SUBSTANCE EVALUATION REPORT

Background document for the purpose of substance evaluation under REACH for Substance name

Toluene

EC No 203-625-9

CAS No 108-88-3

Evaluating Member State: Finland

Dated: 12 November 2013

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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.

In order to ensure a harmonised approach, ECHA in cooperation with the Member States developed risk-based criteria for prioritising substances for substance evaluation. The list of substances subject to evaluation, the Community rolling action plan (CoRAP), is updated and published annually on the ECHA web site[1].

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. Eventually after obtaining the necessary information together with the existing information the evaluating Member State draws conclusion how to use that information for safe use of the substance in question.

The document is prepared as background information by the evaluating Member State Competent Authority for this CoRAP substance in question. The conclusions are provided in the official Conclusion document as required by the article 48 of the REACH Regulation.

Year of evaluation (as given in the CoRAP): 2012

VERSION NUMBER: 1.1 **DATE:** 12.11.2013

Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other: The Registrants have used EU indicative occupational exposure limit value (50 ppm) in place of long-term inhalation DNEL value for workers. The basis for the IOEL value is the SCOEL recommendation from 2001. The EU risk assessment conducted under Regulation (EEC) No 793/93 concluded 2-fold lower reference value (~20 ppm) for toluene (EU RAR, 2003). As a conclusion of the substance evaluation, the Finnish CA recommends that the Registrants take into account the reference values from the EU RAR in their chemical safety assessment and ensure that the risk management measures currently in place adequately control worker exposure to toluene. If the Registrants decide to not follow these proposals the Registrants are recommended to add adequate justifications in their registration dossier. These recommendations were communicated to the Registrants during the evaluation. The Finnish CA concluded that it was not necessary to request new information. The Finnish CA recommends that Commission Scientific Committee on Occupational Exposure Limits (SCOEL) will take into account results from the EU RAR (2003) and make a review on whether there is a need to update the recommendation on IOEL values for toluene. At the moment there is no follow up action needed under REACH Article 48.	x

**Include details in the executive summary*

Executive summary

Grounds for concern

The initial grounds for concerns from the justification document in the CoRAP 2012 were the following:

1) Hazard concern

The publicly available data on toluene from ECHA's web site (database on registered substances) indicated that the DNEL (Derived no-effect level) values in the chemical safety assessment of toluene, especially for long-term inhalation toxicity, were high compared to the health based reference values used in the EU risk assessment under Regulation (EEC) No 793/93 prepared by DK in 2003 (EU RAR 2003). This was considered to indicate that the risks of toluene in the registration dossier are evaluated to be lower than in the EU RAR (2003).

The available data also indicated that the repeated dermal dose toxicity study had been waived. The Finnish CA was interested in checking the justification for waiving. The concern was related to systemic toxicity as a consequence of the combined dermal (liquid) and inhalation (vapor) exposure in certain manual tasks. This concern had also been identified in the toluene EU RAR (2003).

Toluene has the notation “skin” in the American conference of governmental industrial hygienists (ACGIH) list of Threshold Limit Values and in the Finnish list of occupational exposure limits (OEL) (1999). Skin notation indicates that toluene can penetrate trough undamaged skin and that the dermal route should be taken into account in risk assessment.

2) Exposure concern and high tonnage

Toluene is a high product volume chemical and has wide dispersive use (worker, professional and consumer uses). In consumer uses toluene is present in various products such as paints, glues, adhesives, varnishes, inks and cleaning agents. The consumer uses were listed in the EU RAR (2003), but it was assumed that at present (2012) there might be new use scenarios and product types. The current restriction for toluene in REACH Regulation (Annex XVII, entry 48, 0.1 % conc. limit) covers adhesives and spray paints in general public products. The intention was to check whether the CSA includes all relevant uses and exposure scenarios (worker, professional and consumer). For example, the information from the Nordic Product Register (SPIN) and Finnish Product Register was planned to be utilised for this task. The secondary aim was to evaluate the quality and adequacy of human exposure assessments in CSA.

The Finnish CA considered substance evaluation as necessary to check whether concerns described above are addressed appropriately in the current registration dossier.

During the evaluation, also data on ototoxicity, especially in conjunction with noise, and on effects on colour vision induced by toluene were considered.

Procedure

The substance evaluation is based on information in the aggregated registration dossier (technical dossier, IUCLID) and the Chemical Safety Report (CSR). The Finnish CA had an informal meeting with the representatives of the Registrants in 10/2012, where initial concerns were discussed. All updates received until 11/2012 were considered. The evaluation is complemented with information provided in a European risk assessment under Regulation (EEC) No 793/93 prepared by DK in 2003 (EU RAR 2003).

The evaluation as well as the documentation in the substance evaluation report focuses on the initial concerns. The evaluation was targeted on:

1) Information related to the identified uses and establishment of exposure scenarios

2) Information on dermal adosorption

3) Information related to the establishment of long-term inhalation DNEL for workers

4) Calculation of risk characterisation ratios (RCRs)

5) Other issues raised during the evaluation

The Finnish CA concluded that no new information has become available since the EU RAR (2003), which would change conclusions for deriving long-term inhalation reference values for workers. The Finnish CA further notes that the EU RAR (2003) includes additional information related to specific studies, which were not included in the registration dossier. This information was collected from the authors of studies when the EU RAR was prepared.

The parts which were not evaluated are stated in the respective sections of the substance evaluation report.

The Finnish CA concluded that it was not necessary to request new data and therefore a draft decision was not prepared. The Registrants were, however, recommended to update certain parts of the Registration dossier by either reconsidering the risk assessment and risk management measures, or by adding adequate justifications. This recommendation was communicated to the Registrants via e-mail in February 2013. The Finnish CA thus concluded the evaluation process by the end of February 2013.

Conclusions

The substance evaluation was targeted on:

1) Information related to the identified uses and establishment of exposure scenarios

The Finnish CA evaluated whether all identified uses reported in the registration dosser were covered in the Chemical Safety Assessment and in Exposure Scenarios. Furthermore, Finnish Chemicals Product Register was used as a reference to identified uses of toluene. The Register was cross-checked to verify whether all of the uses were covered in the Chemical Safety Assessment and subsequently in Exposure Scenarios.

The only use that appeared to be missing was use of toluene in production of plastics. The question, whether the use should be an identified use in the registration dossier or if it was covered by another

exposure scenario, was presented to the Registrants. According to them, toluene is primarily used as a reaction solvent in the production of plastics and this use is covered in the "Manufacture of the substance" exposure scenario. The Finnish CA would like to make a note that this is not necessarily clear, as the title and thus the exposure scenario can also be interpreted to refer only to manufacture of toluene. A more descriptive title would increase the usability of the exposure scenario. **The Finnish CA recommends the Registrant to include clarifying information in the registration dossier. There is no need to request further information.**

2) Information on dermal absorption

The available studies are present in the dossier and no newer or additional data was found. According to the studies, dermal uptake after skin exposure does occur, but to a limited degree. This uptake is taken into account in relevant exposure scenarios. Dermal absorption is also taken into account in occupational exposure limits using skin notation and this is correctly informed in the chemical safety report and the safety data sheet of the lead registrant. **The concern has been clarified and there is no need to request further information or to update the registration dossier.**

3) Information related to the establishment of long-term inhalation DNEL for workers

The Registrant has used EU indicative occupational exposure limit values (IOELV) in place of worker DNEL values for risk assessment purposes. The Registrant has set the long-term inhalation DNEL for workers at 50 ppm (192 mg/m3) based on IOEL TWA - 8 hr value. The basis for IOEL values is the recommendation of the Commission Scientific Committee on Occupational Exposure Limits (SCOEL), for toluene from 2001 (SCOEL 2001). The IOELVs for toluene were published in Directive 2006/15/EC. According to the ECHA guidance (Appendix R.8-13) Registrants may use the IOELVs in place of DNELs unless new scientific information available does not support the use of the IOELV for this purpose.

Toluene has been evaluated under Regulation (EEC) No 793/93, the risk assessment was finalised in 2003 (EU RAR 2003). The Finnish CA concluded that no new information has become available since the EU RAR (2003), which would change conclusions for the reproductive toxicity. There is thus no need to reevaluate the information available. According to Annex I, 0.5 of the REACH Regulation, where available and appropriate, an assessment completed under Regulation (EEC) No 793/93 shall be taken into account in the development of, and reflected in, the chemical safety report. Deviations from such assessments shall be justified.

After the SCOEL recommendation in 2001, toluene has received a harmonized hazard classification as Repr 2; H361d Suspected of damaging the unborn child, in accordance with Regulation (EC) No 1272/2008. Hazard classification is based on the weight of evidence analysis of all available experimental animal data and human data. These studies were evaluated also in the EU RAR (2003). Ng et al. (1992) was one of the key studies used in the hazard classification and in the EU RAR (2003). In the registration dossier of toluene, this study was assigned a reliability score of 4 (not assignable) and it was used as a supporting study. Ng et al., study discusses increased spontaneous abortions associated with exposure to toluene in the workplace at average air concentration levels 88 ppm (range 50-150 ppm). Because of the limitations of the Ng et al. (1992)

study, results may not be used to establish a definite relationship between late spontaneous abortions and toluene exposure. However, results from this study cannot be completely disregarded because also experimental animal studies indicate developmental toxicity such as lower birth weight, delayed postnatal development and developmental neurotoxicity. Several studies indicate similar effects in rat fetuses at similar dose levels. The effects indicating developmental neurotoxicity occurred at higher exposure levels, 1200 ppm and 1800 ppm (Hass et al. 1999 and Hougaard et al., 1999). This effect has not been examined at lower exposure levels and a NOAEC cannot be set. The NOAEC for other developmental effects is 600 ppm (2261 mg/m3). The Finnish CA considers that there is uncertainty whether the NOAEC 600 ppm for reproductive toxicity covers developmental neurotoxicity as well.

