baua:
Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin
Federal Institute for Occupational
Safety and Health

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Tetrahydrofuran

EC No 203-726-8

CAS No 109-99-9

Evaluating Member State(s): Germany

Dated: 29th September 2017

Template Version 2.1
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Evaluating Member State Competent Authority

BAuA
Federal Institute for Occupational Health and Safety
Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
Tel: +49 231 9071 2777
Fax: +49 231 9071 2679
Email: ChemG@baua.bund.de

Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 13 January 2015
Member State concluded the evaluation without any further need to ask more information from the Registrant(s) under Article 46(1) decision.

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

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Tetrahydrofuran (THF) was originally selected for substance evaluation (SEv) in order to clarify concerns about:

- Human health: Carcinogenic properties
- Exposure: Wide dispersive use (worker & consumer)
- High aggregated tonnage

During the evaluation also other concerns were identified. The additional concerns were:

- Missing information in the registration dossiers concerning physico-chemical properties (flammability, peroxide formation)

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

THF is listed in Annex VI of Regulation (EC) 1272/2008 (CLP) as Carc. Cat. 2, H351.

In 2009, France had proposed THF to be classified as Carc. Cat. 2, H351 (under CLP Regulation) or Carc. Cat. 3, R40 (in accordance with the Directive 67/548/EEC). In 2010 RAC had adopted the opinion that THF should be classified as Carc. Cat. 2, H351 (under CLP Regulation; http://echa.europa.eu/documents/10162/2415df29-6d80-4e96-ae25-7da19e92c3aa).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table at the end of this section.

Human Health: Carcinogenic properties

While a number of additional publications on the mechanistic relevance (or lack thereof) of the tumours observed in male rats and female rats for humans were evaluated, final clarity on this matter could not be obtained. In light of the remaining uncertainty, the findings of the evaluating Member State Competent Authority (eMSCA) support the conclusion of the RAC to classify THF as Carc. Cat. 2.

Further conclusions from hazard assessment

In line with the assessment of the Lead Registrant, the current harmonised classification/labelling of THF as per Annex VI of Regulation (EC) 1272/2008 (CLP) was found to not fully cover the classification/labelling that would result from a full evaluation of the toxicological database. In particular, it should be considered to change the current classification as Eye Irrit. 2/H319 to Eye Dam. 1/H318 and to add the following additional classification/labelling: Acute Tox 4/H302, STOT SE 3/H336, EUH019, EUH066. However, owing to the fact that these endpoints do not fall under harmonised classification and labelling (CLH, Article 36(1) of the CLP Regulation), and since the Lead Registrant already supports the correct classification, the eMSCA sees no immediate need for action and will decide at a later point in time whether there is a necessity to prepare an Annex XV dossier to that end.

In the course of this substance evaluation the eMSCA has evaluated the toxicological database with the aim of establishing Derived No Effect Levels (DNELs) for consumers. The acute DNELs derived by the Lead Registrant in his chemical safety report (CSR) were found to be higher than those that would be obtained by following the corresponding REACH

guidance. In particular, assessment factors (AFs) for inter- and intraspecies variability were chosen too low. As a consequence, the eMSCA established DNELs that were about twofold lower than those deduced by the Registrant(s).

Workers

Flammability and formation of an explosive solvent/air mixtures

THF is labelled as highly flammable (H225). The resulting flash point of -21 °C and the boiling point of 65 °C are very low. Because of these physico-chemical properties, under ambient condition the formation of an explosive atmosphere is probable. For comprehensive risk characterisation, additional information about the process conditions like the amount of use, the effectiveness of the air ventilation and effective ignition sources were required by the eMSCA to allow addressing the risk for workers of flammability of THF.

The Registrant(s) provided information on the way how the substance is used (closed system, use in open containers, spraying, pouring, etc). In addition, the Registrant(s) described how such risks of formation of an explosive air/vapour mixture may be minimised or eliminated (e.g. the maximum amount of use, the capacity of the air ventilation system, removal of effective ignition sources, use of explosion-proof equipment, etc). Therefore, the eMSCA regards this risk as properly controlled.

Explosivity because of formation of peroxides

The CLP labelling warns for peroxide formation in THF (EUH019). In order to assess the risk that such peroxide formation presents, information was needed for which uses and under which conditions peroxide formation may occur.
The dossier information did not allow assessing in which cases such a risk may be present. Therefore, the Registrant(s) were requested to supply this missing information.

The Registrant(s) delivered information on scenarios that are relevant in this respect. Therefore, the eMSCA regards this risk as properly controlled.

Consumers

Inconsistencies and data gaps in the CSR regarding consumer exposure scenarios (ES) led the eMSCA to consider that risks could be expected for consumer applications of THF. To clarify this concern, product information (e.g. intended purpose of the product, maximum THF concentrations, packaging size) which allows a proper exposure assessment for the intended and reasonable foreseeable uses were requested from the Registrant(s) in the substance evaluation decision for product categories (PC) PC 1, PC 9a, and PC 35. Furthermore the missing exposure scenarios by one Registrant for PC 3, 4, 9b, 9c, 13, 18, 23, 24, 31 & PC 0 (others: PC 5 & 10) were also requested.

Regarding requests 5-9 of the decision, addressing additional product information and consumer exposure scenarios, the Registrant(s) commented that these might require extensive information from downstream users. They assumed that "default/worst-case value databases might not be readily available for these endpoints. This would require communication with the downstream users, potentially involving a third party agency to maintain confidentiality of the values" (SEv decision on THF).

For this reason a questionnaire was sent to the Downstream User Associations by the Registrant(s) (see confidential Annex). Upon further consideration, the active Registrant(s) updated their registration dossiers and removed the identified consumer uses PC 9a and 35 from the technical dossier as well as from the CSR. The Registrant of the various consumer uses (see above) also updated his registration dossier in line with the joint submission. Only one update is still outstanding.

In consequence, the Registrant(s) support PC 1 (adhesives, glues) for consumer uses only and have submitted new consumer exposure scenarios for these uses.

They also added the following recommendations in the CSR concerning risk management measures (RMMs):

"Product integrated RMM which may be applied in products contain THF are not standardised. As a result of the qualitative risk assessment as a minimum the following RMM are recommended to duly control risk:

- Only use THF which contains stabilisers to prevent peroxide formation
- Max. size packaging = 1 Litre (1000 mL)
- Opening limited to max. 42 mm for packaging over 500 mL (with screw top lid closure) unless packaging contains a lid with built-in applicator where opening should be restricted to a size appropriate for the applicator."

This has to be clearly communicated along the supply chain e.g. by updating the Safety Data Sheets (SDS), so that downstream users are aware of their obligation according to Article 37 (4) of the REACH Regulation in cases where THF 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 THF as outlined in the decision.

As of June 2017, the information on THF disseminated on ECHA's webpages still lists several consumer uses of THF among the registered uses. These identified consumer uses belong to inactive registrations as well as to new registrations after ECHA's Decision was issued on 13th of January 2015. The latter are outside the scope of the current SEv process, that means information coming from these new registrations are not assessed e.g. in the light of consumer safety. The active Registrant(s) that registered THF for the first time after ECHA's decision was issued still mentions consumer uses for which no exposure scenarios are given by the joint CSR e.g. PC0, PC9 and PC35. In the absence of the description of a safe use for those, these Registrant(s) would have to adapt their dossier in order to comply with the legal information requirements.

Nevertheless, it could not be sufficiently clarified whether the exposure scenarios in the CSR cover consumer applications adequately. These need further clarification as their exposure levels could be underestimated. However, at present the eMSCA does not consider these residual uncertainties to trigger further follow-up regulatory action at EU level. An independent verification of data, exposure scenarios and models is sought via a national project.

The available information on the substance and the evaluation conducted has led the evaluating Member State to the following conclusions, as summarised in Table 1 below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level *[if a specific regulatory action is already identified then, please, select one or more of the specific follow-up actions mentioned below]*	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

4. FOLLOW-UP AT EU LEVEL

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

Not applicable.

4.1.1. Harmonised Classification and Labelling

Not applicable.

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

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties	X
Consumer Exposure Actions by the Registrant(s) to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.) The Registrant(s) support PC 1 (adhesives, glues) for consumer uses only.	X

They also add the following recommendations in the CSR: "Product integrated RMM which may be applied in products contain THF are not standardised. As a result of the qualitative risk assessment as a minimum the following RMM are recommended to duly control risk: ▪ Only use THF which contains stabilisers to prevent peroxide formation ▪ Max. size packaging = 1 Litre (1000 mL) ▪ Opening limited to max. 42 mm for packaging over 500 mL (with screw top lid closure) unless packaging contains a lid with built-in applicator where opening should be restricted to a size appropriate for the applicator."	X
Worker Exposure Descriptions by the Registrant(s) on the way how the substance is used (closed system, use in open containers, spraying, pouring, etc). In addition the Registrant(s) described how risks of formation of an explosive air/vapour mixture may be minimised or eliminated (e.g. the maximum amount of use, the capacity of the air ventilation system, removal of effective ignition sources, use of explosion proof equipment, etc). Descriptions by the Registrant(s) for which uses and under which conditions peroxide formation may occur.	X X

5.2. Other actions

It could not be sufficiently clarified whether the exposure scenarios in the CSR cover consumer applications adequately. Their exposure levels could be underestimated especially for the event exposure. Because of the acute effects after inhalation, verification with poison centre data is planned. This national project will start soon. Further activities to reduce uncertainties related to exposure scenarios, data, and models used here are needed.

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

Not applicable

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Tetrahydrofuran was originally selected for substance evaluation in order to clarify concerns about:

- Relevance for humans due to carcinogenic properties of THF
- Wide and dispersive use, consumer use and high workers exposure
- High aggregated tonnage

During the evaluation also other concern was identified. The additional concern was:

- Additional concern arose because of the physico-chemical properties (flammability and potential peroxide formation) of the substance.

Table 3

EVALUATED ENDPOINTS **Endpoint evaluated**	**Outcome/conclusion**
Carcinogenicity	Classification as Carc. Cat. 2/H351 by RAC confirmed in light of uncertainty about the mechanistic relevance for humans of tumours observed in rats and mice.
Hazard Assessment	DNELs need to be lowered using appropriate assessment factors.
Worker exposure	The ESs given in the CSR were checked with regard to completeness, plausibility and documentation including operational conditions (OCs) and information about risk management measures. The Registrant(s) delivered new exposure assessments which fulfil the requirements of the eMSCA.
Consumer exposure	Missing/implausible information regarding consumer products and their application in combination with high exposure levels based on the available data by recalculation of the eMSCA, and missing exposure scenarios for some identified consumer uses led to require further information by a decision. After the Registrant(s) updated their registration dossiers, the consumer use of adhesives, sealants (PC 1) was subject of further assessment by the eMSCA. Based on the new data, it could not be clarified sufficiently whether the exposure scenarios in the CSR cover consumer applications adequately. Their exposure levels could be underestimated.

7.2. Procedure

In 2011, tetrahydrofuran was proposed for substance evaluation in compliance with Article 44(1) of the Regulation (EC) No 1907/2006 (EC 2016) in order to clarify concerns about its carcinogenic potential and its risk to workers and consumers. The use of THF is widespread, e.g. in consumer, professional and industrial settings. Its risk to workers and consumers, based also on its physico-chemical properties i.e. flammability and potential peroxide formation, were assessed in addition. In October 2012 ECHA published the Draft-CoRAP and initiated a substance evaluation for THF.

The substance evaluation started in March 2013. In August 2013 the eMSCA invited the Lead Registrant for an expert meeting in order to discuss the current state of the evaluation and on-going tasks. Due to information gaps in the CSR (e.g. the missing description and assessment of occupational and consumer exposure referred to Appendix 1) the eMSCA had addressed some questions to the Lead Registrant regarding consumer uses, used operational conditions and models as well as for the missing Appendix 1 of the CSR. In consequence, the Lead Registrant has provided the Appendix 1, the description of use for PC 35 and justifications for changed defaults and the chosen tools. Therefore, it was possible to reproduce the exposure estimates for nearly all consumer exposure scenarios.

Although this information was still not part of the CSRs, all data available until the end of December 2013 were considered.

The eMSCA considered that further information was required to clarify the consumer use and worker exposure. Therefore, a draft decision was prepared to request further information regarding those concerns. This draft decision was submitted to ECHA in March 2014. Following the normal procedure of commenting deadlines for Registrant(s) and submission of proposals for amendments by other member states and ECHA, the draft decision was referred to the Member State Committee in October 2014. An unanimous agreement of the Member State Committee on the draft decision was reached in November 2014.

The decision was sent to Registrant(s) in January 2015, asking them to submit an update of the registrations containing the information required by this decision by 20th July 2016.

For this reason the Registrant(s) sent a questionnaire to the Downstream User Associations requiring information regarding use and product information (see confidential Annex and below). Following dossier updates of a few Registrant(s) including the Lead Registrant, the eMSCA started its follow-up period of twelve months to continue its substance evaluation of THF. In December 2016 the eMSCA contacted nineteen concerned Registrant(s) that did not update their dossiers with the requested information concerning consumer uses. Most of those carried out dossier updates until February 2017; one of the announced updates is still missing.

In conclusion, most of the Registrant(s) updated their Registration Dossiers and removed the identified consumer uses PC 9a and 35 or alternatively all consumer uses in the technical IUCLID as well as in the CSR. The Registrant of the various consumer uses also updated his registration dossier in line with the joint submission. As a result of the qualitative risk assessment, integrated risk management measures are recommended and recorded in their CSRs. The consumer uses of adhesives, sealants (PC 1) were subject of further assessment by the eMSCA.

7.2.1. Effects on environment:

The effects on the environment have not been evaluated during this substance evaluation.

