EUROPEAN CHEMICALS AGENCY

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

For 4,4'-Propane-2,2-diyldiphenol, polymer with 2-methyloxirane, CAS No 37353-75-6 (EC No 500-097-4) (BPA 1 – 4.5 PO)

Addressees: Registrant(s)[1] of 4,4'-propane-2,2-diyldiphenol, polymer with 2-methyloxirane (Registrant(s))

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent for comments, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrants holding active registrations on the day the draft decision was sent are not addressees of this decision if they are: i) Registrant(s) who had on that day registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

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

This decision is based on the registration dossier(s) on 5 September 2014, i.e. the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a new substance evaluation process once the present substance evaluation has been completed.

Throughout this document, the abbreviation BPA 1 - 4.5 PO is used for the registered substance (EC No 500-097-4). The substance is a UVCB that can have different compositions. Individual constituents are described by the length of the propoxylated chain, i.e. BPA 2PO, BPA 3PO, etc. Different compositions of the registered substance are described by using the prefix "grade", i.e. "grade BPA 3PO" and "grade BPA 5PO". The different grades are also characterized as UVCB's were the PO number is related to the major constituent in the specific grade of the substance.

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

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Denmark has initiated substance evaluation for **4,4'-propane-2,2-diyldiphenol, polymer with 2-methyloxirane**, CAS No 37353-75-6 (EC No 500-097-4), hereafter referred to as BPA 1-4.5 PO, based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/Suspected CMR (the scope is limited to reproductive toxicity, i.e. fertility and developmental toxicity); Exposure/Wide dispersive use; Aggregated tonnage, BPA 1 - 4.5 PO was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013. The Competent Authority of Denmark was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding possible endocrine disrupting effects as a mode of action for effects on sexual function and fertility, and developmental toxicity including developmental neurotoxicity and developmental immunotoxicity. A concern of toxicity after repeated dose administration was also added. The concerns are based on both the data gaps as well as on substance specific concerns.

The evaluating MSCA considered that further information was required to clarify the following concerns: 1) reproductive toxicity (effects on sexual function and fertility and developmental toxicity), 2) endocrine disruption, especially oestrogenicity, as a mode of action for reproductive toxicity and 3) the concern on developmental neurotoxicity and developmental immunotoxicity due to oestrogenic mode of action, 4) concern on repeated dose toxicity, and 5) exposure. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 18 March 2014.

On 29 April 2014 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrant commenting phase

By 5 June 2014 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay. By the 25 June 2014 one of the Registrant(s) submitted new study reports directly to the evaluating MSCA on a 90-days repeated dose toxicity study (OECD 408) and a prenatal developmental toxicity study (OECD 414) conducted with the monoconstituent substance BPA 2PO (CAS 116-37-0).

In their comments the Registrant(s) suggested that the newly conducted studies on BPA 2PO should be used for read across to BPA 1-4.5 PO for repeated dose toxicity and prenatal developmental toxicity. For the Extended one-generation reproductive toxicity study an alternative testing strategy was proposed starting with the *in vitro* oestrogen receptor agonist test and then, based on the results, decide which type or grade of substance to test (e.g. BPA 2PO, grade 3PO, 5PO, etc.).

By 5 September 2014 the Registrant(s) submitted an update of the registration dossier.

On the 27 October 2014 a meeting was held between the evaluating MSCA and two of the

Registrant(s). At this meeting the Registrant(s) reiterated their previous written comments and also stated that the BPA 5PO grade is not covered by the registrations as it is considered a polymer and that BPA 3PO is the most commonly used grade of the registered substance whereas grade 4PO and 5PO (which was previously selected for further testing in the draft decision) are only used in small quantities.

The evaluating MSCA considered the comments received from the Registrant(s), the submitted study reports and the dossier update.

On basis of this information, Section II was amended. The substance to be tested was changed from grade BPA 5PO to grade BPA 4PO in the three requested *in vivo* studies. Furthermore, additional grades of BPA 1 - 4.5 PO were added to the requested *in vitro* study on oestrogen receptor agonist activity so that the requested testing now includes BPA 2, 3, 4 & 5 PO. The Statement of Reasons (Section III) was changed accordingly and a new section related to the proposed read across to BPA 2PO was inserted. The evaluating MSCA did not amend the required tests in the draft decision with regard to the read across or alternative testing strategy proposed by the Registrant(s).

Commenting by other MSCAs and ECHA
In accordance with Article 52(1) of the REACH Regulation, on the 15 January 2015 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

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

On the 20 February 2015 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

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

Referral to Member State Committee

On 2 March 2015 ECHA referred the draft decision to the Member State Committee.

On 23 March 2015 in accordance to Article 52(2) and Article 51(5), the Registrant(s) provided comments on the proposals for amendment. The Member State Committee took the comments on the proposals for amendment of the Registrant(s) into account.

After discussion in the Member State Committee meeting on 20-23 April 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 23 April 2015.

ECHA took the decision pursuant to Article 52(2) and Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) shall submit the following information using the indicated test method/instructions (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the specified grade/constituent of the

registered substance subject to the present decision:

1. Extended one-generation reproductive toxicity study in rats, oral route (test method: EU B.56./OECD 443), including extension of Cohort 1B to produce the F2 generation and including Cohorts 2A and 2B for developmental neurotoxicity and Cohort 3 for developmental immunotoxicity as further specified in section III. The study shall be conducted with the grade BPA 4PO.

2. Pre-natal developmental toxicity study (test method: EU B.35, OECD 414) in rats or rabbits, oral route. The study shall be conducted with the grade BPA 4PO.

3. Sub-chronic toxicity study (90-day), oral route (test method: EU B.26./OECD 408) in rats. The study shall be conducted with the grade BPA 4PO.

4. Stably transfected transactivation *in vitro* assays to detect oestrogen receptor agonists (test method: OECD TG 455). The study shall be conducted with BPA 2PO and the three grades BPA 3PO, BPA 4PO and BPA 5PO.

For each of the four above mentioned studies, the Registrant(s) shall report the composition of the tested substances together with the obtained results.

5. Information on the registered substance to be reflected in the CSR (The Chemical Safety Report)

    a) Information on personal protective equipment regarding e.g. the type of material, thickness and breakthrough times of the gloves and the duration of use for all exposure scenarios where the use of personal protective equipment is requested.

    b) Documentation that risks to workers and consumers are adequately controlled for all exposure scenarios.

    c) Documentation supporting the claim that releases to the environment from recycling of paper is negligible.

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **07 September 2018** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

0. Read-across approach

Two new studies (sub-chronic toxicity 90-day and pre-natal developmental toxicity) conducted with BPA 2PO (CAS 116-37-0) were submitted directly to the evaluating MSCA following the Registrant(s) commenting on the draft decision.

The Registrant(s) proposed to use a read-across approach, and to use sub-chronic toxicity 90-day and pre-natal developmental toxicity studies conducted on the analogue substance BPA 2PO (which is also a constituent in the registered substance BPA 1-4.5 PO) to fulfill the information requirements for BPA 1-4.5 PO. In order to support its suggested read across,

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

the Registrant(s) have provided a read across justification document attached in Section 13 in the IUCLID dossier. Furthermore, the Registrant(s) have included justification for the proposed read across in their written comments to the draft decision.

