baua:
Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

n-Hexane

EC No 203-777-6

CAS No 110-54-3

Evaluating Member State(s): Germany

Dated: May 2017

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

Before concluding the substance evaluation a Decision to request further information was issued on: 21 May 2014

Further information on registered substances here:

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

DISCLAIMER

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

Foreword

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

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

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

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

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

n-Hexane was originally selected for substance evaluation in order to clarify suspected risks about:

- Human health: CMR and neurotoxicity

- Exposure: Wide dispersive use, high aggregated tonnage

During the evaluation, exposure of workers and consumer exposure were identified as additional concerns. These concerns were addressed in a decision dated 21 May 2014 requiring the registrants to provide additional information on the registered uses and exposure conditions for workers and consumers.[2]

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The substance is listed by Index number 601-037-00-0 in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures for repeated dose toxicity as "STOT RE 2*; H373**", meaning that it is a minimum classification following Annex VI, Section 1.2.1 of CLP, and for reproductive toxicity as "Repr. 2, H361f".

The substance is listed by Index number 601-037-00-0 in Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Directive 67/548/EEC) of CLP as "Xn; R48/20" and as "Repr. Cat. 3; R62".

3. CONCLUSION OF SUBSTANCE EVALUATION

Worker exposure

The additional information regarding the risk of flammability (Requirement 1) submitted by the registrant following the substance evaluation decision contains some RMMs that should be implemented with special regard to the aspect of high flammability of n-hexane. However, they are identical for all exposure scenarios (ES) which still does not allow a straight forward differentiated risk assessment for each individual scenario. As a result, the registrants therefore did not submit the requested information as it was addressed in the decision. Nevertheless, the supplied information together with specific information in the chemical safety assessment (CSA) and in the safety data sheet (SDS) may serve as a basis for a meaningful selection of RMMs by a skilled user. Therefore, the evaluating member state competent authority (eMSCA) considered the supplied information as acceptable despite deviations.

The lead registrant has submitted information on the concerned exposure scenarios regarding effectiveness of protective measures for those cases where default values have not been used to clarify questions in terms of risk management measures (RMMs) such as standard operating procedures (SOPs) as an organisational measure. Therefore, request 2a of the substance evaluation decision is met with deviations, but acceptable.

In addition, the lead registrant has submitted information regarding operational conditions allowing refined assessments for exposure scenarios that were initially regarded as

[2] Substance evaluation decision on n-Hexane:
https://echa.europa.eu/documents/10162/774df00d-2a20-45a2-8fe0-b71a0bcc5680

incomplete by the eMSCA or for which a safe use could not be demonstrated. This information allows a higher tier assessment of the exposure scenarios which were identified by the eMSCA. A refined risk assessment based on this new information showed that the risk is adequately controlled. Therefore, the respective concern related to the request 2b of the substance evaluation decision has been clarified.

Regarding information on the use of PPE (request 3 of the substance evaluation decision), the lead registrant delivered the information concerning the requested specification of glove material, respiratory protection and the duration of use. Therefore, the respective concern has been clarified.

Furthermore, concerning request 4 of the substance evaluation decision the lead registrant did not provide peak exposure estimates/calculations for the process categories (PROCs) specified in the decision. According to the registrant, "peak exposures are unlikely to exceed 100 ppm even for short periods of time". First acute effects for n-hexane could be expected at or above ca. 500 ppm. German Technical Rule for Hazardous Substances 900 "Occupational limit values" contains the provision that short term exposures up to 400 ppm for n-hexane (for 15 min) are considered tolerable in occupational settings. Therefore, the eMSCA considers the reported peak exposure of about 100 ppm as providing sufficient margin of safety with respect to the exposure levels where first acute effects are expected. The eMSCA considered the supplied information as acceptable despite deviations.

Consumer Exposure

At the beginning of the substance evaluation process in 2012, inconsistencies and data gaps in the CSR regarding consumer exposure scenarios led the eMSCA to consider that risks could be expected for consumer application of n-hexane. To clarify this additional concern, plausible exposure scenarios with reproducible exposure estimates and RCRs were requested from the registrants in the substance evaluation decision.

Upon further consideration and discussion with downstream users, the active registrants updated their registration dossiers and removed the identified consumer uses completely in the technical IUCLID as well as in the CSR. **In consequence, the registrants do not support consumer uses any longer.** This has to be clearly communicated along the supply chain e.g. by updating the Safety Data Sheets, so that downstream users are aware of their obligation according to Article 37 (4) of the REACH Regulation in cases where n-hexane is intentionally used for the formulation of consumer products, bearing in mind that the original, now withdrawn chemical safety assessment documentation for consumers provided in the registration dossiers was insufficient to demonstrate no risk for consumer applications of n-hexane as outlined in the decision.

As of February 2017, the disseminated information on ECHA's page on n-hexane still lists consumer uses of n-hexane among the registered uses. This is due to the fact that information from inactive registrations is also disseminated, but this does not reflect the current range of uses supported by the active registrations.

A French survey was conducted among industrial sectors concerning the marketing of consumer products containing n-hexane (information provided as justification for the French proposal for amendment according to Article 51(4) of the REACH Regulation in 2013). A potential risk for consumers was identified in some consumer products belonging to the categories PC1, PC3, PC8, PC9, PC24 and PC35 with the current concentration limit of 3 % (triggering classification of a mixture as a Category 2 reproductive toxicant according Annex I (Table 3.7.2) of the Regulation (EC) No 1272/2008).

A "Survey of n-hexane" as part of the LOUS review by the Danish EPA (Mikkelsen et al., 2014) recorded several consumer products which contain n-hexane. They concluded that consumers may be exposed to "relatively high concentrations on a short term basis" due to the volatility of the substance and its presence in several spray products.

It can be assumed that n-hexane is present in consumer products and that consumer exposure is likely. But it is currently unclear whether n-hexane is mainly contained in

consumer products because (a) downstream users in the supply chain may have no knowledge that the consumer uses are no longer supported by the registrants (although the dissemination page suggests differently), (b) it is a constituent of other registered substances, and/or (c) occurs as impurity in other registered substances (which can "make up no more than 20 % (w/w)", ECHA-GD 2011) (further details are provided in the confidential annex). Likewise, it is unknown in which concentrations and products it is supplied to consumers. Therefore, the concerns identified regarding consumers could not be completely clarified. In case that the withdrawal of the supported uses in consumer products is effective, it has to be concluded that no risk for consumers arises from this registration. Whether the withdrawal of the originally registered uses will be completely effective for the market should be controlled by surveillance authorities. In addition and apart from the substance evaluation process, further data generation is necessary. With further information the authorities would be able to perform a general risk assessment of n-hexane that will consider all sources of n-hexane including dietary exposure and exposure from impurities in other registered substances.

The available information on the substance and the evaluation conducted has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

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

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

Upon assessment of the existing information on the neurotoxicity of n-hexane in humans the eMSCA considers it sufficient to indicate that classification of n-hexane as STOT RE 1 is appropriate. The legal classification of n-hexane for repeated dose toxicity is "STOT RE 2*; H373", meaning that it is a minimum classification following Annex VI 1.2.1 of Regulation (EC) No 1272/2008 (CLP). As stated in CLP, this (minimum) classification shall be applied if none of the following conditions are fulfilled:

- The manufacturer or importer has access to data or other information as specified in Part 1 of Annex I that lead to classification in a more severe category compared to the minimum classification. Classification in the more severe category must then be applied.

Following the rules set down in Annex VI and the data available, n-hexane appears to fulfil the criteria for classification as "STOT RE 1; H372".

The existing information on n-hexane is sufficient to conclude that n-hexane produces significant functional changes in the peripheral nervous system of humans following

repeated exposure through inhalation. Available human data demonstrated that the incidence of peripheral neuropathy can reliably be attributed to prolonged occupational exposure to n-hexane. The classification of n-hexane as "STOT RE 2; H373" shall be considered as a minimum classification. The availability of sufficient information on the neurotoxicity of n-hexane in humans indicates that a classification as "STOT RE 1; H372" may be appropriate. According to the Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (Chapter 3.9.5: Re-classification of substances and mixtures classified for STOT-RE according to DSD and DPD) "…Substances or mixtures classified with R48/23, R48/20 (for vapour), R48/24 and/or R48/25 shall be classified as STOT RE Category 1 because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD".

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

Not applicable.

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

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLP Annex VI Dossier	12/2017	DE

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

n-Hexane was originally selected for substance evaluation in order to clarify concerns about:

- Human health: CMR and neurotoxicity

- Exposure: Wide dispersive use, high aggregated tonnage

During the evaluation, exposure of workers and consumer exposure were identified as additional concerns. These concerns were addressed in a decision dated 21 May 2014 requiring the registrants to provide additional information on the registered uses and exposure conditions for workers and consumers.

Table 3

Evaluated endpoints	
Endpoint evaluated	**Outcome/conclusion**
CMR	Carcinogenicity was evaluated due to a concern regarding the potential of n-hexane to cause cancer in humans. The eMSCA concludes that non-classification for carcinogenicity is appropriate. Concern not substantiated. No further action. Mutagenicity was evaluated due to a concern regarding the potential of n-hexane to cause cancer in humans. The eMSCA concludes that non-classification for mutagenicity is appropriate. No further action. Reproductive Toxicity was evaluated due to a concern regarding the potential of n-hexane of damaging fertility in humans. The eMSCA concludes that the harmonised C&L is appropriate. No further action.
Neurotoxicity	Neurotoxicity confirmed, harmonised C&L process to be initiated.
Exposure of workers	Registrants delivered additional information and the concerns addressed were clarified. No further action.
Consumer exposure	Although the active registrants do not support consumer uses anymore, it can be assumed that n-hexane is still present in some consumer products and that consumer exposure is likely. However, both the source substances and the concentration in these products are currently unclear (see also section 7.13.3). Therefore, the concerns identified regarding consumers could not be completely clarified.

7.2. Procedure

The substance evaluation started in the year 2012. n-Hexane was evaluated regarding the aspects human health and exposure. During the evaluation two main areas of concern were identified: Worker exposure and consumer exposure. At the end of the initial evaluation year the eMSCA prepared a draft decision with further information requirements which was

finalised in the Member State Committee and taken by ECHA and sent to the registrants of n-hexane on 21 May 2014 with a deadline for provision of the new information until November 2014.

7.2.1.1. **Human Health**

The evaluation of the toxicity of n-hexane has been based on the registration dossiers as well as on reviews by a variety of international bodies/regulatory programs and original publications. Data available up to November 2015 for all endpoints have been assessed.

7.2.1.2. **Risk Communication, Labelling**

The Labelling of n-hexane as provided by the lead registrant was reviewed based on the Classification and Labelling as listed under Index number 601-037-00-0 in Annex VI, Part 3, Table 3.1 of Regulation (EC) No 1272/2008.

7.2.1.3. **Worker exposure**

Occupational exposure data are taken from literature sources which were selected based on timeliness of the assessment and representativeness for EU countries. An additional focus in the evaluation of literature was the time trend of occupational exposure to n-hexane.

The exposure scenarios for worker as provided by the registrants in the CSR were checked whether they are exhaustive, plausible and well documented with regard to operational conditions and information about risk management measures.

The evaluating MSCA considered the following aspects of particular importance for exposure scenarios for worker:

- sufficient description of operational conditions and risk management measures including personal protection equipment
- the order of priority for protective and prevention measures shall comply with the order as laid down in Directive 98/24/EG Art.6(2)
- the period of usage of personal protective equipment shall not exceed the specified maximum duration

Some exposure scenarios for worker were recalculated with ECETOC TRA for comparison. Thereby the efficiency values of risk management measures as used by the registrant(s) and justifications for variations were reviewed. The results are included in the confidential part of this report.

7.2.1.4. **Consumer Exposure**

In order to identify possible risks the CSR was checked to assess whether the exposure scenarios and risk characterisation ratios for consumers are exhaustive, plausible and well documented regarding relevant uses, exposure routes and targeted population groups. The efficiency of already implemented risk management measures was evaluated for clarification whether further risk management options are needed. Furthermore data lacks were identified and used default values and justifications for variations were checked.

The exposure assessment for consumers based on the recorded exposure scenarios, operational conditions and exposure estimates in the CSR of the registrant(s). For comparison, the evaluating MSCA also carried out own consumer exposure estimates according to ECHA Guidance on Information Requirements and Chemical Safety Assessment R.15 (ECHA R.15, 2010) on the basis of the operational conditions (OC) in the CSR. The results were compared to the exposure estimates in the CSR.

