SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

p-Xylene

EC No 203-396-5

CAS No 106-42-3

and

o-Xylene

EC No 202-422-2

CAS No 95-47-6

and

m-Xylene

EC No 203-576-3

CAS No 108-38-3

Evaluating Member State(s): Germany

Dated: 25 August 2021

Evaluating Member State Competent Authority

BAuA
Federal Institute for Occupational Safety and Health
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Year of evaluation in CoRAP: 2015

Before concluding the Substance Evaluation, Decisions to request further information were issued on 17 March 2016.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The three xylene isomers o-xylene, m-xylene and p-xylene were originally selected for substance evaluation in order to clarify the following concerns:

- Suspected reprotoxicant
- Suspected sensitiser
- Consumer use
- Cumulative exposure
- High (aggregated) tonnage
- High RCR
- Wide dispersive use

During the evaluation, the following additional concerns were identified:

- respiratory irritation
- aspiration hazard
- Risk Characterisation Ratios > 1 were obtained when comparing several consumer uses with the corresponding acute or chronic DNELs, based on neurobehavioural effects, and
- Risk Characterisation Ratios > 1 were obtained when comparing several worker uses with the corresponding chronic DNELs, based on neurobehavioural effects.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

For all three xylene isomers, dossier evaluation was conducted by ECHA and the following decisions were adopted:

o-xylene:

1) Decision of 18 April 2013 requesting a pre-natal developmental toxicity (PNDT) study in rats via inhalation.[2]
2) Decision of 16 December 2014 requesting information on composition, spectral data as well as ready biodegradability, long-term toxicity testing on fish and effects on terrestrial organisms.[3]
3) Decision of 21 February 2019 requesting a 90-d study in rats and a PNDT study in a second species, both via the oral route.[4]

m-xylene:

1) Decision of 18 April 2013 requesting a PNDT study in rats via inhalation.[5]
2) Decision of 16 December 2014 requesting information on composition, spectral data as well as ready biodegradability, long-term toxicity testing on fish and effects on terrestrial organisms.[6]
3) Decision of 21 February 2019 requesting a 90-d study in rats and a PNDT study in a second species, both via the oral route.[7]

p-xylene:

1) Decision of 18 April 2013 requesting a PNDT study in rats via inhalation.[8]

[2] https://echa.europa.eu/documents/10162/eb1e3e4f-649d-b298-7c63-03848edb784f
[3] https://echa.europa.eu/documents/10162/b83fe5bf-2c3e-be9f-8158-9ec204faa44b
[4] https://echa.europa.eu/documents/10162/71facfdf-5051-f6b0-5526-29a0c6c789c3
[5] https://echa.europa.eu/documents/10162/0efa2c88-7122-2653-7ee4-1013b34af0c5
[6] https://echa.europa.eu/documents/10162/5df5873e-69c5-f7ce-852b-bcd3ff89cc5a
[7] https://echa.europa.eu/documents/10162/57ca8e55-5368-a804-f3e5-f2fa2231ecb7
[8] https://echa.europa.eu/documents/10162/0efa2c88-7122-2653-7ee4-1013b34af0c5

2) Decision of 16 December 2014 requesting information on composition, spectral data as well as ready biodegradability, long-term toxicity testing on fish and effects on terrestrial organisms.[9]
3) Decision of 21 February 2019 requesting a 90-d study in rats and a PNDT study in a second species, both via the oral route.[10]

3. CONCLUSION OF SUBSTANCE EVALUATION

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	X
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

The result of the substance evaluation was a significantly lower DNEL compared to the currently valid limit values. Risks for a series of uses of xylenes in occupational settings cannot be excluded (obtained RCRs > 1). Therefore, an adaptation of the EU-wide occupational exposure limit (OEL) for xylenes may be necessary.

Consumer uses for the xylene isomers subject to substance evaluation have been removed by most registrants. The consideration whether follow-up action is required will be based on the uses of the xylenes isomeric mixtures (EC number 905-562-9, EC number 905-588-0, CAS RN 1330-20-7,) which are included in the CoRAP and are supposedly of higher relevance for consumer exposure.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

[9] https://echa.europa.eu/documents/10162/4651f1cd-88d2-90a2-1d28-d6f35defc0e2
[10] https://echa.europa.eu/documents/10162/13fa3a4c-3d9c-6ed9-8c76-c203bfd49c7b

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Amendment of European Indicative OEL Value (IOELV) for xylenes	N/A	SCOEL/RAC

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The three xylene isomers o-xylene, m-xylene and p-xylene were originally selected for substance evaluation in order to clarify the following concerns:

- Suspected reprotoxic
- Suspected Sensitiser
- Consumer use
- Cumulative exposure
- High (aggregated) tonnage
- High RCR
- Wide dispersive use

During the evaluation, the following additional concerns were identified:

- respiratory irritation
- aspiration hazard
- Risk Characterisation Ratios > 1 were obtained when comparing several consumer uses with the corresponding acute or chronic DNELs, based on neurobehavioural effects, and
- Risk Characterisation Ratios > 1 were obtained when comparing several worker uses with the corresponding chronic DNELs, based on neurobehavioural effects.

Table 3

EVALUATED ENDPOINTS	
Endpoint	**Outcome/conclusion**
All toxicity endpoints	The registrants' read-Across approach was insufficiently justified, but eMSCA considers the rationale to be plausible in principle. This has been formally addressed by ECHA via a dossier evaluation. (CCH).
Acute toxicity	No concern. However data in humans and animals suggest that classification as STOT SE 3 (H336: May cause drowsiness or dizziness) should be considered by registrants/notifiers.
Irritation/corrosion	Concern confirmed. Classification for respiratory irritation should be considered by registrants/notifiers.
Sensitisation	Concern clarified. Xylene isomers are not considered skin sensitisers according to CLP.
Repeated Dose Toxicity	Concern on ototoxicity clarified: confirmed for p-xylene, but the required doses are above CLP STOT RE 2 classification thresholds. If the other two xylene isomers would also have the potential to cause this effect, even higher doses (> 1800 ppm) would be required.
Genotoxicity	No concern.
Carcinogenicity	No concern.
Reproductive toxicity	Concern unresolved. Since no immediate concern for developmental toxicity was evident from the available database, closing this data gap was transferred to Dossier Evaluation. Data on developmental toxicity in a second species (rabbits) as well as additional read-across justification were provided by the registrants after conclusion of this substance evaluation by the eMSCA. Although this information has not been assessed in depth by the eMSCA and is not reflected in this report, the PDNT study the registrant provided did not demonstrate developmental toxicity.

EVALUATED ENDPOINTS	
Endpoint	**Outcome/conclusion**
Aspiration hazard	Concern confirmed. Classification for aspiration hazard should be considered by registrants/notifiers.
Consumer exposure	It can be assumed that xylenes are present in consumer products and consumer exposure is likely. On the other hand, consumer uses for the xylene isomers subject to substance evaluation have been removed by most registrants. However, these uses may still be relevant for isomeric mixtures of xylenes which are registered separately. A new, lower DNEL has been derived by the eMSCA which can be adjusted for shorter exposure duration over a day and/or infrequent use over a year (instead of averaging out the event exposure over a year). As a result, the eMSCA concludes that for a series of previously registered uses, risks to consumers may not be excluded (anticipated RCRs >1). The eMSCA considers that this DNEL should be applied for future exposure assessments by the registrants of the pure xylene isomers subject to substance evaluation as well as isomeric mixtures of xylenes which so far have not been subject to formal substance evaluation.
Occupational exposure	Concern confirmed. Applying the new DNEL derived by the eMSCA, risks for a series of uses of xylenes in occupational settings cannot be excluded (Obtained RCRs > 1). The eMSCA considers that an adaptation of the EU-wide occupational exposure limit (OEL) for xylenes may be necessary.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, o-, m-, and p-xylene were included on the Community rolling action plan (CoRAP) for evaluation in 2015. The Competent Authority of Germany was appointed to carry out the evaluation. The substance evaluation started on 17 March 2015.

Based on the fact that the registrants have used a read-across/category approach for the evaluation of the xylenes, in the following chapters the toxicity of the three xylene isomers (o-xylene, EC number 202-422-2/ CAS RN 95-47-6; m-xylene, EC number 203-576-3/ CAS RN 108-38-3; p-xylene, EC number 203-396-5/ CAS RN 106-42-3) is evaluated together.

In addition to the three xylene isomers, the data matrix used for the read-across/category approach contains data on "xylene" (EC number 215-535-7/ CAS number 1330-20-7) from which in the industrial process the individual isomers are obtained by further purification steps. Different qualities of xylene are on the market and test data have been obtained with xylene of varying composition: aside from the o-, m-, and p-isomers, xylene also contains a significant amount of ethylbenzene (EC number 202-849-4/ CAS RN 100-41-4). For the former, the DE CA has declared its intention to potentially perform an SEv at a later stage, for the latter, data have been assessed by the DE CA in the context of an EU RAR (German MSCA, 2008); unless directly used by the registrants for registration of the individual xylene isomers, these data are not reported again in this Substance Evaluation report.

In the following, unless specific xylene isomers are addressed, the name "xylene" will be used to designate multi-constituent substances which contain the three individual isomers and ethylbenzene. Where known, purity and composition of the test materials (and, in case of "xylene", their constituents) are provided in the tabular summaries of the toxicological studies.

Human health hazard assessment: A thorough literature search for all xylene isomers and mixed xylenes was undertaken by the eMSCA in 2015 using web-based databases (TOXLINE, ISI Web Of Science, Scopus). Since the registration dossiers are based on a category approach, a need was identified to evaluate the available data base for communalities/differences between the individual category members. Therefore, all relevant human health endpoints as addressed by the requirements specified in Annexes VII-X to the REACH regulation have been addressed in this substance evaluation. A detailed documentation of the application of ECHA's Read-Across Assessment Framework (RAAF) can be found in Annex 1, section7.16.. Before starting the finalisation of this document in February 2019, an additional search in the PubMed and Scopus databases was performed to identify any relevant new studies submitted between 2012 and 2019.

Exposure assessment for consumers: In order to clarify health risks derived from the use of consumer products that contain xylene isomers, the CSRs and the technical IUCLID dossiers were checked as to whether the exposure scenarios are comprehensive, inherently conclusive, and complete regarding the identified uses, operational conditions, and targeted population groups. In parallel to the SEv process, the registrants carried out a downstream user survey regarding consumer uses, asking for product categories which should be further supported and the concentration of xylenes present in the final products. A thoroughly revised consumer exposure assessment and risk characterisation was provided to the eMSCA in October 2015, and also evaluated and reported here. However, only very few registrants have updated their registration dossiers regarding these results until March 2016. Therefore, all identified uses are still supported by the registrants and the required information refers to these.

For all three xylene isomers, substance evaluation decisions were taken by ECHA and sent to the respective registrant(s) on 30 March 2017, asking them to submit an update of the registration dossiers containing the required information.[11] In conclusion, most of the registrant(s) updated their Registration Dossiers and removed the identified consumer uses in the technical IUCLID as well as in the CSR.

It can be assumed that xylenes are present in consumer products and consumer exposure is likely. Consumer products may be produced using only one of the xylene isomers, but use of mixed xylenes often would appear more likely for economic reasons. However, these mixed xylenes are registered as separate substances under REACH which were not the subject of this evaluation.

Exposure assessment for workers: The occupational exposure assessment of the eMSCA is essentially based on model estimates provided in the lead CSR. The lead registrant assessed inhalation and dermal exposure of workers by using the tier 1 model ECETOC TRA v3. It has to be noted that the registrants did not provide any measurement data on workplace exposure. However, measured workplace exposure data from Germany have been evaluated in a study by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2016) and used as a basis for the worker exposure assessment. A detailed documentation of the exposure scenarios can be found in section 7.12.1.1.

The eMSCA formally concluded the follow-up assessment of the new information in April 2019. The draft conclusion and substance evaluation report was provided to ECHA on 14 April 2020. Prior to publication of the final report by ECHA in 2021, further information has been made available in the registrations following compliance check procedures for the three substances (cf. p. 8, Part A: 2. Overview of other processes/EU legislation).

[11] SEV decision on o-xylene, 30 March 2017: https://echa.europa.eu/documents/10162/af586a59-eb77-fb3c-4f8f-35781cf507cd; SEV decision on m-xylene, 30 March 2017: https://echa.europa.eu/documents/10162/6124be44-e7d4-7db0-eab7-7262ad81d5d8; SEV decision on p-xylene, 30 March 2017: https://echa.europa.eu/documents/10162/cb44ae93-1dcc-4191-2e26-b76d94444e94

The decisions by ECHA requested the following studies for all three substances:

1. Sub-chronic toxicity study (9o-day), oral route (Annex IX, Section 8.6.2. ;test method: OECD TG 4O8) in rats with the registered substance

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.

This information has not been assessed by the eMSCA and is not reflected in detail in this report. However, ECHA has, in April 2021, formally concluded the compliance check and confirmed that the PNDT study submitted by the registrants is complying with the requested information.

7.3. Identity of the substance

Table 4

P-XYLENE: SUBSTANCE IDENTITY	
Public name:	p-Xylene
EC number:	203-396-5
CAS number:	106-42-3
Index number in Annex VI of the CLP Regulation:	601-022-00-9
Molecular formula:	C_8H_{10}
Molecular weight range:	106.16 g/mol
Synonyms:	Benzene, 1,4-dimethyl- 1,4-Dimethylbenzene 4-Methyltoluene

Type of substance: Mono-constituent
Structural formula:

Table 5

O-XYLENE: SUBSTANCE IDENTITY	
Public name:	o-Xylene
EC number:	202-422-2
CAS number:	95-47-6
Index number in Annex VI of the CLP Regulation:	601-022-00-9
Molecular formula:	C_8H_{10}
Molecular weight range:	106.16 g/mol
Synonyms:	Benzene, 1,2-dimethyl- 1,2-Dimethylbenzene o-Methyltoluene

Type of substance: Mono-constituent
Structural formula:

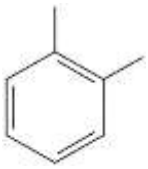
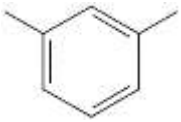


Table 6

M-XYLENE: SUBSTANCE IDENTITY	
Public name:	m-Xylene
EC number:	203-576-3
CAS number:	108-38-3
Index number in Annex VI of the CLP Regulation:	601-022-00-9
Molecular formula:	C_8H_{10}
Molecular weight range:	106.16 g/mol
Synonyms:	Benzene, 1,3-dimethyl- 1,3-Dimethylbenzene m-Methyltoluene

Type of substance: Mono-constituent

Structural formula:



7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES OF P-XYLENE	
Property	**Value**
Physical state at 20 °C and 101.3 kPa	Colourless liquid
Melting/freezing point	13.2 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Boiling point	138.4 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Vapour pressure	1167 Pa at 25 °C, Handbook data from Handbook of vapour pressures and heats of vapourisation of hydrocarbons and related compounds 1971
Water solubility	156 mg/L at 25 °C, Handbook data from Handbook of aqueous solubility data 2003
Partition coefficient n-octanol/water (Log K^{ow})	log K_{OW} = 3.15, Hansch C, Leo A, Hoekman D., American Chemical Society, 1995
Flashpoint	27 °C c.c., Handbook data from The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, 14th edition
Autoflammability Auto-ignition temperature	528 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Flammability Flammability upon ignition (solids) Flammability in contact with water and pyrophoric properties	 Testing not necessary, substance is a liquid. The molecular structure of p-xylene does not contain any groups that indicate potential reactivity with water or pyrophoric properties and handling of the substance indicates that this is the case.
Lower and Upper Explosion limits	1.1–7%, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Explosive properties	Non-explosive
Oxidising properties	Non-explosive

Table 8

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES OF O-XYLENE	
Property	**Value**
Physical state at 20 °C and 101.3 kPa	Colourless liquid
Melting/freezing point	-25.2 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Boiling point	144.5 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Vapour pressure	882 Pa at 25 °C, Handbook data from Handbook of vapour pressures and heats of vapourisation of hydrocarbons and related compounds 1971
Water solubility	170.5 mg/L at 25 °C, Handbook data from Yalkowsky SH and He Y, Aqueous solubility data, 2003
Partition coefficient n-octanol/water (Log K_{ow})	log K_{OW} = 3.12, Hansch C, Leo A, Hoekman D., American Chemical Society, 1995
Flashpoint	32 °C c.c., Handbook data from The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, 14th edition
Autoflammability Auto-ignition temperature	463 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Flammability Flammability upon ignition (solids) Flammability in contact with water and pyrophoric properties	 Testing not necessary, substance is a liquid. The molecular structure of o-xylene does not contain any groups that indicate potential reactivity with water or pyrophoric properties and handling of the substance indicates that this is the case.
Lower and Upper Explosion limits	0.9–6.7%, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Explosive properties	Non-explosive
Oxidising properties	Non-oxidising

Table 9

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES OF M-XYLENE	
Property	**Value**
Physical state at 20 °C and 101.3 kPa	Colourless liquid
Melting/freezing point	–47.9 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Boiling point	139.1 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Vapour pressure	1106 Pa at 25 °C, Handbook data from Handbook of vapour pressures and heats of vapourisation of hydrocarbons and related compounds 1971
Water solubility	146 mg/L at 25 °C, Handbook data from Handbook of aqueous solubility data 2003
Partition coefficient n-octanol/water (Log K_{ow})	log K_{OW} = 3.2, Hansch C., Leo A., Hoekman D., American Chemical Society, 1995
Flashpoint	27 °C c.c., Handbook data from The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, 14th edition
Autoflammability Auto-ignition temperature	527 °C, Handbook data from CRC handbook of chemistry and physics. 89th ed.

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES OF M-XYLENE	
Property	**Value**
Flammability Flammability upon ignition (solids) Flammability in contact with water and pyrophoric properties	Testing not necessary, substance is a liquid. The molecular structure of m-xylene does not contain any groups that indicate potential reactivity with water or pyrophoric properties and handling of the substance indicates that this is the case.
Lower and Upper Explosion limits	1.1–7%, Handbook data from CRC handbook of chemistry and physics. 89th ed.
Explosive properties	Non-explosive
Oxidising properties	Non-oxidising

7.5. Manufacture and uses

7.5.1. Quantities

Table 10

AGGREGATED TONNAGE (PER YEAR) OF P-XYLENE				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☒ > 1000,000 t	☐ Confidential

Table 11

AGGREGATED TONNAGE (PER YEAR) OF O-XYLENE				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☒ 100,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential	

Table 12

AGGREGATED TONNAGE (PER YEAR) OF M-XYLENE				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☒ 100,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential	

7.5.2. Overview of uses

In Table 13, the identified uses for the xylene isomers according to the ECHA dissemination website are listed: last review by eMSCA in April 2020.

Table 13

USES OF O-,P- AND M-XYLENE	
	Use(s)
Uses as intermediate	

USES OF O-,P- AND M-XYLENE	
	Use(s)
p-Xylene	• Use as an intermediate • Intermediate/solvents – Manufacture of Intermediate under SCC
o-Xylene	• Use as an intermediate • Intermediate/solvents – Manufacture of Intermediate under SCC
m-Xylene	• Use as an intermediate
Formulation ***p-Xylene***	• Formulation & (re)packing of substances and mixtures • Distribution • Use as a laboratory reagent • Explosives manufacture and use • Formulation & (re)packing of substances and mixtures
o-Xylene	• Distribution • Use as a laboratory reagent • Explosives manufacture and use
Uses at industrial sites ***p-Xylene***	• Manufacture • Distribution of a substance • Uses in Coatings • Uses in Cleaning Agents • Use in Oil and Gas field drilling and production operation • Use as binders and release agents • Use as a fuel • Rubber production and processing • Explosives manufacture and use • Use in Laboratories
o-Xylene	• Manufacture • Distribution of a substance • Uses in Coatings • Uses in Cleaning Agents • Use in Oil and Gas field drilling and production operation • Use as binders and release agents • Use as a fuel • Rubber production and processing • Explosives manufacture and use • Use in Laboratories
m-Xylene	• Manufacture • Distribution of a substance
Uses by professional workers ***p-Xylene***	• Uses in Coatings • Uses in Cleaning Agents • Use in Oil and Gas field drilling and production operations • Use as binders and release agents • Use as a fuel • Use in laboratories
o-Xylene	• Uses in Cleaning Agents • Use in Oil and Gas field drilling and production operations • Use as binders and release agents • Use as a fuel • Use in laboratories
Consumer Uses	Most of the Registrant(s) have deleted consumer uses in their registration dossiers after receipt of the substance evaluation decision. However, according to the information provided on the dissemination website within "Chemical Substance Search" (on 2015-12-02, status: latest update on 28 November 2015 and on 2019-05-02, latest update on 17 April 2019) by ECHA, the following consumer uses of the three xylene isomers (o-, m-, and p-) are recorded: *Use in coatings:* ▪ PC 1: Adhesives, sealants ▪ PC 4: Anti-freeze and de-icing products ▪ PC 8: Biocidal products (e.g. disinfectants, pest control)

USES OF O-,P- AND M-XYLENE	
	Use(s)
	▪ PC 9a: Coatings and paints, thinners, paint removes ▪ PC 9b: Fillers, putties, plasters, modelling clay ▪ PC 9c: Finger paints ▪ PC 15: Non-metal-surface treatment products ▪ PC 18: Ink and toners ▪ PC 23: Leather tanning, dye, finishing, impregnation and care products ▪ PC 24: Lubricants, greases, release products ▪ PC 31: Polishes and wax blends ▪ PC 34: Textile dyes, finishing and impregnating products; including bleaches and other processing aids *Use in cleaning products:* ▪ PC 3: Air care products ▪ PC 4: Anti-freeze and de-icing products ▪ PC 8: Biocidal products (e.g. disinfectants, pest control) ▪ PC 9: Not specified ▪ PC 24: Lubricants, greases, release products ▪ PC 35: Washing and cleaning products (including solvent based products) ▪ PC 38: Welding and soldering products (with flux coatings or flux cores), flux products *Use as agrochemical:* ▪ PC 12: Fertilisers ▪ PC 27: Plant protection products *Use as a fuel* ▪ PC 13: Fuels There are no consumer uses advised against.
Article service life	N/A

7.5.2.1. Uses by workers/professionals

The three xylene isomers are important industrial chemicals which are used as intermediates in the manufacture of other substances and also as solvents, e.g. in mixtures for coatings, cleaning agents, or as oil field drilling agents. All of the three isomers are used in the industrial sector. p-Xylene and m-xylene are also used in the professional sector mainly in coatings, cleaning agents, binders, release agents and as fuels.

7.5.2.2. Consumer use

In parallel to the substance evaluation process, the registrants conducted a downstream user survey regarding consumer uses, asking for product categories which should be further supported.

As a result, the registrants indicated to the eMSCA no need to support the consumer uses for o- and p-xylene in cleaning products and as agrochemicals any longer, as well as for the specific product categories 8 and 9c in coatings. Furthermore, they identified no consumer-related uses for m-xylene. They informed the German CA accordingly in October 2015.

Xylenes are used as solvents. Consumer products may be produced using only one of the xylene isomers, but use of mixed xylenes appears more likely in many cases. However, based on the above survey, the registrants identified consumer uses with o- and p- xylene and in fact the product data bases of Germany, Slovenia, Switzerland, and Sweden listed a small number of products for each of the three isomers. For some of these products it was not possible to distinguish between consumer and professional use.

In March 2016, the eMSCA noted that only very few registrants had updated their registration dossiers regarding the results of the downstream user survey, and that many of the consumer uses were still supported (see Table 13).

All national product databases list the isomers as a common ingredient of paints, lacquers, thinners, and removers. The purpose of the coatings seems to be mainly to protect wood and metals with different application methods, e.g. by spraying.

The SPIN database[12] indicated in 2013 a "probable exposure" with an "intermediate range of applications" (NO, SE) or a "very wide range of applications" (DK) and a "very probable use in article productions", respectively. The SPIN database has listed the following use categories: paints, lacquers and varnishes, adhesives, binding agents, fillers, reprographic agents, non-agricultural pesticides and preservatives, colouring agents, construction materials, fuels, and solvents.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 14

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
601-022-00-9	o-xylene [1] p-xylene [2] m-xylene [3] xylene [4]	202-422-2 [1] 203-396-5 [2] 203-576-3 [3] 215-535-7 [4]	95-47-6 [1] 106-42-3 [2] 108-38-3 [3] 1330-20-7 [4]	Flam. Liq. 3 Acute Tox. 4* Acute Tox. 4* Skin Irrit. 2	H226 H332 H312 H315	*	C
601-023-00-4	ethylbenzene	202-849-4	100-41-4	Flam. Liq. 2; Acute Tox. 4*; STOT RE 2 Asp. Tox 1	H225 H332 H373 (hearing organs) H304		

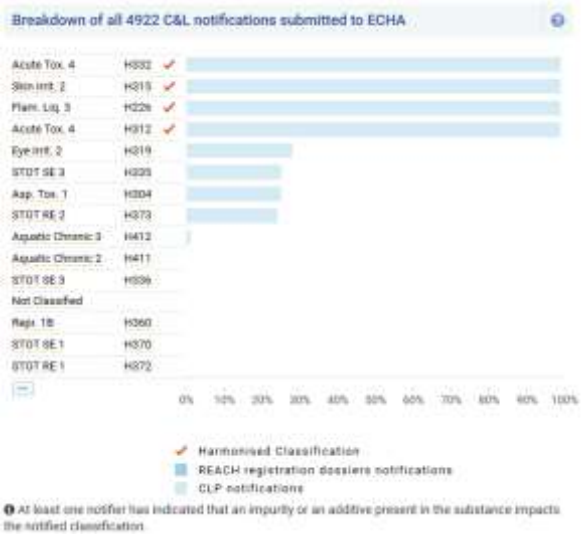
Note C: Some organic substances may be marketed either in a specific isomeric form or as a mixture of several isomers.