Evaluation of the proposed read across
According to information submitted by the Registrant(s) BPA 1 – 4.5 PO contains constituents with propoxylation degrees from 2 to 9.

According to REACH Annex XI, section 1.5 application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by **interpolation** to other substances in the group (read-across approach). The reference substance(s) should have physicochemical, toxicological and ecotoxicological properties likely to be similar or follow a regular pattern as a result of structural similarity.

BPA 1 – 4.5 PO is one substance (UVCB) under REACH, but from a scientific perspective the substance contains a range of different constituents which are members of a homologues series and in that respect the UVCB can be compared with a 'chemical category'.

For every propoxylation degree 3 carbons are added, so the total number of carbons in the two side-chains on Bisphenol A, i.e. total number of carbons in the sidechains, go from 6 (BPA 2PO) to 27 (BPA 9PO). Doing read-across from BPA 2PO to BPA 1-4.5 (grade 3 and 5) is in reality extrapolating from a monoconstituent substance with a low PO degree (2PO) to a "category" of constituents with propoxylation degrees from 2 to 9, i.e. from the lowest 'PO degree boundary' (2PO) and up to a considerably higher PO degree (9PO), containing for example up to 30% 5PO (grade 5). Generally, interpolation rather than extrapolation is preferred in read across for reliability reasons as it is also stated in REACH Annex XI section 1.5. and in the ECHA R.6 guidance (R.6.2.2.2). It may in certain cases be possible that data are available for a significant number of members of a category but are not available for a boundary chemical. In this case a limited extrapolation to the boundary substance may be considered as in an analogue approach, with its own justification. The potential for greater uncertainty in applying the analogue approach should then additionally be addressed.

In relation to various toxicological effects it can theoretically be different BPA PO constituents that drive the individual effect of the UVCB substance. Trend analysis for properties of relevance for the specific endpoint for the BPA PO constituents should be explored to investigate whether their toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity (R.6.1.7.8 Step 5 – Read-across). Theoretically, in a chemical 'category' there may be endpoint / property specific sub-grouping, where for example one sub-group may have a given effect / property while another sub-group does not.

ECHA finds that the justification for read across is not sufficient in relation to indicating that interpolation can be performed from BPA 2PO to BPA 1 – 4.5 . The justification provided by the registrant for read-across from BPA 2PO to BPA 1 – 4.5 PO does not take into consideration that:

- Absorption is essential for toxicity, but it is well-known that chemical substances can exert effects despite limited absorption. If constituents with higher propoxylation degrees for example have greater affinity to bind to specific receptors, this may drive an effect for the substance which may more than outweigh the possible lower absorption of these higher propoxylated constituents than those with a lower propoxylation degree.

- The possible endpoint specific pattern in changing potency is not addressed in the justification, neither in terms of empirical observations (trend analysis without scientific explanation) nor with an attempt to provide a scientific explanation. The Registrant(s) argue that the broad spectrum of observed effects in the reproductive screening studies could be caused by parental toxicity. However, there is no documentation to support that statement.

- Read-across justifications should always be endpoint specific as completely different mechanisms (Adverse Outcome Pathways) may be involved for the individual effect endpoints. Read across to one or more analogues may be scientifically justified for one property/toxicity endpoint, but this in itself does not prove that the same is the case for another property/toxicity endpoint. No specific arguments as to why all types of "systemic toxicity" endpoints (repeated dose, developmental and reproductive toxicity and regardless of duration of exposure / test design) can be read across has been provided by the registrant.

- Constituents with higher propoxylation degrees may, although possibly absorbed to a smaller extent than BPA 2PO, still be absorbed to a significant degree. No information/documentation has been provided on how much the different propoxylated constituents are absorbed and may become systemically available.

- Constituents with higher propoxylation degrees may have slower metabolisation and depuration/excretion rates than BPA 2PO. Hence, it is based on available information not possible to conclude whether some of the higher propoxylated bisphenols may reach higher internal (body) concentrations than BPA 2PO.

- The two OECD 422 studies with BPA 2PO and BPA 5PO, respectively, and the new OECD 408 and 414 studies with BPA 2PO, do not contain data suggesting that BPA 2PO should be worst case in relation to repeated dose, reproductive and/or developmental toxicity. On contrary, the observed findings on the oestrous cycle in the OECD 422 study with BPA 5PO were not seen in the OECD 408 study with BPA 2PO.

The proposed read across from BPA 2 PO to BPA 1 – 4.5 is considered as a remote and therefore possibly imprecise extrapolation, which needs careful endpoint-specific considerations in relation to possible trends among the constituents relating to potency of involved toxicity endpoints or toxicity profile, including if possible potency of toxicity related modes or mechanisms of action with the increase of the PO degree. Therefore, the concern for repeated dose, developmental and reproductive toxicity, as initially identified for BPA 1 - 4.5 PO, has not been resolved by the new information submitted for BPA 2PO. As a consequence, the draft decision was not amended with regard to the proposed read across from BPA 2PO for 90 days repeated dose toxicity and prenatal developmental toxicity.

The Registrant(s) submitted comments to a Proposal for Amendment (PfA) on the read across section in which he states that the draft decision lacks transparency since the NOAEL values reported by the Registrant(s) for the two OECD 422 studies on BPA 2PO and grade 5PO had not been taken into consideration by the evaluating MSCA. More specifically, the Registrant(s) argued that the lower reported NOAEL value for BPA 2PO (125 mg/kg bw/day) compared to that of grade BPA 5PO (500 mg/kg bw/day) indicates that the BPA substituted with shorter propoxyl chains are more toxic than those with longer propoxyl chains and that BPA 2PO therefore can be used for read across to BPA 1-4.5 PO.
The NOAELs on BPA 1 – 4.5 PO reported by the Registrant(s) are not considered to be appropriate. The OECD TG 422 test (with grade 5 PO) revealed repeated dose toxicity at 120 mg/kg bw/day (dilatation of lacteals in small intestine observed at 120 mg/kg bw/day in both males and females), and reproductive toxicity at 500 mg/kg bw/day (increased rate of oestrous cycle disorder in females). Moreover, developmental findings of decreased pup

body weights were observed at 500 mg/kg bw/day. The parental (P) females showed no changes in body weight during premating, pregnancy or the lactation period and thereby no maternal toxicity was seen in any of the dose groups.

This leads to the following NOAELS:
Repeated dose toxicity NO(A)EL: 30 mg/kg bw/day
Reproductive toxicity NOAEL: 120 mg/kg bw/day
Maternal NOAEL: 500 mg/kg bw/day
Developmental toxicity NOAEL: 120 mg/kg bw/day.