To assess if risks are adequately controlled, the risk characterisation ratios were recalculated once on the basis of the recorded exposure estimates and DNELs in the CSR and once again on the basis of the exposure estimates by the evaluating MSCA.

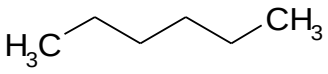
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	n-hexane
EC number:	203-777-6
CAS number:	110-54-3
Index number in Annex VI of the CLP Regulation:	601-037-00-0
Molecular formula:	C_6H_{14}
Molecular weight range:	86.18 g/mol
Synonyms:	Hexane Hexyl hydride n-Hexan Skellysolve B UN 1208

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Table 5

Overview of physicochemical properties	
Property	**Value**
Physical state at 20°C and 101.3 kPa	liquid
Vapour pressure	10 kPa at 9.8°C 20 kPa at 25°C 30 kPa at ~ 35°C
Water solubility	0.0098 g/l
Partition coefficient n-octanol/water (Log Kow)	4 at 20°C, pH = 7 shake-flask method, Standard temperature and pressure assumed
Flammability	*idem*
Explosive properties	*idem*

Oxidising properties	*idem*
Granulometry	The granulometry study does not need to be conducted as the substance is marketed or used in a non solid or granular form.
Stability in organic solvents and identity of relevant degradation products	In accordance with column 1 of REACH Annex IX the stability in organic solvents study is not required as stability of the substance is not considered to be critical.
Dissociation constant	*idem*

7.5. Manufacture and uses

7.5.1. Quantities

According to information provided by ECHA, n-hexane is used the total tonnage band of `10 000-100 000 tonnes per annum`.

Table 6

AGGREGATED TONNAGE (per year)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	x 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

7.5.2. Overview of uses

Table 7

USES Use(s)	
Uses as intermediate	
Formulation	
Uses at industrial sites	Formulation, Distribution, Formulation and (re)packing, Use in coatings, Use in cleaning agents, Blowing agents, Functional Fluids, Polymer processing, Mining Chemicals
Uses by professional workers	Use in coatings, Use in cleaning agents, Polymer processing, Use in Laboratories, Use as Functional Fluids, Use as fuel
Consumer Uses	Disseminated and assessed during Substance Evaluation: 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 28: Perfumes, fragrances PC 39: Cosmetics, personal care products. **According to Annex II (entry 999) of the European cosmetics regulation No 1223/2009, n-hexane is prohibited in cosmetic products.** The registrants have deleted all consumer uses in their registration dossiers after the substance evaluation decision to clarify the additional concerns regarding consumer exposure.
Article service life	

In addition to the identified uses from the registration(s) given above the following uses were extracted from literature sources.

According to Mears and Eastman (Kirk-Othmer 2005), the largest volume applications for n-hexane are the use as fuel and for extraction of oil from seeds, for example from soybeans or peanuts. Other than that, n-hexane is used as solvent and reaction medium for "manufacture of polyolefins, synthetic rubbers, and some pharmaceuticals".

In the Occupational Disease Report published by DGUV the use of n-hexane as solvent in lacquer, resins, glues (especially fast-drying glues) and adhesives is mentioned (BK1317).

Most of the applications in industrial and professional settings described in chapter 7.12. of this report cover the use of n-hexane in preparations or mixtures. Therefore, some examples for typical n-hexane concentration are summarized in the following.

In the Occupational Disease Report concentrations of n-hexane in preparations as listed in Table 8 are reported.

Table 8

PERCENT OF N-HEXANE IN PREPARATIONS AS REPORTED IN THE OCCUPATIONAL DISEASE REPORT [BK1317]		
Year of survey		**Percent of n-hexane**
1997	Lacquers, fast-drying (Industrial production of lacquers for wires/cables)	Gasoline with up to 4.5% n-hexane is used
n.a.	Contact adhesive (Flooring for trucks/ commercial vehicles)	1%
n.a.	Thinner	1%
n.a.	Contact adhesive (Construction work)	3%

Baldasseroni et al. reported concentrations of n-hexane in solvents and glues of leather and shoe factories in Italy (Baldasseroni 2003). Their findings are summarized in Table 9.

Table 9

PERCENT OF N-HEXANE IN GLUES AS REPORTED BY BALDASSERONI ET AL. [BALDASSERONI2003]				
Year of survey	**No. of glues analysed**	**Percent of n-hexane containing glues**	**Percent of n-hexane in the solvents mixtures, Mean**	**Range [%]**
1982-1983	36	63.8	19.3	4-66
1988-1989	21	76.2	16.1	3-46
1994	16	56.2	12.6	1-50
1997	43	72.1	10.1	0.1-60.0

A detailed list of products supplied to industrial and professional users was provided by the Federal Office of Public Health (FOPH), Switzerland. The largest number of products is assigned to the sector "sealants and glues" while the second largest number can be found in the sector "solvents, paint remover, degreaser, thinner". The content of n-hexane in these products exceeds 50% by weight in some cases. The sectors, the number of products and the percent of n-hexane are listed in in the confidential part of this report.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

n-Hexane is listed by Index number 601-037-00-0 in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as follows:

Table 10

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
601-037-00-0	n-hexane	203-777-6	110-54-3	Flam. Liq. 2 Repr. 2 Asp. Tox. 1 STOT RE 2 * Skin Irrit. 2 STOT SE 3 Aquatic Chronic 2	H225 H361f *** H304 H373 ** H315 H336 H411	STOT RE 2; H373: C ≥ 5 %	
* For certain hazard classes, including acute toxicity and STOT repeated exposure, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under this Regulation. In these cases the classification in this Annex shall be considered as a minimum classification. ** The classification under 67/548/EEC indicating the route of exposure has been translated into the corresponding class and category according to this Regulation, but with a general hazard statement not specifying the route of exposure as the necessary information is not available. *** Hazard statements H360 and H361 indicate a general concern for effects on both fertility and development: 'May damage/Suspected of damaging fertility or the unborn child'. According to the criteria, the general hazard statement can be replaced by the hazard statement indicating only							

the property of concern, where either fertility or developmental effects are proven to be not relevant.
In order not to lose information from the harmonised classifications for fertility and developmental effects under Directive 67/548/EEC, the classifications have been translated only for those effects classified under that Directive.

Note: Considering the availability of sufficient information on the neurotoxicity of n-hexane in humans, a classification as "STOT RE 1; H372" is justified. According to the Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (Chapter 3.9.5: Re-classification of substances and mixtures classified for STOT-RE according to DSD and DPD) "…Substances or mixtures classified with R48/23, R48/20 (for vapour), R48/24 and/or R48/25 shall be classified as STOT-RE Category 1 because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD".

The legal classification of n-hexane for repeated dose toxicity is "STOT RE 2*; H373**", meaning that it is a minimum classification following Annex VI 1.2.1 of Regulation (EC) No 1272/2008 (CLP). As stated in CLP, this (minimum) classification shall be applied if none of the following conditions are fulfilled:

- The manufacturer or importer has access to data or other information as specified in Part 1 of Annex I that lead to classification in a more severe category compared to the minimum classification. Classification in the more severe category must then be applied.

Following the rules set down in Annex VI and the data available, n-hexane has to be classified as "STOT RE 1; H372".

7.6.2. Self-classification

- In the registration(s):

Table 11

CLASSIFICATION ACCORDING TO REGULATION (EC) NO 1272/2008 AS PROVIDED BY THE LEAD REGISTRANT			
Hazard class and category	**Hazard statement**	**Specific concentration limits***	
Flam. Liq. 2 Asp. Tox. 1 Repr. 2 STOT RE 2 STOT SE 3 Skin Irrit. 2 Aquatic Chronic 2	H225 H304 H361 H373 H336 H315 H411	> 25 %	Flam. Liq. 2 Asp. Tox. 1 Repr. 2 STOT RE 2 STOT SE 3 Skin Irrit. 2 Aquatic Chronic 2
The concentration limits given by the registrant(s) are not compliant with Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) nor with Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Directive 67/548/EEC) of Regulation (EC) No 1272/2008. The legal classification of n-hexane for repeated dose toxicity is "STOT RE 2, H373**", meaning that it is a minimum classification following Annex VI 1.2.1 of Regulation (EC) No 1272/2008 (CLP). As stated in CLP, this (minimum) classification shall be applied if none of the following conditions are fulfilled: The manufacturer or importer has access to data or other information as specified in Part 1 of Annex I that lead to classification in a more severe category compared to the minimum classification. Classification in the more severe category must then be applied. Following the rules set down in Annex VI and the data available, n-hexane appears to fulfil the criteria for classification as STOT RE 1.			

7.7. Environmental fate properties

Not part of the evaluation.

7.8. Environmental hazard assessment

Not part of the evaluation.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

7.9.1.1. **Absorption**

Absorption following oral and dermal exposure of n-hexane in humans and laboratory animals can be inferred from the presence of n-hexane and its metabolites in exhaled air, serum, and urine (ATSDR 1999, US EPA 2005, MAK 1997, Krasavage 1980 cf. chapter 5.6.1.1). Absorption of n-hexane into the human blood in relation to total respiratory uptake was about 17% (ATSDR 1999, US EPA 2005).

7.9.1.2. **Distribution**

In rats and humans n-hexane is widely distributed to the body tissues but not concentrated significantly by any of those tissues (API 1990, MAK 1997, ATSDR 1999). The various metabolites are distributed from the blood to various organs and tissues, including the peripheral nerve system (sciatic nerve), testes, liver, kidney, and brain (ATSDR 1999, US EPA 2005).

7.9.1.3. **Metabolism**

n-Hexane is extensively metabolized in the liver without qualitative differences between humans and test animals (US EPA 2005, MAK 1997, WHO 1991). The major metabolites in urine, predominantly in conjugated form, are considered to be 4,5-dihydroxy-2-hexanone for humans and 2- and 3-hexanol for rat, rabbit and monkey (MAK 1997). 2,5-Hexanedione is believed to be the major toxic metabolite produced in humans following acid hydrolysis of urine samples (Perbellini et al. 1981).

7.9.1.1. **Excretion**

Exhaled breath and urine were the two primary routes for the excretion of n-hexane and its metabolites from rats and humans (API 1990, ATSDR 1999, US EPA 2005). A mean elimination half-life of 13 to 14 hours for urinary excretion of 2,5-hexanedione by humans and 7 hours by rats has been reported. The neurotoxic metabolite 2,5-hexanedione may therefore accumulate in the human body following repeated exposure to n-hexane (MAK 1997, WHO 1991).

7.9.2. Acute toxicity and Corrosion/Irritation

The registrants concluded the substance may be fatal if swallowed and enters airways and may cause drowsiness or dizziness, and based on the available information, the eMSCA can support this conclusion.

The registrants concluded the substance is irritating to skin, and based on the available information, the eMSCA can support this conclusion.

7.9.3. Sensitisation

The registrants concluded the substance is not sensitising, and based on the available information, the eMSCA can support this conclusion.

