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Helsinki, 30 March 2017

Substance name: o-xylene
EC number: 202-422-2
CAS number: 95-47-6
Date of Latest submission(s) considered[1]: 10 June 2016
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of o-xylene (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

1. Requested information

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following information on the registered substance:

Exposure related requests – Consumers

1) Refined exposure parameters (including use and product descriptions, operational conditions, product-integrated risk management measures, and where necessary measurements of release during use) for the exposure assessment and risk characterisations concerning single exposure events for all contributing scenarios of consumer use in coatings, cleaning agents,and fuels (identified consumer uses Chemical Product Categories (PC) 1, 3, 4, 9a, 9b, 9c, 13, 15, 18, 23, 24, 31, 34, 35, and 38).

2) Refined exposure parameters (operational conditions and where necessary measurements of release during use) for the exposure assessment and risk characterisation concerning inhalation by using finger paints (PC 9c) and modelling clay (PC 9b).

3) A precise description of the designated purpose of consumer products which are intended to be covered by the exposure scenario of "glues, DIY-use (carpet glue, tile glue, wood parquet glue)" with a justification why the chosen operational conditions of this subcategory are appropriate to describe these consumer uses.

You shall provide an update of the registration dossier(s) containing the requested information and, where relevant, an update of the Chemical Safety Report by **6 April 2018**.

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[1] This decision is based on the registration dossier(s) on the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

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The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3 and 4. Appendix 5 contains a list of registration numbers for the addressees of this decision. This Appendix is confidential and not included in the public version of this decision.

2. Appeal

You can appeal this decision 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[3] by Leena Ylä-Mononen, Director of Evaluation

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

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Appendix 1: Reasons

Based on the fact that the you have used a read-across/category approach for your assessment of the xylenes, the three xylene isomers (o-xylene, CAS 95-47-6/EC 202-422-2; m-xylene, CAS 108-38-3/EC 203-576-3; p-xylene, CAS 106-42-3/EC 203-396-5) have been evaluated together. Based on the evaluation of all relevant information submitted on the three Xylene isomers and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the concern for consumer exposure.

Exposure related requests - Consumers

1) Refined exposure parameters (including use and product descriptions, operational conditions, product-integrated risk management measures, and where necessary measurements of release during use) for the exposure assessment and risk characterisation concerning single exposure events for all contributing scenarios of consumer use in coatings, cleaning agents, and fuels (identified consumer uses PC 1, 3, 4, 9a, 9b, 9c, 13, 15, 18, 23, 24, 31, 34, 35, and 38).

o-Xylene is classified as Acute Tox. 4 (H332: Harmful if inhaled). Therefore, the Registrant(s) derived chronic and acute derived no-effect level (DNEL). In your exposure assessment, however, only chronic effects have been assessed by averaging the event exposure over time. An exposure assessment for acute effects is missing for all contributing consumer exposure scenarios. In this context it needs to be noted that the REACH Guidance Chapter R.8 (ECHA, 2012a) sets out: *"The actual daily dose is independent of the exposure frequency. This means that if for a certain scenario, worker or consumer exposure is for instance only for a number of days per year, the exposure value is the actual dose on the exposure days, and not the daily dose averaged out (and thus divided) over the whole year."*

Derivation of acute and chronic DNELs by the evaluating MSCA based on studies by Olson et al. and Korsak et al.[4] with neurotoxicity as the most critical endpoint leads to values of ca. 7 ppm or 30 mg/m^3 for single 4 h exposure (to be adjusted for longer or shorter duration using Modified Haber's Law, cf. IR&CSA guidance R.8), and 0.12 ppm or ca. 0.5 mg/m^3 for long-term (i.e. chronic, 24 h) exposure, respectively (see Appendix 4, section 2 for details on DNEL derivation by the evaluating MSCA).

It is noted that these values are far lower than the DNELs derived by you which in the view of the evaluating MSCA were obtained using inappropriate methodology (e.g. using

[4] These studies were carried out with p-xylene and m-xylene, respectively, but are used for all three xylene isomers in line with the read-across hypothesis presented by the Registrant(s).