7.6.2. Self-classification

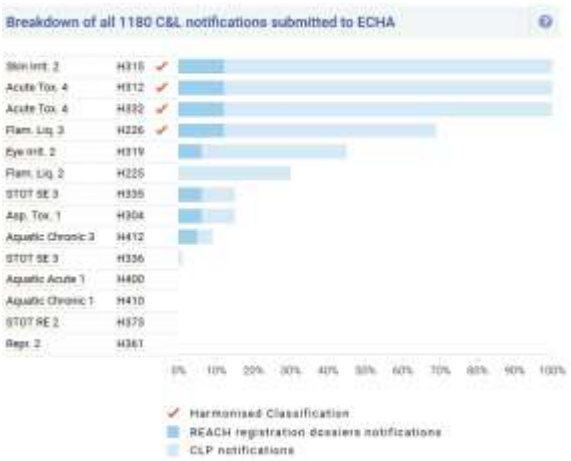
Below, self-classifications for xylene (mixed isomers), the individual xylene isomers, and ethylbenzene are reported as obtained from the ECHA dissemination website on 30 April 2019:

[12] SPIN: "Substances in Preparations in Nordic Countries": http://spin2000.net/

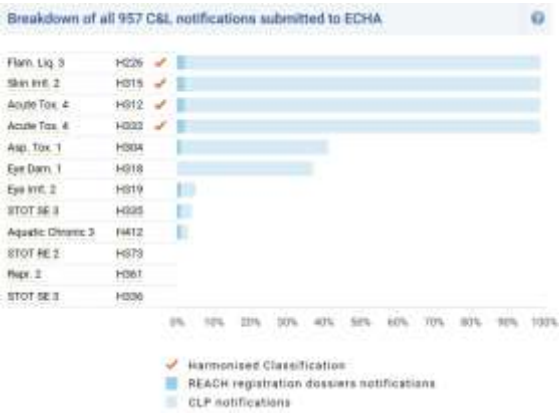
xylene (mixed xylenes, EC 215-535-7):



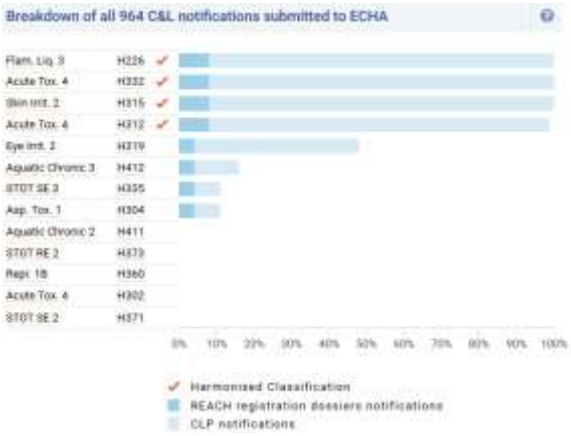
o-xylene (EC 202-422-2):



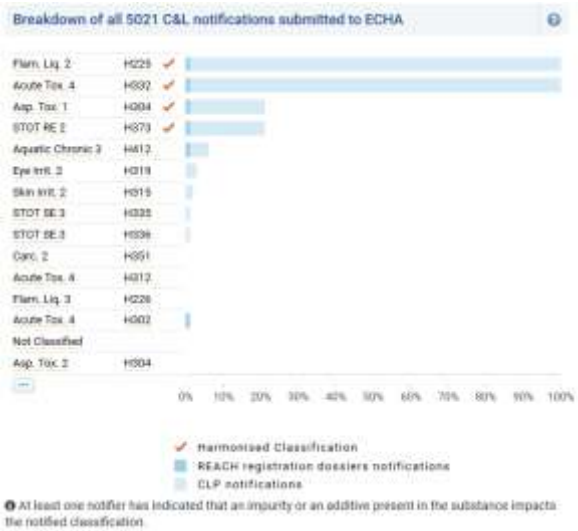
m-xylene (EC 203-576-3):



p-xylene (EC 203-396-5):



ethylbenzene (EC 202-849-4):



7.7. Environmental fate properties

Not assessed in this evaluation.

7.8. Environmental hazard assessment

Not assessed in this evaluation.

7.9. Human health hazard assessment

Introductory notes

The following parameters have been used for dose conversion:

1 mg xylene isomer/m^3 is equivalent to 0.23 ppm. Conversely, 1 ppm xylene isomer corresponds to 4.40 mg/m^3

Where needed, the following specific weight values were used:

o-Xylene: 0.881 g/mL, m-xylene: 0.866 g/mL, p-xylene: 0.861 g/mL, ethylbenzene: 0.867 g/mL, and mixed xylenes: ~0.86 g/mL (Römpp, 2015).

In many older publications, purity of the test material was only reported verbally, therefore the following assumptions were made:

"Laboratory grade" is assumed to refer to at least 95% purity, "analytical grade" is assumed to refer to at least 99% purity.

The final data matrix containing the key results for each endpoint for the five substances in the category (o-, m-, p-xylene, ethylbenzene, xylene) considered during the assessment by the eMSCA can be found in section 7.9.10. A tabular documentation of the assessment of the read-across/category approach according to ECHA's Read-Across Assessment Framework RAAF, (ECHA, 2017) is provided in Annex 1 (section 7.16).

A number of reviews on the toxicity of xylenes are available in the published literature e.g. (ACGIH, 2001; ATSDR, 2007; Bang, 1984; Bell et al., 1992; Bonde, 1992; Crookes et al., 1993; DECOS, 1991; ECETOC, 1986; ECETOC, 1997; Health Council of the Netherlands, 2001; IARC, 1989; Kandyala et al., 2010; Low et al., 1989; NIWL, 2005; USEPA, 1989; Vainio et al., 1985; Ware, 1988; WHO, 1997; Wiger, 1992). A summary of most of the studies reviewed for this SEv report can be found in these papers, therefore only a tabular overview is provided in the subsequent sections.

7.9.1. Toxicokinetics

7.9.1.1. Non-human data

Table 15

SUMMARY OF STUDIES ON TOXICOKINETICS, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Absorption & Distribution			
Oral			
Single oral dose o-, m-, or p-xylene, gavage, 8.47 mmol/kg bw, SD rat Repeated oral dose o-, m-, or p-xylene, gavage, 8.47 mmol/kg bw, 2 wk, 5 d/wk. SD rat Single oral dose m-xylene, gavage, 16.94 mmol/kg bw, SD rat Repeated dose m-xylene, gavage, 16.94 mmol/kg bw, 2 wk, 5 d/wk, SD rat	After single or repeated administration of 8.47 mmol p-xylene /kg bw to rats, blood/brain C_{max} and AUC were much higher (brain: almost 2-fold) than with o-/m-xylene Depending on the isomer, T_{max} was in the range of 2-4 h after single administration (smallest for p-xylene). Single administration of 16.94 mmol m-xylene/kg bw yielded a comparable C_{max} but a 2-fold higher AUC as compared to 8.47 mmol p-xylene/kg bw. For all xylene isomers, at 8.47 mmol /kg bw, blood and brain levels after repeated	None	(Gagnaire et al., 2007)

SUMMARY OF STUDIES ON TOXICOKINETICS, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Single oral dose p-xylene, gavage, 8.47 mmol/kg bw, guinea pigs Repeated oral dose p-xylene, gavage, 8.47 mmol/kg bw, 2 wk, 5 d/wk. guinea pig Repeated oral dose p-xylene, gavage, 16.94 mmol/kg bw, 2 wk, 5 d/wk, guinea pig Single exposure p-xylene via whole-body inhalation, 1800 ppm, 4 h, SD rat Single exposure p-xylene via whole-body inhalation, 1800 ppm, 4 h, guinea pig Purity: > 99% (all isomers)	exposure were ≤ those obtained after single administration. Repeated administration of 16.94 mmol m-xylene/kg bw yielded C_{max} and AUC values comparable to those obtained with 8.47 mmol/kg bw p-xylene. The ratio between brain and blood levels expressed as µg/g (blood) or µg/g (brain) was found to be around 2-3 at all dose levels and most time points. Regardless of dosing scheme, C_{max} and AUC in rats were always found to be much higher than those in guinea pigs.		
Dermal			
Dermal absorption in hairless rat skin in vitro Xylene Purity: 98.0%	Steady state flux reported as 0.22 mg/cm²/h Steady state reached after ~ 4 h under "infinite dose" scenario Cf. section 7.9.1.3 for a more detailed discussion	Identity of test substance unclear	(Ahaghotu et al., 2005)
Inhalation			
Inhalation kinetics study in SD rats 12 h/d, 1-3 d Samples were taken immediately after end of exposure on days 1-3 and 12 h after exposure on d 3 ("recovery") o-Xylene, purity > 99%, 100 ppm	Blood 1 d: 9.1 ± 1.4 µmol/kg 2 d: 7.8 ± 1.3 µmol/kg 3 d: 10.3 ± 0 9 µmol/kg Recovery: 0.1 ± 0.1 µmol/kg Brain 1 d: 22.4 ± 0.4 µmol/kg 2 d: 22.6 ± 3.0 µmol/kg 3 d: 28.6 ± 7.3 µmol/kg Recovery: not detected Liver 1 d: 13.5 ± 1.0 µmol/kg 2 d: 14.3 ± 0.6 µmol/kg 3 d: 22.4 ± 4.6 µmol/kg Recovery: 0.2 ± 0.1 µmol/kg Kidney 1 d: 63.2 ± 7.9 µmol/kg 2 d: 76.2 ± 32.7 µmol/kg 3 d: 95.2 ± 47.0 µmol/kg Recovery: 1.5 ± 0.7 µmol/kg Perirenal fat 1 d: 1173 ± 126 µmol/kg 2 d: 1108 ± 71 µmol/kg 3 d: 1228 ± 253 µmol/kg Recovery: 71 ± 35 µmol/kg		(Zahlsen et al., 1992)
Metabolism & Excretion			
Oral			

SUMMARY OF STUDIES ON TOXICOKINETICS, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Toxicokinetics in phenobarbital pre-treated rats vs. control m-Xylene, purity not reported	Metabolism *in vitro* increased by PB pre-treatment already at the lower dose of 0.01 mL/kg (8.64 mg/kg or 0.081 mmol/kg)	None	(Kaneko et al., 1995)
Inhalation			
Effect on enzymes in vitro (kidney, liver, lung microsomes) and in vivo (rat, 3-d inhalation) o-Xylene (purity > 99%) m-Xylene (purity 98,7%) p-Xylene (purity > 99%) Xylene (2% o-, 64.5% m-, 10% p-xylene, 23% ethylbenzene) Ethylbenzene (purity > 99%) 200 ppm each	*In vitro*: Increased O-deethylation of 7-ethoxyresorufin, hydroxylation of n-hexane and benzo[a]pyrene *In vivo*: Induction of P450 and NADPH-cytochrome c reductase m-Xylene strongest, p-xylene less potent regarding P450 than the other test chemicals Enzyme induction of phenobarbital type	None	(Toftgard and Nilsen, 1982)
Metabolism study (5 d, 6 h/d, rat, inhalation) Mixtures of m-xylene and ethylbenzene (purity not reported) (0/75+25/300+100/600+200 ppm)	Major metabolites of m-xylene: methylhippuric acid, dimethylphenols, methylbenzyl alcohol "In conclusion, the mutual effects characteristic for mixed exposure to XYL + EB were, in a conspicuous manner, enhanced with the dose."	None	(Elovaara et al., 1984)
Study on pulmonary microsomal alterations,SD rats, 300 ppm, 6 h/d, for 1, 3, or 5 d p-Xylene, purity 99.7%	Initial increase in conjugated dienes, decrease in P450 content, benzyloxyresorufin O-dealkylase, 2-aminofluorene N-hydroxylase, and extracellular surfactant Returned to normal by day 3 except for 2-aminofluorene N-hydroxylase Core membrane fluidity and aryl hydrocarbon hydroxylase (AHH) increased after 3 d. AHH increased by 41% after 5 d.	None	(Silverman and Schatz, 1991)
Metabolism in vivo (6 h inhalation of 300 ppm by Wistar rats, either pretreated (1 h/d, 6 d) or untreated) m-Xylene, 99%, 300 ppm	Blood concentration at end of exposure: Untreated: 135 ± 10 µmol/L Pre-treated: 148 ± 16 µmol/L Concentration in perirenal fat at end of exposure: Untreated: 2.49 ± 0.57 µmol/g Pre-treated: 1.77 ± 0.26 µmol/L Concentration in perirenal fat 12 h after end of exposure: Untreated: 0.31 ± 0.20 µmol/g Pre-treated: 0.33 ± 0.12 µmol/L Urinary metabolites: Methylhippuric acid (MHA) 2,4-Diphenol (2,4-DMP) Urinary excretion of MHA during and after exposure (n=6): 0-6.5 h, untreated: 115 ± 8 µmol/animal 6.5-24 h: 141 ± 30 µmoL/animal 0-6.5 h, pre-treated: 104 ± 29 µmol/animal 6.5-24 h: 217 ± 73 µmoL/animal	None	(Liira et al., 1991)

SUMMARY OF STUDIES ON TOXICOKINETICS, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
	Urinary excretion of 2,4-DMP during and after exposure (n=6): 0-6.5 h, untreated: 14.4 ± 1.6 µmol/animal 6.5-24 h: 19.3 ± 3.6 µmoL/animal 0-6.5 h, pre-treated: 13.6 ± 4.5 µmol/animal 6.5-24 h: 27.5 ± 5.8 µmoL/animal Urinary excretion of thioethers (n=6): 0-6.5 h, untreated: 1.28 ± 0.4 µmol/animal 6.5-24 h: 4.06 ± 2.60 µmoL/animal 0-6.5 h, pre-treated: 1.05 ± 0.78 µmol/animal 6.5-24 h: 2.80 ± 2.36 µmoL/animal Liver GSH (n=6): Control: 6.48 ± 0.15 µmol/animal Pre-treated: 5.96 ± 0.43 µmol/animal Microsomal protein and aniline hydroxylase slighty lower, P450 indifferent, PROD, EROD, ECOD higher compared to control (n=6)		
Toxicokinetics in phenobarbital pre-treated rats vs. control after oral administration m-Xylene, purity not reported	Metabolism increased by PB pre-treatment, significant effect of enzyme induction only at high dose (400 ppm), not at the low dose (40 ppm)	None	(Kaneko et al., 1995)
Other routes			
Effect on liver glutathione in Wistar rats in vitro and in vivo (i.p. administration) o-, m-, and p-Xylene, purity not reported (presumed to be 99%)	*In vitro*: No direct conjugation of o-xylene with glutathione in vitro, but conjugation after bioactivation (not specified) *In vivo*: Hepatic glutathione reduction vs. control: ca. 35% for m- and p-xylenes, ca. 75% for o-xylene Metabolism - Excretion of thioethers: o-xylene >>> m-xylene > p-xylene o-Xylene: Thioether characterised as mercapturic acid. Only minor amounts of mercapturic acids formed for m-/p-xylene	None	(van Doorn et al., 1980)
Subacute i.p. study in rats 3 d, 10 mmol/kg bw m-Xylene, purity > 99% p-Xylene,purity > 99% Ethylbenzene, purity > 99%	Small differences in activity Treatment caused slight increases in body wt, liver wt m-Xylene caused slightly stronger effects than p-xylene but relevance and significance are unclear 10 mmol/kg bw x 3 d is a LOEC	Not relevant for quantitative risk assessment due to i.p. administration	(Backes et al., 1993)

SUMMARY OF STUDIES ON TOXICOKINETICS, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Study on the induction of mixed functional oxidases (CYP450, AHH) in liver and lung (SD rats, acute i.p. injection, 1 g/kg bw) o-Xylene (purity 99.7%)	Blood T_{max}: 1 h post-dose C_{max}: 0.482 ± 0.061 µmol/g Liver T_{max}: 3 h post-dose C_{max}: 2.720 ± 0.790 µmol/g Total P450 increased, CYP1A1 activity (EROD) slightly and CYP2B1 activity (BROD) markedly increased at 6 and 12 h p.a. Lung T_{max}: 3 h post-dose C_{max}: 0.899 ± 0.194 µmol/g Total P450, CYP1A1, CYP2B1 and AHH activity decreased at all time points, max. at 3 h p.a.	None	(Park et al., 1994)
Toxicokinetics in phenobarbital pre-treated rats vs. control after i.p. administration m-Xylene, purity not reported	Metabolism *in vitro* increased by PB pre-treatment, significant effect of enzyme induction only at high dose (400 ppm), not at the low dose (40 ppm)	None	(Kaneko et al., 1995)

7.9.1.2. Human data

Table 16

SUMMARY OF STUDIES ON TOXICOKINETICS, HUMAN DATA			
Method/Study Type	**Results**	**Remarks**	**Source**
Absorption & Distribution			
Dermal			
Dermal absorption, immersion of one or both hands into m-xylene for 15 min m-Xylene, 95%	Rapid absorption, peak concentration in venous blood draining the site of exposure reached 4-6 min post-exposure Absorption rate estimated at ~2 µg/cm²/min (~120 µg/cm²/h), basis for estimation is however unclear Three times higer absorption in individual with hand eczema Excretion of m-methylhippuric acid detectable until 72 h post-exposure	"Infinite dose" experiment, complete mass balance is missing	(Engström et al., 1977)
Dermal absorption, immersion of one or both hands into m-xylene for 15 min m-Xylene (purity: 95%), m-xylene + isobutanol, m-xylene + isobutanol + water	Analogous to results by (Engström et al., 1977), cf. above Mixture results not relevant for this evaluation.	None	(Riihimäki, 1979)
Dermal absorption in human volunteers, 27 cm², for 3 min Inhalation exposure, 40 nmol/L (~4.2 mg/m³), for 10 min m-Xylene, purity not reported	Fast permeation Flux within the exposure period: 46 nmol/cm²/min (~5 µg/cm²/min, ~300 µg/cm²/h)	Flux: Steady state reached? Metabolism not accounted for	(Kezic et al., 2001)

SUMMARY OF STUDIES ON TOXICOKINETICS, HUMAN DATA			
Method/Study Type	**Results**	**Remarks**	**Source**
		Divergent statements on air concentration in inhalation experiment Overall considered unreliable	
Inhalation			
Metabolism study, inhalation 8 h at ~ 0.2 mg/L or ~ 0.4 mg/L o-, m-, p-xylene alone or to a 1:1:1 mixture of these isomers by male volunteers Purity not reported	Pulmonary retention ~ 60-70% Main metabolite fraction (95-99%) consists of methylhippuric acids (MHA) MHA levels decrease strongly after end of exposure, ~ 70% excretion within 24 h, trace amounts observable after 4-5 d Minor metabolite fractions contain xylenols In the mixture, p-xylene was metabolised faster than the other two isomers.	None	(Šedivec and Flek, 1976)
Inhalation absorption for a total of 2 h (140 min, including 20 min break after 30 min), male volunteers 870 mg/m^3 (~198 ppm) for 30 min at rest, followed by a 20 min break, followed by 90 min at 50 W (light activity) 435 mg/m^3 (~99 ppm) for 30 min at rest followed by each 30 min at 50, 100, and 150 W (moderately heavy activity) Xylene: o-xylene: 8.8%, m-xylene: 49.4%, p-xylene: 1.4%, ethylbenzene: 40.4%	Absorption ~ 60% of inhaled dose Expired xylene amounted to ~ 4-5% Increase of xylene blood levels with higher workload Arterial blood/alveolar air partitioning coefficient: ~ 30-40 after about 1 h of exposure under exercise, lower at rest	Not reliable for quantitative risk assessment (incomplete mass balance, metabolism not accounted for)	(Åstrand et al., 1978)
Biomonitoring in 4 female histology laboratory assistants exposed to average Median ambient air concentrations: Workplace 1 (3 F): 42 ppm EB, 12 ppm o-xylene, 70 ppm m- + p-xylene Workplace 2 (1 F): 37 ppm EB, 11 ppm o-xylene, 61 ppm m- + p-xylene Xylene: 6.72% o-xylene, 52.63% m-xylene, 15.24% p-xylene, 25.25% ethylbenzene	Blood levels (mg/L) at end of working day: Workplace 1: Ethylbenzene: 0.7-0.8, o-xylene: ~ 0.2, (m+p)-xylene: 1.2-1.5 Workplace 2: Ethylbenzene: 0.5, o-xylene: ~ 0.1, (m+p)-xylene: ~ 1.0 2-Ethylphenol identified as ethylbenzene metabolite, whereas 2,4 dimethyl phenol was not found	None	(Angerer and Lehnert, 1979)

SUMMARY OF STUDIES ON TOXICOKINETICS, HUMAN DATA			
Method/Study Type	**Results**	**Remarks**	**Source**
Toxicokinetics in 6 male volunteers following inhalation exposure, for 4 h Xylene, composition and purity not reported, 200 mg/m^3, mean absolute dose received: 355.6 (296.2 – 459.2) mg, Ethylbenzene, purity not reported, 20 – 200 mg/m^3), purity not reported	Excretion modelled to follow biphasic pattern Wide variability in blood and urine levels of xylene, methylhippuric acid, and ethylbenzene. Not usable for quantitative risk assessment	Composition of test material unclear Reporting of results for EB ambiguous (two dose levels were tested, only one result reported	(Janasik et al., 2008)
Inhalation toxicokinetics study in 5 male volunteers, 1 x 6 h/d, at 12.5 and 25 ppm (1/8 or 1/4 of Camadian time-weighted average exposure value, TWAEV), with 1 wk break between exposures m-Xylene (≥ 99% purity) Ethylbenzene (purity 99%)	Principal verification and improvement of PBTK models for the time-course of exhaled unchanged parent (m-xylene, EB) and typical metabolite biomarkers (m-MHA, mandelic acid, MA) in urine. Exhaled parents: Concentrations approaching steady state towards end of exposure period. Doubling exposure concentrations roughly produced 2-fold concentrations. Comparable levels for m-xylene and ethylbenzene Urinary metabolites: Concentrations approaching steady state 24 h p.a. Doubling exposure concentrations roughl y produced 2-fold concentrations. Comparable levels for m-MHA and MA	None	(Marchand et al., 2015)
Metabolism & Excretion			
Inhalation			
Metabolism study, inhalation 3 h or 3 h/1 h break/4 h m-, p-Xylene, purity not reported	Demonstration of the formation of methylhippuric acids as metabolites of m- and p-xylene	None	(Ogata et al., 1970)

SUMMARY OF STUDIES ON TOXICOKINETICS, HUMAN DATA			
Method/Study Type	**Results**	**Remarks**	**Source**
Metabolism study, inhalation 8 h at ~0.2 mg/L or ~0.4 mg/L to o-,m-, p-xylene alone or to a 1:1:1 mixture of these isomers by male volunteers Purity not reported	Pulmonary retention ~ 60-70% Main metabolite fraction (95-99%) consists of methylhippuric acids (MHA) MHA levels decrease strongly after end of exposure, ~70% excretion within 24 h, trace amounts observable after 4-5 d Minor metabolite fractions contain xylenols In the mixture, p-xylene was metabolised faster than the other two isomers.	None	(Šedivec and Flek, 1976)
Biomonitoring of 121 workers employed in dip-coating of metals Ambient air containing (8 h TWA GM/GSD): 0.8/3.9 ppm o-xylene, 2.1/3.37 ppm m-xylene, 0.9/3.66 ppm p-xylene, 0.8/2.26 ppm toluene, 0.9/3.22 ppm EB	Metabolites identified: Xylenes: MHA Toluene: Hippuric acid, Ethylbenzene: Mandelic acid, phenylglyoxylic acid Urinary MHA levels increased with some proportionality to ambient air concentration of the respective xylene isomer At the same ambient air concentration, p-xylene produced higher urinary levels of the corresponding MHA than the m- and o-isomers.	None	(Kawai et al., 1991)
Biomonitoring of 175 workers, cf. (Uchida et al., 1993) Ambient air containing (8 h TWA GM/GSD): 1.2/30.4 ppm o-xylene, 7.3/99.3 ppm m-xylene, 3.8/45.4 ppm p-xylene, 0.8 ppm toluene, 2.7 ppm ethylbenzene	Increase of MHA formation with TWA ambient air concentration confirmed (cf. (Kawai et al., 1991)). Smoking and drinking found to reduce urinary MHA levels	None	(Inoue et al., 1993)
Biomonitoring of 12 workers	Time of conversion to MHA: p (up to 6 h) < m (up to 18 h) < o (after 18 h); m-MHA present in over-proportionate amount	Conclusion of authors (m-xylene conversion is preferred over others) is not supported. Could be explained by faster metabolisation of p-xylene	(Miller and Edwards, 1999)
PBTK modelling combined with human data (acute inhalation of deuterated xylenes, 2 h) o-, m-, p-Xylene: 98%	Clearance: o: 116 ± 34 L/h m: 129 ±33 L/h p: 117 ± 23 L/h $T_{1/2}$ o: 38.5 ± 18.2 h m: 33.0 ± 11.7 h p: 30.3 ± 10.2 h	No real difference between isomers, m-xylene has slightly higher clearance, high interindividual variability	(Adams et al., 2005)
Toxicokinetics in 6 male volunteers following inhalation exposure, for 4 h Xylene, composition and purity not reported,	Excretion modelled to follow biphasic pattern Wide variability in blood and urine levels of xylene, methylhippuric acid, and ethylbenzene.	Composition of test material unclear Reporting of results for EB ambiguous (two dose levels were	(Janasik et al., 2008)

SUMMARY OF STUDIES ON TOXICOKINETICS, HUMAN DATA			
Method/Study Type	**Results**	**Remarks**	**Source**
200 mg/m^3, mean absolute dose received: 355.6 (296.2 – 459.2) mg Ethylbenzene, purity not reported, 20 – 200 mg/m^3	Not usable for quantitative risk assessment	tested, only one result reported	

In 2007, the US Agency for Toxic Substances and Disease Registry (ATSDR) concluded that *"xylenes, because of their lipophilic properties, are rapidly absorbed by all routes of exposure, rapidly distributed throughout the body, and, if not metabolized, quickly eliminated in exhaled air. In humans, absorption has been estimated as > 50% through the lungs following inhalation exposure and < 50% through the gastrointestinal system. In humans exposed by inhalation, up to 2% of the absorbed dose may be absorbed through the skin. The major pathway for metabolism involves mixed function oxidases in the liver, resulting mainly in the formation of isomers of methylhippuric acid that are eliminated in the urine [...]. Xylenes tend not to accumulate in the body, but they may be sequestered briefly in fat tissues due to their lipophilicity; elimination of xylene is slower in individuals with a greater percentage of body fat."* (ATSDR, 2007)

Below, some aspects with relevance to specific issues in this evaluation are further discussed.

7.9.1.3. Summary of toxicokinetics

7.9.1.3.1. Absorption

7.9.1.3.1.1. Oral

No reliable data are available that would allow quantification of oral absorption. The US ATSDR estimates < 50%, but the basis for this estimate is unclear (ATSDR, 2007). As a worst-case assumption in line with the REACH guidance, 50% absorption will be used when converting an external oral dose to a systemically available one, while in theory 100% would have to be used when converting a systemically available to an external oral dose (not relevant in the context of this dossier).

7.9.1.3.1.2. Inhalation

No reliable non-human data are available from which the percentage of xylene absorbed via inhalation could be estimated.

Available studies in humans lack complete mass balances. Estimates of the percentage of dose absorbed via inhalation therefore range from 60-100%. As a worst-case assumption, 60% absorption will be used when converting an external air concentration to a systemically dose following inhalation, while 95% will be used when converting a systemic dose to an external air concentration.

7.9.1.3.1.3. Dermal

Dermal absorption studies in humans are available only for m-xylene. (Engström et al., 1977) estimated a flux of 120 µg/cm^2/h, the basis for this estimate is, however, unclear and a complete mass balance is missing. (Kezic et al., 2001) estimated a flux of 300 µg/cm^2/h based on additional modelling assumptions which are not fully clear and therefore negatively impact on the reliability of this result. All of these studies likely underestimate dermal absorption.

The lead registrant by means of applying the QSAR model proposed by (ten Berge, 2009) calculated a worst-case estimate of 15% dermal absorption for all xylenes, but no

documentation was provided to clarify how this result was achieved (the said model does not predict an absorbed percentage directly).

(Ahaghotu et al., 2005) carried out an *in vitro* dermal absorption study in hairless rats exposed to an excess ("infinite") dose of (mixed?) xylene(s). A volume of 0.5 mL of 98% pure radiolabelled xylene was applied to an exposure area of 0.636 cm^2 for 8 h.

None of these studies fully represent the dermal absorption to be expected during real-life dermal exposure of workers or consumers. Therefore, a reasonable worst case scenario needs to be developed.

Given that with the exception of acute lethality studies no dermal toxicity studies are available for the xylene isomers, the eMSCA considered that a dermal absorption rate would be needed only for the purpose of judging the risk of dermal exposure based on systematic concentrations derived from oral or inhalation studies, but not vice versa.

In this sense, a reasonable worst-case estimate of dermal absorption should represent the highest amount reasonably assumed to be absorbed. The eMSCA found that the study by (Ahaghotu et al., 2005) was the most reliable to be used for this purpose and, being based on data, more suitable than the 100% default assumption suggested by the REACH guidance.

The content of xylene in all relevant compartments was reported as mean and standard deviation (SD) for the time-points of 0.25, 0.5, 1, 2, 3, 4, and 8 h. Due to rather low substance concentrations in the respective compartments, there was quite some variability. As a worst-case scenario was sought for, the eMSCA decided to

- use all compartments except the donor cell for the estimation (i.e. also the *stratum corneum* fraction was included),
- for any given time-point sum up the individual compartment contents expressed as mean plus three standard deviations to cover a high percentile of the probability distribution (for a normal distribution this would correspond to the 99.7th percentile), and
- in the end use the value for the time-point showing the highest sum for further risk assessment.