7.9.4. Repeated dose toxicity

7.9.4.1. Non-human information following oral exposure

Table 12

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, ORAL EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
Subchronic, no guideline available, non-GLP **n-hexane** (99 %) Oral route (gavage) once daily (5 days /week) **Rat**, CD (SD) BR, 5 M 90 d (0, 568, 1135 mg/kg bw/d) 120 d (3973 mg/kg bw/d)	NOEL: 568 mg/kg bw/d LOEL: 1135 mg/kg bw/d based on reduced body weight gain NOAEL: 1135 mg/kg bw/d LOAEL: 3973 mg/kg bw/d based on neurological effects (hindlimb paralysis, multifocal axonal swellings, adaxonal myelin infolding, paranodal myelin retraction)	Key study examination for body weight, clinical signs, mortality, and neurological effects histopathology on testes, epididymis, and nerve tissue	Krasavage et al., 1980

7.9.4.2. Non-human information following inhalative exposure

Table 13

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, INHALATIVE EXPOSURE, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
Subchronic Limit Test, no guideline followed, non-GLP **n-hexane** (99 %) **Rat**, Wistar, 7 M Inhalation (vapour) 16 weeks daily (12 h/day) 0, 3000 ppm	LOAEC: 3000 ppm (10800 mg/m³) based on ↓ bwg, ↑ mortality, neurological effects: ↓ Motor nerve conduction velocity (MCV), ↑ distal latency, damaged tibial nerve and dorsal trunk of the tail nerve	Key study examination for body weight, clinical signs, mortality, and neurological effects histopathology on testes, epididymis, and nerve tissue	Takeuchi et al., 1980
Subchronic, equivalent or similar to OECD TG 413, non-GLP **n-hexane** (99 %) Inhalation (vapour) **Mouse**, B6C3F1, 18 M/18 F	NOEC (males): 500 ppm (1760 mg/m³) LOEC (females): 500 ppm (1760 mg/m³) based on nasal lesions	No respiratory effects at 500 ppm according to ATSDR 1999. Minimal olfactory epithelium changes or no effects at 1000 ppm according to study authors.	Dunnick et al., 1991

13 weeks daily (5 days /week, 6 h/day) 0, 500, 1000, 4000, 10000 ppm 13 weeks daily (5 days /week, 22 h/day) 1000 ppm	LOEC (males): 1000 ppm (3520 mg/m³) based on nasal lesions NOAEC (males/females): 4000 ppm (14080 mg/m³) LOAEC (males/females): 10000 ppm (35200 mg/m³) based on neurological effects (decreased locomotor activity, paranodal swellings of tibial nerve)	Minimal toxicity to the respiratory system from 1000 ppm according to US EPA 2005. Histopathological changes from 4000 ppm according to WHO 1991. Inflammation and regeneration of respiratory and olfactory epithelium, and metaplasia of olfactory epithelium from 10000 ppm. Similar lesions of less severity in femals in 4000 ppm and 1000 ppm (3520 mg/m³) in 22 h exposure group.	
Chronic inhalation study, non-guideline, GLP pure n-hexane or **mixed hexanes** **Rat**, Sprague-Dawley, 19 M Inhalation (vapour) Dynamic whole body 6 months daily (7 d/week, 22 h/day) 0, 125, 250, 500, 1500 ppm, positive control (n-hexane)	No NOAEC LOAEC: 500, 1500, and positive control based on differences in liver weights 500 ppm n-hexane pure: axonal degeneration, myelin vacuolation, muscle atrophy Positive control: abnormal gait	Supporting study Type of hexane administered in groups not defined. necrosis of liver, degenerative and regenerative renal changes for all dose groups	Test Labatory, 1983
Chronic inhalation study, non-guideline, GLP pure n-hexane or **mixed hexanes** **Rat**, Sprague-Dawley, 20 sex not specified Inhalation (vapour) Dynamic whole body 24 weeks (7 d/week, 22 h/day) 0, 500, 1000 ppm, positive control (500 ppm n-hexane)	No NOAEC LOAEC: 500 ppm mixed hexanes & positive control: abnormal gait and reduced average body weight	Supporting study Type of hexane administered in groups not defined. necrosis of liver, degenerative and regenerative renal changes for all dose groups	Test Labatory, 1983
Subchronic, non-guideline, non-GLP **n-hexane** (> 99 % pure) **Rat**, Wistar, 8 M Inhalation (vapour) 16 weeks daily (12 h/day) 0, 500, 1200, 3000 ppm	NOAEC: 500 ppm (1762 mg/m³) LOAEC: 1200 ppm (4230 mg/m³) based on reduced body weight gain, neurological effects: degeneration of peripheral nerves, ↓ motor nerve conduction velocity (MCV)	Principal study according to U.S. EPA/635/R-03/012 www.epa.gov/iris reduced S-100 protein in peripheral nerves ≥ 500 ppm reduced S-100 protein in muscles ≥ 3000 ppm	Huang et al., 1989

7.9.4.3. **Human information**

Table 14

OVERVIEW OF EPIDEMIOLOGICAL DATA, HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
cohort study (retrospective) **Human**, 57 M/2 F press proofing workers employed for at least 2 months, mean age 25.8 years with a standard deviation of 10.2 years. occupational exposure in factory study period not given cleaning solvents containing n-hexane at concentrations ranging from 10–65 % n-hexane air concentrations up to 190 ppm	15 workers with polyneuropathy and 2 asymptomatic workers with abnormal MCVs. Associations between frequency of polyneuropathy and abnormal MCV and n-hexane concentration in the cleaning solvents and between the frequency of polyneuropathy and n-hexane air concentrations > 100 ppm (> 352 mg/m³). Significant reduction in the MCV among workers exposed to air concentrations < 25 ppm (< 88 mg/m³).	Key study Referent neurological data were collected from 150 healthy individuals. (50 persons from three age groups, 10–35, 36–50, and 51–80 years, sex not stated). Prolonged exposure due to overtime work	Wang et al., 1986
case control study (prospective) **Human**, 40 workers randomly chosen occupational exposure in 4 small shoe factories without protective equipment for about 7 h/d glue or solvent that contained over 50% n-hexane Air concentrations were not measured. 1 urine sample per study subject at end of weekly shift	mild or nonspecific symptoms of polyneuropathy Dose-response relationship of 2,5-hexanedione concentration in urine for the electroneuromyography (ENM) scores (decreased conduction velocities). A threshold value of 7.5 mg/L was closely related to the incidence of abnormalities. 3 workers with lower concentrations of 2.5-hexanedione (3.0, 3.3, and 4.5 mg/L) displayed ENM changes	Key study Reference values were obtained from 41 unexposed individuals. The threshold value of 7,5 mg/L was derived from the observation that the majority of ENM effects was seen above this value.	Governa et al., 1987
cohort study (retrospective) **Human**, 24 M/71 F shoe factory workers, employment time: 4 months to 29 years (mean 10.2, SD 9.7), age: 16-58 years (mean 29.6, SD 12.3) long term occupational inhalation exposure in shoe factory exposure time 1-25 years (mean 9.1, SD 8.0) hydrocarbon mixture containing n-hexane, cyclohexane, methyl ethyl ketone, and ethyl acetate: TWA for n-hexane of 108 breathing zone samples: 243 mg/m³ (69 ppm) in the mildly exposed group and 474 mg/m³ (134 ppm) in the highly exposed group	Neurological symptoms occurred more frequently among the exposed than the unexposed workers. Increases in the frequency of self-reported sleepiness, dizziness, weakness in the limbs, paresthesia (burning or tingling sensation in limbs), and hypoesthesia (partial loss of sensation and/or diminished sensibility). increased motor nerve action potential (MAP) duration and decreased MCV in the median and ulnar nerves related to hydrocarbon exposure	Supporting study Comparison to 52 unexposed workers from the same factory Gender, age, and employment time were similar in the exposed and referent groups	Mutti et al., 1982

7.9.4.4. **Summary and discussion of repeated dose toxicity**

The evidence of target organ toxicity through repeated exposure to n-hexane was obtained from animal testing and epidemiological data. None of the tests on repeated dose toxicity was carried out in accordance with EU Regulation (EC) No 440/2008 or current OECD guidelines for the testing of chemicals. However, by means of a weight of evidence approach the information provided in the registration dossiers is sufficient to conclude that n-hexane produces significant toxicity in humans following repeated exposure through inhalation. Significant neurotoxic effects observed in at least 90-day repeated-dose studies conducted in experimental animals are seen at concentrations ≥ 500 ppm. Valid tests according to current guidelines on concentrations below 500 ppm (including the dose range below guidance values for classification) are not available. On the other hand, human data demonstrated that the incidence of peripheral neuropathy can reliably be attributed to prolonged occupational exposure to n-hexane. (ATSDR 1999, WHO 1991, US EPA 2005).

n-Hexane is classified as STOT RE 2, H373: "May cause damage to organs through prolonged or repeated exposure." according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as a minimum classification and as Xn, R48/20: "Harmful: danger of serious damage to health by prolonged exposure through inhalation." according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008.

The eMSCA considers the existing information on the neurotoxicity of n-hexane in humans sufficient to conclude that n-hexane produces significant functional changes in the peripheral nervous system of humans following repeated exposure through inhalation. Following the rules set down in Annex VI and the data available, n-hexane appears to fulfil the criteria for classification as "STOT RE 1; H372".

7.9.5. Mutagenicity

7.9.5.1. **In vitro data**

Table 15

OVERVIEW OF EXPERIMENTAL IN VITRO GENOTOXICITY STUDIES						
Method **Guideline**	**Test system** **(Organism, strain)**	**Concentrations tested (give range)**	**Results** **+ S9**	**– S9**	**Remarks (give information on cytotoxicity and other)**	**Refe-rence**
OECD TG 471 (GMbact) GLP	**n-hexane** S. typhimurium TA 1535, TA 1537, TA 98, TA 100	up to 1000 µg/plate with and w/o metabolic activation: S9	neg	neg	cytotoxicity not determined S9 from aroclor 1254 induced male rat liver or Syrian hamster liver	Dunnick, et al., 1991
OECD TG 476 (GMvitro) non-GLP	**n-hexane** (100 % assumed) Mouse lymphoma L5178Y cells vehicle: DMSO	up to 500 µg/plate with and w/o metabolic activation: S9	neg	slight in-crease in 2 conc. weak muta-gen	cytotoxicity ≥ 350 µg/plate no information on the kind of S9 mix given	Phillips Petroleum Company 1982

OECD TG 476 (GMvitro) GLP	**n-hexane** (100 % assumed) Mouse lymphoma L5178Y cells vehicle: DMSO	up to 200 µg/plate with and w/o metabolic activation: S9	neg	neg	cytotoxicity not determined no information on the kind of S9 mix given	API, 1981
OECD TG 471 (GMbact) Non-GLP	**n-hexane** S. typhimurium TA 1535, TA 1537, TA 92, TA 94, TA 98, TA 100 vehicle: DMSO	up to 10000 µg/plate with and w/o metabolic activation: S9	neg	neg	no cytotoxicity S9 from rats treated with polychlorinated biphenyls	Ishidate, et al., 1984
OECD TG 471 (GMbact) Non-GLP	**n-hexane** (99 %) S. typhimurium TA 1535, TA 1537, TA 97, TA 98, TA 100 vehicle: 95% ethanol	3300 - 330000 µg/plate with and w/o metabolic activation: S9	neg	neg	No information on cytotoxicity S9 from aroclor 1254 induced rats and hamsters	Mortelmans, et al., 1986

7.9.5.1. **In vivo data**

Table 16

OVERVIEW OF EXPERIMENTAL IN VIVO GENOTOXICITY STUDIES						
Method Guideline	**Test substance Route of exposure Duration**	**Species, Strain, Sex, No/group**	**Dose levels**	**Result Target organs**	**Remarks**	**Refe-rence**
Mouse Dominant Lethal Assay, no guideline available, non-GLP	**n-hexane** Inhalation (vapour) 6 h/d, 5 d/wk 8 weeks	Mouse (CD-1) 3 M a total of 4 groups	0, 100, and 400 ppm vehicle: filtered air	neg no dominant lethal mutations	Key study	API 1980
OECD TG 475 (Cytvivo, Cab) GLP	**commercial hexane** (52 % n-hexane) Inhalation (vapour), nose-only 6 h/d 5 days	Rat (Sprague-Dawley) 5 M/5 F	0, 900, 3000, 9000 ppm (0, 3168, 10560, 31680 mg/m³)	neg no increase in cell aberrations	Supportin g study Animals sacrificed 3 or 21 hrs after exposure	API 1990

7.9.5.2. **Conclusion on genotoxicity**

The registrants concluded the substance is not genotoxic, and based on the available information, the eMSCA can support this conclusion. This is supported by reviews of international bodies/regulatory programs (ATSDR 1999, WHO 1991, US EPA 2005, MAK 1997, HSDB 2012).

