Helsinki, 18 December 2017

Addressee: [redacted]

Decision number: CCH-D-2114378524-42-01/F
Substance name: benzaldehyde
EC number: 202-860-4
CAS number: 100-52-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26.04.2016
Registered tonnage band: Over 1000 tonnes per year

**DECISION ON A COMPLIANCE CHECK**

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **High-pressure liquid chromatogram or gas chromatogram (Annex VI, Section 2.3.6.), as specified in Appendix 1;**
2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2, test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**
3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3; test method: OECD TG 476 or OECD TG 490) with the registered substance; provided that the study requested under 2. has negative results;**
4. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2; test method: EU B.31/OECD TG 414) in a first species (rats or rabbits), oral route with the registered substance;**
5. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2; test method: EU B.31/OECD TG 414) in a second species (rats if first species was rabbits or rabbits if first species was rats), oral route with the registered substance;**
6. **Extended one-generation reproductive toxicity study (Annex IX/X, Section 8.7.3; test method: OECD TG 443) in rats, oral route, with the registered substance, specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity); and**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**
7. **Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1; test method: Daphnia sp. Acute immobilisation test, EU C.2/OECD TG 202) with the registered substance;**

8. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2; test method: Alga, growth inhibition test, EU C.3/OECD TG 201) with the registered substance;**

9. **Identification of PNEC and risk characterisation (Annex I, Section 3.3.1. and 6.): revise PNECs for freshwater, marine water, intermittent releases, freshwater sediment, marine sediment and soil using the assessment factors recommended by ECHA Guidance R.10 for PNEC derivation and revise the risk characterisation accordingly *or* provide a detailed justification for not using the recommendations of ECHA guidance in PNEC derivation.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **25 June 2020**. You also have to update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

**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] by Claudio Carlon, Head of Unit, Evaluation E2

[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.

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**Appendix 1: Reasons**

IDENTIFICATION OF THE SUBSTANCE

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

1. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.)**

According to Annex VI, Section 2.3.6 of the REACH Regulation, a registration dossier shall contain a high-pressure liquid chromatogram or a gas chromatogram for the identification and quantification of the constituents of the substance, as reported in IUCLID section 1.2. Adequate information needs to be present in the registration dossier to meet this information requirement.

You have identified the substance as a mono-constituent substance. According to the compositional information provided in IUCLID section 1.2, the substance consists of one main constituent [redacted] (concentration range [redacted]%) and 3 impurities ([redacted]) each with concentration range [redacted]%. You have provided a gas chromatogram (document "[redacted]") in IUCLID section 1.4 which includes the description of the method, a peak table with the expected retention times for various peaks (identified with acronyms), and two chromatographic pictures. The Peak area percentage values have not been provided.

ECHA notes the following deficiencies in the chromatogram:

(i) The chromatographic picture indicates a multitude of peaks, which is not expected for a highly pure mono-constituent substance with a main constituent having a concentration range of [redacted]% (w/w) as reported in IUCLID section 1.2.
(ii) The peak area percentage values have not been provided in the analytical report.
(iii) The chemical names corresponding to the acronyms reported in the peak table (under the column "Peak name") have not been provided.

ECHA concludes that the chromatogram attached in section 1.4 of your registration dossier does not confirm the identity and composition of the substance as per the requirements laid down in Annex VI, section 2 of the REACH Regulation. Consequently, it is necessary to provide additional information to confirm the identity and composition of the substance.

In your comments you agreed the data do not appropriately establish the substance purity and identity, and you indicated that your registration dossier will be updated with reliable information.

Therefore, you are requested to submit the following information on your substance as manufactured or imported:

- The area percentage of each significant peak in the chromatogram shall be provided and shall be linked to a chemical name (without relying solely on an acronym).
- The chromatographic information should be revised so that the peaks in the chromatogram and the associated peak area percentage values can be clearly linked to the compositional information reported in section 1.2 of the technical dossier.
- The chromatographic information must be sufficient to verify the composition reported in section 1.2 of the dossier. Furthermore, you shall ensure that the reported information is consistent throughout the dossier.

The requested information shall be included in section 1.4 of the technical dossier.

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

For the endpoints "Pre-natal developmental toxicity (Annex IX/X, Section 8.7.2)" and "Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3)", your registration dossier contains adaptation arguments in form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your Grouping and read-across approach in general before the individual endpoints (sections 4, 5 and 6).

**Grouping and read-across approach for toxicological information**

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration.
Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests.

Thus physicochemical properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical properties is only a part of the read-across hypothesis, and it is

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]: (1) (Bio)transformation to common compound(s) and (2) Different compounds have the same type of effect(s).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

## A. Description of the grouping and read-across approach proposed by the Registrant

You seek to adapt the human health information requirements for "Pre-natal developmental toxicity (Annex IX/X, Section 8.7.2)" and "Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3)" by applying a read-across approach according to Annex XI, Section 1.5.

You consider to achieve compliance with the REACH information requirements for the registered substance benzaldehyde (EC No 202-860-4) using data of structurally similar substances: benzyl alcohol (EC No 202-859-9), benzoic acid (EC No 200-618-2), sodium benzoate (EC No 208-534-8) and benzyl acetate (EC No 205-399-7) (hereafter the 'source substances').

