Helsinki, 18 July 2016

Addressee: [redacted]

Decision number: CCH-D-2114337628-41-01/F
Substance name: Cis-2-tert-butylcyclohexyl acetate
EC number: 243-718-1
CAS number: 20298-69-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 12.04.2013

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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD TG 408) in rats with the registered substance; modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy;**

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

3. **Long-term toxicity to terrestrial invertebrates (Annex IX, Section 9.4.1., column 2; test method: Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*), OECD TG 222, or Enchytraeid reproduction test, OECD TG 220, or Collembolan reproduction test in soil, OECD TG 232) with the registered substance;**

4. **Long-term toxicity testing on plants (Annex IX, Section 9.4.3., column 2; test method: Terrestrial plants, growth test, OECD TG 208, with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species), or, Soil Quality – Biological Methods – Chronic toxicity in higher plants, ISO 22030) with the registered substance;**

5. **Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD TG 216) with the registered substance;**

6. **Identification of PNEC and risk characterisation (Annex I, Section 3.3.1. and 6.): revise PNECs for freshwater and marine water using results of only**

relevant and reliable aquatic toxicity studies and revise the risk characterisation accordingly.

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 **25 July 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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), oral route (Annex IX, Section 8.6.2.)

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 "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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. Pursuant to last paragraph of column 2 of that Section, further studies may be required by the Agency in case of, for instance, indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422). However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days. Furthermore, the technical dossier does not contain an adaptation in accordance with column 2 of Annex IX, Section 8.6.2. or with the general rules of Annex XI for this standard information requirement.

In the comments to the draft decision, you indicated that the provided OECD TG 422 screening study was performed with extended exposure duration (77 days for males and 104 days for females) and you provided a weight of evidence analysis considering that "*further testing on this endpoint does not appear scientifically necessary and that the available information is sufficient for an adequate hazard characterization and a CSA where the exposure to the substance is adequately controlled.*"

ECHA notes the following shortcomings of this argumentation:

- An adaptation according to Annex XI, Section 1.2. requires "*sufficient evidence from several independent sources*". However, you provided only one source of information (OECD TG 422). Hence, a basic element of a weight of evidence adaptation is not met.
- Histopathological examination was performed on all organs showing gross lesions and all organs/tissues as required according to OECD TG 422 as well as on ovaries, prostate and peripheral nerves which are required for a sub-chronic toxicity study. However, the following organs/tissues which need to be examined in a sub-chronic toxicity study were not investigated in the provided study: mammary gland, pituitary, and pancreas. You did not address the impact of the missing histopathological evaluation for those organs on your conclusion.
- The provided study was performed with 12 animals per sex and dose. Histopathological examination of reproductive organs (ovaries, uterus, testes, epididymides, seminal vesicles and prostate) and of all organs showing gross lesions was performed on all animals. However, for other organs histopathological examination was performed with 5 animals per sex and dose as described in OECD TG 422. Since for a sub-chronic toxicity study histopathological examination is required for 10 animals per sex and dose, the OECD TG 422 screening study has a lower statistical power to detect effects on those organs for which only 5 animals per sex and dose were examined. You did not address this issue.