7.9.6. Carcinogenicity

7.9.6.1. **Non-human Carcinogenicity Data following inhalative exposure**

Table 17

OVERVIEW OF EXPERIMENTAL STUDIES ON CARCINOGENICITY, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
OECD TG 451 (Oncogenicity) GLP **commercial hexane** (52 % n-hexane) Inhalation (vapour), whole body 2 years, 6 hrs/day, 5 days/week (total of 504 exposures) **Mouse** (B6C3F1) 50 M/50 F per group 0, 900, 3000, 9018 ppm (0, 3168, 10560, 31680 mg/m³)	NOAEC (carcinogenicity): 3000 ppm (10560 mg/m³) F 9018 ppm (31680 mg/m³) M LOAEC (carcinogenicity): 9018 ppm (31680 mg/m³) female Carcinogenicity in females (↑ liver masses, ↑ nodules), dose-related increases in hepato-cellular adenomas and carcinomas in strain with high spontaneous incidences of liver tumours (CLP Guidance)	Key study Read-across based on grouping of substances (category approach) borderline statistical significance (US EPA 2005), questionable relevance for humans (Daughtrey 1999)	API 1995
OECD TG 451 (Oncogenicity) GLP **commercial hexane** (52 % n-hexane) Inhalation (vapour), whole body 2 years, 6 hrs/day, 5 days/week (total of 511 exposures) **Rat** (Fischer 344) 50 M/50 F per group 0, 900, 3000, 9016 ppm (0, 3168, 10560, 31743 mg/m³)	NOAEC (carcinogenicity): 9016 ppm (31743 mg/m³) M/F Carcinogenicity/Systemic effects: No neoplastic effects LOAEC (Local toxicity): 900 ppm (3168 mg/m³) M/F based on effects on nasal-turbinal tissue: Intracytoplasmic eosinophilic material in the respiratory epithelial cells, and sustentacular cells of the olfactory epithelium.	Key study Read-across based on grouping of substances (category approach)	API 1995

7.9.6.2. **Conclusion on Carcinogenicity**

The registrants concluded the substance is not carcinogenic, and based on the available information, the eMSCA can support this conclusion.

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

7.9.7.1. Non-human information on fertility following inhalative exposure

Table 18

OVERVIEW OF EXPERIMENTAL STUDIES ON FERTILITY EFFECTS, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
OECD TG 416 (2-Gen.), GLP **commercial hexane** (52 % n-hexane) Inhalation (vapour), whole body 6 hrs/day, 5 days/week 7 days/week during breeding **Rat** (Sprague-Dawley) 25 M/25 F per group 892, 2995, 9019 ppm (0, 3168, 10560, 31680 mg/m³)	NOAEC (development): 3000 ppm (10560 mg/m³) LOAEC (development): 9000 ppm (31680 mg/m³) based on reduced body weight and body weight gain in F1, F2 NOAEC (fertility): > 9000 ppm (31680 mg/m³)	Key study Read-across based on grouping of substances (category approach) no adverse effects in offspring without adverse maternal effects; maternal body weight significantly reduced in the high-dose group of the F1 parental generation	API 1991
respiratory treatment, no guideline non-GLP **n-hexane** Inhalation (vapour), whole body single 24-h: 17 M 16-h/d, 2, 4, 6 or 8 d: 3M 16-h/d, 6 d/w, 1, 2 or 3 w: 8 M 16-h/d, 6 d/w, 4 or 5 w: 6 M 16-h/d, 6 d/w, 6 w: 3 M **Rat** (Sprague-Dawley) 5000 ppm (17600 mg/m³)	24 hrs and 8 days: Lesions in testis and epididymides: focal degeneration of spermatocytes, exfoliation of elongated spermatids, degenerating germ cells 6 weeks: aplasia of germinal epithelium, complete atrophy of seminiferous tubules	Key study recovery time after the end of treatment from 2 days to 29 weeks, depending on the original exposure duration after 5 weeks most animals began to show clinical symptoms of polyneuropathy	De Martino 1987

7.9.7.1. Non-human information on developmental toxicity

Table 19

OVERVIEW OF EXPERIMENTAL STUDIES ON DEVELOPMENT, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
Developmental Toxicology Study, no guideline followed, non-GLP **n-hexane** (99.5 %) Inhalation (vapour), whole body 20 h/day, daily, during GD 6-20 **Rat** (Sprague-Dawley) 30 pregnant F/10 virgin F per dose	NOAEC (maternal): 200 ppm (704 mg/m³) based on reduced body weight gain NOAEC (development): 200 ppm (704 mg/m³) based on reduced reduced foetal weight gain	Key study	Pacific Northwest Laboratory, 1987

0, 200, 1000, 5000 ppm (0, 704, 3520, 17600 mg/m³)			
Developmental Toxicology Study, no guideline followed, non-GLP **n-hexane** (99.2 %) Inhalation (vapour), whole body 20 h/day, daily, during GD 6-17 **Mouse** (CD-1) 30 pregnant F/10 virgin F per dose 0, 200, 1000, 5000 ppm (0, 704, 3520, 17600 mg/m³)	NOAEC (maternal): 1000 ppm (3520 mg/m³) based on reduced body weight gain and reduced relative uterus weight No NOEC (development): increase in number of late foetal resorptions at 5000 ppm (17600 mg/m³), reduced gravid uterine weight at 200 ppm (704 mg/m³) and 5000 ppm (17600 mg/m³)	Key study significant increase in intrauterine death only in the 200 ppm (704 mg/m³) group	Pacific Northwest Laboratory, 1988
Perinatal Toxicity, Limit test similar to OECD TG 414, non-GLP **n-hexane** (99.0 %) Inhalation (vapour), whole body 6 h/d, GD 8-12: 7 females 6 h/d, GD 12-16: 9 females 6 h/d, GD 8-16: 8 females **Rat** (Fischer 344) 0, 1000 ppm (0, 3520 mg/m³)	No NOEC (development): decreased body weight in first 7 weeks of life	Supporting study maternal toxicity not examined	Bus 1979
Embryo and Foetal Development no guideline followed, non-GLP **n-hexane** (99 %) Oral (gavage), vehicle: cotton seed oil GD 6-15, sacrifice GD 18 **Mouse** (CD-1) Once daily: 0 (37 F), 0.26 (13 F), 0.66 (6 F), 1.32 (6 F), 2.20 (14 F) g/kg bw/d 3 x daily: 0 (24 F), 2.17 (24 F), 2.83 (25 F), 7.92 (34 F), 9.90 (33 F) g/kg bw/d	NOAEC (maternal): 2170 mg/kg bw/day (nominal) based on reduced body weight gain and mortality from 2200 mg/kg bw/day (nominal) NOAEC (development): 2830 mg/kg bw/day (nominal) reduced foetal weight from 7920 mg/kg bw/day (nominal)	Supporting study	Marks 1980

7.9.7.2. **Conclusion on reproductive toxicity**

The evidence of reproductive toxicity of n-hexane was obtained from animal testing. A GLP compliant 2-generation study of commercial hexane (52% n-hexane) in rats according to OECD Guideline 416 and a non-guideline inhalation study in male rats with varying exposure durations of n-hexane are available for assessment of effects on fertility. Exposure of rats to commercial hexane for two generations resulted in reduced body weight and body weight gains in F1 and F2 litters at the highest dose of 9000 ppm (31680 mg/m³) but no adverse effects on reproduction corresponding to a NOAEC (based on n-hexane) above 4680 ppm (16474 mg/m³) (API 1991, Daughtrey 1994). At a comparable dose of 5000 ppm (17600 mg/m³) n-hexane progressive increases in testicular and epididymal lesions were observed with prolonging exposure time of male rats (De Martino 1987). Deficiencies in the study e.g. testing with only one dose, low animal numbers, make the quality of evidence less convincing.

Although the registrants concluded the substance is suspected of damaging fertility, the eMSCA, after taking into account all available information in a weight-of-evidence approach (giving more weight on the guidance-conforme 2-generation study) concludes that no further information needs to be requested under this substance evaluation.

7.9.8. Hazard assessment of physico-chemical properties

Assessment for worker

Pursuant to Article 14(4a) of the REACH regulation, exposure assessment and risk characterisation is to be performed on the substance that fulfils the criteria for certain hazard classes or categories set out in Annex I of regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (the CLP regulation). n-hexane is classified as "Flam. Liq. 2; H225" according to Annex VI of regulation (EC) No 1272/2008 and thereby fulfils the criteria for hazard class 2.6. General provisions for the assessment are laid down in Annex I of the REACH regulation.

REACH Annex I (General provisions for assessing substances and preparing chemical safety reports) requires in Chapters 2, 5 and 6 an assessment of the hazards of physicochemical properties of the reported substance.

In the registration dossiers the endpoints regarding PC properties are correctly included in Part B1.3.

However, the exposure scenarios and the related PROCs suggest uses with amounts that vary over a wide range. This variability has implications for which RMMs are to be used regarding flammability and explosion risks.

None of the Risk Management Measures related to the various scenarios reflect a differentiation (neither explicitly, nor as a reference to other regulations) taking into account the amount of material concerned. However, such a differentiation (e.g. regarding grounding, building structures, etc.) is an essential part of a comprehensive risk management scenario.

The additional information regarding the risk of flammability submitted by the registrant/s following the substance evaluation decision contains some RMMs that should be implemented with special regard to the aspect of high flammability of n-hexane. However, they are identical for all ES which still does not allow a straight forward differentiated risk assessment for each individual scenario. As a result, the registrants therefore did not submit the requested information as it was addressed in the decision. Nevertheless, the supplied information together with specific information in the CSA and in the SDS may serve as a basis for a meaningful selection of RMMs by a skilled user. Therefore, the eMSCA considered the supplied information as acceptable despite deviations.

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

7.9.9.1. Overview of typical dose descriptors for all endpoints

According to Chapter R.8 of the REACH Guidance on information requirements and chemical safety assessment, a DNEL for the leading health effect needs to be derived for every relevant human population and every relevant route, duration and frequency of exposure, if feasible.

The registrant(s) has given an overview of available dose-descriptors per endpoint. The dose-descriptors have been gathered from the available and relevant experimental animal

studies in the registration dossier. Out of this database together with the information published in reviews of international bodies/regulatory programs (ATSDR 1999, WHO 1991, US EPA 2005, MAK 1982, MAK 1997, HSDB 2012) suitable studies and typical dose descriptors for derivation of DNEL values are selected.

A review of all available dose descriptors per each toxicity endpoint indicates that the major concern associated with acute and chronic exposures to n-hexane is neurotoxicity; these are the most prominent effects observed at the lowest exposure levels in both experimental animals as well as in epidemiological studies. Table 20 summarizes the studies which were used for derivation of the long-term systemic DNELs.

Table 20

OVERVIEW OF DOSE DESCRIPTORS PER ENDPOINT USED FOR DNEL DERIVATION				
Endpoint of concern	**Type of effect**	**Critical studies**	**Corrected dose de-scriptors**	**Justifi-cation / Remarks**
Repeated dose toxicity: sub-acute / sub-chronic / chronic	Biomonitoring results (end of weekly shift): mild or non-specific symptoms of polyneuropathy (electroneuromyo-graphic abnormalities in the peripheral muscles) associated with urinary ex-cretion of 2,5-hexanedione at levels ≥ 7.5 mg/L. The relationship between 2,5-hexanedione excretion as a biomarker of exposure and n-hexane air concentration was established in another study (Perbellini & Bartolucci, 1985), thus linking the urinary excretion of 7.5 mg/L 2,5-hexanedione with atmospheric exposures to 250 mg/m^3 n-hexane.	prospective case control study in small collectives of workers exposed to hexane for about 7 h/d without wearing protective equipment (Governa et al 1986).	LOAEC: 7.5 mg/L 2,5-hexanedione in urine (cor-responding to a LOAEC of 250 mg/m^3 n-hexane in the air) Value used by SCOEL for IOEL derivation	Study used by SCOEL (together with other supporting informa-tion) as a principle study for IOEL deri-vation (SCOEL 1995).
Repeated dose toxicity: sub-acute / sub-chronic / chronic	Reduced body weight gain and neurological effects noted at exposures ≥ 1200 ppm (LOAEC: 4230 mg/m^3)	non-guideline inhalation toxicity study in Wistar rats (males only) exposed daily to n-hexane vapors (purity > 99 %) for 12 h/day, 16 weeks (Huang et al, 1989)	NOAEC: 500 ppm (1762 mg/m^3)	Study used by US EPA as a principle study for RfC derivation (USEPA 2005).
Repeated dose toxicity: sub-acute / sub-chronic / chronic	Treatment related reduced body weight gain and decreased food consumption seen at dose levels ≥ 13.2 mmol/kg bw/d (LOAEL 1135 mg/kg bw/d)	non-guideline oral toxicity study in COBS CD (SD) BR rats (males only) exposed daily to n-hexane (purity 99%) by gavage 5 d/week for 13 weeks	NOAEL: 6.60 mmol/kg bw/d (568 mg/kg bw/d)	Krasavage et al. 1980 is the only oral n-hexane exposure study of subchronic duration.