You have provided read-across documentation as a separate attachment, in section 13 of the registration dossier, entitled "[redacted]".

You use the following arguments to support the prediction of properties of the registered substance from data for reference substance(s) within the group by interpolation to other substances in the group: (1) this grouping of substances is based on previous toxicological evaluations by expert panels and regulatory authorities; (2) these substances are all rapidly metabolised and excreted via a common pathway within 24 hours; (3) the substances have similar structure, physico-chemical properties and toxicology.

According to you, the source substances and the registered substance "*are closely related structurally*". "*This [category] is based on the fact that* in vivo *the major pathway of metabolic detoxification involves oxidation to yield benzoic acid*". You also note that "*the physicochemical data such as aggregate state, melting point, vapour pressure, and dissociation constant differ substantially for the substances depending on the nature of the functional group (alcohol-, aldehyde-, carboxyl-)*".

You justify the used of the category approach on the "*similar metabolic pathway of the category members* in vivo", and because the "*systemic toxicity [of the members of the category], driven by the same metabolic product, has proven to be the same*" for the above-mentioned information requirements.

ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the properties of the registered substance from the above-mentioned source substances.

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

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## B. ECHA analysis of the grouping and read-across approach

ECHA has the following observations on your justification of the read-across:

1) You have provided a listing of previous toxicological evaluations by expert panels and regulatory authorities, but have not provided the toxicological evaluations themselves. However, the reference to these previous evaluations does not provide a basis for adaptation under Annex XI, Section 1.5 since none of these previous evaluations has applied the requirements of Annex XI, Section 1.5 for predicting the properties of the registered substance.

2) You provided the "*widely accepted*" metabolic pathway of benzaldehyde (based on ACGIH, 1986), linking benzyl acetate, benzyl alcohol, benzaldehyde, benzoates and benzoic acid. Although the referenced article has not been provided in the registration dossier, ECHA accepts that it is likely that benzoate is formed from benzaldehyde via a metabolic oxidation pathway, and notes that you have not provided any evidence that this *in vivo* oxidation is the only (bio)transformation pathway acting on benzaldehyde. If there is another metabolic pathway for benzaldehyde which has not been described in you registration dossier, this would contradict your read-across hypothesis.

   Furthermore, you have not shown that (bio)transformation of benzaldehyde to benzoate is sufficiently rapid and complete, to exclude systemic bioavailability and internal exposure to benzaldehyde itself. You make reference to a report (published in the International Journal of Toxicology, 2006) stating that "*Bray* et al. *(1951) reported that Benzaldehyde is metabolised to benzoic acid by first-order kinetics at a velocity rate constant of 0.33/h (in rabbits) [...]*". You provided a limited summary of this study so that there is not sufficient information provided to make an independent assessment of the statement. Nonetheless, this statement suggests that benzaldehyde would be systemically available and would remain present in the systemic circulation for an appreciable time, with a half-life of ~1.5 hours.

   You also reported a non-GLP, non-guideline basic toxicokinetics study (key study, with reliability 2) performed in rats (Kutzman *et al.*, 1979) with the registered substance. Five female rats were exposed to $^{11}$C-labelled benzaldehyde in vapour for 2 min (inhalation route) at a single dose of 2.5 µg. No control group was selected. At 1.5 min, 5 min, 12 min, 20 min and 40 min after exposure, one dosed animal was killed. The kinetics and biodistribution were studied based on the decay characteristics of short-lived gamma-emitting radioisotopes. The following results were reported:
   Absorption: Inhaled the test substance was rapidly absorbed and at 1.5 min after exposure, only 1.2% of the administered dose was resident in the respiratory tract, with 0.8% in the lungs;
   Distribution: The test substance was quickly distributed with the peak radioactivity in the organs occurring at 1.5 min after exposure;
   Excretion: The test substance was rapidly excreted in the urine, via the renal system with the kidneys containing 17% of the total administered activity at 5 min. You noted that "*because inhaled the test substance was rapidly excreted into the urine, the percentage of the administered dose retained by the animals until the time of sacrifice was largely dependent upon when the rat last urinated and the amount of urine present in the bladder.*" "*The biological half-life of the test substance in the blood of exposed rats was 8.1 minutes, and elimination of radiolabel from most organs paralleled the clearance of the test substance from the blood. Organs with a limited blood flow eliminated the test substance more slowly with a net loss of radiolabel recorded only after 5 to 12 minutes following exposure.*"
   ECHA notes that on the basis of the information provided, there is not sufficient information to make an independent assessment of the study. Furthermore, the study

provides limited value information in terms of sensitivity (only one animal per timepoint) and the study is not part of the read-across approach. However it seems to provide results on biological half-life which may be contradicting those of the report above.

ECHA concludes that you did not adequately address important aspects such as the toxicokinetics of the parent substances and their metabolic fate and the resulting possible differences in their metabolite profiles.