Developing nervous system is particularly sensitive to chemical exposure. Organic solvents such as toluene have an affinity for lipid-rich tissues and can readily cross the placenta. In addition to effects seen in developing animals, neurotoxicity has also been demonstrated in adult animals and in humans. Neurophysiological effects in workers have been found to be the most sensitive endpoints for toluene. Toluene has a harmonized hazard classification for effects on central nervous system (STOT SE 3; H336: May cause drowsiness or dizziness; STOT RE 2; H373: May cause damage to organs). For fertility the Registrant has provided data which indicate a NOAEC value of 600 ppm (2261 mg/m3) for fertility (i.e., decreased sperm count and reduced epididymal weight). The Finnish CA considers that due to the remaining uncertainties in the Ng et al. study (1992) and because the developmental neurotoxicity has not been evaluated for exposure levels below 1200 ppm, this additional uncertainty consisting of limited dose-response data and data quality should be taken into account in the risk characterization.

The Registrant has set the long-term inhalation DNEL for workers at 50 ppm (192 mg/m3) based on IOEL TWA - 8 hr value. The SCOEL recommendation for IOEL values is mainly based on data from epidemiological studies (SCOEL 2001). TWA - 8 hrs (50 ppm, 192 mg/m3) for toluene is based on LOAEC value (60 ppm, 230 mg/m3) for neurobehavioral effects in humans (subjective effects on how the person feels). It is concluded that an exposure limit of 50 ppm (192 mg/m3) would also protect against potential fetotoxicity. The SCOEL recommendation does not, however, refer to all available experimental animal studies for reproductive toxicity which were included in the EU RAR (2003).

Currently, it is not clear how available experimental animal results especially for reproductive toxicity and the results from the EU RAR (2003) under Regulation (EEC) No 793/93 have been taken into account in the chemical safety assessment. The Finnish CA is of the opinion that the animal NOAEC 600 ppm (2250 mg/m3) and human LOAEC 88 ppm (330 mg/m3) should be used in parallel to derive a long-term DNEL for workers using a weight of evidence analysis as it was used in the EU RAR (2003). The current long-term inhalation DNEL 50 ppm (192 mg/m3) for workers provides a 2-fold lower margin of safety than was concluded in the EU RAR (Table 1). The Registrant has not provided justification for deviation from the EU risk assessment carried under Regulation No 793/93. The risk characterization should cover adequately developmental toxicity in humans and protect also vulnerable subpopulations.

Table 1. Required minimal Margin of Safety (MOS) for workers in the EU RAR 2003 (reproductive toxicity)

Sensitive end point	**Route**	**Dose descriptor**	**MOS_{min}**	**Reference value**
development, fertility	inhalation	NOAEC 600 ppm (2250 mg/m3)	30	20 ppm
abortions	inhalation	LOAEC 88 ppm (330 mg/m3)	5	17.6 ppm

The Finnish CA notes that the methodology used by SCOEL to establish IOEL values differs from the methodology used for DNEL derivation in REACH; for example handling of uncertainty varies. The applied assessment factor for derivation of IOEL TWA - 8 hr value was not explicitly stated or justified in the SCOEL recommendation for toluene. The SCOEL has applied an assessment factor below 2 to cover uncertainty due to remaining intraspecies differences between workers. This factor is lower than the one presented in the ECHA guidance, the recommended ECHA's factor being 5. The Finnish CA is in the opinion that the Registrant has not followed the recommendations of ECHA`s Guidance R.8 and has not provided full justification for the derivation of long-term DNELs for workers (see Annex I, 1.4.1 of the REACH Regulation).

Therefore, the Registrant is, recommended to justify the deviation from the risk assessment completed under Regulation (EEC) No 793/93 (See Annex I, 0.5 of the REACH Regulation). In addition the Registrant is recommended to fully justify the long-term inhalation DNEL derivation for workers provided in the chemical safety report by specifying (see Annex I, 1.4.1 of the REACH Regulation)

- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
- the DNELs reflecting the likely route(s), duration and frequency of exposure.

If a justification for the deviation from the risk assessment completed under Regulation (EEC) No 793/93 is not given and the choice of the information used for current long-term inhalation DNEL derivation for workers is not fully justified, the Registrant should use the results from the EU RAR (2003) to derive the long-term inhalation DNEL for workers and reassess related risks.

The concern has been clarified and the Finnish CA recommends to update the registration dossier, taking into account the issues mentioned above. The Finnish CA recommends that Commission Scientific Committee on Occupational Exposure Limits (SCOEL) will take into account results from the EU RAR (2003) and make a review on whether there is a need to update the recommendation on IOEL values for toluene.

4) Calculation of risk characterisation ratios (RCRs)

The comparison of the toluene DNEL with the results of the exposure assessment in different use categories shows that exposures are in most cases well below the derived DNEL. In a couple of use categories however, the RCR value is nearly at the level of DNEL (see Table 2 in Annex:

Confidential information). When taking into account the uncertainties in derivation of the long-term DNEL for workers and exposure assessments, it is not evident that safe use is demonstrated there. Therefore, it would be essential for registrant to demonstrate and justify more transparently that the safe use is ensured also in the scenarios where RCR is very close to 1. **There is no need to request further information. However, the Finnish CA recommends that the Registrant includes a clarifying justification in the registration dossier and makes a reassessment of the appropriateness of the relevant risk management measures (RMM) to ensure that the RMMs currently in place adequately control worker exposure to toluene.**

5) Other issues raised during the evaluation

The Finnish CA concluded that the data available on effects on colour vision is not robust and that based on the studies present in the registration dossier, permanent impairment of colour vision is not likely when IOEL values are not exceeded. **The concern has been clarified and there is no need to request further information or to update the registration dossier.**

Concerning ototoxicity, the Finnish CA concluded that the systemic NOAEC provides adequate protection. There are indications of synergistic effects due to simultaneous exposure to toluene and noise, but it is not possible to address this kind of co-exposure through REACH-legislation. Existence of this co-exposure is communicated in the lead registrants' Safety Data Sheet and there is thus **no need to request further information or to update the registration dossier**.

Statement of reasons.

Not applicable, as a draft decision was not prepared.

CONTENTS

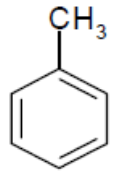
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 2: Substance identity

Public Name:	Toluene
EC number:	203-625-9
EC name:	Toluene
CAS number (in the EC inventory):	108-88-3
CAS number:	
CAS name:	Toluene
IUPAC name:	Toluene, methylbenzene
Index number in Annex VI of the CLP Regulation	601-021-00-3
Molecular formula:	C_7H_8
Molecular weight range:	92,15 g/mol
Synonyms:	*1-methylbenzene, phenyl methane, toluol, methyl benzol, methacide*

Structural formula:



1.2 Composition of the substance

Name: Toluene

Description: aromatic hydrocarbon

Degree of purity: ≥ 99%

Table 3: Constituents

Constituents	Typical concentration	Concentration range	Remarks
Name and EC number			

Table 4: Impurities

Impurities	Typical concentration	Concentration range	Remarks
Name and EC number			

Table 5: Additives

Additives	Typical concentration	Concentration range	Remarks
Name and EC number			

1.3 Physico-chemical properties

Table 6: Overview of physicochemical properties

Property	Description of key information	Value used for CSA / Discussion
Physical state	liquid at 20°C and 101.3 kPa Colour: data not reported Odour: benzene like	
Melting / freezing point	The melting point of toluene is -95°C	**Value used for CSA:** 178 K at 101.3 kPa The Merck Index is a peer reviewed handbook and is considered reliable and suitable for use as the key study for this endpoint. In addition, this reference was used as the key study in the EU RAR (2003) for toluene. The supporting study (CRC, 2008) is also a peer reviewed handbook and supports the value reported in the key study.
Boiling point	The boiling point of toluene is 110.6°C	**Value used for CSA:** 384 K at 101.3 kPa The Merck Index is a peer reviewed handbook and is considered reliable and suitable for use as the key study for this endpoint. In addition, this reference was used as the key study