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a less sensitive point of departure (PoD), using occupational exposure limits (OELs) to derive consumer DNELs, using inappropriate assessment factor (AF)).

Based on the operational conditions and risk management measures in the Chemical Safety Report (CSR), calculations by the evaluating MSCA lead to exposure levels exceeding the acute DNEL. The available data is therefore not sufficient to clarify the concern regarding acute risks for consumers.

In your comments you claim that you have updated your registration dossiers and deleted the cleaning use. You also announce a future update to delete the uses of coatings and fuels. However, not all Registrant(s) have yet submitted the respective updates and deleted the uses. Hence, in order to assess if there is an acute risk for consumers related to these uses the requested information is needed.

Therefore, you shall provide refined exposure parameters (including use and product descriptions, operational conditions, product-integrated risk management measures, and where necessary measurements of release during use) for the exposure assessment and risk characterisations concerning single exposure events for all contributing scenarios of consumer use in coatings, cleaning agents and fuels (identified consumer uses PC 1, 3, 4, 9a, 9b, 9c, 13, 15, 18, 23, 24, 31, 34, 35 and 38). It is noted that the evaluating MSCA will use this information also for higher tier exposure assessments for frequently used products by considering the findings of Johnson & Lucica (2012).

2) Refined exposure parameters (operational conditions and where necessary measurements of release during use) for the exposure assessment and risk characterisation concerning inhalation by using finger paints (PC 9c) and modelling clay (PC 9b).

You have not considered the consumer exposure via inhalation by using finger paints and modelling clay. They assumed the release to air to be negligible without any justification. o-xylene is volatile with a vapour pressure of 882 Pa at 25 °C. The REACH Guidance Chapter R.15 (ECHA, 2012b) states that *"for non-aerosol products, instantaneous release of 100% of any substance with vapour pressure ≥10 Pa is assumed."*

Due to the circumstance that you waived the exposure scenario for finger paints and modelling clay, operational conditions are still missing. A preliminary assessment by the evaluating MSCA based on a low tier model indicates that risks especially for children cannot be ruled out. However, evaporation from liquids and solid products is an evaporation from mixtures which follows other kinetics compared to the pure substance. Thus the available data is not sufficient to clarify the concern.

In your comments you claim that you have updated your registration dossiers and deleted the uses of o-xylene in finger paints and modelling clay. However, not all Registrant(s) have yet submitted the respective updates and deleted the uses. Hence, in order to assess if there is a risk for consumers related to these uses the requested information is needed.

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Therefore, you shall provide refined parameters (operational conditions and where necessary measurements of release during use) for the exposure assessment and risk characterisation concerning inhalation by using finger paints (PC 9c) and modelling clay (PC 9b).

3) A precise description of the designated purpose of consumer products which are intended to be covered by the exposure scenario of "glues, DIY-use (carpet glue, tile glue, wood parquet glue)" with a justification why the chosen operational conditions of this subcategory are appropriate to describe these consumer uses.

You performed the consumer exposure assessment by using the ECETOC TRA consumer exposure tool. The subcategory "glues DIY-use (carpet glue, tile glue, wood parquet glue)" of PC 1 (adhesives, sealants) in this tool is related to defaults of high product amount (15 kg) and exposure time (6 h) concerning tile glue. The defaults have been taken from the RIVM-Do-IT-Yourself Product Fact Sheet (ter Burg et al., 2007).

You differ from these defaults by using much lower product amounts leading also to lower exposure levels without further justification.

The gluing of carpets, tiles, or wood parquet, which is related to higher product amounts and therefore to higher exposure, is not covered by your exposure scenario, and risks derived from these applications can currently not be ruled out. The requested data will clarify the designated purpose of DIY glues containing o-xylene and support clarification of the initial concern regarding consumer risks.

In your comments you indicate that the use of o-xylene in glues, DIY-use will be removed from the registration dossiers with a future update. However, these updates have not been received so far and the use is still supported. Hence, in order to assess if there is a risk for consumers related to this use the requested information shall be provided.