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

ECHA has evaluated the most appropriate route of administration for the study. ECHA observes that based on the information provided in the registration dossier the substance is a solid handled exclusively in liquid form of low vapour pressure (9.7 Pa). Several uses with spray application are reported in the registration dossier. The substance is not classified for skin or eye irritation. Based on those results you have concluded that "*There is also no indication for the substance being a long-term local irritant after repeated exposure and therefore it is not a respiratory irritant (see comments in IUCLID 7.3).*" However, ECHA notes that since the substance is metabolised to acetic acid by carboxylesterases which are also expressed in the upper respiratory tract, respiratory tract irritation could be expected following inhalation exposure. However ECHA notes that the substance is used as a fragrance, i.e. in very low concentrations in those liquid formulations. Therefore local inhalation effects are unlikely. ECHA notes further that oral route of administration is the preferred route used in repeated dose toxicity study in order to maximise systemic availability. Hence, ECHA considers that testing for sub-chronic toxicity should be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26/OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In the OECD 422 screening study a dose related increase in relative kidney weight was observed in mid and high dose male rats. Effects observed on kidney weights and urea-concentrations were considered by you to be related to alpha 2u-microglobulin nephropathy which was confirmed by immunocytochemical staining of the alpha 2u-microglobulin protein in the cortical tubular epithelial cells. Since humans do not excrete alpha-2u-globulin, this mode of action is not relevant to humans. However, ECHA considers that this additional analysis is also necessary to conclude whether any possible effects on kidney in the Repeated dose 90-day oral toxicity study are relevant to humans or not. For this reason, ECHA decided to include in the request for a sub-chronic toxicity study urinalysis (which is optional in paragraph 30 of OECD 408, and the relevant part of Section 1.5.2.2. of EU Method B.26) to investigate kidney function, and a full histopathological examination (paragraph 36 of OECD 408, Section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats; modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(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 sought to adapt this information requirement according to Annex XI, Section 1. using the following justification:
- *"In accordance with Section 1 of REACH Annex XI the developmental toxicity study according to OECD TG 414 is not scientifically justified, because in the available combined and extended repeated dose - reproductive screening study (OECD 422) no adverse effects on reproductive and developmental toxicity were noted up to the limit dose of 500 mg/kg bw. Furthermore, Verdox, did not show adverse effects on systemic toxicity up to the limit dose of 500 mg/kg bw."*
- *"Though the formation of acetic acids is expected for Verdox, acetic acid (C2) has two hydrogen atoms at the C-2 position and is thus not branched (see Fig. below from* [redacted] *and see attachment in the IUCLID 7.6 Endpoint summary). This means that the acetic acid formed is will not be causing malformations. In addition, acetic acid is a natural constituent of the body and is therefore also not expected to cause malformations. In the REACH registration on acetic acid it is shown that acetic acid does not cause developmental toxicity up to 1600 mg/kg bw [http://...])."*
- *"Malformations may be due to genetic damage. Verdox is negative in all genotoxicity assays and has no alert for genotoxicity and thus malformations in offspring caused by genetic damage are not expected."*

While you have not explicitly claimed a specific 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. This adaptation requires that there may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property. ECHA notes, however, that from the information provided by you it cannot be assumed or concluded that the substance will not lead to pre-natal developmental toxicity.

More specifically, the pre-natal developmental toxicity study investigates foetuses for skeletal and visceral alterations before natural delivery. These key parameters are not investigated in the OECD 422 screening study.

Furthermore ECHA notes that, when concluding your justification, you correctly note that the absence of findings in an OECD 422 study does not exclude adverse findings in an OECD 414 study (underlining added): *"It can be concluded that Verdox has a low potential to cause developmental effects based on the absence of such effects in the extended OECD TG 422. Possibly with the exception of malformations which may be better detected in an OECD 414. In view of the absence of reproductive, developmental and systemic effects at the limit dose of 500 mg/kg bw and the absence of genotoxicity further testing is not warranted in an OECD 414, because C&L for developmental toxicity is unlikely and the low order of (systemic) toxicity shown for Verdox (NOAEL 500 mg/kg bw, highest dose tested)".*

ECHA also notes that the absence of reproductive or other systemic effects at the highest dose tested in the studies provided by you does not necessarily exclude pre-natal toxic effects.

Furthermore, even if you refer to the information that the metabolite acetic acid is not a teratogen, this information is not included in the registration and no adequate information on pre-natal developmental toxicity for the other metabolite, 2-tert-butyl cyclohexanol, is provided. With regard to the last argument, it is to be noted that also non-genotoxic substances can induce malformations. Hence, this is not an argument to disregard potential pre-natal developmental toxic effects of the registered substance.

In the comments to the draft decision, you indicated that the current reasoning will be strengthened and that an Annex XI weight of evidence will be used to further support the expected absence of developmental toxicity.