Property	Description of key information	Value used for CSA / Discussion
		in the EU RAR (2003) for toluene. The supporting study (CRC, 2008) is also a peer reviewed handbook and supports the value reported in the key study.
Relative density	The density of toluene is 0.866 g.cm-3 at 20°C	**Value used for CSA:** 866 at 20°C The Merck Index is a peer reviewed handbook and is considered reliable and suitable for use as the key study for this endpoint. In addition, this reference was used as the key study in the EU RAR (2003) for toluene. The density of toluene is 0.866 g.cm-3 at 20°C. The supporting study (CRC, 2008) is also a peer reviewed handbook and supports the value reported in the key study.
Vapour pressure	The reported vapour pressure of toluene is 0.448 PSI (3088.9Pa) at 70°F (21.1°C) and 0.599 PSI (4130.0Pa) at 80°F (26.6°C).	**Value used for CSA:** 3089 Pa at 294 K The handbook of vapour pressure and heats of vaporization of hydrocarbons and related compounds (Zwolinski and Wilhoit, 1971) is a peer reviewed handbook and is considered reliable and suitable for use as the key study for this endpoint.In addition, this vapour pressure is similar to the vapour pressure reported in the EU RAR. The supporting study (CRC, 2008) is also a peer reviewed handbook and supports the value reported in the key study.
Partition coefficient n-octanol/water (log value)	The log Kow of toluene is 2.73	**Value used for CSA:** Log Kow (Log Pow): 2.73 at 20 °C Exploring QSAR , Hydrophobic, Electric, and Steric Constants by Hansch et al. (1995) is a peer reviewed handbook and is

Property	Description of key information	Value used for CSA / Discussion
		considered reliable and suitable for use as the key study for this endpoint. The supporting study (CRC, 2008) is also a peer reviewed handbook and supports the value reported in the key study.
Water solubility	The solubility of toluene is 573-587 mg/l at 25°C	The handbook of aqueous solubility data by Yalkowsky and He (2003) is a peer reviewed handbook and so can be considered reliable and suitable for use as the key study for this endpoint. The supporting study (CRC, 2008) is also a peer reviewed handbook and supports the value reported in the key study.
Flash point	The flash point of toluene is 4.4°C	**Value used for CSA:** 277.6 K at 1013 hPa The Merck Index is a peer reviewed handbook and is considered reliable and suitable for use as the key study for this endpoint. The supporting study (CRC, 2008) is also a peer reviewed handbook and supports the value reported in the key study.
Autoflammability / self-ignition temperature	The self ignition temperature of toluene is 480°C	**Value used for CSA:** 753 K at 1013 hPa The CRC handbook of chemistry and physics is a peer reviewed handbook and is considered reliable and suitable for use as the key study for this endpoint. The supporting study (ICSC, 2002) is also a peer reviewed handbook and supports the value reported in the key study.
Viscosity	The viscosity of toluene at 25°C is	The CRC handbook of chemistry and physics is a peer reviewed

Property	Description of key information	Value used for CSA / Discussion
	0.56 mPa s	handbook and is considered reliable and suitable for use as the key study for this endpoint. In addition, this reference was used as the key study in the EU RAR (2003) for toluene. The supporting study (EHC, 1985) is also a peer reviewed handbook and supports the value reported in the key study.

Data waiving

Information requirement: Granulometry

Reason: other justification

Information requirement: Surface tension

Reason: other justification

Information requirement: Flammability

Reason: study scientifically unjustified.

Information requirement: Explosive properties

Reason: other justification

Information requirement: Stability in organic solvents and identity of relevant degradation products

Reason: other justification

Information requirement: Dissociation constant

Reason: study scientifically unjustified

2 MANUFACTURE AND USES

2.1 Quantities

Table 7: Aggregated tonnage (per year)

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

2.1.1 Manufacturing processes

See IUCLID dossier for information on manufacturing process.

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

Table 8. Uses by workers in industrial settings

Identified Use (IU) name	**Use descriptors**
Manufacture	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 1: Manufacture of substances ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Sector of end use (SU)** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 9: Manufacture of fine chemicals SU 0: Other: 3
Distribution	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation)

Identified Use (IU) name	Use descriptors
	PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 1: Manufacture of substances ERC 3: Formulation in materials ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 5: Industrial use resulting in inclusion into or onto a matrix ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) ERC 6b: Industrial use of reactive processing aids ERC 6c: Industrial use of monomers for manufacture of thermoplastics ERC 6d: Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers ERC 7: Industrial use of substances in closed systems **Sector of end use (SU)** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 9 Manufacture of fine chemicals SU 0: Other: 3
Use as an intermediate	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) **Sector of end use:** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 9: Manufacture of fine chemicals SU 0: Other: 3
Use in cleaning agents	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 7: Industrial spraying

Identified Use (IU) name	Use descriptors
	PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 10: Roller application or brushing PROC 13: Treatment of articles by dipping and pouring **Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 0: Other: 3
Use as fuel	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 16: Using material as fuel sources, limited exposure to unburned product to be expected **Environmental release category (ERC):** ERC 7: Industrial use of substances in closed systems **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys)
Use in coatings	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 7: Industrial spraying PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 13: Treatment of articles by dipping and pouring PROC 14: Production of preparations or articles by tabletting, compression, extrusion,

Identified Use (IU) name	Use descriptors
	pelletisation PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 0: Other: 3
Use in oilfield drilling and production operations	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities **Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 0: Other: 3
Use in binders and release agents	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 6: Calendering operations PROC 7: Industrial spraying PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 10: Roller application or brushing PROC 13: Treatment of articles by dipping and pouring PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation **Environmental release category (ERC):** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Sector of end use:** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 9: Manufacture of fine chemicals SU 0: Other: 3

Identified Use (IU) name	Use descriptors
Use as a laboratory reagent	**Process category (PROC):** PROC 10: Roller application or brushing PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 2: Formulation of preparations ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 0: Other: 3
Use in functional fluids	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **Environmental release category (ERC):** ERC 7: Industrial use of substances in closed systems **Sector of end use:** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 9: Manufacture of fine chemicals SU 0: Other: 3
Use in rubber production and processing	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 6: Calendering operations PROC 7: Industrial spraying PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 13: Treatment of articles by dipping and pouring PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 15: Use as laboratory reagent PROC 21: Low energy manipulation of substances bound in materials and/or articles

Identified Use (IU) name	Use descriptors
	Environmental release category (ERC): ERC 1: Manufacture of substances ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles ERC 6d: Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers **Sector of end use:** SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) SU 9: Manufacture of fine chemicals SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 0: Other: 3
Formulation	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 2: Formulation of preparations **Sector of end use:** SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 0: Other: 3

2.2.2 Use by professional workers

Table 9. Use by professional workers

Identified Use (IU) name	Use descriptors
Use in roads and construction	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 7: Industrial spraying

	PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 11: Non industrial spraying PROC 13: Treatment of articles by dipping and pouring **Environmental release category (ERC):** ERC 8d: Wide dispersive outdoor use of processing aids in open systems ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix **Sector of end use:** SU 0: Other: 22
Use in cleaning agents	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 10: Roller application or brushing PROC 11: Non industrial spraying PROC 13: Treatment of articles by dipping and pouring **Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems ERC 8d: Wide dispersive outdoor use of processing aids in open systems **Sector of end use:** SU 0: Other: 22
Use in fuels	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 16: Using material as fuel sources, limited exposure to unburned product to be expected **Environmental release category (ERC):** ERC 9a: Wide dispersive indoor use of substances in closed systems

	ERC 9b: Wide dispersive outdoor use of substances in closed systems **Sector of end use:** SU 0: Other: 22
Use in coatings	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 10: Roller application or brushing PROC 11: Non industrial spraying PROC 13: Treatment of articles by dipping and pouring PROC 15: Use as laboratory reagent PROC 19: Hand-mixing with intimate contact and only PPE available. **Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems ERC 8d: Wide dispersive outdoor use of processing aids in open systems **Sector of end use:** SU 0: Other: 22
Use in binders and release agents	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 6: Calendering operations PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 10: Roller application or brushing PROC 11: Non industrial spraying PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation **Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems ERC 8d: Wide dispersive outdoor use of processing aids in open systems **Sector of end use:** SU 0: Other: 22

Use in laboratory reagents	**Process category (PROC):** PROC 10: Roller application or brushing PROC 15: Use as laboratory reagent **Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems **Sector of end use:** SU 0: Other: 22
Use in functional fluids	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 20: Heat and pressure transfer fluids in dispersive, professional use but closed systems **Environmental release category (ERC):** ERC 9a: Wide dispersive indoor use of substances in closed systems ERC 9b: Wide dispersive outdoor use of substances in closed systems **Sector of end use:** SU 0: Other: 22
Agrochemical use	**Process category (PROC):** PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 11: Non industrial spraying PROC 13: Treatment of articles by dipping and pouring **Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems ERC 8d: Wide dispersive outdoor use of processing aids in open systems **Sector of end use:** SU 0: Other: SU 22

2.2.3 Uses by consumers

Table 10. Uses by consumers

Identified Use (IU) name	Use descriptors
Use in coatings	**Chemical product category (PC):** PC 1: Adhesives, sealants PC 4: Anti-freeze and de-icing products PC 8: Biocidal products (e.g. disinfectants, pest control) 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 PC 0: Other: 5, 9, 10, PC34 covers PC5 and PC10 **Environmental release category (ERC):** ERC 8a: Wide dispersive indoor use of processing aids in open systems ERC 8d: Wide dispersive outdoor use of processing aids in open systems **Sector of end use:** SU 0: Other: SU 21
Use in fuels	**Chemical product category (PC):** PC 13: Fuels **Environmental release category (ERC):** ERC 9a: Wide dispersive indoor use of substances in closed systems ERC 9b: Wide dispersive outdoor use of substances in closed systems Subsequent service life relevant for that use? : yes

2.3 Uses advised against

The uses are provided in Section 2.2. Other uses are not recommended.

