Helsinki, 31 August 2016

Adressee: [redacted]

Decision number: CCH-D-2114332338-51-01/F
Substance name: 3-ethoxy-4-hydroxybenzaldehyde
EC number: 204-464-7
CAS number: 121-32-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28.02.2013

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. **Dissociation constant (Annex IX, Section 7.16; test method: OECD TG 112), with the registered substance;**

2. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14 /OECD TG 471) using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 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), provided that the study requested under point 2. has negative results, with the registered substance;**

4. **Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD TG 421 or 422) in rats, oral route with the registered substance;**

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2; test method: EU B.31/OECD TG 414) in rats or rabbits, oral route with the registered substance;**

6. **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;**

7. **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;**

8. **Identification of DNEL(s) and risk characterisation (Annex I, Section 1.4. and 6):**
   - **deriving acute and long-term DNEL(s);**
   - **for workers and for the general population;**
   - **inhalation, dermal, and oral route;**
   - **systemic and local effects;**

- **using the study giving rise to the highest concern (according to Annex I, Section 1.1.4.);**
- **using the assessment factors and other recommendations of ECHA guidance R.8 or a full justification for not using the recommendations of ECHA guidance R.8. for DNEL derivation;**
  and revising risk characterisation accordingly; and

9. **Exposure assessment and risk characterisation (Article 14(6), Annex I, Section 5.1.1., in conjunction with Annex II, 0.1.2. and 8.2.2.2. (b) (d) and 6.) for human health:**
   - **provide documentation for the recommended personal protective equipment, *i.e.* Skin and body protection;**
   - **specify the type of glove material, thickness and breakthrough times;**
   - **specify the type and quality of the protective suit.**

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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **07 March 2018.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

[For the final decision: 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 Leena Ylä-Mononen, Director of Evaluation

[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. Dissociation constant (Annex IX, Section 7.16.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) 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.

"Dissociation constant" is a standard information requirement as laid down in Annex IX, Section 7.16 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 provided pKa values predicted by a QSAR model (SPARC), providing solely the following: "-5.01 corresponds to ionisation of the aldehyde (calculated) 7.84 corresponds to ionisation of the OH (calculated)". You did not provide any further information.

You did not fulfil the conditions under Annex XI 1.3 regarding the use of QSARs, as no detailed information was provided regarding the QSAR model used. Additionally, the estimated pKa value suggests that the substance will dissociate at environmentally relevant pH (pKa of 7.84), and according to ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R7a (version 4.0 July 2015) "*If an estimated pKa value suggests that the substance will dissociate significantly at environmentally relevant pH, a test may be required to confirm the result*". Therefore, an experimental study should be performed.

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.

In your comments to the draft decision, you provided further details [redacted]. ECHA considers that the information in the comment does not fulfil the conditions of Annex XI 1.3 regarding the use of QSARs, as still no adequate and reliable documentation has been provided. You can find in ECHA Guidance on information requirements and chemical safety assessment Chapter R.6 instructions regarding QSAR Reporting Formats. Furthermore, the predicted pKa value is 7.84, and as already mentioned above, ECHA Guidance on information requirements and chemical safety assessment, Chapter R7a, recommends that an experimental study should be provided to confirm the estimated pKa values, if in the range of environmentally relevant pH. However, ECHA does not exclude the possibility to accept a predicted value if the conditions set out in Annex XI, Section 1.3. of the REACH Regulation are fulfilled in a future dossier update.

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: Dissociation constant in water (test method: OECD TG 112).

2. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) Adequate and reliable documentation of the study is provided.