It should be noted, however, that the repeated dose toxicity NO(A)EL is referred to as a parental NOAEL by the Registrant(s). However, it is deemed that this should be a NO(A)EL for repeated dose toxicity. The reason for the "A" in parenthesis in this NO(A)EL is that the slides of dilatation of lacteals in the small intestine observed at 120 mg/kg bw/day were not available to the evaluating MSCA to be able to assess if this minimal severity (slight grading) may be considered as non-adverse.

Consequently, the draft decision was not amended based on these comments by the Registrant(s).

1. Extended one-generation reproductive toxicity study

Only limited information on reproductive toxicity is available and no higher tier reproductive toxicity studies according to REACH, Annex X, Section 8.7.3 have been conducted with the registered substance.

An extended combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) by oral gavage in male and female SD rats (Crj: CD(SD)) is reported for the grade BPA 5PO. The test was conducted with dose levels of 0, 30, 120 and 500 mg/kg body weight/day for 42 days for male and 42-53 days for female starting from 2 weeks before mating to day 4 of lactation. The test revealed repeated dose toxicity at 120 mg/kg body weight/day (dilatation of lacteals in small intestine observed at 120 mg/kg/day in both males and females), and reproductive toxicity at 500 mg/kg body (indications of increased rate of oestrous cycle disorder in females). Moreover, developmental findings of decreased pup body weights were observed at 500 mg/kg/day. The parental (P) females showed no changes in body weight during premating, pregnancy or the lactation period and thereby no maternal toxicity was seen in any of the dose groups.

In their comments to the draft decision the Registrant(s) mentioned that the study report for OECD 422 for grade BPA 5PO (provided by the Ministry of Health, Labour and Welfare of Japan) was still partial since the final report had not yet been issued. According to the Registrant(s) it was not possible to review the oestrous cycle disorder of each female since the individual tables were not available in the draft report. In addition, the Registrant(s) mentioned that although a statistically significant difference for the mean duration of the oestrous cycle was noted between the control females group and the one given 500 mg/kg bw/day, it is worthy to note that quantitatively this difference is minimal (4.1 vs. 4.2 days, respectively) with close standard deviations (0.4 vs 0.6, respectively). The calculated 95th percentile corresponds to a mean range of 3.3- 4.88 days for the control group and of 3-5.3 days for the high dose-group.

The evaluating MSCA based its review on the version of the OECD 422 test report which was sent by the lead Registrant to the evaluating MSCA in an e-mail on the 27th of May 2013. According to the Registrant himself this is the final and published version of the test report. The report has not been translated from Japanese, but all tables and figures are in English.

The individual tables on the oestrous cycle disorder are available in this version and are to be found in Appendix 36-1, 36-2 and 36-3 (page 171-173 in the study report). Therefore individual evaluation is to some extent possible. It is correct that quantitatively the difference is minimal (4.1 vs. 4.2 days, respectively) with rather small standard deviations (0.4 vs 0.6, respectively). The mean oestrous cycle (days) is calculated as the mean number of days from metoestrus to the next metoestrus. However, such mean values are quite insensitive. When looking at the individual data it is clear that all animals with disorders are in the high dose group (500 mg/kg). From these tables it seems clear what the nature of the observed effect is i.e. more days of dioestrous (stage 5) or some cycles without prooestrus (stage 1). The oestrus cycle was (most likely) examined during the premating period.

In addition, the Registrant(s) have reported the results from an OECD 422 (oral gavage) with the substance BPA 2PO (CAS 116-37-0), a mono-constituent substance that also appears as a constituent in the registered substance. In this study dose levels used were 125, 250 and 500 mg/kg/day. The mating, fertility and conception indices were lower for females at 500 mg/kg, along with a lower number of corpora lutea. A high mortality and limited number of litters available for evaluation likely contributed to this finding. Moreover, when also taking into account evidence of impaired spermatogenesis in males observed at 250 and 500 mg/kg, a treatment related effect cannot be excluded. It should be noted that BPA 2PO was not analysed for oestrogenic activity including oestrus cycle disorder in this study.

In their comments to the draft decision the Registrant(s) mentioned the results from the newly conducted OECD 408 study (Sub-chronic toxicity study (90-day), oral route (gavage) in rats) with BPA 2PO (CAS 116-37-0) conducted with the dose-levels of 0, 20, 60 and 180 mg/kg bw/day. In this study, oestrous cycle length was normal for all examined females at 20, 60 and 180 mg/kg bw/day. In addition, the spermatogenic staging profiles were normal for all animals assessed at the dose-levels of 20, 60 and 180 mg/kg bw/day. According to the Registrant(s) this would confirm that the impaired spermatogenesis and histopathological findings in the prostate gland, seminal vesicles, coagulation gland and ovaries observed concomitantly with non-reproductive organs in the parental generation in the OECD 422 study with BPA 2PO was linked to the observed high toxicity.

The evaluating MSCA agrees that the OECD 408 study on BPA 2PO did not identify an abnormal oestrous cycle length at the highest tested dose of 180 mg/kg/day and that spermatogenic staging profiles were normal for all animals assessed in this study. It should be noted, however, that the OECD 408 study used lower doses (only up to 180 mg/kg bw/day) than those that caused effects on the oestrous cycle length for grade BPA 5PO (500 mg/kg bw/day) and impaired spermatogenesis in males for BPA 2PO (250 mg/kg bw/day) in the OECD 422 studies. On the other hand, the OECD 408 employed a longer exposure time and higher number of animals and therefore normally has a higher sensitivity. The results of the OECD 408 study could also be seen as a counter argument to the read across hypothesis provided by the Registrant(s) as it indicates that BPA 2PO does not represent "worst case" for certain reproductive toxicity endpoints. In conclusion, there is still a remaining concern, especially for the higher propoxylated constituents in BPA 1 -4.5 PO.

The screening study on reproductive toxicity for grade BPA 5PO indicates a possible reproductive toxicity effect of BPA 1 - 4.5 PO. However, the findings do not fulfil the criteria for reproductive toxicity classification. Nevertheless, the findings concerning indications of an increased rate of oestrus cycle disorder in females (grade BPA 5PO) in the screening study cause a concern for endocrine disruption *in vivo*. Further evaluation by QSAR model predictions on oestrogen receptor interference (see Annex 1) strengthens the concern that BPA PO may cause reproductive toxicity and endocrine disruption through binding of constituents of BPA 1 - 4.5 PO to the oestrogen receptor.

Specification of the study and study design
To clarify the indications of concern on reproductive toxicity (both for adverse effects on sexual function and fertility and developmental toxicity) which could be via endocrine disrupting modes of action and a concern for endocrine disruption modes of action itself as indicated in the available extended OECD 422 screening study and supported by QSAR predictions, an extended one-generation reproductive toxicity study (B.56, OECD 443) is the preferred test. This test is expected to provide relevant information on reproductive toxicity and systemic toxicity *in vivo* especially related to the concerns indicated in the available studies (effects on sexual function and fertility, developmental toxicity, endocrine disruption mode of action, and systemic toxicity). OECD 443 includes parameters for adverse effects on reproduction and a number of endocrine sensitive parameters which may be used to inform about endocrine disrupting modes of action.