Therefore, you shall provide a precise description of the purpose of consumer products which are intended to be covered by the exposure scenario of "glues, DIY-use (carpet glue, tile glue, wood parquet glue)" with a justification why the chosen operational conditions of this subcategory are appropriate to describe these consumer uses.

A proposal for amendment (PfA) was received during the MSCA/ECHA commenting phase requesting a revision of the requests for consumer exposure by providing a more robust and scientifically adequate point of departure for the recalculation of consumers DNELs. The evaluating MSCA took note of the PfA and provided further explanation on the adequacy of the DNEL derivation and the underlying study in section 1 of Appendix 4. The evaluating MSCA also took note of your supportive comments on the submitted PfA which, however, did not provide any new information. Hence, the decision was not further amended.

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected CMR properties, wide-dispersive use and consumer and worker exposure, o-xylene CAS No 95-47-6 (EC No 202-422-2) was included in the Community Rolling Action Plan (CoRAP) for substance evaluation to be evaluated in 2015. The updated CoRAP was published on the ECHA website on 17 March 2015. The Competent Authority of Germany (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the following concern: consumer and worker exposure. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 17 March 2016.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

ECHA notified you of the draft decision and invited you to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

By 10 June 2016 some Registrant(s) submitted update(s) of the registration dossier(s). The evaluating MSCA took the information in the updated registration dossier(s) into account, and it is reflected in the Reasons (Appendix 1). The information requirements to provide refined exposure parameters of coating products for polishing, wax/cream & spray as well as regarding the frequent use of air care products, instant and continuous action have been removed from section 1, Requested information, of this decision.

Proposals for amendment by other MSCAs and ECHA and referral to Member State Committee

The evaluating MSCA notified the draft decision to the Competent Authorities of the other Member States and ECHA for proposal(s) for amendment (PfA).

Subsequently, the evaluating MSCA received PfAs to the draft decision. Based on the received PfA the evaluating MSCA removed the information requirement related to worker exposure from section 1, Requested information. The PfA(s) on the remaining information requirements 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(s).

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Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-52 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

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.

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Appendix 4: Reasoning on the DNEL derivation by the evaluating MSCA

1. Reasoning why the evaluating MSCA found the IOELV published by SCOEL in 1992 unsuitable for risk characterisation under REACH

On whether using an IOELV for DNEL derivation under REACH is possible or even obligatory

The process of Substance Evaluation is intended to provide Member States (MS) – on the basis of one or more initial concerns - with a means to perform their own risk assessment for the substance under scrutiny. In performing the risk characterisation (RC), an MSCA needs to follow the legal text as well as the available REACH guidance. Specifically, under section R.8.1.1 the guidance states that *"REACH requires a RC for the leading health effect (i.e. the toxicological effect that results in the most critical DNEL) for a given exposure pattern (duration, frequency, route and exposed human population) associated with an exposure scenario (ES)."*

This quotation describes the general procedure for risk characterisation under REACH whereas using an indicative occupational exposure limit values (IOELV) as surrogate derived no-effect level (DNEL) is an exception to this rule. According to the IR&CSA guidance R.8 (Version 2.1 of November 2012, Appendix R.8-13) registrants are allowed *"[...] to use an IOEL as a DNEL [...], unless new scientific information [...] does not support the use of the IOEL for this purpose"*. The latter could be because information not considered by the Scientific Committee on Occupational Exposure Limits (SCOEL) (e.g. because it only became available after the SCOEL assessment) *"[...] leads to another value being derived which requires different risk management measures (RMMs) and operational conditions (OC)"*.

It is clear from that text, that using the IOELV as a surrogate DNEL is only an option, where the IOELV is not in conflict with other scientific information not considered by SCOEL and leading to the calculation of a lower DNEL.

Anyhow, use of IOELVs as surrogate DNELs is limited to workplace exposure, while for consumer exposure in general lower DNELs will be established even from the same toxicological Points of Departure (PoD) *inter alia* due to the assumption of higher intraspecies variabililty and a longer potential daily exposure time.