In your comments you agreed to include in an updated registration dossier, further information by populating the empty fields of the dossier to better represent the details of the existing data from each of these published ADME studies with benzaldehyde, as you indicated that *"although all of these published studies are considered as good quality Klimisch category 2 peer reviewed reports, none of them are GLP or conducted according to OECD test guideline 417. For some of them, we recognize that there is a lack of numerical or graphical data to fully demonstrate rates of biotransformation (Bray et al., 1951). In some of the studies, no control group was included (Kutzman et al., 1980)."*

You also added that *"the Consortium considers that these data provide useful supportive evidence to indicate that the half-life of benzaldehyde in the body is short, and that the principal pathway of metabolism of benzaldehyde includes oxidation to yield benzoic acid. Since the Consortium cannot provide a Klimisch category 1 robust study summary, we propose a tiered-approach to ECHA to first clarify the ADME of benzaldehyde by conducting a GLP toxicokinetic study in accordance with OECD guideline 417" and that "the results of this definitive GLP ADME study with benzaldehyde will provide robust support for the previously-published ADME studies and will therefore demonstrate that the read across hypothesis is valid."* ECHA acknowledges your intention to provide an additional more robust study to support your read-across hypothesis in an update of your registration dossier, while addressing the REACH provisions related to alternatives to animal testing and animal testing as a last resort. However the information provided in the upcoming update will only be reviewed after the deadline indicated in the final decision has passed.

When considering that bioavailability of benzaldehyde is likely, it should be explained why systemic exposure to benzaldehyde would not significantly influence the toxicological properties under consideration. However, you did not include any such explanation. In this respect, ECHA further notes that the structural differences between benzaldehyde and benzoate are significant: whereas benzaldehyde contains an aldehyde function, benzoate bears a carboxylate group instead. It is emphasised that an aldehyde function exerts a significantly different reactivity compared to a carboxylate group, namely high reactivity towards nucleophiles, such as the reaction of amino groups of peptides/ proteins with aldehydes by nucleophilic addition to yield Schiff base. Such reactivity is not observed for carboxylate groups. You have not explained why these structural differences and their inherent different reactivity result in similar toxicological properties with respect to reproductive and pre-natal developmental toxicity. Therefore, the provided explanation does not provide a reliable basis for predicting the properties of benzaldehyde from benzoate which does not rely upon conversion to benzoate.

3) Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical and toxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical and toxicological properties does not always lead to predictable or similar human health properties in other endpoints.

So you have not established why a prediction for other human health/ environmental properties is reliable. Additionally you have noted that "*the physicochemical data such as aggregate state, melting point, vapour pressure, and dissociation constant differ substantially for the substances depending on the nature of the functional group (alcohol-, aldehyde-, carboxyl-)*". This shows that the physicochemical data differ, and so the (eco)toxicological properties would be expected to differ as a result of these changes.

Furthermore, you have provided study records for repeated dose toxicity studies which show significant differences with respect to toxicological effects:
(i) Benzaldehyde effects: in a 13-week gavage study (1990), rats and mice (males and females) were given the registered substance by gavage, at five different doses. More deaths were observed in males than in females at the top dose (800 mg/kg bw/day): 6/10 male rats versus 3/10 female rats and 9/10 male mice versus 1/10 female mice. In both species, compound-related lesions included degeneration and necrosis of renal tubules. In addition in rats, lesions included necrosis in the hippocampus, in the cerebellum, in the liver epithelium and hyperplasia and or hyperkeratosis in the forestomach. The NOAEL was set at 200 mg/kg bw/day in rats, and at 600 mg/kg bw/day in mice.
(ii) Benzoic acid effects: in a 4-generation study (1960) on benzoic acid (2 doses in feed), no effects were observed in any generation on growth, organ weights, or fertility. From other parameters, you reported that "*it can be assumed that as a minimum the brains, heart, liver, kidney, testis and were examined*". The NOAEL was set at >750 mg/kg bw/day.

At comparable doses, benzaldehyde (800 mg/kg bw/day) causes effects (deaths, effects in the brain, degeneration of the liver, necrosis of the liver (males only), and degeneration or necrosis of the tubular epithelium in the kidney also occurred at the highest dose), whereas benzoic acid (750 mg/kg bw/day) causes no effect.
Such differences may indeed stem from qualitative differences (i.e. exposure to different substances) and/or quantitative differences (e.g. exposure of target tissues to different concentrations of a substance).

The observed differences provide prima facie evidence that benzaldehyde exerts different effects than benzoic acid. Therefore, ECHA concludes that the presented evidence contradicts your hypothesis that the target and source substance have the same toxicological properties, and on this basis also, it is not possible to predict the toxicological properties under consideration.

4) Additionally, ECHA considers that the characterisation of the tested substances in the source studies needs to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/ or impurities of the tested material(s). In the ECHA practical guide "*How to use alternatives to animal testing to fulfil your information requirements (Chapter 4.4 on Read-Across)*", it is recommended to follow the Guidance on identification and naming of substances und REACH (version 2.0, December 2016) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

ECHA notes that the source substances are identified by their chemical names and CAS numbers. However, the impurity profiles of the source substances cannot be assessed using the information provided in the registration dossier and, hence, ECHA cannot verify the suitability of the substances for read-across. As the structural similarity between the source substances and the target substance cannot be established, prediction of toxicological properties is not possible.

5) Annex XI, Section 1.5 requires for studies used for read-across purposes that "*adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3)*" is ensured and that you provide "*adequate and reliable documentation*".

