ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 26 April 2017

Addressee: [redacted]

Decision number: CCH-D-2114359254-48-01/F
Substance name: ANISALDEHYDE
EC number: 204-602-6
CAS number: 123-11-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 13.05.2013
Registered tonnage band: 100-1000T

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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

3. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./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);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

4. **Robust study summary of long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5., Annex I, Sections 0.5. and 3.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) reported in the OECD Screening Information Dataset dossier;**

5. **Robust study summary for Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; Annex I, Sections 0.5. and 3.1.5.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) reported in the OECD Screening Information Dataset dossier.**

You are required to submit the requested information in an updated registration dossier by **2 November 2020** except for the information requested under point 1 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **3 May 2018**. You may only commence the extended one-generation reproductive toxicity study as requested under point 3 after **2 August 2018**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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 Kevin Pollard, Head of Unit, Evaluation E1

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

Appendix 1: Reasons

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

You have not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your provided information with respect to this provision.

Adaptation of the standard information requirement

You have provided in the IUCLID section 7.5.1. summaries of the following oral studies conducted with exposure duration of more than 28 days and indicated as reliable (Rel. 1 or 2):

- Key study: "combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test" in Sprague-Dawley rats (OECD TG 422; GLP; oral gavage), registered substance, [redacted] 2000 (study report), Rel. 1, NOEL 20 mg/kg/day (lowest dose tested).
- Supporting study: 27-28 weeks oral study in Osborne-Mendel rats (non-guideline, non-GLP), registered substance, Hagan et al. 1967 (publication), Rel. 2, NOAEL 1000 ppm (67 mg/kg bw/day; only dose tested)
- Supporting study: 15 weeks oral study in Osborne-Mendel rats (non-guideline, non-GLP), registered substance, Hagan et al. 1967 (publication), Rel. 2, NOAEL 10000 ppm (670 mg/kg bw/day; only dose tested)

You have further provided in the IUCLID section 7.5.1., information on studies with the registered substance which you disregarded in your evaluation:

- reference to Baer and Griepentrog 1967 (publication), "*documentation insufficient for assessment*", NOAEL 10000 ppm
- reference to Boichuk and Davidenko 1993 (publication), "*publication in Russian language*"
- reference to Trubeck 1958, "*Only secondary source, TS was a mixture containing 4-methoxybenzaldehyde*"

ECHA notes that you have not provided a conclusion for the weight of evidence adaptation. ECHA understands that you conclude on a NOAEL of 20 mg/kg bw/d based on the OECD TG 422 screening study (with exposure duration less than 90 days) while in the supporting studies with 27-28 weeks and 15 weeks, no effects were observed at doses of 67 and 670 mg/kg bw/day, respectively.

ECHA has evaluated the information you provided according to REACH Annex XI, Section 1.2., and assessed whether you have provided "*sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion*" with respect to the information requirement of Annex IX, Section 8.6.2., for the registered substance.

ECHA has further evaluated the information according to ECHA Guidance R.4.4., by considering whether the criteria given in that guidance i.e. relevance, reliability and adequacy for the purpose apply to the information you have provided. ECHA has also evaluated whether the provided information is consistent and covers the relevant aspects of information on exposure duration, dose/concentration, number of animals used, and relevant parameters as investigated in a sub-chronic toxicity study (90 days) required at Annex IX, Section 8.6.2.

ECHA notes that the "combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test" ([redacted], 2000) by the oral route provides reliable information on the potential systemic effects (e.g. organ weights, histopathology, haematology) of the registered substance. However, it does not provide the information investigated in a sub-chronic toxicity study (according to OECD TG 408), because the exposure duration of this study is less than 90 days and hence the hazard effect(s) likely to arise from repeated exposure over prolonged period of time is/are not covered.

To address "*the chronic potential of the substance*", you have provided two supporting non-guideline studies (Hagan, 1967) by the oral route (diet) with exposure duration of 27-28 weeks and 15 weeks. However, ECHA notes that these studies have much lower statistical power than that of a standard sub-chronic toxicity study, because only 5 animals per sex and dose were investigated. Furthermore, both studies were performed with a single dose (67 and 670 mg/kg bw/d, respectively) which did not reach the limit dose level. In addition, the following parameters that are required to be investigated in a sub-chronic toxicity study (i.e. according to OECD TG 408) were not investigated: clinical chemistry, measurement of platelet count and blood clotting time/potential, organ weights (such as adrenals, epididymides, uterus, ovaries, thymus, brain), and histopathological examination (such as those organs mentioned before; and spinal cord, pituitary, thyroid, parathyroid, oesophagus, salivary glands, stomach, small and large intestines (including Peyer's patches), pancreas, trachea and lungs, aorta, gonads, female mammary gland, prostate, urinary bladder, lymph nodes, peripheral nerve, skin and eyes). In addition, you did not provide information on stability of the substance in the diet.