2.3.1 Uses by workers in industrial settings advised against

The uses are provided in Section 2.2.1. Other uses are not recommended.

2.3.2 Use by professional workers advised against

The uses are provided in Section 2.2.2. Other uses are not recommended.

2.3.3 Uses by consumers advised against

The uses are provided in Section 2.2.3. Other uses are not recommended.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
601-021-00-3	toluene	203-625-9	108-88-3	Flam. Liq. 2 Repr. 2 Asp. Tox. 1 STOT RE 2 * Skin Irrit. 2 STOT SE 3	H225 H361d*** H304 H373** H315 H336	GHS02 GHS08 GHS07 Dgr	H225 H361d *** H304 H373 ** H315 H336			

3.2 Self classification

See 3.1. Harmonised Classification.

ENVIRONMENTAL FATE PROPERTIES

Not evaluated.

3.3 Degradation

Not evaluated.

3.3.1 Abiotic degradation

Not evaluated.

3.3.1.1 Hydrolysis

Not evaluated.

3.3.1.2 Phototransformation/photolysis

Not evaluated.

3.3.1.2.1 Phototransformation in air

Not evaluated.

3.3.1.2.2 Phototransformation in water

Not evaluated.

3.3.1.2.3 Phototransformation in soil

Not evaluated.

3.3.2 Biodegradation

Not evaluated.

3.3.2.1 Biodegradation in water

Not evaluated.

3.3.2.1.1 Estimated data

Not evaluated.

3.3.2.1.2 Screening tests

Not evaluated.

3.3.2.1.3 Simulation tests (water and sediments)

Not evaluated.

3.3.2.1.4 Summary and discussion of biodegradation in water and sediment

Not evaluated.

3.3.2.2 Biodegradation in soil

Not evaluated.

3.3.3 Summary and discussion on degradation

Not evaluated.

3.4 Environmental distribution

Not evaluated.

3.4.1 Adsorption/desorption

Not evaluated.

3.4.2 Volatilisation

Not evaluated.

3.4.3 Distribution modelling

Not evaluated.

3.4.4 Summary and discussion of environmental distribution

Not evaluated.

3.5 Bioaccumulation

Not evaluated.

3.5.1 Aquatic bioaccumulation

Not evaluated.

3.5.2 Terrestrial bioaccumulation

Not evaluated.

3.5.3 Summary and discussion of bioaccumulation

Not evaluated.

3.6 Secondary poisoning

Not evaluated.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Finnish CA`s comments and remarks

The Finnish CA concludes that for toluene vapors the dermal route is not considered to be very important, but liquid toluene can be absorbed through the skin. The available studies are present in the dossier and no newer or additional data was found. According to the studies, dermal uptake after skin exposure does occur, but to a limited degree. This uptake is taken into account in relevant exposure scenarios. Dermal absorption is also taken into account in occupational exposure limits using skin notation and this is correctly informed in chemical safety report and safety data sheet of the lead registrant. **The concern has been clarified and there is no need for request further information or update registration dossier.**

Relevant data in the registration dossier on toxicokinetics is included in italics for information only.

4.1.1 Non-human information

Table 11. Overview of experimental studies on absorption, metabolism, distribution and elimination

Method	***Results***	***Remarks***	***Reference***
rat (various) *Oral, dermal and inhalation* *The data for toxicokinetics, metabolism and distribution of toluene conform with the requirements of Annex VIIA of Directive 67/548/EEC*	*Main ADME results:* *absorption: Oral ~100%; Inhalation ~50% (dependent upon pulmonary ventilation); Dermal (in vitro rat skin, liquid toluene) 8.5 nmol/cm2min (0.78µg/cm2min)* *distribution: Toluene is distributed to various tissues, the amount depending on the tissue/blood partition coefficient, the duration and level of exposure, and the rate of elimination.* *metabolism: Biotransformation of toluene occurs mainly by oxidation. The endoplasmic reticulum of liver parenchymal cells is the principal site of oxidation which involves the P450 system.* *elimination: About 20% of the absorbed toluene is eliminated via the lungs in expired air. The remainder is rapidly metabolised in the liver and excreted as conjugated metabolites in the urine (mainly as hippuric acid).*	*2 (reliable with restrictions)* *supporting study* *Composite record* ***Test material (EC name): toluene***	*Benignus VA, Muller KE, Barton CN and Bittikofer JA (1981)* *Sato A, Nakajima T (1978)* *Carlsson A, Lindqvist T (1977)* *Tsuruta H (1982)* *EU RAR (2003)* *ASTDR (2000)*

Estimated data on toxicokinetics are summarised in the following table:

Table 12. Overview of estimated data on toxicokinetics

Method	***Results***	***Remarks***	***Reference***

Dermal absorption *Dermal absorption was predicted using a model based on QSAR.*	*Percutaneous absorption rate:* *3.6 % (maximum dermal flux = 0.000581 mg/cm2/min)*	*2 (reliable with restrictions)* *supporting study* *(Q)SAR* ***Test material (EC name): toluene***	*ten Berge, W. (2009)*

4.1.2 Human information

The exposure-related observations in humans are summarised in the following table:

Table 13. Overview of exposure-related observations on basic toxicokinetics and/or dermal absorption in humans

Method	***Results***	***Remarks***	***Reference***
Endpoint addressed: basic toxicokinetics	*Toluene is absorbed rapidly from the lung (approximately 50% absorbed), but uptake from skin exposure is limited. Toluene is almost completely absorbed from the gastrointestinal tract. Toluene is readily metabolised, mainly to benzoic acid. A proportion of around 20% of absorbed toluene is eliminated in expired air and the remaining 80% is metabolised and excreted in the urine.*	*2 (reliable with restrictions)* *supporting study* ***Test material (EC name): toluene***	*Sato A, Nakajima T (1978)* *Carlsson A, Lindqvist T (1977)* *Woiwode W, Drysch K. (1981)* *ASTDR (2000)* *EU RAR (2003)*

4.1.3 Summary and discussion on toxicokinetics

Absorption

The major uptake of toluene vapour is through the respiratory system. Toluene is absorbed rapidly via inhalation and the amount absorbed (approximately 50%) depends on pulmonary ventilation. Studies in humans (e. g. Carlsson and Lindqvist, 1977) have shown that at rest a three-hour exposure to toluene vapour will result in an uptake amounting to approximately 50% of the inhaled toluene. Data from experimental exposure of volunteers show that physical work results in increased toluene uptake (Carlsson, 1982). Using a 50 W workload, exposure to 300 mg/m^3 (80 ppm) toluene for 2 hours toluene uptake was 2.4 times higher than the uptake at rest. In rats during a 3 hour exposure to 575 ppm (2167 mg/m^3) blood and brain toluene levels reached estimated asymptotic levels in 53 and 58 minutes, respectively (Benignus et al., 1981).

Toluene is almost completely absorbed from the gastrointestinal tract.

Distribution

Toluene is distributed to various tissues, the amount depending on the tissue/blood partition coefficient, the duration and level of exposure, and the rate of elimination.

Metabolism

Biotransformation of toluene occurs mainly by oxidation. The endoplasmic reticulum of liver parenchymal cells is the principal site of oxidation which involves the P450 system. Analysis of blood and urine samples from workers and volunteers exposed to toluene via inhalation in concentrations ranging from 100 to 600 ppm (377-2,261 mg/m^3) indicate that of the biotransformed toluene, ~ 99% is oxidised via benzyl alcohol and benzaldehyde to benzoic acid. The remaining 1% is oxidised in the aromatic ring, forming ortho-, meta- and para-cresol (Woiwode and Drysch, 1981).

Elimination

In the rat, elimination of toluene is rapid with most toluene eliminated from fat after 12 hours. Within a few hours after termination of exposure the blood and alveolar air contains very little toluene. A proportion (around 20%) of the absorbed toluene is eliminated in the expired air. The remaining 80% of the absorbed toluene is metabolised in the liver by the P450 system, mainly via benzyl alcohol and benzaldehyde to benzoic acid. Benzoic acid is conjugated with glycine and excreted in the urine as hippuric acid.

Dermal absorption

The capability of liquid toluene to penetrate the skin was investigated in isolated rat skin (Tsurutu, 1982). At steady state, a penetration of 8.5 nmol/cm^2 min (0.78µg/cm^2 min) was determined indicating that dermal uptake occurs to a very limited degree. In five volunteers exposed to toluene by immersing a hand up to the wrist in liquid toluene for 30 minutes, maximum concentrations of toluene in blood (0.17 mg/L) were found 30 minutes after start of the exposure. The maximum blood toluene concentration was maintained for 10-15 minutes after exposure had ended and was a quarter of that achieved in a 2 hour inhalation exposure to 100 ppm (377 mg/m^3) toluene vapour (Sato and Nakajima, 1978). These results demonstrate that liquid toluene can be absorbed through the skin.

Dermal absorption of liquid toluene was predicted using a model which considers absorption as a two stage process, permeation of the stratum corneum followed by transfer from the stratum corneum to the epidermis (ten Berge, 2009). The QSAR for each process was derived by fitting each model equation to experimentally derived values using an iterative non-linear least squares approach. Dermal flux and percent absorption were predicted using physicochemical values (see section 4) determined at approximately 25°C. The model predicted a maximum flux of 0.0000581 mg/cm^2/min giving a dermal absorption value of approximately 3.6% of the amount applied as liquid toluene.

