ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-2114288006-49-01/F Helsinki, 7 October 2014

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 1,3-dioxolane, CAS No 646-06-0 (EC No 211-463-5), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for 1,3-dioxolane, CAS No 646-06-0 (EC No 211-463-5), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more tonnes per year. This decision does not take into account any updates submitted after 12 June 2014, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 22 October 2013.

On 27 November 2013 ECHA sent the draft decision to the Registrant and invited him in accordance with Article 50(1) of the REACH Regulation to provide comments on the draft decision. That draft decision was based on submission number [redacted]

On 13 January 2014 ECHA received comments from the Registrant on the draft decision.

On 13 January 2014 the Registrant updated his registration dossier with the submission number [redacted]

The ECHA Secretariat considered the Registrant's comments and update.
On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 12 June 2014 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.

Subsequently, proposals for amendment to the draft decision were submitted.

On 18 July 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and did not amend the draft decision.

The present decision relates solely to a compliance check requesting information in form of *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.), pre-natal developmental toxicity study (Annex X, Section 8.7.2.) and revised DNELs for workers and for the general population (Annex I, Section 1.4.1.). The other information requirement for two-generation reproductive toxicity study with the inclusion of the developmental immunotoxicity cohort as described in the OECD testing Guideline 443, paragraph 51 and a splenic lymphocyte subpopulation analysis as described in OECD 443, paragraph 65 (Annex X, Sections 8.7.3 and 8.6.4) is addressed in a separate decision although all requirements were initially addressed together in the same draft decision.

On 28 July 2014 ECHA referred the draft decision to the Member State Committee.

By 18 August 2014, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposals for amendment into account.

A unanimous agreement of the Member State Committee on the draft decision relating to *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.), pre-natal developmental toxicity study (Annex X, Section 8.7.2.) and revised DNELs for workers and for the general population (Annex I, Section 1.4.1.) was reached on 1 September 2014 in a written procedure launched on 21 August 2014.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annexes VII, IX and X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. /OECD 471) as specified in section III.A.1 below;
2. Pre-natal developmental toxicity study (Annex X, 8.7.2.; test method: EU B.31./OECD 414) in rabbits, oral route.

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. Information related to chemical safety assessment and chemical safety report

Pursuant to Articles 41(1)(c), 41(3), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

1. Revised DNELs for workers and for the general population using the assessment factors recommended by ECHA and re-assessment of related risks or a full justification for not using the recommended assessment factors in DNEL derivation (Annex I, 1.4.1.).

C. Deadline for submission of the information

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **14 October 2015**.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

1. *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.)

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.

According to paragraph 13 of the current OECD 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.

The dossier contains four negative *in vitro* gene mutation tests in bacteria (OECD 471). However, all of these tests contain deviations (e.g. "insufficient replication", "Strain *E. coli* not tested") and none of them used E.coli WP2 strains or S. typhimurium TA102. Furthermore, in none of the tests special measures were implemented to compensate the high volatility of the substance. Therefore, the information provided for the endpoint *In vitro* gene mutation tests in bacteria is insufficient to fulfil the information requirement.

ECHA concludes that a test using E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 has not been submitted by the Registrant and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria. Furthermore due to the other deviations pointed out in the previous paragraph, ECHA concludes it necessary to perform a test following OECD 471 test guideline (updated 1997) in its entirety.

The Registrant, in his comments submitted according to Article 50(1) of the REACH Regulation, considers that OECD 471 study in the dossier pre-dated the 1997 update of OECD 471 and, therefore, is compliant with the guideline at the time. Furthermore, he considers that since all the *in vitro* and *in vivo* assays in the dossier are negative, the substance has low genotoxicity potential. ECHA notes that the major drawback of all OECD 471 tests in the dossier is that no measures were taken to compensate the high volatility of the substance. Furthermore, in none of the tests E.coli WP2 strains or S. typhimurium TA102 was used. The fact that the dossier contains several *in vitro* studies for the endpoint chromosome aberration, does not remove the need to carry out an OECD 471 in five strains which addresses gene mutation in bacterial cells. Therefore, the dossier has a data gap for this endpoint.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 471).

2. Pre-natal developmental toxicity study (Annex X, 8.7.2.)

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

The technical dossier contains information on a pre-natal developmental toxicity studies in rats by the oral route using the registered substance as test material.

However, there is no information available for a pre-natal developmental toxicity study in a second species.

The technical dossier does not contain any adaptation in accordance with column 2 of Annex X, Section 8.7. or with the general rules of Annex XI for this standard information requirement.

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

The test in the first species was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rabbit is 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 rabbit as a second species to be used.

The Registrant, in his comments submitted according to Article 50(1) of the REACH Regulation, considers that the studies already in the dossier (including a one-generation study) fulfil the the data requirements. He also notes that review of other endpoints suggests that "*there does not appear to be a significant difference in sensitivity in any of the species tested for different endpoints*". Furthermore, he argues that since in the 90-day study adverse effects were seen at a lower dose level than in the OECD 414 in rats, it is very unlikely that testing in a second species would bring any new information. ECHA notes that even though the dossier contains two studies in which it is possible to investigate developmental toxicity, both of them are done in rats. Since at this tonnage level the standard requirement is a pre-natal developmental toxicity study (OECD 414) in two species, the study in rabbits is required. The dossier does not contain any studies or information that would indicate that rat is more sensitive than rabbit in pre-natal developmental toxicity. The Registrant has not included a justified adaptation argument for the information requirement of a Pre-natal developmental toxicity study in a second species.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 414) in rabbits by the oral route.