ECHA notes the following shortcomings of this argumentation:

- You conclude that in the provided reproductive screening study according to OECD TG 422 no adverse effects on reproductive and developmental toxicity and on systemic toxicity were noted. ECHA refers to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2 which emphasizes that a screening study does not provide sufficient information on prenatal developmental toxicity: "*This study* [OECD TG 414] *is specifically designed to provide information on substance-induced effects on growth and survival of the foetuses, and increased incidences in external, skeletal and soft tissue malformations and variations in foetuses* (see ECHA Guidance R.7.6.2.2.2.). *The screening studies provide initial information of the effects on male and female reproductive performance as well as on developmental toxicity during and shortly after birth.* [...] *An evaluation of the screening tests (OECD TGs 421 or 422) has confirmed that these tests are useful for initial hazard assessment and can contribute to decisions on further test requirements (*[redacted]*).* [...] *With regard to developmental toxicity, these screening tests do not provide sufficient information on prenatal developmental toxicity because the pups are not examined for external, skeletal and visceral anomalies as in the prenatal developmental toxicity study (EU B.31, OECD TG 414). In addition, the pups in the screening studies are delivered naturally and the dams may cannibalise malformed pups. In the prenatal developmental toxicity study caesarean section is performed to avoid any cannibalism and to allow an appropriate evaluation of the foetuses. In addition, the statistical power of the screening study is lower than that of the prenatal developmental toxicity study. Therefore, a screening study cannot be used to fulfil the standard information requirement of a prenatal developmental toxicity study (EU B.31, OECD TG 414)* (see ECHA Guidance R. R.7.6.4.2.1). Hence, a screening study is not suitable to conclude on the absence of pre-natal developmental toxic effects.
- In addition, ECHA notes that the study has not been conducted up to the limit dose of 1000 mg/kg bw/day, which is generally considered as limit dose in the test methods as well as for considering adverse effects on reproductive toxicity and their potential relationship to systemic toxicity. Thus, your argument that no developmental toxicity was noted up to 500 mg/kg bw/day is not alone sufficient to conclude/assume that the substance is not a pre-natal developmental toxicant.
- You commented that neither the registered substance nor its metabolites belong to a category of substance (SAR) which may cause malformations. However, the information based on SAR does not exclude the possibility that the registered substance or its metabolite(s) might lead to pre-natal developmentally toxic effects other than malformations. Thus, this information is not sufficient to conclude/assume

that the substance has or has not a hazardous property regarding pre-natal developmental toxicity.

- Furthermore, you refer to the REACH registration on the metabolite acetic acid for which no pre-natal developmental toxicity was observed. However, you did not provide information on pre-natal developmental toxicity on the other metabolites of the registered substance. Thus, absence of pre-natal developmental toxicity cannot be assumed/concluded based on information on only one metabolite.
- You indicated that since there is no alert for genotoxicity for the registered substance, malformations in offspring caused by genetic damage are not expected. ECHA notes that genotoxicity may be one cause of pre-natal developmental toxicity; however, all effects that interfere with normal embryonic development could potentially lead to pre-natal developmental toxicity.
- You are further citing that malformations are often associated with maternal toxicity or other developmental effects ([redacted]), which have not been identified for the cyclic acetates ([redacted]). However, you did neither provide study summaries for pre-natal developmental toxicity studies of other cyclic acetates nor a read-across justification or other substance-specific justification why and how for this specific case the absence of maternal toxicity and other developmental effects as investigated in OECD TG 422 study would allow to conclude on the absence pre-natal developmental toxicity (including malformations). Hence, this source of information cannot be regarded as sufficiently supported by data.
- Regarding to the low order of systemic toxicity, ECHA notes that the registered substance is absorbed, shows some effects (increased liver weights in male and female animals and increased alpha 2u nephropathy in male rats) at lower dose level than a limit dose. In addition, human exposure - including consumer exposure - occurs. Hence, exposure of pregnant women to the registered substance can be expected. This further supports the need to investigate pre-natal developmental toxicity.

Therefore, individually and taken together, the provided information and justification to adapt the prenatal developmental toxicity study is not sufficient to allow an assumption or conclusion that the substance has or has not a particular dangerous property with respect to pre-natal developmental toxicity, i.e., on growth, survival, external, skeletal and soft tissue malformations and variations. 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 assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, July 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid handled exclusively in liquid form of low vapour pressure, ECHA concludes that testing should be performed by the oral route.

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

3. Long-term toxicity to terrestrial invertebrates (Annex IX, Section 9.4.1., column 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.