The following sub-sections of this Appendix analyse whether the PoDs used by SCOEL for deriving the IOELV for xylenes are still the most relevant ones and whether in deriving the IOELV appropriate modification and assessment factors (AF) were used that are in line with those recommended by the REACH legal text and guidance.

Analysis of the PoDs used for IOEL derivation by SCOEL in 1992

The IOELV derived by SCOEL in 1992 is justified as follows: *"The critical effects of xylene are irritation and CNS effects. Mild irritation of the eye and upper respiratory tract has been reported in some individuals exposed to xylene for 15 – 30 mins at a level of 100 ppm (442 mg/m^3) in volunteer studies (Carpenter et al., 1975; Hastings et al., 1984).*

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Symptoms of CNS effects also start to occur at exposure levels of around 100 ppm (442 mg/m³) (Savolainen et al, 1979, 1980a+b, 1981; Gamberale et al., 1978; Olson et al., 1985)." The evaluating MSCA notes that the studies by Savolainen et al. 1979, 1980a, and 1980b resulted in Lowest-observed adverse effect concentrations (LOAECs) of ca. 100 ppm, 90 ppm, and 150 ppm, respectively, but did not establish No-observed adverse effect concentrations (NOAECs). Olson et al. (1985) established a NOAEC at 68 ppm, but failed to show a LOAEC. At 100 ppm, the study by Gamberale et al. (1978) established a NOAEC at 100 and a LOAEC at 300 ppm. By and large, the conclusion by SCOEL that with respect to central nervous system (CNS) effects the studies cited in their assessment demonstrated LOAECs in the order of 100 ppm in humans is therefore supported by the evaluating MSCA.

Comparison of IOEL and potential DNEL to be derived according to REACH based on the same PODs as used by SCOEL in 1992

According to the available documentation, SCOEL applied the following rationale for establishing the 8-h TWA IOEL value in 1992: *"[...] The studies cited above, indicating a LOAEL of 100 ppm (442 mg/m³) for mild irritation and possible effects in humans, were considered to be the best available basis for setting exposure limits. An uncertainty factor of 2 was considered to be sufficient because the effects observed at the LOAEL were minimal. The recommended 8-hour TWA for xylene is 50 ppm (221 mg/m³)."*

The evaluating MSCA notes that in several essential aspects the way in which the 8-h TWA IOEL was established by SCOEL in 1992 deviates from the way in which DNELs are set under REACH:

- Although an 8-h IOELV is derived, actual daily exposure time in the studies mentioned above was generally shorter than 8 h, requiring a corresponding modification of the PoD under REACH, but this apparently was not done in the SCOEL assessment. Notably, in the cited studies by Savolainen et al. a variable dosing scheme was used (two 3-h exposures per day, interrupted by a break; on some days, a higher concentration was applied in the afternoon), precluding their use for reliable quantitative dose-response assessment. Gamberale et al. (1978) or Olson et al. (1985) applied single, 70 minute or 4-h exposure schemes, respectively.

- LOAECs from acute (Gamberale et al.; Olson et al.) or subacute (Savolainen et al.) studies were used for deriving a chronic limit value without applying an additional AF for exposure duration.

- No AF for intraspecies variability (under REACH: 5 for workers, 10 for consumers) was applied, although in all of the experiments only a small number of volunteers was exposed, which is not representative of all of human intraspecies variability.

- An AF of 2 was chosen for LOAEC-to-NOAEC extrapolation, although the IR&CSA R.8 guidance foresees default factors of 3-10.

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As explained further in section 2 below, in order to e.g. derive an acute, 8-h inhalation DNEL for consumers based on the results by Olson et al. (1985) under REACH, an overall AF of 20 (2 to correct exposure time to 8 h, 10 for intraspecies variability) needs to be applied to the NOAEC of 68 ppm, resulting in a rounded 8-h DNEL value of 3 ppm (1 ppm for a 24-h DNEL accordingly), which is 33 times lower than the short-term exposure limit (STEL) of 100 ppm. In fact, this exactly represents the acute DNEL established by the evaluating MSCA in the substance evaluation report.