Dermal absorption from toluene vapours is not likely to be an important route of exposure.

4.2 Acute toxicity

Not evaluated.

4.2.1 Non-human information

Not evaluated.

4.2.1.1 Acute toxicity: oral

Not evaluated.

4.2.1.2 Acute toxicity: inhalation

Not evaluated.

4.2.1.3 Acute toxicity: dermal

Not evaluated.

4.2.1.4 Acute toxicity: other routes

Not evaluated.

4.2.2 Human information

Not evaluated.

4.2.3 Summary and discussion of acute toxicity

Not evaluated.

4.3 Irritation

Not evaluated.

4.3.1 Skin

Not evaluated.

4.3.2 Eye

Not evaluated.

4.3.3 Respiratory tract

Not evaluated.

4.3.4 Summary and discussion of irritation

Not evaluated.

4.4 Corrosivity

Not evaluated.

4.5 Sensitisation

Not evaluated.

4.5.1 Skin

Not evaluated.

4.5.2 Respiratory system

Not evaluated.

4.5.3 Summary and discussion on sensitisation

Not evaluated.

4.6 Repeated dose toxicity

Not evaluated.

4.6.1 Non-human information

Not evaluated.

4.6.1.1 Repeated dose toxicity: oral

Not evaluated.

4.6.1.2 Repeated dose toxicity: inhalation

Not evaluated.

4.6.1.3 Repeated dose toxicity: dermal

Not evaluated.

4.6.1.4 Repeated dose toxicity: other routes

Not evaluated.

4.6.2 Human information

Not evaluated.

4.6.3 Summary and discussion of repeated dose toxicity

Not evaluated.

4.7 Mutagenicity

Not evaluated.

4.7.1 Non-human information

Not evaluated.

4.7.1.1 In vitro data

Not evaluated.

4.7.1.2 In vivo data

Not evaluated.

4.7.2 Human information

Not evaluated.

4.7.3 Summary and discussion of mutagenicity

Not evaluated.

4.8 Carcinogenicity

Not evaluated.

4.8.1 Non-human information

Not evaluated.

4.8.1.1 Carcinogenicity: oral

Not evaluated.

4.8.1.2 Carcinogenicity: inhalation

Not evaluated.

4.8.1.3 Carcinogenicity: dermal

Not evaluated.

4.8.2 Human information

Not evaluated.

4.8.3 Summary and discussion of carcinogenicity

Not evaluated.

4.9 Toxicity for reproduction

Finnish CA`s comments and remarks

The Finnish CA concluded that no new information has become available since the EU RAR (2003), which would change the conclusions for deriving long-term inhalation reference value for workers. The basis of the long-term inhalation DNEL for workers is information on reproductive toxicity. There is no need to re-evaluate the available information and therefore relevant parts of the CSR are included in italics for information only. The Finnish CA further notes that EU RAR (2003) includes additional information related to specific studies, which was not included in the registration dossier. This information was collected from the authors of studies when the EU RAR was prepared.

See discussion on DNELs in more detail in section 5.13.2.

4.9.1 Effects on fertility

4.9.1.1 Non-human information

The results of experimental studies are summarised in the following table:

Table 14. Overview of experimental studies on fertility

Method	***Results***	***Remarks***	***Reference***
rat (Crl:CD[SD]BR) male/female *two-generation study* *inhalation: vapour (whole body)* *0, 375, 1875, 7500 mg/m^3 (target concentration)* *0, 102, 497, 2020 ppm (analytical conc. (average over 39 weeks of exposure))* *Exposure: 6 h/day (7 days/week)* *OECD Guideline 416 (Two-Generation Reproduction Toxicity Study)*	*NOAEC (systemic toxicity) (P): 500 ppm (male/female) (slightly lower body weight gain 2000 ppm)* *NOAEC (systemic toxicity) (P): 1875 mg/m³ air (nominal) (male/female) (slightly lower bodyweight gain at 7500 mg/m^3)* *NOAEC (reproduction) (P): 2000 ppm (male/female) (no effects on fertility, reproductive performance or maternal/ pup behaviours at 2000 ppm (highest dose tested))* *NOAEC (reproduction) (P): 7500 mg/m³ air (nominal) (male/female) (no effects on fertility, reproductive performance or maternal/ pup behaviours at 7500 mg/m^3 (highest dose tested))*	*2 (reliable with restrictions)* *key study* *experimental result* ***Test material (EC name): toluene***	*Publication 1 (see annex: confidential information)*

	NOAEC (F1): 500 ppm (male/female) (lower body weight at birth and body weight gain prior to weaning) *NOAEC (F1): 1875 mg/m³ air (nominal) (male/female) (lower body weight at birth and body weight gain prior to weaning)* *NOAEC (F2): 500 ppm (male/female) (lower body weight at birth and body weight gain prior to weaning)* *NOAEC (F2): 1875 mg/m³ air (nominal) (male/female) (lower bodyweight at birth and body weight gain prior to weaning)*		
rat (Sprague-Dawley) male/female *fertility* *inhalation: vapour (whole body)* *600 or 2000 ppm (2261 or 7537 mg/m^3) (nominal conc.)* *Exposure: 6 h/day (7 days/week Male rats were exposed for 90 days (60 days pre-mating, during mating period and until termination on day 91); female rats were exposed from 14 days before mating, during the mating period and until day 7 of gestation)* *Male and female rats were exposed to toluene vapour and effects on their fertility were investigated. Toxicity with respect to testicular and reproductive functions was examined.*	*NOAEC (P): 600 ppm (male) (based on decreased sperm count and reduced epididymides at 2000 ppm)* *NOAEC (P): 2261 mg/m³ air (nominal) (male) (based on decreased sperm count and reduced epididymides at 7537 mg/m^3)*	*2 (reliable with restrictions)* *key study* *experimental result* ***Test material (EC name): toluene***	*Ono A, Sekita K, Ogawa Y, Hirose A, Suzuki S, Saito M, Naito K, Kaneko (1996)*

4.9.1.2 Human information

The exposure-related observations in humans are summarised in the following table:

Table 15. Exposure-related observations on toxicity to reproduction / fertility in humans

Method	***Results***	***Remarks***	***Reference***
Study type: cross sectional study *Type of population: occupational* *Details on study design: Rates of late*	*The results of this study suggest an increased risk of late spontaneous abortions associated with exposure to toluene at levels around 88 ppm*	*4 (not assignable)* *supporting study*	*Ng TP, Foo SC, Yoong T (1992)* *Foo, SC, Phoon, WO, Khoo, NY*

Method	*Results*	*Remarks*	*Reference*
spontaneous abortion (12-28 weeks) determined using a reproductive questionnaire were compared in 55 women with 105 pregnancies exposed to toluene (mean 88 ppm, range 50-150 ppm), 31 women (68 pregnancies) working in the same factory in departments where much lower exposure to toluene occurred (range 0-25 ppm), and an external community control group of 190 women (444 pregnancies) attending antenatal and postnatal clinics. *Endpoint addressed: toxicity to reproduction / fertility*	*(range 50-150 ppm). The finding achieved statistical significance in comparisons with the low exposure group.*	***Test material (EC name): toluene***	*(1988)* *EU RAR (2008)* *SCOEL (2001)* *European Commission (2000)*

4.9.2 Developmental toxicity

4.9.2.1 Non-human information

The results of experimental studies are summarised in the following table:

Table 16. Overview of experimental studies on developmental toxicity

Method	*Results*	*Remarks*	*Reference*
rat (Wistar (Bor: Wisw/spf, TNO)) *inhalation: vapour (whole body)* *0, 300, 600, 1000, 1200 ppm (nominal conc.)* *0, 1131, 2261, 3768, 4522 mg/m^3 (nominal conc.)* *0, 271, 628, 951, 1167 ppm (analytical conc.)* *Exposure: 6h/day (day 9-21 of pregnancy)* *Pregnant rats exposed to toluene by whole body inhalation from day 9-21 of pregnancy. Rats were allowed to litter and offspring assessed for range of developmental effects including learning ability and fertility.*	*NOAEC (offspring behaviour): 1200 ppm (no adverse effects seen on behaviour of rat offspring following exposure during late embryonic and foetal development)* *NOAEC (offspring behaviour): 4522 mg/m³ air (nominal) (no adverse effects seen on behaviour of rat offspring following exposure during late embryonic and foetal development)* *NOAEC (maternal toxicity): 600 ppm (lower maternal body weight gains at 1000 and 1200 ppm)* *NOAEC (maternal toxicity): 2261 mg/m³ air (nominal) (lower maternal bodyweight gain at 3768 and 4522 mg/m^3)* *NOAEC (developmental toxicity): 600 ppm (lower offspring body weight at birth and delayed vaginal opening following maternal exposure at 1000 ppm)* *NOAEC (developmental toxicity): 2261 mg/m³ air (nominal) (lower*	*2 (reliable with restrictions)* *key study* *experimental result* ***Test material (EC name): toluene***	*Thiel R and Chahoud I (1997)*