The respective values are given in Table 17.

Table 17

DISTRIBUTION OF XYLENE IN THE DIFFERENT COMPARTMENTS OF THE SKIN AND IN THE RECEPTOR CELL AS OBSERVED IN (AHAGHOTU ET AL., 2005)*

Time (h)	Receptor cell (%)	Stratum corneum (%)	Epidermis (%)	Dermis (%)	Lateral skin (%)	Sum (%)
0.25	0.012	0.009	0.01	0.008	1.599	1.638
0.5	0.023	0.030	0.006	0.022	3.099	3.180
1	0.021	0.049	0.009	0.045	0.951	1.075
2	0.079	0.069	0.014	0.11	0.930	1.202
3	0.137	0.114	0.017	0.107	0.012	0.387
4	0.193	0.107	0.013	0.182	0.080	0.575
6	0.231	0.093	0.018	0.120	0.047	0.509
8	0.342	0.103	0.016	0.083	0.052	0.596

* Based on the results for 6 replicates for each time point, all percentage values are mean + 3 SD, i.e. they represent the 99.7th percentile if normal distribution is assumed

As can be seen, the highest value of 3.180% was obtained at t = 0.5 h. Given the applied volume (0.5 mL), a density of 0.871 g/mL, and a purity of 98%, this amounts to a total absorbed mass of:

$$0.0318 \times 0.5 \text{ mL} \times 0.871 \text{ g/mL} \times 0.98 = 13.57 \text{ mg}$$

after 0.5 h. Based on an exposure area of 0.636 cm^2, a worst-case assumption of the dermal flux therefore amounts to:

$$13.57 \text{ mg}/0.636 \text{ cm}^2/0.5 \text{ h} = 43 \text{ mg/cm}^2/\text{h}$$

Further arguments that this value constitutes a worst-case scenario include *inter alia*:

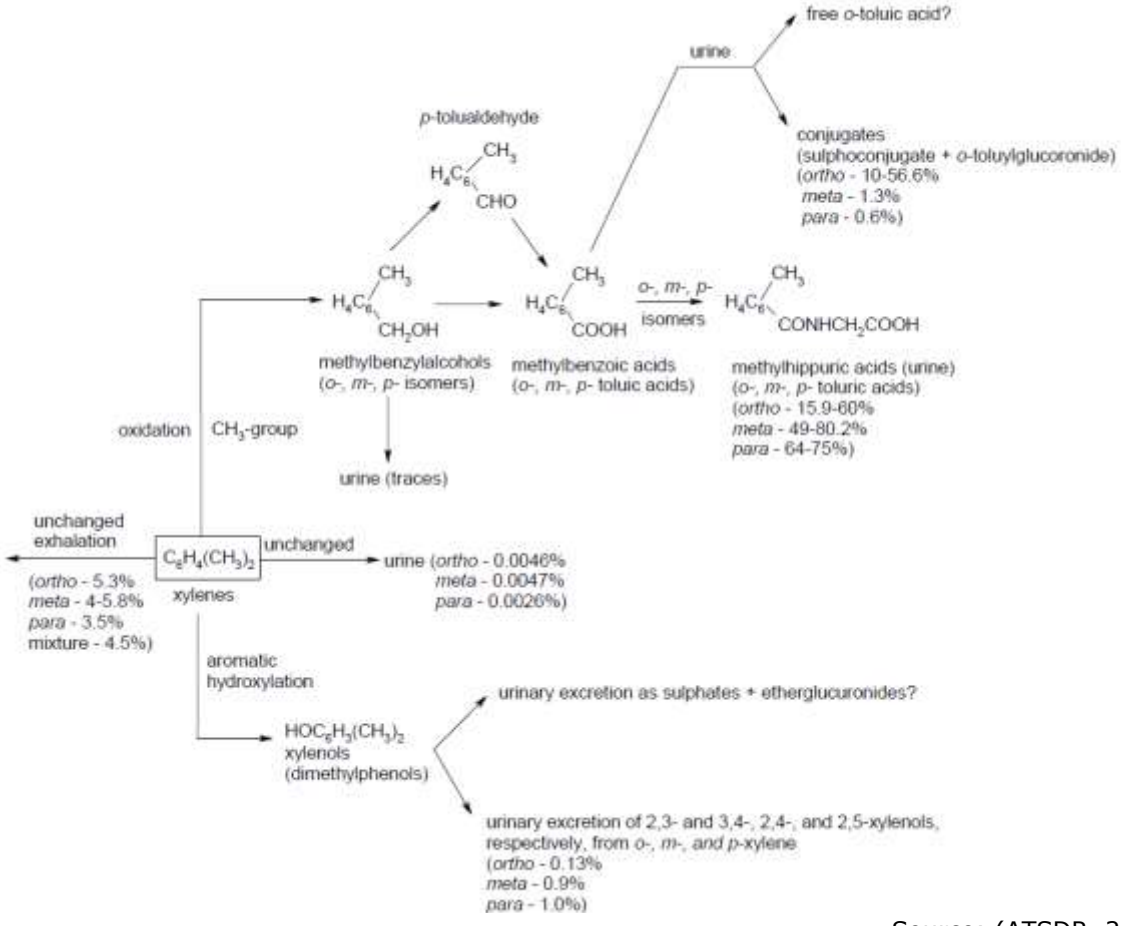
- with a total of 8 h, the exposure time was long enough to account for any impact of xylenes on the barrier function of the skin,
- the occlusive design of the study excluded volatilisation which can be expected for the real-life situation, and
- most of the real-life scenarios will not be "infinite dose" cases, i.e. the concentration gradient driving dermal absorption can be expected to be less steep.

7.9.1.3.2. Distribution

Xylenes are widely distributed and intermediately stored to some degree in fat tissue (e.g. perirenal fat).

7.9.1.3.3. Metabolism

Phase I reactions include oxidation to hydroxy-, carbonyl-, and ultimately oxocarbonyl derivatives, followed by phase II conjugations, most prominently with glycine to form the corresponding methylhippuric acids. A schematic overview is given in the figure below.



Source: (ATSDR, 2007)

In mixtures, isomers and ethylbenzene appear to compete for the same CYP enzymes and conjugation partners. The involvement of ADH suggests a possible mixture effects with ethanol and other solvents.

7.9.1.3.4. Excretion

The major fraction of absorbed xylene isomers is excreted in the form of the corresponding methylhippuric acids (ethylbenzene: mandelic acid) while a smaller fraction is exhaled unchanged. Some studies show the presence of corresponding dimethylphenols. (NTP, 1986) postulates route-specific differences, but the data base seems to be too weak to support this.

7.9.1.3.5. Differences between xylene isomers, ethylbenzene

Conjugation and excretion are fastest for p-xylene and ethylbenzene, followed by m-xylene and o-xylene. Competitive metabolism might lead to difficulties in reliably predicting blood levels from single isomers vs. mixed isomers. Potential sex-specific differences are not covered by the human database. Similar results as for the three xylene isomers have been reported for ethylbenzene (German MSCA, 2008).

7.9.2. Acute toxicity

Table 18

SUMMARY OF STUDIES ON ACUTE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Oral			
Acute oral toxicity, Wistar rats Application per gavage, undiluted, in corn or olive oil. Post-exposure period: 14 d Xylene (Purity: 19% o, 52% m, 24% p, ethylbenzene: not specified) Ethylbenzene: Purity: ≥ 98%	LD_{50} (xylene, male rats): 4300 mg/kg bw LD_{50} (ethylbenzene, male and female rats): 3500 mg/kg bw	Sparse documentation, no group dose levels/results given	(Wolf et al., 1956)
Acute oral toxicity, Wistar rats Application per gavage undiluted or in corn oil. Post-exposure period: 14 d m-Xylene, ethylbenzene (purity: not reported)	LD_{50} (m-xylene, male rats): 6677 (5404-8253) mg/kg bw LD_{50} (ethylbenzene, rats): 4734 (4413-5081) mg/kg bw	Sparse documentation, no group dose levels/results given	(Smyth et al., 1962)
Acute oral toxicity, Long-Evans rats Post-exposure period: 14 d Mixed xylenes (purity: not reported)	LD_{50}: 7.5-13.3 mL/kg (6450-11438 mg/kg bw)	Sparse documentation, no group dose levels/results given	(Hine and Zuidema, 1970)
Acute oral toxicity, single dose, oral gavage, rats, mice Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	Rats: Mortality at ≥ 4000 mg/kg bw LD_{50} = 3523 (2707-4587) mg/kg bw Mice: Mortality at 6000 mg/kg bw LD_{50} = 5627 (4675-6646) mg/kg bw (M) LD_{50} = 5251 (4583-6014) mg/kg bw (F)	None	(NTP, 1986)

SUMMARY OF STUDIES ON ACUTE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Acute oral neurotoxicity, Long-Evans rats, single gavage dose of 0-125-250-500-1000 mg/kg bw p-Xylene, purity not reported	Significant amplitude depression of flash-evoked potentials (FEP) at ≥ 250 mg/kg bw	None	(Dyer et al., 1988)
Dermal			
Acute dermal toxicity, NZW rabbits m-Xylene, ethylbenzene (purity: not reported)	LD_{50} (m-xylene, rabbits): 12211 mg/kg bw LD_{50} (ethylbenzene, rabbits): 15433 mg/kg bw	Sparse documentation, no group dose levels/results given. Inhaled concentrations are nominal, not analytically verified, i.e. LC_{50} might have been lower	(Smyth et al., 1962)
Acute dermal toxicity, NZW rabbits Xylene (purity: not reported)	LD_{50}: ~5.0 mL/kg (~4300 mg/kg bw)	Sparse documentation, no group dose levels/results given	(Hine and Zuidema, 1970)
Inhalation			
Inhalation: 4 h whole-body exposure Xylene (purity: not reported)	LC_{50}: 4670-8640 ppm	Sparse documentation, no group dose levels or individual group results are given	(Hine and Zuidema, 1970)
4 h Acute inhalation study in rats and cats 4 h Range-finding inhalation experiments in rats (actual dose ca. 0-2-4-8-16-32 mg/L) and dogs (actual dose ca. ca. 0-2-4-8 mg/L) Determination of odour threshold and sensory responses Xylene: 7.63% o-, 65.01% m-, 7.84 p-xylene, 19.27% ethylbenzene	4 h LC_{50}, male rats: 6700 (5100-8500) ppm All 4 cats died within 2 hr → LC_{50} (cat) << 9500 ppm Range-finders: ≥ ~4 mg/L or ~909 ppm caused slight incoordination in rats and lacrimation in dogs Odour threshold: ~1 ppm "Not objectionable" dose: 110 ppm	Density of mixed xylenes used in this study: 0.87 g/mL	(Carpenter et al., 1975)
Acute inhalation study in mice 1 x 6 h, 14 d observation period o-Xylene: purity 98% m-Xylene: purity 97% p-Xylene: purity 98%	o-Xylene: LC50 = 4595 ppm (4468-4744) m-Xylene: LC50 = 5267 ppm (5025-5490) p-Xylene: LC50 = 3907 ppm (3747-4015) 1.5-fold values when extrapolated to 4 h exposure: o-Xylene: LC50 = 6893 ppm (6702-7116) m-Xylene: LC50 = 7901 ppm (7538-8235) p-Xylene: LC50 = 8235 ppm (5621-6023)	None	(Bonnet et al., 1979)

SUMMARY OF STUDIES ON ACUTE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Acute inhalation study rats 1 x 6 h, 14 d observation period o-Xylene: purity 98% m-Xylene: purity 97% p-Xylene: purity 98%	o-Xylene: LC_{50} = 4330 ppm (4247-4432) m-Xylene: LC_{50} = 5984 ppm (5796-6181) p-Xylene: LC_{50} = 4591 ppm (4353-5049) 1.5-fold values when extrapolated to 4 h exposure: o-Xylene: LC_{50} = 6495 ppm (6371-6648) m-Xylene: LC_{50} = 8976 ppm (8694-9272) p-Xylene: LC_{50} = 6887 ppm (6530-7574)	None	(Bonnet et al., 1982)
Acute inhalation, 4 h, rat, 14 d post-exposure observation period p-Xylene, purity not reported	LC_{50}: 6247 ppm (combined) 5922 ppm (F)/6580 ppm (M)	None	[redacted] 1986)
Acute inhalation, female SD rats, 4 h exposure, 24 h post-exposure observation period Xylene, purity 99%, composition: o-, m-, and p-xylene, relative content not specified	Not taken for risk assessment due to insufficient post-exposure observation	None	(Lundberg et al., 1986)
Acute inhalation (4 h) neurotoxicity, Long-Evans rats p-Xylene, purity not reported	Significant amplitude depression of Flash-Evoked Potentials (FEP) at ≥ 1600 ppm	None	(Dyer et al., 1988)
Acute inhalation (OECD 403), rat, 4 h, ~40,000 mg/m³ or 9094 ppm p-Xylene, purity 98%	Time until first lethality (LT_0) = 0.5 h	None	(Klimisch et al., 1988)
Acute inhalation neurotoxicity test, male Wistar rats (ca. 3000 ppm analytical), mice, (ca. 2600 ppm analytical), 6 h o-, m-, p-Xylene (95%)	Clear effect on rotarod performance in rats Strong depression of respiratory rate in mice	None	(Korsak et al., 1990)
Acute inhalation hepatotoxicity study in male F344 rats at 0 or 1600 ppm, 6 h/d for 1 or 3 d p-Xylene (purity ≥ 99.0%)	No histopathological evidence of hepatic damage Little or no effect on the serum levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, ornithine carbamyl transferase, alkaline phosphatase, and total bilirubin. Increase in relative liver weight on d 1 post-exposure (both 1 and 3 d exposure) P450 increased by both p-xylene exposure regimens on d 1 post-exposure; returned to control levels by d 3 following single and by d 2 following 3-d exposure	None	(Simmons et al., 1991)

SUMMARY OF STUDIES ON ACUTE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Acute inhalation toxicity in, male Wistar rats (4 h/d) and , Balb/C mice (6 h/d, sex not reported), for 1 d m-Xylene (purity not reported)	Concentration-dependent disturbance of rotarod performance in rats, EC50 = 1982 (15430-2565) ppm Concentration-dependent increase in motor activity in rats, LOAEC = 500 ppm Concentration-dependent decrease in respiratory rate in mice, EC_{50} = 1360 ppm/5984 mg/m^3	None	(Korsak et al., 1993)
Acute inhalation nephrotoxicity study in rats, 4 h, 3000 ppm o-Xylene, assumed 99% pure	Increase in urinary γ–glutamyl transferase, alkaline phospatase, N-Acetyl-beta-D-glucosaminidase, glucose and in urinary output	None	(Morel et al., 1998)

Table 19

SUMMARY OF STUDIES ON ACUTE TOXICITY, HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Inhalation			
Tests of numerical ability, reaction time (simple and choice), short-term memory, and critical flicker fusion Series 1: 15 males, 0-435-1300 mg/m^3 (~0-100-300 ppm), for 70 min Series 2: 8 males, 0-1300 mg/m^3 (~300 ppm) including 30 min work at 100 W , 1 x for 70 min Xylene (p-xylene 12.8%, o-xylene 12.1%, m-xylene 54.4%), and ethylbenzene 20.7%.	Series 1: No effect on behaviour. total uptake of xylene estimated to be on average 180/540 mg, respectively Series 2: Evidence of performance decrement in three of the performance tests. Physical work induced an increase in the total uptake up to an average of 1,200 mg NOAEC (70 min) = 100 ppm	None	(Gamberale et al., 1978)
Acute inhalation, human, 4 h (3 h in the morning, 40 min break, 1 hour in the afternoon) exposure to TWA of 8.2 µmol/L (869 mg/m^3 or ~200 ppm) 1.: Constant concentration 2.: Fluctuating concentration with peaks (up to ~400 ppm) m-Xylene, purity 95%	Impairment of body balance and audiomotor coordination after peak exposures	None	(Savolainen et al., 1984)
Acute inhalation CNS toxicity study in 16 male volunteers, 2.84 mmol/m^3 (~300 mg/m^3 or 68 ppm), for 4 h p-Xylene, purity not reported	Simple reaction time, short term memory, and choice reaction time at 0, 1 and 4 h into exposure were all unaffected	Key study for acute DNEL derivation (NOAEC)	(Olson et al., 1985)

SUMMARY OF STUDIES ON ACUTE TOXICITY, HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Acute inhalation neurotoxicity study in 9 male volunteers, 3 h exposure – 40 min break – 40 min exposure 1.: Constant conc.200 ppm 2.: Fluctuating conc. with peaks (135-400 ppm) for first 20 min, then constant at 200 ppm m-Xylene, purity 95%	Decrease in Visually Evoked Potentials (Flash VEPs) upon physical activity, no effects on Brain-stem Auditory Evoked Potentials (BAEP)	None	(Seppalainen et al., 1989)
Acute inhalation neurotoxicity study in 10 male volunteers, 100 ppm, 4 h Xylene, composition/purity not reported	Effects on Simple Reaction Time (SRT) and Choice Reaction Time (ChRT)	Key study for acute DNEL derivation (LOAEC)	(Dudek et al., 1990)
Two inhalation neurotoxicity studies in male volunteers, TWA concentration of 200 ppm, either at a constant rate or fluctuating with peaks (up to ~400 ppm), sedentary or under physical activity (100 W) m-Xylene, 95%	400 ppm peaks decreased body sway and prolonged simple visual reaction times in sedentary subjects , and auditory choice reaction times when combined with physical exercise (200 ppm: no effect)	None	(Laine et al., 1993)

7.9.2.1. Summary of acute toxicity

Experimental data are available for all isomers for the inhalation route, for m-xylene, ethylbenzene and mixed xylenes also for the oral and dermal routes of administration.

While the available data base supports the CLH as Acute Tox. 4 for the inhalation route as well as no classification for acute oral toxicity, the rationale behind the existing CLH for xylenes (isomers and mixed) as Acute Tox. 4 for the dermal route is not clear.

Non-lethal toxicity of xylene isomers or mixed xylene can be observed in the form of acute neurobehavioural effects. In rats, (Dyer et al., 1988) observed a significant amplitude depression of flash-evoked potentials (FEP) after single oral gavage administration of ≥ 250 mg/kg bw or single inhalation exposure for 4 h to ≥ 1600 ppm p-xylene. (Korsak et al., 1990) noted a decrease in rotarod performance in rats and a strong depression of the respiratory rate after inhalation of ca. 3000 ppm (rats) and 2600 ppm (mice) with all xylene isomers.

In addition, a number of experiments (Dudek et al., 1990; Gamberale et al., 1978; Laine et al., 1993; Olson et al., 1985; Savolainen et al., 1984; Seppalainen et al., 1989) have studied xylene-related neurobehavioural effects related to learning performance, reaction time or motor coordination in humans after single acute exposure. (Dudek et al., 1990) observed effects of mixed xylene on simple and choice reaction time after a 4-h exposure at 100 ppm, while (Olson et al., 1985) reported 68 ppm as a NOAEC for p-xylene with respect to these effects.

Both the data in animals and humans suggest the need for classification/labelling for STOT SE 3, H336 ("May cause drowsiness or dizziness").

The value of 68 ppm is taken forward to risk assessment as the most relevant Point of Departure (PoD) for acute effects after single inhalation exposure in humans (cf. section 7.9.11.1).

7.9.2.2. Irritation/corrosion

Table 20

SUMMARY OF STUDIES ON IRRITATION/CORROSION IN NON-HUMANS			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Skin			
Skin irritation in rabbits Skin: Repeated exposure of ear and belly for 10-20 exposures over 2-4 wk Xylene (purity: 19% o, 52% m, 24% p, ethylbenzene: not specified) Ethylbenzene: Purity: ≥ 98%	Xylene: Moderate to strong irritation, "moderate necrosis" (development of oedema and superficial necrosis,; this resulted in a "chapped" appearance and exfoliation of large patches of skin) Ethylbenzene: Moderate to strong irritation, "moderate necrosis"	Evidence of skin irritation, but not clear regarding corrosion Unclear for eye irritation/corrosion	(Wolf et al., 1956)
Skin irritation in rabbits m-Xylene, ethylbenzene, purity/composition not reported	Indications of skin irritation, but results are not usable for classification and labelling due to lack of sufficient information	None	(Smyth et al., 1962)
Skin irritation in NZW rabbits Xylene, purity/composition not reported	Suggests skin irritation, but results cannot be directly transferred to current classification and labelling (only mean prinmary irritation index is given) Interpreted by registrant as irritant	None	(Hine and Zuidema, 1970)
Skin irritation in NZW, undiluted, semi-occlusive p-Xylene, purity 99%	Irritating, not corrosive	Only registrant's summary available, no single animal scores or detailed effect description Unclear whether CLP classification threshold for irritation is exceeded	(Chevron Chemical Company, 1973)
Skin irritation in NZW rabbits, occlusive (abraded and intact) o-Xylene, purity not reported	Irritating, not corrosive	Only registrant's summary available, no single animal scores or detailed effect description Unclear whether CLP classification threshold for irritation is exceeded	([redacted] 1983a)
Determination of non-irritant concentrations ("limit concentrations") in rabbit skin o-, m-, p-Xylene, ethylbenzene, purity not reported	All tested substances were below Dir 83/467/EEC classification thresholds at ≤ 50% dilution	Reliable with restrictions, only limit concentrations, no individual scores are given	(Jacobs et al., 1987)
Mechanistic skin irritation study in F344 rats, 1h exposure m-Xylene, purity not reported	Interleukin-1alpha (IL-1α) and inducible nitric oxide synthase levels were increased immediately and 4	None	(Gunasekar et al., 2003)

SUMMARY OF STUDIES ON IRRITATION/CORROSION IN NON-HUMANS			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
	hours after exposure, respectively		
Skin irritation in vivo, hairless rats 15 µL on ~3 cm^2, for 4 d, every 2 h for 8 h/d, unocclusive Xylene (purity 98%)	Strong increase in Trans-Epidermal Water Loss (TEWL); erythema score 2.0 Histopathology: stratum corneum swelling and disruption, infiltration of markers of inflammation Almost 4-fold increase in blood IL-1α and 5-6-fold increase in skin TNFα	Identity of test material unclear	(Ahaghotu et al., 2005)
Skin irritation in vivo, hairless rats Single, occlusive, 1 h Repeated, unocclusive, 15 µL on ~ 3 cm^2, for 4 d, every 2 h for 8 h/d m-Xylene, purity not reported	Strong increase in TEWL IL-1α elevated 2.5- and 3.8-fold (occlusive/unocclusive) TNFα elevated about 2.4- and 6.0-fold (occlusive/unocclusive) MCP levels in skin increased ~1.7- and 1.8-fold (occlusive/unocclusive)	Authors' conclusion: Long-term exposure to small amounts can induce more skin irritation and cytokine response than occlusive exposure	(Chatterjee et al., 2005)
Skin irritation in pigs, single (1 d) and repeated (4 d) exposure o-Xylene, ethylbenzene, purity > 98%	No erythema, only slight oedema, no significant difference vs. control regarding epidermal thickness or number of epidermal layers.	None	(Muhammad et al., 2005)
Eye			
Eye irritation in rabbits Two drops of liquid applied to one eye, no washing, observations at 3 min, 1 h, 1 d, 2 d, 7 d) Xylene (Purity: 19% o, 52% m, 24% p, ethylbenzene: not specified) Ethylbenzene: Purity: ≥ 98%	Xylene: slight conjunctival irritation, very slight, transient corneal injury Ethylbenzene: slight conjunctival irritation, no corneal injury	Unclear results for eye irritation/corrosion	(Wolf et al., 1956)
Eye irritation in rabbits m-Xylene, ethylbenzene, purity/composition not reported	Indications of eye irritation, but results are not usable for classification and labelling due to insufficient information	None	(Smyth et al., 1962)
Eye irritation in NZW rabbits Xylene, purity/composition not reported	Indications of eye irritation, but results are not directly usable for classification and labelling due to intransparent scoring system. Interpreted by registrant as irritant	None	(Hine and Zuidema, 1970)

SUMMARY OF STUDIES ON IRRITATION/CORROSION IN NON-HUMANS			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Eye irritation in NZW rabbits, unwashed eye Volume/concentration not reported o-Xylene, purity not reported	No effects on cornea and iris, Conjunctival redness and swelling observed, but scores were below classification threshold All effects reversed by 7 d post-exposure	None	[redacted] 1983d)
Eye irritation in NZW rabbits, washed eye Volume/concentration not reported o-Xylene, purity not reported	No effects on cornea and iris Conjunctival redness and swelling observed, but scores were below classification threshold All effects reversed by 7 d post-exposure	Only registrant's summary available, no single animal scores are given Unclear whether CLP classification threshold for irritation is exceeded	([redacted] 1983e)
Respiratory tract			
Mouse sensory irritation test (1 min exposure) Mixed xylenes: 7.63% o-, 65.01% m-, 7.84 p-xyene, 19.27% ethylbenzene	Mouse: Depression of respiratory rate at ≥ 1300 ppm	None	(Carpenter et al., 1975)
Sensory irritation after inhalation in male Swiss OF_1 mice, ca. 5 min exposure time o-Xylene, ethylbenzene. "high purity"	RD_{50} (concentration corresponding with 50% decrease in respiratory rate): Ethylbenzene: 1432 ppm o-xylene: 1400 ppm	None	(De Ceaurriz et al., 1981)
Respiratory tract irritation in mice, 7700 mg/m^3 (~1750 ppm) analytical o-Xylene, purity not reported	"Very slight to slight respiratory tract irritation"	Only registrant's summary available, no single animal scores or detailed effect description Unclear whether CLP classification threshold for irritation is exceeded	[redacted] 1983b)
Respiratory tract irritation in mice, 8725 mg/m^3 (~1980 ppm) analytical p-Xylene, purity not reported	"Slight to severe respiratory irritation"	Only registrant's summary available, no single animal scores are given Unclear whether CLP classification threshold for irritation is exceeded	([redacted] 1983c)

Table 21

SUMMARY OF STUDIES ON IRRITATION/CORROSION IN HUMANS			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Inhalation irrritation test in 150 male human volunteers, 430-860-1720 mg/m^3 (ca. 100-200-400 ppm), for 30 min Xylene: 7.63% o-, 65.01% m-, 7.84 p-xylene, 19.27% ethylbenzene (as in Carpenter et. al. 1975)	No significant dose-related effects on subjective reports of irritation, respiratory rate, eye blinking rate or performance of behavioural tests		(Hastings, 1984)
Analysis of symptoms in 107 xylene-exposed workers (107 M, 86 F)	Increased prevalence of subjective reports of irritation symptoms (CNS, eyes, skin, throat), with only limited dose correlation No effects on haematopoietic system	Quality of exposure measurements cannot be judged	(Uchida et al., 1993)
Two case reports of ocular injury after exposure to xylene	Strong ocular injury after eyes were exposed to paint. Impossible to judge whether xylene was the responsible agent	Not usable for risk assessment	(Ansari, 1997)
Acute inhalation study in 28 male and 28 female volunteers at 50 ppm, 2 h m-Xylene, purity not reported	Both men and women showed signs of irritation (subjective self-reporting on graded scale) Slight decrease in pulmonary function (Forced Expiratory Volume in 1 second, FEV_1; Forced Vital Capacity, FVC) Women appear to be slightly more sensitive to these effects No effects on acoustic rhinometry, markers of inflammation or blinking frequency	None	(Ernstgård et al., 2002)

7.9.2.3. Summary of irritation/corrosion

Based on the available data, individual xylene isomers, ethylbenzene and mixed xylenes are considered unlikely to possess corrosive properties.