ECHA further notes that in the provided OECD TG 422 study main effects were observed in the gastrointestinal tract (irritation) from 100 mg/kg bw/day and in the liver (hepatocellular hypertrophy) at 500 mg/kg bw/day. Also some hematological changes were reported at 100 and 500 mg/kg bw/day and a decreased absolute and relative weight of epididymis at 500 mg/kg bw/day. However, in the supporting studies (Hagan, 1967), no effects on the liver were reported at 670 mg/kg bw/day, and relevant organs (e.g., gastrointestinal tract, epididymis) were not investigated. Hence, there is no information on the severity of such effects after repeated exposure over prolonged period of time.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agree to update the registration dossier and to better reflect the conclusion for a weight of evidence adaptation according to Annex XI, Section 1.2.

With respect to the insufficient information stemming from the supportive studies (Hagan, 1967), you comment that "*However in REACH Annex XI, Section 1.2, it is clearly stated that a conclusion can be drawn even if the information from each single source alone might be regarded insufficient to support this notion.*" ECHA acknowledges this condition. However, ECHA reminds that – as explained above - the information would need to cover the relevant aspects of information on exposure duration, dose/concentration, number of animals used, and relevant parameters as investigated in a sub-chronic toxicity study (90 days) required at Annex IX, Section 8.6.2.

You further comment that "*in one supportive study no evident increase in severity of toxicity was observed after dosing approx. 670 mg/kg/d, which represents a dose above the LOAEL of the OECD TG 422. Furthermore, the respective dosing period of 15 weeks was significantly longer than the study duration of the 90 day study, requested by ECHA. The absence of adverse effects after dosing anisaldehyde above the defined NOAEL of the OECD TG 422 study (approx. 67 mg/kg bw/d) for an extensively longer exposure period of 27-28 weeks, did not indicate a potential reduction of the NOAEL or additional systemic toxicity due to exposure elongation. This needs to be assessed together with the data of the OECD TG 422 study (considered reliable by ECHA), whose exposure duration (6-7 weeks) bridges between a subacute (4 week) exposure and the exposure duration of the ECHA requested 90 day study.*" ECHA acknowledges that the exposure duration in the supporting studies (15 and 27-28 weeks) were longer than the exposure duration required in the 90-day study. However, as already mentioned above, relevant organs like the epididymis, which was affected in the OECD TG 422 screening study, were not investigated. Hence, the supporting studies can neither be used to conclude on "*no evident increase in severity of toxicity*" nor to conclude that those studies "*did not indicate a potential reduction of the NOAEL or additional systemic toxicity.*"

You further commented that "*Although the exposure length does not reach the study requirements of an OECD TG 408 study, it is considered to be a sub-chronic toxicity study as well (Prieto 2005).*" ECHA notes that you referred to a publication from *Prieto 2005* to support your claim that the OECD TG 422 screening study is considered to be a sub-chronic toxicity study. However, this publication is not publically available. Furthermore, the REACH legal text clearly states that at Annex IX, a sub-chronic toxicity study (90-day) study is an information requirement. In this regard, ECHA notes that in the OECD TG 422 screening study exposure to the test material is up to 4 weeks for male rat and 6-7 weeks for female rat. Hence, between sexes there is significant difference in the length of exposure to the test material in comparison to the 90-day study – especially for males. Therefore, the OECD TG 422 screening study cannot be considered as sub-chronic toxicity study (90-day study).

In addition, you commented on the effects observed in the OECD TG 422 screening study. You consider the effects listed from the OECD TG 422 screening study as irrelevant and mostly questionable in terms of relevance to humans. Specifically, you state that the haematological changes (platelet counts) were of questionable relevance since other parameters of the hematopoetic system were not affected (bone marrow, prothrombine time) and no severe liver injury such as necrosis was observed.
You also state that the decrease in epididymides weights were not correlated with histopathological findings, and irritation of the forestomach in rat is rodent specific due to bolus application of anisaldehyde via gavage. In addition, you indicate that these findings were not reported in a 14 day study in rats ([redacted], 2011).