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

Due to its high vapour pressure, the main route of exposure to n-hexane is inhalation. In addition, several recent studies indicate that dermal contact with the liquid can be an important route of exposure as well. Considering the use of n-hexane and the resulting exposure routes for workers and consumers, long-term systemic DNELs must be derived for inhalation, oral and dermal routes of exposure.

The REACH Guidance Chapter R.8, Appendix R.8-13 specifies that a community/national occupational exposure limit (OEL) may be used in place of developing a DNEL when such guidance value is available, provided exposure route and duration are the same, and there is no newer scientific information that would lead to a different result requiring the implementation of specific RMM. In the case of n-hexane, an EU indicative occupational exposure limit (IOEL) of 72 mg/m^3 has been adopted (SCOEL 1995). This IOEL (8-hour TWA) is set to protect workers for systemic effects from long-term inhalation exposures to n-hexane. The IOEL is based on results from a biomonitoring study establishing that electroneuromyographic abnormalities in the peripheral muscles occur in workers exposed to ≥ 250 mg/m^3 (70 ppm) n-hexane, supported with further workplace observations reporting electrophysiological changes at atmospheric concentrations of 50 to 100 ppm (179 to 358 mg/m^3) n-hexane (SCOEL 1995). So far there are no newer studies identified that would suggest a different result, therefore the IOEL of 72 mg/m^3 can be used as a worker long-term inhalation exposure DNEL for systemic effects. Using the IOEL of 72 mg/m³ as a starting point, a dermal DNEL of 10.3 mg/kg bw/day can be calculated by multiplying the IOEL by 10 m^3 (the volume of air breathed in a working day) and divided by 70 kg (the average worker's body weight); as default equal rates of respiratory and dermal absorption is assumed.

Alternatively, the long-term inhalation and dermal DNELs for systemic effects in workers can be calculated according to the standard procedure outlined in Chapter R.8 of the REACH Guidance. Starting point is a NOAEL of 500 ppm (1762 mg/m^3) for the endpoint neurotoxicity established in a key inhalation study with rats (Huang et al. 1989; see Table 21 for study details). Specifics on the calculation procedure and the use of assessment factors are provided in Table 21, and a comparison of the IOEL with the respective DNELs can be found in Table 24. The calculated DNELs of 98.7 mg/m^3 and 14.1 mg/kg/d for protecting workers from systemic effects of n-hexane via inhalation and dermal exposures, respectively, are close to (and slightly above) the values derived from human biomonitoring studies thus providing additional support for using the IOEL of 72 mg/m^3 as a long-term inhalation DNEL. Despite several general shortcomings of epidemiological studies related mostly to uncertainties in the precise exposure estimate and potential co-exposure to other workplace chemicals, reliable human data are considered under REACH as the most relevant source for hazard assessment. Among their merits are that the route of exposure, dose levels and mode of action are usually relevant for the population that should be protected, and no inter-species extrapolation is needed (REACH Guidance Chapter R.8, Appendix R.8-15).

An overview of current occupational exposure limits of n-hexane in various EU member states and Switzerland (as of March 2012) can be found in Table 22.

Table 21

ALTERNATIVE CALCULATION OF THE LONG-TERM INHALATION AND DERMAL DNELS FOR SYSTEMIC EFFECTS IN WORKERS EXPOSED TO N-HEXANE BASED ON ANIMAL DATA	
Route and type of effect	**DNEL Calculation (Workers)**
	Starting point is a NOAEL of 500 ppm (1762 mg/m^3) for the endpoint neurotoxicity established in a key subchronic inhalation study (12 h/day, 7 day/week, for16 weeks) in rats (Huang et al. 1989)
Inhalation Long Term, Systemic	Inhalation $NOAEC_{human}$= Inhalation $NOAEC_{rat}$*(12/8)*(7/5)*(6.7/10) Inhalation $NOAEC_{human}$= 1762*1.4=2467 mg/m^3 ($ABS_{inh,rat}/ABS_{inh,human}$=1) AF for difference in duration of exposure: **2** (DNEL is based on a 16-week subchronic study)

	AF for interspecies differences:	**1** for allometrical scaling [1]
		2.5 for remaining uncertainties
	AF for intra species differences:	**5** (for workers)
	Overall AF:	**2*1*2.5*5=25**
		DNEL: 2467/25 = 98.7 mg/m³ (27.6 ppm)
Dermal Long Term, Systemic	Dermal $NOAEL_{human}$= Inhalation $NOAEC_{human}$*(10 m^3/day)/70 kg bw	
	Inhalation $NOAEC_{human}$= Inhalation $NOAEC_{rat}$*(12/8)*(7/5)*(6.7/10) = 2467 mg/m^3	
	Dermal $NOAEL_{human}$ = 2467*10/70 = 352.4 mg/kg/d ($ABS_{inh,rat}/ABS_{derm,human}$=1)	
	AF for difference in duration of exposure:	**2** (DNEL is based on a 16-week subchronic study)
	AF for interspecies differences:	**1** for allometrical scaling [1]
		2.5 for remaining uncertainties
	AF for intra species differences:	**5** (for workers)
	Overall AF:	**2*1*2.5*5 = 25**
		DNEL: 352.4/25 = 14.1mg/kg/d

[1] inhalation NOAECs are compared directly after adjustments for differences in exposure pattern/duration (12/8)*(7/5) and increased pulmonary ventilation rates during light work (6.7/10)

Table 22

OCCUPATIONAL EXPOSURE LIMITS OF N-HEXANE IN VARIOUS EU MEMBER STATES AND SWITZERLAND (adapted from GESTIS International Limit values data base, http://limitvalue.ifa.dguv.de; last accessed on 25.09.12)

	Limit value - Eight hours		Limit value - Short term	
	ppm	mg/m³	ppm	mg/m³
Austria	20	72	80	288
Belgium	20	72		
Denmark	25	90	50	180
European Union	**20**	**72**		
France	**20**	**72**		
Germany (AGS)	50	180	400 (1)	1440 (1)
Germany (DFG)	50	180	400	720
Hungary		72		
Italy	20	72		
Japan	50			
Poland		72		
Spain	20	72		
Sweden	25	90	50	180
Switzerland	50	180	400	1440

The Netherlands		72		144
United Kingdom	20	72		

Remarks:

European Union	Bold type: Indicative Occupational Exposure Limit Values and Limit Values for Occupational Exposure
France	Bold type: Restrictive statutory limit values
Germany (AGS)	(1) 15 minutes average value
Germany (DFG)	STV 15 minutes average value

The general population long-term exposure DNELs for systemic effects can be derived from the IOEL for n-hexane. The inhalation DNEL of 3 mg/m³ is calculated from the IOEL of 72 mg/m³ by multiplying by 10/20 to correct for differences between worker and general population ventilation rates, 5/7 to correct for days per week and 8/24 to correct for hours per day potentially exposed, and 3.5/10 to use the default assessment factor of 10 to account for intraspecies differences among the general population instead of 3.5 for workers. The dermal and oral DNELs of 1 mg/kg bw/day can be calculated starting from the inhalation DNEL by multiplying by 20 m³ (the volume of air a person breathes in a day) and dividing by 60 kg (average body weight of general population); as default equal rates of respiratory, oral, and dermal absorption is assumed yielding identical values.

Alternatively, the long-term oral, inhalation and dermal DNELs for systemic effects in the general population can be calculated according to the standard procedure outlined in Chapter R.8 of the REACH Guidance. Starting point for the oral DNEL is a NOAEL of 568 mg/kg bw/d for the endpoint systemic toxicity established in a key gavage study with rats (Krasavage et al. 1980). Starting point for the inhalation DNEL is a NOAEC of 500 ppm (1762 mg/m³) for the endpoint neurotoxicity established in a key inhalation study with rats (Huang et al. 1989). Dermal DNELs have been calculated from both of the above studies. Specifics on the calculation procedure and the use of assessment factors are provided in Table 21, and a comparison of the IOEL-derived values with the DNELs based on data from studies with experimental animals can be found in Table 23. The calculated DNELs for protecting the general population from systemic effects of n-hexane via oral, inhalation and dermal exposures, respectively, are close to (and above) the values derived from human biomonitoring studies thus providing additional support for using the IOEL of 72 mg/m³ as point of departure.

Table 23

ALTERNATIVE CALCULATION OF THE LONG-TERM ORAL, INHALATION, AND DERMAL DNELS FOR SYSTEMIC EFFECTS IN GENERAL POPULATION EXPOSED TO N-HEXANE BASED ON ANIMAL DATA	
Route and type of effect	**DNEL Calculation (General population)**
	Starting point is a NOAEL of 568 mg/kg/d from the (in the dossier) provided 90-day oral study in rats (Krasavage et al. 1980; endpoint systemic toxicity)
Oral Long Term, Systemic	Oral $NOAEL_{human}$= Oral $NOAEL_{rat}$*($ABS_{oral,rat}/ABS_{oral,human}$) Oral $NOAEL_{human}$= 568 mg/kg/d ($ABS_{oral,rat}/ABS_{oral,human}$=1) AF for difference in duration of exposure: **2** (DNEL is based on a 90-day subchronic study) AF for interspecies differences: **4** for allometrical scaling **2.5** for remaining uncertainties AF for intra species differences: **10** (for general population) Overall AF: **2*4*2.5*10 = 200** **DNEL: 568/200 = 2.8 mg/kg/d**

	Starting point is a NOAEL of 500 ppm (1762 mg/m³) for the endpoint neurotoxicity established in a key subchronic inhalation study (12 h/day, 7 day/week, for16 weeks) in rats (Huang et al. 1989)
Inhalation Long Term, Systemic	Inhalation $NOAEC_{human}$= Inhalation $NOAEC_{rat}$*(12/24) Inhalation $NOAEC_{human}$= 1762*0.5 = 881 mg/m³ ($ABS_{inh,rat}/ABS_{inh,human}$=1) AF for difference in duration of exposure: **2** (DNEL is based on a 16-week subchronic study) AF for interspecies differences: **1** for allometrical scaling (inh. NOAELs compared directly) **2.5** for remaining uncertainties AF for intra species differences: **10** (for general population) Overall AF: **2*1*2.5*10 = 50** **DNEL: 881/50 = 17.6 mg/m³ (5 ppm)**
	Starting point is a NOAEL of 568 mg/kg/d from the (in the dossier) provided 90-day oral study in rats (Krasavage et al. 1980; endpoint systemic toxicity)
Dermal Long Term, Systemic	Dermal $NOAEL_{human}$= Oral $NOAEL_{rat}$*($ABS_{oral,rat}/ABS_{derm,human}$) Dermal $NOAEL_{human}$= 568 mg/kg/d ($ABS_{oral,rat}/ABS_{derm,human}$=1) AF for difference in duration of exposure: **2** (DNEL is based on a 90-day subchronic study) AF for interspecies differences: **4** for allometrical scaling **2.5** for remaining uncertainties AF for intra species differences: **10** (for general population) Overall AF: **2*4*2.5*10 = 200** **DNEL: 568/200 = 2.8 mg/kg/d**
	Starting point is a NOAEL of 500 ppm (1762 mg/m³) for the endpoint neurotoxicity established in a key subchronic inhalation study (12 h/day, 7 day/week, for16 weeks) in rats (Huang et al. 1989)
Dermal Long Term, Systemic	Dermal $NOAEL_{human}$= Inhalation $NOAEC_{rat}$*(12/24) *(20 m³/day)/60 kg bw Dermal $NOAEL_{human}$ = 1762*0.5*20/60 = 294 mg/kg/d ($ABS_{inh,rat}/ABS_{derm,human}$=1) AF for difference in duration of exposure: **2** (DNEL is based on a 16-week subchronic study) AF for interspecies differences: **1** for allometrical scaling (inh. NOAELs compared directly: Inhalation $NOAEC_{human}$= Inhalation $NOAEC_{rat}$*(12/24)) **2.5** for remaining uncertainties AF for intra species differences: **10** (for general population) Overall AF: **2*1*2.5*10 = 50** **DNEL: 294/50 = 5.9mg/kg/d**