With respect to the information requirement for extended one-generation reproductive toxicity (Annex X, Section 8.7.3.), ECHA notes that you have provided a non-GLP, non-guideline four-generation study with the source substance benzoic acid in rats in which only some reproduction parameters were assessed: "*Percentage of infertility, delayed sexual maturation, litter size, total pups, surviving pups.*" However, according to the OECD testing guideline, comprehensive examinations on functional fertility such as mating and gestation indices and male and female reproductive systems is required including, in particular, examination of the oestrous cycle; sperm parameters; organ weights of uterus, ovaries, testes, epididymides, prostate, seminal vesicles with coagulating glands and their fluids and prostate, thyroid, pituitary, adrenal glands; histopathology of vagina, uterus with cervix, ovaries, testis, epididymis, seminal vesicles, prostate, and coagulating gland. ECHA notes that these key parameters have not been examined.
Furthermore, ECHA notes that the dose level setting, which is a key parameter, does not comply with the requirements of OECD TG 416 because only two doses were used (0.5% and 1%), no rationale for dose selection has been provided and no toxicity was observed at the highest dose.

With respect to the information requirement for pre-natal developmental toxicity according to Annex IX/X, Section 8.7.2., ECHA notes that you have provided four non-GLP, pre-natal developmental toxicity studies with the source substance sodium benzoate in mice, rats, hamsters and rabbits which are designated as equivalent or similar to OECD TG 414. ECHA notes that the exposure duration deviates from that prescribed in the current test guideline because it was from day 6 through day 15 of gestation in rats and mice, from day 6 through day 10 of gestation in hamsters, and from day 6 to day 18 of gestation in rabbits. OECD TG 414 states that the study "*is not intended to examine solely the period of organogenesis, (e.g. days 5-15 in the rodent, and days 6-18 in the rabbit) but also effects from preimplantation [...] through the entire period of gestation to the day before caesarean section.*" Hence, the effects from preimplantation through the entire period of gestation, which is a key parameter foreseen to be investigated, is not covered. According to ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017), R.7.6.4.2.2, "*If a study is conducted according to an old test method and thus uses a shorter administration period than current test methods, it is important that there is no indication challenging the exposure period used. Thus, if there is a concern suggesting that a longer exposure period would have revealed developmental toxicity or more profound findings affecting also lower dose levels that were not observed using shorter exposure duration, this should be addressed*".

However, ECHA notes that you have not explained whether a longer administration period is not deemed necessary for the registered substance. Furthermore, according to OECD TG 414, "*unless limited by the physical/chemical nature or biological properties of the test substance, the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering.*"

However, you have not reported any rationale for dose selection and according to the study records no effects have been observed for any species at the highest dose administered. In this respect ECHA notes that the highest dose tested was 175 mg/ kg bw/ day in rats and mice, 300 mg/kg bw/day in hamsters, and

250 mg/ kg bw/ day in rabbits only, and that a limit test according to OECD TG 414, paragraph 16, was not performed. Therefore, ECHA concludes that the dose level setting was inadequate to investigate pre-natal developmental toxicity for the registered substance. Moreover, due to limited reporting in all four study records, ECHA cannot assess which examinations have been actually performed on maternal animals and offspring. It is also noted that you have stated that the performed studies deviate in "*foetal examinations*" but you did not specify in detail which examinations were and were not conducted.

ECHA concludes that the source studies do not provide the information required by Annex IX/X, Section 8.7.2. (pre-natal developmental toxicity) and Annex X, Section 8.7.3. (extended one-generation reproductive toxicity), because they do not meet the requirements of Annex XI, Section 1.5.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

ECHA considers that your comment does not provide a basis for considering that the read-across is acceptable, since you accept that "*After re-evaluation of the available data for the ADME of benzaldehyde [*they agree that*] the published data are somewhat limited*" and that you "*understand that the dossier has apparent gaps in information*".

ECHA acknowledges your intention provide more robust information to support your read-across hypothesis in an update of your registration dossier.

**C. Conclusion**

The adaptation of the standard information requirements for pre-natal developmental toxicity (Annex IX/X, Section 8.7.2.) and extended one-generation reproductive toxicity (Annex X, Section 8.7.3.) in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5.

In your closing comments, you added that: "*The consortium believes that these results [GLP ADME/ OECD TG 417 study] should be obtained prior to launch any new developmental or reproductive toxicological studies. Until contradictory results coming from the results of the toxicokinetic study, we feel that all the other data requirements have been adequately addressed, and believe that any additional testing would be duplicative of existing data, and would therefore go against the underlying directive of the REACH regulation to "... replace, reduce or refine testing on vertebrate animals", and the idea that animal testing should be used as a last resort.*"

ECHA acknowledges your intention to provide additional information in an update of your registration dossier to better support your read-across hypothesis, and as a first step prior to deciding whether the studies OECD TG 414 in two species and the OECD TG 443 are necessary. However, the information is currently not available and if submitted, it will only be reviewed after the deadline indicated in the final decision has passed.

Therefore, ECHA rejects the read-across adaptations in the technical dossier for pre-natal

developmental toxicity and extended one-generation reproductive toxicity.