However, ECHA considers the findings from the OECD TG screening 422 study as relevant indicators to raise concern for the potentially severe effect(s) after prolonged exposure. As such, the absence of effects in other parameters of the hematopoetic system, no necrosis in the liver, and no histopathological effects in epididymides do not rebuttal or nullify the potential effect of the test substance after repeated exposure over a longer period of time. ECHA also considers that the absence of effects in the 14-day study is not a valid explanation to undermine the findings of the OECD TG 422 study since the 14-day study was conducted with shorter exposure duration than the OECD TG 422 study. In addition, ECHA notes that the 14-day repeated dose toxicity study was tested up to the limit dose level of 1000 mg/kg bw/day and effects such as changes in liver weight were observed at 250 mg/kg bw/day and above. Hence, ECHA does not support your conclusion on absence of effects in the 14-day study.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that "*we do not agree with ECHAs view, that the present data are not sufficient to assume/conclude on the hazardous properties of anisaldehyde following sub-chronic exposure. Furthermore, we disagree with ECHAs conclusion, that the weight of evidence is rejected due to the limitations and deviations of the supporting studies with longer exposure durations from current standard sub-chronic toxicity studies (such as the OECD TG 408). If this would be ECHAs reasoning, then a weight of evidence approach could only been made with a database, that covers all aspects of a current test guideline, making the weight of evidence approach unfeasible. In line, the ECHA guidance R4.4. states, that further information on that particular endpoint may not be necessary even if several pieces of inadequate data exist, i.e. repeated dose toxicity studies with deficiencies as cited in the ECHA draft decision.* [..] *We agree, that no consistent findings in the target organ liver were observed and local irritative effects in the forestomach were not assessed in all pieces of data. However, no indication for a reduction in the NOAEL or additional systemic toxicity exist due to exposure elongation and the findings cited by ECHA are mostly of questionable (human) relevance. Therefore, the available data are considered adequate to describe the REACH endpoint of concern and in order to avoid animal testing as outlined in (REACH Article 25.1.), ECHAs reasoning is rejected.*"

In contrast, "absence of evidence" is not equal to "evidence of absence" and for the reason mentioned above, ECHA considers that the information from the individual sources (i.e, the two-supporting studies and one-key study) alone or together do not weight sufficiently to cover the standard information according to Annex IX, Section 8.6.2.. Therfore, they do not lead to the assumption/conclusion that the substance has or has not a particular dangerous property.

ECHA concludes that the evidence you provided to adapt the standard information requirement for a sub-chronic toxicity study is not sufficient to assume/conclude on the hazardous properties of the registered substance following sub-chronic exposure as required according to REACH Annex XI, Section 1.2. Hence, your adaptation of the information requirement is rejected.
Therefore, 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.

Route of administration

ECHA has evaluated the most appropriate route of administration for the study. In the draft decision sent to you, ECHA has requested testing by the inhalation route due to a concern that the substance could lead to respiratory tract irritation in case of human inhalation exposure. In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation, you explained why you consider that there is "*no clear evidence for a respiratory tract irritation*". You further clarified that the concentrations to which humans are exposed by the inhalation route are low. More specifically you indicate that "*for air care products (PC3), liquid and solid-electrical products were determined to have final anisaldehyde concentrations of* [redacted]*%, whereas air care spray product concentrations were also found to be below* [redacted]*%.*" Based on the low concentration reported for air care products, ECHA agrees that the inhalation route does not appear to be the most appropriate route of administration. You further comment that the dermal route is the most likely route for human exposure. However, ECHA notes that no significant dermal toxicity was reported in the 14-day dermal toxicity study ([redacted] 2011), which may indicate low or no dermal absorption. Hence, ECHA considers that the criteria of Annex IX, Section 8.6.2, column 2 are not fully met. In addition, according to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3, the oral route is the preferred route of administration. Furthermore, route-to-route extrapolation is allowed because the provided information indicates no specific effects following dermal administration. ECHA also considers that the oral route causes less distress to test animals than dermal administration which requires dermal occlusion. Therefore, ECHA considers that the oral route is the most appropriate route of administration. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Comment on deadline

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you have stated that conducting a sub-chronic toxicity study (90-day) by inhalation route would require a total of 24 months for completion of the study including the preconditions from the date of order.

However, following your comment and for the reason mentioned above, ECHA has changed the route of administration from inhalation to oral, and no further preparatory tests for an inhalation study will be required.

Therefore, ECHA has not amended the decision with respect to the deadline.

Species for testing

According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Conclusion

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: Sub-chronic oral toxicity: 90-day study (test method: EU B.26. / OECD TG 408) in rats.

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

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

Adaptation of the standard information requirement

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence.

You have provided in IUCLID section 7.8.2. the following reliable information which you flagged as "weight of evidence":

- "Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" in Sprague-Dawley rats (OECD TG 422; GLP; oral gavage), [redacted], 2000 (study report), Rel. 1, NOEL 20 mg/kg/d (maternal toxicity), NOEL 100 mg/kg bw/d (developmental toxicity).

