EUROPEAN CHEMICALS AGENCY

Helsinki, 21 February 2019

Addressee: [redacted]

Decision number: CCH-D-2114461359-41-01/F
Substance name: p-xylene
EC number: 203-396-5
CAS number: 106-42-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28/03/2018
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

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

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit), oral route with the registered substance.**

You are required to submit the requested information in an updated registration dossier by **1 March 2021** except for the information requested under point 1 for a Sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **28 February 2020**. 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 and advice and further observations are provided in Appendix 3.

The scope of this compliance check decision is limited to the standard information requirements for Toxicological Information of Annexes VII to X of the REACH Regulation. However, this decision does not address the information requirement of the extended one-generation reproductive toxicity study according to Annex X, Section 8.7.3. of the REACH Regulation.

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Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to 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, Hazard Assessment C4

[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

TOXICOLOGICAL INFORMATION

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

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1 and 3).

Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the following endpoint:

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

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]: (1) (Bio)transformation to common compound(s) - the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed, and (2) Different compounds have the same type of effect(s) - the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties or follow a regular pattern (trend) as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance p-xylene (EC No 203-396-5) using data of structurally similar substances o-xylene (EC No 202-422-2), m-xylene (EC No 203-576-3), Xylene (EC No 215-535-7) and ethylbenzene (EC No 202-849-4) (hereafter the 'source substances').

Currently, the lead registration dossier for the source substance Xylene defines two compositions which contain either [redacted]% or [redacted]% ethylbenzene. However, ECHA notes that this lead registration is for the substance Xylene with EC number 215-535-7 which is defined as a mixture of o-, m- and p-xylene isomers containing [redacted]% ethylbenzene. Therefore, the composition containing [redacted]% ethylbenzene is disregarded and only the composition containing [redacted]% ethylbenzene is considered in this compliance check.

You have provided a read-across documentation as a separate attachment entitled "[redacted]" (referred to as "*category justification document*" below). Furthermore you have provided another read-across documentation as separate attachment entitled "[redacted]" (referred to as "*analogue-approach justification document*" below).

The category justification document is included in the registration dossiers of the category members o-, m-, and p-xylene but not in that of the category member Xylene. ECHA notes, however, that the IUCLID dossier for Xylene refers to the identical category proposed by the LOA REACH Consortium and, therefore, ECHA considered that the category justification document also applies to the registration of Xylene.

ECHA understands that the category justification document relates to reading across toxicological data within the category consisting of o-, m-, and p-xylene and Xylene. Whereas the analogue-approach justification document relates to reading across data on reproductive toxicity for o-, m-, p-xylene and Xylene from the source substance ethylbenzene.

For the category read-across, you use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: on the basis of structural similarity, and similarity in toxicokinetics, physico-chemical, toxicological properties, and classification, it is possible to predict the human health

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

properties of the registered substance. As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties and that the identification of trends between category members is possible for the above-mentioned information requirements. ECHA considers that this information is your category read-across hypothesis.

For the analogue-approach read-across from ethylbenzene, you use the following arguments to support the prediction of properties of the registered substance from data for ethylbenzene: on the basis of common functional groups (structural similarity), metabolism to common breakdown products, and similar patterns of toxicity (similarity in toxicological properties), it is possible to predict the human health properties of the registered substance for reproductive toxicity. As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties for reproductive toxicity. ECHA considers that this information is your analogue-approach read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument for both the category and the analogue read-across is that the similarity in chemical structure and in some of the physico-chemical, toxicological properties and classification between the source and registered substances is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical, toxicological properties and classification does not necessarily lead to predictable or similar human health properties in other endpoints. Your justification based on these similarities has not established why the prediction is reliable for the human health endpoints for which the read across is claimed.

You have proposed similar toxicokinetics as a basis for predicting the properties of the registered substance. This proposition is inadequately supported (see below). Knowledge of both the toxicokinetics and toxicodynamic properties of a substance are necessary to predict its toxicological properties, with the exception of those cases where a substance is not systemically available. Thus a hypothesis addressing solely toxicokinetic properties does not provide a reliable basis for predicting the toxicodynamic properties of the substance, and hence the substance's toxicological properties.