7.2.2. Effects on human health – workers/consumers

7.2.2.1. Toxicity

The substance evaluation with respect to human health was comprehensive, addressing all human health endpoints as required according to REACH Regulation, Annex VII-X.

This substance evaluation referred to the CSR and the IUCLID endpoint records submitted by the Lead Registrant for THF. In addition, it also considered a number of reference assessments and reports available up to December 2013.

7.2.2.2. Exposure assessment and risk characterisation - workers

Occupational exposure information presented and discussed in chapter 7.12. and in the confidential Annex was taken from the registration dossiers. The exposure scenarios for workers as provided by the Registrant(s) in the chemical safety report were checked whether they are exhaustive, plausible and well documented with regard to operational conditions and information about risk management measures.

The eMSCA considered the following aspects of particular importance for ESs for workers:

- Sufficient description of operational conditions and RMMs including personal protection equipment (PPE).
- Sufficient reasoning for the use of efficiency factors used for the exposure assessment.

- 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).
- Flammability and possible peroxide formation

7.2.2.3. Exposure assessment and risk characterisation - consumers

In order to identify possible risks, the CSRs and the technical IUCLID dossiers were checked whether the exposure scenarios and risk characterisation ratios (RCRs) 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.

7.2.3. Conclusion

7.2.3.1. Conclusions regarding environment

The effects on the environment have not been evaluated during this substance evaluation.

7.2.3.2. Conclusions regarding human health

While a number of additional publications on the mechanistic relevance (or lack thereof) of the tumours observed in male rats and female rats for humans were evaluated, final clarity on this matter could not be obtained. In light of the remaining uncertainty, the findings of the eMSCA support the conclusion of the RAC to classify THF as Carc. Cat. 2.

In line with the assessment of the Lead Registrant, the current harmonised classification/labelling of THF as per Annex VI of Regulation (EC) 1272/2008 (CLP) was found to not fully cover the classification/labelling that would result from a full evaluation of the toxicological database. In particular, it should be considered to change the current classification as Eye Irrit. 2/H319 to Eye Dam. 1/H318 and to add the following additional classification/labelling: Acute Tox 4/H302, STOT SE 3/H336, EUH019, EUH066. However, owing to the fact that these endpoints do not fall under CLH (Article 36 of the CLP Regulation), and since the Lead Registrant already supports the correct classification, the eMSCA sees no immediate need for action and will decide at a later point in time whether there is a necessity to prepare an Annex XV dossier to that end.

In the course of this substance evaluation the eMSCA has evaluated the toxicological database with the aim of establishing DNELs for consumers. The acute DNELs derived by the Lead Registrant in his CSR were found to be higher than those that would be obtained by following the corresponding REACH guidance. In particular, the chosen assessment factors for inter- and intraspecies variability were too low. As a consequence, the eMSCA established DNELs that were about twofold lower than those deduced by the Registrant(s). For human health hazard assessment in relation to workers, the justification of DNELs was given particular attention. For the risk assessment the use of the Indicative Occupational Exposure Limit (IOEL) as a long term inhalation DNEL was found not to be justified. Therefore, DNELs were derived by the eMSCA for long-term systemic effects on the basis of the available data according to the REACH IR & CSA Guidance Document R.8 (ECHA, 2012).

THF is labelled as highly flammable (H225). The flash point of -21°C and the boiling point of 65°C are very low. Because of these physico-chemical properties the formation of an explosive atmosphere under ambient condition is probable. By itself, the mere possibility of formation of an explosive atmosphere does not give enough information to determine the likelihood and severity of an event occurring due to the physico-chemical properties of the substance. In addition, the CLP labelling warns of peroxide formation in THF (EUH019). In order to assess the risk that such peroxide formation presents, information was needed for which uses and under which conditions peroxide formation may occur. The Registrant(s) supplied this missing information in an update, which allows to assess in which cases such a risk may be present.

For comprehensive worker risk characterisation, additional information about the process conditions such as the amount of use, the effectiveness of the air ventilation and effective ignition sources were required by the eMSCA. Uses where the following Process Categories (PROCs) are included were considered likely to present a risk: PROC 5, PROC 7, PROC 8a, PROC 10, PROC 11, PROC 13, PROC 14, PROC 15, PROC 19 and PROC 20. This information was supplied by the Registrant(s) and enabled the eMSCA to complete its risk assessment. The eMSCA regards this risk as properly controlled.

As discussed in chapter 7.12. and in the confidential Annex of this report, data evaluated in the registration dossiers indicate that the risk associated with the use of THF or THF containing formulations by workers can be adequately controlled by implementation of appropriate RMMs at the workplaces. The previously missing information was supplied by the Registrant(s) and enabled the eMSCA to complete its risk assessment. Adequate risk management measures at workplaces are recommended.

Due to additional informal information by the Lead Registrant, in most cases the exposure estimates were reproducible. Nevertheless there are high uncertainties regarding the identified consumer products and the plausibility of the exposure scenarios. Furthermore the Registrant(s) did not address some important aspects: the reasonable foreseeable uses, the aggregated exposure, and the expected exposure times in the exposure scenarios which are important to obtain the total exposure. On the basis of the provided data the eMSCA was not able to carry out higher tier exposure estimates to decide whether possible health risks can be expected or not. Therefore, additional information was required in a decision.

Where calculations were possible, the low tier assumptions made in the consumer exposure assessment for those consumer uses originally supported and the DNELs derived by the eMSCA resulted in risk characterisation ratios > 1 for:

- the majority of consumer-related scenarios with respect to acute inhalation or dermal exposure,
- all consumer-relevant scenarios with respect to combined acute dermal and inhalation exposure,
- one consumer-related scenario with chronic dermal exposure,
- two out of three consumer-related scenarios with combined chronic dermal and inhalation exposure, and
- aggregated risk characterisation of consumer-related scenarios for PC 35 with combined chronic dermal and inhalation exposure.

After updating their registration dossiers in 2016 and 2017, the Registrant(s) now support PC 1 (adhesives, glues) for consumer uses only. The revised consumer exposure scenarios were assessed by the eMSCA. Although the Registrant(s) recommended in their updated CSRs a maximum packaging size of 1 L, this information is not in line with the chosen application form, and their operational conditions do not seem plausible. Therefore, the scenarios do not cover consumer applications adequately, and their exposure levels could be underestimated. Some more clarifying information with regard to consumer uses PC 1 was asked from Registrant(s) within the course of finalising the evaluation. Further, one use that was listed under PC 1 by the Registrant(s) should be registered as PC 9a in the opinion of the eMSCA based on the ECHA-GD R.12 (ECHA, 2010b) with an additional exposure scenario.

7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	tetrahydrofuran
EC number:	203-726-8
CAS number:	109-99-9
Index number in Annex VI of the CLP Regulation:	603-025-00-0
Molecular formula:	C_4H_8O
Molecular weight range:	72.1057 g/mol
Synonyms:	*THF*

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

Structural formula:

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICO-CHEMICAL PROPERTIES		
Property	**Value**	**Remarks**
Physical state at 20°C and 101.3 kPa	Colourless liquid with an ether-like odour	LyondellBasell Industries, 2009
Melting/freezing point	-108.44°C at 1013 hPa	Lide, D.R., 2009
Boiling point	65°C at 1013 hPa	Lide, D.R., 2009
Vapour pressure	17 kPa at 20°C	Kroschwitz, J., Kirk, R.E., Othmer, D.F., 2001
Water solubility	miscible in water	Kirk, R.E. 2004
Partition coefficient n-octanol/water (log value)	0.45 at 25°C	OECD Guideline 107 (Partition Coefficient (n-octanol / water), Shake Flask Method) BASF AG 1988
Viscosity	0.456 mPa/s at 25°C 0.359 mPa/s at 50°C.	Lide, D.R., 2009

Stability in organic solvents and identity of relevant degradation products		In accordance with column 1 of REACH annex IX stability of organic solvents and identity of relevant degradation products is not required as the stability of tetrahydrofuran is not considered critical.
Dissociation constant		According to Annex XI of the REACH regulation the dissociation constant test is not required as it is not scientifically necessary: the structure of tetrahydrofuran indicates that dissociation is unlikely to occur. According to ECHA Chapter 7 guidance, measurement of pKa is irrelevant as the substance cannot dissociate due to a lack of relevant functional groups.
Flash point	-21°C	
Flammability	Highly flammable	

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

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

7.5.2. Overview of uses

THF has a wide dispersive use (worker/professional and consumer uses). This substance is used in the following products: washing & cleaning products, adhesives and sealants, coating products and pharmaceuticals and has an industrial use resulting in manufacture of another substance (use of intermediates). Further, THF is registered for polymer production and is used in the following areas: formulation of mixtures and/or re-packaging.

In consumer uses, THF is present in various products such as paints, lacquers, paint removers, adhesives, and cleaning agents often in high concentrations. The identified consumer uses were compared to information coming from the national product data bases of Germany, Switzerland and the Nordic countries.

In Germany, THF is listed as ingredient in "adhesives & sealants", especially in plastic adhesives and as welding aid for plastics with a maximum concentration of about 90% as well as in "washing & cleaning agents", especially in "leather and shoe care products" with an maximum concentration of 30%. The SPIN database (2013) indicates a "probable exposure" with an "intermediate range of applications" and a "very probable use in article

productions". The SPIN database has listed the following use categories: solvents; adhesives, binding agents; cleaning/washing agents; paints, lacquers and varnishes; photo chemicals. In Switzerland, especially the product category "adhesive & sealants" is listed for consumer use. Furthermore their database also listed paints/lacquers; washing/cleaning agents; solvent/degreaser/thinners/paint removers with unknown assignment. The Danish Environmental Agency detected THF positively in small amounts in several consumer products: roof glue/roof adhesive (Nilsson et al., 2004), "slimy toys" (Svendsen et al., 2005), emission from hair dryers and computers (Mortensen, 2005), and sex toys (Nilsson et al., 2006).

In conclusion, there was a match between the registered PC 1, 9a, 35, 23 and information coming from the national product databases. However, there are uncertainties about the product types of single product categories and their applications, which are necessary to assess the reported exposure scenarios in the CSR. According to internet searches the purpose of THF in PVC-cement is well known and verifiable with the information coming from the CSR. For all other PCs no specific information could be identified – neither in the CSR nor in secondary sources.

After removing nearly all consumer uses in their registration dossiers, it is now unclear whether consumer uses are sufficiently covered by the identified consumer use of PC 1 (adhesives, glues), in particular due to the paper of (Fowles et al., 2013). The review reported on an inventory of customer uses performed by manufactures in addition to screened internet sources. Based on these results, eleven worker and two consumer exposure scenarios were identified: "Consumer uses of THF in cleaning products (ES#12) and Consumer uses of products containing THF: PVC primer, PVC cement, paint stripper, adhesives, lacquers, coatings (ES#13)". It was also noted that each consumer ES comprises one or more product categories.

Table 7

USES	Use(s)
Manufacture	PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent
Uses as intermediate	
Formulation	
Uses at industrial sites	• Coatings • Polymer Production • Functional Fluids - Corrosion Inhibitors • Cleaning Agents • Metal working fluids / rolling oils • Fuel

USES	Use(s)
	• Use in laboratories • Formulation & Packing of Preparations and Mixtures Containing THF • Process Solvent PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 7: Industrial spraying PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 13: Treatment of articles by dipping and pouring PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 15: Use as laboratory reagent PROC 17: Lubrication at high energy conditions and in partly open process PROC 19: Hand-mixing with intimate contact and only PPE available PROC 21: Low energy manipulation of substances bound in materials and/or articles
Uses by professional workers	• Use in Coatings • Use in Cleaning agents • Use in Laboratories • Use as Functional Fluids - Corrosion Inhibitors PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 3: Use in closed batch process (synthesis or formulation) PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation

USES	Use(s)
	(charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 11: Non industrial spraying PROC 13: Treatment of articles by dipping and pouring PROC 15: Use as laboratory reagent PROC 19: Hand-mixing with intimate contact and only PPE available. PROC 20: Heat and pressure transfer fluids in dispersive, professional use but closed systems
Consumer uses	In 2013 (during the first year of substance evaluation) the search for information provided on the dissemination website by ECHA within "Chemical Substance Search" (on 2013-11-28, status: latest update on 28 November 2013), led to the identification of consumer uses of THF in PC 1: Adhesives, sealants PC 3: Air care products PC 4: Anti-freeze and de-icing products PC 9a: Coatings and paints, thinners, paint removers PC 9b: Fillers, putties, plasters, modelling clay PC 9c: Finger paints PC 13: Fuels 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 35: Washing and cleaning products (including solvent based products). According to the information provided on the dissemination website within "Chemical Substance Search" (on 2017-06-16, status: latest update on 2017-06-06) the disseminated uses have not changed. However, the Registrant(s) subject to the draft decision have deleted consumer uses in their registration dossiers after the substance evaluation decision with exception of PC 1.
Article service life	

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 8

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)		
603-025-00-0	tetrahydrofuran	203-726-8	109-99-9	Flam. Liquid 2 Eye Irrit. 2 STOT SE 3 Carc. Cat. 2	H225 H319 H335 H351	 C ≥ 25% C ≥ 25%	

(last update of entry: 3rd ATP of Annex VI to the CLP regulation)

7.6.2. Self-classification

According to the CSR, the Lead Registrant proposes the following additional classification:

Acute Tox 4/H302, Eye Dam. 1/H318, STOT SE 3/H336, EUH019

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

Except where otherwise noted, unpublished studies/reports were mostly available as abstract or as a study summary in the technical dossier only. Names of the study authors were sometimes lacking, where original study reports were not available.

