EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 28 April 2021

Addressees
Registrant(s) of JS_133-14-2 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
06/03/2019

Registered substance subject to this decision ("the Substance")
Substance name: Bis(2,4-dichlorobenzoyl) peroxide
EC number: 205-094-9
CAS number: 133-14-2

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***02 February 2023*** *from the date of the decision*.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex IX of REACH

1. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

2. Transgenic rodent somatic and germ cell gene mutation assay (Annex IX, Section 8.4., column 2; test method: OECD TG 488 from 2020[1]) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach; germ cells and duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.

   OR

   In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum.

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annex IX of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH, the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

[1] The updated OECD TG 488, adopted on 26 June 2020, is available on OECD website at https://www.oecd-ilibrary.org/docserver/9789264203907-en.pdf?expires=1596539942&id=id&accname=guest&checksum=D552783C4CB0FC8045D04C88EFFBFA66.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons to request information required under Annex IX of REACH

1. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided the following justification to omit the study: "According to the REACH regulation, vertebrate animal testing must be restricted to the necessary minimum. No effects of the parent were observed up to the water solubility limit in either acute testing covering three endpoints (algae, Daphnia and fish) or chronic testing covering two endpoint (algae and Daphnia). Based on these results, no hazard is observed for the aquatic compartment and the chronic fish test is concluded unnecessary to conduct".

We have assessed this information and identified the following issues:

In general, a registrant may adapt the standard testing regime in accordance with the specific rules set out in column 2 of Annexes VII to X (if applicable) or the general rules set out in Annex XI. For the present information requirement, column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

You have adapted this information requirement by referring to the minimisation of vertebrate animal testing under REACH. Your adaptation does not refer to any of the general adaptation possibilities under Annex XI. Minimisation of vertebrate animal testing is not provided for as an adaptation possibility under the general rules for adaptation set out in Annex XI. It is therefore unclear what adaptation possibility you refer to under Annex XI.

Your adaptation is therefore rejected. On this basis, the information requirement is not fulfilled.

In your comments on the draft decision, you agree to conduct the requested test as specified in the decision, but you remark that, due to the Substance properties, you expect that analytical monitoring of the test concentrations will not be technically feasible.

To fulfil the information requirement, a study must comply with the OECD TG 210 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, among others, the following specifications must be met:

- the analytical measurement of the test concentrations is compulsory;
- a reliable and sufficiently sensitive analytical method for the quantification of the test material in the test solutions must be available, including reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range; and
- where the dissolved fraction cannot be analytically measured (e.g. when solubility is below a quantifiable level), a statement from an analytical chemist in the study report must be provided to confirm that the analytical methods used were state of the art, and a justification as to why lower detection limits were not feasible (any preliminary analytical efforts should also be described in the report).

You indicate that the Substance is difficult to test due to the low water solubility and high adsorption potential. Therefore, similarly to the aquatic toxicity studies provided in your dossier, you expect that it is technically not feasible to monitor test and/or stock solution concentration.

You have not provided any details on the analytical methods to be used in the requested study (including their specificity, recovery efficiency, precision, limits of determination), nor a statement from analytical chemist explaining why the test substance or its degradation products could not be detected.

ECHA understands the analytical difficulties inherent to a poorly water soluble and adsorptive Substance. In the absence of information on the analytical methods and a statement explaining the reasons behind the failure to measure the test substance in the solution, we are not in the position to assess if the analytical methods would be reliable and sufficiently sensitive in the test to be conducted and if the absence of analytical monitoring would be justified.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

The Substance is difficult to test due to the low water solubility (0.02993 mg/L), adsorptive properties (Log Koc = 4.8) and potentially unstable (claimed to be prone to hydrolysis). OECD TG 210 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 210. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

In your comments on the draft decision you indicate that monitoring of the test concentration may not be possible. However, as stated above, you have not provided documentation which would justify the deficiency. Therefore, analytical monitoring is still required. Furthermore, you indicate in the dossier, that the Substance is considered to be "potentially prone to hydrolysis", and that the hydrolysis products are "most likely 2,4,- di-chloro benzoic acid". While you have not indicated if the difficulties in analytical monitoring would apply to the hydrolysis product(s), ECHA encourages you to consider OECD GD 23 recommendations regarding degradation products and identify and quantify the degradation products to facilitate the interpretation of test results for test chemicals that degrade in the test system.