Furthermore, in IUCLID section 7.8.2. you provided secondary references cited from OECD SIDS Benzoates, Final Report April 2004 which you flagged as "weight of evidence" and "read across" and for which you indicated that the oringinal data are not available.

- "Teratologic evaluation of FDA 71-37 (sodium benzoate)" in the rat (EPA OPPTS 870.3700), [redacted], 1972, Rel. 4, "*original data not available*";
- "Teratologic evaluation of FDA 71-37 (sodium benzoate)" in the mouse (EPA OPPTS 870.3700), [redacted], 1972, Rel. 4, "*original data not available*";
- "Teratologic evaluation of FDA 71-37 (sodium benzoate)" in the hamster (EPA OPPTS 870.3700), [redacted], Inc, 1972, Rel. 4, "*original data not given*";
- "Studies on effects of sodium benzoate on fetuses and offspring of Wistar rats" (no information on test method). Onodera et al. 1978, Rel. 4, "original data not available".

You have provided the following as read across justification: "*No valid data on developmental toxicity are available for the key metabolite anisic acid. However information from developmental toxicity studies performed with another benzyl derivative with similar structural features as the key metabolite anisic acid, i. e. benzoic acid, was taken for further assessment of this endpoint via read across. The respective structure only differs in an additional methoxy group in para-position. In terms of systemic toxicity after single or repeated administration, the toxicological profile of benzoic acid shares similarities with 4-methoxybenzaldehyde (see also OECD SIDS for Benzoates). Acute toxicity is comparably low with LD50 values observed in rats between 2000 and 5000 mg/kg bw. Systemic toxicity after repeated administration of benzoic acid via feed was generally lower as seen for 4-methoxybenzaldehyde, however the liver has been identified as target organ for both substances.*

Differences in potencies might be explainable by differences in ADME after administration via feed versus gavage. Furthermore, similarities exist in pharmacokinetics of orally administered benzoic acid and 4-methoxybenzaldehyde. Benzoic acid is metabolized and excreted predominantly as glycine conjugate and to a lower extent as benzoylglucuronide. A limited capacity for glycine conjugation of benzoates was described at high dose levels only in the OECD SIDS. However AUCs for benzoic acid in humans were reported to increase disproportional with dose, while that for hippuric acid increased proportionally (see Kubota et al.; J. Chromatography 425, 67-75, 1988). It is therefore suggested that transformation of orally administered benzoic acid to hippuric acid is a saturable process. If administered as sodium and potassium salts, benzoic acid is expected to immediately dissociate and form benzoic acid in an aqueous envimonment. On the basis of these similarities the following data on sodium benzoate were taken into consideration via read across in a weight of evidence".

ECHA has first evaluated the information you provided on read-across and then the information you provided on weight of evidence.

Read-across

ECHA has evaluated the information you provided on read-across according to the provision of REACH Annex XI, Section 1.5. ECHA has considered whether the information you have provided is sufficient to predict the properties of the registered substance with respect to pre-natal developmental toxicity from the analogue substance sodium benzoate (CAS no: 532-32-1). ECHA understands that this analogue substance is a salt of benzoic acid which has a common functional group with the main metabolite of the registered substance, anisic acid.

ECHA notes the following:

You indicated that "*No valid data on developmental toxicity are available for the key metabolite anisic acid. However information from developmental toxicity studies performed with another benzyl derivative with similar structural features as the key metabolite anisic acid, i. e. benzoic acid, was taken for further assessment of this endpoint via read across.*

ECHA notes that the information you provided is flagged as "*original data not available*". In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation, you explain that "*the Klimisch score 4 indicated in IUCLID has been used to express the circumstance that the information has been taken from literature, which do not give sufficient experimental details and which are listed in secondary literature (Klimisch 1997)*". The developmental toxicity studies by [redacted], (1972) are indicated in the IUCLID of OECD SIDS "*have been evaluated and classified with a reliability score of 1 (valid without restriction; Guideline study, according to EPA OPPTS 870.3700) in the attached IUCLID of the SIDS document, which further adds to the confidence, that the information is relevant*" and the dossier will be updated with these information.

ECHA reminds you that according to REACH Annex XI, Section 1.5., adequate and reliable documentation is required.

