able to severely inhibit spermatogenesis and to affect reproduction in zebrafish.	Corradetti et al (2013)