"Effects on terrestrial organisms" is a standard information requirement as laid down in Annex IX, Section 9.4. of the REACH Regulation. Adequate information on effects on short-term toxicity to invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity to plants (Annex IX, Section 9.4.3.) needs to be present in the technical dossier for the registered substance to meet the information requirements. Column 2 of Annex IX, Section 9.4 specifies that long-term toxicity testing shall be considered by the Registrant instead of short-term, in particular for substances that have a high potential to adsorb to soil or that are very persistent.

You have sought to adapt the standard information requirements of Annex IX, section 9.4.1. using the following justification: "*No studies on the toxicity of the substance to soil macro-organisms are available. According to column 2 of REACH (Regulation 1907/2006/EC) Annex IX, the equilibrium partitioning method may be applied to assess the hazard to soil organisms if actual toxicity data is not available. According to column 2 of REACH Annex X, long-term toxicity testing on soil organisms shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on terrestrial organisms. Based on the available measured Koc value of 1300 L/kg w.w the substance will have moderate potential to adsorb to soil. Therefore, the screening approach, in which soil risks are estimated using aquatic toxicity data using the equilibrium partitioning method, is justified. Using the available information for the substance and a PNECsoil derived by equilibrium partitioning, the chemical safety assessment does not reveal a need for further investigation (the environmental risk assessment for all intended uses shows that the risk is controlled). Therefore, studies on the short and long-term effects on soil macro-organisms are waived.*"

Based on the data provided in the registration dossier, ECHA notes that the registered substance is not highly adsorptive, not very toxic to aquatic organisms, but is nevertheless very persistent in soil (default setting for not readily biodegradable substances, when information on half-life of the substance in the soil is not available). Thus, based upon the available aquatic toxicity information and the physico-chemical properties of the substance and in relation to section R.7.11.6., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), ECHA considers that the substance would fall into soil hazard category 3. In the context of an integrated testing strategy for soil toxicity, the Guidance advocates performing an initial screening assessment based upon the Equilibrium Partitioning Method (EPM), together with a confirmatory long-term soil toxicity test. The Predicted No-Effect Concentration screening (PNECscreen) is calculated through EPM on the basis of aquatic toxicity data only.

As concluded under section 5 below, PNECs for freshwater and marine water should be based on results of only relevant and reliable aquatic toxicity studies. Furthermore, ECHA notes that according to the integrated testing strategy for soil toxicity an additional assessment factor of 10 should be applied to PNECscreen for substances falling into soil hazard category 3. Consequently, ECHA notes that the screening assessment for the soil compartment based on the revised PNEC for freshwater and with an applied additional assessment factor of 10 would indicate a risk, i.e. for some Exposure Scenarios, predicted environmental concentration in soil reported in the Chemical Safety Report (CSR) would exceed the PNECscreen for soil.

Therefore, the screening assessment conducted for the soil compartment through the EPM method based on aquatic toxicity data would indicate a potential risk for the soil compartment. Consequently, the risk characterisation done according to Annex I would indicate the need to investigate further effects on terrestrial organisms, requiring terrestrial toxicity testing.

According to the evidence presented within the Registration dossier, the substance is likely to be very persistent (default setting for not readily biodegradable substances). Therefore ECHA considers that the column II adaptation for Annex IX, section 9.4 regarding long-term testing instead of short-term testing, is applicable to this substance.

According to the Guidance on information requirements and substance safety assessment, Chapter R.7c, Table R.7.11-2 (November 2014), when a risk is indicated through the screening assessment, long-term toxicity tests according to the standard information requirements of Annex X (invertebrates and plants) shall be conducted for the substance falling into soil hazard category 3. However, in the absence of such risk (based on the screening assessment), only one study (either invertebrates or plants) would need to be conducted. Therefore, ECHA concludes that a long-term toxicity testing with terrestrial invertebrates is necessary.

In the comments to the draft decision according to Article 50(1) you proposed to use weight of evidence reasoning to support categorisation of the substance as not persistent in the environment (specifically, in soil). Furthermore, you considered that the substance is not highly adsorptive to soil and is not very toxic to the aquatic organisms. Therefore, you concluded that the substance can be assigned to soil hazard category 1 and screening risk assessment for the soil compartment based on EPM from aquatic toxicity information would be applicable for the substance.