You further stated that "*The respective structure only differs in an additional methoxy group in para-position".*

ECHA considers that in order to meet the provisions in Annex XI, Section 1.5., to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible. However, you did not provide information on how the structural difference (aldehyde *versus* acid and no substituent versus *para*-methoxy substituent) may impact the toxicity profile - with special emphasis on developmental toxicity - of the substances and thus affect the possibility to predict the properties of the target substance from the data of the analogue substance.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you responded that "*The impact of the structural difference "no substituent versus para-methoxy substituent" on the endpoint developmental toxicity cannot be fully elucidated without comparison of results from definitive developmental toxicity studies with both substances. However, the toxicological profile of the substance without substituent (i.e. bezoates) has been compared with the profile of anisaldehyde, which is immediately metabolitzed to anisic acid. Although it cannot be fully answered, if the differences in potencies after repeated oral administration stems from different test substance application procedures or differences in structural features, the absence of any developmental toxicity in 4 species (rat, rabbit, mouse and hamster) give confidence to cover this remaining uncertainty. In addition to the comparative toxicological profiles, striking similarities in the metabolization and excretion exist between anisic acid and benzoic acid such as saturable glycine conjugation and excretion as hippuric acid.*"

ECHA notes that the available information from the OECD TG 422 screening study performed with the registered substance showed developmental effects (post-implantation losses), whereas in the developmental toxicity studies with sodium benzoate no developmental effects were observed.

Thus, the provided explanation is not considered as sufficient to establish a scientific credible link between the structural similarity and the prediction but is contradicted by the information you provided.

Weight of evidence

Furthermore, ECHA has evaluated your weight of evidence information according to REACH Annex XI, Section 1.2., and assessed whether you have provided "sufficient weight of evidence from several independent sources of information leading to the assumption/ conclusion that the substance has or has not a particular dangrous property" with respect to the information requirement of Annex X, Section 8.7.2. for the registered substance.

ECHA has further evaluated the information according to ECHA Guidance R.4.4. by considering whether the criteria given in that guidance i.e. relevance, reliability and adequacy for the purpose apply to the information you have provided. ECHA has also evaluated whether the provided information is consistent and covers the relevant aspects of information on on "developmental toxicity" as specified at Annex X, Section 8.7.2.

ECHA considers the information generated from the read across studies ([redacted], 1972; and Onodera, 1978) as an independent source of information within the weight of evidence evaluation.

However, the information from those studies can not be considered as supporting information for a weight of evidence approach for the registered substance because the read-across is rejected as mentioned above. Hence, ECHA cannot take into account the read-across information in the evaluation of your weight of evidence adaptation.

ECHA further notes that the main weight of evidence information you provided in the technical dossier is the study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that *"we disagree with ECHAs argument, that only one remaining study is available for the weight of evidence approach taken and as outlined above, we consider the secondary references cited from OECD SIDS Benzoates relevant and worth to be included in the weight of evidence approach. Taken these references into account, key parameters of a pre-natal developmental toxicity study like examinations of fetuses for skeletal and visceral alterations are covered with studies in 4 different species (i.e. rat, rabbit, mouse and hamster)".*

However, as explained above, in light of developmental effects observed with the registered substance, your read-across adaptation to structural different analogue substances showing no pre-natal developmental toxicity effects is rejected. Hence, such studies are also not appropriate to be used in a weight of evidence approach and to conclude that the registered substance does not lead to pre-natal developmental toxic effects.

Conclusion of the adaptation

Thus, ECHA concludes that the information you have provided to adapt the information requirement of Annex IX, Section 8.7.2 according to the general rule for adaptation of Annex XI, Sections 1.2 and 1.5, are not suffient and therfore your adaptation of the information requirement is rejected.

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.

Species

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.

Route of administration

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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Conclusion

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 (rat or rabbit) by the oral route.

3. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method EU 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 IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.

If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 5.0, December 2016), further cited as ECHA guidance..

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

You have provided in IUCLID section 7.8.1. the following reliable information which you flagged as "key study":

- "Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" in Sprague-Dawley rats (OECD TG 422; GLP; oral gavage), registered substance, [redacted], 2000 (study report), Rel. 1, NOEL 20 mg/kg/d (maternal toxicity), NOEL 100 mg/kg bw/d (developmental toxicity)

Furthermore, in IUCLID section 7.8.1. you provided secondary references cited from OECD SIDS Benzoates, Final Report April 2004 which you flagged as "supporting study" and "read across" and for which you indicated that the "*oringinal data are not available*". Hence, you did not flag those studies as "reliable":

- "*4-generation study*" in rats (not guideline, not GLP, oral feed), read across substance (benzoic acid; CAS no: 65-85-0) in the rat, Kieckebusch, 1960 (secondary source), Rel. 4, "*original data not available*"

Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is an information requirement if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other conecerns in reation to with reproductive toxicity.