All xylene isomers possess CLH as Skin Irrit. 2, therefore no further action is required despite the fact that the available data mostly consist of very old studies with insufficient reporting and/or scoring systems not directly compatible with the GHS/CLP system.

With respect to eye irritation, Draize tests (with and without washing of the treated eyes) are available for o-xylene [redacted] 1983d; [redacted] 1983e). In both of these studies, no effects on cornea and iris were observed. Effects on the conjunctiva were below CLP classification thresholds and were fully reversed by 7 d post-exposure at the latest. Studies available for mixed xylenes (Hine and Zuidema, 1970; Wolf et al., 1956) and m-xylene (Smyth et al., 1962) provide some indication of at least mild eye irritation, but do not allow to conclude on whether classification thresholds were exceeded. All in all, these studies are sufficient to exclude a potential for severe eye damage (CLP Cat. 1). In the view of the eMSCA, they also do not give rise to a sufficiently strong concern justifying initiation of CLH for eye irritation (CLP Cat. 2).

For respiratory tract irritation, however, the available data in animals (depression of respiration rate in mice in [redacted]

[redacted], 1983b; [redacted] 1983c) indicate a possible need for classification as STOT SE/H335. Studies in humans (Ansari, 1997; Ernstgård et al., 2002; Hastings, 1984; Uchida et al., 1993) have shown that respiratory irritation (in the form of sensory irritation) can be observed in humans exposed to xylenes, too. However, most of these findings were based on subjective reporting and could not be objectivated by measurements (beyond a slight effect on pulmonary function reported in (Ernstgård et al., 2002) at 50 ppm, which was not associated with effects on rhinometry, inflammation markers or blinking rate and is therefore not considered as a suitable starting point for acute risk assessment).

7.9.3. Sensitisation

Table 22

SUMMARY OF STUDIES ON SKIN SENSITISATION			
Method/Study substances **Type/Test**	**Results**	**Remarks**	**Source**
Human maximisation patch test in 25 prisoners , 1 mL undiluted Induction: 5 x (24 h pretreatment with SDS followed by 48 h patch exposure of undiluted test substance) Challenge: 1 h pretreatment with SDS followed by 48 h exposure with 25% dilution Xylene, composition and purity not reported	Negative, but test may not be sensitive enough: - Test design apparently produces baseline inflammation reaction; xylene not identified as irritant - Challenge with 25% dilution - 90% of the "test collective" were black prisoners, the author notes that white (Caucasian) individuals with less pigmented skin might be more sensitive Supporting evidence that mixed xylene does not possess strong skin sensitisation properties Interpretation as proving absence of sensitising potential in humans taken over by ECVAM (European Commission, 2008) and ICCVAM (ICCVAM, 2009)	Non-compliant with today's EU ethical standards Used in validation of the LLNA test for regulatory purposes	(Kligman, 1966)
LLNA Xylene, purity/composition not reported	Positive EC_3 not reported in publication, but apparently 95.8% acc. to RIFM DB/(Urbisch et al., 2015)	None	(Basketter et al., 1996)
Expert statement	Weight-of-Evidence justification that xylenes are non-sensitising	None	(Basketter and Kimber, 2010)
In vitro tests for skin sensitisation: Direct Peptide Reactivity Assay (DPRA) KeratinoSens© LuSens MUSST mMUSST h-CLAT Xylene, purity 98.5%, composition not given	All tests reported negative	None	(Bauch et al., 2011; Bauch et al., 2012; Urbisch et al., 2015)

7.9.3.1. Summary of sensitisation

Both ECVAM and ICCVAM consider – apparently based on the HMT results reported in (Kligman, 1966) – that the positive LLNA test result for (mixed) xylene is in fact a false positive. For this reason they have used xylene as an LLNA performance standard for identifying tests performing better than the LLNA (European Commission, 2008; ICCVAM, 2009).

An expert statement is available (Basketter and Kimber, 2010) in which a Weight-of-Evidence approach is used to demonstrate the absence of a skin sensitisation potential of the xylenes using the following reasoning:

- Despite its wide-dispersive use and in contrast to irritation, no clinical reports of humans sensitised by xylenes were found by the authors.
- There are also no known structural alerts triggering concern for a sensitisation potential of xylenes.
- Human predictive test data demonstrated no sensitisation of humans in the Human Maximisation Test (HMT, (Kligman, 1966)).
- An LLNA test with 100% xylene resulted in a Stimulation Index (SI) of 3.1, barely above the cutoff for classification of 3.0. The authors have reviewed the database for xylene and concluded that xylene was a false positive.
- In addition the eMSCA has noted that a number of in vitro tests linked to the OECD Adverse Outcome Pathway (OECD, 2012) for skin sensitisation have been performed (Bauch et al., 2011; Bauch et al., 2012; Urbisch et al., 2015). These tests - all being negative - may be seen as a strong indicator that xylenes are unlikely to cause skin sensitisation via the aforementioned AOP. Strictly speaking, this does, however, not completely rule out the possibility that xylenes could be skin sensitisers via a different, as yet unknown, mechanism/AOP.

In summary, with remaining uncertainties acknowledged, the eMSCA considers the totality of information sufficient to conclude that xylenes most likely are no or only very weak skin sensitisers.

- No data on respiratory sensitisation are available for the xylenes. Given that all known respiratory sensitisers are also skin sensitisers (and xylenes are not considered to be) and that no reports on respiratory hypersensitivity as a consequence of exposure to xylenes have been found, the eMSCA concludes that there is currently no specific concern that xylenes could be respiratory sensitisers.

7.9.4. Repeated dose toxicity

Table 23

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Oral			
Subacute			
Subacute oral gavage study in rats, 14 d 0-125-250-500-1000-2000 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	Mortality from 2000 mg/kg bw/d Dose-related decrease in body weight of male, but not female rats, > 10% only at the highest dose NOAEL = 1000 mg/kg bw/d	Only macroscopic pathology performed	(NTP, 1986)
Subacute oral gavage study in mice, 14 d 0-250-500-1000-2000-4000 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	Mortality at 4000 mg/kg bw/d Prostration and shallow breathing during wk 1 at 2000 mg/kg bw/d NOAEL = 1000 mg/kg bw/d	Only macroscopic pathology performed	(NTP, 1986)

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Subacute oral gavage study in rats, 10 d, 0-250-1000-2000 mg/kg bw/d o-, m-, and p-Xylene, purity 99%	Body weight gain decreased by 5-10% at 2000 mg/kg bw/d for all isomers Effects on absolute and relative liver weight at ≥ 1000 mg/kg bw/d NOEL = 250 mg/kg bw/d NOAEL = 1000 mg/kg bw/d Further effects on thymus (o-, m-xylene), spleen, and brain (p-xylene) weight in different treatment groups, but mostly slight and without clear dose-related trend	Only macroscopic pathology performed	(Condie et al., 1988)
Subchronic			
Repeated dose oral toxicity study in female rats, gavage, 1/d, 5d/wk, 6 mo Ethylbenzene: Purity: ≥ 98%	Increase in liver and kidney weight with "slight" histopathological changes at ≥ 408 mg/kg bw/d	None	(Wolf et al., 1956)
Subchronic hepatotoxicity, diet, aging rats, 1, 2, 3 or 6 mo, 200 mg/kg feed o-Xylene, purity 99%	Changes in hepatocyte ultrastructure (vacuoles, surface invaginations) observed with all compounds and in both study segments Adversity of effects unclear	None	(Bowers et al., 1982)
Subchronic (13-wk) oral gavage study in rats, 13 wk, 5 d/wk 0-62.5-125-250-500-1000 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	Body weight decrease in both sexes NOAEL (> 10% bw reduction) = 500 mg/kg bw/d	None	(NTP, 1986)

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Subchronic (13-wk) oral gavage study in mice 0-125-250-500-1000-2000 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	Clinical signs (weakness, lethargy, short and shallow breathing, unsteadiness, tremors, paresis) at 2000 mg/kg bw/d Body weight gain decreased by > 5% at 2000 mg/kg bw/d Mortality at 2000 mg/kg bw/d	None	(NTP, 1986)
Subchronic oral gavage study in rats, 90 d 0-150-750-1500 mg/kg bw/d Xylene, composition: 17.6% o-, 62.3% m-/p-xylene, 20% ethylbenzene	Decreased body weight gain in males at 1500 mg/kg bw/d Increase in absolute and relative liver and kidney weight at ≥ 750 mg/kg bw/d Dose-related slight increase/exacerbation in incidence of nephropathy in females Adversity of these findings unclear NO(A)EL = 150 mg/kg bw/d	None	(Condie et al., 1988)
Chronic			
Combined chronic and carcinogenicity oral gavage study in rats, 103 wk, 5 d/wk 0-250-500 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	Decreased survival vs. control in males from both treatment groups, significant at 500 mg/kg bw/d NOAEC = 250 mg/kg bw/d	None	(NTP, 1986)
Combined chronic and carcinogenicity (2-yr) oral gavage study in mice 0-500-1000 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	Clinical signs (hyperactivity) at 1000 mg/kg bw/d (acute effect)	None	(NTP, 1986)
Inhalation			
Subacute			
Repeated dose vapour inhalation study in rats, guinea pigs, monkeys, and dogs, 8 h/d, 5 d/wk, 6 wk to ~763 ppm o-Xylene, purity not reported	High dose, 6 wk: mortality on days 2 and 3 Increase in leukocytes, potential effect on bw Relation to treatment unclear, no control groups present	Unreliable due to insufficient reporting Not used for risk assessment	(Jenkins et al., 1970)
Subacute inhalation enzyme induction study in male Wistar rats, 2 wk, 5 d/wk, 6 h/d 2.0-16.1-30.3 µmol/L (equivalent to 50-400-750 ppm) m-Xylene, purity not reported	Increase in brain NADPH-diaphorase and azoreductase levels and cerebral RNA NOEC = 50 ppm/LOEC = 400 ppm Decrease in cerebral glutathione activity already at 50 ppm (LOEC)	None	(Savolainen and Pfäffli, 1980)

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
	Adversity of these effects cannot be established		
Subacute inhalation test in rats 2000 ppm for 3 d, 6 h/d 6 rats/group o-, p-Xylene: 99%, m-xylene: 98.5%, xylene: o: 2%/m: 64%/p: 10% ethylbenzene: 23%	Endpoint: changed neurotransmitter levels in different nervous tissues LOAEC 2000 ppm	Limited set of parameters, differences between isomers	(Andersson et al., 1981)
Subacute (30-d) inhalation study in male SD rats 0-200-400-800 ppm Xylene, composition and purity not reported	Acetylcholine levels in striatum and whole brain decreased and brain glutamine levels increased at 800 ppm	Questionable reliability due to lack of clear dose response	(Honma et al., 1983)
Subacute inhalation study in mice, 4 d, 6 h/d 0-600-1000 ppm p-Xylene, purity unknown	No effect on serum aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase activities, Significant increase in total P450 levels in the liver	Only abstract available Effect levels of pure p-xylene unclear	(Selgrade et al., 1993)
Subacute inhalation neurotoxicity study in rats, 6 h/d, 5 d/wk for 4 wk 0-100 ppm Battery of neurobehavioural tests: Radial maze test 1 wk pre- and on days 14-18 post-exposure; open-field activity on day 8 pre- and on day 25 post-exposure; passive avoidance on days 39-48 post-exposure;Hot-plate test on days 50 and 51 post-exposure Active avoidance on days 54 and 60 post-exposure. m-Xylene, purity not reported	No impact on radial maze performance Significantly higher spontaneous locomotor activity in the open field, impaired passive avoidance learning and significantly longer paw-lick latencies 24 h after footshock (but no significant impact without shock). Acquisition, but not retention, of the two-way active avoidance response significantly impaired	None	(Gralewicz and Wiaderna, 2001)
Subacute inhalation ototoxicity study in rats, 3 wk, 6 h/d, 5 d/wk 1800 ppm o-, m-, p-Xylene methylhippuric acids (MHAs) mercapturic acids (MBAs)	Among the three isomers, only p-xylene was cochleotoxic at the tested dose level. A 39-dB permanent threshold shift was obtained over the tested frequency range from 8 to 20 kHz. Outer hair cells were largely injured, no significant morphological change within spiral ganglia	isomer-specific difference in effect or potency	(Maguin et al., 2006)

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Subchronic			
Repeated dose vapour inhalation study in rats, guinea pigs, monkeys, and dogs, 90-127 d continuous exposure to ~77 ppm) o-Xylene, purity not reported	Increase in leukocytes, potential effect on bw Unclear whether relation to treatment, no control groups present	Not reliable due to lack of sufficient reporting Not used for risk assessment	(Jenkins et al., 1970)
Subchronic inhalation (6 h/d, 5 d/wk, 13 wk), rats, dogs, 0-180-460-810 ppm) Xylene: 7.63% o-, 65.01% m-, 7.84 p-xylene, 19.27% ethylbenzene	Rats and dogs: Under the limited scope of this study, 810 ppm or ~3500 mg/m^3 was the NOAEC in both species	Reliable with restrictions only: no GLP, no details of animal husbandry, no single animal data etc.	(Carpenter et al., 1975)
Subchronic inhalation study in male rats, 6 h/d, 5 d/wk 1.) 0-1000 ppm for 3 mo 2.) 0-100 ppm for 6 mo m-Xylene, 95%	Decreased rotarod performance in both experiments Decreased spontaneous motor activity after 100 ppm x 6 mo At 1000 ppm x 3 mo, also slight decrease in lymphocytes and increase in monocytes of unclear significance LOAEC = 1000 ppm (3 mo) LOAEC = 100 ppm (6 mo)	No histopathology performed No dose without effect	(Korsak et al., 1992)
Subchronic inhalation study in rats, 3 mo, 5 h/d, 6 h/wk 0-50-100 ppm m-Xylene, purity not reported	Significant decrease in Hb, RBC and WBC (all < 10%), significant decrease in rotarod performance at 1, 2 and 3 months at 100 ppm, significant decrease in latency of the paw-lick response (plate behaviour) at 50 ppm NOAEC < 50 ppm LOAEC = 50 ppm	Key study for chronic DNEL derivation	(Korsak et al., 1994)
Subchronic inhalation study in Wistar rats, 3 mo, 5 h/d, 6 h/wk Tests on spontaneous neocortical spike and wave discharges (SWD) and spatial learning in an eight-arm radial maze. SWD activity was assessed on the basis of the number and duration of SWD bursts in one-hour EEG recordings performed before the exposure, on day 28, 56 and 84 of exposure, and then on day 14, 28, 42, and 84 post-exposure. 0-100-1000 ppm m-Xylene, purity unknown	Learning deficit in maze test two months post-exposure at 1000 and 100 ppm Development of the age-related SWD activity significantly retarded LOAEC = 100 ppm	None	(Gralewicz et al., 1995)
Subchronic inhalation neurotoxicity study in male SD rats, 6 h/d, 6 d/wk, 13 wk	p-Xylene: Moderate to severe ototoxicity in rats exposed at 900 and 1800 ppm. Body weight gain reduction at ≥ 900 ppm	Isomer-specific difference in effect or potency	(Gagnaire et al., 2001)

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, NON-HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Morphological investigations 8 wk post-exposure (vs. pre-exposure values) 450-900-1800 ppm o-, m-, p-Xylene, purity > 99%	Increased auditory thresholds observed at 2, 4, 8 and 16 kHz in rats exposed to 1800 p-xylene. Auditory threshold shifts (35 to 38 dB) did not reverse after eight weeks of recovery. Moderate and severe loss of outer hair cells of the organ of Corti occurred in animals exposed to 900 and 1800 ppm p-xylene respectively. No ototoxicity for other isomers NOAEC (p-xylene): 450 ppm NOAEC (m-,o-xylene): 1800 ppm	LOAEC of 900 ppm corresponds to 4 mg/L, which is below the classification threshold for STOT RE 2 Assuming 24 h/d 7 d/wk exposure and extrapolating to chronic exposure results , a human DNEL of 2 ppm or 8,5 mg/m^3 results	
Subchronic inhalation study in rats, 5 h/d, 6 d/wk, for 13 wk + 8 wk post-exposure period 200-400-600-800 ppm (ethylbenzene) 250-500-1000-2000 ppm (mixed xylenes) Xylene 1 (o-, p-xylene, ethylbenzene: 20% each, m-xylene: 40%, mixed from > 99% pure compounds) Xylene 2: (p-xylene, ethylbenzene: 10% each, o-xylene: 30%, m-xylene: 50%, mixed from > 99% pure compounds) Ethylbenzene, purity > 99%	Ethylbenzene: Increased auditory thresholds at ≥ 400 ppm; moderate to severe losses of outer hair cells of the organ of Corti at all tested concentrations Xylene: increased auditory thresholds and losses of outer hair cells. Concentrations of ethylbenzene in mixed xylenes necessary to cause a given ototoxicity were 1.7–2.8 times less than those of pure ethylbenzene. Outer hair cell loss more sensitive endpoint than LOAECs (ototoxicity): Ethylbenzene: 200 ppm Xylene 1: 250 ppm Xylene 2: 1000 ppm NOAECs: Ethylbenzene: < 200 ppm Xylene 1: < 250 ppm Xylene 2: 500 ppm	Confirmation that ethylbenzene and p-xylene are drivers for ototoxicity of mixed xylenes → mixed xylenes should be classified depending on p-xylene and ethylbenzene content	(Gagnaire et al., 2007)
Other routes			
Subacute hepatotoxicity, i.p., young rats, 3 d, 73 mg/kg bw o-Xylene, purity 99%	No effect on hepatocyte ultrastructure	None	(Bowers et al., 1982)

Table 24

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Subacute inhalation study in 8 male human volunteers Eight male volunteers were exposed on 5 consecutive days and 1 day after the weekend to m-xylene vapour at either a constant (Study I) or a periodically varying (Study II) concentration of 3.7-8.2 µmol/L (90-200 ppm, time-weighted average) The effects of exposure on psychophysiological functions, such as reaction time, manual coordination and body balance, and EEG were studied The same tests were completed on two non-exposure days for control purposes in both studies, in which physical exercise of 100 W was included. m-Xylene	Exposure to m-xylene already at a concentration of 3.7 µmol/L (90 ppm) had acute deleterious effects on psychophysiological functions of non-adapted subjects EEG indicated lowered vigilance during exposure to varying concentrations with peak exposures of 8.2 µmol/L Slight exercise, especially at the beginning of the exposure, seemed to antagonise the effects of xylene, particularly when the concentration fluctuated. Unclear picture with respect to tolerance.	Unclear results, limited usability	(Savolainen et al., 1980)
175 Xylene-exposed workers (107 men and 68 women) were selected as those (1) who underwent all examinations and (2) for whom the sum of the three xylene isomers accounted for 70% or more of the total exposure (on a ppm basis). Geometric mean: 14 ppm Arithmetic mean: 21 ppm As controls, 241 nonexposed workers (116 men and 125 women) were recruited either from the same factories or from factories in the same regions.	Increased prevalence of subjective symptoms in the exposed workers apparently related to effects on the central nervous system and to local effects on the eyes, the nose, and the throat, although dose-dependency of the symptoms was evident in only a limited number of cases, possibly because the intensity of exposure was rather low. Haematology and serum biochemistry findings with respect to liver and kidney functions were generally negative	Questionable because of subjective symptoms and insufficient delineation from exposure to other agents Not used for risk assessment	(Uchida et al., 1993)
Xylene-induced ototoxicity in humans in 30 exposed and 30 non-exposed laboratory workers Peripheral auditory measures: pure-tone audiometry and distortion product otoacoustic emissions; behavioral measures of central auditory function; pitch pattern sequence test, adaptive test of temporal resolution, dichotic digit test, masking level difference test; auditory brainstem response was used to objectively evaluate the function of the auditory pathways at the brainstem level. Speech perception in quiet and in noise was evaluated using the Hearing In Noise Test (HINT).	Significantly worse pure-tone thresholds, pitch pattern sequence test, dichotic digit test, HINT, and auditory brainstem response (absolute and interpeak latencies) test results in exposed vs. nonexposed participants No significant differences for distortion product otoacoustic emissions, adaptive test of temporal resolution, or the masking level difference test Significant correlation between the concentrations of methyl hippuric acid in urine and pure-tone thresholds (2 to 8 kHz) was found in xylene-exposed workers. Also, participants with high cumulative doses of xylene exposure presented with poorer test results than participants with low cumulative dose of xylene exposure.	Proves relevance for humans	(Fuente et al., 2013)

SUMMARY OF STUDIES ON REPEATED DOSE TOXICITY, HUMAN DATA			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Cross-sectional study on auditory function in a group of workers exposed to organic solvent mixture at a paint factory One hundred and sixty-one workers (77 exposed/84 unexposed)	Hearing impairment in both ears of exposed workers compared with unexposed workers. Adjusted for age and chronic pathologies, waves III and V, and interpeak interval latencies were increased ($p < 0.05$) in both ears in the exposed group. Despite low solvent mixture concentrations and noise levels, a concurrent ototoxicity and neurotoxicity condition may be observed	Limited value for risk assessment of xylenes	(Juárez-Pérez et al., 2014)

7.9.4.1. Summary of repeated dose toxicity

Repeated dose studies are available for the oral and inhalation route. No studies with repeated dermal administration were identified in the registration dossiers or the published literature.

Studies along the oral route (Condie et al., 1988; NTP, 1986; Wolf et al., 1956) mainly demonstrated effects on organ and body weight as well as – at very high doses not relevant for classification and labelling – clinical signs of severe toxicity (prostration, shallow breathing, lethality).

However, under the scope of this SEv, the eMSCA considers the oral route less relevant and risk assessment is therefore focused on exposure via inhalation.

Neurofunctional/neurobehavioural impairment has been identified as the most sensitive endpoint for risk assessment. In animals, repeated inhalation of xylenes was found to impact on learning (Gralewicz and Wiaderna, 2001; Gralewicz et al., 1995), reaction time, motor coordination (Korsak et al., 1992; Korsak et al., 1994) and activity (Korsak et al., 1992), and increased sensitivity to pain expressed as a decreased latency of the paw-lick response in rats when placed on a hot (54.5 °C) metal plate (Korsak et al., 1994). While the relevance of these effects for humans in principle has been demonstrated in acute studies (cf. section 7.9.2), no human studies using repeated exposure are available for these endpoints (with the exception of (Savolainen and Pfäffli, 1980), which was found unsuitable for risk assessment).

The most sensitive endpoint was the reduced latency of response in the hot plate test indicating increased sensitivity to pain. At the end of a 13-wk (5 d/wk, 6 h/d) inhalation experiment with m-xylene, (Korsak et al., 1994) observed a statistically significant ($p \leq 0.05$) effect already at the lowest concentration tested of 50 ppm, which therefore has to be considered a LOAEC. (Gralewicz and Wiaderna, 2001) showed that 50 days after the end of a 13-wk (5 d/wk, 6 h/d) exposure at 100 ppm, no statistically significant decrease in latency vs. controls was observed, which indicates that the effect likely does not represent irreversible neurological damage and therefore does not have to be considered for STOT RE classification.

With respect to STOT RE classification, one of the initial concerns of the DE MSCA under SEv was ototoxicity. Ototoxicity was demonstrated in rats for p-xylene at ≥ 800 ppm (13 wk, 5 d/wk, 6 h/d; (Gagnaire et al., 2001)) or 1800 ppm (3 wk, 5 d/wk, 6 h/d; (Maguin et al., 2006), only one dose level tested), while 1800 ppm, the highest concentration tested in both experiments, was a NOAEC for the o- and m-isomers. The relevance for humans has been shown by (Fuente et al., 2013) and (Juárez-Pérez et al., 2014) who reported significantly lower hearing ability in exposed vs. non-exposed workers; these studies, however, cannot be used for quantitative risk assessment.

As a consequence of these findings, no classification/labelling for STOT RE is indicated for any of the single xylene isomers.

In 2012, Vyskocil and co-workers reviewed the available data on the ototoxic potential of a number of industrial chemicals. With respect to the xylenes, the authors concluded:

"Absence of noise.

One study on volunteers was identified (Seppalainen et al., 1989). ABR tests showed no ototoxic effect when 200 ppm of m-xylene was inhaled for 3 h. Seven studies were identified in rats of different strains. An ototoxic effect was observed in five of six inhalation studies (Crofton et al., 1994; Gagnaire and Langlais, 2005; Gagnaire et al., 2001; Maguin et al., 2006; Pryor et al., 1987) and one oral study (Gagnaire and Langlais, 2005) by four different tests. Three studies from the same laboratory showed the ototoxic effect depending on the duration of exposure. A LOAEL of 800 ppm was observed after 6 weeks of exposure (Pryor et al., 1987). Two studies compared the ototoxicity of three xylene isomers (Gagnaire et al., 2001; Maguin et al., 2006). No ototoxic effect was observed after a subchronic exposure of up to 1800 ppm o- or m-xylene, but it was observed after exposure to 900 ppm p-xylene in one study and 1800 ppm in the other.

Presence of noise.

No study with realistic exposure concentration was identified.

Conclusion.

Only one human study was identified showing no ototoxic effect after short-term exposure. In rats xylene affects the auditory function. Further studies with sufficient data on the exposure of workers to xylene isomers are necessary to make a definitive conclusion. Given the current evidence from animal studies, we recommend considering p-xylene and consequently a mixture of xylene isomers as possibly ototoxic. No human or animal study on ototoxic interaction between xylenes and noise was identified" (Vyskocil et al., 2012).