For consumers, even accepting the studies by Savolainen et al., ignoring for a moment the problems mentioned above as well as numerous uncertainties, and assuming the daily exposure scheme in theses 2-wk studies would have been 6 h without interruption and changing exposure concentrations, by default still an overall AF of ≥ 670 (24/6 for daily exposure time, 7/5 for number of exposure days per week, ≥ 2 for LOAEC-to-NOAEC extrapolation, 6 for subacute-to-chronic extrapolation and 10 for intraspecies variability) would need to be applied to the LOAEC of ca. 100 ppm in order to establish a chronic 24 h, 7 h/d consumer inhalation DNEL in accordance with the assessment rules under REACH. Notably, the resulting DNEL would almost be the same as the DNEL established by the evaluating MSCA based on animal data, i.e. it would fall in the order of 0.15 ppm.

Other PODs for risk assessment not considered by the SCOEL assessment in 1992

The evaluating MSCA notes that the most recent reference cited for the IOELV derivation by SCOEL in 1992 dates from 1987.

a) Human data

As mentioned above and in line with SCOEL, the evaluating MSCA derived the acute inhalation DNEL based on the studies by Olson et al. (1985) and Gamberale et al. (1978). These results are further supported by the study of Dudek et al. (1990) showing a LOAEC of 100 ppm (but no NOAEC) regarding effects on Simple and Choice Reaction Times following a single 4-h exposure. This study was not mentioned in the 1992 SCOEL assessment, probably because it was published after the deadline for accepting studies for that evaluation, nevertheless it is in line with the use of a LOAEC of 100 ppm as a PoD for setting a human acute DNEL.

b) Animal data

You claim that animal data should not be used for risk assessment of xylenes due to differences in metabolism between animals and humans. The evaluating MSCA notes that these alleged differences are not further discussed in the CSR. Moreover, you did not provide any proof, either in the CSR or in your comments, that a potentially different spectrum of metabolites could be responsible for CNS effects seen only in animals, but not humans. To the contrary, the evaluating MSCA notes that effects on essentially the same CNS-related neurobehavioural targets (memory, reaction time, motor

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coordination), are seen in humans and animals as a result of xylene exposure, with additional endpoints in animals (hot plate test) which are not tested in humans. The evaluating MSCA therefore concludes that the you did not provide convincing evidence that risk assessment for xylenes should only be performed based on human, but not animal data.

Relevant studies from the animal data base not included by SCOEL

Most notably, the two studies on which the evaluating MSCA has based its derivation of the chronic DNELs (cf. section 2 of this Appendix), i.e. Korsak et al. (1994) and Gralewicz and Wiaderna (2001) have not been available to SCOEL for their assessment.

In addition to these two reports, *inter alia* the following studies demonstrating CNS effects in animals using a repeat-dose exposure scheme could not have been included in the SCOEL assessment: Korsak et al. (1992), Gralewicz et al. (1995), Gagnaire et al. (2001, 2007). Moreover, a number of studies on reproductive toxicity have either not been covered by SCOEL [e.g. Hudak and Ungvary (1978), Ungvary et al. (1980), [redacted]] or have become available only after the SCOEL assessment, i.e. Hass and Jakobsen (1993), Hass et al. (1995, 1997), Faber et al. (2006), or Saillenfait et al, (2006). In many of these studies, LOAECs < 500 ppm are demonstrated. If appropriate modification and AFs were applied, many of these studies would lead to DNELs clearly lower than those derived by you based on the SCOEL assessment. As a consequence, the evaluating MSCA does not agree your claim (in your comments to the draft decision) that "no studies that materially change the basis of the evidence that SCOEL used to determine the 8 hour TWA and 15 minute STEL" were available.