ECHA considers that adverse effects on reproductive organs and/or other concerns in relation with reproductive toxicity are observed with the registered substance. More specifically, in the provided "combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test" (OECD TG 422) performed with the registered substance significant reduction in absolute and relative weight of epididymis and a significant reduction in fertility index, numer of pregnant dams, number of pups born, delivery index, and number of liveborns at lactation day 0 and 4 were reported at the highest dose group (500 mg/kg bw/d). Furthermore, a dose dependent, statistically non significant reduction in number of corpora lutea was reported. You have concluded that "*overall, these findings at the high dose of 500 mg/kg bw/d 4-methoxybenzaldehyde are indicative for post-implantation losses*".

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you "*do not agree with ECHAs conclusion, that the significant reduction in absolute / relative epididymis weights and the reduction in number of corpora lutea can be considered as biologically relevant adverse effects*". You explain that "*the decreased epididymis weights are single findings, that were not correlated with any histopathology of this organ and the biological relevance of this finding is therefore questionable*".

With respect to corpora lutea, ECHA acknowledges your comment. However, ECHA notes that the decrease in the epididymis weights - both absolute and relative to body weight – were reported as statistically significant finding rather than as a minor change. ECHA notes that the exposure period of the male animals in this OECD TG 422 study was only up to 4 weeks which is much less than that required by the extended one-generation reproductive toxicity study. Hence, with the longer duration of exposure, the potential for severe effect on the reproductive organ as well as on fertility shall not be excluded. Furthermore, OECD TG 422 is a screening study rather than a definitive study with respect to investigating reproductive toxicity potential of a chemical. Therefore, ECHA consider that the reduction in the epididymis weights in the screening study raises a concern that merits further investigation.

Furthermore, you explain that to your understanding the "*clear adverse findings consisted of increased number of non-pregnant animals leading to a reduction in the fertility index and decreased numbers of pups born/delivery index at the high dose (500 mg/kg bw/d).*" You consider these adverse effects as secondary to acidosis that occurred due to the disproportionate increase in the endogenous level of anisic acid. You also state that "*since occupational and consumer exposure to anisaldehyde is low, an endogenous formation of anisic acid levels at toxicologically relevant concentrations in humans is highly unlikely*".

ECHA agrees with you that the findings from the OECD TG 422 screening study (increased number of non-pregnant animals leading to a reduction in the fertility index and decreased numbers of pups born/delivery index at the high dose group) can be interpreted as adverse findings. However, ECHA notes that these effects were reported only in the presence of slight local irritiation (squamous cell hyperplasia) which is likely secondary to the gavage administration. With regard to this, ECHA would like to point out that the extended one-generation toxicity study must be conducted via dietary route of administration and such irritation effect might be avoided.

In addition, ECHA considers that your claim of the observed effects as secoundary to acidosis as hypothetical claim and not suported by factual evidence.

Furthermore, ECHA notes that the OECD TG 443 states the dose level that clearly exhibit saturation shall be avoided if the human exposure is expected to be well below the point of saturation. You have not provided exposure estimation in the chemical safety report and the potential level of exposure of the human population to anisaldehyde is therfore not known. However, the uses described in the registration dossier (both worker and consumer uses) show a high potential, *i.e.* likelyhood, for exposure. Hence, based on the current available information, ECHA cannot exclude the potential for high exposure of worker and consumer to anisaldehyde. Therefore, internal exposure to toxicologically relevant concentrations in humans can not be excluded.

You further comment that "*according to the OECD TG 422, dose levels should be selected taking into account any existing toxicity and (toxico-) kinetic data available. Based on the current knowledge on the toxicokinetic behavior of anisaldehyde, some doses chosen in the present OECD TG 422 study overwhelm the detoxifying mechanisms of the test animals and have no relevance to human exposure. Therefore, the adverse findings specified by ECHA do not represent relevant human concerns in relation with reproductive toxicity and the request of an EOGRTS is therefore not justified*".

ECHA agrees that the dose selection for the OECD TG screening 422 study shall take into account any existing toxicity and (toxico-) kinetic data available. ECHA notes from your record in IUCLID that you considered the result from a dose range finding study in order to set the dose level for the available OECD TG 422 screening study. ECHA considers that the possibility of human exposure at the dose level that potentially overwelm the detoxifying system can not be excluded for the reason explained above. Hence, based on the current information the adverse findings from the OECD TG 422 study trigger a relevant concern for humans that requires further investigation.

Thus, an extended one-generation reproductive toxicity study is considered an information requirement for the registered substance.

ECHA notes that you have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.3. Instead, you have provided information with the registered substance and with read across substance that could be interpreted as an adaptation according to Annex XI, Section 1.1.2., use of existing data and Section 1.5, read across.