DNEL derivation: Summary Workers

Table 24

OVERVIEW OF THE STUDIES AND CORRESPONDING ASSESSMENT FACTORS USED FOR IOEL AND DNEL CALCULATION											
Endpoint	**Species**	**POD**	**Modified Dose**	**Assessment Factors (AF)**							**DNEL**
				Inter-species							
				All Sc.	Rem. Diff.	Intra-species	Exp. Duration	Dose Resp.	Data Quality	Over-all AF	
Long Term Systemic Effects, Inhalation											
IOEL	human	LOAEC	250 mg/m³							3.5	**72 mg/m³**
16 week inhalation study (neuro-toxicity)	rat	NOAEC 1762 mg/m³	2467 mg/m³	1	2.5	5	2	1	1	25	**98.7 mg/m³**
Long Term Systemic Effects, Dermal											
IOEL (neuro-toxicity)	human	IOEL	72 mg/m³							7	**10.3 mg/kg/d**
16 week inhalation study (neuro-toxicity)	rat	NOAEC 1762 mg/m³	352.4 mg/kg/d	1	2.5	5	2	1	1	25	**14.1 mg/kg/d**

DNEL derivation: Summary General Population

Table 25

OVERVIEW OF THE STUDIES AND CORRESPONDING ASSESSMENT FACTORS USED FOR DNEL CALCULATION											
Endpoint	**Species**	**POD**	**Modified Dose**	**Assessment Factors (AF)**							**DNEL**
				Inter-species							
				All Sc.	Rem. Diff	Intra-species	Exp. Duration	Dose Resp.	Data Quality	Over all AF	
Long Term Systemic Effects, Oral											

IOEL (neuro-toxicity)	human	LOAEC	9.9 mg/ kg/d			10				10	**1.0 mg/kg /d**
90-day oral study (systemic toxicity)	rat	NOAEL	568 mg/k g/d	4	2.5	10	2	1	1	200	**2.8 mg/kg /d**
Long Term Systemic Effects, Inhalation											
IOEL (neuro-toxicity)	human	LOAEC	29.8 mg/ m^3			10				10	**3.0 mg/m^3**
16 week inhalation study (neurotox icity)	rat	NOAEC	881 mg/ m^3	1	2.5	10	2	1	1	50	**17.6 mg/m^3**
Long Term Systemic Effects, Dermal											
IOEL (neuro-toxicity)	human	LOAEC	9.9 mg/ kg/d			10				10	**1.0 mg/kg /d**
90-day oral study (systemic toxicity)	rat	NOAEL	568 mg/k g/d	4	2.5	10	2	1	1	200	**2.8 mg/kg /d**
16 week inhalation study (neuro-toxicity)	rat	NOAEC	294 mg/k g/d	1	2.5	10	2	1	1	50	**5.9 mg/kg /d**

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

Based on the submitted data the legal classification of n-hexane was confirmed by the lead registrant. The available data show that n-hexane affects the nervous system of humans following repeated exposure through inhalation. The availability of sufficient information on the neurotoxicity of n-hexane in humans indicates that a classification as STOT RE 1 may be appropriate. According to the Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (Chapter 3.9.5: Re-classification of substances and mixtures classified for STOT-RE according to DSD and DPD) "…Substances or mixtures classified with R48/23, R48/20 (for vapour), R48/24 and/or R48/25 shall be classified as STOT-RE Category 1 because less adverse effects and higher guidance values are required for classification according to CLP compared to DSD". This provision has not been followed.

The legal classification of n-hexane for repeated does toxicity is "STOT RE 2*; H373", meaning that it is a minimal classification following Annex VI 1.2.1 of Regulation (EC) No. 1272/2008 (CLP). As stated in CLP, this (minimum) classification shall be applied if none of the following conditions are fulfilled:

- The manufacturer or importer has access to data or other information as specified in Part 1 of Annex I that lead to classification in a more severe category compared to the minimum classification. Classification in the more severe category must then be applied

Following the rules set down in Annex VI and the data available, n-hexane appears to fulfil the criteria for classification as "STOT RE 1; H372".

7.10. Assessment of endocrine disrupting (ED) properties

Not part of the evaluation.

7.11. PBT and VPVB assessment

Not part of the evaluation.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

The occupational exposure data presented in this chapter were taken from literature sources which were selected based on timeliness of the assessment and representativeness for the EU countries. An additional focus in the evaluation of literature was the time trend of occupational exposure to n-hexane. In general, occupational exposure to n-hexane can occur through inhalation, ingestion and skin contact. However, ingestion as exposure pathway will be neglected in the following discussion assuming that standard occupational hygiene measures are implemented at typical workplaces.

Usually inhalation is assumed to be the main source of occupational exposure (BK 1317) although there is still a debate about the influence of uptake via dermal route. For example there are indications that uptake of liquid n-hexane through the skin could increase the total body burden (Prieto 2003).

7.12.1.1.1. Overview of uses and exposure scenarios

Data presented in this chapter are taken from selected literature sources and cover the following uses of n-hexane:

- Use in shoe industry
- Use in furniture industry
- Use in printing industry
- Use in paper and pulp industry
- Use in automotive industry/ vehicle repair shops

Furthermore, data taken from "BK Report" by the German Social Accident Insurance (DGUV) are summarized in this chapter (BK 1317). In this report, activity based exposure information from different industry sectors are evaluated. The activities cover spreading/ painting, adhesive bonding/ gluing and mixing in preparations/filling.

The discussion of the exposure scenarios as presented by the registrant/s is provided in the confidential annex to this SEV report.

7.12.1.1.2. Scope and type of exposure

Monitoring data

The occupational exposure data presented and discussed in this chapter are taken from literature sources which were selected based on timeliness of the assessment and representativeness for EU countries. An additional focus in the evaluation of literature was the time trend of occupational exposure to n-hexane

Table 26 shows data as provided in the Occupational Diseases Report 1317 by German Social Accident Insurance (DGUV). The table is provided in German language and was translated into English. As mentioned above, the airborne concentration of n-hexane was measured in different industry sectors during comparable activities, e.g. while workers were mixing or spreading a substance or preparation. The data from certain time periods were summarized and statistically evaluated by DGUV. In Figure 1 the 50th and 90th Percentile of the n-hexane concentration of the respective collective are presented and compared to the indicative occupational exposure limit (IOEL) as recommended by the EU scientific committee (SCOEL).

In summary, the values provided by IFA do not exceed the occupational exposure limits.

Table 26

DATA ON OCCUPATIONAL EXPOSURE TO N-HEXANE AS PROVIDED IN THE OCCUPATIONAL DISEASES REPORT 1317 BY GERMAN SOCIAL ACCIDENT INSURANCE (DGUV)				
Groups (Field of activity)	**Number of measurement data**	**Number of companies**	**50th Perc. [mg/m^3]**	**90th Perc. [mg/m^3]**
Period 1985-1991				
Production of Preparations (Mixing, Stirring, Filling)	125	46	2	40
Painting/ Spreading	12	10	< a.B.*	< a.B.*
Adhesive Bonding (Plastic material industry, Metal industry, Electrical industry, Wood industry, Upholstered furniture industry)	575	119	7	39
Adhesive Bonding (Leather industry, Shoe industry)	153	30	13	35
Period 1992 – 1997				
Production of Preparations (Mixing, Stirring, Filling)	99	49	1	22
Painting/ Spreading	22	14	< a.B.*	< a.B.*
Adhesive Bonding (Plastic material industry, Metal industry, Electrical industry, Wood industry, Upholstered furniture industry)	460	153	3	14
Adhesive Bonding (Leather industry, Shoe industry)	327	78	4	18
Period 1997-2002				
Production of Preparations (Mixing, Stirring, Filling)	44	26	2	12
Painting/ Spreading	-	-	-	-

Adhesive Bonding (Plastic material industry, Metal industry, Electrical industry, Wood industry, Upholstered furniture industry)	89	40	4	12
Adhesive Bonding (Leather industry, Shoe industry)	40	14	5	24
*indicates that the respective percentile of the data set is below the analytical limit of quantification				

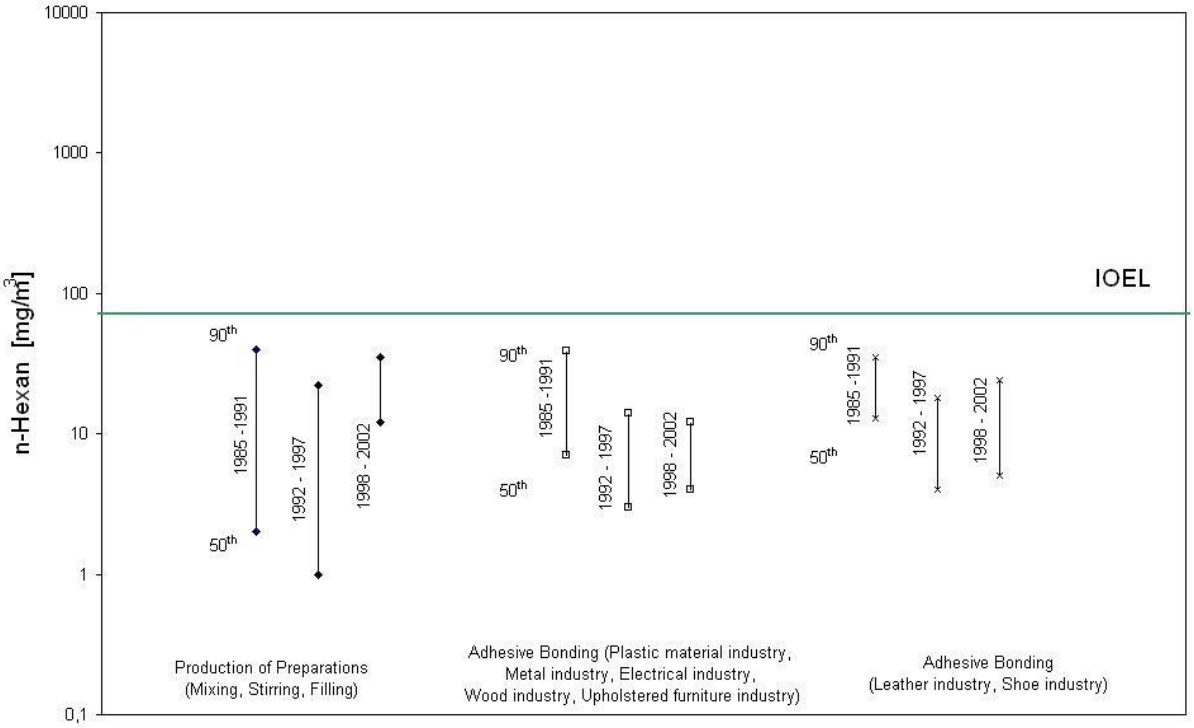


Figure 1: Data on occupational exposure to n-hexane as provided in the Occupational Diseases Report 1317 by German Social Accident Insurance (DGUV).

In Figure 2 airborne hexane concentrations as measured in a furniture industry setting, a printing industry settings and in a number of car refinishing shops are compared with occupational exposure limits. The personal measurements carried out in the furniture industry setting reflect the concentration of hexane arising from adhesive bonding. Please note that each point represents a single measurement.

Two stationary measurements were carried in a printing industry setting. In this setting hexane is used in a mixture of different organic solvents. Both values and the mean value are shown in Figure 2.

The statistical evaluation of data collected in car refinishing shops covers 176 stationary measurements and 372 personal measurements. In Figure 2 the maximum values as well as the mean values are presented.

In summary, the IOEL as recommended by the EU scientific committee [SCOEL] is exceeded by the maximum value of the personal measurements. However, the mean value is two orders of magnitude lower indicating a very broad range.