B. Information related to the chemical safety assessment and chemical safety report

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.

1. Revised DNELs for workers and for the general population using the assessment factors recommended by ECHA and re-assessment of related risks or a full justification for not using the recommended assessment factors in DNEL derivation (Annex I, 1.4.1.)

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 provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

The assessment factors (AF) applied by the Registrant and the default assessment factors recommended in the ECHA Guidance[1] are given in detail in the Annex attached to this decision.

ECHA observes that the Registrant has not followed the recommendations of ECHA's Guidance R.8 and has not provided a full justification for the derivation of DNELs in line with Annex I, 1.4.1. In particular, ECHA notes that the Registrant has used 3 for workers and 5 for general population as an intraspecies assessment factor, whereas according to ECHA Guidance the intraspecies assessment factor for workers is 5 and for general population 10.

As explained above, the information provided on DNEL for the registered substance in the chemical safety report does not meet the general provisions for preparing a chemical safety report as described in Annex I, 1.4.1. because the assessment factors used are neither in accordance with ECHA *Guidance on information requirements and chemical safety assessment* Volume 8, Chapter R.8. nor fully justified. Consequently it is necessary to revise the DNELs or to provide a full justification.

The Registrant is given two options:

The Registrant shall revise the DNELs for workers and for the general population by applying the assessment factors recommended by ECHA that are appropriate in this case. Subsequently, the Registrant shall re-assess related risks.

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

In the alternative, the Registrant shall, in accordance with Annex I, 1.4.1, provide a full justification for the 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.

The Registrant, in his comments submitted according to Article 50(1) of the REACH Regulation, noted that the assessment factors cited in the Annex are not identical with those of the registration dossier. ECHA acknowledges that some of the detailed assessment factors were not consistent with those contained in the registration dossier. Those inconsistencies have been revised in the Annex. These changes have not, however, affected the outcome of the ECHA assessment.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit in the chemical safety report either of the following information: Revised DNELs for workers and for the general population using the assessment factors recommended by ECHA and re-assessment of related risks *or* a full justification for not using the recommended assessment factors in DNEL derivation.

Notes for consideration by the Registrant

The results of the study requested under section II.A. shall be taken into account when revising the DNELs.

C. Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation reproductive toxicity study (Annex X, Sections 8.7.3. and 8.6.4). As this study is not covered in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. The Registrant is reminded of his responsibility and that of joint Registrants to ensure that the joint registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given 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 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 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 an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Leena Ylä-Mononen
Director of Evaluation

Annex

Assessment factors (AF) applied by the Registrant:

For workers - systemic long term – inhalation route:
- Interspecies extrapolation: 4
- Intraspecies extrapolation: 3
- Exposure duration: 2
- Dose response: 1
- Quality of the database: 1
  (overall AF: 24)

For workers - systemic long term – dermal route:
- Interspecies: 4
- Intraspecies: 3
- Exposure duration: 2
- Dose response:1
- Quality od the database: 1
  (overall AF: 24)

For the general population - systemic long term – inhalation route:
- Interspecies extrapolation: 4
- Intraspecies: 5
- exposure duration: 2
- Dose response: 1
- Quality of the databse: 1
  (overall AF: 40)

For the general population - systemic long term – dermal route:
- Interspecies extrapolation: 4
- Intraspecies extrapolation: 3
- Exposure duration: 2
- Dose response: 1
- Quality of the database: 1
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  (overall AF: 24)

For the general population - systemic long term – oral route:
- Interspecies extrapolation: 4
- Intraspecies extrapolation: 5
- exposure duration: 6
- Dose response: 1
- Quality of the databse: 1
  (overall AF: 120)

The default assessment factors recommended in the ECHA Guidance[2]:

For workers - systemic long term – inhalation route:
- interspecies: 2.5 (remaining differences between species non related to allometry)
- intraspecies: 5 (workers)

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

- exposure duration: 2 (sub-chronic to chronic)
  (overall AF: 25)

For workers - systemic long term – dermal route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 5 (workers)
- exposure duration: 2 (sub-chronic to chronic)
- absorption difference dermal-oral[3]: 1
  (overall AF: 100)

For the general population - systemic long term – inhalation route:
- interspecies: 2.5 (remaining differences between species non related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 2 (subchronic to chronic)
  (overall AF: 50)

For the general population - systemic long term – dermal route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 2 (subchronic to chronic)
- absorption difference dermal-oral[5]: 1
  (overall AF: 200)

For the general population - systemic long term – oral route:
- interspecies - allometric correction: 4 (rat to human)
- interspecies - remaining differences: 2.5 (non-related to allometry)
- intraspecies: 10 (general population)
- exposure duration: 6 (sub-acute to chronic)
  (overall AF: 200)

[3] In the absence of substance specific information, the ECHA Guidance R.8 (section R.8.4.2) recommends that a factor of 1 be applied for the extrapolation of the results from the oral route to the dermal route. In general, dermal absorption will not be higher than oral absorption and by default, the same bioavailability for experimental animals and humans should be assumed.