ECHA has first evaluated the information you provided on key study ([redacted], 2000) with respect to Annex IX, Section 1.1.2. and then the information you provided on read across (Kieckebusch, 1960) according to Annex IX, Section 1.5.

ECHA notes that the adaptation according to Annex XI, 1.1.2., requirement includes "*adequate and reliable coverage of the key parameters*", and "*exposure duration*" as the conditions (among others) to be considered if the data - in this case the OECD TG 422 study - would be equivalent to the data generated by the corresponding test methods referred to in Article 13 (3), in this case extended one generation reproductive toxicity study.

ECHA considers if the information from OECD TG 422 screening study with the registered substance ([redacted], 2000) would meet the information requirement according to Annnex XI, 1.1.2. ECHA notes that the OECD TG 422 screening study does not cover key elements such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. Hence, the data generated from the OECD TG 422 screening study is not considered as equivalent to the data generated from the extended one generated reproductive toxicity study and consequesntly, does not meet the general rule for adaptation of Annex XI, Section 1.1.2. Therefore, your adaptation of the information requirement is rejected.
Furthermore, ECHA has evaluated the information you provided on read-across according to the providion of REACH Annex XI, Section 1.5. ECHA has considered wheather the information you have provided is sufficient to predict the properties of the registered substance with respect to extended one generation reproductive toxicity study from the analogue substance (benzoic acid; CAS no: 65-85-0). ECHA notes you have not provided a read across justification for the source and the registered substance. However, ECHA notes that you have provided justification to read across between sodium benzoate and the registered substance. In this justification you have considered that sodium benzoate is a salt of benzoic acid which has a common functional group with the main metabolite of the registered substance (anisic acid) and further considered to use the information generated from benzoic acid to the registered substance.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you conclude that "*furthermore, the supporting data of a 4-generation study with the read across substance benzoic acid do further substantiate the absence of such a concern. As testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort (REACH Article 25.1.), we disagree with ECHAs study requirement*".

However, ECHA considers that the justification you have provided to read across between benzoic acid to the registered substance is not sufficient for the reason stated above (see request 3).

Furthermore, ECHA considered the information on the result of the "*4-generation study*" (Kieckebusch, 1960) with respect to the requirement of Annex XI, Section 1.5. ECHA notes that you have disregarded these studies by indicating "not assignable" (reliability 4) and "original data not available". You have not provided sufficient record for this study in IUCLID and under the "*details on the study*" section of IUCLID you have recorded that "*taking into account the reputation of the investigators a high quality has to be assumed*".

As such, ECHA notes the following:

- the present information on those studies is not adequate for the purpose of classification and labelling and/or risk assessment;
- it cannot be verified if the key parameters are adequately and reliably covered which are addressed in the corresponding test method referred to in Artcile 13(3);
- and
- You did not provide adequate and reliable documentation of the applied methods;
- You did not provide robust study summaries (as required by REACH Annex I, Section 1.1.4).

Hence, ECHA consider that the data from this study is not sufficient to meet the information requirement of Annex IX, Section 1.5.

Therefore, Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints extended one generation reproductive toxicity study in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects the adaptations based on Annex XI, 1.5.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you state that "*we agree, that the OECD TG 422 does not cover all key elements of an EOGRTS, however, this study provides relevant information for the endpoint "Toxicity to reproduction". We do not agree, that no read across justification was provided for the source (benzoic acid) and anisaldehyde and the reasoning is given above. However, we will submit a read across justification document to achieve a better transparency. For the other aspects raised here, see our comments to ECHA concern 2. Overall, we consider the data submitted to be an adequate basis for predicting the properties of anisaldehyde from the data with the source substance and object to the study requirement as outlined by ECHA in the draft decision*".

However, 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. Thus, an extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3., is required. The following refers to the specifications of this required study.

b) The specifications for the required study

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among to other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA guidance.. The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

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 the ECHA guidance, the starting point for deciding on the length of the 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.

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.