Table 27

DATA ON OCCUPATIONAL EXPOSURE TO N-HEXANE FROM DIFFERENT LITERATURE SOURCES				
Source	**Number of measurement data**	**[mg/m³]**		**Comment**
"Occupational exposure to hazardous substances during furniture production" [GA 54]	6 (personal)	5.00; 2.80; 2.95; 2.86; 0.43; 0.36		8h TWA, no further statistical evaluation
"Exposure to hazardous substances in the flexographic printing industry" [GA 54]	2 (static)	0.2; 0.6		8h TWA, no further statistical evaluation
"Genotoxic risk of workers in car refinishing shops" [Fb 887]	174 (static)	Mean: 0.83	Max: 21.32	Standard error: 0.25 mg/m³
	372 (personal)	Mean: 1.00	Max: 110	Standard error: 0.49 mg/m³

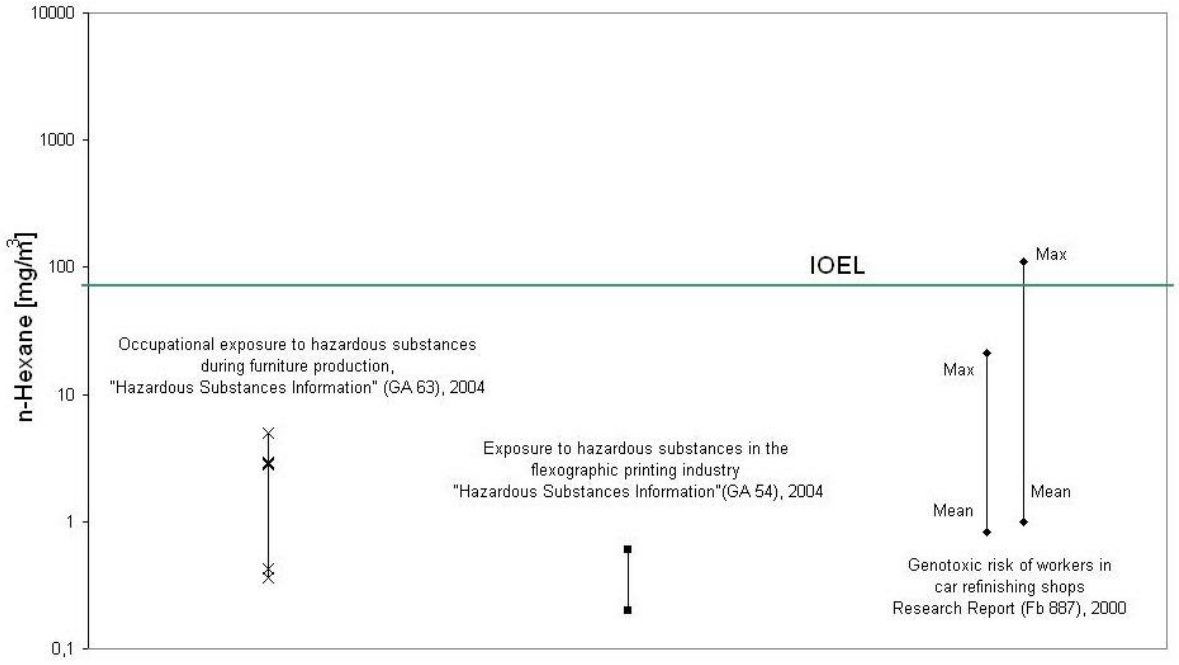


Figure 2: Data on occupational exposure to n-hexane from different literature sources

In measurements of n-hexane concentrations as provided in different literature sources are presented and compared to occupational exposure limits. Please note that this limit value was in some cases not in force when the measurements were carried out. The data were statistically evaluated differently by the authors; therefore the data points are labelled in detail.

Caldwell carried out a literature analysis comprising n-hexane measurements published in the period 1961-1998. The sources used cover a variety of industry sectors and end-use applications. The numbers presented in Figure 2 were extracted from a total of 86 and 1309 discrete breathing zone data points. The maximum measured concentration and the weighted arithmetic mean exceed the IOEL value (Caldwell 2000).

Wilson et al. published a number of task based exposure concentration values measured in the breathing zone of workers in a vehicle repair shop. The measurements cover the use

of organic substances containing n-hexane as solvent for cleaning or degreasing. Each data point represents one sample collected during the time necessary for the technician to initiate and complete the respective task. Therefore the measurements should be considered to reflect short term rather than long term exposure (Wilson 2007).

Coble et al. evaluated the time trend of occupational exposure to various agents including n-hexane in paper and pulp industry (Coble 2001). They analysed measurements as carried out within a monitoring program by the Occupational Safety and Health Administration (OSHA) in the United States. The data evaluation for n-hexane comprises 40 measurements. Based on a linear regression analysis of personal measurements the authors concluded that there is a significant reduction in worker exposure to n-hexane although the magnitude of decrease might be overestimated due to the small number of measurements and the mathematical model. In Figure 2, the geometric mean values of the exposure for the initial year 1980 and final year 1998 are presented.

Mayan et al. present data about the exposure of shoe manufacturing workers to n-hexane (Mayan 2001). n-Hexane is usually used as cleaning agent or in glues in this industry. In Figure 2 the time-weighted average concentration of personal n-hexane measurements in the air as calculated from 45 workplaces is presented. The maximum value of the measured concentrations as well as the 90th percentile and the geometric mean of the measured concentrations exceed the IOEL as derived by SCOEL.

Maizlish et al. evaluated the exposure of workers to mixtures of organic solvents, n-hexane amongst them (Maizlish 1987). The authors carried out measurements of the concentration of solvents in the workers breathing zone at four plants, namely two furniture production plants, a car refinishing shop and an offset printing shop. In Figure 2, the average full shift concentration of n-hexane is plotted. Only the n-hexane concentration measured in the offset printing plant exceeds the IOEL value.

As obvious from Figure 2 the limit values are exceeded in some cases, for example in the shoe manufacturing plant described by Mayan et al. and the offset printing plant described by Maizlish et al. (Mayan 2001, Mazlish 1987). An important factor for the exceeding of limit values as described by the authors is the lack of technical and personal risk management measures implemented at the respective settings. For instance, as stated by Mayan et al. "in this industry workers regularly handled several glues based on organic solvents and in the workplace there was inadequate ventilation."(Mayan 2001). Maizlish et al. highlight the fact that the high n-hexane concentration in the offset printing plant was a result of a miss-installed ventilation system, which "recirculated contaminated pressroom air which led to heavy contamination" (Mazlish 1987). Wilson et al. (Wilson 2007) described that "ambient air movement through large, roll-up doors served as primary source for ventilation in the work areas. None of the 10 shops used local exhaust ventilation for removal of solvent vapours from the work area, and no technician was observed using respiratory protection."

Table 28

DATA ON OCCUPATIONAL EXPOSURE TO N-HEXANE AS PROVIDED IN DIFFERENT LITERATURE SOURCES			
Source	**Number of measurement data**	**[mg/m3]**	**Comment**
Caldwell et al., AIHAJ (2000), 61: 881-894: Hydrocarbon Solvent Exposure Data: Compilation and Analysis of the Literature	AM: 86 WAM: 1309	Min.: 0 Weighted arithmetic Mean (WAM): 92.9 Arithmetic Mean (AM): 65 Max: 1426	
Wilson et al.:	23 (personal)	12; 31; 15; 8; 96; 50; 55; 49; 43; 20; 31; 100;	Task-based measurements

J.Occ. Environ. Hyg. (2007), 4: 301-310: Worker Exposure to Volatile Organic Compounds in the Vehicle Repair Industry		23; 21; 2; 51; 14; 21; 60; 47; 49; 49; 31	in the workers breathing zone
Coble et al.: Appl. Occ. Environ. Hyg. (2001), 16(2):263-270: Time Trends in Exposure Measurements from OSHA Compliance Inspections of the Pulp and Paper Industry	40	Geometric Mean (initial year): 408.97 Geometric Mean (final year): 6.69	
Mayan et al.: Appl. Occ Environ Hyg. (2010),16(7): 736–741: Biological Monitoring of n-Hexane Exposure in Portuguese Shoe Manufacturing Workers	Samples collected from 45 workplaces	Min.: 21.15 Geometric Mean: 87.06 90th Percentile:211.48 Max.: 246.73	8h TWA, Measurements in the workers breathing zone
Maizlish et al.: Brit. J. Ind. Med (1987), 44:14-25: A neurological evaluation of workers exposed to mixtures of organic solvents		Mean (Plant 1): 3.52 Mean (Plant 2): 3.52 Mean (Plant 3): 3.52 Mean (Plant 4):137.47	Measurements in the workers breathing zone

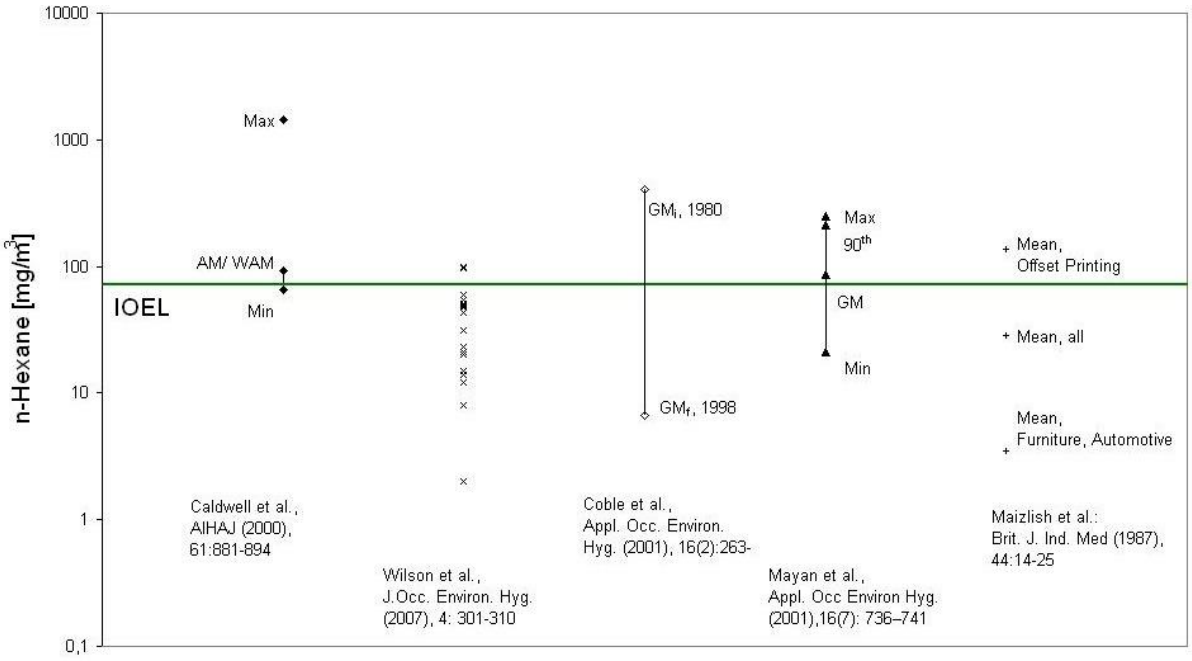


Figure 3: Data on occupational exposure to n-hexane as provided in different literature sources.

There is only limited information about the dermal exposure available. Nevertheless, biomonitoring studies give some indications about the contribution of dermal exposure to the total body burden.

Dermal uptake of vaporous n-hexane is low. Kezic et al. estimated the whole body skin uptake in comparison to the inhalation uptake from the same atmosphere on the base of biomonitoring exposure studies to be 0.1 % to the total uptake (Kezic 2000).

Nevertheless low molecular organic solvents like n-hexane are capable of damaging the skin by solvation of lipids followed by alteration of the lipid bilayers (Sartorelli 2000). The extent of the effect on the absorption of lipophilic solvents is less clear. Higher

concentrations of the biomarker of n-hexane where found in urine of exposed workers who did not use gloves and give hint at dermal uptake (Neghab 2011, Prieto 2003). The subject of dermal uptake is contrarily discussed by the German Senate Commission for the Testing of Harmful Working Materials (The MAK Collection for Occupational Health and Safety) (MAK) because of the good correlation between the n-hexane concentration in air and the concentration of the biomarker of the employees who do wear and who do not wear gloves. In the case of dermal absorption a lower correlation coefficient is expected. On the other hand if the exposure goes on steadily and the dermal uptake is of lower importance the correlation coefficients should differ only slightly.

Prieto et al. studied free and total 2,5-hexandione in urine of workers exposed to n-hexane in the shoe industry. In the atmosphere at the workplaces besides n-hexane further solvents were present (Prieto 2003). The average air concentrations of these solvents did not exceed the German Occupational Exposure Limit (AGW) (TRGS 900), but the average concentration of total 2,5-hexandione in urine of 5.84 mg/l (range between 0.3 to 32.5) exceeded the German biological limit value (BGW) of 5 mg/l (TRGS 903). Accumulation of biomarker concentration over the course of a week was noticed. The average values increased from day to day with the highest on Friday.