The technical dossier contains the following information:

i. Experimental result on the registered substance, 1984, reliability 2 (reliable with restrictions), test similar to OECD 471, Reported deviations from current test guideline: no data on negative and positive controls; no data on test item purity; no data on cytotoxicity; the study was only performed with metabolic activation; the study was not conducted according GLP; and only four strains tested (TA92, TA94, TA100, TA1535, TA1537), Registrant's conclusion: 'Negative with metabolic activation'.
ii. Experimental result on the registered substance, 1982 (NTP), reliability 2 (reliable with restrictions), test similar to OECD 471, Reported deviations from current test guideline: no data on negative controls; no data on test item purity; the study was not conducted according GLP; and no cross-linking strain tested (TA98, TA100, TA1535, TA1537, TA1538), Registrant's conclusion: 'Negative with and without metabolic activation'.
iii. Experimental result on the registered substance, 1982 (RIFM), reliability 2 (reliable with restrictions), test similar to OECD 471, Reported deviations from current test guideline: no data on negative controls; no data on test item purity; the study was not conducted according GLP; and only four strains tested (TA98, TA100, TA1535, TA1537), Registrant's conclusion: 'Negative with and without metabolic activation'.
iv. Experimental result on the registered substance, 1979, reliability 3 (not reliable), test similar to OECD 471, Reported deviations from current test guideline: Not enough detail on test conditions; not the normal positive controls; the study was not conducted according GLP; and only four strains tested (TA98, TA100, TA1535, TA1537), Registrant's conclusion: 'Negative with and without metabolic activation'.

v. Experimental result on the registered substance, 1983, reliability 3 (not reliable), test similar to OECD 471, Reported deviations from current test guideline: No information about the tested doses; the study was not conducted according GLP; and no cross-linking strain tested (TA98, TA100, TA1535, TA1537, TA1538), Registrant's conclusion: 'Negative with and without metabolic activation'.
vi. Experimental result on the registered substance, 1987, reliability 4 (not assignable), test similar to OECD 471, Reported deviations from current test guideline: Not enough information on study conditions (passed on publication in Japanese); the study was not conducted according GLP; and only two strains tested (TA97, TA102), Registrant's conclusion: 'Negative with and without metabolic activation'.
vii. Experimental result on the registered substance, 1989, reliability 4 (not assignable), test similar to OECD 471, Reported deviations from current test guideline: Not enough information on study conditions; the study was not conducted according GLP; and no cross-linking strain tested (TA98, TA100, TA1535, TA1537, TA1538), Registrant's conclusion: 'Negative with and without metabolic activation'.
viii. Experimental result on the registered substance, 1979, reliability 4 (not assignable), non-Guideline (Principle of the test: 'rec-assay'), Reported deviations: Publication in Japanese, only a summary is available; Not enough information on the study; and the study was not conducted according GLP, Registrant's conclusion: 'Negative with and without metabolic activation'.
ix. Experimental result (under specific investigations: other routes in IUCLID), 1986, reliability not specified, non-Guideline (Principle of the test: a bacterial mutagenicity test in two strains: *E. Coli* (uvrA, trpE) and *S. typhimurium* TA98 (uvrB, hisD)). The registrant's conclusion "*is that under the specified conditions the results are negative; However, there is not enough information do consider this as a valid study for example are positive controls missing thus we do not know if the assay worked or not. Also there is no metabolic activation*".

You have provided the tests as listed in points i) to ix) above, none of the tests where conducted according to GLP. In addition, since the tests were conducted, significant changes have been made to OECD TG guideline 471 and this means that the studies do not meet the current guideline, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used. These should include four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by *E. coli* WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

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.

In your comments to the draft decision you agreed to conduct the requested study.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

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)(d) and 13(4) 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.

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 the infromation requiremnt Annex VIII, Section 8.4.2.; and negative results for the infromation requirement Annex VII, Section 8.4.1. (see request 2 above). Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) Adequate and reliable documentation of the study is provided.

The technical dossier contains the following information:

i. Experimental result on the registered substance, 1983, reliability 3 (not reliable), non-Guideline (Principle of the test: mouse lymphoma assay), Reported deficiencies: Not enough information on study; and the study was not conducted according GLP; Registrant's conclusion: 'Ambiguous with metabolic activation and negative without metabolic activation'.
ii. Experimental result on the registered substance, 1989, reliability 4 (not assignable), non-Guideline (Principle of the test: mouse lymphoma assay), Reported deficiencies: Not enough information on study; and the study was not conducted according GLP; Registrant's conclusion: 'Positive with and without metabolic activation'.