7.9.1. Toxicokinetics

7.9.1.1. Non-human information

Table 9

OVERVIEW OF NON-HUMAN INFORMATION ON TOXICOKINETICS CONSIDERED FOR THIS EVALUATION						
Method/ Guideline	**Route**	**Species, Strain, Sex, No/group**	**Dose levels, Duration of exposure**	**Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)**	**Remarks**	**Reference**
In vitro						
Comparative *in vitro* metabolism No guideline GLP	NA	Mice (B6C3F1, M/F), rats (F344, M/F) All preparations had a protein content between 17 and 22 mg/mL	Incubation of liver microsomes with 70 µM THF for 5 min	All species: only a single metabolite, γ-hydroxybutyric acid (GHB), was identified The following values are given for mice/rats: $t_{1/2}$(THF): 9.0/40.1 min Clearance (THF): 160.5/30.6 mL/min/kg (method 1) 205.4/30.6 mL/min/kg (method 2) No sex-specific differences observed Reaction rates were linear with protein content	Clearance *in vitro* was comparable in rats and humans, higher in mice Due to the analytical-chemical methodology used for determination, further metabolites might have been missed	([redacted] 2000), unpublished (study report available)
In vivo						
Investigation of brain and perirenal fat burden and selected enzyme levels after repeated exposure No guideline Likely non-GLP (no data)	Inhalation (vapour)	Rat, Wistar, M, 5	0-200-1000-2000 ppm, 2-18 wk, 5 d/wk, 6 h/d	a) Brain and perirenal fat burden increased with dose. For the same dose, burden decreased with exposure duration (tolerance). Brain and perirenal fat burden were linearly correlated b) Induction of 7-ethoxycoumarin deethylase (liver, kidney, all dose levels). Increase in NADPH-cytochrome c reductase at 2000 ppm.	None	(Elovaara et al., 1984)

OVERVIEW OF NON-HUMAN INFORMATION ON TOXICOKINETICS CONSIDERED FOR THIS EVALUATION						
Method/ Guideline	**Route**	**Species, Strain, Sex, No/group**	**Dose levels, Duration of exposure**	**Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)**	**Remarks**	**Reference**
Determination of THF blood levels following single exposure No guideline Likely non-GLP (no data)	Oral, gavage	Rat, Wistar, M, 3 (18 in total) Rabbit, N.N., M, 2	Single dose, 0.3 g/kg bw (as 10% aqueous solution) Single dose, 0.7 g/kg bw	C_{max} ca. 1 h (rats) $t_{1/2}$ between 4 and 6 h (rats and rabbits) Ratio tissue/blood levels ca. 0.5-1.5 (rats and rabbits, various tissues) Apparent distribution ca. 1-1.3 L/kg	None	(Hara et al., 1987)
Disposition and pharmacokinetics study No guideline GLP	Oral, gavage	Rat, F344, M+F, 5 (urine, faeces, tissue, cage wash, residual feed analysis), 3 (blood), 2 (CO_2 and volatile organics) Mouse, B6C3F1, M+F, 3	Single dose, 50-500 mg/kg bw (nominal, analytical values 38-46/429-496 mg/kg bw) Target gavage volumes were 4 mL/kg bw for rats and 8 mL/kg bw for mice	Absorption *Rats*: T_{max}(plasma) ca. 3-4 h at the low dose, 3-8 h at the high dose; C_{max} ca. 4fold lower at the low vs. high dose *Mice*: T_{max}(plasma) ca. 0.5 h at the low dose, ca. 1 h at the high dose; C_{max} ca. 4fold lower at the low vs. high dose In both species, THF content in red blood cells (but not in plasma) increased between 24 and 48 h samples, until a plateau (ca. 1/10 µg eq./g at the low/high dose in both species) was reached Metabolism Results qualitatively suggest the presence of a probably acidic metabolite in urine, but the study authors failed to identify or quantify this metabolite. Distribution/elimination *Rats*: plasma $t_{1/2}$ ca. 50-55 h in both the low and high dose group; much higher (10-20fold) in red blood cells (data for low dose only); mean of ≤ 48/≤ 20% of radioactivity exhaled as CO_2, ≤ 3.5/≤ 2.1% excreted in urine, and ≤ 0.9/≤ 1.4% in faeces, ≤ 14.1/≤ 7.9% remained in carcass and tissues at 50/500	Overall, reported results are of limited use for risk assessment considering the very low number (sometimes only 2) of animals per group, large intra-group variability and the overall low recovery. In particular, these results do not provide a reliable basis for identifying sex- or species-specific differences in toxico-kinetics	([redacted] 1998), unpublished (study report was available)

OVERVIEW OF NON-HUMAN INFORMATION ON TOXICOKINETICS CONSIDERED FOR THIS EVALUATION						
Method/ Guideline	**Route**	**Species, Strain, Sex, No/group**	**Dose levels, Duration of exposure**	**Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)**	**Remarks**	**Reference**
				mg/kg bw. Highest residues at 168 h in liver, fat, and adrenals. Total recovery was 26-33% in high dose and 61-68% in low dose rats *Mice*: plasma $t_{1/2}$ ca. 50-55 h in low dose mice of both sexes and high dose males; ca. 100 h in high dose F, but result is unreliable (high SD); $t_{1/2}$ in red blood cells much higher, but not reliably quantifiable; Mean of ≤ 75/51% of radioactivity exhaled as CO_2, ≤ 5.3/≤ 3.8% excreted in urine, at 50/500 mg/kg bw; 21.1% as volatile organics at the low dose; recovery: 43-62% in high dose mice. Missing fractions were attributed to ineffective trapping of volatile organics (VOC); in one experiment in low dose mice using a different setup, VOC fractions amounted to 18/25%, leading to an overall recovery of 85/109%)		

p.e. = post exposure

Absorption

In the ADME study in rats and mice ([redacted] 1998), the main part of absorption occurred within the first hours after administration of 50 or 500 mg/kg bw and was faster in mice (ca. 0.5/1 h) than in rats (2-4/4-8 h). Occasionally apparent sex-specific differences were observed with plasma parameters, but these results are not reliable due to small group sizes and high intra-group variability. Due to experimental problems, in particular with respect to low recoveries most likely due to inefficient trapping of volatile organic chemicals (VOC), this study does not provide a reliable basis for exact quantification of the orally absorbed amount of THF. Judging from the low radioactivity found in faeces as well as from the low-dose mouse experiment (with improved trapping). However, it is prudent to assume that absorption at 50 mg/kg bw was quantitative, i.e. > 90%. For the higher dose level, percentages might have been lower but this cannot be established with certainty. Based on a density of 0.886 g/mL, the applied dilutions correspond to ca. 1.4 or 14% (v/v) dilutions for rats, and 0.7 or 7% (v/v) for mice. Conclusions for higher concentrations cannot be drawn.

There are no reliable non-human data on the rate of dermal absorption or uptake via inhalation.

Metabolism

A plausible metabolism scheme is presented in (US EPA, 2012), cf. Fig. 1. The metabolite γ-hydroxybutryric acid (GHB), a neurotoxicant also known as a drug of abuse ('liquid ecstasy'), has been detected *inter alia* by (Cartigny et al., 2001) and ([redacted] 2000).

Distribution and elimination

While (Hara et al., 1987) found plasma half-lives around 4-6 h in rats and rabbits, in ([redacted] 1998), $t_{1/2}$ values ranged around 50 h in both rats and mice (with an unreliable outlier of 100 h in female high-dose mice). In the latter study, half-lives in red blood cells were also determined but found to be much higher. The toxicological relevance of this finding is unclear. The main route of elimination of administered radiolabel in this study was via exhalation, either as CO_2 or in the form of (unidentified) VOC. It might be speculated whether the VOC fraction contained an (unknown amount) of not metabolised THF. In the same study, highest tissue radioactivity in low-dose mice was observed during the first 1-2 h following gavage administration, indicating rapid distribution after uptake. Highest residues 168 h post-exposure were found in liver, adrenals, and fat (both rats and mice, both dose levels). (Elovaara et al., 1984) showed that THF levels in brain and perirenal fat of rats are increased in a dose-related fashion (while the relative ratio in both compartments is roughly maintained). On the other hand, these levels decrease with continuing exposure, perhaps due to increased elimination based on induction of CYP450, EROD, and PROD [cf. also (Van Ravenzwaay et al., 2003)].

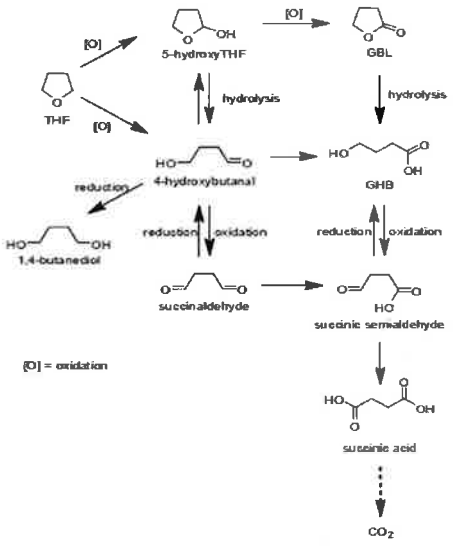


Fig. 1: Postulated metabolism for THF [from (US EPA, 2012)]

7.9.1.2. Human information

Table 10

OVERVIEW OF HUMAN INFORMATION ON TOXICOKINETICS CONSIDERED FOR THIS EVALUATION						
Method/ Guideline	**Route**	**Test Subjects**	**Dose levels, Duration of exposure**	**Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)**	**Remarks**	**Reference**
In silico						
Seven-compartment (lungs, muscles and skin, fat, brain, kidneys, liver, others) PBPK model	Inhalation	NA	Data were estimated for a time-point immediately after the end of an 8 h-shift at 200 ppm THF	Predicted THF levels: 5.1 ppm (breath), 4.1 mg/L (venous blood), 7.2 mg/L (urine). Predicted partition coefficients: Air/Water: 163.3 ± 2.3, Air/Olive oil: 226.2 ± 5.9, Air/Blood: 145.3 ± 3.7	Fairly good agreement with some, but not all experimental results. C_{max} tends to be underestimated	(Droz et al., 1999)
In vitro						
Comparative *in vitro* metabolism No guideline GLP	NA	Humans (mixed pool) Protein content 20 mg/mL	Incubation of liver microsomes with 70 µM THF for 5 min	Only a single metabolite, □-hydroxybutyric acid (GHB), was identified $t_{1/2}$: 28.63 min Clearance: 27.31 mL/min/kg (method 1); 28.59 mL/min/kg (method 2) Reaction rates were linear with protein content	Animal data see previous section Metabolisation rate (THF → GHB) in rats and humans comparable, but > 5 times higher in mice Due to the analytical-chemical methodology used for determination, further metabolites might have been missed	([redacted] 2000)

OVERVIEW OF HUMAN INFORMATION ON TOXICOKINETICS CONSIDERED FOR THIS EVALUATION						
Method/ Guideline	**Route**	**Test Subjects**	**Dose levels, Duration of exposure**	**Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)**	**Remarks**	**Reference**
In vitro dermal absorption study GLP	Dermal	Cadaver skin from 3 donors (2 M, 1 F, age 44-61)	Exposure with 10 and 30% aqueous THF and with 100% THF for 10 and 60 min and with 10% aqueous THF for 14 h Contact between skin and receptor fluid interrupted immediately post-exposure Skin was flushed twice before further processing	Application of 100% THF resulted in loss of membrane integrity, results are not usable for risk assessment Results for 10 and 60 min exposure to dilutions are not usable due to experimental flaws (evaporation with 10% for 10 min; immediate removal of receptor fluid at end of exposure, residual skin content was only counted after purging the skin twice) Results for 14 h exposure to 10% THF: K_p: 0.012-0.021 cm/h Flux: 1.1-2.0 mg/cm^2/h However, average overall recovery was only 58%	Experiment designed to come close to an 'infinite dose' experiment Significant deviations from standard OECD 428/EU B.45 guideline setup Results are not suitable for deriving absorption percentages or for performing route-to-route extrapolation	([redacted] 2005)

OVERVIEW OF HUMAN INFORMATION ON TOXICOKINETICS CONSIDERED FOR THIS EVALUATION						
Method/ Guideline	**Route**	**Test Subjects**	**Dose levels, Duration of exposure**	**Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)**	**Remarks**	**Reference**
In vivo						
No guideline Likely non-GLP (no data)	Dermal (from vapour phase)	Four human volunteers	2 exposures in T-shirt and shorts at 150 ppm for 4 h 1st exposure: whole-body exposure 2nd exposure: skin only (inhalation excluded by wearing air-fed breathing masks)	The following levels are given for skin only/whole body as the range observed in the four volunteers: Blood: 0-0.8/13-28 µmol/L (immediately p.e.) Breath: 1.3-4/153-463 nmol/L (mean of four samples taken within 30 min p.e.) Urine: 0.06-0.31/5.1-8.4 µmol (total collected until 22 h p.e.) Under the conditions of this study, uptake via the skin was estimated to contribute ca. 1-2% of the body burden	None	(Brooke et al., 1998)
^{1}H-NMR analysis of biological fluids in a case of acute poisoning	NA	One case (F, 55 yr)	Intentional ingestion of large (unknown) quantity of THF together with 'psychoactive substances' (zolpidem, fluoxetine)	Values determined in serum/urine were: THF: 813/850 mg/L GHB: 239/2977 mg/L Lactic acid: 342/2286 mg/L	None	(Cartigny et al., 2001)
Biomonit-oring study No guideline, Likely non-GLP (no data)	Inhalation	48-58 workers	NA (environ-mental concentra-tions in the workplace)	Strong interindividual variation in various THF concentrations (mean/SD/range): Environmental (ppm): 24.7/35/0.2-143 Breath (ppm): 1.8/3.8/0-27.3 Blood (µmol/L): 6.3/6.6/0.3-25.6 Urinary THF (µmol/g, creatinine-adjusted): 13.3/17.8/2-97.4	Unclear, whether additional dermal exposure occurred; Poor correlation of breath/ blood/urin-ary levels and environ-mental concen-trations; Limited value for risk assess-ment	(Ong et al., 1991)

Absorption

The results of (Kageyama, 1988) regarding absorption and elimination in humans suggest that about one third of the dose absorbed by inhalation is exhaled as THF (but possible metabolites were not traced).