According to OECD GD 150 (2012) the OECD 443 is the reproductive toxicity standard test guideline, which is preferable for detection of endocrine disrupting mode of action and many related apical endpoints for sexual function and fertility and developmental toxicity are included as it provides an evaluation of a number of endocrine related endpoints in particular in the F1 juvenile and adult animals. OECD TG 443 can provide the following endpoints for oestrogen-mediated activity: Change in anogenital distance (AGD) in male and female pups, changes in oestrus cyclicity (P, F1 females), decreased age at vaginal opening (F1 females) and increased age at preputial separation (F1 males), genital abnormalities in both sexes, changes in weights of (P,F1) uterus, ovaries, testes, epididymides, prostate, seminal vesicles (+ coagulating glands), histopathologic changes in vagina, uterus (+ cervix), ovaries, testis, epididymis, prostate, seminal vesicles and coagulating glands, histopathologic changes (proliferative) in mammary glands, changes in sperm parameters as sperm numbers, sperm motility, sperm morphology (P, F1) (OECD, 2012).

The OECD 443 test design includes a number of modules and flexibility and it can be expanded or reduced to suit specific needs for the substance under investigation and the relevant regulatory framework. In REACH substance evaluation the information requests are based on concern. Thus, the study design of the OECD 443 is justified based on identified substance specific concerns. In addition, the Annexes IX and X, section 8.7.3 of REACH include a description on conditions and triggers for inclusion of extension of Cohort 1B and of inclusion Cohort 2A/2B and/or Cohort 3 in relation to the standard information requirements for substances registered in accordance with the REACH Regulation. Such standard information requirements may based on specific concerns be extended under substance evaluation.

Inclusion/exclusion of the extension of Cohort 1B
The findings observed in existing studies causing a concern for reproductive toxicity (both sexual function and fertility and development) and a possibly underlying mode of action (oestrogenicity) can be potentially assessed/confirmed in an one-generation study set up without extending the Cohort 1B to mate the animals to produce the F2 generation, because the findings (oestrous cycle disorder) were already observed in a prolonged OECD 422 study, which is a kind of one-generation study. However, as there is concern on the consumer and professional exposure and an oestrogenic mode of action, which may cause more severe effects on reproduction especially in the F1 generation than only the already observed indications of disturbance in oestrous cycle in the P (F0) generation, it is considered necessary to include the extension of Cohort 1B. Inclusion of the extension of Cohort 1B allows to evaluate the potential effects on reproductive performance of the F1 animals which are exposed already during critical life stages in utero and early postnatal periods. This is also in line with Column 2 of section 8.7.3 of Annexes IX and X of REACH describing the conditions when the extension of Cohort 1B is triggered (significant exposure

of consumers or professional in combination with indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies or non-animal approaches).

In their comments the Registrant(s) state that they are currently working on a revision of the Chemical Safety Report (CSR) which will lead to a removal of the consumer use of the substance, and therefore a lower exposure than the one used in order to justify an EOGRTS with an extension of cohort 1B.

This decision is taken on the basis of the information and documentation available in the registration dossiers and has therefore not been amended based on the Registrant(s) intention on a future update. Furthermore, it is noted that according to Column 2 of section 8.7.3 of Annexes IX and X of REACH triggering of F2 depends not only on consumer use but also on exposure to professionals. Where the Registrant(s) update their registration dossiers justifying and demonstrating that there are neither consumer nor professional uses covered in the registration dossiers leading to significant exposure, taking into account consumer exposure from articles, the F2 generation may be omitted in the EOGRTS study design.

Inclusion/exclusion of Cohort 2A/2B
A tendency towards increased activity and signs of impaired habituation was seen in males in the existing extended OECD 422 study (grade BPA 5PO) which supports further elucidating testing for neurodevelopmental toxicity.

In addition, indications of oestrous cycle disturbances has been observed in the OECD 422 study with BPA 5PO which suggests a potential for endocrine MoA. This is further supported by QSAR predictions for oestrogen receptor interference. Hence, inclusion of cohorts for developmental neurotoxicity (Cohort 2A and 2B) would allow evaluation of potential effects on the sexual dimorphic development of the brain (e.g. behaviour) which may be vulnerable to disruption by oestrogenic substances (Ferguson et al. 2000; Patisaul et al. 2008).

Inclusion/exclusion of Cohort 3
No significant changes were detected in the weight of the spleen or thymus and no abnormalities were detected in bone marrow or lymph nodes in the available screening study (OECD 422) with grade BPA 5PO that could indicate a concern for developmental immunotoxicity. However, OECD 422 is not designed for investigation of developmental immunotoxicity and these results cannot be used to conclude that the substance does not cause developmental immunotoxicity. Oestrogenic endocrine disruptors may modulate the immune system (e.g. Calemine et al., 2003; Adori et al., 2010). Thus, based on the findings suggesting effects on the oestrous cycle (which may be caused by an oestrogenic mode of action), inclusion of the DIT Cohort is requested. It is furthermore noted that the request to include the cohorts in the requested EOGRTS is not only related to standard information requirements of REACH but also to the fact that the registered substance is undergoing a concern driven substance evaluation where the requests may go beyond the information requirements of REACH.

Duration of premating exposure
The extension of Cohort 1B is included to the study design. Cohort 1 B animals (F1) will have an implicit 10 weeks premating exposure duration which covers the complete spermatogenesis and folliculogenesis before mating and thus allows to evaluate fully the potential effects on reproductive performance in Cohort 1B animals. Thus, two weeks premating exposure duration seems to be adequate for the parental (F0) animals if the F2 generation is included. However, in the case the F2 generation is not included, the starting point for considering the premating period shall be 10 weeks unless a shorter premating period of at least two weeks can be scientifically justified.

Selection of exposure route
The relevant route of exposure is considered to be oral.

Selection of the dose levels
The highest dose should be selected with the aim to induce overt maternal toxicity at the highest selected dose level inducing for example a decreased body weight gain but not death or suffering of the parental animals. This is in line with OECD 443.

Evaluation of comments received from the Registrant(s)
The Registrant(s) have proposed an alternative testing strategy in which the *in vitro* oestrogen receptor agonist assay (OECD 455) is conducted before the extended one-generation reproductive toxicity study (OECD 443). This would serve to identify the constituent/grade of BPA PO with the highest affinity/binding to oestrogen receptors which would then be selected as test item in the OECD 443 study. In case the four compounds do not exhibit any affinity for ER binding, the Registrant(s) propose to test BPA 2PO in the extended one-generation study as this constituent according to their read across hypothesis represents the worse-case due to its better bioavailability.