The most relevant dose descriptors taken forward for DNEL derivation are listed in section 7.9.11. (

Table 29

7.9.5. Genotoxicity

Table 25

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
In vitro			
***In vitro* sister chromatid exchange assay** (human lymphocytes) Xylene Test concentration: 152 µg/mL Purity: No information on relative composition.	Negative ± metabolic activation No increase of chromosomal aberrations	Many deviations from OECD guideline TG 479 (e.g. no test with metabolic activation).	(Gerner-Smidt and Friedrich, 1978)
Bacterial gene mutation assay Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100 Test concentrations: 0.001, 0.01, 0.1, 1.0 and 5.0 µg/plate (with/without metabolic activation) Purity: 11.4% o-xylene, 52.07% m-xylene, 0.31% p-xylene, 36.8% ethylbenzene	Negative ± metabolic activation Cytotoxicity: no information	Not in accordance with OECD TG 471 (e.g.: no E. coli strain was tested). Lack of detailed information	([redacted] 1978a)
Saccharomyces cerevisiae gene mutation assay Xylene Test strain: D4 Test concentrations: 0.001, 0.01, 0.1, 1.0 and 5.0 µg/plate (± metabolic activation) Purity: 11.4% o-xylene, 52.07% m-xylene, 0.31% p-xylene, 36.8% ethylbenzene	Negative ± metabolic activation Cytotoxicity: no information	Due to the lack of detailed information it is not clear, whether the test is in complete accordance with OECD TG 480 (e.g.: no information on a second experiment; no information on replicates/concentration).	([redacted] 1978a)
***In vitro* mammalian cell gene mutation test** (MLA, L5178Y cells) Xylene Test concentrations: 0.0064, 0.0125, 0.025, 0.05, 0.075 and 0.1 µL/mL (without metabolic activation) Test concentrations: 0.025, 0.05, 0.075, 0.1 and 0.15 µL/mL (with metabolic activation) Purity: 11.4% o-xylene, 52.07 % m-xylene, 0.31 % p-xylene, 36.8 % ethylbenzene	Negative ± metabolic activation Cytotoxicity: no information	Due to the lack of detailed information it is unclear whether the test is in complete accordance with OECD TG 476.	[redacted] 1978a)
Bacterial gene mutation test Xylene	Negative	Only limited information (abstract) is available.	(Lebowitz et al., 1979)

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
Purity: No information on relative composition.			
***In vitro* gene mutation test** (MLA, L5178Y cells) Xylene Purity: No information on relative composition.	Negative	Only limited information (abstract) is available.	(Lebowitz et al., 1979)
Bacterial gene mutation test m-Xylene S. typhimurium tester strains: TA 98, TA 100 Test concentrations: 0.03, 0.3, 3.0 and 30 µmol/plate (equivalent to 3.2, 32.0, 320 and 3200 µg/plate) (± metabolic activation) Purity: No information	Negative ± metabolic activation Cytotoxicity: at 30 µmol/plate	Not in accordance with OECD TG471 (e.g.: only two Salmonella typhimurium strains were tested; no E.coli strain was tested; no information on negative/solvent controls).	(Florin et al., 1980)
p-Xylene S. typhimurium tester strains: TA 98, TA 100 Test concentrations: 0.03, 0.3, 3.0 and 30 µmol/plate (equivalent to 3.2, 32.0, 320 and 3200 µg/plate) (± metabolic activation) Purity: No information.	Negative ± metabolic activation Cytotoxicity: at 30 µmol/plate	None	(Florin et al., 1980)
Bacterial gene mutation test o-Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100 Test concentrations: 20, 50, 100, 200 and 500 µg/plate (± metabolic activation) Purity: No information.	Negative ± metabolic activation Cytotoxicity: No increased toxic effects up to the highest tested concentration ± metabolic activation	Deviations from OECD TG471 (e.g.: no E.coli strain was tested; only one experiment without metabolic activation; taking into account the lack of toxicity no justification was given why concentrations higher than 500 µg/plate were not tested).	(Bos et al., 1981)
m-Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100 Test concentrations: 20, 50, 100, 200 and 500 µg/plate (± metabolic activation) Purity: No information.	Negative ± metabolic activation Cytotoxicity: No increased effects up to the highest tested concentration without metabolic activation.	None	(Bos et al., 1981)
p-Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100 Test concentrations: 20, 50, 100, 200 and 500 µg/plate (± metabolic activation) Purity: No information.	Negative ± metabolic activation Cytotoxicity: No increased effects up to the highest tested concentration without metabolic activation.	None	(Bos et al., 1981)

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
DNA repair in bacteria (micro suspension assay) Xylene E. coli strains:WP2, WP2 uvrA^{-}, WP67, CM611, WP100, W3110 and p3478	Negative ± metabolic activation	Only limited information is available (no guideline available).	(McCarroll et al., 1981b)
DNA repair in bacteria (micro suspension Rec-assay) Xylene Strain: Bacillus subtilis	Negative ± metabolic activation	Only limited information is available (no guideline available).	(McCarroll et al., 1981a)
Bacterial gene mutation test o-Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 98, TA 100 Test concentrations: 1.0, 3.3, 10.0, 33.0, 100 µg/plate (without metabolic activation) Test concentrations: 3.3, 10.0, 33.0, 100 and 333.3 µg/plate (with metabolic activation) Purity: 97 %	Negative ± metabolic activation Cytotoxicity: No effects up to the highest tested concentration without metabolic activation.	Deviations from the OECD TG 471 (e.g.: no E.coli strain was tested; it has not been tested up to relevant toxic concentrations).	(Haworth et al., 1983)
m-Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 98, TA 100 Test concentrations: 0.3, 1.0, 3.3 10.0 and 33.0 µg/plate (± metabolic activation) Purity: 97%	Negative ± metabolic activation Cytotoxicity: No increased effects up to the highest tested concentration without metabolic activation	None	(Haworth et al., 1983)
p-Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 98, TA 100 Test concentrations: 1.0, 3.3, 10.0, 33,0 and 100.0 µg/plate (without metabolic activation) Test concentrations: 3.3, 10.0, 33.0, 100.0 and 200.0 µg/plate (with metabolic activation) Purity: 97%	Negative without metabolic activation Cytotoxicity: TA 100 and TA 1537 at 200.0 µg/plate with metabolic activation	None	(Haworth et al., 1983)
Bacterial gene mutation test p-Xylene S. typhimurium tester strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100 and E.coli WP2 Test concentrations: 1.0, 5.0, 10.0, 50.0, 100.0 µg/plate (without metabolic activation) Purity: 98%	Negative ± metabolic activation Cytotoxicity: without metabolic activity ≥ 50 µg/plate; with S9-mix > 100 µg/plate	Due to the lack of detailed information it is unclear whether the test is in complete accordance with OECD TG 471 (e.g. no information on second experiment).	(Shimizu et al., 1985)
Bacterial gene mutation test Xylene	Negative ± metabolic activation	Deviations from OECD TG 471 (e.g.: no E.coli strain was tested; not	(NTP, 1986)

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
S. typhimurium tester strains: TA 1535, TA 97, TA 98 and TA 100 Test concentrations: 3.0, 10.0, 33.0, 100.0 and 200.0 µg/plate (without metabolic activation) Purity: 9% o-xylene, 60% m-xylene, 14% p-xylene, 17% ethylbenzene		tested up to relevant toxic concentrations).	
***In vitro* chromosomal aberration test** (CHO cells) Ethylbenzene Test concentrations: 75.0, 100.0 and 125.0 µg/ml Purity: No information.	Negative ± metabolic activation Cytotoxicity: no information	Early standard protocol is not in accordance with OECD TG 473.	(NTP, 1986)
***In vitro* sister chromatid exchange assay** (CHO cells) Ethylbenzene Test concentrations: 75.5, 99.5 and 125.0 µg/ml Purity: No information.	Negative ± metabolic activation Cytotoxicity: no information	Early standard protocol is not in accordance with OECD TG 479.	(NTP, 1986)
DNA repair in bacteria (umu-test) Xylene S. typhimurium strain: TA1535/pSK 1002 Test concentration: 36 µg/mL Purity: No information.	Negative	Only limited information is available (no guideline available).	(Nakamura et al., 1987)
Bacterial gene mutation test Xylene S. typhimurium tester strains: TA 1535, TA 97, TA 98, TA 100 Test concentrations: 3.3, 10.0, 33.0, 100.0 and 200.0 µg/plate (without metabolic activation Purity: 83.1%	Negative ± metabolic activation Cytotoxicity: slight effects with and without S9-mix at 200 µg/plate	Deviation from current OECD TG 471 (no E.coli strain was tested).	(Zeiger et al., 1987)
***In vitro* mammalian chromosomal aberration test** (CHO cells) Xylene Test concentrations: 20.1, 50.3 and 100.5 µg/mL (without metabolic activation) Test concentrations: 15.1, 20.1 and 50.3 µg/mL (with metabolic activation) Purity: 83.1% (commercial mixture: no information on relative composition)	Negative ± metabolic activation Cytotoxicity: No effects with and without metabolic activation	Due to the lack of detailed information it is unclear whether the test is in complete accordance with OECD TG 473 (e.g. no information on second experiment).	(Anderson et al., 1990)
***In vitro* sister chromatid exchange assay** (CHO cells)	Negative ± metabolic activation	Due to the lack of detailed information it is not clarified whether the test is in complete	(Anderson et al., 1990)

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
Xylene Test concentrations: 5.0, 16.7 and 50.0 µg/mL(without metabolic activation) Purity: 83.1% (commercial mixture; no information on relative composition)	Cytotoxicity: No effects with and without metabolic activation	accordance with OECD TG 479.	
***In vitro* mammalian cell gene mutation test** (MLA, L5178Y cells) Xylene Test concentrations:16.0, 24.0, 32.0, 40.0, 45.0, 48.0, 60.0, 75.0, 90.0 and 105.0 µg/mL (without metabolic activation) Purity: Commercial mixture.	Weakly positive without metabolic activation at the highest tested concentration of 105.0 µg/mL in two experiments. Cytotoxicity: Extremely toxic at 105.0 µg/mL in two expriments (relative total growth 6% or 13%).	The weakly positive result is of limited relevance because the mutagenic effect (average mutation frequency: 2.6) was induced in two experiments only at the highest concentration which also induce extreme cytotoxicity.	(Myhr et al., 1990)
***In vitro* comet assay** (Freshly isolated human peripheral lymphocytes) o-Xylene Test concentrations: 50.0, 100.0 and 200.0 µM (without metabolic activation) Purity: No information.	Positive at concentrations of 100.0 and 200.0 µM Cytotoxicity: Cell viability > 95% Solubility: Limited at concentrations > 200 µM	The positive test results are questionable in their relevance due to many limitations. Limitations: - No guideline available. - No standardized evaluation (visual evaluation by a person: intensity of the tails as evaluation criteria according to an intensity score from class 0 (undamaged) to class 4 (severely damaged). - No use of a metabolic activation system. - No historical controls are available.	(Chen et al., 2008)
m-Xylene Test concentrations: 50.0, 100.0 and 200.0 µM (without metabolic activation) Purity: No information.	Positive at concentrations of 100.0 and 200 µM Cytotoxicity: Cell viability > 95% Solubility: Limited at concentrations > 200 µM	None	(Chen et al., 2008)
p-Xylene Test concentrations: 50.0, 100.0 and 200.0 µM (without metabolic activation) Purity: No information. Ethylbenzene Test concentrations: 50.0, 100.0 and 200.0 µM (without metabolic activation) Purity: No information.	Positive at concentrations from 50 µM upwards Cytotoxicity: Cell viability > 95% Solubility: Limited at concentrations > 200 µM	None	(Chen et al., 2008)

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
	Positive at concentrations of 100 and 200 µM Cytotoxicity: Cell viability > 95% Solubility: Limited at concentrations > 200 µM		
In vivo			
Rodent dominant lethal test (in vivo test) Xylene Test animals: male/female rats (strain: Long-Evans) Exposure: i.p. (once; males) Doses: 1.0 mL/kg bw Purity: No information on relative composition.	Negative	Due to the lack of detailed information it is not clarified whether the test is in complete accordance with OECD TG 478.	[redacted] 1973)
Rodent dominant lethal test (in vivo test) Xylene Test animals: male/female mice (strain: Swiss Webster) Exposure: i.p. (once; males) Doses: 1.0 mL/kg bw Purity: No information on relative composition.	Negative	Due to the lack of detailed information it is not clarified whether the test is in complete accordance with OECD TG478.	([redacted] 1973)
***In vivo* chromosome aberration test** Xylene Test animals: mMale rats Target cells: Bone marrow cells Exposure: i.p (once) Sampling time: 6, 24 and 48h after dosing Doses: 0.044, 0.147 and 0.441 mL/kg bw Purity: 11.4% o-xylene, 52.07% m-xylene, 0.31% p-xylene, 36.8% ethylbenzene	Negative	Due to the lack of detailed information it is not clarified whether the test is in complete accordance with OECD TG 476 (e.g. no justification why only males were tested; choice of tested doses is not comprehensible).	([redacted] 1978a)
In vivo chromosome aberration test Xylene Test animals: Rats Target cells: Bone marrow cells Exposure: i.p	Negative	Only limited information (abstract) is available.	(Lebowitz et al., 1979)

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
Purity: No information on relative composition.			
***In vivo* chromosome aberration test** Xylene Test animals: Rats Target cells: Bone marrow cells Exposure: Inhalation (6 h daily, 5 days/week for 9, 14 and 18 weeks) Sampling time: After 9, 14 and 18 weeks after exposure Doses: 300 ppm Purity: No information on relative composition.	Negative	Only limited information (abstract) is available.	(Donner et al., 1980)
Sex-linked recessive lethal test in Drosophila melanogaster m-Xylene, o-xylene, ethylbenzene Purity: No information. Xylene Purity: technical grade xylene (18.3% ethylbenzene)	Negative: m-xylene, o-xylene, Ehylbenzene Weakly positive: Xylene	Only limited information (abstract) is available. Due to the lack of detailed information it is not clear whether the test is in complete accordance with OECD TG 477 nor can the relevance of the weakly positive result be evaluated.	(Donner et al., 1980)
Analysis of sperm abnormalities o-Xylene Test animals: rats (strain: Sprague Dawley) Exposure: i.p. (twice, 24 h apart) Doses: 0.5 and 1.5 mL/kg bw (430 and 1290 mg/kg bw) Sampling time: 5 weeks after injection Purity: No information.	Negative (at both tested doses if rats housed at temperatures of 20-24 °C) Positive (only 0.5 mL/kg bw were tested; rats housed at temperatures between 24-30 °C) Conclusion by the authors: No conclusive evidence for mutagenic effects but for biological activity of o-xylene	No mutagenicity/ genotoxicity test (crucial deficiency: lack of a positive control)	(Washington et al., 1983)
Human study **Sister chromatid exchange assay** Xylene Subjects: Workers occupationally exposed to xylene; control group Purity: technical mixture (o-, m-, p-xylenes; 6-15% ethylbenzene)	Negative	None	(Pap and Varga, 1987)

SUMMARY OF GENOTOXICITY STUDIES			
Method/Study Type/Test substance	**Results**	**Remarks**	**Source**
Mammalian erythrocyte micronucleus test Test animals: Male mice (strain: NMRI) Target cells: Bone marrow Exposure: i.p.; each dose was administered twice (24 hours apart) Doses: The respective highest tested dose does not exceed 70% of the LD50 (LD50: 1.55 mL/kg bw (o-xylene); 2,003 mL/Kg bw (m-xylene); 2.45 mL/kg bw (p-xylene) Sampling time: 6 h after second injection o-Xylene, (2x) 0.12, 0.25, 0.37 and 0.50 mL/kg bw 2x) 106, 220, 329 and 440 mg/kg bw), purity: 98% m-Xylene, (2x) 0.37, 0.5, 0.62 and 0.75 mL/kg bw (105–650 mg/kg bw), purity: 98% p-Xylene, (2x) 0.37, 0.5, 0.62 and 0.75 mL/kg bw (319, 431, 534 and 646 mg/kg bw) Purity: 98%	Negative Negative Negative	Deviations from OECD TG 474 (e.g. no justification why only males were tested; no justification why the respective highest tested dose is lower than the MTD; divergent sampling time after two-time administration)	(Mohtashamipur et al., 1985)

7.9.5.1. Summary of genotoxicity

Assuming that the mixed xylenes in the respective tests contained all single xylene isomers in sufficient amounts (as a rule this information is not available) read-across of the results to single xylene isomers can be accepted (otherwise there would be numerous data gaps).

Based on a synopsis of all data, the weakly positive test result in Drosophila is not considered relevant.

Possible concerns based on the positive results from the *in vitro* Comet assays with the single isomers are alleviated by the available *in vivo* tests (micronucleus test with the single isomers, chromosome aberration test, SCE, and Dominant Lethal test with xylene). Moreover some doubts are cast on the reliability of the results of the *in vitro* Comet assay.

In conclusion the eMSCA finds that the available data do not point at a genotoxic concern for mixed xylenes or any of the individual xylene isomers.

A tabular overview of the results from the genotoxicity studies performed with the members of the xylene/ethylbenzene category members can be found in the matrix table in section 7.9.10.

7.9.6. Carcinogenicity

Table 26

SUMMARY OF STUDIES ON CARCINOGENICITY			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Combined chronic and carcinogenicity oral gavage study in rats, 103 wk, 5 d/wk 0-250-500 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	NOAEL carcinogenicity = 500 mg/kg bw/d (highest dose tested)	None	(NTP, 1986)
Combined chronic and carcinogenicity (2-yr) oral gavage study in mice 0-500-1000 mg/kg bw/d Xylene: 9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene	NOAEL carcinogenicity = 1000 mg/kg bw/d (highest dose tested)	None	(NTP, 1986)
BALB/c-3T3 cell transformation assay Xylene, purity/composition not reported	Evaluated as inactive	None	(Matthews et al., 1993)

7.9.6.1. Summary of carcinogenicity

In 1986 the US National Toxicity Program has performed two oral combined chronic toxicity and carcinogenicity studies in rats and mice, in which no increased incidence of tumours in treated groups up to the highest dose of 500 (rats) or 1000 (mice) mg/kg bw/d was observed. In conjunction with the synopsis of the available data base on genotoxicity, the eMSCA finds that at this point in time, there is no concern about a carcinogenic potential of the xylene isomers.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Table 27

SUMMARY OF STUDIES ON TOXICITY TO REPRODUCTION			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Developmental toxicity			
Inhalation study on pre-natal development in CFY rats, 24 h/d, gestation days 9-14 1000 mg/m^3 (230 ppm) Xylene (10% o-xylene, 50% m-xylene, 20% p-xylene, 20% ethylbenzene)	No effect on incidence of malformations Increase in skeletal variations (extra ribs, fused sternebrae)	Exposure only from d9 –d14	(Hudak and Ungvary, 1978)
Pre-natal development inhalation study in rats, gestation days 6-15, 0-100-400 ppm Xylene (36.08% ethylbenzene, 0.3% p-xylene, 52.07% m-xylene, 11.4% o-xylene)	Slight dose-related increase of resorptions (33-40-52% at 0-100-400 ppm), statistical significance unclear Significant increase in skeletal variations (mostly retarded ossification) at 400 ppm	Exposure only from d6-15	([redacted], 1978b)

SUMMARY OF STUDIES ON TOXICITY TO REPRODUCTION			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Inhalation study on pre-natal development in CFY rats, 24 h/d, gestation days 7-14 0-150-1500-3000 mg/m^3 (0-34-340-680 ppm) Satellite groups for toxicokinetics (only exposed on gestation day 18) o-, m-, p-Xylene ≥99%	Xylenes found in foetal blood and amniotic fluid 680 ppm, all isomers: maternal toxicity, decreased foetus wt, skeletal retardation, decreased activity of succinic dehydrogenase, alkaline and acid phosphatase, and glucose 6-phosphatase, Dose-dependent retardation of foetuses, p- > o- > m-xylene m-/p-Xylene: extra ribs, preimplantation loss at 680 ppm p-Xylene: postimplantation loss at 680 ppm o-Xylene without effect on extra ribs, implantation, or pre- and postimplantation foetal losses, but on foetal wt and number of weight-retarded foetuses at ≥ 340 ppm	Exposure only from d7 –d14	(Ungvary et al., 1980)
Pre-natal development gavage study in CD 1 mice, 3 /d, gestation days 6-15 2.4-3.0-3.6 mL/kg bw/d Xylene (60.2% m-xylene, 9.1% o-xylene, 13.6% p-xylene, and 17.0% ethylbenzene)	Mortality (12/38 dams) and significant decrease in average weight gain during pregnancy, significantly greater percentage of resorptions at 3.6 mL/kg bw/d Decrease in foetal weights at ≥ 2.4 mL/kg/d Significantly greater average percent of malformed foetuses (major malformation: cleft palate) at all dose levels	Very high doses close to LD_{50} with high maternal mortality	(Marks et al., 1982)
Pre-natal development inhalation study in SD rats, gestation days 7-16 Auditory startle test, maze test 3500-7000 mg/m^3 (800-1600 ppm) p-Xylene, purity ≥ 99%	Maternal weight gain decreased during treatment period at 1600 ppm No effects on litter size or weight, growth rate, acoustic startle response, or "figure 8" maze activity	Exposure only from d7 –d16	(Rosen et al., 1986)
Embryotoxicity in vitro Xylene, purity ≥ 99%, composition: 60% p-, 22% o-xylene, 18% ethylbenzene	No increased incidence of malformations, but dose-related embryotoxicity	Results cannot be transferred to the in vivo situation in a quantitative way.	(Brown-Woodman et al., 1991)
Pre-natal development in Wistar rats, days 4-20 of gestation, 500 ppm Xylene, purity and/or composition not reported	No maternal toxicity No exposure-related differences except for delayed ossification of os maxillare Xylene-exposed pups displayed higher body weight and impaired rotarod performance	Only one dose level	(Hass and Jakobsen, 1993)
Pre-natal development vapour inhalation study in rats including neurological parameters, 6 h/d, gestation days 7-20, 0-500 ppm	No pregnancy-related parameters affected	Only one dose level	(Hass et al., 1995)

SUMMARY OF STUDIES ON TOXICITY TO REPRODUCTION			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Xylene (19% o-xylene, 45% m-xylene, 20% p-xylene, 15% ethylbenzene)	Decrease in absolute brain weights of pups, delay in development of the air righting reflex, impairment of performance on the rotarod and in the water maze		
Wistar rats, 6 h/d, gestation days 7-20, 0-500 ppm Xylene, (19% o-xylene, 45% m-xylene, 20% p-xylene, 15% ethylbenzene)	At the age of 16 weeks, the exposed offspring showed impairments in the Morris maze when the platform was relocated in the pool. Impaired performance after platform relocation was also observed in exposed offspring at 28 and 55 weeks of age, although the difference was not statistically significant at 55 weeks LOAEC 500 ppm	Only one dose level	(Hass et al., 1997)
Pre-natal development inhalation study in SD rats, 6 h/d, gestation days 6-20 0-100-500-1000-2000 ppm Ethylbenzene, o-, m-, p-xylene and mixed xylenes (15.3% ethylbenzene, 21.3% o-xylene, 43.9% m-xylene, 19.4% p-xylene), all ≥ 99.5% pure	All agents caused a reduction in maternal body weight gain at 1000 and 2000 ppm Decreased corrected weight gain and food consumption at 1000 and 2000 ppm ethylbenzene, o-, m- or p-xylene, and at 2000 ppm xylene. No evidence of teratogenic effects after exposure for any substance up to 2000 ppm Foetal toxicity (significant decreases in foetal bw) at ≥ 500 ppm o-xylene or technical xylene, and ≥ 1000 ppm or greater of ethylbenzene, m-, or p-xylene. Significant increase in mean percentage of foetuses per litter with skeletal variations at 2000 ppm ethylbenzene, o- and p-xylene	None	(Saillenfait et al., 2003)
Fertility			
One-generation study, rats Whole body vapour inhalation 0-60-250-500 ppm for 131 d pre-mating, 20 d during mating, from d 1-20 of gestation (mated females only) and from day 5-20 of lactation (only females who delivered) Xylene, purity: 87-92%, detailed composition not reported	No impact of treatment on fertility Slightly (< 10%) decreased foetal weight, skeletal variations at 500 ppm NOAEC 250 ppm LOAEC 500 ppm	None	([redacted] 1983)
Analysis of sperm abnormalities in SD rats, i.p., 1 x 0.5 or 1.5 mL/kg bw Sperm examination 5 wk post-exposure o-Xylene	Morphological abnormalities: amorphous heads, and banana-like heads Alleged relationship with housing temperatures	Poorly documented, unreliable, not usable for risk assessment	(Washington et al., 1983)

SUMMARY OF STUDIES ON TOXICITY TO REPRODUCTION			
Method/Study Type/Test substances	**Results**	**Remarks**	**Source**
Two-generation reproductive toxicity study in SD rats, 6 h/d from ≥ 70 d before mating through lactation of F1 pups 0-25-100-500 ppm On lactation days 1-4, females received EB in corn oil via oral gavage at dose levels of 26, 90, and 342 mg/kg bw/d, calculated from a PBPK model to provide similar maternal blood AUC as provided by inhalation Ethylbenzene, "stability and purity confirmed"	No effect on survival or clinical observations Decreased body weight gain in male F_0 and F_1 rats of the 500 ppm group in both generations No adverse effects on reproductive performance in either generation: male and female mating and fertility indices, pre-coital intervals, spermatogenic endpoints, ovarian follicle counts, reproductive organ weights, lengths of oestrous cycle and gestation, live litter size, No effect on pup weights, developmental landmarks, and postnatal survival, or macroscopic pathology		(Faber et al., 2006)

7.9.7.1. Developmental toxicity

In several studies on developmental toxicity in rats, xylenes caused skeletal variations as well as effects on foetal body weight and foetal neurobehaviour. While maternal toxicity is not always explicitly reported in sufficient detail, it can be assumed that all of the adverse effects observed only occurred at dose levels much higher than those required to trigger neurotoxicity in maternal animals. The overall NOAEC/LOAEC for foetal weight effects was 100/340 ppm.

Based on these observations and the nature of the effects, there are currently no indications that for xylenes classification with respect to developmental effects is required.

The eMSCA notes that at the time of conclusion of the SEV, all developmental studies available had been performed in rats, while at this tonnage level under REACH a study in a second (non-rodent) species is required. As no specific concern for developmental toxicity was found, this issue is seen to lie outside the scope of SEv and was therefore forwarded to ECHA to be clarified under CCH.

7.9.7.2. Fertility

A one-generation with xylene showed no effects on fertility-related parameters [redacted] 1983) after exposure of rats to concentrations up to 500 ppm. However this study is not equivalent to a two- or extended one-generation study as required by REACH at this tonnage level.

The registrant(s) have waived this requirement by performing read-across to a published two-generation study in rats performed with ethylbenzene (Faber et al., 2006), which did not show relevant effects on fertility up to 500 ppm. As explained below (section 7.9.10), read-across to ethylbenzene is considered plausible in principle by the eMSCA, while the justification provided by the registrant(s) was found insufficient.

7.9.7.3. Summary on Reproductive Toxicity

At the conclusion of the eMSCA's assessment in April 2020, no specific concern was established with regard to developmental toxicity. Since then, new information was provided by the registrants with regard to read-across and developmental toxicity studies in rabbits.

This information has not been assessed in-depth by the eMSCA or otherwise reflected in this report. However, ECHA has, in April 2021, formally concluded the compliance check and confirmed that the PNDT study submitted by the registrants is complying with the requested information.

7.9.8. Aspiration hazard

Only one specific study (Hine and Zuidema, 1970) with respect to aspiration hazard is available, however, the test was only able to demonstrate lethality after aspiration, but not the likelihood of aspiration itself.

Nevertheless, according to the CSR, the kinematic viscosity of all xylene isomers is in the range of 0.58-0.76 mm^2/s at 25 °C which suggests that the criterion for classification given in the CLP regulation (≤ 22.5 mm^2/s at 40 °C) is clearly met.

In line with the lead registrants the eMSCA therefore concludes that all xylene isomers as well as mixed xylenes should be classified/labelled as "Asp. Tox 1/H304: May be fatal if swallowed and enters airways".

The eMSCA considers that this should be reflected in the self-classification.

7.9.9. Hazard assessment of physico-chemical properties

o-Xylene, m-xylene and p-xylene are classified as flammable liquid. Therefore a risk assessment of the likelihood and the severity of an event occurring due to physicochemical hazard properties is needed. Flashpoint, explosion limits, vapour pressure, critical chemical reactions are important factors to evaluate the risk. The severity of an event will be also triggered by the substance amount of use per task/in the process and the process condition like temperature, pressure, concentration, ventilation and duration.

7.9.10. Evaluation of the Read-Across-/Category Approach

An overview of the data available for the xylene/ethylbenzene category is given in the matrix table below.

For a comparison of physico-chemical properties, cf. section 7.4.