	offspring body weight at birth and delayed vaginal opening following maternal exposure at 3768 mg/m^3)		
rat (Crl: CD (SD) BR VAF/Plus) *inhalation: vapour (whole body)* *0 (control), 250, 750, 1500 or 3000 ppm (0, 938, 2812, 5625 or 11250 mg/m^3) (nominal conc.)* *0, 250, 748, 1519, 3009 ppm (analytical conc.)* *Exposure: 6 h/day (gestation day 6-15 (GD 6-15) where day of positive smear/vaginal plug was taken as day gestation day 0 (GD0))* *EPA OTS 798.4350 (Inhalation Developmental Toxicity Screen)*	*NOAEC (maternal toxicity): 750 ppm (nominal) (lower body weight and adverse clinical signs at 1500 ppm and 3000 ppm)* *NOAEC (maternal toxicity): 2812 mg/m³ air (nominal) (lower body weight and adverse clinical signs at 5625 and 11250 mg/m$^{3)}$* *NOAEC (developmental toxicity): 750 ppm (nominal) (lower foetal body weight at 1500 ppm and 3000 ppm)* *NOAEC (developmental toxicity): 2812 mg/m³ air (nominal) (lower foetal body weight at 5625 and 11250 mg/m^3)*	*2 (reliable with restrictions)* *key study* *experimental result* ***Test material (EC name): toluene***	*Publication 2 (see annex: confidential information)*
rat (Sprague-Dawley) *inhalation: vapour (whole body)* *0, 500 or 1500 ppm (nominal conc.)* *0, 1880 or 5650 mg/m3 (nominal conc. (http:// www.cdc.gov/niosh/docs/2004-101/calc.htm; based on mwt = 92.14))* *Exposure: 6 h/day (day 6-20 of pregnancy)* *Pregnant rats exposed to two concentrations of toluene vapour by whole body inhalation from day 6-20 of pregnancy. Foetal parameters were evaluated on GD21.*	*NOAEC (maternal toxicity): 1880 mg/m³ air (nominal) based on: test mat. (Corrected maternal body weight was significantly decreased by 40% in dams exposed to 5650 mg/m3)* *NOAEC (teratogenicity): 1880 mg/m³ air (nominal) based on: test mat. (Malformations (described as "mainly diaphragmatic hernia") were present in 2 foetuses from litters from 2 dams exposed to 5650 mg/m3 (not statistically significant))* *NOAEC (developmental toxicity): 1880 mg/m³ air (nominal) based on: test mat. (Foetal body weight reduced by 7% in litters from dams exposed to 5650 mg/m3, but no effects of treatment on numbers of implantations, dead implants, resorptions or live foetuses)*	*2 (reliable with restrictions)* *supporting study* *experimental result* ***Test material (EC name): toluene***	*Saillenfait, A-M, Gallissot, F, Sabate, J-P, Bourges-Abella, N and (2007)*
rabbit (Himalayan) *inhalation: vapour (whole body)* *0, 30, 100, 100, 300, 500 ppm (nominal conc.)* *0, 30, 102, 100, 299 and 501 ppm (analytical conc.)* *0, 113, 377, 1131, 1884 mg/m^3 (nominal conc.)* *Exposure: 6 h/day (days 6-18 of*	*NOAEC (maternal toxicity): 500 ppm (no effects at highest dose tested)* *NOAEC (maternal toxicity): 1884 mg/m³ air (nominal) (no effects at highest dose tested)* *NOAEC (teratogenicity): 500 ppm (no effects at highest dose tested)* *NOAEC (teratogenicity): 1884 mg/m³ air (nominal) (no effects at*	*2 (reliable with restrictions)* *key study* *experimental result* ***Test material (EC name): toluene***	*Klimisch H-J, Hellwig J, Hofmann A (1992)*

gestation) *OECD Guideline 414 (Prenatal Developmental Toxicity Study)*	*highest dose tested)*		
rat (Mol:WIST) *inhalation: vapour (whole body)* *1200 ppm (4522 mg/m^3) (nominal conc.)* *1206 ± 18 ppm (analytical conc.)* *Exposure: 6 h/day (day 7 of gestation to day 18 lactation)* *Rats were exposed to toluene from day 7 of pregnancy until day 18 postnatally. Developmental and neurobehavioral effects in the offspring were investigated.*	*LOAEC (developmental toxicity): 1200 ppm (nominal) (lower birth weight in the absence of maternal toxicity at the only dose tested)* *LOAEC (developmental toxicity): 4522 mg/m³ air (nominal) (lower birth weight in the absence of maternal toxicity at the only dose tested)*	*2 (reliable with restrictions)* *supporting study* *experimental result* ***Test material (EC name): toluene***	*Hass U, Lund SP, Hougaard KS and Simonsen L (1999)*

4.9.2.2 Human information

The exposure-related observations in humans are summarised in the following table:

Table 17. Overview of exposure-related observations developmental toxicity in humans

Method	***Results***	***Remarks***	***Reference***
Study type: review of epidemiological evidence *Type of population: occupational in pregnant women and pregnant toluene abusers* *Details on study design: Papers were reviewed which investigated toluene abuse during pregnancy and toluene specific occupational studies. The reproductive outcomes of concern in these studies were primarily spontaneous abortion (SA), congenital malformation (CM), or decreased fertility/fecundity.* *Endpoint addressed: developmental toxicity / teratogenicity*	*This review examined the epidemiological evidence for adverse reproductive outcomes from occupational studies that presented toluene-specific findings. Clinical investigations of the reproductive effects of toluene abuse were also examined. It was concluded that the literature cannot be used to definitively establish a causal relationship between toluene exposure and spontaneous abortion or congenital malformation or the magnitude of the lowest effect level.*	*2 (reliable with restrictions)* *supporting study* ***Test material (EC name): toluene***	*Bukowski JA (2001)*

4.9.3 Summary and discussion of reproductive toxicity

Relevant parts of the CSR are included in Annex: Confidential information.

4.10 Endocrine disrupting properties

Not evaluated.

4.11 Other effects

Finnish CA`s comments and remarks

The Finnish CA concludes that among other neurophysiological effects, toluene induced impairment of the auditory function including morphological changes in experimental animal studies. Auditory toxicity has also been studied in humans, but these studies are not appropriate for determining a LOAEC/NOAEC. The Finnish CA concludes that the systemic NOAEC provides adequate protection against ototoxicity.

There are indications from several studies of synergistic effects due to simultaneous exposure to toluene and noise, but it is not possible to address this kind of co-exposure through REACH-legislation. Existence of this co-exposure is communicated in the lead registrants SDS.

The data available on effects on colour vision is not robust and based on the studies present in the registration dossier, permanent impairment of colour vision is not likely when IOEL values are not exceeded.

There is no need to request further information or to update the registration dossier.

4.11.1 Non-human information

4.11.1.1 Neurotoxicity

Not evaluated.

4.11.1.2 Immunotoxicity

Not evaluated.

4.11.1.3 Specific investigations: other studies

4.11.2 Human information

4.11.3 Summary and discussion of specific investigations

Relevant parts of the CSR are included in Annex: Confidential information.

4.12 Combined effects

Not evaluated.

4.13 Derivation of DNEL(s) / DMEL(s)

Finnish CA`s comments and remarks

The Registrant has used EU indicative occupational exposure limit values (IOELV) in place of worker DNEL values for risk assessment purposes. The Registrant has set the long-term inhalation DNEL for workers at 50 ppm (192 mg/m3) based on IOEL TWA - 8 hr value. The basis for IOEL values is the recommendation of the Commission Scientific Committee on Occupational Exposure Limits (SCOEL), for toluene from 2001 (SCOEL 2001). The IOELVs for toluene were published in Directive 2006/15/EC. The NOAEC values in the registration dossier derived from the hazard characterization are mentioned to be for information only.

The IOELVs are not mandatory values in the EU and the member states may implement different values (lower, equal or higher) in their national legislations. For example, the eight hours national occupational exposure limit value for toluene in Finland, Norway and Denmark is 25 ppm and in Belgium and France 20 ppm. In Finland the exposure limit value was lowered from 50 ppm to 25 ppm in 2009 based on the weight of evidence analysis of studies where increased rate of abortions in workers, effects on workers' color vision and other neurophysiological effects were seen. In 2007 American conference of governmental industrial hygienists (ACGIH) lowered their recommendation for TLV-TWA (8 hrs) value from 50 ppm to 20 ppm (75 mg/m3). ACGIH TLV-TWA value is set to protect from subclinical changes in color vision and potential for spontaneous abortion in female workers.

According to the ECHA guidance (Appendix R.8-13) Registrant may use the IOELVs in place of DNELs unless new scientific information available does not support the use of the IOELV for this purpose. This could be because information is more recent than the information that was used to set IOELV and because it leads to another value being derived which requires different risk management measures and operational conditions. When there is new scientific information which indicates that the IOEL does not provide the appropriate level of protection required by REACH, then the Registrant should develop a DNEL based on this new information whilst also taking account of the scientific information that was used as a basis for the adoption of the IOELV.

Toluene has been evaluated under Regulation (EEC) No 793/93, where the risk assessment was finalised in 2003 (EU RAR 2003). At the same time with this procedure, the SCOEL was preparing a recommendation on IOEL values for the Commission. The Finnish CA considers that no new information has become available since the EU RAR (2003), which would change conclusions for reproductive toxicity, on which the DNEL derivation is based on. There is no need to re-evaluate available information. According to Annex I, 0.5 of the REACH Regulation, available information from assessments carried out under other international and national programmes shall be included in the chemical safety assessment. Where available and appropriate, an assessment carried out under Community legislation (e.g. risk assessments completed under Regulation (EEC) No 793/93) shall be taken into account in the development of, and reflected in, the chemical safety report. Deviations from such assessments shall be justified.