You have provided the tests as listed above, none of the tests where conducted according to GLP and none of the tests are considered reliable. In addition, none of the studies meet the current guideline, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. 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 considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments to the draft decision you did not object to conduct the requested study.

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. has negative results.

4. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

"Screening for reproductive/developmental toxicity" is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, 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 screening study for reproductive/ developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement by providing the following justification for the adaptation [redacted]

ECHA considers your adaptation to be a weight-of-evidence approach. According to Annex XI, Section 1.2. ECHA understand that the weight-of-evidence consists of two lines of evidence:

i. In the available oral sub-chronic toxicity (OECD 408, GLP, 1992) study on the registered substance, no effects on reproductive organs have been reported. The substance has a low toxicity and the NOAEL has been established at 1000 mg/kg/day (based on spleen effects at 2000 mg/kg/day).

ii. Read-across from supporting substance (structural analogue or surrogate) from [redacted], 1990, reliability 2 (reliable with restrictions), non-Guideline (Principle of the test: 'no data on the principles followed', appears similar to a reproductive and developmental toxicity screening test), Deficiencies compared to the current guideline (OECD 421/422): not specified, Registrant's conclusion: NOAEL maternal toxicity 250 mg/kg/day (basis not reported); NOAEL teratogenicity 500 mg/kg/day (highest dose tested).

ECHA concludes that this weight-of-evidence does not meet the general rules for adaptation of Annex XI, Section 1.2. The reasons are listed below:

(a) A sub-chronic toxicity (90-day) study does not investigate the same parameters as a Screening study for reproductive/developmental toxicity. The screening study investigates parameters related to reproductive performance and developmental toxicity; these parameters are not investigated in a sub-chronic toxicity study.
(b) Read-across from a structural analogue in principle can be used as part of a weight-of-evidence. ECHA notes that you have merely asserted that the properties of [redacted] can be read across to those of the registered substance. However, there is no further justification provided, thus ECHA considers that there is a failure to provide adequate and reliable documentation of the applied method, as required by Annex XI, 1.5. ECHA considers that you have not explained as to how and why the effects of the registered substance in a Screening study for reproductive/developmental toxicity can be predicted using the results obtained with the proposed analogue substance [redacted].
(c) ECHA notes that the study provided on [redacted] appears to be similar to a Screening study for reproductive/developmental toxicity. However, as noted in point ii) the principle of this study is not specified. ECHA notes has significant deficiencies when compared to the current OECD 421/422 test guidelines these include: Not enough information on study details; Premating exposure one week versus 'minimum of two weeks prior to mating' in the guideline; study conducted on females only; no data on mating procedure, indices, statistics, historical control data etc.; and the study was not conducted according to GLP and the study was not conducted according GLP. ECHA concludes that the study as such does not have adequate and reliable coverage of all key parameters addressed by the current OECD 421/422 test guidelines. Therefore, this study does not provide all necessary information about the key parameters covered by the guideline study as required by the standard information requirements.

Taking the results of the analysis (a) to (c) into account, ECHA concludes that the lines of evidence as explained under (i) and (ii) can not be considered to present sufficient weight of evidence for the presence or absence of the particular dangerous property as investigated by the current OECD 421/422 test guidelines. 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 the test methods OECD TG 421/422, the test guideline is designed for use with the rat and the substance is administered orally unless other routes of administration are considered more appropriate. ECHA considers these default parameters appropriate and testing should be performed on the rat by the oral route.

In your comments to the draft decision you agreed to conduct a study according to OECD TG 421.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) in rats by the oral route; or Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

5. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

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 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.