2. Transgenic rodent somatic and germ cell gene mutation assay or *In vivo* mammalian alkaline comet assay

Under Annex IX, Section 8.4, column 2 of REACH, the information requirement for an appropriate *in vivo* somatic cell genotoxicity study is triggered if 1) there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and 2) there are no appropriate results already available from an *in vivo* somatic cell genotoxicity study.

In relation to the first condition, your dossier contains positive results for the *in vitro* gene mutation study in bacteria, which raise the concern for gene mutation.

In relation to the second condition, your dossier contains no data from an *in vivo* somatic cell genotoxicity study.

As regards the first condition, in your comments to the original draft decision you indicated that the "*positive mutagenic reactions were only seen in the Ames test in the absence of S9, and were not observed in the presence of S9*". Additionally you stated that the "*Response in a strain without metabolic activation, would mostly also lead to a response with metabolic activation (converse is not expected).*" Finally you noted that the observed effects were "*very small*", "*not consistent over the different experiments performed*" but "*statistically significant, in only one of the three experiments, and in two of the three experiments in case of TA100*".

In the proposal for amendment (PfA), submitted by one of the Member States Competent Authorities (MSCAs), the Ames test result was considered as being positive. More specifically it was noted that the first experiment revealed statistically significant increases in the frequency of revertant colonies in *S. typhimurium* strains TA100, TA1535 and TA98 with a dose-response relationship for TA100 and TA98. As regards the negative results of the second experiment, it was noted that this experiment should not be taken into account as in the dossier it is indicated that there were technical issues with this experiment. As for the third experiment, which was performed with the strains showing increases in experiment one (TA100, TA1535 and TA98), there was a statistically significant increase in the frequency of TA98 revertant colonies, reported at the upper dose levels of the test item confirming the findings of the first experiment. In the PfA it was also noted that even though "*the observed increase was small and below a factor of 2*", this alone should not lead to the conclusion that the test result is negative (Levy *et al.*, 2019[3]) as the "*significant results were generally above the upper limit of the in-house vehicle/untreated historical control range*".

In your comments to the PfA you again stated there was only a "*weakly mutagenic response in the Ames test to one strain of bacteria (TA98) in the absence of S9-mix at levels showing precipitation*". Moreover you indicated that this result was only noted in the direct plate incorporation, but was not observed with the pre-incubation method, which you claim as the "*more sensitive*" method. As regards the technical issues of the second experiment flagged in the PfA you indicated that there was a technical issue which required the test system without S9 to be partly repeated but after that also the second experiment was correctly performed in full.

Moreover, in your comments on the PfA you referred to the test method OECD TG 471 where it is indicated that "*Biological relevance of the results should be considered first. [...] However, statistical significance should not be the only determining factor for a positive response.*" You also referred to the Levy *et al.* (2019) publication and emphasized that "*the workgroup was not able to reach consensus recommendations*". However, it was recommended that a combination of approaches such as a fold-increase or statistics, can be used in combination with historical control values and expert judgment.

Following the considerations raised in the PfA and your comments, we acknowledge that the pre-incubation method is a more sensitive test method however we cannot disregard the results obtained with the plate incorporation method. As regards your comments on experiment 2 we still note that in the dossier, in the tabulated data there is reference that for experiment 2 (without S9) there were technical issues.

In the comments on the PfA you indicate that in experiment 3 "*the positive results were repeated only for TA98*". Therefore, we consider that the Ames test results obtained for the TA98 strain in experiments one and three, without metabolic activation, showed 1) a concentration-related increase over the range tested, and 2) a reproducible increase at one or more concentrations in the number of revertant colonies per plate.

[3] Levy *et al.*, 2019, *Recommended criteria for the evaluation of bacterial mutagenicity data (Ames test)*, Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Volume 848, December 2019, 403074: https://www.sciencedirect.com/science/article/pii/S1383571819300774

Moreover, we acknowledge your comments concerning the consideration of the "*biological relevance*" of the result but also the "*combination of approaches*" recommended in the publication by Levy et al. (2019). When taking together the information submitted in the dossier and in your comments, we still consider the result obtained for TA98 as being positive, not only because there was a dose related and reproducible result but also because the increase in revertant colonies for TA98 was actually over two-fold.

In your comments to the original draft decision you emphasized that the positive result was only obtained when the Substance was tested without the metabolic activation system. However we note that, according to OECD TG 471, a result is considered positive if there are concentration-related and reproducible increases in at least one of the test conditions.