Results of (Brooke et al., 1998) showed that when individuals were exposed to THF vapour at levels in the range of contemporary occupational exposure limits (OELs), uptake via the skin only made a small contribution to the overall body burden in relation to absorption by inhalation. However, a complete mass balance was not obtained in this study, thus no absolute quantification of inhaled dose is possible.

The study by ([redacted] 2005) on the dermal absorption in humans *in vitro* showed strong deviations from the relevant OECD test guideline 428/EU test method B.45 with respect to experimental study design:

- As the volume of THF placed on the skin was far too high (800 µL/0.8 cm^2, mimicking an 'infinite dose' approach; cf. EU test method B.45: ≤ 10 µL/cm^2), meaningful absorption percentages cannot be derived.
- Treated skin and receptor fluid were separated immediately after end of exposure time, i.e. after 10 or 60 min (instead of 24 h sample time).
- After removal of receptor fluid, two successive integrity tests (i.e. flushing with tritiated water) were performed with the treated skin before submitting it to scintillation counting, thus purging twice any potential residual THF from the skin.
- In one experiment (10% for 14 h), total recovery of radioactivity was low (58%). Thus, the flux rates and K_p values derived from this study are not reliable.

In addition, due to the 'infinite dose-like' approach, experiments with 100% THF showed disintegration of the barrier function of the skin *in vitro*. As a consequence of these deviations and difficulties, the study is not suitable for a reliable conclusion on the dermal absorption rate of THF in humans *in vivo*.

Metabolism

In the context of investigating a case of intentional self-poisoning, (Cartigny et al., 2001) confirmed the presence of GHB as a metabolite of THF in humans. ([redacted] 2000) showed that the metabolisation rate of THF to GHB in incubated liver microsomal fractions was comparable in rats and humans, while it was more than five times faster in mice.

Distribution and elimination

(Droz et al., 1999) developed a PBTK model for THF. Predicted THF levels (for details cf. Table 10 above) after exposure by inhalation to 200 ppm THF over an 8 h shift were compared with published biomonitoring data. The predicted results were in fairly good agreement with some, but not all experimental results. In particular, blood C_{max} values in urine and also breath tended to be underestimated.

(Ong et al., 1991) reported biomonitoring results for 48-58 workers. Due to a high variability of results (cf. Table 10) and poor correlation of breath/blood/urinary THF levels with environmental concentrations this study has only very limited value for risk assessment.

7.9.1.3. Summary of toxicokinetics

- Absorption of THF via the oral and dermal routes is high, perhaps quantitative (i.e. close to 100%), while exact quantification is not possible due to limitations of the available data. For absorption via inhalation, no data are available, but presumably absorption is also high. For route-to-route extrapolation, similar(ly high) absorption rates have to be assumed for all routes.

- Oral absorption in mice appears to occur slightly faster than in rats.
- Tissue distribution is fast with highest fractions of administered radiolabel observed in liver, adrenals, and fat.
- As a prominent metabolite of THF, γ-hydroxybutyric acid was observed in several studies.
- Clearance of radiolabel from plasma occurs at ca. the same rate in rats and mice, while *in vitro*, clearance of THF was faster in mice vs. rats/humans.
- Exhalation appears to be the most important route of excretion of THF, either unchanged or as CO_2 (existence of further volatile metabolites is unknown).

7.9.2. Acute toxicity and Corrosion/Irritation

7.9.2.1. Acute toxicity

Non-human information

The following studies were evaluated: ([redacted] 1979c; [redacted] 2009; [redacted] 1978; [redacted], 1980; Horiguchi et al., 1984; Katahira et al., 1982a; Kimura et al., 1971; Malley et al., 2001; Ohashi et al., 1982a; Ohashi et al., 1982b). Apparently, (Malley et al., 2001) is the published version of ([redacted] 1999) and ([redacted] 1996).

Acute toxicity: oral

In ([redacted] 1978), mortality was observed already at the lowest dose of 500 mg/kg bw (1/3 M, 2/3 F). It is unclear whether all fatalities can be related to treatment with THF. Based on the oral LD_{50} of 1650 mg/kg bw derived from this study, classification as Acute Tox. 4 appears to be required (which is confirmed in the CSR of the Lead Registrant).

Acute toxicity: inhalation

Based on ([redacted] 1979c), ([redacted] 1980), and (Katahira et al., 1982a) (and also (Horiguchi et al., 1984), for which only abstracts were available), classification for acute toxicity (in the sense of the CLP Acute Tox hazard class) via the inhalation route is not required for THF.

According to (Malley et al., 2001), the no observed adverse effect concentration (NOAEC) for acute narcotic effects after inhalation was found to be 2500 ppm. However, at this dose level reaction to an acoustic stimulus was diminished (NOAEC: 500 ppm). From these findings – which were observed in a similar fashion in further studies – classification/labelling as STOT SE 3/H336 can be deduced. Again, this classification is currently not included in Annex VI of the CLP regulation, but provided in the CSR of the Lead Registrant.

Acute toxicity: dermal

Based on ([redacted] 2009), classification for acute toxicity (in the sense of the CLP 'Acute Tox' hazard class) via the dermal route is not required for THF.

Acute toxicity: other routes

No data

Human information

Human data on acute toxicity were not evaluated for this dossier.

Summary

Classification with Acute Tox 4/H302 and STOT SE 3/H336 has been proposed by the Lead Registrant and this is supported by the eMSCA.

7.9.2.2. Irritation

Skin

With respect to the CLP classification criteria, the results from ([redacted] 1978) do not point at a need for classification/labelling of THF for skin irritation. Final judgement however is not possible, as a) scoring was performed only at 24 and 72, but not at 48 h and b) the test protocol did not include a 14-d post-exposure observation period by means of which reversibility of the erythemas/oedemas present at 72 h could have been confirmed.

In the technical dossier the acute dermal toxicity study in rats ([redacted] 2009) is mentioned as a further proof of the absence of irritation after dermal contact with THF, but neither the species used nor the time-points of evaluation fit in with current guideline requirements. (Jochmann, 1961) quotes earlier work of other authors:

> *'GROSS found strong local irritation of the rabbit ear (erythema, oedema, signs of corrosion, healing with formation of scars) following painting with undiluted as well as 50% aqueous THF solution, weak irritation occurred with a 20%, no irritation was seen with a 10% aqueous solution. Feeding a 20% aqueous solution to rabbits very strongly irritated the stomach and intestinal mucosae (inflammation, necrosis and haemorrhage of the gastric mucosa, diarrhoea).'* [translated from German by the eMSCA]

Ultimately these results cannot be verified. In particular there is huge uncertainty regarding the composition/purity of the test material (apparently the respective tests were performed before 1938). Not purified or unstable THF forms strongly irritant peroxides and there is no information whether (and if so, which) stabilisers might have been used in order to prevent peroxide formation, also supported by (Hofmann and Oettel, 1954). This possible explanation is supported by (Hofmann and Oettel, 1954):

> *,Skin irritation experiments in humans with different batches of technical THF resulted in distinctly different* [degrees of] *irritation. Interestingly stronger irritation occurred only where THF was allowed to evaporate from the skin. Thus, while THF itself is practically non-irritant, impurities remaining on the skin after evaporation of the solvent or transformation products formed only there appear to be responsible for the irritant effect. As peroxides are readily generated in THF as in ether, [...] stronger irritation [...] could have been caused [...] by such peroxides.'*

Another hypothetical explanation for the above findings could lie in a defatting effect of THF in the sense of the EU hazard phrase EUH066 ('Repeated exposure may cause skin dryness or cracking'). Chemically related substances such as diethyl and diisopropyl ethers or 1,4-dioxane are classified/labelled with EUH066. On the other hand, THF is not classified in this way, but a defatting effect has been reported, e.g. in many MSDSs available over the internet (whereas this effect apparently is not discussed in the registration dossier).

Eye

Following application of THF to the eyes of rabbits in ([redacted] 1978), several animals suffered from (sometimes severe) damage of the cornea and conjunctiva, which did not reverse until day 7 post-exposure. For classification it is not relevant, that post-exposure observation did not last for 21 d (as requested by the corresponding OECD guideline), as for the observed grade 4 damage of the cornea, irreversibility can be assumed, cf. the most recent version of the EU test method regulation (EG) 440/2208, method B.5, section 1.4.2.7.1.:

> '[...] *Animals should be kept on test no longer than necessary once definitive information has been obtained. Animals with the following eye lesions post-*

> *instillation should be humanely killed: corneal perforation or significant corneal ulceration including staphyloma; blood in the anterior chamber of the eye; grade 4 corneal opacity which persists for 48 hours; absence of a light reflex (iridial response grade 2) which persists for 72 hours; ulceration of the conjunctival membrane; necrosis of the conjunctivae or nictitating membrane; or sloughing. This is because such lesions generally are not reversible.'*

In addition, corneal opacity is also reported in (Katahira et al., 1982a) after exposure of rats to a concentration of 5000 ppm THF via inhalation.

In the view of the eMSCA and in line with the Lead Registrant's evaluation in the registration dossier the current legal classification of Eye Irrit. 2 should be changed to Eye Dam1/H318.

Respiratory tract

THF currently is legally classified as STOT SE 3/H335 for respiratory irritation, with the exact justification not being available to the authors of this dossier.

Again, (Jochmann, 1961) quotes findings of previous authors:

> *'With inhalation of vapours containing THF he* [the author Gross, cf. above] *observed irritation (salivation, licking of the snout, lacrimation, forced closing of eyelids) on accessible mucosae of the experimental animals already from concentrations of 10 mg/L* [ca. 3.300 ppm]. [...] *In his inhalation experiments Gross also saw* [...] *local irritation of the lungs, in one case even pneumonia with suppurative pleuritis'* [translated from German].

In rats, doses of 100 and 200 ppm elicited slight (reddening of nose and eyelids), and 5000 ppm strong irritation symptoms (oedemata and corneal opacity, increased salivation, discharge and haemorrhage of the nasal mucosa) (Horiguchi et al., 1984; Katahira et al., 1982a). Upon 4 h exposure, very high air levels (12.000 ppm) caused paralysis of nasal cilia in rabbits, associated with histopathological damage of cilia and nasal mucosa [(Ohashi et al., 1982a), only available as abstract].

(Ohashi et al., 1982b) exposed rats to 0, 100, or 5000 ppm THF vapour for 1 d, 1 wk, or 3 wk. One day exposure to 100 ppm did not have a significant effect on ciliary function. After 1 wk at 100 ppm the frequency of ciliary beats in the nasal mucosa was slightly (11%) reduced vs. controls, and the nasal epithelium displayed morphological changes such as vacuolisation, compound cilia, and epithelial protuberances. After three weeks at this concentration, a reduction (11%) of the ciliary beating frequency in the tracheal mucosa was observed, whereas ciliary frequency in the nasal mucosa was reduced by 39% vs. controls. Morphologically the nasal mucosa presented with strong vacuolisation, cilia were missing, and membranes of cilia-bearing cells were partly destroyed.

Finally, after a week at 5000 ppm reduction of ciliary beating frequency in the trachea amounted to 18% (nose 28%), after three weeks the reduction in the trachea was 24%, while in the nasal mucosa no ciliary activity was notable anymore.

As a comprehensive description of the experimental conditions is only available in Japanese, a judgement of the reliability of these results is hard to give. Furthermore these results are in contradiction with newer studies, above all (NTP, 1998), in which no morphological damage in nasal or tracheal epithelium was reported after exposure of rats up to 1800 ppm of THF for 14 wk to 2 yr.

If the results of Ohashi et al. after repeated administration were taken seriously, however, classification as STOT RE (perhaps even category 1) might have to be considered. In this context, (Muttray et al., 2006) report occupational cases of hyp- or anosmia (reduction or loss of the ability to perceive odours). Anosmia is a possible criterion for STOT RE. However, the study leaves room for doubt whether the observed findings can be traced with sufficient reliability to THF as the sole causative.

The eMSCA currently finds that there is no sufficient basis for a classification of THF as STOT RE based on damage of respiratory epithelia.

Summary

Available data on skin irritation do not call for classification, while – in line with the view of the Lead Registrant - the existing classification for eye damage should be changed from Eye Irrit. 2 to Eye Dam. 1.

The basis for the existing classification as STOT SE 3/H335 could not be elucidated but it is not proposed to change this classification.

Classification with EUH066 should be considered based on structural similarity to other defatting agents.

7.9.3. Sensitisation

7.9.3.1. Skin

The Local Lymph Node Assay [([redacted] 1997) in connection with ([redacted] 2008)] for THF concentrations of 10, 25, and 50% w/w gave a negative result. Irritation was not reported at these concentrations. While it is unclear why 100% THF has not been tested, it might be speculated that avoidance of possible irritation was the reason.

7.9.3.2. Respiratory system

No specific information on this endpoint is available, but the eMSCA considers THF unlikely to be a respiratory sensitizer, both due to the absence of any known structural alert for skin or respiratory sensitisation and the lack of any respective report in humans in spite of decades of high tonnage use of this solvent in the chemical industry.

