EUROPEAN CHEMICALS AGENCY

Helsinki, 12 March 2020

Addressees
Registrants of Biphenyl-4,4'-diol listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
31/10/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Biphenyl-4,4'-diol
EC number: 202-200-5
CAS number: 92-88-6

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)]

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***19 September 2022.***

A. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rabbit), oral route, with the Substance;

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, with the Substance, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;
   - Cohorts 2A and 2B (Developmental neurotoxicity); and
   - Cohort 3 (Developmental immunotoxicity).

You must report the study performed according to the above specifications. Any expansions of the study design must be scientifically justified.

Conditions to comply with the requests

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation. Therefore you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information they are required to submit to fulfil the information requirements for their registration.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

Appeal

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

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons for the requirement applicable to all the Registrants subject to Annex X of REACH

This decision is based on the examination of the testing proposals you submitted.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Examination of the testing proposal

Pre-natal developmental toxicity (PNDT) studies on two species is a standard information requirement under Annex X, Section 8.7.2 to REACH.

You have submitted a testing proposal for a PNDT study in a second species (rabbits) according to OECD TG 414 by the oral route with the Substance.

You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that the proposed study fulfils the information requirement.

Species and route

The study in the first species was carried out with rats. The rat or the rabbit is the preferred species under the OECD TG 414[2]. The study should be performed with the rabbit as a second species.

You proposed administration by the oral route. ECHA agrees with your proposal. The oral route is the most appropriate route of administration to investigate reproductive toxicity[5].

Outcome

Under Article 40(3)(a) of REACH, you are requested to carry out the proposed test with the Substance.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

Examination of the testing proposal

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to REACH. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats. You have provided the following justification and specification of the study design according to the criteria described in Column 2 of Section 8.7.3, Annex X, and detailed in ECHA Guidance R.7a: "*The study will be performed in rats according to OECD guideline 443 in compliance with GLP. The test substance Biphenyl-4,4'-diol will be administered by the oral route. The basic configuration of EOGRTS will be performed as based on the toxicological profile of the substance there are no concern-driven scientific triggers for the performance of the F2 generation (extension of Cohort 1B), developmental neurotoxicity (DNT; cohorts 2A and 2B) and/or developmental immunotoxicity (DIT; cohort 3) cohorts.*

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.

** Extension of cohort 1B: no indications [...] that endocrine disruption is a relevant mode of action for the substance. [...].*
** Inclusion of Cohorts 2A and 2B: not justified [...] as no neurotoxic potential of the test material [...].*
** Inclusion of Cohort 3: not justified [...] as [...] (i) the substance has not caused biologically significant changes in haematology/clinical chemistry and/ or organ weight associated with immunotoxicity [...], (ii) the substance has not caused significant effects to immunology organs [...]."*

You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

The proposed study design fulfils the information requirement, and the following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You did not specify the premating exposure duration. Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance R.7a

You stated that *"doses will be selected based on the results of a range-finding study. The highest dose level will be selected with the aim to induce some toxicity, in order to allow a conclusion on whether potential effects on reproduction are considered to be secondary, non-specific con sequence of other toxic effects seen."*

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level must aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study.

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and shall be included.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

You proposed not to include Cohorts 2A and 2B because you considered that the existing studies have not reported any neurotoxic potential of the Substance.

However, two Member States submitted proposals for amendments considering that the criteria to include Cohorts 2A and 2B are met.

ECHA notes that the Substance weakened the mean grip strength (by 34%) in females at 500 mg/kg bw/day in an OECD TG 408 study suggesting that there may be a concern for developmental neurotoxicity. This is supported by information from a structurally analogous substance bisphenol A (BPA; CAS No. 80-05-7). The Substance and BPA both contain two phenyl moieties with hydroxyl groups in *para* positions, and therefore there is structural analogy. The publicly available information on developmental neurotoxicity-related effects caused by BPA is extensive but inconsistent, complex and having some quality issues. However, one of the references in the review from Patisaul (2019)[3], referred to in the proposal for amendment, describes a recent assessment which is based on a systematic review and meta-analysis on studies investigating hyperactivity in children prenatally exposed to BPA (Rochester *et al.*, 2018)[4]. The results of this assessment show reliably a concern for developmental neurotoxicity, and it includes also the results from the GLP study according to OECD TG 426 with BPA (which does not individually show any concern for developmental neurotoxicity; Stump *et al.*, 2010[5]). This systematic review and meta-analysis on hyperactivity in children prenatally exposed to BPA consists of 29 rodent and 3 human studies, and it shows evidence of a relationship between early life exposure to BPA and hyperactivity in male rodents and in both human sexes. The overall confidence in the body of evidence was reported to be high for the animal studies and moderate for the human studies. The final rating of presumed hazard to human health was reached.

The developmental neurotoxicity cohorts 2A and 2B must be conducted because there is a particular concern on (developmental) neurotoxicity.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.
You proposed not to include Cohort 3.

