EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114321209-57-01/F Helsinki, 30 March 2016

DECISION ON TESTING PROPOSAL(S) SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For 2,2-dimethyl-1,3-dioxolan-4-ylmethanol, EC No 202-888-7 (CAS No 100-79-8), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for 2,2-dimethyl-1,3-dioxolan-4-ylmethanol, EC No 202-888-7 (CAS No 100-79-8), submitted by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study; oral in rat (OECD TG 414);
- Long-term toxicity to aquatic invertebrates (OECD TG 211);
- Toxicity to soil microorganisms (OECD TG 216 and 217)
- 90-day oral toxicity study (OECD TG 408);
- Earthworm, Acute Toxicity Tests (OECD TG 207).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year.

This decision does not take into account any updates after 02 November 2015, i.e. 30 calendar days after the end of the commenting period.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

ECHA received the registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 22 December 2014.

ECHA held a third party consultation for the testing proposals from 17 April 2015 until 4 June 2015. ECHA did not receive information from third parties.

ECHA notified the Registrant of the draft decision on 25 August 2015 and invited him to provide comments.

ECHA did not receive any comments on the draft decision by 01 October 2015.

On 21 January 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route;
2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211);
3. Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216 and Annex IX, Section 9.4.2.; test method: Soil microorganisms: carbon transformation test, EU C.22/OECD 217).

The Registrant shall carry out the following additional tests pursuant to Article 40(3)(c) and 13(4) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

4. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD 413) 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;
5. Long-term toxicity on terrestrial invertebrates (Annex IX, Section 9.4..1., column 2.; test method: Either Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*), OECD 222), or Enchytraeid reproduction test OECD 220, or Collembolan reproduction test in soil OECD 232).

while the originally proposed tests for 90-day oral toxicity study (OECD TG 408) and Earthworm, Acute Toxicity Tests (OECD TG 207) proposed to be carried out are rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Note for consideration by the Registrant

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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 the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **6 April 2018** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance.

A. Tests required pursuant to Article 40(3)

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

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD 414.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant proposed testing in rats. He proposed testing by the oral route. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.
"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the

technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for long-term toxicity testing on aquatic invertebrates *Daphnia magna* reproduction test, OECD TG 211 with the following justification: "*In accordance with the adaptations for information requirements stipulated in Column 2 of Annex IX of REACH, long term toxicity testing on fish is not deemed necessary unless the CSA would indicate the opposite. Based on the currently available information, namely that the substance exhibits low acute toxicity to fish and is inherently biodegradable, there is no indication that there would be a need for long-term fish testing. Moreover in the meantime, long-term toxicity testing on invertebrates (OECD211) is proposed in the current registration dossier. If, based on the outcome of the Daphnia study additional studies would be triggered, the information requirements for this endpoint will be updated accordingly*". ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially more sensitive than aquatic invertebrates.
In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, long-term fish testing may need to be conducted. The registrant has indicated in his justification that he intends to follow the integrated testing strategy.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study using the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

Notes for consideration by the Registrant

Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, the Registrant shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, the Registrant shall submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, Section 9.1.6. If the Registrant comes to the conclusion that no further investigation of effects on aquatic organisms is required, he shall update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, Section 9.1.6.

3. Effects on soil micro-organisms (Annex IX, Section 9.4.2, column 2)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed tests.

'Effects on terrestrial organisms' is a standard information requirements as laid down in Section 9.4 of Annex IX. The information for this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information

requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The Registrant must address the standard information requirements set out in Annex IX, Section 9.4., for different taxonomic groups: short-term toxicity testing on invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity testing on plants (Annex IX, Section 9.4.3.). Column 2 of Section 9.4 of Annex IX 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.

The Registrant has submitted a testing proposal for generating information on toxicity to soil microorganisms (OECD TG 216 and 217) to meet the information requirements of Annex IX, Section 9.4.2. with the following justification: "*The physicochemical data indicate that the substance is not adsorptive (log Koc <1.25) or bioaccumulative (log Kow = 0.3) and very soluble in water (172 g/L). Consequently, a significant distribution into the soil compartment and a significant (long-term) exposure of terrestrial organisms is not expected to be relevant. Hence, long-term toxicity information on terrestrial organisms is not considered required and short-term toxicity testing is proposed*".

According to section R.7.11.3.1, Chapter R.7c of the ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), the proposed carbon and nitrogen transformation tests are both designed to detect long-term adverse effects of a substance on the process of carbon or nitrogen transformation in aerobic soils. As according to the information provided in the registration dossier the registered substance has uses as an agrochemical, both tests according OECD 216 and OECD 217 are needed in order to detect the long-term adverse effects of the registered substance on soil micro-organisms .

ECHA considers that the proposed studies are appropriate to fulfil the information requirement of Annex IX, Section 9.4.2. of the REACH Regulation.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed studies with the registered substance subject to the present decision: Effects on soil micro-organisms (test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216 and test method: Soil microorganisms: carbon transformation test, EU C.22/OECD 217).