7.9.4. Repeated dose toxicity

The following studies were considered: ([redacted] 2001; Chhabra et al., 1990; Horiguchi et al., 1984; Jochmann, 1961; Katahira et al., 1982b; Kawata and Ito, 1984; Komsta et al., 1988; Malley et al., 2001; NTP, 1998; Ohashi et al., 1982b; Van Ravenzwaay et al., 2003). The study by (Chhabra et al., 1990) is also reported in (NTP, 1998). Below, only the most relevant results from these studies are reported.

7.9.4.1. Repeated dose toxicity: oral

(Komsta et al., 1988) administered dose levels of 0, 10, 100, or 1000 mg THF/L drinking water to Sprague-Dawley rats over a period of 28 d. With the exception of a slight, dose-related increase in body weight of females and a higher incidence of anisokaryosis (with unclear toxicological relevance) in females of the 1000 mg/L group, no substance-related effects of THF were reported. As a whole this study is of only limited value, because the highest drinking water concentration applied corresponded to a dose level of only 100 mg/kg bw/d and thus was chosen too low (in the sense of the respective OECD test guideline).

As oral uptake is not a central issue with the known uses of THF, requesting a valid oral study is however currently not regarded necessary.

7.9.4.2. Repeated dose toxicity: inhalation

Subacute

In ([redacted] 2001) mice inhaled THF vapour in concentrations of 0, 200, 600, and 1800 ppm for four weeks (5 d/wk, 6 h/d) via head-nose inhalation. Respective satellite groups were sacrificed after the first five exposures, or after five days plus a 21 d recovery time. The

focus of this study was on a possible proliferative effect of THF (method: BrdU labelling). Results are provided in Table 11.

Table 11

CELL PROLIFERATION RATE IN LIVER OF MICE AFTER TREATMENT WITH THF [data from summary of (BASF, 2001) by Lead Registrant]			
Group	**200 ppm**	**600 ppm**	**1800 ppm**
	Overall*		
5 exposures	110	132	217
5 exposures + 3 wk regeneration	124	103	96
20 exposures	101	103	141
Zone 3 (centrilobular)			
5 exposures	147	188	401
5 exposures + 3 wk regeneration	170	148	137
20 exposures	133	134	230
Zone 2 (mid-zonal)			
5 exposures	98	117	183
5 exposures + 3 wk regeneration	No data available, but acc. to Lead Registrant, 'no such observations [i.e. of a proliferative nature] were made'		
20 exposures			

*All positively labelled cells per liver lobule counted together; number of labelled cells (in percent vs. control = labelling index (LI)

At 1800 ppm, a proliferative effect on liver cells was demonstrated both after 5 and 20 exposures, which however seemed to be of a reversible nature (at least after 5 exposures, no data available after 20 exposures). The apoptotic index (AI, determined by TUNEL staining) was not significantly influenced by THF treatment. The mitotic index (MI, haematoxylin/eosin staining) was slightly but significantly elevated in zone 3 (centrilobular) in the high concentration group after 5 and significantly after 20 exposures. The MI was also significantly elevated in the high concentration group in Zone 2 after 5 and after 20 exposures. However, the MI was even higher in zone 2 (mid-zonal) in the medium concentration group after 20 exposures, thus showing no relationship to inhaled concentrations. The overall NOAEC for these effects in mice was 600 ppm.

In the uterus, number of labelled cells, AI, and MI were not significantly affected by THF treatment.

In male rats, increased cell proliferation was found in the proximal renal tubuli, accompanied by deposition of α2u-globulin in the renal cortex (proven by immune-histochemical analysis; the NOAEC for this was 200 ppm). In contrast to females, male rats showed an increase in apoptotic index.

(Van Ravenzwaay et al., 2003) report another experiment in female mice, this time using dose levels of 0, 1800, and 5400 ppm with and without pre-treatment with 1-aminobenzotriazole (ABT, for inhibition of CYP450, EROD und PROD enzymes). At 5400 ppm the onset of 'deep narcosis' was observed. In contrast to ([redacted] 2001), cell proliferation here was measured using the PCNA method (there: BrdU labelling). Induction of microsomal enzymes by THF was clearly confirmed. While the rate of proliferation was markedly increased in zone 3 at 5400 ppm both with and without ABT pre-treatment, an increase in zone 2 was only noted with ABT.

Subchronic

In rats which inhaled 0, 100, 200, 1000, or 5000 ppm THF vapour for 12 weeks, (Katahira et al., 1982b) [or (Horiguchi et al., 1984), respectively] reported effects on the liver at ≥

200 ppm (increase in serum GOT/ASAT by ca. 20-30%, statistically significant at ≥ 1000 ppm). At 5000 ppm, also serum GPT/ALAT (to almost twice the control value), cholesterol, and bilirubin were increased, body weight was reduced and marked signs of local irritation accompanied by morphological changes of the mucosa occurred. In addition, signs of narcosis up to the extent of coma were observed. In contrast, only mild mucosal irritation was reported up to and including 200 ppm.

The effects on liver enzymes were not seen in rats which received 3000 ppm THF for 12 wk (Kawata and Ito, 1984). In the kidneys from the same group, the authors observed proteinaceous casts and hyaline droplets.

(Chhabra et al., 1990) administered 0, 66, 200, 600, 1800 or 5000 ppm THF vapour to mice and rats over a period of 14 wk (6 h/d, 5 d/wk).

In rats, adverse effects were recorded only at the highest dose level (5000 ppm). Narcosis (‚ataxia') was the predominant effect, furthermore reduced thymus and spleen weight as well as haematological and clinico-chemical changes and lesions of the forestomach (acanthosis, inflammation) were reported. The NOAEC was 1800 ppm.

In mice slightly increased liver weight (M: + 6%/+ 13% at 600/1800 ppm; F: + 6% only at 1800 ppm) and clearly reduced thymus weight (only F: -15/- 22% at 600/1800 ppm) were observed up to a concentration of 1800 ppm. Histopathologically – by using standard staining techniques – no correlates were seen.

Narcosis was noted at ≥ 1800 ppm. At 5000 ppm mortality occurred, furthermore reduced body weight, slightly (F: + 13%) to clearly (M: + 25%) increased liver weight, strongly reduced thymus (F) and spleen weight (M + F), minimal to mild centrilobular cytomegaly in the liver, uterus atrophy and degeneration of the „X" zone of the adrenal cortex were reported. The overall NOAEC in this study was 600 ppm.

In the context of their investigation of acute and subchronic neurotoxicity, (Malley et al., 2001) exposed rats to 0, 500, 1500, or 3000 ppm THF vapour over a period of 14 weeks. Aside from sedation (diminished response to an acoustic stimulus at ≥ 1500 ppm), no functional or morphological neurotoxic effects were found up to the highest concentration tested. Already at the lowest concentration signs of irritation (red or brown spots around the snout, nose, or eyes) were recorded. The relevance of these findings is unclear, as similar observations have not been reported at a comparable dose level in other studies. Other adverse effects were not reported, however, only organs with neurological relevance were subject to pathological examination in this study.

Chronic (without carcinogenicity)

Chronic experiments over two years in mice and rats (0, 200, 600 und 1800 ppm per whole body exposure) are reported in (NTP, 1998) or (Chhabra et al., 1998). These studies were performed primarily as carcinogenicity studies, i.e. with a reduced spectrum of examined parameters. For example, no organ weights were determined, and haematological or clinico-chemical investigations were left out. However, a full histopathological examination was carried out.

Neoplastic and pre-neoplastic lesions are discussed below in the section on carcinogenicity. Apart from (pre-)neoplasms, no further adverse effects were seen in rats. Almost all male animals (but also between 84 and 96% of all females) displayed signs of nephropathy. However, no remarkable differences were found between animals form the control and treated groups.

At the highest concentration, narcosis was seen in mice. Survival rate in males of the highest dose group was significantly reduced, which was attributed by the study authors to the lesions of the urogenital tract found in males at this dose level (increased incidence of 'suppurative inflammation' of kidney, prostate, and foreskin; hydronephrosis; hyperplasia of the epithelium of the urinary bladder).

In summary, for effects other than (pre-)neoplastic lesions, the respective NOAECs were 1800 ppm (rats) and 600 ppm (mice).

7.9.4.3. Repeated dose toxicity: dermal

No repeat-dose studies with dermal administration are available.

7.9.4.4. Repeated dose toxicity: other routes

No data for other routes are available.

7.9.4.5. Human information

No human repeat-dose data were evaluated.

7.9.5. Mutagenicity

7.9.5.1. Non-human information

A comprehensive database is available for this endpoint. The following studies were considered in this evaluation: (Abbott et al., 1991; [redacted] 1979a; [redacted] 1979b; [redacted] 2010; Galloway et al., 1987; Hatch et al., 1983; Hermida et al., 2006; Loureiro et al., 2005; Matthews et al., 1993; McMahon et al., 1979; Mirsalis et al., 1983; Mortelmans et al., 1986; NTP, 1998; Shelby and Witt, 1995; Valencia et al., 1985). These studies were only subject to cursory assessment, because several reviews [e.g. (ECHA, 2010a; NTP, 1998; US EPA, 2012)] had already concluded that they do not point at a genotoxic effect of THF.

The only exception is the study by (Hatch et al., 1983), which reports a positive test result with THF in a ‚DNA viral transformation test' in embryonic cells of the Syrian hamster. However, while the same authors have published the results for other test substances in more extensive publications, only an abstract of a presentation is available, and the absence of any detailed information on the experimental results makes it impossible to judge on its relevance.

(Loureiro et al., 2005) and (Hermida et al., 2006) demonstrated that THF can form adducts with DNA bases *in vitro* following metabolisation to 4-hydroxybutanal. The relevance of these findings *in vivo* is however unclear.

7.9.5.2. Human information

No human data on mutagenicity were available.

7.9.5.3. Summary and discussion of mutagenicity

The available data do not suggest a genotoxic potential of THF.

7.9.6. Carcinogenicity

7.9.6.1. Non-human information

Carcinogenicity: oral

No oral carcinogenicity data were available for this evaluation.

Carcinogenicity: inhalation

For this endpoint, the following studies were considered: (Alden, 1986; Bahnemann, 2000; [redacted] 1998; [redacted] 2009; Bruner et al., 2010; Chhabra et al., 1998; Fenner-Crisp et al., 2011; French MSCA, 2009; Gamer et al., 2002; Hard et al., 2013; Hard et al., 2012; IARC, 1999; Lock and Hard, 2004; Melnick et al., 1996; Seely and Hard, 2008; Swenberg and Lehman-McKeeman, 1999; Van Ravenzwaay et al., 2003). (Bruner et al., 2010) apparently

is the published version of ([redacted] 2009), while (Chhabra et al., 1998) presents the results of (NTP, 1998).

In the original NTP studies [(Chhabra et al., 1998; NTP, 1998)], a substance-related increase in kidney tumours in male rats and in liver tumours in female mice was diagnosed.

Kidney lesions in male rats

First, non-neoplastic kidney lesions in rats as observed in (NTP, 1998) are presented in Table 12.

Table 12 Non-neoplastic kidney lesions in male rats after exposure to THF via inhalation for two years [reproduced from (NTP, 1998)]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	3 (6%)	3 (6%)	2 (4%)	5 (10%)
Fibrosis	1 (2%)			
Inflammation, suppurative				1 (2%)
Metaplasia, osseous				1 (2%)
Nephropathy, chronic	48 (96%)	50 (100%)	50 (100%)	50 (100%)
Thrombosis	1 (2%)		1 (2%)	3 (6%)
Cortex, necrosis			1 (2%)	3 (6%)
Pelvis, dilatation	2 (4%)	1 (2%)		
Pelvis, transitional epithelium, hyperplasia	16 (32%)	13 (26%)	16 (32%)	18 (36%)
Pelvis, transitional epithelium, inflammation, suppurative		1 (2%)		1 (2%)
Renal tubule, degeneration	1 (2%)			
Renal tubule, hyperplasia	7 (14%)	5 (10%)	6 (12%)	7 (14%)
Renal tubule, inflammation, suppurative	1 (2%)			
Renal tubule, mineralization	8 (16%)	7 (14%)	2 (4%)	5 (10%)
Renal tubule, pigmentation, hemosiderin				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Hemorrhage	2 (4%)	1 (2%)		2 (4%)
Inflammation, suppurative	2 (4%)	1 (2%)		
Transitional epithelium, hyperplasia	2 (4%)	1 (2%)		3 (6%)

With respect to chronic-progressive nephropathy (CPN), no relevant difference between controls and treated groups is seen. This is also visible in a more differentiated presentation of CPN severity (Table 13).

Table 13 Degree of CPN severity in rats for controls and treated groups [(NTP, 1998), reproduced from (Bruner et al., 2010)]

Group incidence and severity of chronic progressive nephropathy (CPN) in the 2-year carcinogenicity study of tetrahydrofuran (reproduced from Hard, 2005).

Dose (ppm)	Number of animals per group	Number of animals examined	Severity grade of CPN[a]								
			0	1	2	3	4	5	6	7	8
Males											
0	50	48	0[b]	2	0	2	4	4	14	9	13
			(0)	(4)	(0)	(4)	(8)	(8)	(29)	(19)	(27)
1800	50	48	0	0	0	0	1	8	18	8	13
			(0)	(0)	(0)	(0)	(2)	(17)	(38)	(17)	(27)
Females											
0	50	47	0	0	1	8	18	13	6	1	0
			(0)	(0)	(2)	(17)	(38)	(28)	(13)	(2)	(0)
1800	50	49	0	1	2	8	19	11	7	1	0
			(0)	(2)	(4)	(16)	(38)	(22)	(14)	(2)	(0)

[a] 0, no lesions; 1, minimal; 2, mild; 3, low-moderate; 4, mid-moderate; 5, high-moderate; 6, low-severe; 7, high-severe; 8, end-stage.
[b] Number of animals diagnosed with severity grade of CPN; percentage in parenthesis.