**2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)**

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.
An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided two study records for *in vitro* mammalian chromosome aberration tests, one (1986) being the key study, whereas the other (1982) is designated as supporting study. However, neither the key study nor the supporting study provide the information required by Annex VIII, Section 8.4.2., because they were not performed according OECD TG 473. In the 1986 study, only 100 cells and in the 1982 study only 162 cells were scored, instead of "at least 300 cells" cells as prescribed in the OECD TG 473. Furthermore, for both tests you did not provide any data on mitotic index together with a rationale for top concentration, and did not present the tabulated data. The scoring of only 100 and 162 cells represents a significant deviation, which consequently significantly impacts the statistical analysis and renders the results of the tests questionable. Moreover, ECHA cannot conclude whether the concentrations selected for the study were appropriate as no data on mitotic index nor rationale for top concentration was provided. ECHA also notes that the 1982 study was performed in the presence of metabolic activation only and therefore does not provide any information on possible effects in absence of metabolic activation. In view of the significant deviations described above, ECHA concludes that the two studies submitted do not fulfil the standard information requirement according to Annex VIII, Section 8.4.2.

In addition to the two *in vitro* chromosome aberration tests, you have also provided (i) two study records for sister chromatid exchange assays in mammalian cells (one key and one supporting study), (ii) one study record for a single cell gel/comet assay in mammalian cells for detection of DNA damage (supporting study) and (iii) one study record for a DNA damage and repair assay, unscheduled DNA synthesis in mammalian cells *in vitro* (supporting study).

In the IUCLID section 7.6.2 ("*Genetic toxicity in vivo*"), you have also provided three records, with reliability scores of 2 or 4: (i) two records for a *Drosophila melanogaster* Sex-linked recessive lethal (SLRL) assay (1985), (ii) wing somatic mutation and recombination test (SMART) of *Drosophila melanogaster* and (iii) an Ames test of metabolites of benzaldehyde extracted from rat urine (1979). Finally you also provided a reliability-4 *in vitro* sister chromatid exchange study (1989) which was not further assessed.

However, none of these *in vitro* and *in vivo* assays provides the information required by Annex VIII, Section 8.4.2., because these assays neither identify agents that cause structural chromosome aberrations nor detect micronuclei in the cytoplasm of interphase cells.
As explained above, the information provided on this endpoint for the registered substance does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In your comments, you agree that the current information does not meet the information requirement, and you indicate that you will provide an update of the dossier, tying together the various studies to demonstrate how they meet the specific endpoint requirements. ECHA acknowledges your intention to provide additional information in an update of your

registration dossier. However, the information is currently not available and if submitted, it will only be reviewed after the deadline indicated in the final decision has passed.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* cytogenicity study in mammalian cells (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

### 3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "*if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2.*" is obtained. ECHA notes that the registration dossier contains negative results for one of these information requirements, i.e. *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.), but it does not contain appropriate study records for the information requirement *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study according to Annex VIII, Section 8.4.2. (see request 2). Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under point 2 has negative results.

In the technical dossier you have provided a study record for a non-guideline mammalian cell gene mutation assay (1989), designated as key study. However, this study does not provide the information required by Annex VIII, Section 8.4.3., because no data on the relative total growth (RTG) nor rationale for selecting the top concentration has been provided. Therefore, ECHA cannot conclude whether the study design (selection of concentrations) was appropriate. ECHA also notes that the study was performed in the absence of metabolic activation only and it does not provide any information on possible effects in the presence of metabolic activation.
Furthermore, no tabulated data is presented and, therefore, it is not possible to verify whether the increase in the mutant frequency is higher than the threshold 126 global evaluation factor (GEF value), i.e. your overall conclusion "*positive at slightly toxic doses*" cannot be verified. Based on the information provided, ECHA concludes that this study deviates significantly from the OECD TG 476. In view of the significant deviations described above, ECHA concludes that the test does fulfil the information requirement of Annex VIII, Section 8.4.3.

In addition to the key study above, you have provided a study record for a non-GLP mammalian cell gene mutation assay (1997), designated as supporting study. You classified this study as reliability 4 (not assignable). ECHA concludes that also this study does not provide the information required by Annex VIII, Section 8.4.2. because no tabular results, no reporting on cytogenicity, no rational for selection of concentrations has been provided. Furthermore, the study is unreliable and was performed without positive control.
In the IUCLID section 7.6.2 ("*Genetic toxicity in vivo*"), you have also provided three records, with reliability scores of 2 or 4: (i) two records for a *Drosophila melanogaster* Sex-linked recessive lethal (SLRL) assay (1985), (ii) wing somatic mutation and recombination test (SMART) of *Drosophila melanogaster* and (iii) an Ames test of metabolites of benzaldehyde extracted from rat urine (1979). However, all these *in vivo* assays do not provide the information required by Annex VIII, Section 8.4.3., because these assays do not detect gene

mutations in mammalian cells.

As explained above, the information provided on this endpoint for the registered substance does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In your comments, you agree with ECHA that the studies presented have significant deviations from the current OECD TG 476, and therefore do "*not take issue with performing a contemporary OECD 476*".

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 or OECD TG 490) provided that the study requested under point 2 exhibits negative results.