Alleged shortcomings of the studies by Korsak et al. (1994) and Gralewicz and Wiaderna (2001) used by the evaluating MSCA for DNEL derivation

In their comments to the draft decision, the Registrant(s) rejected the study by Korsak et al. due to an allegedely "missing dose response" for the endpoint latency of the paw-lick response. The corresponding reaction times were as follows; control: 12.2 ± 3.1 s, 50 ppm: 8.7 ± 3.8 s, and 100 ppm: 8.6 ± 2.7 s. The results for both dose groups were statistically significantly different from control ($p \leq 0.05$). The evaluating MSCA notes that contrary to the Registrant(s)' comment there is a clear dose-response relationship for this effect, e.g. a reduction of reaction times with increasing dose. While the difference between 50 and 100 ppm is quite small, this could be explained by the assumption that there is a physiological limit for the reduction of response time and that this limit might already almost have been reached at 50 ppm.

In the PfA received in the MSCA and ECHA consultation phase it was also expressed that the study by Korsak et al. (1994) lacked scientific robustness and adequacy as it had "several limitations and many confounding factors for scientifically robust derivation of DNELs (e.g. not GLP, do not follow guidelines, have limitation in design (mixture vs individual isomer – m-xylene, dosing, number of animals per group and dose not

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reported, no control group included)".

The evaluating MSCA notes that first of all with respect to not following GLP this is as true for the study by Korsak et al. as for any of the studies used in the SCOEL assessment. Still the study is considered of sufficient quality to be used in risk assessment under REACH and its reliability is considered as Klimisch code 2 (reliable with restrictions). The laboratory in which the study was performed belongs to a renowned independent Polish Occupational Health Institution (cf. http://www.imp.lodz.pl/home_en) under the Polish Ministry for Health functioning as the Polish WHO Collaboration Centre for Occupational and Environmental Health (apparently appointed WHO reference centre since 1975).

It is also as true for the Korsak et al. (1994) study as it is true for the studies used in the SCOEL assessment that no specific guideline was followed. This can be explained by the fact that the relevant OECD test guideline 424 has only been introduced in 1997. i.e. 3 years after publication of the Korsak et al. paper. In the view of the evaluating MSCA, however, the publication by Korsak et al. provides enough information to conclude that the experiment has been performed to acceptable scientific standards.

As regards the read-across between individual xylene isomers and the mixed isomers, the evaluating MSCA [in line with your position] considers the hypothesis plausible [despite deficits in the justification brought forward by you], and thus this is not seen as a limitation. Furthermore also the SCOEL assessment evaluated xylenes as a group.

For the rest of the alleged limitations the evaluating MSCA would like to clarify that Table 5 on page 164 in Korsak et al., (1994) reports the dose levels used, the number of animals per treated group and in the control group, the latency of the paw-lick response (in seconds ± SD) and the results of statistical significance testing.

The evaluating MSCA concludes that none of the alleged limitations mentioned in the PfA was confirmed to a degree that would preclude the use of the study in the context of xylene risk assessment.

You also claim that the results by Gralewicz and Wiaderna (2001) did not show a difference in paw-lick response. The evaluating MSCA notes that the two results cannot be compared directly, since in Korsak et al. (1994) the hot plate test was performed directly after the end of the three-month exposure period, while in Gralewicz and Wiaderna (2001), the test was only performed two weeks after the end of exposure. However, the evaluating MSCA finds that the two results, when taken together, suggest reversibility of the effect, which however does not rule out its relevance for risk assessment.

Summary

In summary, the evaluating MSCA concludes that the derivation of the SCOEL IOELV in 1992 was performed according to assessment standards deviating from those applied

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under REACH today. Moreover, since the most recent publication cited by SCOEL dates from 1987, a significant number of studies relevant for risk assessment which became available over the last 30 years have not been included. You failed to provide convincing support for the claim that risk assessment of xylenes should only be performed based on human and not animal data. Also the reasons given by you for non-acceptance of the key study used for chronic DNEL derivation by the evaluating MSCA have not been sufficiently substantiated. The evaluating MSCA therefore concludes that neither the comments received by you nor the PfA do lead to a change in the established DNELs.