On this somewhat arbitrary scale, male controls show a mean degree of severity of 6.2, vs. 6.5 in the 1800 ppm group. Overall, female animals have a lesser mean degree of severity, but again without a treatment-related difference (controls: 4.4, 1800 ppm: 4.3).

Table 14 (neoplasms) shows an increased number of adenomas at ≥ 600 ppm, at 1800 ppm also two carcinomas were diagnosed. It is obvious that neither incidence nor degree

of CPN differ between treated groups and controls. Counting adenomas and carcinomas together, a dose-related trend ($p < 0.04$) of increase in incidence is found.

Table 14 Neoplastic lesions in the kidney of male rats after exposure to THF via inhalation for two years [reproduced from (NTP, 1998)]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Number Examined Microscopically	50	50	50	50
Nephropathy, Chronic[a]	48 (3.0)[b]	50 (2.9)	50 (3.1)	50 (3.0)
Renal Tubule, Adenoma				
Overall rate[c]	1/50 (2%)	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted rate[d]	8.3%	16.7%	18.8%	18.6%
Terminal rate[e]	1/12 (8%)	1/6 (17%)	0/5 (0%)	0/6 (0%)
First incidence (days)	733 (T)	733 (T)	631	668
Logistic regression test[f]	P=0.213	P=0.602	P=0.159	P=0.262
Renal Tubule, Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Renal Tubule, Adenoma or Carcinoma[g]				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	8.3%	16.7%	18.8%	38.3%
Terminal rate	1/12 (8%)	1/6 (17%)	0/5 (0%)	1/6 (17%)
First incidence (days)	733 (T)	733 (T)	631	668
Logistic regression test	P=0.037	P=0.602	P=0.159	P=0.065

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals with kidney examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[g] Historical incidence for 2-year NTP inhalation studies with chamber controls (mean ± standard deviation): 6/652 (0.9% ± 1.3%); range, 0%-4%

An international expert working group of (industry) pathologists has reviewed these findings based on the original tissue samples ([redacted] 2009; Bruner et al., 2010). The group concluded that a) neoplasms originally categorised as carcinomas should be re-classified as adenomas and b) differentiation between ‚simple' and ‚atypical' (i.e. pre-neoplastic) hyperplasia (ATH) was required. The results of this re-evaluation are given in Table 15.

Table 15 Re-classification of the kidney lesions in male rats in (NTP, 1998) acc. to an international expert group of industry pathologists ['PWG', (Bruner et al., 2010)]

Summary of diagnoses of male F344 rat kidney lesions from the 2-year study of tetrahydrofuran (THF) conducted by NTP (NTP Study No. 05181-03). Comparison of NTP and PWG findings.

Kidney lesion	THF exposure groups			
	0 ppm	200 ppm	600 ppm	1800 ppm
	NTP observations[a]			
	(50)[b]	(50)	(50)	(50)
Adenoma, renal tubule	1[c]	1	4	3
Carcinoma, renal tubule	0	0	0	2
Hyperplasia, renal tubule	5	5	6	7
CPN[d]	48	50	50	50
Minimal	6	–	–	1
Mild	11	–	–	19
Moderate	11	–	–	9
Severe	21	–	–	21
	PWG findings			
	(50)[b]	(5)	(9)	(50)
Adenoma, renal tubule	2	0	2	7
Hyperplasia, renal tubule	4	2	4	1
CPN	49	–	–	50
Minimal	6	–	–	5
Mild	12	–	–	16
Moderate	12	–	–	9
Severe	19	–	–	20

[a] Data reproduced from tabulated summaries provided by the NTP.
[b] Number of animals examined.
[c] Lesion incidence.
[d] CPN, chronic progressive nephropathy. The NTP severity grades for groups 2 and 3 have not been included.

Also here, no relevant difference in severity of CPN is observed. On this – again arbitrary – four-step scale controls show a mean degree of severity of 2.9, while the 1800 ppm group displays a lower mean severity of only 1.9. The incidence of hyperplasia under 'PWG findings' refers to ATH only. Still the total number of adenomas in the 1800 ppm group is increased, as is the combined incidence of adenoma and hyperplasia.

On the other hand, if ATH and adenomas are seen as a continuum, only a minimal increase of these lesions is found overall. A trend test resulted in a p-value of > 0.05. At the same time, the degree of severity clearly is shifted towards adenoma. As in Table 16 only the highest dose group shows this effect clearly, the medium dose (600 ppm) is set as NOAEC.

In summary, at 1800 ppm a slight increase in combined incidence and severity of pre-neoplastic and (benign) neoplastic lesions was observed, the NOAEC was 600 ppm.

It is noted that on first sight the incidence of (pre-neoplastic) ATH in the controls was unusually high. (Hard et al., 2012) analysed a possible association between ATH and severity of CPN (using an 8-step scale) in the control groups of previous NTP studies. Also the controls in (NTP, 1998), were examined and for male rats, a degree of severity of 6.5 ± 1.5 is reported. For this CPN severity an ATH incidence of 8% still appears quite high, but not completely unrealistic (Table 16).

Table 16 Correlation between CPN severity and the incidence of Atypical Tubular Hyperplasia [ATH; reproduced from (Hard et al., 2012)]

	Grade of CPN severity								
Lesion type	0	1	2	3	4	5	6	7	8
Males									
CPN[a]	0	3	22	11	24	189	402	415	170
ATH	0	0	0	0	0	0	1 (0.3)	19 (4.6)	23 (13.5)
Adenoma	0	0	0	0	0	0	1 (0.3)	7 (1.7)	18 (10.6)
Carcinoma	0	0	0	0	0	0	0	0	0
Combined ATH and RTT	0	0	0	0	0	0	2 (0.5)	26 (6.3)	41 (24.1)
Females									
CPN[a]	14	45	93	79	130	343	306	139	6
ATH	0	0	0	0	0	0	1 (0.3)	4 (2.9)	0
Adenoma	0	0	0	0	0	0	0	1 (0.7)	1 (16.7)
Carcinoma	0	0	0	0	0	1 (0.3)	0	0	0
Combined ATH and RTT	0	0	0	0	0	1 (0.3)	1 (0.3)	5 (3.6)	1 (16.7)
Both sexes combined									
CPN[a]	14	48	115	90	154	532	708	554	176
ATH	0	0	0	0	0	0	2 (0.3)	23 (4.2)	23 (13.1)
Adenoma	0	0	0	0	0	0	1 (0.1)	8 (1.4)	19 (10.8)
Carcinoma	0	0	0	0	0	1 (0.2)	0	0	0
Combined ATH and RTT	0	0	0	0	0	1 (0.2)	3 (0.4)	31 (5.6)	42 (24.0)

Percentage incidence shown in parentheses.
Abbreviations: ATH, atypical hyperplastic lesions; CPN, chronic progressive nephropathy; RTT, renal tubule tumors.
[a] Number of rats for each severity grade.

Fibroadenomas in the mammary glands of female rats

In female rats, an increased incidence of fibroadenomas was observed at ≥ 600 ppm (Table 17).

Table 17 Incidence of fibroadenomas in the mammary glands of female rats after exposure to THF via inhalation for 2 years [(NTP, 1998)]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Mammary Gland: Fibroadenoma				
Overall rate	23/50 (46%)	22/50 (44%)	29/50 (58%)	31/50 (62%)
Adjusted rate	68.8%	61.3%	73.1%	79.3%
Terminal rate	15/25 (60%)	12/25 (48%)	16/26 (62%)	18/26 (69%)
First incidence (days)	634	478	519	478
Life table test	P=0.066	P=0.468N	P=0.227	P=0.113
Logistic regression test	P=0.031	P=0.478N	P=0.211	P=0.056
Cochran-Armitage test	P=0.038			
Fisher exact test		P=0.500N	P=0.158	P=0.080

For this finding, already in-study controls showed a clearly higher incidence than historical controls (27.6 ± 7.7%). Nevertheless, a dose-related trend with $p < 0.05$ is noted in two out of three trend tests. In the background document to their Final Opinion on the Classification and Labelling of THF (ECHA, 2010a) the RAC concludes:

> *'Mammary gland fibroadenoma is a relatively common benign tumour finding in female Fischer 344 rats (NTP historical control range relevant to the THF study was 16 - 42%). There was a marginally positive treatment-related trend for this tumour type with female rat exposure to THF (NTP, 1998). However, pair wise comparisons were not statistically significant. In addition, the concurrent control group also gave a tumour frequency above the historical control range. It seems doubtful, therefore, that the findings in the mammary gland were toxicologically significant.'*

The authors of the original study (NTP, 1998) argue:

> *'The incidences of fibroadenoma in female rats exposed to 600 or 1,800 ppm tetrahydrofuran were slightly greater than those in the chamber controls (chamber controls, 23/50; 200 ppm, 22/50; 600 ppm, 29/50; 1,800 ppm, 31/50; Table B3).*

The trend was marginally significant (P < 0.031), but the pairwise comparisons were not. The neoplasm incidences in all groups (including chamber controls) exceeded the historical control range for this neoplasm in NTP inhalation studies [...]. *These high neoplasm incidences were likely due to the fact that the animals in this study were unusually heavy, and the incidence of mammary gland fibroadenoma is strongly correlated with body weight* [...]. *There was also no evidence of an increase in the incidences of malignant mammary gland neoplasms in female rats (5/50, 5/50, 5/50, 3/50* [...]*). Male rats exposed to 1,800 ppm also had a slightly greater incidence of mammary gland fibroadenoma than that in the chamber controls (0/50, 2/50, 3/50, 4/50* [...]*), but this difference was not statistically significant. Neither of these marginal increases in mammary gland neoplasm incidences were considered to be chemical related.'*

Given the above uncertainties, these findings were therefore not considered for DNEL derivation by the eMSCA. In terms of classification/labelling for carcinogenicity, the existing harmonised classification as Carc. Cat. 2 already reflects the potential relevance, but also the doubts about this relevance, of all neoplasms observed in the animals studies for humans.

Liver lesions in female mice

Table 18 presents the incidences of non-neoplastic and neoplastic lesions in the liver of female mice as a consequence of chronic treatment with THF via inhalation. Already from 200 ppm upwards

- the incidence of hepatocellular adenomas,
- the incidence of hepatocellular carcinomas, and
- the combined incidence of adenomas and carcinomas

were increased. In the highest dose group (1800 ppm) the incidence of multiple adenomas and carcinomas was clearly increased.

Table 18 Neoplastic and non-neoplastic lesions of the liver in female B6C3F1 mice following exposure to THF via inhalation for two years [reproduced from (NTP, 1998)]

	Chamber Control	200 ppm	600 ppm	1,800 ppm
Female				
Number Examined Microscopically	50	50	50	48
Eosinophilic Focus	7	9	7	11
Hematopoietic Cell Proliferation	0	1 (2.0)	2 (2.5)	3 (1.7)
Necrosis	3 (2.0)	0	0	7 (1.9)
Hepatocellular Adenoma (includes multiple)				
Overall rate	12/50 (24%)	17/50 (34%)	18/50 (36%)	31/48 (65%)
Adjusted rate	35.9%	47.1%	52.5%	76.8%
Terminal rate	8/29 (28%)	14/33 (42%)	11/26 (42%)	23/32 (72%)
First incidence (days)	648	640	469	399
Logistic regression test	P<0.001	P=0.249	P=0.188	P<0.001
Hepatocellular Adenoma, Multiple				
Overall rate	2/50 (4%)	3/50 (6%)	5/50 (10%)	12/48 (25%)
Hepatocellular Carcinoma (includes multiple)				
Overall rate	6/50 (12%)	10/50 (20%)	10/50 (20%)	16/48 (33%)
Adjusted rate	16.5%	26.3%	30.0%	40.8%
Terminal rate	2/29 (7%)	6/33 (18%)	5/26 (19%)	10/32 (31%)
First incidence (days)	478	552	544	562
Logistic regression test	P=0.012	P=0.234	P=0.229	P=0.014
Hepatocullular Carcinoma, Multiple				
Overall rate	2/50 (4%)	4/50 (8%)	1/50 (2%)	6/48 (13%)
Hepatocellular Adenoma or Carcinoma[i]				
Overall rate	17/50 (34%)	24/50 (48%)	26/50 (52%)	41/48 (85%)
Adjusted rate	46.3%	61.3%	69.1%	93.0%
Terminal rate	10/29 (34%)	18/33 (55%)	15/26 (58%)	29/32 (91%)
First incidence (days)	478	552	469	399
Logistic regression test	P<0.001	P=0.188	P=0.086	P<0.001

a Number of animals with lesion
b Average severity of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
c Historical incidence for 2-year NTP inhalation studies with chamber controls (mean ± standard deviation): 200/947 (21.1% ± 11.6%); range, 4%-46%
d Number of animals with neoplasm per number of animals with liver examined microscopically
e Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
f Observed incidence in animals surviving until the end of the study
g In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards lesions in animals dying prior to kill as nonfatal. A negative trend or lower incidence in an exposure group is indicated by N.
h Historical incidence: 358/947 (37.8% ± 12.5%); range, 11%-60%
i Historical incidence: 200/937 (21.3% ± 11.9%); range, 3%-54%

By comparison, Table 18 shows historical control incidences. In (NTP, 1998), in-study controls were close to the historical mean for carcinomas, and about one standard deviation above mean for adenomas and for adenomas and carcinomas combined. At 200 and 600 ppm, incidences already were (sometimes more than) two standard deviations above the historical control mean, just below the upper bound of the historical control range. At 1800 ppm incidences were clearly outside the historical control range.