You have sought to adapt this information requirement. You provided the following justification for the adaptation: "[redacted]

ECHA considers your adaptation to be a weight-of-evidence approach according to Annex XI, Section 1.2. ECHA understands that the weight-of-evidence consists of the following evidence:

i. Read-across from supporting substance (structural analogue or surrogate) from [redacted], 1990, reliability 2 (reliable with restrictions), non-Guideline (Principle of the test: 'no data on the principles followed', appears similar to a reproductive and developmental toxicity screening test), Deficiencies compared to the current guideline (OECD 421/422): not specified, Registrant's conclusion: NOAEL maternal toxicity 250 mg/kg/day (basis not reported); NOAEL teratogenicity 500 mg/kg/day (highest dose tested).
ii. Read-across from supporting substance (structural analogue or surrogate) from [redacted], 1988, reliability 3 (not reliable), non-Guideline (Principle of the test: Teratogenicity in mice on day 11 of gestation), Deficiencies: *'For this study, reliability 3, because test conditions are poorly described and are not in accordance with the recognised guidelines. Moreover, the pregnant females were exposed once at day 11 of gestation. The GLP are not mentioned'.*
iii. Read-across from supporting substance (structural analogue or surrogate) from [redacted], 1988, reliability 3 (not reliable), non-Guideline (Principle of the test: Chicken embryo assay), Deficiencies: *'For this study, reliability 3 because the study was poorly described and not followed recognized guidelines'.*

ECHA concludes that this adaptation does not meet the general rules for adaptation of Annex XI, Section 1.2. The reasons for this conclusion are listed below:

(a) Read-across from a structural analogue can, in principle, be used as part of a weight-of-evidence. However, ECHA notes that you have merely asserted that the properties of [redacted] can be read across. However, there is no further justification provided, thus ECHA considers that there is a failure to provide adequate and reliable documentation of the applied method, as required by Annex XI, 1.5. ECHA considers that you have not explained as to how and why the effects of the registered substance in a pre-natal developmental toxicity study can be predicted using the results obtained with the proposed analogue substance [redacted].
(b) A pre-natal developmental toxicity study does not investigate the same key parameters as the available study on [redacted] which appears similar to a Screening study for reproductive/developmental toxicity with severe deficiencies (see 4. (c) above). Therefore, even if the read-across was adequately documented and justified, the study intended to be read across do not have adequate and reliable coverage of all key parameters addressed by the current OECD 414 test guideline.
(c) For the studies listed in point ii) and iii) above, ECHA notes that you consider these studies as 'not reliable' and ECHA considers that you have failed to demonstrate as to why and how these studies contribute to the weight-of-evidence for the key parameters addressed by a pre-natal developmental toxicity study according to OECD test guideline 414. The statement provided in this regard *"However, the results were similar and indicated no teratogen effects"* is not a sufficient reason to accept results of studies considered to be "not reliable".

Taking the results of the analysis (a) to (c) into account, ECHA concludes that the lines of evidence as explained under (i) to (iii) can not be considered to present sufficient weight-of-evidence for the presence or absence of the particular dangerous property as investigated by the current OECD 414 test guideline. 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 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 rats or rabbits as a first species.

According to the test method EU B.31/OECD TG 414, the test substance is usually administered orally. On the basis of this default consideration, ECHA considers testing should be performed by the oral route.

In your comments to the draft decision you agreed to conduct the requested study.

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.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

"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.

The technical dossier includes an unreliable (reliability score 3 provided by the Registrant) experimental study performed with the registered substance and a 2009 key study performed with the analogue substance [redacted] according to OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test. The Registrant reported that "*An old study on 24 hours with Ethylvanillin is available and is not sufficient to fill the gap. So the analogue approach with* [redacted] *is applied because of the similarity of the structure, the physico-chemical properties and the level of toxicity observed in the different available studies. For this study, reliability 2 because, the study was according to the OECD guideline and GLP*".