The evaluating MSCA considers that the results of the OECD 422 study with grade BPA 5PO gives a concern for reproductive toxicity for grades of the registered substance with longer PO chain lengths. The observed effects in this study could be caused by an oestrogenic mode of action as indicated by QSAR model estimates but a number of other mechanisms could also or alternatively be involved. In addition, the OECD 455 test is an *in vitro* test which does not investigate the potential for metabolic activation and the potential effects of such metabolites. A negative result in this test does therefore not indicate that BPA 2PO is "worst case" with regard to reproductive toxicity. A metabolic activating system such as S9 could if feasible and not interfering with the integrity of the test system potentially be added in the *in vitro* OECD 455 study, but such an approach would still not be able to provide definite conclusions since it has not been validated. Predictions in the OECD (Q)SAR Application Toolbox indicates that metabolites with a phenol group may have ER properties. In conclusion, it is considered that there is sufficient concern to warrant further testing on reproductive toxicity on a grade of the registered substance which contains longer PO chain length constituents.

Different grades of BPA 1 – 4.5 PO differ in their composition with regard to mean length of the propoxylated side chains. No toxicokinetic test data is available; however, QSAR predictions and general considerations suggest that the shorter chained constituents may be taken up faster but also metabolised and excreted faster than the longer chained constituents. It is in this context noted that the available OECD 422 data on grade BPA 5PO (having a large fraction of longer PO chains) shows that this grade of the registered substance can cause toxic effects and therefore is bioavailable. This is also supported by QSAR predictions (see Annex 1). In addition, QSAR predictions for oestrogen receptor binding and androgen receptor (AR) antagonism (see Annex 1) predicts an increased probability (please note that potency is not predicted) for activity with longer chain lengths of propoxylated groups.

However, the Registrant(s) have stated that grade BPA 5PO is considered as a polymer under REACH. Grade BPA 3PO, and even more so grade BPA 4PO, can also contain constituents with longer chain lengths of propoxylated groups (up to 9PO). Therefore, the requested OECD 443 should be conducted with the grade BPA 4PO as the test material because this grade contains maximum relative amount of constituents with higher PO chain lengths which are of concern with regard to oestrous cycle disorder and are predicted in QSAR models to have an increased probability for oestrogen receptor binding compared to

shorter chain length constituents.

After the MSCA/ECHA commenting period the Registrant(s) submitted comments in which he agrees to the proposal for amendment made from one Member State that the request for an Extended One-generation Reproductive Toxicity study with DNT and DIT cohorts should be removed from this decision and that the evaluating MSCA should reconsider the design of this study once more data become available. In contrast, to the proposal for amendment made by the MSCA the Registrant(s) did not agree that the 90 days study should be conducted first in order to get more information on BPA 1-4.5 PO. Instead the Registrant(s) reiterated the testing strategy that was already proposed in the Registrant(s) comments to the draft decision in which the *in vitro* study (OECD 455) would be conducted first.

The evaluating MSCA had already addressed the testing strategy proposed by the Registrant(s) and the draft decision was therefore not further amended.

Conclusion
An extended one-generation reproductive toxicity study with BPA 4PO at relevant dose levels is foreseen to generate data both on adverse effects on sexual function and fertility and developmental toxicity and oestrogenic mode of action. New data may allow improving risk assessment and arriving at a more robust conclusion regarding hazard classification.

The Registrant(s) are advised to conduct OECD 408 (also requested by this decision) before OECD 443 in order to use the first mentioned study as a range-finding study.

According to the test method OECD 443, the rat is the preferred species and the test substance is usually administered orally. It is considered that these default parameters are appropriate and testing should be performed in the rat by the oral route.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using BPA 4PO as the test substance subject to this decision:

- Extended one-generation reproductive toxicity study in rats, oral route (test method: OECD 443), including extension of Cohort 1B to produce the F2 generation and Cohorts 2A and 2B for developmental neurotoxicity and Cohort 3 for developmental immunotoxicity on the grade BPA 4PO.

The Registrant(s) shall report the exact composition of the tested substance together with the obtained results (see also section IV).

2. Pre-natal developmental toxicity study

Only limited information on prenatal developmental toxicity is available and no higher tier study according to REACH, Annex IX, Section 8.7.2 (i.e. OECD 414) has been conducted with the registered substance BPA 1 – 4.5 PO. Following the Registrant(s) commenting on the draft decision, however, a prenatal developmental toxicity study (OECD 414) was submitted for BPA 2PO (CAS 116-37-0) and the Registrant(s) proposed this study to be used for read across to BPA 1 - 4.5 PO. However, it is for this endpoint not clear that the compound BPA 2PO represents the worst-case (see arguments in relation to this under the read across section), and the read across hypothesis as presented by the Registrant(s) is therefore not supported.

The combined repeated dose toxicity study with the reproduction/developmental toxicity

Screening Test (OECD 422), conducted with grade BPA 5PO, showed developmental findings with a decrease of pup body weights observed at 500 mg/kg/day. The P females showed no changes in body weight during premating, pregnancy or the lactation period and thereby no maternal toxicity was seen in any of the dose groups.

In their comments the Registrant(s) had included a table with additional data on pup body weights. They also stated that no individual data is available preventing from a possible investigation in terms of maternal body weight and litter pups weight. Finally, they stated that although some statistically significant mean body weight differences between pups of the control dams and those of the dams given 500 mg/kg bw/day, it should be noted that between days 0 and 4, body weight gain was also observed for this latter group.

The additional data presented by the Registrant(s) in their comments was already available to the evaluating MSCA at the time of evaluation. It is a subdivision of Table 28 in the final Japanese report of this OECD 422 study (Study No.06-119) and the individual tables (only litter means) are to be found in Appendix 39-1, 39-2, 39-3 and 39-4 (page 182-185 in the study report). Therefore an evaluation of the pup weights is to some extent possible. Overall a decreased weight was seen in the 500 mg/kg group both at birth and at PND 4. However, this is only analysed separately for the two sexes. Decreased birth weight was significant in females while the males only showed a trend towards decreased birth weight. Day 4 body weight was significantly decreased in males, while the females only show a trend towards decreased day 4 bodyweight (Table 28). The reduced weights for the pups are not a result of decreased weight or reduced weight gain in the P females because such decreases do not occur.

OECD TG 422 is a screening assay that is designed to generate limited information concerning the effects of a test chemical on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition. It is not an alternative to, nor does it replace the existing Test Guidelines (OECD TGs 414 and 416, EU B.31 and B.35). These screening tests are not meant to provide complete information on all aspects of reproduction and development. Furthermore, the number of animals per dose group is limited which affects the statistical power of the study to detect an effect. Hence there is a data gap in comparison with the standard information requirements under REACH for reproductive toxicity which causes concern.

Furthermore, the potential endocrine modulating effect of BPA 1 – 4.5 PO also strengthens the concern for developmental effects that needs to be investigated in the prenatal developmental toxicity study (OECD 414).

The Registrant(s) in their comments mentioned that the design of the OECD 414 does not allow to investigate the effects considered of concern by the evaluating MSCA, i.e. oestrous cycle disorder, decreased pups weight in the early days and impaired spermatogenesis (although the concern for this latter according to the Registrant(s) has been definitely ruled out by the 90-day toxicity study performed with BPA 2PO).