**4. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species**

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

A "pre-natal developmental toxicity study" for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing 4 study records for a pre-natal developmental toxicity non-GLP study (OECD TG 414) with the analogue substance sodium benzoate, performed in 4 different species (rat, mouse, hamster and rabbit) ([redacted], 1972).

As explained above in this decision, your read-across adaptation of the information requirement is rejected. In addition, ECHA observes that the reported reliability of the four studies above was set at 2, because of (i) the limited study summary (publication in a peer-reviewed journal), (ii) the study is predating the approved guidelines, and (iii) the deviation related to exposure period and fetal examinations. ECHA notes that the reporting of the studies is limited rendering their assessment difficult.

You have also provided two study records (with reliability 4) for the publications by Watanuki and Sakaguchi K. (1981) and Abramovici and Rachmuth-Roizman (1983), which were both performed with the registered substance. The reporting for the study record of Watanuki and Sakaguchi is very limited, e.g. the principle of the study used is not reported and seems limited to investigate effects on rat embryo fibroblasts. The Abramovici and Rachmuth-Roizman study investigated the embryotoxic effect of a single dose of the test substance on young chick embryos.

You reported the two studies as being "*disregarded due to major methodological deficiencies*". ECHA agrees that these two study records do not inform on induction of developmental toxicity including effects on growth, survival, external, skeletal and visceral malformations and variations due to exposure during the whole prenatal period and the potential relationship of effects to maternal toxicity. Therefore, these study records do not fulfil the standard information required by Annex IX, Section 8.7.2., because they are not reliable and do not cover key parameters and exposure duration of a pre-natal developmental toxicity study (see Annex XI, Section 1.1.2.).

In your comments, you refer to the comments already provided in the read-across and category approach section. However, there is no current basis proposed whereby the read-across could be considered acceptable, and so the studies on read-across substances would not be acceptable.

You subsequently addressed the merit of the individual studies provided for the three information requirements (sections 4, 5 and 6). In Appendix B you refer to the information on benzoic acid to fulfil the requests for the 2 PNDT studies. Without prejudice to their adequacy for benzoic acid, it remains that the read-across is defective.

You also refer to a compliance check process regarding another substance belonging to the category proposed (namely benzoic acid). This does not fulfil the three information requirements (sections 4, 5 and 6) for the registered substance either. Hence ,ECHA considers that the three information requirements (sections 4, 5 and 6) have not been fulfilled.

ECHA acknowledges your intention to provide additional information in an update of your registration dossier. However, the information is currently not available and if submitted, it will only be reviewed after the deadline indicated in the final decision has passed.

Consequently, as explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* version 46.0, July 20175, R.7a, chapter R.7.6.2.3.2 (version 6.0, July 2017). Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rats or rabbits) by the oral route.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

As discussed under request 4 above, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing 4 study records for a pre-natal developmental toxicity non-GLP study (OECD TG 414) with the analogue substance sodium benzoate, performed in 4 different species (rat, mouse, hamster and rabbit) ([redacted], 1972).

As explained above in this decision, your read-across adaptation of the information requirement is rejected.

In addition, ECHA observes that the reported reliability of the four studies above was set at 2, because of (i) the limited study summary (publication in a peer-reviewed journal), (ii) the study is predating the approved guidelines, and (iii) the deviation related to exposure period and fetal examinations. ECHA notes that the reporting of the studies is limited rendering their assessment difficult.

You have also provided two study records with reliability 4 for the publications by Watanuki and Sakaguchi K. (1981) and Abramovici and Rachmuth-Roizman (1983). As detailed under request 4, these study records do not fulfil the standard information required by Annex X, Section 8.7.2., column 2, because they are not reliable and do not cover key parameters and exposure duration of a pre-natal developmental toxicity study .

In your comments, you refer to the comments already provided in the read-across and category approach section. However, there is no current basis proposed whereby the read-across could be considered acceptable, and so the studies on read-across substances would not be acceptable.

You subsequently addressed the merit of the individual studies provided for the three information requirements (sections 4, 5 and 6). In Appendix B you refer to the information on benzoic acid to fulfil the requests for the 2 PNDT studies. Without prejudice to their adequacy for benzoic acid, however it remains that the read-across is defective.

You also refer to a compliance check process regarding another substance belonging to the category proposed (namely benzoic acid). This does not fulfil the three information requirements (sections 4, 5 and 6) for the registered substance either. Hence, ECHA considers that the three information requirements (sections 4, 5 and 6) have not been fulfilled.

ECHA acknowledges your intention to provide additional information in an update of your registration dossier. However the information is currently not available and if submitted, it will only be reviewed after the deadline indicated in the final decision has passed.

Hence, the information provided on this endpoint for the registered substance does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species selected in the first pre-natal developmental toxicity study (as per the request 4. above).

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment*,

R.7a, chapter R.7.6.2.3.2 (version 6.0, July 2017). Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rat if first species was rabbit or rabbit if first species was rat) by the oral route.

*Notes for your consideration*

You are reminded that before performing a pre-natal developmental toxicity study in a second species, you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and the general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

*a) The information requirement*

The basic test design of an extended one-generation reproductive toxicity study (test method B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3.
Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing one study record for a multigeneration reproductive toxicity study (no test guideline reported) with the analogue substance, sodium benzoate.