More analytically, the read-across argumentation reports that "*The ecotoxicity potential of Ethylvanillin for aquatic invertebrates and algae is performed by a read-across approach with* [redacted]. *This approach is justified by the information below:*

1) Structural similarity

[redacted]

2) Similar bioavailability

[redacted]

3) Similar ecotoxicity potential

[redacted]

ECHA notes that the physicochemical properties, structural similarity and predicted mechanism of action for source and target substances seem comparable. However, your statement that the proposed read-across approach [redacted] is not substantianted by facts, due to the lack of reliable aquatic toxicity data for both source and target substances. More specifically, the short-term *daphnia* study performed for the registered substance [redacted], is a reliability 3 (not reliable) 24-hour study. Furthermore, there is evidence [from the measured LogKow values and from supporting QSAR models: ECOSAR v1.1 and QSAR Toolbox v3.3] that the selected source substance will, actually, be less toxic than the target substance.

Thus, the proposed read-across approach does not fulfil Annex XI, Section 1.5 criteria and 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.

In your comments to the draft decision, you refer to the three arguments (i.e. structural similarity, similar bioavailability, and similar ecotoxicity profile) [redacted]

[redacted]

[redacted]

With regard to your comments ECHA notes the following:

- Regarding the conservative nature of the proposed read-across, ECHA acknowledges that you agree [redacted] read-across approach is associated with uncertainties;
- Regarding the proposed [redacted] ECHA considers that this is at your discretion. However, if you follow this approach, you will need to justify why [redacted] is adequate to address the additional uncertainties introduced by the read-across approach. Furthermore, any revision of [redacted] shall be followed by a subsequent revision/ amendment of the relevant parts of the risk assessment in the Chemicals Safety Report;
- Regarding the proposed change of [redacted] this is also at your discretion. However, ECHA notes that any study provided in the dossier should, in all cases:
  - *be adequate for the purpose of classification and labelling and/or risk assessment,*
  - *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),*
  - *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and*
  - *adequate and reliable documentation of the applied method shall be provided*

  ECHA fails to understand how [redacted] ECHA considers that [redacted] unless the study meets the requirements of Article 13(3).
- [redacted] ECHA does not wish to speculate on the results of a test that has not yet been performed;

- Regarding the use of ECOSAR [redacted] ECHA notes that the argument was used in a supportive way, in order to further highlight the underlying uncertainties in your overall approach. In other words, such models may be used to further assess whether differences in toxicity of some importance can be expected that may also impact classification and/or risk assessment. ECHA acknowledges that the training sets used in these models are rather small, but disagrees that there are no similar compounds with the source and target in these training sets;
- [redacted] the difference between source and target substances may be low but, nevertheless, the target substance is expected to be more toxic than the source. You have not adequately explained how big any such difference in toxicities may be.

ECHA conludes that the arguments brought forward in your comments do not provide sufficient information to allow for an adequate and reliable prediction of the ecotoxicological properties of the registered (target) substance based on the properties of the source substance.

You are reminded that this decision does not take into account any updates submitted after 27 October 2015. All the new information in the latest update of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation

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.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

"Growth inhibition study in 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.

The technical dossier includes a study performed with the analogue substance [redacted]) according to OECD Guideline 201 (Alga, Growth Inhibition Test). For the reasons explained in sub-paragraph 6. above, the proposed read-across approach does not fulfil Annex XI, Section 1.5 criteria and 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.

In your comments to the draft decision, you refer to the same issues as in your comments for the short-term *Daphnia* test. You further note that "*In case a new test on Daphnids would be performed, this new result will be used to update the justification of the read-across approach with* [redacted] *for this endpoint*".

For the reasons already reported in paragraph 6 of this statement of reasons, ECHA will assess the compliance of the new information in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

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.

Notes for your consideration for the requested aquatic toxicity studies

Due to the potential dissociation of the substance at environmentally relevant pH condition you should consult the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R7b, Table R.7.8-3 (summarising aquatic toxicity testing of difficult substances) for both choosing the design of the requested aquatic toxicity tests requested under sections 6. and 7., and for the calculation and expression of the results. More specifically, if the study requested under section 1. (Dissociation constant, Annex IX, 7.16) confirms that the pKa falls within the normal pH range of the aquatic tests requested, the following advice from the OECD Guidance document should be followed: "*a preliminary test, to determine the potential for differing toxicity of the two or more forms of the substance, should be considered*". In case such preliminary test(s) would indicate different toxicity of the two forms of the test substance, "*The definitive test should be conducted at a pH consistent with the more toxic form of the substance whilst remaining within the range required to maintain the health of the control*" as outlined in the OECD Guidance.