Based on the above we conclude that the first condition is met as the *in vitro* gene mutation study in bacteria is positive.

Therefore, the two conditions set out in Annex IX, Section 8.4, column 2 are met and the information requirement for an appropriate *in vivo* somatic cell genotoxicity study is triggered.

In your comments to the original draft decision and on the PfA you concluded that the relevance of performing the *in vivo* study is "*highly doubted*" considering (1) "*the small effects observed in the Ames test*", (2) the negative result obtained in the *in vitro* gene mutation in mammalian cells study, and (3) "*the lack of significant exposures to industrial worker and no consumer exposures*".

We note that at Annex IX the *in vivo* somatic cell genotoxicity study is triggered if there is a positive *in vitro* result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already. As explained above both of these criteria are met. Therefore your statements (1) and (2) above cannot be used to waive this information requirement (Annex IX, Section 8.4., column 2).

As regards your statement (3) we consider that you refer to an option to omit testing according to Annex XI Section 3. We note that as stated in Annex XI, Section 3, testing in accordance with Annexes IX and X may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report (CSR), by providing an adequate and scientifically-supported justification based on a thorough and rigorous exposure assessment in accordance with Section 5 of Annex I and by communicating the specific conditions of use through the supply chain. Any one of the following criteria 3.2.(a),(b) or (c) shall be met:

a) The first criterion 3.2(a) requires "*absence of or no significant exposure in all scenarios of the manufacture and all identified uses*". Moreover, relevant PNECs or DNELs are to be derived and exposure results are to be well below the derived PNECs or DNELs;
b) The second criterion 3.2(b) requires a demonstration that "*throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f)*" apply;
c) The third criterion 3.2(c) sets out conditions which have to be fulfilled for a substance incorporated in an article.

ECHA has assessed the information in the dossier and notes the following:

a) You have performed qualitative and quantitative exposure assessment in your dossier. We note that a number of work activities are not performed in closed systems and the prevention of exposure is also based on the use of personal protective equipment. Your quantitative exposure assessment is based solely on modelling with ECETOC TRA v. 3 which is generally a conservative exposure tool, but also very uncertain. For example we note that in your quantitative exposure assessment you have estimated exposure as high as [redacted] for inhalation and 5.5 mg/kg bw/day for dermal

exposure route for PROC 10 in the contributing scenario (CS) 11 in exposure scenario (ES) 4. This does not support "*absence of or no significant exposure*".

According to ECHA Guidance R.5, the absence of or no significant exposure should be demonstrated for all identified uses with a high level of certainty which can be achieved with an appropriate higher tier exposure tool or with representative measured data. In this regard, according to ECHA Guidance R.14 (R.14.6.1) "*Uncertainty of the exposure estimate needs to be considered to ensure that the conditions of use are sufficiently covered by the exposure estimate. Depending on the level of uncertainty around the various factors contributing to the exposure estimate and resulting RCR, it is recommended to refine (re-iterate) the exposure by alternative means, to reduce the uncertainty. This may include for example modelled exposure from higher tier models, sensitivity considerations regarding input data in models, and by inclusion of or resorting to (additional) measurement data in a weight of evidence approach to increase reliability of the outcome and to guarantee safe use.*"

Moreover, when comparing your exposure estimates with the respective DNELS, ECHA does not consider these RCRs to be well below one. For example, the highest RCR [redacted] for PROC 10 in CS 11 in ES 4 is close to 1. Whilst an RCR <1 demonstrates safe use for a registered substance where the toxicological endpoints are fulfilled, this is not sufficient for omitting standard testing requirements. For that purpose, the exposure assessment needs to show that exposures are always well below the derived DNEL and the assessment needs to take into account the increased uncertainty resulting from the omission of the information requirement. Therefore, the current data in the dossier does not support your claim of "*lack of significant exposures*".

b) The work activities are not performed under strictly controlled conditions.

c) The Substance is not incorporated into an article.

Based on the above none of the criteria of Annex XI, Section 3.2. (a), (b) or (c) are met.

Therefore, the information you provided in the dossier does not meet the general rules for adaptation of Annex XI, Section 3, as none of the criteria of that adaptation are currently fulfilled.