ECHA notes that Section 1.2 of the Annex XI of the REACH Regulation sets out the prerequisites of weight of evidence approaches as follows:
"There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion".

Thus, an evidence based approach involves an assessment of the relative values/weights of different pieces of the available information that have been retrieved and gathered. The weight given to the available evidence depends on factors such as the quality of the data, consistency of results, nature and severity of effects, relevance of the information for the given regulatory endpoint.

If the weight of evidence approaches proposed are themselves based on sources of

information such as QSAR, grouping and read-across or existing studies, these sources of information are themselves adaptations described in respective sections of Annex XI and subject to specific conditions. The fulfillment of all or parts of these conditions determines the quality and reliability of these sources of information for assuming or concluding that a substance has or has not a particular dangerous property.

For instance, the quality and reliability of the (Q)SAR models can be assessed in the light of the criteria established in Section 1.3. of Annex XI to the REACH Regulation. Adequate and reliable documentation should provide information on the scientific validity of the approach. The justification for using the (Q)SAR information should be based on the use of the QSAR Reporting Formats described in ECHA Guidance on information requirements and chemical safety assessment (May 2008), Chapter R.6 (Section R.6.1.6.). Required (Q)SAR Model Reporting Format and (Q)SAR Prediction Reporting Format are essential to provide a comprehensive description of the reliability and use of the (Q)SAR during the chemical safety assessment, including the classification of a given substance for a specific endpoint.

Similarly, the information used for predicting fate/ecotoxicological properties from reference substance(s) (read-across approach) should be justified and documented in line with the requirements of Annex XI, Section 1.5.

ECHA observes that a weight of evidence proposed by you to address degradation of the substance might be plausible. However, ECHA notes that there is no sufficient information reported neither in the registration dossier nor in your comment on the lines of evidence proposed to be used for supporting categorisation of the substance as not persistent in the environment. Thus, ECHA considers that there is no sufficient information reported on various lines of evidence that would allow an independent assessment of the relevance and realibility of the available information.

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

The earthworm reproduction test (OECD TG 222), Enchytraeid reproduction test (OECD TG 220), and Collembolan reproduction test (OECD TG 232) are each considered capable of generating information appropriate for the fulfilment of the information requirements for long-term toxicity testing to terrestrial invertebrates. ECHA is not in a position to determine the most appropriate test protocol, since this decision is dependent upon species sensitivity and substance properties. You are to apply the most appropriate and suitable test guideline among those listed above.

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: Long-term toxicity to terrestrial invertebrates (test method: Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*), OECD TG 222, or Enchytraeid reproduction test, OECD TG 220, or Collembolan reproduction test in soil, OECD TG 232).

ECHA observes that in the comments to the draft decision according to Article 50(1) you stated that the OECD soil toxicity test guidelines are not applicable due to the volatile nature of the substance. ECHA notes that some of OECD and ISO soil toxicity test guidelines (e.g. OECD 220, OECD 222, OECD 232 and ISO 22030) are not applicable to volatile substances, i.e. defined in these guidelines "*as substances for which Henry's law constant or*

air-water partitioning coefficient is greater than 1, or to substances with vapour pressure exceeding 0.0133 Pa at 25 °C". ECHA considers that the value for vapour pressure given in the above mentioned test guidelines is too low and is probably an editorial error. ECHA (November 2012) submitted a note to the OECD Secretariat regarding a potential inconsistency in OECD test guidelines on soil invertebrates. Currently the discussion on correction of vapour pressure value in the OECD test guidelines on soil organisms is on-going with the OECD Secretariat (as noted by you drafts of OECD soil toxicity test guidelines with revised advice for testing volatile substances are publicly available on the OECD website). Based on values of physico-chemical properties of the substance provided in the registration dossier ECHA estimated by using the EUSES 2.1.1 model the air-water partitioning coefficient (dimensionless Henry's law constant) of the substance to be 0.0434 m^3/m^3 (i.e. less than 1). Therefore, ECHA considers that your substance should not be considered as a volatile and the requested soil toxicity tests have to be provided.

4. Long-term toxicity testing on plants (Annex IX, Section 9.4.3., column 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.