Co-exposure to additional solvents may result in increasing biomarker concentrations. Mayan et al. examined additionally mixed workplace exposure to hexane isomers, MEK, acetone, toluene and ethyl acetate and estimated that 2,5-hexanedione excretion could nearly be doubled in that case (Mayan 2001).

Baldasseroni et al. used data from a biomonitoring registry of the Province of Florence in Italy to asses the exposure of employees in leather and shoe industry to n-hexane in the period from 1991 to 1998 (Baldasseroni 2003). Analytical data of the biomarker 2,5-hexandione of about 16 000 samples from 6 650 exposed subjects were involved in the study. The used analytical method quantified the total 2,5-hexandione level. The authors found a reduction of urinary 2,5-hexandione of 31.9 % over the investigated time span. Only 0.8 % of the number of urinary 2,5-hexandione analyses exceeded the biological exposure value of 4.3 mg/l defined by the authors (in comparison the German Biological Limit Value (Biologischer Grenzwert, BGW): 5 mg/l). The reduction of urinary 2,5-hexandione is attributed to the reduction of n-hexane in glues and replacement with other solvents or water based glues, the improvement of hygiene conditions in the workplaces and better working-training programmes. Various biases were discussed in the article. An unintended selection is possible due to repeated sampling or higher number of tests according to legal regulations. No information on the technology, the conditions at the workplaces, exposure via ambient air and the workload is given. Nevertheless the mentioned trend of decreasing levels of 2,5-hexandione in urine of workers exposed to n-hexane appears plausible.

In summary, exceedances of the limit values were reported in some cases of measurements of airborne n-hexane and biomonitoring measurements as presented in this section. However, in most of these cases risk managment measures have become apparent as a key issue. As discussed before, in cases where the limit threshold of airborne n-hexane was exceeded the lack of technical and personal hygiene measures was mentioned by the authors of the respective publications. The influences of hygiene measures – although the general trend of reduction of n-hexane in glues and biases within the data evaluation are mentioned – is also considered as important factor in the discussion of biomonitoring data.

Modelled data

The modelled data as provided by the registrant/s are discussed in the confidential part of this report.

Comparison of monitoring and modelled data

See confidential part of this report.

7.12.1.2. **Consumer**

7.12.1.2.1. Overview of uses and exposure scenarios

The SPIN database (2012) indicates a "very probable exposure" with a "wide range of applications". In principal mixtures for consumer applications coming from different data bases were covered by the PCs in the CSR. Only for PC 35 – "Washing and cleaning products (including solvent bases products)" there are uncertainties whether it is covered completely by other PCs of the Use Descriptor System in the CSR.

A French survey was conducted among industrial sectors concerning the marketing of consumer products containing n-hexane (information provided as justification for the French proposal for amendment according to Article 51(4) of the REACH Regulation in 2013). A potential risk for consumers was identified in some consumer products belonging to the categories PC1, PC3, PC8, PC9, PC24 and PC35 with the current concentration limit of 3 % (triggering classification of a mixture as a Category 2 reproductive toxicant according Annex I (Table 3.7.2) of the REGULATION (EC) No 1272/2008).

A "Survey of n-hexane" as part of the LOUS review by the Danish EPA (Mikkelsen et al., 2014) recorded several consumer products which contain n-hexane. They concluded that consumers may be exposed to "relatively high concentrations on a short term basis" due to the substance volatility and presence in several spray products.

n-Hexane is not registered for consumer articles. Only limited information on articles is available in the literature. E.g. it was measured in scented toys (Glensvig D et al., 2006). It could be assumed that the identified use as PC 28 (fragrance, perfumes) is related to scented articles. It was also measured in electrical and electronic products (Mortensen PB, 2005). However, the emitted concentrations were below the acceptable air concentration of n-hexane.

Pursuant to the chemical safety requirements in Annex II of the European toy safety directive No 2009/48/EC, which come into force on 20 July 2013, CMR substances are not allowed in accessible parts of toys, unless they are present in individual concentrations which do not exceed the specified limits. For reprotoxic substances of GHS category 2, there is currently a generic concentration limit of 5%. From 1 June 2015 a generic concentration limit of 3% has to be applied.

The European standard EN 71-9 on the "Safety of toys - Part 9: Organic chemical compounds - Requirements" contains concentration limits for volatile organic solvents including a limit value for emission of 1.8 mg/m^3 for n-hexane. Although this is not a legally binding value, the conformity with harmonised standards provides a presumption of conformity with the requirements of the toy safety directive. However, in contrast to other European standards, the EN 71-9 has not been harmonized and officially published so far at the EU level, although it is already applied and accepted by EU member states.

In order to identify possible risks the CSR was checked whether the exposure scenarios for consumers are exhaustive, plausible and well documented regarding relevant uses, exposure routes and targeted population groups. The efficiency of already implemented risk management measures was evaluated for clarification whether further risk management options are needed.

The outcome of the assessment is recorded in the confidential part.

Inconsistencies and data gaps in the CSR regarding consumer exposure scenarios led the eMSCA to consider that risks could be expected for consumer application of n-hexane. To clarify this additional concern, plausible exposure scenarios with reproducible exposure estimates and RCRs were requested from the registrants in the substance evaluation decision.

Upon further consideration and discussion with downstream users, the active registrants updated their registration dossiers and removed the identified consumer uses completely in the technical IUCLID as well as in the CSR. **In consequence, the registrants do not support consumer uses any longer.**

It can be assumed that n-hexane is present in consumer products and consumer exposure is likely. But it is currently unclear whether n-hexane is mainly contained in consumer products because (a) downstream users in the supply chain may have no knowledge that the consumer uses are no longer supported by the registrants (although the dissemination page suggests differently), (b) it is a constituent of other registered substances, and/or (c) occurs as impurityin other registred substances (which can "make up no more than 20 % (w/w)", ECHA-GD 2011) (for further details see confidential annex). Likewise, it is unknown in which concentrations and products it is supplied to consumers. Therefore, the concerns identified regarding consumers could not be completely clarified. In case that the withdrawal of the supported uses in consumer products is effective, it has to be concluded that no risk for consumers arises from this registration. Whether the withdrawal of the originally registered uses will be completely effective for the market should be controlled by surveillance authorities. In addition and apart from the substance evaluation process, further data generation is necessary. With further information the authorities would be able to perform a general risk assessment of n-hexane that will consider all sources of n-hexane including dietary exposure and exposure from impurities in other registered substances.

7.12.2. Environment

Not part of the evaluation.

7.12.3. Combined exposure assessment

Not assessed.

7.13. Risk characterisation

7.13.1. Human Health

n-Hexane is listed in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008) as aspiration hazard category 1 (H304: May be fatal if swallowed and enters airways) and irritating to the skin category 2 (H315: Causes skin irritation). For these hazard categories, the available data do not allow a quantitative approach to risk characterization, and according to the REACH guidance on information requirements and chemical safety assessment, Part E, a qualitative assessment should be performed. In addition, a quantitative risk characterisation of workplace and consumer exposures to n-hexane with respect to its short- and long-term systemic effects (neurotoxicity) has been conducted based on exposure assessments and the DNELs given in Table 24 and Table 25.

7.13.2. Workers

Exposure to n-hexane at the workplace occurs mainly via inhalation of its vapours and/or via dermal contact with the liquid. Analysis of publicly available data (see exposure

information described in chapter 9.1.1) indicates that the risks associated with the use of n-hexane can be sufficiently controlled if appropriate risk management measures (RMM) are implemented and adequately communicated. With respect to the uses reported in the registration dossiers and the resulting exposures to n-hexane, quantitative risk characterisation was performed by comparing individually the inhalation and dermal exposure estimates for each exposure scenario (ES) with the respective systemic DNELs (i.e., assessing initially the risk characterization ratios (RCR) for both dermal and inhalation pathway separately). Subsequently, the health risks associated with combined exposures to n-hexane via both pathways are assessed through the summation of the respective RCRs (i.e., for those exposure scenarios involving both inhalation and dermal contact).

Specifically, the inhalation exposure estimates were compared to the long-term inhalation DNEL for systemic effects of 72 mg/m^3, while dermal exposure is compared to the respective long-term dermal DNEL of 10.3 mg/kg bw/d. n-Hexane is classified for skin irritation. Therefore, eye and dermal irritancy should be controlled by the use of appropriate RMMs such as technical, organizational, and personal protective measures. Details of the RMMs are provided for each ES. Under these conditions no local dermal effects are expected.

In addition, n-hexane is classified as STOT SE 3 (H336: May cause drowsiness or dizziness) for its acute effects (narcosis). Therefore, the long-term systemic DNEL should also ensure that workers are adequately protected during short-term peak exposures. In cases where peak exposures exceed significantly the long-term systemic DNEL, the REACH Guidance Chapter R.8, Appendix R.8-8 specifies that "… the DNEL for acute toxicity could be set for a reference period of 15 minutes at 1-5 times the value (default 3) of the long-term DNEL." Therefore, several exposure scenarios leading to peak exposures greater than 360 mg/m^3 (5 times the long-term systemic DNEL) were specifically addressed as a point of concern in this evaluation report (see confidential Annex).

Individual exposure scenarios / contributing scenarios (CS) where potential risks were identified (i.e., RCRs exceeding significantly 1) are summarized in the confidential part of the report. A review indicates that in a lot of cases inhalation exposures during industrial and professional applications of n-hexane are well controlled, and the respective exposure estimates are close to or below the long-term inhalation DNEL for systemic effects of 72 mg/m^3. However, several exceptions are observed during both professional and industrial use of n-hexane where the inhalation DNEL is exceeded. On the other hand, the calculated dermal exposures are frequently above the long term dermal DNEL of 10.3 mg/kg bw/d thus contributing considerably to the overall n-hexane exposure and associated health risks. Examples include both industrial as well as the professional application of n-hexane**.** Considering several uncertainties associated with the magnitude of dermal uptake of n-hexane and its potential contribution to the overall exposure estimate specific attention should be given to RMMs aimed at more efficient control of dermal exposures to liquid n-hexane. With respect to the aggregated n-hexane exposure via both dermal and inhalation pathways, in most instances the combined RCR exceeds significantly 1 indicating that the risks are not sufficiently controlled. In these cases the exposure scenario needs to be reassessed and refined in terms of providing more detailed information (Tier 2 approach) or applying additional safety measures. Please note that in many cases problems and uncertainties regarding the description of safety measures as provided in the exposure scenario were identified by the evaluating MSCA and are discussed in the confidential part of this report.

During discussions the lead registrant has submitted refined information that allows a higher tier assessment of the ES which were identified by the eMSCA. A refined risk assessment based on this new information showed that risk is adequately controlled. Therefore, the respective concerns have been clarified.

7.13.3. Consumers

In order to identify possible risks the registration dossiers was checked whether the risk characterisation including recorded RCR-values and qualitative descriptions is exhaustive, plausible and well documented regarding consumer exposure scenarios and the DNEL for all relevant endpoints.

Based on the current inconsistencies of exposure levels as well as of the derivation of appropriate DNELs it is impossible to fully assess the risks arising from consumer applications based on the data available in 2012.

The risk characterisation performed based on the data available in 2012 is discussed in the confidential part of this document.

After the registrants' withdrawal of all consumer uses in 2015, no risk assessment can be performed because of missing data.

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7.15. Abbreviations

Table 29

LIST OF ABBREVIATIONS	
AF	Assessment Factor
AGS	German Committee for Hazardous Substances
APF	Assigned Protection Factor
bw	Body weight
CS	Contributing Scenario (within an ES)
CSA	Chemical Safety assessment
CSR	Chemical Safety Report
d	day(s)
DNEL	derived no-effect level
EC	Effective Concentration
ENM	Electroneuromyography
ES	Exposure Scenario
F	Female
FOPH	Federal Office of Public Health (Switzerland)
GD	Gestational Days
h	hour(s)

i.v.	intravenous
IOEL	Indicative Occupational Exposure Limit
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
M	Male
MAP	Motor Nerve Action Potential
MCV	Motor Nerve Conduction Velocity
MEK	methyl ethyl ketone
NO(A)EC/L	No observed (adverse) effect concentration/level
OC	Operational Conditions
PC	Product category
PND	Postnatal Day
POD	Point of Departure
PROC	Process category
PPE	Personal Protective Equipment
RMM	Risk Management Measures
RPE	Respiratory Protection
SCOEL	Scientific Committee Occupational Exposure Limit
SD	Standard Deviation
V	Volume
w	week