As explained above in this decision, your read-across adaptation of the information requirement is rejected.
In addition, ECHA points out that the reported reliability of the above study (Kieckebusch W. and Lang K., 1970) is set at 2, because of (i) the limited study summary (publication in a peer-reviewed journal), (ii) the study is predating the approved guidelines, and (iii) the deviation related to number of doses, and general examinations beyond body weights.

In the technical dossier you have also provided a study record for an early study on fertility (no test guideline reported) with the registered substance. The reported reliability of this publication (Sporn *et al.*, 1967) is set at 2, as it is a non-GLP 32-week one-generation study, in rats, treated orally (gavage), using 10 rats and one dose of 5 mg/kg bw/day (in oil). The endpoints examined included the number of pregnant females, number of offspring born, pup body weight at days 7 and 21 post partum, and pup viability. Ten control animals received only the vehicle oil. ECHA considers that the reporting is very limited and notes that you conclude that the *"treatment did not affect reproduction"* although *"fewer females in the*

*treated group became pregnant*". However, the significance of this finding in the parental and first generation data is unknown. No data or statistical analyses were performed, and the authors concluded that treatment did not cause a significant change in any of the parameters measured.

In your comments, you refer to the comments already provided in the read-across and category approach section. However, there is no current basis proposed whereby the read-across could be considered acceptable, and so the studies on read-across substances would not be acceptable. You are subsequently addressing the merit of the individual studies provided for the three information requirements (sections 4, 5 and 6). In Appendix C you refer to an expert review of the 1960 publication on benzoic acid and of the 13-week studies on benzyl acetates. Since the read-across between the source and registered substances is not acceptable, ECHA considers that there is no need to examine in details the quality or merit of the studies at this stage.

You also refer to a compliance check process regarding another substance belonging to the category proposed (namely benzoic acid). This does not fulfil the three information requirements (sections 4, 5 and 6) for the registered substance either. Hence, ECHA considers that the three information requirements (sections 4, 5 and 6) have not been fulfilled.

ECHA acknowledges your intention to provide additional information in an update of your registration dossier. However the information is currently not available and if submitted, it will only be reviewed after the deadline indicated in the final decision has passed.

Consequently this study record does not provide the information required by Annex X, Section 8.7.3., because it is not reliable, reporting is very limited, and the study does not cover key parameters of an extended one-generation reproductive toxicity study, as required by Annex XI, Section 1.1.2, such as the number of doses and the number of animal per dose (in the provided study only 10 animals were exposed to one dose). Hence, the information provided on this endpoint for the registered substance does not meet the information requirement.

Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required.

The following refers to the specifications of this required study.

*b) The specifications for the study design*

*Premating exposure duration and dose-level setting*

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

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 on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels

and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

It is recommended that results from a range-finding study (or range finding studies) for the extended one-generation reproductive toxicity study are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

*Species and route selection*

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment,* R.7a, chapter R.7.6.2.3.2 (version 6.0, July 2017). Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

One Member State Competent Authority proposed to amend the draft decision to take into consideration the "*results of an* in vitro *[genotoxicity] study [which] should be awaited before stating on the final design of the EOGRTS to see if an* in vivo *test is needed. Indeed the extension of cohort 1B to include the F2 generation shall be proposed if the substance displays genotoxic effects in somatic cell mutagenicity test* in vivo.*"*

In your comments to the proposal for amendment, you were *"very appreciative of the thoughtful approach to not rushing into the execution of the EOGRTS when other data requested in the Draft Decision may help in designing the EOGRTS in a way that minimizes animal use."*

However, based on available information the evidence for potential mutagenic Category 2 classification appears weak, given also that the metabolite benzoic acid was classified without genotoxicity concerns and that available studies on the registered substance and its metabolite did not raise any concerns on carcinogenicity. As there are no indications that the substance may display genotoxic effects in somatic cells, from existing *in vivo* studies, no *in vivo* studies available and no indication that *in vivo* studies are required at this stage, ECHA considers that column 2, first paragraph, lit. (b), first indent of section 8.7.3., Annex X to extend Cohort 1B to include a F2 generation, is not met.

In this respect, ECHA is of the opinion that, if the draft decision only contains requests for *in vitro* genotoxicity tests, sequential testing (namely with *in vivo* genotoxicity testing) is not required as, such approach does not meet the REACH trigger (see above) and would result in a significant delay for receiving information on reproductive toxicity. Therefore, no sequential testing is requested because the draft decision only contains requests for *in vitro* genotoxicity tests. Finally as the likelihood for positive results in *in vivo* genotoxicity studies seems to be low, the EOGRTS design is based on the data available in the registration dossier at the time of assessment.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;

- Dose level setting shall aim to induce some 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.

*Notes for your consideration*

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion.

Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, December July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

ECOTOXICOLOGICAL INFORMATION
In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation
The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

## 7. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

"Short-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex VII, Section 9.1.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have provided a non-GLP study from a publication (Bringmann and Kuhn, 1977), where no guideline was followed and the duration of the test was of 24 hours.
Even while pointing the shortcomings of the study, ECHA is of the opinion that you cannot use this study as a key study. The robust study summary does not provide sufficient information to establish the reliability of the results used and this impacts also on the PNEC derivation. In addition, the OECD TG 202 is performed at least for 48 hours; thus, between 24 hours and 48 hours, the toxicity effects could have increased and the EC50 increased extensively. In the absence of 48-hour coverage and reliable documentation, the study does not meet the requirement set forth under Annex XI, Sections 1.1.2 (3) and (4) of the REACH Regulation.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes your agreement to perform the test requested in the draft decision.