Table 19 Occurrence of liver tumours in female B6C3F1 mice in chronic NTP studies (NTP, 1998)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	11/49	4/49	15/49
Acetonitrile	4/49	7/49	9/49
Allyl Glycidyl Ether	1/50	5/50	6/50
2-Chloroacetophenone	4/50	8/50	12/50
l-Epinephrine Hydrochloride	2/50	1/50	3/50
Chloroethane	0/49	3/49	3/49
Hexachlorocyclopentadiene	5/49	4/49	9/49
CS2 (*o*-Chlorobenzalmalononitrile)	4/50	7/50	11/50
Ozone	20/50	15/50	27/50
Total	51/446 (11.4%)	54/446 (12.1%)	95/446 (21.3%)
Standard deviation	12.5%	8.1%	14.8%
Range	0%-40%	2%-30%	6%-54%
Overall Historical Incidence			
Total	114/937 (12.2%)	103/937 (11.0%)	200/937 (21.3%)
Standard deviation	9.7%	6.7%	11.9%
Range	0%-40%	0%-30%	3%-54%

[a] Data as of 12 May 1995

According to the NTP study report, for all listed parameters (adenoma, carcinoma, adenoma + carcinoma) a statistically significant, dose-related trend was found. On the other hand, in pairwise comparisons of treated groups with controls, statistical significance with $p < 0.05$ was only attained for the highest dose group. However, from a scientific point of view, such a pairwise comparison only provides limited information because it ignores both the whole dose-response relationship and the sample character of individual dose groups (i.e. the random nature of that sample and the limits of its representativeness for 'all rats'). Thus, whenever possible, always the complete dose-response relationship should be considered. On the other hand, as incidences at the low- and mid-dose were inside the historical control range, it appears prudent in the present case to set the mid-dose of 600 ppm as the NOAEC for liver tumour formation in female mice after chronic inhalation of THF.

Mechanistic considerations

Kidney tumours in male rats

Based on the comprehensive database on mutagenicity, a direct genotoxic effect of THF appears unlikely. The available data support the assumption that THF stimulates tumorigenesis by an increase in cell proliferation. While not ultimately proven, such a mode of action is generally assumed to be associated with a threshold and thus, derivation of a derived minimal effect level (DMEL) is not required.

Against the background of these more general considerations the available literature extensively discusses whether an exact mechanism can be identified and whether this may or may not allow for a conclusion on the relevance of this mechanism for humans.

α2u-globulin associated nephropathy

(Swenberg and Lehman-McKeeman, 1999) have described α2u-globulin associated nephropathy as a mechanism of carcinogenesis in the renal tubuli of male rats. α2u-Globulin is a protein which is formed in male rats with high species- and sex-specificity. If a plausible justification is given that kidney tumours observed in a carcinogenicity study in male rats can be reliably and without doubt be traced back to this mechanism, then,

according to the current scientific tenet, relevance for humans is unlikely. In (IARC, 1999) the criteria are given which must be met to arrive at this conclusion:

1. *Lack of genotoxic activity (agent and/or metabolite) based on an overall evaluation of in-vitro and in-vivo data*
2. *Male rat specificity for nephropathy and renal tumorigenicity*
3. *Induction of the characteristic sequence of histopathological changes in shorter-term studies, of which protein droplet accumulation is obligatory*
4. *Identification of the protein accumulating in tubule cells as α2u-globulin*
5. *Reversible binding of the chemical or metabolite to α2u-globulin*
6. *Induction of sustained increased cell proliferation in the renal cortex*
7. *Similarities in dose–response relationship of the tumour outcome with the histopathological end-points (protein droplets, α2u-globulin accumulation, cell proliferation)*

For THF these criteria are not completely fulfilled:

- Also in male mice dose-related effects on kidney and urogenital tract were observed [albeit no kidney tumours, (NTP, 1998)].
- Vacuolisation of protein was found in sections of kidney tissue in all relevant studies, but only in some of these studies α2u-globulin was reliably identified via immune-histochemical staining.
- (Reversible) Binding of THF to α2u-globulin was not demonstrated.
- Likewise, similarities in the dose-response relationship between α2u-globulin accumulation and the histopathological endpoints were not sufficiently demonstrated.

In addition, (Melnick et al., 1996) point out that the causality of α2u-globulin accumulation for the increase in cell proliferation and formation of adenoma is possible, but not finally proven. Alternatively this finding could be (a male rat-specific) observation accompanying another, not necessarily rat-specific, mechanism.

Chronic-progressive nephropathy

Another possible mechanism for the observed kidney lesions in male rats might be found in an amplification of an existing CPN by THF. From the results of (NTP, 1998), however, such an exacerbation is not evident (cf. section 7.9.4):

- Overall, the severity of CPN was amplified neither in male, nor in female rats.
- Consequently, in this study there was also no correlation between severity of CPN and incidence of ATH and/or adenomas.

In summary, therefore, a mechanism for the generation of kidney tumours in male rats cannot be established with sufficient certainty. As a consequence the relevance of these tumours for humans cannot be ruled out with sufficient certainty. This view is supported by (ECHA, 2010a) (Background Paper to the RAC opinion on the classification/labelling of THF):

> *'The Risk Assessment Committee, however, found that definitive evidence for either of these 2 non-genotoxic mechanisms being involved was lacking. It was therefore not possible to dismiss this carcinogenic hazard in considering the classification of THF.'*

Liver tumours in female mice

It is known that the mouse strain used in the NTP studies ($B6C3F_1$) displays a comparatively high spontaneous tumour rate with respect to neoplasms of the liver. The results from (NTP, 1998), at least in the high dose group, show incidences clearly outside the historical control range. However, in the absence of observed genotoxicity, a threshold mechanism is assumed.

In principle, according to the rules for dealing with historical controls as provided in section 3.6.2.3.2 (a) on page 304 of the „Guidance on the Application of the CLP Criteria" (http://echa.europa.eu/documents/10162/13562/clp_en.pdf), the liver tumours in mice would need to be considered for classification and labelling purposes. Further below in the same document the following statement is made:

> *„Where the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories […]".*

It is noted that in the available toxicological database, further (kidney) tumours in rats were noted which could in fact be seen as 'supplementary evidence' for the carcinogenic potential.

On the other hand, (ECHA, 2010a) did not assess the tumours in mice as relevant for humans. The high spontaneous rate in the respective mouse strain is given as the main justification.

On summary, there are at least substantial doubts about whether the liver tumours in mice should be used as a basis for risk assessment in humans and these doubts are correctly reflected by the current classification/labelling of THF as Carc. Cat. 2.

In terms of quantitative risk assessment, the question of whether or not the liver tumours in mice are considered as relevant is of a secondary nature as the NOAEC for these effects (600 ppm) is the same as that for narcosis. Thus a DNEL derived from this Point of Departure (PoD) is protective of both.

Carcinogenicity: dermal

No dermal carcinogenicity data were available for this evaluation.

7.9.6.2. Human information

No human carcinogenicity data were available for this evaluation.

7.9.6.3. Summary of carcinogenicity

In summary, the current classification and labelling for THF as a category 2 carcinogen as assigned by the RAC in 2010 is confirmed. Although a number of newer publications has been evaluated in the context of this SEV, neither ultimate confirmation of the relevance of the observed tumours in rats and mice for humans nor the opposite was possible.

While the mechanisms responsible for THF-related tumorigenesis still are not fully elucidated, the available database points at the stimulation of cell proliferation as a relevant factor. In light of a comprehensive database of genotoxicity studies showing no genotoxic potential of THF, it appears prudent to assume that a threshold dose/concentration can be assumed, below which no carcinogenicity will be observed.

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

The following study reports were considered for this evaluation: (1994; 1980; Hellwig et al., 2002; Mast et al., 1989; Mast et al., 1992; 1988). (Hellwig et al., 2002) apparently is the published version of (

1996). (Mast et al., 1992) is the published version of ([redacted] 1988), and at least parts of this work have also been reported in (Mast et al., 1989).

7.9.7.1. Effects on fertility

Non-human information

Both in a one- ([redacted] 1994) and a two-generation study [(Hellwig et al., 2002) or ([redacted] 1996)], THF was administered via drinking water.

In ([redacted] 1994) rats received 0, 4000, 8000, or 12000 ppm. In both sexes during pre-mating (7 weeks) and in females during gestation this was equivalent to dose levels of ca. 0, 450, 800, or 1100 mg/kg bw/d. During lactation, uptake of THF by F0 females was 0, 714, 1264, or 1847 mg/kg bw/d, respectively. In the mid- and high-dose groups animals of both sexes showed a clear, statistically significant reduction in water intake during all phases of substance treatment. Feed intake of males was slightly reduced pre-mating, but overall the parental generation did not display a treatment-related effect on body weight. Relative kidney weight was statistically significantly increased in males of the high- and females of the mid- and high-dose groups. No substance-related effects on reproductive outcome were observed. Body weight development was statistically significantly reduced in the offspring of the mid- and high-dose groups. The NOAEL in this study was 450 mg/kg bw/d.

In the two-generation study by (Hellwig et al., 2002) administered drinking water concentrations were 0, 1000, 3000, and 9000 ppm (equivalent to ca. 0, 100, 300, and 700 mg/kg bw/d before mating, 100, 300, and 800 mg/kg bw/d in females during gestation and 200, 500, and 1300 mg/kg bw/d in females during lactation). At 9000 ppm, water and feed intake were reduced in both parental generations in all phases of the study. In addition, females of the F0 (all study phases) and the F1 generation (lactation) displayed reduced body weight development. Increased absolute and relative kidney weight was noted in male and female animals of the 9000 ppm group, but these findings did not have a histopathological correlate. THF treatment had no effect on reproduction parameters. Offspring of both generations showed a slightly (< 10%) reduced body weight development during lactation. Otherwise no detrimental effects of THF treatment on offspring development were observed, apart from a slightly higher incidence of delayed eye opening on gestation day (GD) 15 in F1 pups. However the toxicological relevance of this finding in isolation is considered low.

Human information

No human data were available for this endpoint.

7.9.7.2. Developmental toxicity

Non-human information

The available studies used administration via inhalation. In a pilot study ([redacted] 1980), 6-7 rats per group (control: 14) were treated with THF concentrations of 0, 200, 500, 1000, 2500, or 5000 ppm on GDs 6-15. From 1000 ppm sedation in the form of a reduced reaction to an acoustic stimulus was observed in the mothers, at 5000 ppm lethargy and coordination problems were noted, accompanied by a complete absence of a reaction to an acoustic signal. At this concentration, pup weight was reduced; ossification of the sternum was less progressed than in the controls. The NOAEC for maternal toxicity was 500 ppm, while it was 2500 ppm for embryotoxicity.

(Mast et al., 1992) [or (Mast et al., 1989; [redacted] 1988), respectively] exposed rats and mice on GDs 6-19 (rats) or 6-17 (mice) by inhalation to concentrations of 0, 600, 1800, or 5000 ppm. In both experiments pregnant and non-pregnant females were treated.

In rats, maternal body weight was significantly reduced in the highest dose group on GD 20. This effect was not observed in virgin females. At the same concentration, also body weight in pups of both sexes was significantly reduced. The NOAEC for maternal and embryotoxicity was 1800 ppm.

In mice, treatment with 5000 ppm was stopped on GD 11 because of high mortality; a total of 25-30% of both pregnant and non-pregnant females died at this concentration. From 1800 ppm narcosis was observed, body and uterus weight of pregnant females were reduced at this concentration. At and above 1800 ppm also the number of viable foetuses per litter was diminished and the number of resorptions was increased; at 5000 ppm only a single litter with liveborn pups remained. The NOAEC for maternal and embryotoxicity obtained from this study was 600 ppm.

Human information

No human data for this endpoint were available.

7.9.7.3. Summary and discussion of reproductive toxicity

Treatment of rats and mice with THF did not cause effects on fertility or teratogenicity. In the presence of maternal toxicity manifested as body weight reduction and/or narcosis, also pup weights were reduced. At a comparatively high concentration of 5000 ppm, in mice severe maternal and embryotoxicity was observed. The overall NOAEC from these studies is 600 ppm based on the results from pre-natal development study in mice.

7.9.8. Endocrine disrupting properties

Neither the effects observed in the regular toxicity studies with THF nor any other available information pointed at a specific endocrine mechanism of action of this chemical. Therefore, no specific evaluation of endocrine disrupting properties was performed.

7.9.9. Other effects

7.9.9.1. Non-human information

Neurotoxicity

For this endpoint, the following studies were available: (Kawata et al., 1986; Maher et al., 2003; Malley et al., 2001; Werawattanachai et al., 2007). The results of the acute and subchronic inhalation study by (Malley et al., 2001) have already been reported above.

(Kawata et al., 1986) investigated catecholamine levels in the rat brain following administration by inhalation of THF concentrations of 3000 or 15000 ppm over various durations. At 15000 ppm noradrenaline (NA) levels decreased immediately and significantly, while dopamine (DA) levels were increased. Following inhalation of 3000 ppm for 3 h/d, 5 d/wk, NA and DA levels were significantly increased, an effect, which was more prominent after 18 than after 8 wk of exposure.

(Maher et al., 2003) determined the TD_{50} for the rotarod test (692 mg/kg bw) and the righting reflex (489 mg/kg bw) in mice after administration of 300-1000 mg/kg bw *i.p.* In (Werawattanachai et al., 2007) this work was continued; a development of tolerance with respect to the sedative/narcotic effect after THF pre-treatment for 14 days was reported. Due to the route of administration, however, the obtained results cannot be used for quantitative risk assessment.

Immunotoxicity

No data were available for this endpoint.

Specific investigations: other studies

No other studies were available for this endpoint.