It is reiterated that the data gap in comparison with the standard information requirements under REACH for prenatal developmental toxicity causes a concern on its own. Furthermore, it is considered that the requested study is relevant to investigate the concern for potential endocrine disrupting effects of BPA 1 – 4.5 PO. The Prenatal Developmental toxicity study (OECD TG 414), which is included in Level 4 in the OECD conceptual framework for evaluating chemicals for endocrine disruption (OECD, 2012), involve repeated dosing of pregnant females and therefore potential exposure of the developing foetus. This test guideline is designed especially to investigate malformations, foetal survival and intra-uterine death after implantation (resorptions). In studies where dosing is started before

implantation, pre-implantation loss may also be assessed. The pregnant animals are killed prior to the expected day of delivery (gestation day 21 in the rat) to avoid that the dams eat malformed or stillborn pups. The guideline specifies that investigations of the foetuses should be with particular attention to the reproductive tract (OECD, 2001). This *in vivo* assay provides relevant developmental toxicity data and includes some endpoints that may detect endocrine disruption (e.g. abnormalities of male and female genitalia) (OECD, 2012).

The observed increased rate of oestrous cycle disorder in females was caused by the grade BPA 5PO, and QSAR predictions for oestrogen receptor binding and AR antagonism (see Annex 1) predicts an increased probability for activity with increasing chain lengths of propoxylated groups. However, the Registrant(s) have stated that grade BPA 5PO is considered as a polymer under REACH. Grade BPA 3PO, and even more so grade BPA 4PO, can also contain constituents with longer chain lengths of propoxylated groups (up to 9PO). Therefore, the requested OECD 443 should be conducted with the grade BPA 4PO as the test material because this grade contains maximum relative amount of constituents with higher PO chain lengths.

According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. It is considered that these default parameters are appropriate and testing should be performed by the oral route with the rat or the rabbit.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision:

- Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31, OECD 414). The study shall be conducted with the grade BPA 4PO and the exact composition of the tested substance shall be reported together with the obtained results.

3. Sub-chronic toxicity study (90 days)

At the time of evaluation the Registrant(s) had not provided any study record of a sub-chronic repeated dose toxicity study in the dossier that would meet the REACH standard information requirement. Instead, two combined repeated dose toxicity studies with the reproduction/developmental toxicity screening test (OECD 422) were provided for grade BPA 5PO of the registered substance and for PBA 2PO (CAS 116-37-0), a mono-constituent substance that also appears as a constituent in the registered substance. A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test can, however, not replace a sub-chronic toxicity study, because, amongst other reasons, the administration period is considerably shorter than for a sub-chronic toxicity study (typically 56 days versus 90 days) and because there is a higher statistical power in the sub-chronic toxicity study.

Following the Registrant(s) commenting on the draft decision, however, a 90 day repeated dose toxicity study (OECD 408) was submitted for BPA 2PO (CAS 116-37-0). Dose-levels of 0, 20, 60 and 180 mg/kg bw/day were used and according to the Registrant(s) no relevant treatment-related findings were observed for clinical signs, clinical biochemistry, histopathological or reproductive parameters up to the dose-level of 180 mg/kg bw/day.

The Registrant(s) proposed this study to be used for read across to BPA 1 - 4.5 PO and states that BPA PO substances exhibit the same properties and that in terms of bioavailability and systemic toxicity the compound BPA 2PO represents the worst-case. In addition the Registrant(s) states that general considerations and QSAR predictions suggest that the shorter chained constituents will be more bioavailable than the longer chained

constituents and this presumption has been confirmed with the results of the two available OECD 422 (and dose-range finding) studies performed on BPA 2PO and the grade BPA 5PO.

However, it is for this endpoint not clear that the compound BPA 2PO represents the worst-case (see arguments in relation to this under the read across section), and the read across hypothesis as presented by the Registrant(s) is therefore not supported.

In addition to the data gap for subchronic toxicity, which constitute a concern in itself, a concern for systemic toxicity was identified in the OECD 422 study conducted with grade BPA 5PO (dilatation of lacteals, effects on the small intestine). Based on both of these identified concerns (data gap and effects in small intestine) the Registrant(s) are requested to submit information on a 90 days sub-chronic repeated dose toxicity study.

The observed effects in the screening study (dilatation of lacteals and increased rate of oestrus cycle disorder in females) was observed for grade PBA 5PO. The requested OECD 408 should therefore be conducted with a grade of BPA 1 – 4.5 PO that covers constituents in the same PO chain length range. In addition, a 90 days sub-chronic repeated dose toxicity study is now available for BPA 2PO (CAS 116-37-0), which has been registered individually under REACH. BPA 2PO is also a constituent in BPA 1 – 4.5 PO (CAS 37353-75-6) and a read across justification between the two substances has been included in the registration dossier for BPA 1 – 4.5 PO. According to the OECD guidance on grouping of chemicals (OECD, 2007), interpolation between members in a category is preferred to extrapolation because it is the more reliable approach. Also from this perspective it would be preferable to use a grade of BPA 1 – 4.5 PO with longer PO chain lengths as test material in order to cover the higher propoxylated constituents.

However, the Registrant(s) have stated that grade BPA 5PO is considered as a polymer under REACH. Grade BPA 3PO, and even more so grade BPA 4PO, also contains constituents with longer chain lengths of propoxylated groups (up to 9PO). Therefore, the requested OECD 443 should be conducted with the grade BPA 4PO as the test material because this grade contains maximum relative amount of constituents with higher PO chain lengths.

The doses used in the study should be identical or close to the doses that were used in the screening study with BPA 5PO (i.e. 30, 120 and 500 mg/kg bw/day). The registrant(s) are advised to conduct OECD 408 before OECD 443 in order to use the first mentioned study as range finding study to the latter.

The Registrant(s) provided comments to a proposal for amendment (PfA) from ECHA in which they state that a Subchronic Toxicity Study (90 day) would not provide additional vital information in addition to that already derived from the requested Extended One-generation Reproductive Toxicity study (OECD 443) for assessment reproductive toxicity which is the intial identified concern to be clarified under the substance evaluation.

The evaluating MSCA agreed to the PfA from ECHA and revised the draft decision accordingly. The text relating to a concern for reproductive toxicity as a justification to request the Subchronic Toxicity Study, i.e. it removed. However, it is noted that beside the justification relating to reproductive toxicity two other lines of reasoning are also used to justify the request for the Subchronic Toxicity Study. These are an identified concern for repeated dose toxicity for BPA 1-4.5 PO (dilatation of lacteals, effects on the small intestine) and a data gap for repeated dose toxicity (given that the proposed read across from BPA 2PO is not supported by the evaluating MSCA). These two latter justifications were mentioned in the original draft decision and are stated more explicitly in this decision following the PfA from ECHA. In addition, the repeated dose toxicity has been included as a separate concern to be clarified under substance evaluation in Section I of this decision.

Consequently, the request for an OECD 408 is maintained.

According to the test method OECD 408, the rat is the preferred rodent species. It is considered that this default parameter is appropriate and testing should be performed on the rat.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision:

- Sub-chronic toxicity study (90-day), oral route (test method: EU B.26./OECD 408) in rats. The study shall be conducted with the grade BPA 4PO.