"Effects on terrestrial organisms" is a standard information requirement as laid down in Annex IX, Section 9.4. of the REACH Regulation. Adequate information on effects on short-term toxicity to invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity to plants (Annex IX, Section 9.4.3.) needs to be present in the technical dossier for the registered substance to meet the information requirements. Column 2 of Annex IX, Section 9.4 specifies that long-term toxicity testing shall be considered by the Registrant instead of short-term, in particular for substances that have a high potential to adsorb to soil or that are very persistent.

You have sought to adapt the standard information requirements of Annex IX, section 9.4.3. using the following justification: "*No studies on the toxicity of the substance to terrestrial plants are available. According to column 2 of REACH (Regulation 1907/2006/EC) Annex IX, the equilibrium partitioning method may be applied to assess the hazard to soil organisms if actual toxicity data is not available. According to column 2 of REACH Annex X, long-term toxicity testing on soil organisms shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on terrestrial organisms. Based on the available measured Koc value of 1300 L/kg w.w the substance will have moderate potential to adsorb to soil. Therefore, the screening approach, in which soil risks are estimated using aquatic toxicity data using the equilibrium partitioning method, is justified. Using the available information for the substance and a PNECsoil derived by equilibrium partitioning, the chemical safety assessment does not reveal a need for further investigation (the environmental risk assessment for all intended uses shows that the risk is controlled). Therefore, studies on the short and long-term effects on terrestrial plants are waived.*"

Based on the data provided in the registration dossier, ECHA notes that the registered substance is not highly adsorptive, not very toxic to aquatic organisms, but is nevertheless very persistent in soil (default setting for not readily biodegradable substances, when information on half-life of the substance in the soil is not available). Thus, based upon the available aquatic toxicity information and the physico-chemical properties of the substance and in relation to section R.7.11.6., Chapter R.7c of the ECHA *Guidance on information*

requirements and chemical safety assessment (version 2.0, November 2014), ECHA considers that the substance would fall into soil hazard category 3. In the context of an integrated testing strategy for soil toxicity, the Guidance advocates performing an initial screening assessment based upon the EPM, together with a confirmatory long-term soil toxicity test. The PNECscreen is calculated through EPM on the basis of aquatic toxicity data only.

As concluded under section 5 below, PNECs for freshwater and marine water should be based on results of only relevant and reliable aquatic toxicity studies. Furthermore, ECHA notes that according to the integrated testing strategy for soil toxicity an additional assessment factor of 10 should be applied to PNECscreen for substances falling into soil hazard category 3. Consequently, ECHA notes that the screening assessment for the soil compartment based on the revised PNEC for freshwater and with an applied additional assessment factor of 10 would indicate a risk, i.e. for some Exposure Scenarios predicted environmental concentration in soil reported in the CSR would exceed the PNECscreen for soil.

Therefore, the screening assessment conducted for the soil compartment through the EPM method based on aquatic toxicity data would indicate a potential risk for the soil compartment. Consequently the risk characterisation done according to Annex I would indicate the need to investigate further effects on terrestrial organisms, requiring terrestrial toxicity testing.

According to the Guidance on information requirements and substance safety assessment, Chapter R.7c, Table R.7.11-2 (November 2014), when a risk is indicated through the screening assessment, long-term toxicity tests according to the standard information requirements of Annex X (invertebrates and plants) shall be conducted for the substance falling into soil hazard category 3. However, in the absence of such risk (based on the screening assessment), only one study (either invertebrates or plants) would need to be conducted. Therefore, ECHA concludes that a long-term toxicity testing with terrestrial plants is necessary.

In the comments to the draft decision according to Article 50(1) you proposed to use weight of evidence reasoning to support categorisation of the substance as not persistent in the environment (specifically, in soil). Furthermore, you proposed to strengthen the PNEC for freshwater that would be used for the calculation of PNEC for soil via EPM method. In line with ECHA's considerations in sections 3 (above) and 5 (below) ECHA considers that it is necessary to provide information on the long-term toxicity to soil organisms.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.
OECD TG guideline 208 (Terrestrial plants, growth test) considers the need to select the number of test species according to relevant regulatory requirements, and the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For long-term toxicity testing, ECHA considers six species as the minimum to achieve a reasonably broad selection. Testing shall be conducted with species from different families, as a minimum with two monocotyledonous species and four dicotyledonous species, selected according to the criteria indicated in the OECD TG 208 guideline. You should consider if testing on additional species is required to cover the information requirement.