Table 28

MATRIX TABLE FOR HUMAN HEALTH ENDPOINTS					
Endpoint	**o-Xylene**	**m-Xylene**	**p-Xylene**	**Ethylbenzene*** **	**Xylene**
Acute toxicity					
Oral					
Acute oral LD_{50}** (mg/kg bw)	No data	5404-8253 (rat)	No data	3500-5081 (rat)	2707-11438 (rat) 4583-6646 (mouse)
Non-lethal effects observed after acute oral application from (mg/kg bw):	No data	No data	250 (rat)	No data	No data
CLH	**None**	**None**	**None**	**None**	**None**
Additional self-classification***	**None**	**None**	**None**	**None**	**None**
Classification acc. to eMSCA	**NC**	**NC**	**NC**	**NC**	**NC**

MATRIX TABLE FOR HUMAN HEALTH ENDPOINTS					
Endpoint	**o-Xylene**	**m-Xylene**	**p-Xylene**	**Ethylbenzene*** **	**Xylene**
Dermal					
Acute dermal LD_{50}** (mg/kg bw)	No data	14100 (rabbit)	No data	15500-17800 (rabbit)	4300 (rat)
Non-lethal effects reported after acute dermal application from (mg/kg bw):	No data	No data	No data	No data	No data
CLH	**Acute Tox. 4**	**Acute Tox. 4**	**Acute Tox. 4**	**None**	**Acute Tox. 4**
Additional self-classification***	**None**	**None**	**None**	**None**	**None**
Classification eMSCA	**NC**	**NC**	**NC**	**NC**	**NC**
Inhalation					
Acute inhalation LC_{50}** (ppm)	6371-6648 Mortality observed from ~4000 ppm x 6 h (rat) 6702-7116 Mortality observed from ~4000 ppm x 6 h (mouse)	<< 8000-9272 Mortality observed from ~5200 ppm x 6 h (rat) 7538-8235 Mortality observed from ~4000 ppm x 6 h (mouse)	4740-7574 Mortality observed from ~3300 ppm x 6 h (rat) 3907-6023 Mortality observed from ~3600 ppm x 6 h (mouse)	~4000 (rat)	4670-8640 (rat) << 9500 (cat)
Acute effects observed after inhalation application from (ppm):	No data	No data	1600 (rat) 2500 (mouse)	No data	200 (human) 909 (rat) 909 (dog)
CLH	**Acute Tox. 4**	**Acute Tox. 4**	**Acute Tox. 4**	**Acute Tox. 4**	**Acute Tox. 4**
Additional self-classification***	**None**	**None**	**None**	**None**	**None**
Classification eMSCA	**Acute Tox. 4 STOT SE 3 (H336)**	**Acute Tox. 4 STOT SE 3 (H336)**	**Acute Tox. 4 STOT SE 3 (H336)**	**Acute Tox. 4 STOT SE 3 (H336)**	**Acute Tox. 4 STOT SE 3 (H336)**
Irritation/Corrosion					
Skin					
Skin irritation/corrosion	Irritant (rabbits) Non-irritant (pigs)	Irritant (rabbits)	Irritant (rabbits)	Irritant (rabbits) Non-irritant (pigs)	Irritant (rabbits)
CLH	**Skin Irrit. 2**	**Skin Irrit. 2**	**Skin Irrit. 2**	**None**	**Skin Irrit. 2**
Additional self-classification***	**None**	**None**	**None**	**Skin Irrit. 2**	**None**
Classification acc. to eMSCA	**Skin Irrit. 2**	**Skin Irrit. 2**	**Skin Irrit. 2**	**Skin Irrit. 2**	**Skin Irrit. 2**
Eye					

MATRIX TABLE FOR HUMAN HEALTH ENDPOINTS					
Endpoint	**o-Xylene**	**m-Xylene**	**p-Xylene**	**Ethylbenzene*** **	**Xylene**
Eye irritation/corrosion	Unclear, considered irritant by registrant	Unclear, considered irritant by registrant	No data	Irritant	Unclear, considered irritant by registrant
CLH	**None**	**None**	**None**	**None**	**None**
Additional self-classification***	**Eye Irrit. 2**	**Eye Dam. 1 Eye Irrit. 2**	**Eye Irrit. 2**	**Eye Irrit. 2**	**Eye Irrit. 2**
Classification acc. to eMSCA	**NC**	**NC**	**NC**	**Eye Irrit. 2**	**NC**
Respiratory tract					
Sensory irritation (RD_{50} mouse, ppm)	1467	No data	No data	1432	≥ 1300
Respiratory tract irritation	Slightly irritant (mouse)	NA	NA	Irritant	NA
CLH	None	None	None	None	None
Additional self-classification***	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**
Classification acc. to eMSCA	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**	**STOT SE 3 (H335)**
Skin sensitisation					
DPRA	No data	No data	No data	No data	Negative
Keratinosens	No data	No data	No data	No data	Negative
LuSens	No data	No data	No data	No data	Negative
MUSST	No data	No data	No data	No data	Negative
mMUSST	No data	No data	No data	No data	Negative
HMT	No data	No data	No data	Negative	Negative
LLNA	No data	No data	No data	No data	Positive (weak)
Buehler	No data	No data	No data	No data	No data
GPMT	No data	No data	No data	No data	No data
HPT	No data	No data	No data	No data	Negative
CLH	**None**	**None**	**None**	**None**	**None**
Additional self-classification***	**None**	**None**	**None**	**None**	**None**
Classification acc. to eMSCA	**NC**	**NC**	**NC**	**NC**	**NC**
Repeated Dose Toxicity					
Oral					
Subacute	NOEL = 250 mg/kg bw/d (liver wt) NOAEL = 1000 mg/kg bw	NOEL = 250 mg/kg bw/d (liver wt) NOAEL = 1000 mg/kg bw	NOEL = 250 mg/kg bw/d (liver wt) NOAEL = 1000 mg/kg bw	No data	NOAEL = 1000 mg/kg bw/d (rats, mice) Mortality from 2000 mg/kg bw/d, 14 d)

MATRIX TABLE FOR HUMAN HEALTH ENDPOINTS					
Endpoint	**o-Xylene**	**m-Xylene**	**p-Xylene**	**Ethylbenzene*** **	**Xylene**
Subchronic	No data	No data	No data	NOAEL = 150-500 mg/kg bw/d (rat, 13 wk, bwg decrease, liver/kidney wt) NOAEL = 1000 mg/kg bw (mice, mortality at 2000 mg/kg bw/d) 6-mo NOAEL < 408 mg/kg bw/d (rats)	NOAEL = 150-500 mg/kg bw/d (rats) NOAEL = 1000 mg/kg bw/d (mice)
Chronic	No data	No data	No data	No data	NOAEL = 250 mg/kg bw/d (2 yr rat, decreased survival) NOAEL = 500 mg/kg bw/d (2 yr mouse, clinical signs)
Dermal					
Subacute	No data	No data	No data	No data	No data
Subchronic	No data	No data	No data	No data	No data
Chronic	No data	No data	No data	No data	No data
Inhalation					
Subacute	LOAEC 2000 ppm (3 d neurotransmitter) NOAEC 1800 ppm (ototxicity, HDT)	LOAEC 100 ppm (behaviour/learning) LOAEC 2000 ppm (3 d neurotransmitter) NOAEC 1800 ppm (ototoxicity, HDT)	LOAEC 2000 ppm (3 d neurotransmitter) LOAEC 1800 ppm (ototoxicity)	No data	LOAEC 2000 ppm (3 d neurotransmitter)
Subchronic	NOAEC = 1800 ppm (ototoxicity, HDT)	LOAEC = 1000 ppm (3 mo. rat, rotarod, motor activity) LOAEC 100 ppm (6 mo., rat) NOAEC ≥ 1800 ppm (ototoxicity)	NOAEC = 450 ppm LOAEC = 900 ppm (ototoxicity)	NOAEC < 200 ppm (ototoxicity)	90-d NOAEC ca. 810 ppm (rats, 6 h/d, 5 d/wk, highest dose tested) NOAEC < 250-500 ppm (ototoxicity)
Chronic	No data	No data	No data	No data	No data
CLH	**None**	**None**	**None**	**STOT RE2 H373 (hearing organ)**	**None**

MATRIX TABLE FOR HUMAN HEALTH ENDPOINTS					
Endpoint	**o-Xylene**	**m-Xylene**	**p-Xylene**	**Ethylbenzene*** **	**Xylene**
Additional self-classification***	**STOT RE2 H373 (hearing organ)**	**STOT RE2 H373 (hearing organ)**	**STOT RE2 H373 (hearing organ)**	**None**	**STOT RE2 H373 (hearing organ)**
Classification acc. to eMSCA	**NC**	**NC**	**NC**	**STOT RE 2/H373 (hearing organ)**	**STOT RE 2/H373 (hearing organ)**
Genotoxicity					
In vitro					
Bacterial gene mutation test	Negative	Negative	Negative	No data	Negative
DNA repair in bacteria	No data	No data	No data	No data	Negative
Saccharomyces cerevisiae gene mutation assay	No data	No data	No data	No data	Negative
In vitro mammalian cell gene mutation test	No data	No data	No data	No data	Negative
In vitro chromosomal aberration test	No data	No data	No data	Negative	Negative
In vitro sister chromatid exchange assay	No data	No data	No data	Negative	Negative
In vitro comet assay	Positive	Positive	Positive	Positive	No data
In vivo					
In vivo micro-nucleus test	Negative	Negative	Negative	No data	No data
In vivo chromosome aberration test	No data	No data	No data	No data	Negative
Rodent domi-nant lethal test	No data	No data	No data	No data	Negative
Sex-linked recessive lethal test in *Drosophila melanogaster*	Negative	Negative	No data	Negative	Positive (weak)
Human study (Sister chromatid exchange assay)	No data	No data	No data	No data	Negative
CLH	**None**	**None**	**None**	**None**	**None**
Additional self-classification***	**None**	**None**	**None**	**None**	**None**
Classification acc. to eMSCA	**NC**	**NC**	**NC**	**NC**	**NC**

MATRIX TABLE FOR HUMAN HEALTH ENDPOINTS					
Endpoint	**o-Xylene**	**m-Xylene**	**p-Xylene**	**Ethylbenzene*** **	**Xylene**
Reproductive Toxicity					
Developmental Toxicity					
Oral	No data	No data	No data	No data	Decrease in foetal wt and malformations together with high maternal toxicity from 2 mg/kg bw/d (mice)
Dermal	No data	No data	No data	No data	No data
Inhalation	680 ppm: Only maternal tox (rat)	680 ppm: Maternal tox, extra ribs, implantation losses (rat)	680 ppm: Maternal tox, extra ribs, implantation losses (rat) 1600 ppm NOAEc for developmental neurotoxicity	No data	LOEC = 230 ppm: extra ribs, fused sternebrae (rat) LOAEC = 500 ppm impaired learning/motor activity of pups
CLH	**None**	**None**	**None**	**None**	**None**
Additional self-classification***	**None**	**None**	**None**	**None**	**None**
Classification acc. to eMSCA	**NC**	**NC**	**NC**	**NC**	**NC**
Fertility					
Oral	No data	No data	No data	NOAEC inhalation, 2-gen. rat 500 ppm	NOAEC inhalation, one-generation rat, 500 ppm?
Dermal	No data	No data	No data	No data	No data
Inhalation	No data	No data	No data	No data	No data
CLH	**None**	**None**	**None**	**None**	**None**
Additional self-classification***	**None**	**None**	**None**	**None**	**None**
Classification acc. to eMSCA	**NC**	**NC**	**NC**	**NC**	**NC**
Aspiration Hazard					
CLH	**None**	**None**	**None**	**Asp. Tox 1**	**None**
Additional self-classification***	**Asp. Tox 1**	**Asp. Tox 1**	**Asp. Tox 1**	**None**	**Asp. Tox 1**
Classification acc. to eMSCA	**Asp. Tox 1**	**Asp. Tox 1**	**Asp. Tox 1**	**Asp. Tox 1**	**Asp. Tox 1**

* Part of this information was derived from (German MSCA, 2008)
** Ranges are derived from upper/lower 95% confidence limits as reported
***Self-classifications which in the view of the eMSCA appeared to be obviously unjustified are omitted (in most cases this concerned only one single notifier and never more than 2% of the notifications)

Despite the fact that the justification/ reporting of the read-across approach in the registration dossiers was found to be insufficient, the eMSCA considers that the above table

shows qualitatively that the different isomers and ethylbenzene more or less elicit comparable effects in animals and humans over a variety of endpoints. Most prominently this seems to hold for the acute neurobehavioural effects, which provide the most sensitive starting points for acute toxicity risk assessment.

On a quantitative basis, some differences are observed between the three isomers, however a clear trend was not observed and to some degree, dose selection may be responsible for this observation (many older studies did not establish a NOAEC or LOAEC). One exception is given by ototoxicity, for which the available data show that p-xylene is much more potent than o- or m-xylene (however they not allow to conclude that these two isomers could not be ototoxic at high doses > 1800 ppm).

An assessment of the read-across approach in terms of ECHA's Read-Across Assessment Framework (ECHA, 2017) can be found in section 7.16 (Annex 1).

Given the apparent plausibility of read-across, the eMSCA finds that a request for an update of the read-across justification lied outside the scope of SEv and therefore asked ECHA to open a dossier evaluation on this issue.

7.9.11. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Oral exposure to xylenes is not relevant under the scope of this dossier. In addition, with the exception of acute dermal LD_{50} studies and studies on dermal absorption, no other dermal studies are available, therefore risk assessment for dermal exposure, where applicable, should be performed via route-to-route extrapolation from inhalation studies.

The spectrum of adverse effects observed in animals and/or humans after inhalation of xylene isomers or mixed xylene comprises:

- Neurotoxicity
- Irritation of skin and respiratory tract
- Specific Target Organ Toxicity - ototoxicity (p-xylene, ethylbenzene, mixed xylenes)
- Embryo-/foetotoxicity
- Effects on body weight gain and organ weight
- General moribundity and lethality, teratogenicity

Out of the experiments listed in Table 18 to Table 27

(section 7.9.2 to 7.9.8), Table 29 shows those inhalation studies principally qualifying as potential candidates to be used as starting points (Points of Departure, PoDs) for risk assessment, i.e. those considered sufficiently reliable. The studies are grouped according to the respective time-frame (acute/subacute, subchronic, chronic) and listed in the order of ascending LOAECs. Where different isomers were found to display different NOAECs/LOAECs, the isomer with the lowest LoAEC was chosen.

Table 29

SUMMARY OF POTENTIAL STARTING POINTS FOR RISK ASSESSMENT BASED ON AVAILABLE INHALATION STUDIES*			
Reference/design, species/test substance	**Endpoint**	**NOAEL/NOAEC**	**LOAEL/LOAEC**
Acute			
(Ernstgård et al., 2002) 1 x 2 h, human m-Xylene	Subjective self-reporting of irritation Slight decrease in pulmonary function (Forced Expiratory Volume in 1 second, FEV_1; Forced Vital Capacity, FVC) No effects on acoustic rhinometry, markers of inflammation or blinking frequency Adversity unclear	< 50 ppm	50 ppm
(Olson et al., 1985) 1 x 4 h, human p-Xylene	Simple reaction time, short term memory, and choice reaction time at 0, 1 and 4 h into exposure were all unaffected	68 ppm	> 68 ppm
(Dudek et al., 1990) 1 x 4 h, human Xylene	Effects on Simple Reaction Time (SRT) and Choice Reaction Time (ChRT)	< 100 ppm	100 ppm
(Gamberale et al., 1978) 1 x 70 min, human Xylene	Impact on numerical ability, reaction time (simple and choice), short-term memory, and critical flicker fusion under physical activity	100 ppm	300 ppm
(Savolainen et al., 1984) 1 x (3 h exposure – 40 min break – 60 min exposure) at constant and fluctuating concentrations, human m-Xylene	Impairment of body balance and audiomotor coordination after peak exposures	200 ppm	400 ppm
(Seppalainen et al., 1989) 1 x (3 h exposure – 40 min break – 40 min exposure) at constant and fluctuating concentrations, human m-Xylene	Decrease in Visually Evoked Potentials (Flash VEPs) upon physical activity	200 ppm	400 ppm
(Laine et al., 1993) 1 x 4 h, human m-Xylene	Decreased body sway; prolonged simple visual reaction times in sedentary subjects and auditory choice reaction times when	200 ppm	400 ppm

SUMMARY OF POTENTIAL STARTING POINTS FOR RISK ASSESSMENT BASED ON AVAILABLE INHALATION STUDIES*			
Reference/design, species/test substance	**Endpoint**	**NOAEL/NOAEC**	**LOAEL/LOAEC**
	combined with physical exercise		
(Carpenter et al., 1975) 1 x 4 h, rat, dog Xylene	Slight incoordination in rats and lacrimation in dogs	< 909 ppm	909 ppm
(Dyer et al., 1988) 1 x 4 h, rat p-Xylene	Significant amplitude depression of flash-evoked potentials (FEP)	800 ppm	1,600 ppm
(Korsak et al., 1990) 1 x 6 h, mouse o-, m-, and p-Xylene	Sensory irritation	< 2,600 ppm	2,600 ppm
(Korsak et al., 1990) 1 x 6 h, rat o-, m-, and p-Xylene	Effect on rotarod performance in rats	< 3,000 ppm	3,000 ppm
Subacute			
(Savolainen and Pfäffli, 1980) 2 wk, 5 d/wk, 6 h/d, rat m-Xylene	Increase in brain NADPH-diaphorase and azoreductase levels and cerebral RNA Decrease in cerebral glutathione activity already at 50 ppm Adversity of these findings is unclear, interpreted as adaptive response	< 50 ppm	50 ppm
(Gralewicz and Wiaderna, 2001) 4 wk, 6 h/d, 5 d/wk, rat m-Xylene	Significantly higher spontaneous locomotor activity in the open field, impaired passive avoidance learning and significantly longer paw-lick latencies 24 h after footshock Acquisition of the two-way active avoidance response significantly impaired	< 100 ppm	100 ppm
(Hudak and Ungvary, 1978) PND study in rats, 24 h/d, gestation days 9-14 Xylene	Increase in skeletal anomalies (extra ribs, fused sternebrae)	< 230 ppm	230 ppm

SUMMARY OF POTENTIAL STARTING POINTS FOR RISK ASSESSMENT BASED ON AVAILABLE INHALATION STUDIES*			
Reference/design, species/test substance	**Endpoint**	**NOAEL/NOAEC**	**LOAEL/LOAEC**
(Ungvary et al., 1980) PND study in rats, 24 h/d, gestation days 7-14 o-Xylene	Decreased foetal weight and number of weight-retarded foetuses	34 ppm	340 ppm
([redacted] 1978b) PND study in rats, gestation days 6-15 Xylene	No maternal toxicity or effects on embryos/foetuses Does not fully cover period of organogenesis	100 ppm	400 ppm
(Saillenfait et al., 2003) PND study in rats, 6 h/d, gestation days 6-20 o-Xylene, Xylene	Significant decrease in fetal bw at ≥ 500 ppm o-xylene or mixed xylenes	100 ppm	500 ppm
(Faber et al., 2006) Two-generation study in rats, 6 h/d from ≥ 70 d before mating through lactation of F_1 pups Ethylbenzene	Decreased body weight gain in male F_0 and F_1 rats of the 500 ppm group in both generations	100 ppm	500 ppm
([redacted], 1983) One-generation study in rats Xylene	No effect on fertility or development	250 ppm	500 ppm
(Hass and Jakobsen, 1993) PND study in rats, gestation days 4-20 Xylene	Delayed ossification of os maxillare, higher pup weight, impaired rotarod performance of pups	< 500 ppm	500 ppm
(Hass et al., 1995) PND study in rats, 6 h/d, gestation days 7-20 Xylene	Decrease in absolute brain weights of pups, delay in development of the air righting reflex, impairment of performance on the rotarod and in the water maze	< 500 ppm	500 ppm
(Hass et al., 1997) PND study in rats, 6 h/d, gestation days 7-20 Xylene	Impaired performance of pups in maze test at age 16 and 28 wk	< 500 ppm	500 ppm
(Honma et al., 1983)	Acetylcholine levels in striatum and whole brain	400 ppm	800 ppm

SUMMARY OF POTENTIAL STARTING POINTS FOR RISK ASSESSMENT BASED ON AVAILABLE INHALATION STUDIES*			
Reference/design, species/test substance	**Endpoint**	**NOAEL/NOAEC**	**LOAEL/LOAEC**
30 d, 24 h/d, rat Xylene	decreased and brain glutamine levels increased Questionable reliability due to lack of clear dose response Adversity unclear		
(Rosen et al., 1986) PND study in rats, gestation days 7-16 p-Xylene	Decreased maternal weight gain	800 ppm	1,600 ppm
(Maguin et al., 2006) 3 wk, 6 h/d, 5 d/wk 1800 ppm p-xylene	Ototoxicity: A 39-dB permanent threshold shift was obtained over the tested frequencies range from 8 to 20 kHz. Outer hair cells largely injured	900 ppm	1800 ppm
(Andersson et al., 1981) 3 d, 6 h/d, rat Xylene and o-, m-, p-, isomers	Changed neurotransmitter levels in different nervous tissues	< 2000 ppm	2000 ppm
Subchronic			
(Korsak et al., 1994) 3 mo, 5 h/d, 6 h/wk, rat m-Xylene	Significant decrease in paw-lick response time (hot plate behaviour)	< 50 ppm	50 ppm
(Korsak et al., 1992) 6 mo, 6 h/d, 5 d/wk, rat m-Xylene	Decreased rotarod performance, decreased spontaneous motor activity	< 100 ppm	100 ppm
(Gralewicz et al., 1995) 3 mo, 5 h/d, 6 h/wk, rat m-Xylene	Learnig deficit in maze test two months post-exposure Development of the age-related spike and wave activity significantly retarded (biological significance unclear)	< 100 ppm	100 ppm
(Gagnaire et al., 2007) 13 wk, 6 h/d, 5 d/wk Xylene	Increased auditory thresholds and loss of outer hair cells. Concentrations of ethylbenzene in xylene necessary to cause a given ototoxicity were 1.7–2.8	< 250 – 500 ppm (depending on composition, i.e. ethylbenzene and, to a lesser	250 - 1000 ppm (depending on composition, i.e. ethylbenzene and, to a lesser

SUMMARY OF POTENTIAL STARTING POINTS FOR RISK ASSESSMENT BASED ON AVAILABLE INHALATION STUDIES*			
Reference/design, species/test substance	**Endpoint**	**NOAEL/NOAEC**	**LOAEL/LOAEC**
	times less than those of pure ethylbenzene	degree, p-xylene content)	degree, p-xylene content)
(Carpenter et al., 1975) 13 wk, 6 h/d, 5 d/wk, rat/dog Xylene	No effects on blood chemistry, food consumption, body weight, urinalysis, macroscopic pathology	810 ppm	> 810 ppm
(Gagnaire et al., 2001) 13 wk, 6 h/d, 6 d/wk p-Xylene	Moderate to severe ototoxicity in rats exposed at 900 and 1800 ppm. Body weight gain reduction at ≥ 900 ppm Increased auditory thresholds observed at 2, 4, 8, and 16 kHz Auditory threshold shifts (35 to 38 dB) did not reverse after 8 weeks of recovery Moderate and severe losses of outer hair cells of the organ of Corti occurred in animals exposed to 900 and 1800 ppm	450 ppm	900 ppm
(Korsak et al., 1992) 3 mo, 6 h/d, 5 d/wk, rat m-Xylene	Decreased rotarod performance, decreased spontaneous motor activity, slight decrease in lymphocytes and increase in monocytes of unclear significance	< 1000 ppm	1000 ppm

* In order of ascending LOAEC; key studies used for DNEL derivation are highlighted

7.9.11.1. DNEL for acute inhalation

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 (Dudek et al., 1990; Gamberale et al., 1978). (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.

In summary, a DNEL for single acute exposure via inhalation should be derived from the NOAEC for neurobehavioural effects of 68 ppm established in the study by (Olson et al., 1985). As the data were obtained from humans, no assessment factor for interspecies variability needs to be assigned. However, an intraspecies variability AF of 5 for workers or 10 for consumers must be set. In addition and in line with the IR/CSA guidance R.8,

where human single exposure duration is expected to be longer or shorter than the 4-h exposure on which the PoD of 68 ppm was based, this PoD needs to be adjusted accordingly using modified Haber's law (C^n x t = const., where n = 1 for extrapolation to longer durations and n = 3 for extrapolation to shorter durations), based on the observation that it may take several hours after the start of exposure until blood and brain levels reach their maximum values on the same day cf. e.g. (Gagnaire et al., 2007; Kaneko et al., 1995). For example, in order to derive an acute 8 h DNEL for consumers from the PoD of 68 ppm, an overall AF of 20 (AF 2 for daily exposure duration, AF 10 for intraspecies variability) has to be applied (resulting in a DNEL of 3.4 ppm or ca. 15 mg/m^3).

7.9.11.2. DNEL for acute dermal exposure

As reliable dermal toxicity data are lacking, dermal risk characterisation should be performed via route-to-route extrapolation from data obtained from the inhalation route.

7.9.11.3. DNEL for chronic inhalation

7.9.11.3.1. Calculation for workers

The eMSCA derived the DNEL (worker, inhalation, long-term, systemic) according to the specifications given in the REACH guidance chapter R.8 (ECHA, 2012).

The eMSCA consider neurotoxicity to be the most critical toxicological endpoint of xylene isomers. In both, human and rats, similar effects on the central nervous system (CNS) were observed.

The eMSCA derived the DNEL on the basis of the study of (Korsak et al., 1994). For the DNEL calculation only the rotarod studies on rats were taken into consideration. In this study the duration of xylene exposure was 90 days. Rats were exposed to doses of 50 ppm (221 mg xylene/m^3) and 100 ppm (442 mg xylene/m^3) m-xylene and the effects on the motor coordination were studied after 1, 2 and 3 months of exposure. After 1 month of exposure the failure rate concerning a motor coordination disturbance in the respective dose groups reached a level which did not change until the end of the study. Failure rates in the 50 ppm and 100 ppm dose groups were ca. 8 and 35%. In both (Korsak et al., 1994) and the report of the German Committee on Indoor Guide Values (Ausschuss für Innenraumluftwerte, 2015) the failure rate in the 50 ppm dose group is considered as significant but minimal. For this reason the eMSCA sets 50 ppm as the LOAEL and used it as a starting point (Point of Departure, PoD) for the DNEL derivation. By using standard default factors (6/8 h and 6.7/10 m^3) the value was adjusted to the situation at the workplace resulting in a corrected PoD of 25 ppm.

For the following calculation of the DNEL the appropriate assessment factors had to be selected. For this purpose, two acute inhalation studies on rats and humans (Korsak et al., 1993; Olson et al., 1985) were analysed additionally. In (Korsak et al., 1993) also rotarod tests were used to study the effect of m-xylene exposure on the motor coordination in rats. The concentration of 1000 ppm (4400 mg/m^3) was observed as a LOAEL. Using the LOAEC/NOAEC relation found in the subchronic study (Korsak et al., 1994), the concentration of 500 ppm (2210 mg/m^3) was set as a NOAEL herein.

In (Olson et al., 1985) the NOAEL was determined at a concentration of 70 ppm (310 mg/m^3). At this dose group, no effects on reaction time or short-term memory of the test persons were observed after a 4-h exposure to m-xylene. At a concentration of 100 ppm (440 mg/m^3) an adverse effect on the reaction time were noticed. Hence, the concentration of 70 ppm was set as the NOAEL and 100 ppm as the LOAEL.

Consequently, the DNEL (worker, inhalation, long-term, systemic) was derived by the eMSCA by modifying the PoD of 25 ppm by applying the assessment factors for residual interspecies variability of 2.5 and for intraspecies variability of 5 (25 ppm/2.5/5), resulting in a DNEL of 2 ppm (8.8 mg/m^3). The application of an assessment factor for the conversion of LOAEL to NOAEL was waived due to the fact that the observed effects at this LOAEL

were significant but minimal. A detailed overview on the derivations of the long-term DNEL as conducted by the eMSCA is presented in Table 30

Table 30

DETAILED OVERVIEW OF THE DERIVATION OF THE DNEL (WORKER, INHALATION, LONG-TERM, SYSTEMIC) FOR M-XYLENE AS AN EXAMPLE CONDUCTED BY THE eMSCA.		
Description (AF= Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	50 ppm (221 mg/m^3) = LOAEL	The NOAEL results from a subchronic (90 days) inhalation toxicity study in Wistar rats (Korsak et al., 1994). At the lowest dose tested (i. e. at 50 ppm) a minimal but significant decrease in motor coordination (-8 % compared to controls) was observed. This concentration was set as LOAEL.
Modification of the starting point	(6 h / 8 h)* (6.7 m^3/ 10 m^3) ↓ Overall factor = 0.5025	Due to different exposure conditions in the animal experiment and at the workplace both time scaling and a modification due to different respiratory volumes have to be applied according to the REACH guidance R.8.
Modified dose-descriptor	50 ppm * 0.5025 = **25 ppm**	
AF for interspecies differences	2.5	However, a default assessment factor for remaining differences is applied according to the REACH guidance R.8.
AF for intraspecies differences	5	The default factor for workers is applied according to the REACH guidance R.8 because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	1	No assessment factor is applied.
AF related to dose response relationship	-	No assessment factor is applied. The application of an assessment factor for the conversion of LOAEL to NOAEL was waived due to the fact that the observed effects at this LOAEL were significant but minimal.
DNEL	25 ppm/2.5/5 = **2 ppm (8.8 mg/ m^3)**	

The DNEL calculated by the eMSCA is lower than the values given by the registrants.