4. *In vitro* assays to detect oestrogen receptor agonists

During the substance evaluation of BPA 1 – 4.5 PO, the evaluating MSCA identified an additional concern for endocrine disruption. The findings on oestrous cycle disorder in females in the OECD 422 (on the grade BPA 5PO) may be associated with an oestrogenic mode of action. A literature search by the evaluating MSCA revealed only one additional relevant study (Perez *et al.*1998). The authors studied whether BPA-derived compounds with substitution of the hydroxy groups and the central carbon atom are oestrogenic and tested the proliferative effect of BPA and structurally similar molecules commonly employed in plastic materials in MCF7 breast cancer cells. They also studied the potency of these compounds in inducing cell type-specific proteins (progesterone receptor and pS2) and their affinity to bind to the oestrogen receptor extracted from immature rats. For the chemicals used and also bisphenol A propoxylate (P-BPA) they do not specify any CAS number, however, chemical characterization indicates that it is BPA 2PO (CAS 116-37-0). The authors showed that in this assay (MCF-7) BPA 2PO did not seem to have any affinity for binding to the oestrogen receptor (ER), up to a concentration 1 million-fold higher than active concentrations of oestradiol (E2). Moreover, BPA 2PO showed no oestrogenic activity in the range of concentrations tested.

No other relevant mechanistic information is available for the registered substance or its constituents.

The evaluating MSCA has, however, applied a number of relevant QSAR models to predict the sex hormone activity of the individual constituents of BPA PO (see Annex 3).

Binding to the human Estrogen Receptor alpha (hERalpha) *in vitro* was predicted in an in-house Leadscope model based on METI data (hERalpha was produced from *Escherichia coli* by a genetic engineering method and was used for the receptor binding assay with radioisotope-labelled oestradiol as the reference ligand, training set N=595, statistical LGO (leave-groups-out) cross-validation 10*50% gave within the defined applicability domain (AD) sensitivity = 83.7%, specificity = 89.0% and concordance = 86.3%): BPA 2PO to BPA 9PO were all predicted to be positive (within AD). The positive prediction for BPA 2PO was for 2 propoxylated groups on the one side and 0 on the other; for the constituent with 1 propoxylated group on each side the prediction was indeterminate (probability close to positive but below the cut-off that we apply for certainty). Also applied was another Leadscope model based on METI data for activation of the human Estrogen Receptor alpha (hERalpha) *in vitro* (*in vitro* assay, training set N=481, statistical LGO cross-validation 10*50% gave within the defined AD sensitivity = 73.3%, specificity = 84.8% and concordance = 79.8%). In this model a robust prediction could not be obtained for BPA 2PO, and for BPA 3PO to BPA 9PO the predictions did not pick up positive alerts (negative predictions within the AD).

It has been found for alkyl phenols that compounds with higher carbon numbers, p-octylphenol and p-nonylphenol, possess higher oestrogenic capacity, compared to p-propyl-, p-butyl and p-pentylphenol. A similar trend for increasing propoxylation degrees for BPA has to our knowledge not been experimentally verified, however, predictions from the applied hERalpha binding model indicate that the probability (it is noted that potency can not be predicted in this model) for binding to the oestrogen receptor may be increasing with the degree of propoxylation.

Androgen receptor (AR) antagonism was predicted in an in-house Leadscope model (*in vitro* CHO cells with a human vector androgen receptor antagonism, where "a positive" was at least 25% inhibition of the 0.1 nM R1881-induced response reached at noncytotoxic concentrations ≤10 µM training set N=922, statistical LGO cross-validation 10*50% gave within the defined AD sensitivity = 51.7%, specificity = 91.2% and concordance = 80.4%). BPA 2PO was predicted positive (within AD) in the "version" with 2 propoxylated groups on the one side and 0 on the other; for the constituent with 1 propoxylated group on each side the prediction was indeterminate (probability close to positive but below the cut-off that we apply for certainty). BPA 3PO to 7PO also had indeterminate predictions (increasing probability with chain length), and BPA 8PO and 9PO were predicted positive (within AD).

In their comments the Registrant(s) mentioned that predictions from another model in the OECD QSAR Application Toolbox does not support the positive predictions on oestrogen receptor binding which were obtained with the Leadscope models. Except for BPA 1 PO and BPA 2PO 1_0 which both exhibited a free OH linked to one cycle, no alert for ER binding was considered for the other BPA PO substances in this model. Thus, according to the Registrant(s) on the basis of a limited QSAR approach and the negative in vitro test data for BPA 2PO, it seemed difficult to conclude if BPA PO compounds have an affinity to the oestrogen receptors and moreover if this possible affinity is proportional to the length of the chain.

It is currently not possible to definitively conclude that BPA PO compounds have an affinity to the oestrogen receptor. That is why experimental *in vitro* testing for ER properties is requested in order to conclude if the BPA PO constituents have an affinity to the oestrogen receptors under *in vitro* conditions.

Mechanistic information is warranted on oestrogenic agonist activity. The Stably Transfected Human ER Transcriptional Activation Assay for Detection of Estrogenic Agonist-Activity of Chemicals (ER STTA) (OECD 455) should therefore be conducted to cover different chain lengths of propoxylation in the registered substance. The mechanistic information from OECD 455 may be relevant as supporting information to the results of the OECD 443 requested by this decision. However, depending on the outcome of the studies/documentation requested in this decision, further testing may be necessary. Such potential follow up testing could include (but is not limited to) one or more of the following assays: Steroidgenesis in vitro (H295R, OECD 456), Uterotrophic assay (OECD 440), Hershberger assay (OECD 441), Androgenized female stickleback screen (GD 140) or Fish sexual development test (OECD 234).

The Registrant(s) in their comments suggested to test additional constituents/grades of BPA 1 – 4.5 PO (BPA 2PO and the grades BPA 3PO, BPA 4PO and BPA 5PO) in the requested *in vitro* study. ECHA agrees that this would be a sensible approach, and recommends that the grades used in the test are manufactured with as narrow a chain length distribution as possible, as far as this is feasible within reason to achieve during the manufacturing process. In addition, if practically feasible, the potential for metabolic activation could be explored by for example including additional testing of the individual constituents/grades with the addition of S9 or alternatively by testing S9 pre-treated samples of the individual

where most of the components of S9 has been removed (e.g. by chemical precipitation and centrifugation) to avoid interference of S9 on the *in vitro* test system. This, however, shall be seen as a recommendation and not as a requirement.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using BPA 2PO and the three grades BPA 3PO, BPA 4PO and BPA 5PO:

- Stably transfected transactivation *in vitro* assays to detect oestrogen receptor agonists (test method: OECD 455).

In this specific assay it is recommended that the Registrant(s) use grades of BPA 3PO, 4PO and 5PO that are manufactured with as narrow a chain length distribution as possible, as far as this is feasible within reason to achieve during the manufacturing process. The Registrant(s) shall report the exact composition of the tested substances together with the obtained results (see also section IV).