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a sub-chronic toxicity study (90 day) by the oral route with the following justification: "*In accordance with Regulation (EC) No. 1907/2006 (REACH), Annex IX, 8.6.2., a sub-chronic toxicity study (90-day) should be*

proposed to be conducted according to the OECD No. 408 test guideline. The oral route is proposed as there is no expected exposure to the substance as vapours or inhalable aerosols that would justify a study by the inhalation route. The dermal route is also considered not appropriate as no evidence of systemic toxicity were reported in the acute dermal toxicity and the skin irritation study."

It is noted that testing by the oral route of administration could be considered. The registered substance is reported to be a liquid at ambient temperature. However, judging from the information provided by the Registrant, the inhalation route is considered the most appropriate route of administration. Due to the reported vapour pressure of 34 Pa at ambient temperature, formation of vapours might be assumed. Furthermore, uses with spray application that may generate aerosols of inhalable size are described in the technical dossier and/or chemical safety report. For example, industrial spraying (PROC 7) is reported for "Worker contributing scenario" 5, 7, 11, 14, 15, 17, 18, 19, 23, and non-industrial spraying (PROC 11) for for "Worker contributing scenario" 2, 3, 4, 5, 9, 10, 12, 15, 16, 19, 22, 27. Maximum long-term exposure concentration is reported for non-industrial spraying (PROC 11) with [redacted] mg/m^3 with maximum acute exposure concentration of [redacted] mg/m^3 (Table 395 in the chemical safety report). Hence, ECHA does not agree with the Registrant's conclusion that *"there is no expected exposure to the substance as vapours or inhalable aerosols that would justify a study by the inhalation route."* ECHA concludes that exposure of humans via inhalation is likely and testing by the inhalation route is appropriate as specified in Annex IX, Section 8.6.2., column 2. Furthermore, the substance is classified for eye irritation. Hence, local respiratory tract effects following inhalation exposure cannot be excluded.

In the sub-acute oral study (OECD 422) included in the technical dossier at the maximum dose of 1000 mg/kg bw tubular hyaline droplets were observed in male rats. The fact that these effects were only observed in male rats indicates that the registered substance may induce alpha-2u-globulin-mediated nephropathy. Since humans do not excrete alpha-2u-globulin, this mode of action is not relevant to humans. For this reason, ECHA decides to include in the request for a sub-chronic toxicity study urinalysis (which is optional in paragraph 38 of OECD 413) to investigate kidney function, and a full histopathological examination (paragraph 45 of OECD 413), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

According to the test method OECD 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD 413) 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, while proposed test for 90-day oral toxicity study (OECD TG 408) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

5. Long-term toxicity on terrestrial invertebrates (Annex IX, Section 9.4.1. column 2)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

'Effects on terrestrial organisms' is a standar information requirements as laid down in Section 9.4 of Annex IX. The information for this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The Registrant must address the standard information requirements set out in Annex IX, section 9.4., for different taxonomic groups: short-term toxicity testing on invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity testing on plants (Annex IX, Section 9.4.3.). Column 2 of section 9.4 of Annex IX 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.

The Registrant has porposed a short term toxicity test on terrestrial invertebrates (OECD TG 207) to meet the information requirements of Annex IX, Section 9.4.1. with the following justification; "*The physicochemical data indicate that the substance is not adsorptive (log Koc < 1.25) or bioaccumulative (log Kow = 0.3) and very soluble in water (172 g/L). Consequently, a significant distribution into the soil compartment and a significant (long-term) exposure of terrestrial organisms is not expected to be relevant. Hence, long-term toxicity information on terrestrial organisms is not considered required and short-term toxicity testing is proposed.*"

According to section R.7.11.5.3., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), substances that are ionisable or have a log K_{ow}/K_{oc} >5 are considered highly adsorptive, and substances with a half-life >180 days are considered very persistent in soil. ECHA notes that, according to the evidence presented within the Registration dossier, the substance is considered very persistent, which is the default setting for not readily biodegradable substances when the value of the half-life in soil is not available and therefore the substance meets the column 2 adaptation criteria of Annex IX, section 9.4. concerning the use of long-term testing instead of short-term.

Furthermore, based upon the currently available aquatic toxicity information and the physico-chemical properties of the substance, and in relation to section R.7.11.6. of the above mentioned Guidance, 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. Therefore, considering the properties of the substance, ECHA concludes that only a long-term toxicity test on invertebrates (and not the short-term) will provide the adequate information.

The earthworm reproduction test (OECD 222), Enchytraeid reproduction test (OECD 220), and Collembolan reproduction test (OECD 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.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out one of the following additional studies using the registered substance subject to the present decision: Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*) OECD 222,

or Enchytraeid reproduction test OECD 220, or Collembolan reproduction test in soil OECD 232), while the short-term Earthworm, Acute Toxicity Tests (OECD 207) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Notes for consideration by the Registrant

If the results of the proposed toxicity test on aquatic invertebrates leads to the subsequent derivation of a PNECwater, the Registrant may consider the ITS as recommended in section R.7.11.6., Chapter R.7c of the ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), and determine the need for further testing on terrestrial organisms.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Finally, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Claudio Carlon , Head of Unit, Evaluation E2

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