However, a Member State submitted a proposal for amendment considering that the criteria to include Cohort 3 are met, because of existing information on a structurally analogous substance bisphenol A (BPA; CAS No. 80-05-7). The Substance and BPA both contain two phenyl moieties with hydroxyl groups in *para* positions, and therefore there is structural analogy. BPA shows changes in various parameters of innate and adaptive immune system in several experimental studies:

- polarisation of Th cells (Th1 vs Th2) e.g. changes via cytokine production (Youn *et al.* 2002[6], Yoshino *et al.* 2003[7] and 2004[8]),
- reduction in number of regulatory T-cells (Tregs) (Ohshima *et al.* 2007[9] and Yan *et al.* 2008[10]),

[3] Patisaul, H. B. (2019). Achieving CLARITY on bisphenol A, brain and behaviour. Journal of neuroendocrinology, e12730.
[4] Rochester *et al* (2018): Prenatal exposure to bisphenol A and hyperactivity in children: a systematic review and meta-analysis. Environ Int. 114:343-356.
[5] Stump *et al* (2010): Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats. Toxicological sciences 115(1): 167-182.
[6] Youn et al (2002): Evaluation of the immune response following exposure of mice to bisphenol A: induction of Th1 cytokine and prolactin by BPA exposure in the mouse spleen cells. Archives of Pharmacal Research (25) 946–953.
[7] Yoshino et al (2003): Effects of bisphenol A on antigen-specific antibody production, proliferative responses of lymphoid cells, and TH1 and TH2 immune responses in mice. British Journal of Pharmacology (138)1271–1276.
[8] Yoshino et al (2004): Prenatal exposure to bisphenol A up-regulates immune responses, including T helper 1 and T helper 2 responses, in mice. Immunology (112) 489–495.
[9] Ohshima et al (2007): Transmaternal exposure to bisphenol a modulates the development of oral tolerance. Pediatric Research (62)60–64.
[10] Yan et al (2008): Exposure to Bisphenol A prenatally or in adulthood promotes T(H)2 cytokine production associated with reduction of CD4CD25 regulatory T cells. Environmental Health Perspectives (116)514–519.

- changes in macrophage function (Byun *et al.* 2005[11] and Li *et al.* 2018[12]),
- changes in immunoglobulin and autoantibody production (Goto *et al.* 2007[13] and Yoshino *et al.* 2004),
- changes in dendritic cell differentiation and function (Guo *et al* 2010[14]),
- changes in lymphoproliferative responses (Goto *et al.* 2007 and Li *et al.* 2018),
- impaired cellular response to food allergens, and increased susceptibility to intestinal parasitic infection in juveniles after perinatal exposure (Menard *et al.* 2014a[15] and 2014b[16]).

The European Food Safety Authority (EFSA) has reviewed BPA also in regard to its immunotoxic potential in years 2010[17], 2015[18] and 2016[19]. EFSA concluded that based on the uncertainty of the reviewed data, it does not contribute to the derivation of tolerable daily intake value. However, the available information on BPA shows that the *in vivo* exposure to BPA changes the immune responses which have been associated to immune-mediated disorders and diseases. Therefore, ECHA considers that the studies above show a concern for developmental immunotoxicity for the analogous substance BPA, and that inclusion of Cohort 3 is justified for the Substance.

The developmental immunotoxicity Cohort 3 must be conducted because there is a particular concern on (developmental) immunotoxicity.

The literature cited above is based on the proposal for amendment, i.e. the publications were either included as an article, or cited in reviews of Hessel *et al.* 2016[20] or Rogers *et al.* 2013[21] referred to in the PfA.

Species and route selection

You proposed testing by oral route in rats. ECHA agrees with your proposal.

Outcome

Under Article 40(3)(b) of REACH, you are requested to carry out the proposed test under modified conditions, as explained above, with the Substance.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. However, you may expand the study by including the extension of Cohort 1B if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the

[11] Byun et al (2005): Bisphenol A-induced downregulation of murine macrophage activities in vitro and ex vivo. Environmental Toxicology and Pharmacology (19)19–24.
[12] Li et al (2018): CLARITY-BPA: Effects of chronic bisphenol A exposure on the immune system: Part 2–Characterization of lymphoproliferative and immune effector responses by splenic leukocytes. Toxicology, (396)54-67.
[13] Goto et al (2007): Orally administered bisphenol A disturbed antigen specific immunoresponses in the naive condition. Bioscience, Biotechnology, and Biochemistry (71)2136–2143.
[14] Guo et al (2010): Bisphenol A in combination with TNF-alpha selectively induces Th2 cell-promoting dendritic cells in vitro with an estrogen-like activity. Cellular and Molecular Immunology (7)227–234.
[15] Menard et al (2014a): Food intolerance at adulthood after perinatal exposure to the endocrine disruptor bisphenol A. FASEB Journal (28)4893-4900.
[16] Menard et al (2014b): Perinatal exposure to low dose bisphenol A impaired systemic cellular immune response and predisposes young rats to intestinal parasitic infection. PLOS One Nov 21;9(11):e112752.
[17] EFSA (2010): Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A
[18] EFSA (2015): Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs
[19] EFSA (2016): A statement on the developmental immunotoxicity of bisphenol A (BPA): answer to the question from the Dutch Ministry of Health, Welfare and Sport
[20] Hessel, E. V., Ezendam, J., Van Broekhuizen, F. A., Hakkert, B., DeWitt, J., Granum, B., ... & Piersma, A. H. (2016). Assessment of recent developmental immunotoxicity studies with bisphenol A in the context of the 2015 EFSA t-TDI. Reproductive Toxicology, 65, 448-456.
[21] Rogers J.A., Metz L., Yong V.W. Review: Endocrine disrupting chemicals and immune responses: a focus on bisphenol-A and its potential mechanisms. Mol Immunol. 2013 Apr;53(4):421-30.

available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[22].

[22] ECHA Guidance R.7a, Section R.7.6.

Appendix B: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 31 October 2018.

ECHA held a third party consultation for the testing proposals from 26 April 2019 until 10 June 2019. ECHA did not receive information from third parties.

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The decision making followed the procedure of Articles 50 and 51 of REACH, as described below:

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA did not receive any comments within the 30-day notification period.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-68 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix C: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State(s).

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[23].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[24].

[23] https://echa.europa.eu/practical-guides
[24] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[25]

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[26]

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

[25] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[26] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fulfilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.