In particular, ECHA notes that in the read-across studies with the test materials called "mixed xylenes", the ethylbenzene content is [redacted]% and [redacted]% and therefore the test substance does not reflect the composition of the category member Xylene with EC number 215-535-7 which contains by definition only [redacted]% ethylbenzene. Therefore, the content of o-, m- and p-xylene in the test materials mixed xylenes is diminished. You did not explain why potential effects resulting from the individual xylene isomers are not underestimated when reading across the results from mixed xylenes, and ECHA considers that underestimation of the potential effects resulting from the individual xylene isomers when making a prediction based upon the results from mixed xylenes is potentially important. Furthermore and as outlined below, ethylbenzene and the xylene isomers show different toxicological properties and you have not explained how prediction of toxicological properties can be reliably be made from the source substance containing ethylbenzene, in particular if it contains higher amounts of ethylbenzene.

Furthermore, for the category read-across ECHA notes that

a) Xylene is a multi-constituent substance whereas your category definition is limited to mono-constituent substances;

b) [redacted] is the manufacturing process for Xylene whereas your category definition is limited to substances manufactured by [redacted];
c) Xylene can contain up to [redacted]% ethylbenzene whereas your category definition is limited to substances with [redacted]% purity;
d) trends and well-defined toxicokinetic parameters within the category have not been provided although these are the basis for your read-across hypothesis;
e) dissimilar toxicological properties have been observed: in particular an increased auditory threshold and a loss of outer hair cells have been observed for p-xylene but not for other category members ([redacted] 2001) - apparently, a small change in structure seems to result in significantly different toxicological properties.

On the basis of points a), b) and c) above, Xylene is defined as being outside the category of substances. Point d) is missing from your read-across justification which therefore fails to support your read-across hypothesis and for point e), the dissimilarity contradicts your hypothesis of similar toxicological properties and your justification does not address this issue..

For the analogue-approach read-across, ECHA notes that

- the metabolic pathways of xylene isomers and ethylbenzene are significantly different because they do not have a single metabolite in common and you did not demonstrate that these differences are not relevant in terms of toxicity;
- there are qualitative and/or quantitative differences in the toxicological properties of ethylbenzene vs. the xylenes (and which you did not discuss in your read-across justification), i.e., ototoxicity (ethylbenzene has a harmonised classification for STOT RE 2/ H373: hearing organs), and repeat-dose toxicity (OECD TG 408 with ethylbenzene ([redacted] 2006): increased mean corpuscular volume, reduced platelet counts, reduced prothrombin times and reduced thymus weights in females; OECD TG 408 with mixed xylenes ([redacted] 1988): mild polycythaemia and leukocytosis in some of the dose groups, and increased spleen and heart weights) and potentially even carcinogenicity (ethylbenzene shows indications of carcinogenic activity);
- o-, m- and p-xylene give positive results in the *in vitro* comet assay whereas *in vitro* genetic toxicity is negative for mixed xylenes and ethylbenzene.

This contradicts your hypothesis of metabolism to common breakdown products and similar toxicological properties.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that these grouping and read-across approaches do not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, Section 1.5., and these are set out under the endpoint concerned.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities

and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

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

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.

In the technical dossier you have provided a study record for a non-guideline study by [redacted] (2001) investigating ototoxicity in rats exposed to the registered substance p-xylene. However, this study does not provide the information required by Annex IX, Section 8.6.2., because it is limited to determine auditory thresholds and a quantitative morphological study (histocochleogram) and scanning electron microscopy of the organ of Corti. Therefore, there is a failure to provide adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), *i.e.* an OECD TG 408 study, which is not limited to ototoxicity but provides information on toxic effects in the test animals, indicate target organs and the possibility of accumulation, and an estimate of a no-observed-adverse-effect level of exposure which can be used for establishing safety criteria for human exposure. Furthermore, the provided study by [redacted] (2001) does not investigate other neurological endpoints besides ototoxicity and gives no indication of immunological and reproductive effects.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for

- OECD TG 408 study with the analogue substance mixed xylenes containing 20% ethylbenzene ([redacted] 1988),
- three oral NTP studies with the analogue substance mixed xylenes containing 17% ethylbenzene (one 2-year study in rats, two 13-week studies in rats and mice),
- two non-guideline inhalation studies with the analogue substances o- and m-xylene ([redacted] 2001), and
- two non-guideline inhalation studies in rats and dogs with the analogue substance mixed xylenes containing 19.27% ethylbenzene ([redacted] 1975).