Once the requested aquatic toxicity studies are performed, the Chemical Safety Assessment needs to be updated accordingly and, depending on its results, the need for further aquatic and terrestrial toxicity testing needs to be re-evaluated.

8. Identification of DNEL(s) and risk characterisation (Annex I, Section 1.4. 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 1.1.4. of the REACH Regulation requires that the study giving rise to the highest concern shall be used and a robust study summary shall be prepared for that study or studies and included in the technical dossier. In addition, Annex I, Section 1.1.4. requires that if a study giving rise to the highest concern is not used, then this shall be fully justified.

Annex I, 1.4.1 of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:

a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
b) the nature and severity of the effect;
c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
d) and that the DNELs reflect the likely route(s), duration and frequency of exposure.

The ECHA *Guidance on information requirements and chemical safety assessment* Volume 8, Chapter R.8 [2] provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

ECHA notes that you have not derived any DNELs for workers or the general population. You have given the following justification:

"According to the current toxicological profile of Ethylvanillin, the main hazard was irritancy, so local effect for the eyes with Ethylvanillin powder. No other toxic effects were reported and not permit to derive a DNEL. The chemical risk assessment should take into account the main effect with Ethylvanillin powder to protect against irritant effect. A qualitative risk assessment approach is recommended".

ECHA notes that according to Annex I, Section 1.0.1 the objective of the human health assessment shall be

- *'to derive levels of exposure to the substance above which humans should not be exposed. This level is known as the Derived No-Effect Level (DNEL).'*

ECHA notes that a detailed justification shall be given specifying, *inter alia*, the choice of the information used, the routes of exposure (oral, dermal, inhalation) and the duration and frequency of exposure to the substance for which the DNEL is valid.

You are given two options: You shall derive the DNELs for workers and for the general population by applying the assessment factors and other recommendations that are appropriate in this case according to ECHA guidance R.8. Subsequently, you shall re-assess related risks.

In the alternative, you shall, in accordance with Annex I, 1.4.1, provide a full justification for DNELs derived for workers and for the general population provided in the chemical safety report by specifying how the following has been taken into account:

a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
b) the nature and severity of the effect;
c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
d) and that the DNELs reflect the likely route(s), duration and frequency of exposure.

Subsequently, you shall re-assess related risks.

In your comments to the draft decision, you state that a NOAEL derived from the sub-chronic study conducted with the registered substance can be used as a point of departure for the DNEL derivation. ECHA wants to highlight that the study giving rise to the highest concern shall be used as point of departure for the DNEL derivation; this may be one of the studies requested in this decision. For appropriate assessment factors for DNEL derivation see the ECHA Guidance R.8.

With regard to acute DNELs, you state in your comments that the registered substance is not acutely toxic, therefore you argue that there is no need for short-term DNELs for systemic effects whatever the route of exposure and whatever the population. ECHA agrees that acute DNELs do not have to be derived under all circumstances.

[2] Link to ECHA guidance document R.8 is: http://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf

However, if acute DNELs are not derived a justification shall be provided which explains the reasoning for not providing the acute DNELs. For further guidance on how to derive DNELs see ECHA Guidance R.8.

With regard to eye irritation, you state in your comments that it is not possible to derive local DNELs and therefore, qualitative risk assessment was done. ECHA agrees that a qualitative assessment may be done. However, if qualitative assessment is done, a justification shall be provided which explains the reasoning in this assessment. For further guidance on how to conduct qualitative risk assessment see Part E, Section E.3 of the ECHA Guidance on information requirements and chemical safety assessment (http://echa.europa.eu/documents/10162/13632/information_requirements_part_e_en.pdf)

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit in the chemical safety report either of the following information: DNELs for workers and for the general population using the recommendations of ECHA guidance *or* a detailed justification for not using the recommended assessment factors in DNEL derivation. You shall re-assess the related risks accordingly.