Based on the above, there is an information requirement for an *in vivo* somatic cell genotoxicity study which needs to be fulfilled.

i. Test selection

According to the ECHA Guidance Chapter R.7a, Section R.7.7.6.3, the transgenic rodent somatic and germ cell gene mutation assay ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a positive *in vitro* result on gene mutation.

ii. Test design

a) TGR assay

If you perform the TGR assay, according to the test method OECD TG 488, the test must be performed in transgenic mice or rats and the test substance is usually administered orally.

Based on the recent update[4] of OECD TG 488, you are requested to follow the new 28+28d regimen, as it permits the testing of mutations in somatic tissues and as well as in tubule germ cells from the same animals. This updated version provides for a transitional period for the new version. However, ECHA is aware that testing according to the updated OECD TG is already available from CROs and the new study design would provide meaningful germ cell data, so this decision requires the application of the new version.

According to the test method OECD TG 488, the test must be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, glandular stomach and duodenum as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 °C) until the analysis of liver and glandular stomach is completed; the duodenum must then be analysed only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

b) Comet assay

In case you decide to perform the comet assay according to the test method OECD TG 489, the test must be performed in rats. Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

Your comments to the draft decision also referred to the test design:

1) You indicated that you "*strongly advice against oral use*" and that "*there can hardly be any exposure*" in view of the industrial use. Considering that the Substance is classified as a "*strong skin sensitiser*" there is adequate protection to preclude significant dermal exposures. Moreover you claimed that "*the product is a paste with a very low vp which also precludes exposures via inhalation*."

   In your comments you mostly refer to the exposure of the Substance rather than the choice of route to perform the test. You only stated that you "*strongly advice against oral use*" however you have not provided a justification why the oral route is not appropriate for testing. We note that the selection of the oral route is based on the available information on the Substance including the toxicity data (e.g. oral sub-chronic toxicity study (90-day)) available in the dossier and the need for adequate exposure of the target tissue(s), as indicated in OECD TGs 489 and 488. As regards

[4] The updated OECD TG 488, adopted on 26 June 2020, is available on OECD website at https://www.oecd-ilibrary.org/docserver/9789264203907-en.pdf?expires=1596539942&id=id&accname=guest&checksum=D552783C4CB0FC8045D04C88EFFBFA66.

your claims on the exposure to the Substance, as already explained above, the current data in the dossier does not support your claims on "*absence of or no significant exposure*" (Annex XI, Section 3.2(a)) of the Substance.

2) You indicated that the Substance is not a weak acid or base and that the absorption properties are not expected to change at different physiological pH conditions. You also indicated that the possible breakdown/metabolism products are not indicated to be a direct concern.

ECHA notes that for these tests we request by default the collection of the liver and of two site-of-contact tissues (glandular stomach and duodenum). In your comments you simply refer to the properties of the Substance. However, you have not provided any valid justification on why testing on these specific and default site-of-contact tissues cannot be performed using the Substance.

Therefore, based on the above, you should perform either OECD TG 488 or 489, following the above test specifications.

iii. Germ cells

A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483, depending on the concern raised by the substance) may still be required under Annex IX of REACH, in case 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

Therefore, in case you decide to perform the TGR, you must collect the male germ cells (from the seminiferous tubules) at the same time as the other tissues, in order to limit additional animal testing. According to the OECD 488, the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 °C). This duration is sufficient to allow you or ECHA, in accordance to Annex IX, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells.

In case you decide to perform the comet assay, you may consider to collect the male gonadal cells collected from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, in accordance to Annex IX, Section 8.4., column 2, you should consider analysing the slides prepared with gonadal cells.

This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

2. 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.

3. 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 on How to report robust study summaries[5].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity 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.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[6].

[5] https://echa.europa.eu/practical-guides
[6] https://echa.europa.eu/manuals

Appendix C: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 27 March 2020.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and removed the request for *in vivo* mammalian alkaline comet assay or transgenic rodent somatic and germ cell gene mutation assay from the decision. As a consequence the deadline of the decision was also modified.

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 to include the request for *in vivo* mammalian alkaline comet assay or transgenic rodent somatic and germ cell gene mutation assay. As a consequence the deadline of the decision was also modified.

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-73bis written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix D: List of references - ECHA Guidance[7] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

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 where relevant.

Read-across assessment framework (RAAF, March 2017)[8]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

Physical-chemical properties
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.

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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[9]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[7] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[8] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

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

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.