The Registrants propose to use the IOELV (8 hr time-weighted average (TWA)) of 50 ppm (221 mg/m^3) and the IOELV (short-time exposure limit (STEL)) of 100 ppm (442 mg/m^3) as DNELs. These limit values were recommended by SCOEL in 1992 for both the xylene isomers and the mixture and are based on mild irritation of eye and upper respiratory tract and CNS effects in rats and humans (Carpenter et al., 1975; Hastings et al., 1984). According to appendix R.8-13 of ECHA guidance IOELVs can be used for the derivation of DNELs or as a DNEL itself:

"When an EU IOEL exists the registrant may, under conditions as described below, use the IOEL in place of developing a DNEL. But it must be noted that this approach is only applicable as long as there are no newer relevant data available. R.8-13 of ECHA guidance: a registrant is allowed to use an IOEL as a DNEL…, unless new scientific information…does not support the use of the IOEL for this purpose. The registrant may wish to provide details

of the new scientific information to DG EMPL who will take this into consideration as part of the normal procedures for reviewing IOELs."

7.9.11.3.2. Calculation for 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 who displayed a decreased latency in the paw-lick response at the end of a 13 wk, 6 h/d, 5 d/wk exposure. 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. For differing daily exposure durations, modified Haber's law (see above) has to be applied.

Table 31

CRITICAL DNELS/DMELS DERIVED BY OTHERS					
Type of health-based guidance value	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Inhalation					
Acute/Subacute					
MRL ≤ 14 d		(Ernstgård et al., 2002)		2 ppm	(ATSDR, 2007)
DNEL (workers), acute				100 ppm	Lead registrant
DNEL (general population), acute	Neurotoxicity, irritation	IOELV for workers	Not given	260 mg/m^3 60 ppm	Lead registrant
Subchronic					
MRL 15 d – 1 yr				0.6 ppm	(ATSDR, 2007)
Chronic/Long-term					
MRL > 1 yr				0.05 ppm	(ATSDR, 2007)
DNEL (workers), long-term	Mild irritation of eye and upper respiratory tract	(Carpenter et al., 1975; Hastings et al., 1984)	50 ppm (221 mg/m^3)	50 ppm (221 mg/m^3)	Lead registrant
Innenraumrichtwert I (Guidance value for indoor air, with no risk of adverse effects upon lifetime exposure)	Neurotoxicity	(Korsak et al., 1992; Korsak et al., 1994)	100 ppm (LOAEC)	0.02 ppm (0.8 mg/m^3)	(Ausschuss für Innenraumluftwerte, 2015)

CRITICAL DNELS/DMELS DERIVED BY OTHERS					
Type of health-based guidance value	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Innenraumrichtwert II (Guidance value for indoor air, upon exceedance of which risk mitigation is required)	Neurotoxicity	(Korsak et al., 1992; Korsak et al., 1994)	100 ppm (LOAEC)	0.18 ppm (0.1 mg/m^3)	(Ausschuss für Innenraumluftwerte, 2015)
DNEL (general population), long-term	Neurotoxicity, irritation	IOELV for workers	Not given	65.3 mg/m^3 15 ppm	Lead registrant
Dermal					
DNEL (workers), long-term	Neurotoxicity	IOELV for workers	Not given	212 mg/kg bw/d	Lead registrant
DNEL (general population), long-term	Neurotoxicity			125 mg/kg bw/d	Lead registrant
Oral					
General population	Repeated dose toxicity			12.5 mg/kg bw/d	Lead registrant

Table 32

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL***	**Justification/ Remarks**
Consumers/General Population					
Neurobehaviour	Reaction time	(Gamberale et al., 1978) (Olson et al., 1985)	$NOAEC_{human}$ 167 ppm 171 ppm	Acute, 0.25 h** 17 ppm 70 mg/m^3	Adjustment to 0.25 h daily exposure via modified Haber's law (C^3 x t = const.), overall AF = 10
Neurobehaviour	Reaction time	(Gamberale et al., 1978) (Olson et al., 1985)	$NOAEC_{human}$ 105 ppm 108 ppm	Acute, 1 h 11 ppm 50 mg/m^3	Adjustment to 1 h daily exposure via modified Haber's law (C^3 x t = const.), overall AF = 10
Neurobehaviour	Reaction time	(Olson et al., 1985)	$NOAEC_{human}$ 86 ppm	Acute, 2 h 9 ppm 40 mg/m^3	Adjustment to 2 h daily exposure via modified Haber's law (C^3 x t = const.), overall AF = 10
Neurobehaviour	Reaction time	(Olson et al., 1985)	$NOAEC_{human}$ 68 ppm	Acute, 4 h 7 ppm 30 mg/m^3	Overall AF = 10

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL***	**Justification/ Remarks**
Neurobehaviour	Reaction time	(Olson et al., 1985)	$NOAEC_{human}$ 34 ppm	Acute, 8 h 3 ppm 15 mg/m³	Adjustment to 8 h daily exposure via modified Haber's law (C x t = const.), overall AF = 10
Neurobehavioural toxicity	Hypersensi-tivity to pain (hot plate test)	(Korsak et al., 1994)	$LOAEC_{rat}$ 41 ppm	Chronic, 4 h/d 0.5 ppm 2 mg/m³	Adjustment to 4 h daily exposure via modified Haber's law (C^3 x t = const.) and to exposure 7 d/wk, overall AF = 75
Neurobehavioural toxicity	Hypersensitivity to pain (hot plate test)	(Korsak et al., 1994)	$LOAEC_{rat}$ 9 ppm	Chronic, 24 h/d 0.12 ppm 0.5 mg/m³	Adjustment to 24 h daily exposure via modified Haber's law (C x t = const.) and to exposure 7 d/wk, overall AF = 75

*Rounded to first significant figure if the first figure is 2-9, to two significant figures if the first is 1; ** Consistent with the result that would be derived from (Olson et al., 1985)

7.9.12. Conclusions of the human health hazard assessment and related classification and labelling

7.9.12.1. Read-across approach

Table 27 in section 7.9.10 above already provided an overview of the available toxicity data in the form of a matrix table. For building this database, the registrants to a large extent relied on read-across from individual xylene isomers to xylene mixtures and vice versa. Despite the fact that the justification/reporting of the read-across approach in the registration dossiers was found to be insufficient, the eMSCA considers that Table 28 shows qualitatively that the different isomers and ethylbenzene more or less elicit comparable effects in animals and humans over a variety of endpoints and therefore the read-across hypothesis appears to be plausible in principle. Most prominently, this seems to hold for the acute neurobehavioural effects, which provide the most sensitive starting points for acute toxicity risk assessment. Given the apparent plausibility of read-across, the eMSCA found that a request for an update of the read-across justification was outside the scope of SEv. An assessment of the read-across approach in terms of ECHA's Read-Across Assessment Framework (ECHA, 2017) can be found in Annex 1 (section 7.16).

7.9.12.2. ADME

The following worst-case assumption should be used in line with the REACH guidance:

- 50% oral absorption should be used when converting an external oral dose to a systemically available one, while 100% should be used when converting a systemically available to an external oral dose.

- 60% absorption should be used when converting an external air concentration to a systemically dose following inhalation, while a value of 95% should be used when converting a systemic dose to an external air concentration.

- When judging the risk of dermal exposure based on systematic concentrations derived from oral or inhalation studies 43 mg/cm^2/h can be considered as a reasonable worst-case estimate of dermal absorption flux.

Xylenes are widely distributed and intermediately stored to some degree in fat tissue (e.g. perirenal fat). With respect to metabolism, phase I reactions include oxidation to hydroxy-, carbonyl-, and ultimately oxocarbonyl derivatives, followed by phase II conjugations, most prominently with glycine to form the corresponding methylhippuric acids. In isomer mixtures, isomers and ethylbenzene appear to compete for the same CYP enzymes and conjugation partners. The involvement of ADH suggests possible mixture effects with ethanol and other solvents. The major fraction of absorbed xylene isomers is excreted as methylhippuric acids (ethylbenzene: mandelic acid) while a smaller fraction is exhaled unchanged. Some studies show the presence of corresponding dimethylphenols, some postulate route-specific differences, but the data base seems to be too weak to support this. Conjugation and excretion are fastest for p-xylene and ethylbenzene, followed by m-xylene and o-xylene. Competitive metabolism might lead to difficulties in reliably predicting blood levels from single isomers vs. mixed isomers. Potential sex-specific differences are not covered by the human database. Similar results as for the three xylene isomers have been reported for ethylbenzene.

7.9.12.3. Acute toxicity including irritation/corrosion

Experimental data are available for all isomers for the inhalation route, for m-xylene, ethylbenzene and mixed xylenes also for the oral and dermal routes of administration. Non-lethal toxicity of xylene isomers or mixed xylene can be observed in the form of acute neurobehavioural effects. In animals, inter alia depression of flash-evoked potentials (FEP), as well as decrease in hot plate, rotarod and maze test performance were observed. In humans learning performance, reaction time and/or motor coordination can be affected already after single acute exposure. A NOAEC of 68 ppm is taken forward to risk assessment as the most relevant PoD for acute effects after single inhalation exposure in humans. While the available data base supports CLH as Acute Tox. 4 for the inhalation route as well as no classification for acute oral toxicity, the rationale behind the existing CLH for xylenes (isomers and mixed) as Acute Tox. 4 for the dermal route is not clear. Both the data in animals and humans suggest the need for classification/labelling for STOT SE 3, H336 ("May cause drowsiness or dizziness").

Based on the available data, individual xylene isomers, ethylbenzene and mixed xylenes are considered unlikely to possess corrosive properties. According to CLP Annex VI, all xylene isomers are classified as Skin Irrit. 2, therefore no further action is required despite the fact that the available data mostly consist of very old studies with insufficient reporting and/or scoring systems not directly compatible with the GHS/CLP system. With respect to eye irritation, the available studies are considered sufficient to exclude a potential for severe eye damage (CLP Cat. 1). In the view of the eMSCA, they also do not give rise to a sufficiently strong concern justifying initiation of CLH for eye irritation (CLP Cat. 2). For respiratory tract irritation, however, the available data in animals indicate a possible need for classification as STOT SE/H335. Studies in humans have shown that respiratory irritation (in the form of sensory irritation) can be observed in humans exposed to xylenes, too. However, most of these findings were based on subjective reporting and could not be

objectivated by measurements. It is noted that a number of notifiers to the C&L Inventory have chosen to self-classify the xylene isomers in this way.

7.9.12.4. Sensitisation

With remaining uncertainties acknowledged, the eMSCA considers the totality of information sufficient to conclude that xylenes most likely are not skin sensitisers. In this regard the respective initial concern has been clarified. No data on respiratory sensitisation are available for the xylenes. Given that all known respiratory sensitisers are also skin sensitisers (which xylenes are not considered to be) and that no reports on respiratory hypersensitivity as a consequence of exposure to xylenes have been found, the eMSCA concludes that there is currently no specific concern that xylenes could be respiratory sensitisers.

7.9.12.5. Repeated dose toxicity

Repeated dose studies are available for the oral and inhalation route. No studies with repeated dermal administration were identified in the registration dossiers or the published literature. Studies along the oral route mainly demonstrated effects on organ and body weight as well as – at very high doses not relevant for classification and labelling – clinical signs of severe toxicity (prostration, shallow breathing, lethality). However, under the scope of this SEv, the eMSCA considers the oral route less relevant and risk assessment was therefore focused on exposure via inhalation. Neurofunctional/neurobehavioural impairment has been identified as the most sensitive endpoint for risk assessment. In animals, repeated inhalation of xylenes was found to impact on learning, reaction time, motor coordination, and increased sensitivity to pain expressed as a decreased latency of the paw-lick response in rats when placed on a hot metal plate. While the relevance of these effects for humans in principle has been demonstrated in acute studies, no adequate human studies using repeated exposure are available for these endpoints. The LOAEC of 50 ppm for hot plate test behaviour at the end of a 13-wk (5 d/wk, 6 h/d) inhalation experiment with m-xylene was taken forward as the starting point for risk characterisation. This effect likely does not represent irreversible neurological damage and therefore does not have to be considered for STOT RE classification. With respect to STOT RE classification, however, one of the initial concerns of the eMSCA under SEv was ototoxicity, which was demonstrated in rats for p-xylene at ≥ 800 ppm (13 wk, 5 d/wk, 6 h/d) or 1800 ppm (3 wk, 5 d/wk, 6 h/d), while 1800 ppm, the highest concentration tested in both experiments and well above the classification limit for STOT RE 2, was a NOAEC for the o- and m-isomers. The relevance for humans has been shown in studies which reported significantly lower hearing ability in exposed vs. non-exposed workers, but cannot be used for quantitative risk assessment. As a consequence of these findings, no classification/labelling for STOT RE is indicated for any of the single xylene isomers.

7.9.12.6. Genotoxicity

The eMSCA finds that the available data do not point at a genotoxic concern for mixed xylenes or any of the individual xylene isomers.

7.9.12.7. Carcinogenicity

In 1986 the US National Toxicity Program has performed two oral combined chronic toxicity and carcinogenicity studies in rats and mice, in which no increased incidence of tumours in treated groups up to the highest dose of 500 (rats) or 1000 (mice) mg/kg bw/d was observed. In conjunction with the synopsis of the available data base on genotoxicity, the eMSCA finds that at this point in time, there is no concern about a carcinogenic potential of the xylene isomers.

7.9.12.8. Toxicity to reproduction

In several studies on developmental toxicity, xylenes caused skeletal variations as well as effects on foetal body weight and foetal neurobehaviour. While maternal toxicity is not always explicitly reported in sufficient detail, it can be assumed that all of the adverse

effects observed only occurred at dose levels much higher than those required to trigger neurotoxicity in maternal animals. The overall NOAEC/LOAEC for foetal weight effects was 100/340 ppm. Based on these observations and the nature of the effects, there are currently no indications that classification with respect to developmental effects is required for xylenes.

Following conclusion of the substance evaluation but prior to publication of the report, new information from pre-natal developmental studies in rabbits were provided in the registration as a follow-up of a dossier evaluation by ECHA.

This new information was not assessed in detail by the eMSCA and is not reflected in this report. However, ECHA has, in April 2021, formally concluded the compliance check and confirmed that the PNDT study submitted by the registrants is complying with the requested information.

A one-generation study with xylene in rats showed no effects on fertility-related parameters after exposure to concentrations up to 500 ppm. However, this study is not equivalent to a two- or extended one-generation study as required by REACH at this tonnage level. The registrant(s) have waived this requirement by performing read-across to a published two-generation study in rats performed with ethylbenzene, which likewise did not show relevant effects on fertility up to 500 ppm. In summary, potential data gaps for developmental toxicity (second species) and fertility (read-across to a two-generation study with ethylbenzene) have been identified, but no specific concern could be established that would justify requesting further information under SEv in line with the risk paradigm of REACH Art. 50 (4).

7.9.12.9. Aspiration hazard

The kinematic viscosity of all xylene isomers is reported to lie in the range of 0.58-0.76 mm^2/s at 25 °C which suggests that the criterion for classification given in the CLP regulation (≤ 22.5 mm^2/s at 40 °C) is clearly met. The eMSCA therefore concludes that all xylene isomers as well as mixed xylenes should be classified/labelled as Asp. Tox 1 (H304: "May be fatal if swallowed and enters airways)".

7.9.12.10. Physico-chemical properties

o-Xylene, m-xylene and p-xylene are classified as flammable liquids. Therefore, a risk assessment of the likelihood and the severity of an event occurring due to physicochemical hazard properties is needed. Flashpoint, explosion limits, vapour pressure, critical chemical reactions are important factors to evaluate the risk. The severity of an event will be also triggered by the substance amount of use per task/in the process and the process condition like temperature, pressure, concentration, ventilation and duration.

7.10. Assessment of endocrine disrupting (ED) properties

There was no initial concern for ED properties at the beginning of this SEv. No indications of a potential of xylene isomers to cause ED-related effects have been identified in the course of the evaluation of the toxicological database.

7.10.1. Endocrine disruption – Environment

Not assessed during this evaluation.

7.10.2. Endocrine disruption - Human health

There was no initial concern for ED properties at the beginning of this SEv. No indications of a potential of xylene isomers to cause ED-related effects have been identified in the course of the evaluation of the toxicological database.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

The eMSCA agrees with the US Agency for Toxic Substances and Disease Registry in concluding that "no *in vivo* or *in vitro* studies were located regarding endocrine disruption in human and /or animals after exposure to mixed xylenes or individual isomers of xylene. Evidence for endocrine effects has not been seen in studies on reproductive, developmental, or chronic toxicities of xylenes" (ATSDR, 2007).

7.11. PBT and VPVB assessment

PBT and vPvB assessment were outside the scope of this SEv.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Workers

The exposure assessment for workers includes modelled data from the CSRs (as provided by the registrants) that were calculated with ECETOC TRA v3. The exposure scenarios taken into account for this substance evaluation report are taken from the CSRs of the lead registrant (version October 2015). In addition, measurement data from Germany as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) have been evaluated.

7.12.1.1.1. Scope and type of exposure

The CSRs from the lead registrant (version October 2015) includes 17 worker exposure scenarios for o- and p- xylene. Eleven scenarios cover industrial applications und six scenarios cover xylene applications for professional worker. An overview of the exposure scenarios according to the lead registrant is provided for each of the xylene isomers in a confidential annex to the evaluation report.

The vapour pressures of the xylene isomers at 25 °C are 882 Pa for o-xylene, 1052 Pa for m-xylene and 1167 Pa for p-xylene. As xylenes are readily volatile liquids and because they are also used in applications with potentially high exposures (such as solvents and/or cleaning agents), exposure via dermal and inhalation route are likely to occur. However, as the focus of the exposure assessment is based on measurement data, the modelled data for dermal exposure from the CSRs have not been further taken into account. This was not considered necessary because the risk assessments based solely on the measured inhalation data already shows RCRs well above 1 and it is therefore clearly demonstrated that risks are not adequately controlled for a wide range of sectors and uses.

7.12.1.1.2. Occupational exposure data from the German Social Accident Insurance (IFA)

Measured workplace exposure data from Germany have been evaluated in a study by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA, 2016). The data have been gathered from 2005 to August 2016 and were documented in accordance to the measurement system of the German Social Accident Insurance Institutions for exposure assessment (MGU) (Gabriel et al., 2010). Overall, a total of 8449 measurement data for xylene (all isomers, CAS number 1330-20-7) have been evaluated according to industry groups as well as work area groups.

Table 33

provides an overview of the statistical evaluations according to industry groups and work areas. In accordance with REACH Guidance on Information Requirements and Chemical

Safety Assessment Chapter R.14: Occupational exposure assessment, the 90th percentile value (representing the reasonable worst case exposure level of the distribution of the measurement dataset), is used as the exposure value for the risk characterisation.

Table 33

Statistical evaluations according to industry groups and work areas

Industry group	Work area group	Exposure duration	Type of measure-ment	Number of measure-ments	Concentration [mg/m³] 90%-value
Surface coating in painting, varnishing and liquid varnish coating	Airless spraying	≥ 6 h	personal	200	160
			stationary	53	49.8
		< 6 h	personal	36	287.6
	Spraying with pressurised air	≥ 6 h	personal	746	44.4
			stationary	133	20.8
		< 6 h	personal	313	46.4
			stationary	31	24.6
	Spraying unspecified	≥ 6 h	personal	129	37.1
			stationary	30	21
		< 6 h	personal	22	57
	Manual surface coating	≥ 6 h	personal	48	79.6
			stationary	30	62
		< 6 h	personal	44	152
	Machine surface coating	≥ 6 h	personal	28	96.2
			stationary	28	32.8
	Dipping, powder coating and other unspecified surface coating processes	≥ 6 h	personal	142	49
			stationary	95	80
		< 6 h	personal	13	273
			stationary	18	25
	Coating preparation, mixing and drying	≥ 6 h	personal	34	22.6
			stationary	81	34
		< 6 h	personal	17	33
Surface coating in metalworking, mechanical engineering and repair workshops	Airless spraying	≥ 6 h	personal	108	111.4
			stationary	59	106.2
		< 6 h	personal	10	27
	Spraying with pressurised air	≥ 6 h	personal	297	54
			stationary	138	31
		< 6 h	personal	80	97
			stationary	22	36.6
	Spraying unspecified	≥ 6 h	personal	86	65.2
			stationary	35	147
		< 6 h	personal	11	30.6
	Manual surface coating	≥ 6 h	personal	76	100
			stationary	54	25
		< 6 h	personal	16	225.8
	Machine surface coating	≥ 6 h	personal	32	63.4
			stationary	32	26.4
	Dipping, powder coating and other unspecified surface coating processes	≥ 6 h	personal	61	42.9
			stationary	78	36.4
		< 6 h	personal	11	105.5
S u r f	Paint spraying	≥ 6 h	personal	135	30

Statistical evaluations according to industry groups and work areas

Industry group	Work area group	Exposure duration	Type of measure-ment	Number of measure-ments	Concentration [mg/m³] 90%-value
	(chemical/plastics/ rubber industry)		stationary	17	40,2
	Surface coating without paint spraying (chemical/plastics/rubber industry)	≥ 6 h	personal	103	43.7
			stationary	70	38.5
		< 6 h	personal	11	312.7
	Paint spraying in wood industry	≥ 6 h	personal	95	25.5
			stationary	21	22.5
		< 6 h	personal	11	15.2
	Surface coating without paint spraying in wood industry	≥ 6 h	personal	64	20.6
			stationary	27	23.6
	Paint spraying in electrical engineering/precision mechanics, optics	≥ 6 h	personal	136	50.2
			stationary	36	14
		< 6 h	personal	60	89
	Surface coating without paint spraying spraying in electrical engineering/precision mechanics, optics	≥ 6 h	personal	72	19.2
			stationary	47	10.9
		< 6 h	personal	28	301.2
			stationary	19	22.5
	Surface coating (glass and ceramics industry)	≥ 6 h	personal	17	16.3
			stationary	98	36.2
	Surface coating in the leather, textile and paper industries	≥ 6 h	personal	22	108.4
			stationary	16	6.3
	Surface coating in the construction industry and the stone and earth industry	≥ 6 h	personal	38	118.2
			stationary	21	24.6
	Surface coating in metal production and electroplating	≥ 6 h	personal	40	84
			stationary	21	11.6
	Surface coating in wholesale/retail, service/transport and educational establishments	≥ 6 h	personal	47	42.2
			stationary	13	75.7
		< 6 h	personal	28	29.2
Manufacture and processing	Manufacture of preparations for the chemical industry	≥ 6 h	personal	483	79.7
			stationary	168	68.2
		< 6 h	personal	32	27.2
	Production of plastic parts and mechanical and thermal plastics processing in the plastics industry	≥ 6 h	personal	86	5.4
			stationary	74	5.2
		< 6 h	personal	17	32.9
	Manufacture and processing of plastic parts in other industries (moulding, prepreg, laminating, casting, extruding, injection moulding or plastic welding)	≥ 6 h	personal	22	7.9
			stationary	18	4.1
	Rubber products, manufacture and processing	≥ 6 h	personal	67	11.6
			stationary	29	16.8
	Gluing	≥ 6 h	personal	161	15
			stationary	77	13.6

Statistical evaluations according to industry groups and work areas

Industry group	Work area group	Exposure duration	Type of measure-ment	Number of measure-ments	Concentration [mg/m³] 90%-value
		< 6 h	personal	24	14.8
			stationary	17	14
	Mechanical machining processes	≥ 6 h	personal	25	7
			stationary	65	2.8
	Thermal machining processes in metalworking, mechanical engineering and electrical engineering	≥ 6 h	personal	10	128
			stationary	30	18
	Filling, conveying, mixing, weighing in the plastics and rubber industry	≥ 6 h	personal	13	86.9
			stationary	15	17
Manufacture and processing	Assembly, machining, finishing in metalworking, mechanical engineering and repair shops	≥ 6 h	personal	51	14.9
			stationary	43	4.99
	Assembly, machining, finishing in other industries	≥ 6 h	personal	31	15.8
			stationary	27	8.3
	Packing and storage work	≥ 6 h	personal	59	61.1
			stationary	77	13.9
		< 6 h	stationary	15	9.9
Cleaning	Cleaning and stripping of parts and surfaces in electrical engineering/fine mechanics/metal working	≥ 6 h	personal	27	185.9
			stationary	23	14.8
		< 6 h	personal	20	137
			stationary	11	15.8
	Cleaning, degreasing, stripping of parts and surfaces in other industries	≥ 6 h	personal	33	61.1
			stationary	16	18.6
		< 6 h	personal	22	126
	Cleaning of plants and containers	≥ 6 h	personal	59	170
		< 6 h	personal	24	50
			stationary	14	9.72
Special industries and work areas	Laboratories in chemical industry	≥ 6 h	personal	38	29.6
			stationary	21	32.3
	Printing and screen printing	≥ 6 h	personal	151	19.6
			stationary	215	25.5
		< 6 h	personal	28	4.1
			stationary	20	14
	Hospitals and pathologies	≥ 6 h	personal	20	73
			stationary	29	27.4
		< 6 h	personal	18	58
			stationary	17	60.4
	Repair and maintenance	≥ 6 h	personal	24	12.4
			stationary	27	8.2
		< 6 h	personal	13	14.7
	Test benches and controls	≥ 6 h	personal	41	4.8
			stationary	45	3.7
	Waste and sewage disposal and recycling	≥ 6 h	personal	22	18.3
			stationary	29	16.5

Statistical evaluations according to industry groups and work areas					
Industry group	**Work area group**	**Exposure duration**	**Type of measure-ment**	**Number of measure-ments**	**Concentration [mg/m³] 90%-value**
	Shipping industry	≥ 6 h	stationary	94	< LOQ
	Foundries	≥ 6 h	stationary	17	28.3
Further work areas	Further work areas in the chemical, rubber and plastics industry	≥ 6 h	personal	11	29.9
			stationary	16	13
	Further work areas in electrical engineering/ fine mechanics/metal processing and repair workshops	≥ 6 h	personal	36	39.6
			stationary	50	24
		< 6 h	personal	23	12.7
Further work areas	Further work areas in construction and stone and earth industry	≥ 6 h	personal	12	28.4
			stationary	15	29.1
	Further work areas in painting, varnishing and liquid varnish coating	≥ 6 h	personal	25	21
			stationary	30	4.1
	Further work areas in the glass and ceramics industry	≥ 6 h	personal	30	9.6
	Further work areas in the leather, wood and textile industry	≥ 6 h	personal	20	15
			stationary	18	12
	Further work areas in educational institutions, wholesale and retail trade, service and transport industry	≥ 6 h	personal	38	23.2
			stationary	34	18.8
		< 6 h	personal	10	9.5
	Other branches and work areas	≥ 6 h	personal	14	10.2
			stationary	30	16

7.12.1.1.3. Risks from physico-chemical properties

For a clear presentation and overview the eMSCA would prefer to group physical-chemical (PC) parameters in bands, depending on the risk assessment of the exposure scenarios. The combination of these bands will then result in risk levels with associated control measures. Currently, none of the dossiers fulfills this requirement. However, the information contained in the Appendix C of the lead dossier of the joint registration of o-xylene provides some details on the physical-chemical properties and the resulting risks. However, the eMSCA is of the opinion that still more detail would be required to fully meet the REACh requirements.