Notes for your consideration

Regarding Identification of DNEL(s) and risk characterisation, the results of the studies requested with this decision shall be taken into account when deriving the DNELs.

9. Exposure assessment and risk characterisation (Article 14(6), Annex I, Section 5.1.1., in conjunction with Annex II, 0.1.2. and 8.2.2.2. (b) (d) and 6.) for human health

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.

Article 14(6) as well as Annex I, 0.1., 5.1.1., 5.2.4. and 6.2. of the REACH Regulation require registrants to identify and apply appropriate measures to adequately control the risks identified in a CSR. The exposure shall be estimated and risks shall be characterised in the CSR under the assumption that relevant risk management measures have been implemented.

According to Annex I, 0.3., 0.5. and 5.1.1. the applied Risk Management Measures (RMM) have to be described in the CSR. The CSR needs to contain sufficient information to allow ECHA to gain assurance that the risks are adequately controlled and that appropriate risk management measures can be prescribed by actors in the supply chain. Accordingly, the supplier is required to describe the relevant RMM in detail in the Safety Data Sheet in order to minimise the exposure for workers handling the registered substance (e.g. the type of gloves to be worn, protection equipment for parts of the body other than the hand or respiratory protection shall be clearly specified based on the hazard of the substance or mixture and potential for contact and with regard to the amount and duration of exposure in accordance with Annex II, section 8.2.2.2.(b)(i), (ii) and 8.2.2.2.(c) respectively). The information provided in the Safety Data Sheet (SDS) shall be consistent with information in the CSR (Annex II, section 0.1.2. of the REACH Regulation).

ECHA notes that specific detailed information on the recommended personal protective equipment is missing both from the CSR and from the information on safe use within the IUCLID dossier. In the CSR, you indicated the following personal protective equipment is advised e.g. in chapter 9.3.1.2. mentions gloves. While in IUCLID Section 11 has reported: "Eye protection: Safety glasses"; "Skin and body protection: Protective suit", and "The protective equipment must be selected in accordance with current CEN standards and in cooperation with the supplier of the protective equipment."

To ensure the safe use of a substance, Annex I Section 5.1.1 requires a description of the risk management measures to reduce or avoid direct and indirect exposure of humans. Gloves are reported in the CSR as required personal protective equipment to prevent dermal exposure to the substance. Generally, gloves that are capable of preventing exposure to the skin for a pre-determined duration shall be specified. Typically, this information, as a minimum, has to specify the glove material and, depending on the exposure scenarios, may also need to include the breakthrough time and thickness of the glove material.

Protective suit is reported in IUCLID Section 11 as required personal protective equipment to prevent dermal exposure to the substance. Generally, protective suits that are capable of preventing exposure to the skin for a pre-determined duration shall be specified. Typically, this information, as a minimum, has to specify the type of suite and quality.

In your comments you agreed to change the risk assessment and the CSR accordingly.

Therefore, pursuant to Article 41(1)(c) you are requested to:
- provide documentation for the recommended personal protective equipment, *i.e.* Skin and body protection;
- specify the type of glove material, thickness and breakthrough times;
and to revise the risk characterisation accordingly; and
- specify the type and quality of the protective suit.

Notes for your consideration
Regarding how to report the gloves specifications, the information should be included both in section 11 of the technical IUCLID dossier (Guidance on Safe Use), which is the disseminated part of the dossier and in the CSR, where the appropriate measures to adequately control the risk are to be reported.

It is the responsibility of the Registrant to ensure consistency of the information within the CSR, and between the CSR, IUCLID section 11 and the safety data sheet.

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 13 August 2015.

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments, which were sent within the commenting period, and they are reflected in the Reasons (Appendix 1).

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendments.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-47 written procedure and ECHA took the decision according to Article 51(6) 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 requests in this decision, or to fulfil otherwise the information requirements 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 substance used for the new tests 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. 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 tests 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 tests 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 tests to be assessed.