2: Detailed information on DNEL derivation (all xylene isomers) by the evaluating MSCA:

Acute DNEL inhalation:

Consumers:
Experiments in humans have shown that levels of 100 ppm (4 h) for m-xylene or 300 ppm (70 min) for mixed xylenes may negatively impact on reaction time and other neurobehavioural performance parameters in humans under physical activity (Gamberale et al. 1978, Dudek et al. 1990). Olson et al. 1985 showed for p-xylene that 68 ppm was a NOAEC for these effects in humans. The slight irritation-related effects reported by Ernstgård et al. 2002 for 2 h inhalation of 50 ppm m-xylene are not considered as relevant for DNEL-setting, since they rely on subjective reporting while objective parameters (such as blinking rate) failed to demonstrate an adverse effect. Other available studies on irritation do not allow for the determination of a clear threshold/non-irritating air concentration.

Therefore, the evaluating MSCA finds the most relevant starting point (Point of Departure, PoD) should be the concentration of 68 ppm observed as a NOAEC for effects on reaction time in the study by Olson et al. 1985, when humans were exposed to p-xylene for 4 h (for these effects a LOAEC of 100 ppm was established by Dudek et al. 1990 using technical/mixed xylene).

In the selection of appropriate modification and AF, the REACH guidance on DNEL derivation (ECHA 2012) needs to be followed. In short, in order to e.g. derive a DNEL for single acute exposure of consumers, the above PoD first needs to be modified for daily exposure time according to the modified Haber's law ($C^n \times t = const.$, where n = 1 when modifying to longer, and n = 3, when modifiying to shorter exposure times). Next, the modified acute PoD needs to be divided by appropriate AF for interspecies (in case the PoD is derived from non-human species) and intraspecies variability. For instance, in order to derive a DNEL for single acute 8 h exposure of consumers, the above PoD of 68 ppm would need to be modified by applying a factor of 2 for exposure time in combination with an AF for intraspecies variability of 10, resulting in a DNEL of 3.4 ppm (ca. 15 mg/m^3). **For single 4 h exposure, no modification for exposure duration is needed and a DNEL of ca. 7 ppm or 30 mg/m^3 is obtained by applying the AF for intraspecies variability.** For durations shorter than 4 hours, higher DNELS may be used for risk assessment, e.g. for a duration of 0.25 h, application of Modified Haber's law and the intraspecies AF results in a DNEL of ca. 17 ppm or 70 mg/m^3.

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Chronic DNEL inhalation:

Consumers:
Neurobehavioural deficits were observed in rats after subacute and subchronic exposure to ≥ 50 ppm xylene isomers. The most sensitive endpoint in this regard was found in Korsak et al. 1994, where a LOAEC of 50 ppm was determined for rats which displayed a decreased latency in the paw-lick response at the end of a 13 wk, 6 h/d, 5 d/wk exposure. This is taken as evidence of an increased sensitivity to pain caused by repeated exposure to xylenes. From the available data on toxicokinetics it is expected that steady state blood concentrations will have been achieved already after three months of exposure and, as the neurobehavioural effects are perceived as being primarily concentration-dependent in nature, the eMSCA considers that there is no need for setting an extra Assessement Factor for subchronic-to-chronic extrapolation.

In summary, a 24 h/d chronic inhalation DNEL for the general population can be obtained from the PoD by applying a factor of 24/6 to correct from 6 h/d exposure in the animal experiment to 24 h/d human exposure and another factor of 7/5 to account for everyday exposure, by adding an AF of 3 because the PoD is a LOAEC, and by applying inter /intraspecies factors of 2.5/10. As a result, the PoD of 50 ppm has to be divided by an overall AF of 420, which results in a **DNEL value of 0.12 ppm or ca. 0.5 mg/m³**.

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Appendix 5: List of registration numbers for the addressees of this decision. This Appendix is confidential and not included in the public version of this decision.

EC number: 202-422-2
CAS number: 95-47-6
Public name: o-xylene

This decision is addressed to the Registrant(s) of the above substance with active registration pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided below.