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: Long-term toxicity testing on plants (test method: Terrestrial plants, growth test, OECD TG 208, with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species), or, Soil Quality – Biological Methods – Chronic toxicity in higher plants, ISO 22030).

5. Effects on soil micro-organisms (Annex IX, Section 9.4.2.)

"Effects on terrestrial organisms" is a standard information requirement as laid down in Annexes IX and X, section 9.4., of the REACH Regulation. Adequate information on effects on soil micro-organisms (Annex IX, section 9.4.2.), short-term toxicity testing on invertebrates (Annex IX, section 9.4.1.), long-term toxicity testing on invertebrates (Annex X, section 9.4.4.), short-term toxicity testing on plants (Annex IX, section 9.4.3.) and long-term toxicity testing on plants (Annex X, section 9.4.6.) needs to be present in the technical dossier for the registered substance to meet the information requirements.

You have waived the standard information requirements of Annexes IX and X, section 9.4.2. using the following justification: "No studies on the toxicity of the substance to soil microorganism are available. According to column 2 of REACH (Regulation 1907/2006/EC) Annex IX, the equilibrium partitioning method may be applied to assess the hazard to soil organisms if actual toxicity data is not available. According to column 2 of REACH Annex X, long-term toxicity testing on soil organisms shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on terrestrial organisms. Based on the available measured Koc value of 1300 L/kg w.w the substance will have moderate potential to adsorb to soil. Therefore, the screening approach, in which soil risks are estimated using aquatic toxicity data using the equilibrium partitioning method, is justified. Using the available information for the substance and a PNECsoil derived by equilibrium partitioning, the chemical safety assessment does not reveal a need for further investigation (the environmental risk assessment for all intended uses shows that the risk is controlled). Therefore, studies on the short and long-term effects on soil micro-organisms are waived."

You have sought to adapt this information requirement by using the EPM based screening approach. However, ECHA emphasises that the intrinsic properties of soil microbial communities are not addressed through the EPM extrapolation method and therefore the potential adaptation possibility outlined for the information requirement of Annex IX, Section 9.4. does not apply for the present endpoint. Your justification for waiving does not meet the criteria of either the specific adaptation rules of Column 2 of Annexes IX and X, Section 9.4, or the general adaptation rules of Annex XI. Therefore, the adaptations 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 requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes that the tests requested under points (3 and 4) above are not sufficient to address this standard information requirement. ECHA concludes that the effects on soil microorganisms need to be ascertained by performing a relevant test.

According to ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R.7C, Section R.7.11.3.1., p115, the nitrogen transformation test is considered sufficient for most non-agrochemicals.

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: Soil microorganisms: nitrogen transformation test (test method: EU C.21./OECD TG 216).

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

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

Annex I, Section 3.3.1. of the REACH Regulation requires to establish a PNEC for each environmental sphere based on the available information and to use an appropriate assessment factor to the effect values. The ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.10 provides further details and specifically provides default assessment factors that should be applied to derive PNECs.

ECHA observes that for the derivation of PNECs for fresh and marine waters you have assumed that in addition to the short-term aquatic toxicity data, long-term toxicity data with algae and fish are available for the substance. Furthermore, ECHA observes that a long-term No Observed Effect Concentration (NOEC) for fish is calculated by "*using the Critical Body Burden approach*". In the IUCLID Registration dossier, you have calculated a NOEC for fish from acute fish toxicity data through the estimation of Lethal Body Burden (LBB) and used this LBB for the estimation of Critical Body Burden (CBB). For the justification of such approach you have noted following: "*Though Verdox is an ester the neutral organic approach can still be applied, because its ester is not reactive. The ester has no electrophilic groups adjacent to the ester-bond which can increase the reactivity and thus the aquatic toxicity. Also, Verdox hydrolysis in ca 44h and the hydrolysis products: the alcohol and acetic acid, can be considered neutral organics. Though this half-life is outside the criteria for using hydrolysis products for the risk assessment it indicates that in the environment the exposure will be more via the hydrolysis products than the parent substance.*"