Furthermore, the non-guideline read-across studies by [redacted] (2001) which investigate ototoxicity do not provide the information required by Annex IX, Section 8.6.2. as exlained above. The non-guideline read-across studies by Carpenter et al. (1975) do also not provide the information required by Annex IX, Section 8.6.2. because only male animals were used and investigations required by the OECD TG 408 have not been performed (e.g. sensory activity, grip strength and motor activity assessments, ophthalmological examination). There is thus a failure to meet the requirement of Annex XI, 1.1.2, for adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), i.e. OECD TG 408.

Therefore and as explained above in Appendix 1 ("Grouping of substances and read-across approach") of this decision, your adaptation of the information requirement is rejected.

In your comments on the draft decision, you specify that you identified a new GLP compliant sub-chronic toxicity study (90 days) in rat (oral route) with a test substance claimed to fit the substance identity of the registered substance. You intend to use this study to cover the

information requirement for this endpoint as you consider that this study, together with the other studies already included in your technical dossier, are sufficient to characterise the hazards of repeated sub-chronic oral exposure to p-xylene.

ECHA notes that you did not provide a robust study summary for that 90-day study as part of your comments on the draft decision or in your updated dossier. Consequently, ECHA could not evaluate if the information provided in this study is adequate to cover the standard information requirement for this endpoint.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier currently does 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. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

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

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: OECD TG 408) in rats.

Notes for your consideration:

The request for an extended one-generation reproductive toxicity study (EOGRTS) according to Annex X, Section 8.7.3. was removed from this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the EOGRTS, not only for the registered substance but also for other xylene category members. You provided comments to challenge the analysis by ECHA of the required study design. ECHA took into account your arguments and concluded that the results of the repeated dose 90-day oral toxicity study would allow a more robust assessment of the need to include additional cohorts to the standard EOGRTS design.

You should consider submitting a testing proposal for an extended one-generation reproductive toxicity study together with the results of the requested sub-chronic toxicity study (90-day). The testing proposal should include a justification for its study design following ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6 (version 6.0, July 2017), taking into account the results of the sub-chronic toxicity study (90-day).

Alternatively, ECHA may launch a separate compliance check at a later stage addressing the EOGRTS information requirement.

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

"Pre-natal developmental toxicity studies" (test method OECD TG 414) 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 study in rats by the inhalation route using the registered substance as test material ([redacted] 2003).

Furthermore, the registration dossier contains read-across studies investigating prenatal and postnatal developmental toxicity which were all performed in rats: Three OECD TG 414 studies with the source substances o-xylene, m-xylene and mixed xylenes ([redacted] 2003); a prenatal developmental toxicity study equivalent or similar to EPA OPP 83-3 with only two dose groups with the source substance mixed xylenes ([redacted] 1978); four non-guideline studies with the source substance mixed xylenes ([redacted] 1983, [redacted] 1993, [redacted] 1995, [redacted]. 1997).

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

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

In your comment on the draft decision, you agreed to conduct the requested study.

The test in the first species was carried out by using a rodent species (rat). According to the test method OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second 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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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: OECD TG 414) in a second species (rabbit) by the oral route.

Appendix 2: Procedural history

For the purpose of the abovementioned decision making, ECHA does not take into account any dossier updates after **2 April 2018**, 60 calendar days after the end of the commenting period.

The compliance check was initiated on 14 March 2017.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments. You were notified in the Notification letter of 11 December 2017 that the decision-making process and the decision do not take into account any updates after 2 April 2018.

You updated your registration on 28 March 2018 (submission number [redacted]). ECHA took the information in the updated registration into account, and amended the draft decision. The updated information is reflected in the Reasons (Appendix 1).
In your update, you provided an updated CSR in section 13 of your technical dossier. This update of your registration dossier did not include additional information compared to your comments on the draft decision.

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

You provided comments which did not address the Proposals for Amendments. Your comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5). Specifically, the Proposals for Amendment (PfAs) were to change particular wordings in the decision. You did not address these specific PfAs, but rather you explained that you intended to submit dossier updates (for repeat-dose toxicity, toxicity to reproduction, developmental toxicity, read-across justification and the chemical safety report) in March 2018, that ECHA did not receive this information in March, that the dossier was updated with this information in September 2018, and that you wish ECHA to take this information into account. You provided summaries of the relevant information. (ECHA's approach to taking into account dossier updates during the decision-making process is set out above.)

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-63 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.