In view of the biodegradation properties of the substance and no bioaccumulation potential, a short term study, as requested here, seems to be the most appropriate instead of a long term test.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *Daphnia* sp. Acute immobilisation test, EU C.2./OECD TG 202).

**8. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)**

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance, to meet this information requirement.

You have provided several non-GLP studies from publications, all assigned as reliability 4 according to the Klimisch score, two of which have been combined in a weight of evidence approach.

The robust study summaries do not provide sufficient information to establish the reliability of the results used and this impacts also on the PNEC derivation. As a consequence, also the weight of evidence approach proposed and based on Annex XI, Section 1.2 cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes your agreement to perform the test requested in the draft decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Freshwater Alga and Cyanobacteria, Growth Inhibition Test, EU C.3./OECD TG 201).

**9. Identification of PNEC and risk characterisation (Annex I, Section 3.3.1. and 6.)**

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

Annex I, Section 3.3.1. of the REACH Regulation requires to establish a PNEC for each environmental sphere based on the available information and to use an appropriate assessment factor to the effect values.

The ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.10 provides further details and specifically provides default assessment factors that should be applied to derive PNECs.

Further, pursuant to Annex I, Section 3.3.2. if it is not possible to derive the PNEC, then this shall be clearly stated and fully justified.

You have used two aquatic toxicity results from studies which you consider long-term and an assessment factor of 50 for the calculation of PNEC aquatic for freshwater.

ECHA notes that according ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.10 (May 2008), an assessment factor of 50 can be applied when two long-term aquatic toxicity results (e.g. EC10 or NOEC) from freshwater or saltwater species representing two trophic levels (algae and/or crustaceans and/or fish) are available. In your registration dossier you have provided information on long-term toxicity to fish; however, ECHA does not consider this test as fulfilling the requirements for a long-term study according to OECD 210, due to the considerably shorter duration of the test (7 days).
The second long-term study you provided is on long-term toxicity to algae, the issues of which are outlined under point 7 above. Even if the information for this endpoint would have been adequate, ECHA notes that in view of the information provided in the registration dossier, it would not be possible to determine that algae are the most sensitive species in short term studies. Hence, you have selected the incorrect assessment factor.
As explained above, the information provided on PNEC for the registered substance in the chemical safety report does not meet the general provisions for preparing a chemical safety report as described in Annex I, 3.3.1.

Consequently, you are given two options:

(i) Revise the PNECs derived for freshwater by applying the assessment factors recommended by the ECHA Guidance that are appropriate in this case. Furthermore, you are requested to revise other relevant PNECs according to the points considered above, specifically marine water, intermittent releases, freshwater sediment, marine sediment and soil. Subsequently, you shall re-assess related risks.

(ii) Alternatively, provide a full justification for the PNECs derived for freshwater, marine water, intermittent releases, freshwater sediment, marine sediment and soil provided in the chemical safety report in accordance with Annex I, 3.3.1. and ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.10. (May 2008), by specifying how the following has been taken into account:
   a. Intra- and inter-laboratory variation of toxicity data;
   b. Intra- and inter-species variations (biological variance);
   c. Short-term to long-term toxicity extrapolation;
   d. Laboratory data to field impact extrapolation.

A justification for varying the assessment factor could include one or more of the following:
- evidence from structurally similar compounds which may demonstrate that a higher or lower factor may be appropriate;
- knowledge of the mode of action as some substances by virtue of their structure may be known to act in a non-specific manner. A lower factor may therefore be considered. Equally a known specific mode of action may lead to a higher factor;
- the availability of data from a variety of species covering the taxonomic groups of species across at least three trophic levels. In such a case the assessment factors may only be lowered if multiple data points are available for the most sensitive taxonomic group (i.e. the group showing acute toxicity more than 10 times lower than for the other groups).

ECHA notes your agreement to address the PNEC calculation as requested in the draft decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to:

revise PNECs for freshwater, marine water, intermittent releases, freshwater sediment, marine sediment, soil using the default assessment factors and other recommendations of ECHA Guidance R.10 for PNEC derivation and to revise the risk characterisation accordingly,

*or*

provide a detailed justification for not using the recommendations of ECHA Guidance R.10 for PNEC derivation.

*Notes for your consideration*

The results of the studies requested with this decision shall be taken into account when revising the PNECs.

**Appendix 2: Procedural history**

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 10 February 2017, as ECHA rectified and withdrew the previous compliance check decision of 13 June 2016 on your registration dossier for the same substance on 12 October 2016.

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

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

ECHA took into account your comments and did not amend the requests.

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

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

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

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-56 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

**Appendix 3: Further information, observations and technical guidance**

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2019.

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

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

4. In relation to the information required by the present decision, the sample of substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance composition manufactured or imported by the joint registrants.

5. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

6. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.