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

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you conclude that "*However, we disagree with ECHAs proposal, that the highest dose level shall aim to induce some toxicity without taking into account the present data on the toxicokinetic behavior of anisaldehyde. The OECD TG 443 clearly states, that TK data need to be taken into account and care should be taken to avoid doses that clearly exhibit saturation, given, that human exposure is well below the point of saturation".* Furthermore, you highlight from the test method OECD TG 443: "*If TK data are available which indicate dose-dependent saturation of TK processes, care should be taken to avoid high dose levels which clearly exhibit saturation, provided of course, that human exposures are expected to be well below the point of saturation. In such cases, the highest dose level should be at, or just slightly above the inflection point for transition to nonlinear TK behaviour.*"

ECHA notes the OECD TG 443 states that the dose level that clearly exhibit saturation shall be avoided if the human exposure is expected to be well below the point of saturation. You have not provided exposure estimation in the chemical safety assessment and the potential exposure of the human population to anisaldehyde is therefore not known while the uses described in the registration dossier (both worker and consumer uses) show high potential or likelyhood for exposure. Hence, based on the current available information, a potential for high exposure of worker and consumer to anisaldehyde cannot be excluded. Therefore, the dose levels should be selected based on the fertility effects observed in the previous studies.

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

c) Outcome

Based on the available information, 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

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request *1*) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **3 May 2018**. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **2 August 2018** (i.e. within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **2 August 2018,** the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision **2 November 2020**.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA guidance*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design 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.

4. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5., Annex I, Sections 0.5. and 3.1.5.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. 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 not provided any study record of a long-term toxicity on aquatic invertebrates in the dossier that would meet the information requirement of Annex IX, Section 9.1.5.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.5., column 2. You provided the following justification for the adaptation: "*In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long term toxicity testing shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic invertebrates. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 4-Methoxybenzaldehyde reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, a long-term toxicity testing in aquatic invertebrates is not provided.*"

ECHA however notes that there is OECD Screening Information Dataset dossier generated under OECD High Production Volume Chemical Programme publicly available for the registered substance (link available on 27 May 2016: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=83FE0975-A9DC-47CB-B3C1-816977363C80).

In accordance with Annex I, Section 0.5. of the REACH Regulation the chemical safety assessment shall be based on the information on the substance contained in the technical dossier and on other available and relevant information. Available information from assessments carried out under other international and national programmes shall be included. Deviations from such assessments shall be justified.

ECHA notes that in OECD Screening Information Dataset dossier there is a robust study summary reported for Long-term toxicity to aquatic invertebrates study performed according to OECD Guideline 211 (*Daphnia magna* Reproduction Test). ECHA considers that the results of this study give rise to the higher concern on aquatic toxicity than the data reported in your registration dossier. ECHA notes that Annex I, Section 3.1.5. of the REACH Regulation requires that the study giving rise to the highest concern shall be used to draw a conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier.

Thus, there is information publically available giving rise to the highest concern for this endpoint. This data is not considered for the chemical safety assessment of the substance and no justification is provided for a deviation.

Therefore, your adaptation of the information requirement 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.

According to ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7b (version 3.0, February 2016) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you consented to provide this information.

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: robust study summary of Daphnia magna reproduction test (test method: EU C.20./OECD TG 211) reported in the OECD Screening Information Dataset dossier. The chemical safety assessment and report shall be amended accordingly.

5. Robust study summary for Growth inhibition study aquatic plants (Annex VII, Section 9.1.2., Annex I, Sections 0.5 and 3.1.5.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same 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.

In the technical dossier you have provided a study record for "*the acute static growth inhibition test of anisaldehyde to green algae (Scenedesmus subspicatus)*" performed according to the test guideline DIN 38412, Part 9.
ECHA, however notes that there is OECD Screening Information Dataset dossier generated under OECD High Production Volume Chemical Programme publicly available for the registered substance (link available on 27 May 2016: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=83FE0975-A9DC-47CB-B3C1-816977363C80).

In accordance with Annex I, Section 0.5. of the REACH Regulation the chemical safety assessment shall be based on the information on the substance contained in the technical dossier and on other available and relevant information. Available information from assessments carried out under other international and national programmes shall be included. Deviations from such assessments shall be justified.

ECHA notes that in OECD Screening Information Dataset there is a robust study summary of another Growth inhibition study with aquatic plants performed according to the standard OECD Guideline 201 (Alga, Growth Inhibition Test) reported. ECHA considers that the results of this study give rise to the higher concern on aquatic toxicity than the data reported in your registration dossier. Annex I, Section 3.1.5. of the REACH Regulation requires that the study giving rise to the highest concern shall be used to draw a conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier.

Thus, there is information publically available giving rise to the highest concern for this endpoint. This data is not considered for the chemical safety assessment of the substance and no justification is provided for a deviation.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you consented to provide this information.

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: robust study summary of Alga, Growth Inhibition Test (test method: EU C.3./OECD TG 201) reported in the OECD Screening Information Dataset dossier. The chemical safety assessment and report shall be amended accordingly.

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 1 June 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 amended the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment. As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. 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.

3. In relation to the information required by the present decision, the sample of the 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 compositions manufactured or imported by the joint registrants. 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 the 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. 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.