ECHA notes that ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b: Endpoint specific guidance (Version 2.0, November 2014) specifies that internal body burden is an alternative metric for measuring effects. However, the number of shortcomings of body burden approach are noted in this Guidance. Among others it is noted that "*a value for LBB cannot automatically be used to predict a CBB as the MoA may change from narcotic to non-narcotic for certain chemicals over the long term*". It is summarised in the Guidance that "*If there is information on the critical body burden of a substance in an (aquatic) organism this information could help to identify whether or not the chemical is a baseline narcotic chemical or has a more specific mode of action and thus would provide an indication of its aquatic toxicity*". ECHA notes there is no reliable documentary evidence in line with requirements of Annex XI, section 1 provided in your registration dossier proving that the registered substance would pose only narcotic mode of action on aquatic organisms over the long-term duration. Thus, ECHA concludes that these

shortcomings were not addressed in your registration dossier and that the body burden aproach was not used for the purpose noted in the ECHA's Guidance document. Therefore, ECHA concludes that the NOEC estimated for fish is not reliable and cannot be used for the derivation of PNECs for fresh and marine waters.

In the comments to the draft decision according to Article 50(1) you noted about the intention to submit a dossier update with information on long-term toxicity to *Daphnia* which will be used for derivation of PNECs for freshwater and marine water. ECHA acknowledges your intention and notes that there is currently no sufficient information reported on results and conditions of that study. Hence, an independent assessment of the relevance and realibility of the information is not possible.

Furthermore, ECHA notes that you proposed to use weight of evidence reasoning to predict long-term toxicity of the substance to fish. You proposed still to use a critical body burden approach to predict long-term NOEC for fish. You stated that for the registered substance "*the neutral organic approach can still be applied*". To support this statement you have reported the use of internal body burden approach for the analogue substances.

ECHA notes that the internal body burden approach, noted in ECHA's Guidance, Chapter R.7b, is an alternative metric for measuring effects, i.e. "*method for collating lethal concentration, BCF and chronic effects while adhering to the principle of validated guideline studies rather than performing three standard tests under subtly different conditions and trying to combine the results of the studies.*" Furthermore, as already noted above, there is a number of shortcomings of the CBB approach that are mentioned in the guidance. ECHA observes that the shortcomings noted in the guidance document are not sufficiently addressed by you (e.g. there is no information provided which would demonstrate that the substance possesses only a narcotic mode of action during the long-term exposure etc.). Thus, ECHA considers that the body burden approach is not used for the purpose noted in the above mentioned ECHA's guidance document.

Furthermore, ECHA notes that an evidence based approach involves an assessment of the relative values/weights of different pieces of the available information that have been retrieved and gathered. The weight given to the available evidence depends on factors such as the quality of the data, consistency of results, nature and severity of effects, relevance of the information for the given regulatory endpoint. If the weight of evidence approaches proposed are themselves based on sources of information such as QSAR, grouping and read-across or existing studies, these sources of information are themselves adaptations described in respective sections of Annex XI and subject to specific conditions. The fulfillment of all or parts of these conditions determines the quality and reliability of these sources of information for assuming or concluding that a substance has or has not a particular dangerous property.

ECHA notes that there is no sufficient information reported neither in the registration dossier nor in your comment on the lines of evidence proposed to be used for predicting long-term toxicity of the substance to fish. Thus, ECHA considers that there is no sufficient information reported on various lines of evidence that would allow an independent assessment of the relevance and realibility of the information.

ECHA acknowledges your intention expressed in the comments to the draft decision according to Article 50(1) to refine the prediction of environmental concentration of the substance in the soil.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to revise PNECs for freshwater and marine water using results of only relevant and reliable aquatic toxicity studies and revise the risk characterisation 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 5 October 2015. The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

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 proposal(s) for amendment(s).

Subsequently, ECHA received proposal(s) for amendment(s). They are reflected in the Reasons (Appendix 1). ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment. You did not provide any comments on the proposed amendment.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-48 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 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 substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance composition manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. 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.