Based on the results of the EU risk assessment under Regulation (EEC) No 793/93 (EU RAR 2003) Commission recommended risk reduction strategies for toluene (COM 2004/394/EC). One recommendation was addressed to the SCOEL to review the new information contained in the EU RAR (2003) and to recommend whether there is a need to revise the current OEL. It is stated in the registration dossier that the SCOEL had access to the draft EU risk assessment report for toluene, and was therefore aware of the background information contained therein. The SCOEL recommendation is however referring to the Danish draft ESR Assessment from 1998. The final report under Regulation (EEC) No 793/93 was published in 2003. The Finnish CA discussed with the sereteriat of the Commission Scientific Committee on Occupational Exposure Limits (SCOEL) and the secretariat confirmed that SCOEL had access to the draft EU RAR published in 2003 when

drafting the recommendation on toluene. The secretariat informed that for the moment and update of the toluene recommendation is not a prioritized issue.

After the SCOEL recommendation in 2001, toluene has received a harmonized hazard classification as Repr 2; H361d Suspected of damaging the unborn child, in accordance with Regulation (EC) No 1272/2008. Hazard classification is based on the weight of evidence analysis of all available experimental animal data and human data. These studies were evaluated also in the EU RAR (2003). Ng et al. (1992) was one of the key studies used in the hazard classification and in the EU RAR (2003). In the registration dossier of toluene, this study was assigned a reliability score of 4 (not assignable) and it was used as supporting study. Ng et al., study discusses increased spontaneous abortions associated with exposure to toluene in the workplace at average air concentration levels 88 ppm (range 50-150 ppm). Because of the limitations of the Ng et al. (1992) study, results may not be used to establish a definite relationship between late spontaneous abortions and toluene exposure. However, results from this study cannot be completely disregarded because also experimental animal studies indicate developmental toxicity such as lower birth weight, delayed postnatal development and developmental neurotoxicity. Several studies indicate similar effects in rat fetuses at similar dose levels. The effects indicating developmental neurotoxicity occurred at a higher exposure levels 1200 ppm and 1800 ppm (Hass et al. 1999 and Hougaard et al., 1999). This effect has not been examined at a lower exposure levels and NOAEC cannot be set. The NOAEC for other developmental effects is 600 ppm (2261 mg/m3).The Finnish CA considers that there is uncertainty whether the NOAEC 600 ppm for reproductive toxicity covers developmental neurotoxicity as well.

Developing nervous system is particularly sensitive to chemical exposure. Organic solvents such as toluene have an affinity for lipid-rich tissues and can readily cross the placenta. In addition to effects seen in developing animals, neurotoxicity has also been demonstrated in adult animals and in humans. Neurophysiological effects in workers have been found to be the most sensitive endpoints for toluene. Toluene has a harmonized hazard classification for effects on central nervous system (STOT SE 3; H336: May cause drowsiness or dizziness; STOT RE 2; H373: May cause damage to organs). For fertility the Registrant has provided data which indicate NOAEC value of 600 ppm (2261 mg/m3) for fertility (i.e., decreased sperm count and reduced epididymal weight). The Finnish CA considers that due to the remaining uncertainties in the Ng et al. study (1992) and because the developmental neurotoxicity has not been evaluated for exposure levels below 1200 ppm, this additional uncertainty consisting of limited dose-response data and data quality should be taken into account in the risk characterization.

The Registrant has set the long-term inhalation DNEL for workers at 50 ppm (192 mg/m3) based on IOEL TWA - 8 hr value. The SCOEL recommendation for IOEL values is mainly based on data from epidemiological studies (SCOEL 2001). TWA - 8 hrs (50 ppm, 192 mg/m3) for toluene is based on LOAEC value (60 ppm, 230 mg/m3) for neurobehavioral effects in humans (subjective effects on how the person feels). It is concluded that an exposure limit of 50 ppm (192 mg/m3) would also protect against potential fetotoxicity. The SCOEL recommendation does not, however, refer to all available experimental animal studies for reproductive toxicity which were included in the EU RAR (2003).

Currently, it is not clear how available experimental animal results especially for reproductive toxicity and the results from the EU RAR 2003 have been taken into account in the chemical safety assessment. The Finnish CA considers that due to the remaining uncertainties in Ng et al. study (1992) and because the developmental neurotoxicity has not been evaluated in experimental animals at exposure levels below 1200 ppm, additional uncertainty should be considered when deriving long term DNELs. The Finnish CA is of the opinion that the animal NOAEC 600 ppm (2250 mg/m3)

and human LOAEC 88 ppm (330 mg/m3) should be used in parallel to derive long-term a DNEL for workers and general public by using a weight of evidence analysis as it was used in the EU RAR (2003). The current long-term inhalation DNEL 50 ppm (192 mg/m3) for workers provides a 2-fold lower margin of safety than was concluded in the EU risk assessment (Table 18). In the EU RAR, risk characterization was made separately on "toxicity to reproduction (fertility and development)" and "toxicity to reproduction (spontaneous abortions)". They have led to exactly the same risk assessment conclusions. The Registrant has not provided a justification for deviation from the EU RAR (2003). The risk characterization should cover adequately developmental toxicity in humans and protect also vulnerable subpopulations.

Table 18. Required minimal Margin of Safety (MOS) for workers in the EU RAR 2003 (reproductive toxicity)

Sensitive end point	**Route**	**Dose descriptor**	**MOS_{min}**	**Reference value**
development, fertility	inhalation	NOAEC 600 ppm (2250 mg/m3)	30	20 ppm
abortions	inhalation	LOAEC 88 ppm (330 mg/m3)	5	17.6 ppm

The methodology used by SCOEL to establish IOEL values differs from the methodology used for DNEL derivation in REACH; for example handling of uncertainty varies. The applied assessment factor for derivation of IOEL TWA - 8 hr value was not explicitly stated or justified in the SCOEL recommendation for toluene. The SCOEL has applied an assessment factor below 2 to cover uncertainty due to remaining intraspecies differences between workers. This factor is lower than the one presented in the ECHA guidance, the recommended ECHA's factor being 5. The default factors recommended in ECHA guidance were established after ample consultation with stakeholders, taking into account various opinions on the matter. The Finnish CA is in the opinion that the Registrant has not followed the recommendations of ECHA`s Guidance R.8 and has not provided full justification for the derivation of long-term DNELs for workers (see Annex I, 1.4.1 of the REACH Regulation).

Summary:

According to Annex I, 0.5 of the REACH Regulation, available information from risk assessments completed under Regulation (EEC) No 793/93 shall be taken into account in the development of, and reflected in, the chemical safety report. Deviations from such assessments shall be justified. The proposed long-term inhalation DNEL 50 ppm (192 mg/m3) for workers provides a 2-fold lower minimum margin of safety than was concluded in the EU RAR (2003). Currently, it is not clear how available experimental animal results especially for reproductive toxicity and results from the EU RAR (2003) under Regulation (EEC) No 793/93 have been taken into account in the chemical safety assessment. The Finnish CA is in the opinion that the Registrant has not provided justification for deviation from the EU RAR. The SCOEL recommendation does not mention all of

the available experimental animal studies for reproductive toxicity and the applied assessment factor for derivation of IOEL TWA - 8 hr value was not explicitly stated or justified.

Therefore, the Registrant is, recommended to justify the deviation from the risk assessment completed under Regulation (EEC) No 793/93 (see Annex I, 0.5 of the REACH Regulation). In addition the Registrant isrecommended to fully justify the long-term inhalation DNEL derivation for workers provided in the chemical safety report by specifying (see Annex I, 1.4.1 of the REACH Regulation)

- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
- the DNELs reflect the likely route(s), duration and frequency of exposure.

If a justification for the deviation from the risk assessment completed under Regulation (EEC) No 793/93 is not given and the choice of the information used for current long-term inhalation DNEL derivation for workers is not fully justified, the Registrant should use results from the EU RAR (2003) to derive long-term inhalation DNEL for workers and reassess related risks.

The concern has been clarified and Finnish CA recommends to update the registration dossier, taking into account the issues mentioned above. The Finnish CA recommends that Commission Scientific Committee on Occupational Exposure Limits (SCOEL) will take into account results from the EU RAR (2003) and make a review on whether there is a need to update the recommendation on IOEL values for toluene.

4.13.1 Overview of typical dose descriptors for all endpoints

See Table 20 in Annex: Confidential information.

4.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects

The evaluation was targeted on information related to the establishment of long-term inhalation DNEL for workers.