Nevertheless a skilled person will be able to select the right RMMs from the list that is given. We consider this information as acceptable and would recommend to include this Appendix into other dossiers as well.

7.12.1.2. Consumers

In parallel to the SEv evaluation phase, the registrants carried out a downstream user survey regarding consumer uses, asking for product categories which should be further supported and the concentration of xylene present in the final products.

In consequence, they thoroughly revised the consumer exposure assessment and risk characterisation in Chapter 9 of the Chemical Safety Report, which they provided to the eMSCA in October 2015. The registrants removed all identified consumer uses and thereby exposure scenarios of m-xylene and deleted several exposure scenarios for o- and p-xylene. The remaining 30 exposure scenarios were completely revised concerning operational conditions and the model used for exposure estimation. Under the expectation that an update of the registration dossier will follow in due course, the eMSCA decided to take the new data into consideration during the evaluation process.

Therefore only the two xylene isomers o- and p-xylene were the subject of further evaluation while consumer exposure assessment and risk characterisation of m-xylene was considered to be no longer necessary.

For both isomers the registrants provide new exposure scenarios calculated with ECETOC TRA Consumer Exposure Tool, version 3.1. For identical use subcategories, the operational conditions of o- and p-xylene and consequently the exposure estimates are equal. The exposure estimates are transparently documented and reproducible.

In order to identify possible risks, the consumer exposure scenarios were verified concerning appropriateness of exposure models and operational conditions especially in cases, where they differed from the common default values.

Xylenes are classified as Acute Tox. 4 (H332: Harmful if inhaled). Therefore the registrants derived chronic and acute DNELs. However, in their exposure assessment they only assessed chronic effects by averaging the event exposure over time. An exposure assessment for acute effects is missing for all contributing consumer exposure scenarios.

Based on the operational conditions and risk management measures in the Chemical Safety Report, calculations by the eMSCA led to exposure levels exceeding acute DNELs (cf. section 7.13.1.2). The data on record are not sufficient to demonstrate that risk is adequately controlled. “The refinement of exposure assessment may involve appropriate alteration of the operational conditions or risk management measures in the exposure scenario or more precise exposure estimation” (Annex I, 5.1.1 of the REACH Regulation).

For higher tier exposure estimates refined data, e.g. use descriptions, operational conditions, product-integrated risk management measures, and/or measurements of release during use are necessary. Therefore the registrants are required to provide exposure assessments and risk characterisations concerning single exposure events for all contributing scenarios of consumer use with respect to coatings and fuels taking into account both average event and peak exposure.

Furthermore the registrants are required to submit a more precise use description for these exposure scenarios where the chosen operational conditions do not appear appropriate to cover the use and therefore risks derived from these uses cannot be ruled out.

The details of the consumer exposure assessment can be found in the confidential annex of this report.In March 2016, the eMSCA noted that only very few registrants had updated their registration dossiers regarding the results of the downstream user survey, and that many of the consumer uses are still supported. Therefore the eMSCA has amended further information requirements in the draft decision based on the evaluation results obtained until September 2015. These previous results of the evaluation are not reported here in detail. But it can generally be stated that the operational conditions in these exposure scenarios are mainly defaults and therefore higher than those in the revised consumer exposure scenarios. Thus the exposure values are also higher.

In response to these requests, most of the registrants removed consumer uses from their registrations. However, it can be assumed that xylenes are present in consumer products and consumer exposure is likely. Although consumer products can contain solely the pure xylene isomers, the use of the (putatively less expensive) mixed xylenes which are registered as separate substances under REACH and therefore are not formally subjected to this substance evaluation appears more likely. The DE CA has declared its intention to potentially perform an SEv of these mixed xylenes at a later stage.

7.12.2. Environment

Environmental exposure assessment was outside the scope of this SEv.

7.12.3. Combined exposure assessment

Not addressed.

7.13. Risk characterisation

7.13.1.1. Workers

Considering the physicochemical properties of m-, p- and o-xylene and their industrial and professional uses, workplace exposure occurs mainly via inhalation. For quantitative risk characterisation of m-, p- and o-xylene, inhalation exposure estimates were compared with the derived long-term systemic and inhalation DNELs, respectively. The thus obtained risk characterisation ratios (RCR) were then added to calculate the combined RCR for each exposure scenario.

For m-, p- and o-xylene, a long-term systemic DNEL (inhalation) of 8.8 mg/m^3 (2 ppm) was derived. The DNEL value was calculated on the basis of a subchronic inhalation study in rats (Korsak et al., 1994). A detailed overview of how the eMSCA derived this DNEL is given in section 7.9.11.

The registrant used DNELs for workers that are not accepted by the eMSCA. The long-term systemic DNEL for inhalation exposure is by a factor of 25 lower than the one proposed by the registrant.

Applying the new DNEL derived by the eMSCA, risks for a series of uses of xylenes in occupational settings cannot be excluded (Obtained RCRs > 1).

The eMSCA considers that an adaptation of the EU-wide occupational exposure limit (OEL) for xylenes may be necessary.

An overview of the RCRs calculated by the eMSCA with the newly derived DNEL (workers, inhalation, systemic, long-term) is given in Table 34.

Table 34

Overview of RCRs calculated by the eMSCA in critical exposure scenarios using occupational exposure data from IFA

Industry group	Work area group	Exposure duration	Type of measure-ment	Concentration [mg/m³] 90%-value	RCR
Surface coating in painting, varnishing and liquid varnish coating	Airless spraying	≥ 6 h	personal	160	18.2
			stationary	49.8	5.7
		< 6 h	personal	287.6	32.7
	Spraying with pressurised air	≥ 6 h	personal	44.4	5.0
			stationary	20.8	2.4
		< 6 h	personal	46.4	5.3
			stationary	24.6	2.8
	Spraying unspecified	≥ 6 h	personal	37.1	4.2
			stationary	21	2.4
		< 6 h	personal	57	6.5
	Manual surface coating	≥ 6 h	personal	79.6	9.0
			stationary	62	7.0

Overview of RCRs calculated by the eMSCA in critical exposure scenarios using occupational exposure data from IFA

Industry group	Work area group	Exposure duration	Type of measure-ment	Concentration [mg/m³] 90%-value	RCR
		< 6 h	personal	152	17.3
	Machine surface coating	≥ 6 h	personal	96.2	10.9
			stationary	32.8	3.7
	Dipping, powder coating and other unspecified surface coating processes	≥ 6 h	personal	49	5.6
			stationary	80	9.1
		< 6 h	personal	273	31.0
			stationary	25	2.8
	Coating preparation, mixing and drying	≥ 6 h	personal	22.6	2.6
			stationary	34	3.9
		< 6 h	personal	33	3.8
Surface coating in metalworking, mechanical engineering and repair workshops	Airless spraying	≥ 6 h	personal	111.4	12.7
			stationary	106.2	12.1
		< 6 h	personal	27	3.1
	Spraying with pressurised air	≥ 6 h	personal	54	6.1
			stationary	31	3.5
		< 6 h	personal	97	11.0
			stationary	36.6	4.2
	Spraying unspecified	≥ 6 h	personal	65.2	7.4
			stationary	147	16.7
		< 6 h	personal	30.6	3.5
	Manual surface coating	≥ 6 h	personal	100	11.4
			stationary	25	2.8
		< 6 h	personal	225.8	25.7
	Machine surface coating	≥ 6 h	personal	63.4	7.2
			stationary	26.4	3.0
	Dipping, powder coating and other unspecified surface coating processes	≥ 6 h	personal	42.9	4.9
			stationary	36.4	4.1
		< 6 h	personal	105.5	12.0
Surface coating in other industries	Paint spraying (chemical/plastics/ rubber industry)	≥ 6 h	personal	30	3.4
			stationary	40,2	4.6
	Surface coating without paint spraying (chemical/plastics/rubber industry)	≥ 6 h	personal	43.7	5.0
			stationary	38.5	4.4
		< 6 h	personal	312.7	35.5
	Paint spraying in wood industry	≥ 6 h	personal	25.5	2.9
			stationary	22.5	2.6
		< 6 h	personal	15.2	1.7
	Surface coating without paint spraying in wood industry	≥ 6 h	personal	20.6	2.3
			stationary	23.6	2.7
	Paint spraying in electrical engineering/precision mechanics, optics	≥ 6 h	personal	50.2	5.7
			stationary	14	1.6
		< 6 h	personal	89	10.1
	Surface coating without paint spraying spraying in electrical engineering/precision mechanics,	≥ 6 h	personal	19.2	2.2
			stationary	10.9	1.2
		< 6 h	personal	301.2	34.2

Overview of RCRs calculated by the eMSCA in critical exposure scenarios using occupational exposure data from IFA

Industry group	Work area group	Exposure duration	Type of measure-ment	Concentration [mg/m³] 90%-value	RCR
	optics		stationary	22.5	2.6
	Surface coating (glass and ceramics industry)	≥ 6 h	personal	16.3	1.9
			stationary	36.2	4.1
	Surface coating in the leather, textile and paper industries	≥ 6 h	personal	108.4	12.3
			stationary	6.3	0.7
	Surface coating in the construction industry and the stone and earth industry	≥ 6 h	personal	118.2	13.4
			stationary	24.6	2.8
	Surface coating in metal production and electroplating	≥ 6 h	personal	84	9.5
			stationary	11.6	1.3
	Surface coating in wholesale/retail, service/transport and educational establishments	≥ 6 h	personal	42.2	4.8
			stationary	75.7	8.6
		< 6 h	personal	29.2	3.3
Manufacture and processing	Manufacture of preparations for the chemical industry	≥ 6 h	personal	79.7	9.1
			stationary	68.2	7.8
		< 6 h	personal	27.2	3.1
	Production of plastic parts and mechanical and thermal plastics processing in the plastics industry	≥ 6 h	personal	5.4	0.6
			stationary	5.2	0.6
		< 6 h	personal	32.9	3.7
	Manufacture and processing of plastic parts in other industries (moulding, prepreg, laminating, casting, extruding, injection moulding or plastic welding)	≥ 6 h	personal	7.9	0.9
			stationary	4.1	0.5
	Rubber products, manufacture and processing	≥ 6 h	personal	11.6	1.3
			stationary	16.8	1.9
	Gluing	≥ 6 h	personal	15	1.7
			stationary	13.6	1.5
		< 6 h	personal	14.8	1.7
			stationary	14	1.6
	Mechanical machining processes	≥ 6 h	personal	7	0.8
			stationary	2.8	0.3
	Thermal machining processes in metalworking, mechanical engineering and electrical engineering	≥ 6 h	personal	128	14.5
			stationary	18	2.0
	Filling, conveying, mixing, weighing in the plastics and rubber industry	≥ 6 h	personal	86.9	9.9
			stationary	17	1.9
Manufacture and processing	Assembly, machining, finishing in metalworking, mechanical engineering and repair shops	≥ 6 h	personal	14.9	1.7
			stationary	4.99	0.6
	Assembly, machining, finishing in other industries	≥ 6 h	personal	15.8	1.8
			stationary	8.3	0.9
	Packing and storage work	≥ 6 h	personal	61.1	6.9

Overview of RCRs calculated by the eMSCA in critical exposure scenarios using occupational exposure data from IFA

Industry group	Work area group	Exposure duration	Type of measure-ment	Concentration [mg/m³] 90%-value	RCR
			stationary	13.9	1.6
		< 6 h	stationary	9.9	1.1
Cleaning	Cleaning and stripping of parts and surfaces in electrical engineering/fine mechanics/metal working	≥ 6 h	personal	185.9	21.1
			stationary	14.8	1.7
		< 6 h	personal	137	15.6
			stationary	15.8	1.8
	Cleaning, degreasing, stripping of parts and surfaces in other industries	≥ 6 h	personal	61.1	6.9
			stationary	18.6	2.1
		< 6 h	personal	126	14.3
	Cleaning of plants and containers	≥ 6 h	personal	170	19.3
		< 6 h	personal	50	5.7
			stationary	9.72	1.1
Special industries and work areas	Laboratories in chemical industry	≥ 6 h	personal	29.6	3.4
			stationary	32.3	3.7
	Printing and screen printing	≥ 6 h	personal	19.6	2.2
			stationary	25.5	2.9
		< 6 h	personal	4.1	0.5
			stationary	14	1.6
	Hospitals and pathologies	≥ 6 h	personal	73	8.3
			stationary	27.4	3.1
		< 6 h	personal	58	6.6
			stationary	60.4	6.9
	Repair and maintenance	≥ 6 h	personal	12.4	1.4
			stationary	8.2	0.9
		< 6 h	personal	14.7	1.7
	Test benches and controls	≥ 6 h	personal	4.8	0.5
			stationary	3.7	0.4
	Waste and sewage disposal and recycling	≥ 6 h	personal	18.3	2.1
			stationary	16.5	1.9
	Shipping industry	≥ 6 h	stationary	< LOQ	-
	Foundries	≥ 6 h	stationary	28.3	3.2
Further work areas	Further work areas in the chemical, rubber and plastics industry	≥ 6 h	personal	29.9	3.4
			stationary	13	1.5
	Further work areas in electrical engineering/ fine mechanics/metal processing and repair workshops	≥ 6 h	personal	39.6	4.5
			stationary	24	2.7
		< 6 h	personal	12.7	1.4
Further work areas	Further work areas in construction and stone and earth industry	≥ 6 h	personal	28.4	3.2
			stationary	29.1	3.3
		≥ 6 h	personal	21	2.4

Overview of RCRs calculated by the eMSCA in critical exposure scenarios using occupational exposure data from IFA

Industry group	Work area group	Exposure duration	Type of measure-ment	Concentration [mg/m³] 90%-value	RCR
	Further work areas in painting, varnishing and liquid varnish coating		stationary	4.1	0.5
	Further work areas in the glass and ceramics industry	≥ 6 h	personal	9.6	1.1
	Further work areas in the leather, wood and textile industry	≥ 6 h	personal	15	1.7
			stationary	12	1.4
	Further work areas in educational institutions, wholesale and retail trade, service and transport industry	≥ 6 h	personal	23.2	2.6
			stationary	18.8	2.1
		< 6 h	personal	9.5	1.1
	Other branches and work areas	≥ 6 h	personal	10.2	1.2
			stationary	16	1.8

In the opinion of the eMSCA the registrants have to consider the new calculated DNEL (worker, inhalation, systemic, long-term) for the purpose of the risk evaluation and exposure assessment.

Applying the new DNEL derived by the eMSCA, risks for a series of uses of xylenes in occupational settings cannot be excluded (Obtained RCRs > 1).

The eMSCA considers that an adaptation of the EU-wide occupational exposure limit (OEL) for xylenes may be necessary.

7.13.1.2. Consumers

The details given in the sub-sections of this chapter refer to the original risk characterisation as performed by the eMSCA in 2015. The results of this assessment led to a number of consumer exposure-related information requests which, after decision-making at MSC-52, were contained in the final decisions issued for the three xylenes on 30 March 2017. In response to these requests, most, but not all registrants removed consumer uses from their registrations, thereby rendering the corresponding risk characterisation somewhat obsolete.

For the sake of transparency, however, the eMSCA decided that the original risk characterisation results should be communicated as part of this SEV Conclusion document, in order to allow the reader to fully understand the background of the information requests issued during the SEv process.

7.13.1.2.1. Inhalation exposure:

Risk Characterisation Ratios (RCR) have been calculated for consumer exposure via inhalation based on the estimated exposure using the ECETOC TRA tool, v. 3.0 (cf. confidential annex) and the DNELs derived by the registrants and the eMSCA, respectively (cf. section 7.9.11). Overall, 25 coating and 5 fuel-related uses were considered. As for many of the uses there was uncertainty about whether they had to be considered single or repeated events, exposure was compared to both acute and chronic DNELs in a first risk estimation tier.

The results are included in a confidential annex.

For two coating uses potentially occurring on a daily basis, RCRs > 1 (ca. 3 and ca. 41, respectively) were obtained when compared with the chronic, but not with the acute DNELs derived by the eMSCA.

The same was true for two of the fuel-related uses with an estimated frequency of once in two weeks, for which RCRs of 4 were obtained when exposure was compared with the chronic DNEL derived by the eMSCA.

For all 23 remaining coating uses RCRs ≥ 1 were obtained ranging

- from ca. 1.9 to ca. 23 with respect to the acute DNEL derived by the lead registrant,
- from ca. 1.8 to ca. 90 with respect to the chronic DNEL derived by the lead registrant,
- from ca. 1.1 to ca. 325 with respect to the acute DNEL derived by the eMSCA,
- from ca. 13 to ca. 11719 with respect to the chronic DNEL derived by the eMSCA,
- and for the 3 remaining fuel-related uses RCRs
- slightly above 1 (ca. 1.0 to ca. 1.2) with respect to the chronic DNEL derived by the lead registrant and the acute DNEL derived by the eMSCA, or
- around 15 with respect to the chronic DNEL derived by the eMSCA,

were calculated.

It is noted that very high RCRs (up to the order of 10^4) with respect to the chronic DNELs were obtained for uses with short estimated daily exposure duration, sometimes as short as 3 min, where comparison to the chronic DNEL is not meaningful from a toxicological point of view.

With respect to the exceedance of acute DNELs, it has to be noted that many of the corresponding uses were characterised only in a broad or generic fashion and therefore these results represent a preliminary assessment and cannot be taken as proof that actual use poses an unacceptable risk. On the other hand, for many of these uses, repeated occurrence on successive days cannot be ruled out and in these situations risk may be underestimated by using the acute DNEL for risk characterisation.

Overal, these results strongly indicate the need for a refinement of the exposure estimation by describing more precisely the operational conditions associated with the individual consumer uses. For this reason the Substance Evaluation decisions contained a corresponding information request.

7.13.1.2.2. Dermal exposure:

Based on exemplary calculations, the eMSCA considered dermal exposure as a quantitatively smaller contributor to total exposure as compared to inhalation. Since RCRs ≥ 1 were obtained for almost all uses when inhalation exposure was compared already with the corresponding acute DNEL, the eMSCA decided to first request a more precise use description for the respective exposure scenarios before proceeding with dermal risk characterisation.

7.13.1.2.3. Oral exposure:

Oral exposure of consumers to xylenes was not considered relevant by the eMSCA.

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7.15. Abbreviations

ADH	Alcohol Dehydrogenase
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Assesment Element
AF	Assessment Factor
AOP	Adverse Outcome Pathway
ATSDR	(US) Agency for Toxic Substances and Disease Registry
BOELV	Binding Occupational Exposure Limit Value
CA	Competent Authority
CCH	Check of Compliance
CLH	Harmonised Classification and Labelling
CNS	Central Nervous System
CoRAP	Continuous Rolling Action Plan
CYP	Cytochrom P450
eteam	Exposure Assessment Models under REACH
DNEL	Derived No Effect level
DPRA	Direct Peptide Reactivity Assay
EC/D	Effective Concentration/Dose
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
ECVAM	European Centre for the Validation oif Alternative Methods
ED	Endorine Disruptor/Disruption
EEG	Electroencephalogram
(e)MSCA	(evaluating) Member State Competent Authority
ES	Exposure scenario
ETEAM	Evaluation ofTier 1 Exposure Models (Project)
FEP	Flash-Evoked Potential
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
HINT	Hearing In Noise Test
HMT	Human Maximisation Test
ICCVAM	(US) Interagency Coordinating Committee on the Validation of Alternative Methods
IOELV	Indocative Occupational Exposure Limit Value
LC/D	Lethal Concentration/Dose
LLNA	Local Lymph Node Assay
LOA	Lower Olefins and Aromatic Services Team
LOAEL/C	Lowest Observed Adverse Effect Level/Concentration
MRL	Maximum Residue Limit
MSCA	Member State Competent Authority
NO	Norway
NOAEL/C	No Observed Adverse Effect Level/Concentration
NTP	(US) National Toxicology Program
NZW	New Zealand White
OC	Operational Condition
PB	Phenobarbital
PND	Pre-Natal Development
PNEC	Predicted No Effect Concentration
PoD	Point of Departure
PROC	Process Category
QSAR	Quantitative Strcuture-Activity Relationships
RAAF	Read-Across Assessment Framework

RCR	Risk Characterisation Ratio
SCC	Strictly Controlled Conditions
SDS	Sodium Dodecyl Sulfate
SE	1. Sweden; 2. Single Exposure
SEV	Substance Evaluation
SI	Stimulation Index
SPIN	Substances in Products in the Nordic Countries
SRT	Simple Reaction Time
STEL	Short Time Exposure Limit
STOT	Specific Target Organ Toxicity
SWD	Spike and Wave Discharges
TRA	Targeted Risk Assessment
TWA	Time-Weighted Average
UBA	Umweltbundesamt

7.16. Annex 1 – RAAF assessment

The ECHA Read-Across Assessment Framework or RAAF (ECHA, 2017) provides a structure for assessing read-across/category approaches when used for adaptation of standard information requirements in line with REACH Annex XI.

In a first step, the case at hand is assigned to one of six possible scenarios based on whether an analogue or a category approach is used, whether the rationale behind the read-across approach is based on different identical (e.g. one substance is a metabolite oft he other) or different substances, and whether variability in the strength with which source and target substances exert the critical effects are observed. For the case of the xylene/ethylbenzene category, the eMSCA identified RAAF scenario 4 (category approach, different substances, variations in strength of effect(s) observed among source substances prediction based on a regular pattern or worst case approach) as the most appropriate scenario.

Next, depending on which scenario was identified as the most relevant, a number of so-called assessment elements (AE) have to be adressed. AE may be commmon to all scenarios (C.1-C.6) or scenario-specific (in the case of scenario 4: AE 4.1-4.5). Under each assessment element, the read-across justification is examined with respect to certain assessment questions and an acceptability score from 1-5 is assigned.

SCORES	AOs	MEANING OF THE AOs
5	Acceptable with high confidence	Acceptance without reservations in the scientific explanation and documentation addressing the scientific aspects of the AE.
4	Acceptable with medium confidence	Acceptance with minor reservations about the scientific explanation and documentation addressing the scientific aspects of the AE.
3	Acceptable with just sufficient confidence	Acceptance with notable reservations. Minimum level of confidence in the scientific explanation provided in the documentation and addressing the scientific aspects of the AE.
2	Not acceptable in its current form	Acceptance for the AE under consideration may become possible if improved explanations and/or supporting evidence is made available by the registrant.
1	Not acceptable	A major flaw in the approach for the AE under consideration which is not expected to be resolved by the addition of supporting information.

Source: (ECHA, 2017)

Once this assessment has been completed for all AEs, the lowest score obtained in any of the elements determines the overall score, with a minimum score of 3 required for acceptance. Notably the scoring system is tailored to the needs of dossier evaluation which differ from those under SEv. This is particularly relevant for cases at the border between overall scores 3 (just acceptable with minimum level of confidence) and 2 (not acceptable in the present form, but acceptance may be possible with improved explanations): Where read-across justifications are rated with an overall score of 2, ECHA may under dossier evaluation ask for an update of the read-across justification, whereas subject to Article 50 (4), the eMSCA under SEv may only do so, if a specific risk-driven concern is present. As described in more detail in section 7.9.10 above, in the case of the xylene/ethylbenzene category, the eMSCA concluded that the category justification submitted by the registrants is currently insufficient, while the rationale as such appears plausible when looking at the overall data matrix.

As a consequence, the eMSCA has assigned an overall score of 2 to the RAAF-based evaluation and recommended that ECHA under Dossier Evaluation requests an update of the -xylene/ethylbenzene category from the registrants. The scores obtained for the individual AEs are reported in Table 35.

Table 35

RAAF ASSESSMENT OF THE REGISTRANTS' JUSTIFICATION FOR THE XYLENE/ETHYLBENZENE CATEGORY		
Assessment Element	**Score**	**Justification**
Common Assessment Elements		
C.1 Substance characterisation	2	Levels of constituents and impurities in registered substances and test substances used in experimental studies are not discussed in the registrants' justification of the read-across approach. Xylene of different composition has been used in the studies, and impurities in the technical material may include toluene. From a synopsis of the available data matrix the eMSCA concludes that a significant impact on toxicity appears unlikely, therefore appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.
C.2 Structural similarity and structural differences within the category	2	Common structural features are addressed by the registrants in their justification of the read-across approach, but dissimilarities (e.g. different substitution pattern leading to differences in molecular size) are not. However, the eMSCA did not find an indication that these differences lead to a qualitative difference in biological activty, therefore appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.
C.3 Link of structural similarities and structural differences with the proposed regular pattern	2	Not discussed in the read-across justification submitted by the registrants, but the observed effects are well in line with knowledge about alkylbenzenes, and beside the benzene ring, all of the category members only contain methyl or ethyl groups. As a result, the eMSCA finds that appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.
C.4 Consistency of effects in the data matrix	2	Not discussed in the read-across justification submitted by the registrants, only an incomplete data matrix is presented. However, based on the assessment of the data matrix by the eMSCA, it appears likely that appropriate discussion and documentation of these issues by the registrants could raise the score to at least 3.
C.5 Reliability and adequacy of the source studies	2	Not discussed in the read-across justification submitted by the registrants, but eMSCA is of the opinion that overall the available toxicological data base is of sufficient quality to allow for a reliable risk characterisation of the xylene isomers. Therefore it appears likely that appropriate discussion and documentation of this point by the registrants could raise the score to at least 3.
C.6 Bias that influences the prediction	2	Not discussed in the read-across justification submitted by the registrants. There is indeed an apparent issue with regard to selection bias, as e.g. toluene, diethyl- or trimethylbenzenes have not been included in the category. The rationale for this is unclear and needs to be provided by the registrants. On the other hand, data on diethyl- and trimethylbenzenes available from the ECHA dissemination site do not provide an indication that their inclusion would have changed the overall assessment result. Therefore it appears likely that appropriate discussion and documentation of this point by the registrants could raise the score to at least 3.
Scenario-specific Assessment Elements		
4.1 Compounds the organism is exposed to	2	Not discussed in the read-across justification submitted by the registrants. Notably the individual xylene isomers are metabolised to different methylhippuric acids. On the other hand, from a synopsis of the available data matrix the eMSCA concludes that a significant impact on toxicity appears unlikely, therefore appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.
4.2 Common underlying mechanism, qualitative aspects	2	Not discussed in the read-across justification submitted by the registrants, but the observed effects are well in line with common knowledge about the toxicity of alkylbenzenes. As a result, the eMSCA finds that appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.
4.3 Common underlying mechanism, quantitative aspects	2	Not discussed in the read-across justification submitted by the registrants. On a quantitative basis, some differences are observed between the three isomers, however a clear trend was not observed and ethylbenzene and to some degree, dose selection may be responsible for this observation (many older studies did not establish a NOAEC or LOAEC). One exception is given by ototoxicity, for which the available data show that p-xylene is much more potent than o- or m-xylene (however they not allow to conclude that these two isomers could not be ototoxic

RAAF ASSESSMENT OF THE REGISTRANTS' JUSTIFICATION FOR THE XYLENE/ETHYLBENZENE CATEGORY		
Assessment Element	**Score**	**Justification**
		at high doses > 1800 ppm). Overall, appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.
4.4 Exposure to other compounds than those linked to the prediction	2	Not discussed in the read-across justification submitted by the registrants. Cf. AEs C.1 and 4.1. Overall, appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.
4.5 Occurrence of other effects than covered by the hypothesis and justification	2	Not discussed in the read-across justification submitted by the registrants. An evaluation of the data matrix by the eMSCA did, however not provide indications of such effects. Overall, appropriate discussion and documentation of these issues by the registrants could likely raise the score to at least 3.