5. Information on the registered substance to be reflected in the CSR (The Chemical Safety Report)

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information regarding the registered substance subject to the present decision:

a) Information on personal protective equipment regarding e.g. the type of material, thickness and breakthrough times of the gloves and the duration of use for all exposure scenarios where the use of personal protective equipment is requested

Personal protective equipment (PPE) like gloves is mentioned in the CSR in the workers scenarios in the technical dossier (mentioned as "suitable protective gloves"). However, detailed specifications are lacking.

For skin protection, the information required includes amongst others the type of material and its thickness and the typical or minimum breakthrough times of the glove material.

PPEs like gloves are produced of different type of materials, thickness, design etc. and not all are well suited to protect against exposure to all substances, mixtures and materials. A concern is raised if workers are not properly informed to use the right type of e.g. gloves to protect themselves against exposure to chemicals. The use of unsuited material may even result in higher level of exposure, than not using any protection at all, as the inside of contaminated gloves, may be covered with migrated substance – and the skin inside a glove is often humid – corresponding to exposure under occlusion.

The Registrant(s) are therefore pursuant to Article 46(1) ot the REACH Regulation, requested to provide information on type of personal protective equipment where relevant, taking into account e.g. breakthrough times for gloves and clothing.

b) Documentation that risks to workers and consumers are adequately controlled for all exposure scenarios

In the CSR, Chapter 10 the RCRs are presented as <1. It is not transparent if the RCR is e.g. 0.999 or 0.003. A concern is raised in case an RCR is in the very close vicinity of 1 e.g. in cases where a person may be exposed to BPA PO via both working environment, food and as a consumer. As a consequence, the evaluating MSCA cannot evaluate if there is a

concern based on the current exposure level for BPA PO.

Therefore, the Registrant(s) are requested to submit the exact RCR for each scenario.

c) Documentation supporting the claim that releases to the environment from recycling of paper is negligible

In the CSR, Chapter 9, it is stated that "*environmental releases of BPA PO as a result of its presence at low concentrations in toner are negligible*". Although the presence of the substance in the final toner products is relatively low, the total volume of the substance that is used in this product category could potentially give rise to environmental exposure. Recycling of printed paper is known from other substances (e.g. Bisphenol A) to cause releases to the aquatic environment and may also be a relevant environmental release route for BPA 1 – 4.5 PO since it is assumed that a relative large fraction of the total production volume eventually will be bonded to printing paper. The Registrant(s) state that since the quantity in printed paper will be <1 ng/kg no measurable environmental release would be expected to arise as a consequence of the recycling or disposal of printed paper.

The request for additional documentation on releases to the aquatic environment should be seen in context with the hazardous properties of BPA 1 – 4.5 PO. In this regard, the concern relating to potential oestrogenic effects of BPA 1 – 4.5 PO applies also for the environment. Since the oestrogen receptor is conserved across taxonomic classes, the oestrogenic effects in aquatic wildlife should also be investigated. According to the OECD fish testing strategy (OECD Series on Testing and Assessment, No. 171, 2012), a Fish Sexual Development Test (OECD TG 234) could be considered if there is already a moderate suspicion for the substance being endocrinologically active, e.g. if *in vivo* endocrine-related effects have already been observed in another vertebrate taxon, because the mode of action and therefore the likely most sensitive life stage should be known.

According to the registration dossiers the release of BPA 1 – 4.5 PO to the aquatic environment is considered to be negligible. A request is made in this decision for documentation relating to environmental release through recycling of paper containing the BPA PO. Further testing may, therefore, be relevant if the Registrant(s) are unable to provide adequate documentation for negligible environmental exposure or if changes in the uses of BPA PO give rise to increased environmental release of the substance.

The Registrant(s) are requested to update the CSR with a refinement of the exposure scenario for recycling of printed paper. This should either document that releases to the aquatic environment is negligible or, alternatively, lead to an adjustment of the conclusion for environmental releases.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental stud(y/ies), the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on 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. Finally, the test(s) must be shared by the Registrant(s).

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

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). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at: https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/regulations/reach/registration/data-sharing.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrant(s) to perform the stud(y/ies) on behalf of all of them.

VI. Information on right to appeal

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

[redacted]

Leena Ylä-Mononen
Director of Evaluation

Annex 1: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

Annex 2: References

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Annex 3: QSAR predictions for some potential constituents in BPA PO

Constituent	SMILES	Leadscope estrogen reporter gene	Leadscope ER binding	Leadscope AR antagonism	Human GI absorption in % (MC4PC calculations)
BPA 1PO	c1(C(c2ccc(O)cc2)(C)C)ccc(OCC(C)O)cc1	IND (0,58)	POS (0.92)	POS (0.73)	
BPA 2PO_1_1	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)O)cc1	IND (0,35)	IND (0.59)	IND (0.52)	82,7%
BPA 2PO_0_2	c1(C(c2ccc(O)cc2)(C)C)ccc(OCC(C)OCC(C)O)cc1	IND (0,42)	POS (0.95)	POS (0.75)	
BPA 3PO_1_2	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)O)cc1	NEG (0,22)	POS (0.72)	IND (0.54)	79,3%
BPA 4PO_2_2	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)O)cc1	NEG (0,21)	POS (0.81)	IND (0.56)	74,7%
BPA 4PO_1_3	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,21)	POS (0.81)	IND (0.56)	
BPA 5PO_2_3	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,12)	POS (0.88)	IND (0.62)	68,2%
BPA 5PO_1_4	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,12)	POS (0.88)	IND (0.62)	
BPA 6PO_3_3	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,071)	POS (0.93)	IND (0.68)	59,7%
BPA 6PO_2_4	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,071)	POS (0.93)	IND (0.68)	
BPA 6PO_1_5	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,071)	POS (0.93)	IND (0.68)	
BPA 7PO_3_4	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,065)	POS (0.96)	IND (0.68)	49,3%
BPA 7PO_2_5	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,065)	POS (0.96)	IND (0.69)	
BPA 7PO_1_6	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,065)	POS (0.96)	IND (0.69)	
BPA 8PO_4_4	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,059)	POS (0.98)	POS (0.70)	39,4%
BPA 8PO_3_5	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,059)	POS (0.98)	POS (0.70)	
BPA 8PO_2_6	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,059)	POS (0.98)	POS (0.70)	
BPA 8PO_1_7	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,059)	POS (0.98)	POS (0.70)	
BPA 9PO_4_5	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,033)	POS (0.99)	POS (0.75)	31,0%
BPA 9PO_1_8	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,033)	POS (0.99)	POS (0.75)	
BPA 9PO_2_7	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,033)	POS (0.99)	POS (0.75)	
BPA 9PO_3_6	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	NEG (0,033)	POS (0.99)	POS (0.75)	

The last part of the listed consituents (first column) specifies the number of propoxyl group in each of the two side chains, e.g. for 5PO the 5 proproxyl groups may be distributed 1:4 or 2:3 in the two side chains.
All positive (POS) and negative (NEG) predictions are inside the applicability domain of the applied models.

The categorical estimates (positive (POS)/negative (NEG)/indeterminate (IND)) are followed by the probability (p) in parenthesis.