The information in the CSR : see Annex: Confidential information

Table 19. DN(M)ELs for workers

Exposure pattern	***Route***	***Descriptor***	***DNEL / DMEL***	***(Corrected) Dose descriptor *)***	***Most sensitive endpoint***	***Justification***
Acute - systemic effects	*Dermal*	*No-threshold effect and/or no dose-response information available*				*Available data indicate no acute dermal hazard*
Acute - systemic effects	*Inhalation*	*DNEL (Derived No Effect Level)*	*384 mg/m³*	*NOAEC: 384 mg/m³ (based on AF of 1)*		*Acute inhalation systemic DNEL based on the IOELV with no modification*
Acute - local effects	*Dermal*	*No-threshold effect and/or no dose-response information available*				*Available data indicate no acute / short-term local dermal hazard apart from irritation (dose-response relationship not readily quantifiable)*
Acute - local effects	*Inhalation*	*DNEL (Derived No Effect Level)*	*384 mg/m³*	*LOAEC: 384 mg/m³ (based on AF of 1)*		*Acute inhalation local DNEL based on the IOELV with no modification*
Long-term - systemic effects	*Dermal*	*DNEL (Derived No Effect Level)*	*384 mg/kg bw/day*	*IOELV: 384 mg/kg bw/day (based on AF of 1)*		*Long-term dermal systemic DNEL based on the IOELV following route-to-route extrapolation*
Long-term - systemic effects	*Inhalation*	*DNEL (Derived No Effect Level)*	*192 mg/m³*	*NOAEC: 192 mg/m³ (based on AF of 1)*	*neurotoxicity*	*Long-term inhalation systemic DNEL based on the IOELV with no modification*
Long-term - local effects	*Dermal*	*No-threshold effect and/or no dose-response information available*				*No-threshold effect and/or no dose-response information available*
Long-term - local effects	*Inhalation*	*DNEL (Derived No Effect Level)*	*192 mg/m³*	*NOAEC: 192 mg/m³ (based on AF of 1)*	*irritation (respiratory tract)*	*Long-term inhalation local DNEL based on the IOELV with no modification*

**) The (corrected) dose descriptor starting points have been automatically calculated by multiplying the values of the fields "D(N)MEL" and "Assessment factor" provided in the Endpoint summary of IUCLID section 7. Toxicological information. It reflects the value after any corrections, e.g. route-to-route extrapolation. See column "Justification" for the rationale behind such modifications and the use of assessment factors.*

4.14 Conclusions of the human health hazard assessment and related classification and labelling

Human health hazards were not reevaluated. Evaluation perfomed has no effect on harmonised classification and labelling of toluene.

5 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

Not evaluated.

6 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated

6.1 Aquatic compartment (including sediment)

Not evaluated.

6.1.1 Toxicity data

Not evaluated.

6.1.1.1 Fish

Not evaluated.

6.1.1.1.1 Short-term toxicity to fish

Not evaluated.

6.1.1.1.2 Long-term toxicity to fish

Not evaluated.

6.1.1.2 Aquatic invertebrates

Not evaluated.

6.1.1.2.1 Short-term toxicity to aquatic invertebrates

Not evaluated.

6.1.1.2.2 Long-term toxicity to aquatic invertebrates

Not evaluated.

6.1.1.3 Algae and aquatic plants

Not evaluated.

6.1.1.4 Sediment organisms

Not evaluated.

6.1.1.5 Other aquatic organisms

Not evaluated.

6.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not evaluated.

6.1.2.1 PNEC water

Not evaluated.

6.1.2.2 PNEC sediment

Not evaluated.

6.2 Terrestrial compartment

Not evaluated.

6.2.1 Toxicity test results

Not evaluated.

6.2.1.1 Toxicity to soil macro organisms

Not evaluated.

6.2.1.2 Toxicity to terrestrial plants

Not evaluated.

6.2.1.3 Toxicity to soil micro-organisms

Not evaluated.

6.2.1.4 Toxicity to other terrestrial organisms

Not evaluated.

6.2.2 Calculation of Predicted No Effect Concentration (PNEC soil)

Not evaluated.

6.3 Atmospheric compartment

Not evaluated.

6.4 Endocrine disrupting properties

Not evaluated.

6.5 Microbiological activity in sewage treatment systems

Not evaluated.

6.5.1 Toxicity to aquatic micro-organisms

Not evaluated.

6.5.2 PNEC for sewage treatment plant

Not evaluated.

6.6 Non compartment specific effects relevant for the food chain (secondary poisoning)

Not evaluated.

6.6.1 Toxicity to birds

Not evaluated.

6.6.2 Toxicity to mammals

Not evaluated.

6.6.3 Calculation of PNECoral (secondary poisoning)

Not evaluated.

6.7 Conclusion on the environmental hazard assessment and on classification and labelling

7 PBT AND VPVB ASSESSMENT

Not evaluated.

7.1 Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

Not evaluated.

7.1.1 Persistence assessment

Not evaluated.

7.1.2 Bioaccumulation assessment

Not evaluated.

7.1.3 Toxicity assessment

Not evaluated.

7.1.4 Summary and overall conclusions on PBT and vPvB Properties

Not evaluated.

8 EXPOSURE ASSESSMENT

8.1 Human Health

8.1.1 Exposure assessment for worker

8.1.1.1 Overview of uses and exposure scenarios

Finnish CA`s comments and remarks

The Finnish CA evaluated whether all identified uses reported in the registration dosser were covered in the Chemical Safety Assessment and in Exposure Scenarios. Furthermore, Finnish Chemicals Product Register was used as a reference to identified uses of toluene. The Register was cross-checked to verify whether all of the uses were covered in the Chemical Safety Assessment and subsequently in Exposure Scenarios.

The only use that appeared to be missing was use of toluene in production of plastics. The question, whether the use should be an identified use in the registration dossier or if it was covered by another exposure scenario, was presented to the Registrants. According to them, toluene is primarily used as a reaction solvent in the production of plastics and this use is covered in the "Manufacture of the substance" exposure scenario. The Finnish CA would like to make a note that this is not necessarily clear, as the title and thus the exposure scenario can also be interpreted to refer only to manufacture of toluene. A more descriptive title would increase the usability of the exposure scenario. **The Finnish CA recommends the Registrant to include clarifying information in the registration dossier. There is no need to request further information.**

8.1.1.2 Scope and type of exposure

8.1.1.2.1 Monitoring data

Not evaluated.

8.1.1.2.2 Modelled data

Not evaluated.

8.1.1.2.3 Comparison of monitoring and modelled data

Not evaluated.

8.1.2 Exposure assessment for consumer

8.1.2.1 Overview of uses and exposure scenarios

8.1.2.2 Scope and type of exposure

8.1.2.2.1 Monitoring data

8.1.2.2.2 Modelled data

8.1.2.2.3 Comparison of monitoring and modelled data

8.2 Environmental exposure assessment

Not evaluated.

8.2.1 Aquatic compartment (incl. sediment)

Not evaluated.

8.2.1.1 Overview of uses and exposure scenarios

Not evaluated.

8.2.1.2 Scope and type of exposure

Not evaluated.

8.2.1.2.1 Monitoring data

Not evaluated.

8.2.1.2.2 Modelled data

Not evaluated.

8.2.1.2.3 Comparison of monitoring and modelled data

Not evaluated.

8.2.2 Terrestrial compartment

Not evaluated.

8.2.2.1 Overview of uses and exposure scenarios

Not evaluated.

8.2.2.2 Scope and type of exposure

Not evaluated.

8.2.2.2.1 Monitoring data

Not evaluated.

8.2.2.2.2 Modelled data

Not evaluated.

8.2.2.2.3 Comparison of monitoring and modelled data

Not evaluated.

8.2.3 Atmospheric compartment

Not evaluated.

8.2.3.1 Overview of uses and exposure scenarios

Not evaluated.

8.2.3.2 Scope and type of exposure

Not evaluated.

8.2.3.2.1 Monitoring data

Not evaluated.

8.2.3.2.2 Modelled data

Not evaluated.

8.2.3.2.3 Comparison of monitoring and modelled data

Not evaluated.

8.3 Combined exposure assessment

Not evaluated.

9 RISK CHARACTERISATION

9.1 Human Health

Finnish CA`s comments and remarks

The comparison of the toluene DNEL with the results of the exposure assessment in different use categories shows that exposures are in most cases well below the derived DNEL. In a couple of use categories however, the RCR value is nearly at the level of DNEL (see Table 2 in annex for Confidential information). When taking into account the uncertainties in derivation of the long-term DNEL for workers and exposure assessments, it is not evident that safe use is demonstrated there. Therefore, it would be essential for registrant to demonstrate and justify more transparently that the safe use is ensured also in the scenarios where RCR is very close to 1 **There is no need to request further information. However, the Finnish CA recommends that the Registrant includes a clarifying justification in the registration dossier and makes a reassessment of the appropriateness of the relevant risk management measures (RMM) to ensure that the RMMs currently in place adequately control worker exposure to toluene.**

9.1.1 Workers

9.1.2 Consumers

9.1.3 Indirect exposure of humans via the environment

Not evaluated.

9.2 Environment

Not evaluated.

9.2.1 Risk characterisation for PBT

Not evaluated.

9.2.2 Aquatic compartment (incl. sediment)

Not evaluated.

9.2.3 Terrestrial compartment

Not evaluated.

9.2.4 Atmospheric compartment

Not evaluated.

9.2.5 Microbiological activity in sewage treatment systems

Not evaluated.

9.3 Overall risk characterisation

Not evaluated.

9.3.1 Human health (combined for all exposure routes)

Not evaluated.

9.3.2 Environment (combined for all exposure routes)

Not evaluated.

10 OTHER INFORMATION

11 REFERENCES

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12 ABBREVIATIONS