7.9.9.2. Human information

Reports of intoxications of humans are comparatively rare, symptoms can be tracked only rarely to THF beyond doubt [e.g. (Garnier et al., 1989)]. Some publications describe the effect of THF in conjunction with other factors such as anaesthesia (Juntunen et al., 1984) or disease (Van Vlierberghe, 1995). (Muttray et al., 2006) report a case of anosmia and rhinitis which appears to support the experimental findings of Ohashi and others with respect to damage of the airway epithelium in animals; however, the respective patient was also exposed to other solvents and thus a link to THF cannot be established without reasonable doubt.

In all of the above cases there are no reliable data on the amount of THF inhaled/ingested, therefore, derivation of DNELs should be performed based on the available animal studies.

7.9.9.3. Summary and discussion of specific investigations

Overall, no information with direct relevance to quantitative risk assessment was obtained from the additional studies covered in this section.

7.9.10. Combined effects

Not evaluated in this dossier

7.9.11. Hazard assessment of physico-chemical properties

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 physico-chemical properties of the reported substance. Chapter 6.3 ("Risk Characterization") specifically mentions the need to assess the likelihood and severity of an event occurring due to the physico-chemical properties of the substance.

7.9.11.1. Explosivity because of formation of peroxides

According to the available information in the dossier, tetrahydrofuran may form explosive peroxides (classification R19 under Directive 67/548/EEC and the labelling EUH019 under Regulation 1272/2008 (CLP GHS)). This is a property that has to be considered in the risk assessment and risk characterisation.

For most applications, a technical grade THF will be used. For such grades it is common practice to add stabilizing substances that, under normal use conditions, will prevent the formation of peroxides. Therefore, in these cases the risk of explosion because of peroxide formation can be considered to be negligible.

However, the uses of THF listed by the Registrant(s), may give rise to situations where the stabilisation will be diminished. For example, distillation or reprocessing of solvent mixtures may lead to a product that is no longer sufficiently stabilised. In such cases peroxide formation is a risk that needs to be specifically considered.

In order to be able to assess such a risk, the dossier should indicate in which uses a diminished stabilisation (and the risk of peroxide formation) may occur. The Registrant(s) delivered information on scenarios that are relevant in this respect. Therefore, the eMSCA regards this risk as properly controlled.

7.9.11.2. Flammability and formation of explosive solvent/air mixtures

In the dossier, the flash point of tetrahydrofuran is listed as -21.2°C. Tetrahydrofuran is therefore considered to be a Flammable Liquid - category 2 (Under EU GHS and UN GHS classification criteria) and R11 (under Directive 67/548/EEC classification criteria). The classification "highly flammable liquid and vapour" (R11 under Directive 67/548/EEC and H225 under Regulation 1272/2008 (CLP GHS)) indicates there exists the hazard of

formation of an explosive atmosphere. The Registrant(s) considered this in the risk assessment.

In this respect, the Registrant(s) gave information on the way how the substance is used (closed system, use in open containers, spraying, pouring, etc). In addition the Registrant(s) described how such risks of formation of an explosive air/vapour mixture may be minimised or eliminated (e.g. the maximum amount of use, the capacity of the air ventilation system, removal of effective ignition sources, use of explosion proof equipment, etc).

In the opinion of the eMSCA, uses where the following PROCs appear are considered to be likely to present such a risk of flammability / explosivity: PROC 5, 7, 8a, 10, 11, 13, 14, 15, 19, 20.

The information supplied in the THF dossier allows assessing the risks for above mentioned PROCs. Specific information (maximum amount of substance used in an application, air change rate, ignition sources) is given in a common Appendix by using the control banding approach of the German EMKG (easy-to-use-workplace control scheme). For scenarios for industrial use which are regulated by specific requirements under existing Seveso and ATEX directives (96/98/EC, resp. 94/9/EC and 99/92/EC), reference is made to these directives in the common Appendix. Adequate RMMs which prevent fire and explosion risks are communicated for each exposure scenario with fire and explosion risks.

THF is labelled as highly flammable (H225) and the formation of peroxide in high concentrated consumer products is likely. However, exposure scenarios for consumers do not give any indications on already implemented risk management measures. This prevents a conclusive assessment of risks related to these physico-chemical properties. Therefore, the Registrant(s) are required to provide information which product integrated risk management measures are applied to control the risks concerning the high flammability and peroxide formation of tetrahydrofuran during the use of consumer products.

After updating their registration dossiers in 2016 and 2017, the Registrant(s) recommended stabilisers to prevent peroxide formation and smaller containers (max. 1 L) with an opening not greater than 42 mm. These product integrated risk management measures cannot avoid incidents in general, but reduce the potential risk concerning flammability especially for products which contain THF in high concentrations.

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

7.9.12.1. Overview of typical dose descriptors for all endpoints

Overall, three effect types appear potentially relevant for determining the 'Points of Departure' (PoDs), i.e. those dose descriptors most relevant for deriving DNELs for THF:

- Acute sedation/narcosis
- Irritation
- Toxicity after repeated exposure (non-neoplastic/neoplastic)

As for irritation, quantitative risk assessment is possible neither for the target organ eye nor for the respiratory tract. Possible PoDs for narcosis and repeat-dose effects occurring in experimental animals following inhalation of THF are summarised in

Table 20. Concentrations in ppm (mL/m^3) can be converted to mg/m^3 using the molar mass of THF (72.1057 g/mol) and a molar volume of 24.1 L (at 20°C and 101.3 kPa). Thus, 1 ppm corresponds to 2.99, or ca. 3 mg/m^3.

Table 20

OVERVIEW OF AVAILABLE STARTING POINTS ('POINTS OF DEPARTURE', PoDs) FOR DNEL DERIVATION FOR INHALATION TOXICITY					
Study type	**Duration**	**NOAEC**	**LOAEC**	**Critical endpoint at LOAEC***	**Reference**
Studies in rats					
Acute neurotoxicity	Single	500	2500	Reduced reaction to acoustic stimulus	(Malley et al., 2001)
Subacute neurotoxicity	14 wk		1500		
Pre-natal development, pilot study	GD 6-15	500	1000	Reduced reaction to acoustic stimulus	([redacted] 1980)
Pre-natal development	GD 6-19	1800	5000	Reduced maternal and pup body weight	(Mast et al., 1989; Mast et al., 1992; [redacted] 1988)
Subchronic	12 wk	200	1000	Statistically significant increase in serum liver enzymes; narcosis	(Horiguchi et al., 1984; Katahira et al., 1982b)
Subchronic	14 wk	1800	5000	Narcosis, reduced thymus and spleen weight, clinical chemistry, forestomach lesions	(Chhabra et al., 1990)
Carcinogenicity	2 yr	600	1800	Slight increase in atypical hyperplasias and adenomas in the kidney (M)	(Chhabra et al., 1998; NTP, 1998)
Studies in mice					
Pre-natal development	GD 6-17	600	1800	Narcosis, reduced body and uterus weight of pregnant females, reduced number of viable foetuses per litter, and increased number of resorptions	(Mast et al., 1989; Mast et al., 1992; [redacted] 1988)
Subacute, mechanistic	5-20 exposures	600	1800	Cell proliferation in the liver	([redacted] 2001)
Subchronic	14 wk	600	1800	Narcosis**	(Chhabra et al., 1990)
Carcinogenicity	2 yr	600	1800	Narcosis, lesions of urogenital tract, reduced survival rate (M), adenomas and carcinomas of the liver (F)	(Chhabra et al., 1998; NTP, 1998)

* For effects at higher dose levels, cf. section 5; ** In contrast to the conclusion of the CSR, a moderate change in organ weights without corresponding histopathological changes in mice after exposure at 600 ppm after exposure for 14 weeks is not considered adverse.

Sedation/narcosis

In different studies in rats, a reduced reaction to an acoustic stimulus was reported at and above 1000 ppm [([redacted] 2001; [redacted] 1980)]. At ≥ 1800 ppm, mice displayed sedative/narcotic symptoms [(Chhabra et al., 1990; Mast et al., 1992; NTP, 1998), both

in the 14-wk and 2-yr studies]. The relevant NOAEC (from the studies in mice) was 600 ppm or ca. 1800 mg/m³.

Toxicity after repeated exposure

The PoD for acute sedation/narcosis of 600 ppm (ca. 1800 mg/m³, cf. previous section) also covers the effects observed in the pre-natal development study in mice [(Mast et al., 1992)] and those observed in the carcinogenicity studies in rats and mice [(NTP, 1998)], including neoplastic and non-neoplastic lesions.

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

DNELs for consumers

Narcosis

For narcotic effects, current THF levels in nervous tissue are relevant rather than the total body burden (e.g. as AUC). Given the lack of a reliable dose-response relationship for the respective tissue levels, the most appropriate way to account for this in the case of human exposure via inhalation is to express the DNEL as an external concentration and to compare it directly with the external human exposure concentration.

In line with the relevant REACH guidance, no allometric scaling is needed when using external concentrations as the relevant dose metric. Thus, the PoD for this endpoint needs to be corrected by an Assessment Factor (AF) of 2.5 for interspecies and a factor of 10 for intraspecies variation.

In the case of exposure via inhalation only, applying this overall AF of 25 to the established PoD of 600 ppm/1800 mg/m³ results in a

$$DNEL_{Inhalation,Narcosis} = 600 \text{ ppm}/25 = 24 \text{ ppm or ca. } 72 \text{ mg/m}^3$$

This DNEL is roughly two times lower than the one derived for the general public used by the Registrant(s) in the CSR (150 mg/m³, using a lower PoD of only 300 mg/m³ but also a much smaller AF of only 2, which is not in line with the REACH guidance).

The case of dermal exposure is however more complicated. For THF, no dermal studies are available which would allow for a direct conclusion on a ‚safe' dermal dose with respect to sedation/narcosis. In addition, flux rates derived from the study on dermal absorption ([redacted] 2005) are not reliable (cf. section 0).

In the view of the eMSCA, the closest approximation possible can be achieved by calculating the amount of THF taken up per unit time (h) in relation to body weight for the dermal route. This is achieved by dividing the dermal load (in mg/kg bw/d) by the duration of daily exposure (in h/d). It is noted that this approximation bears an element of uncertainty, as it assumes that the complete dermal load is already absorbed during the exposure event. This might be an overestimation, in particular for short event durations.

For the purpose of risk characterisation, dermal uptake (in mg/kg bw/h) can be compared with the DNEL for inhalation expressed in the same dose metric. In the absence of more specific data, this approach includes the assumption that both percentage and speed of absorption are identical for uptake via skin and inhalation. This might be an overestimation regarding the dermal part. Uptake of THF is assumed to be high along all routes (cf. section0). For inhalation of THF, no reliable data on the rate of absorption are available, but given the physical nature of the involved barriers, this rate is not likely to be lower than the one for the dermal route. However, uptake (at least initially) might occur faster via inhalation, while dermal absorption is normally associated with a certain lag time needed for crossing the skin barrier. Unfortunately, the data available from the study by ([redacted] 2005) does not allow for a reliable determination of this lag time.

For all exposures clearly exceeding the lag time it appears reasonable to assume that comparable steady state blood (and tissue) levels will be established via both routes. Uncertainty increases with decreasing exposure duration.

For transformation of the above inhalation DNEL of 72 mg/m³ to the mg/kg bw/h dose metric, 100% bioavailability of THF, a default human breathing rate of 1.37 m³/h, and a body weight of 60 kg are assumed, resulting in a

$$\text{Converted DNEL}_{\text{Inhalation,Narcosis}} = \text{Surrogate DNEL}_{\text{Dermal, Narcosis}} =$$

$$(72\ \text{mg/m}^3 \times 1.37\ \text{m}^3\text{/h})/60\ \text{kg bw} = 1.6\ \text{mg/kg bw/h}$$

Using this dose metric also allows for aggregate risk characterisation with respect to scenarios in which dermal exposure and inhalation occur simultaneously.

Other systemic effects

For other effects, such as e.g. the non-neoplastic lesions in the urogenital tract of mice following chronic exposure, rather total daily dose (in mg/kg bw/d) is the relevant dose metric.

The relevant DNEL for chronic exposure given as an external concentration is again 24 ppm or 72 mg/m³ (based on a PoD of 600 ppm/1800 mg/m³ and applying an overall AF of 25) for an exposure of 6 h/d, 5 d/wk (it would be 4 ppm or 12 mg/m³ for a 24 h/d, 7 d/wk exposure). This is slightly higher than the DNEL of 62 mg/m³ used by the Lead Registrant in the CSR.

Using the above defaults for human inhalation (1.37 m³/h, 100% bioavailability, 60 kg bw) and considering that in (NTP, 1998) mice were treated on a 5 d/wk basis, the chronic DNEL in mg/kg bw/d for a 7 d/wk exposure is:

$$\text{DNEL}_{\text{chronic}} = [(72\ \text{mg/m}^3 \times 1.37\ \text{m}^3\text{/h} \times 6\ \text{h/d})/60\ \text{kg bw}] \times 5/7 = 7\ \text{mg/kg bw/d}$$

This DNEL is ca. two times lower than the one derived by the Lead Registrant in the CSR (15 mg/kg bw/d). This DNEL can also be used for dermal risk characterisation by comparing it to the dermal burden (in mg/kg bw/d).

DNELs for Workers

The routes of occupational exposure to tetrahydrofuran are inhalation and dermal contact.

An IOEL for THF of 150 mg/m³ (8-hour TWA) exists and is derived based on local effects as reduction in ciliary beating in rabbit and irritation of the nose and eyes of the rat (SCOEL, 1992). An assessment of the results of the studies used for IOEL derivation is not possible because a detailed description of the experimental conditions are not available or only in Japanese. Furthermore these results are in contradiction with newer studies, in which no morphological damage in nasal or tracheal epithelium was reported after exposure of rats to THF for 14 weeks to 2 years (NTP, 1998).

Therefore, the long-term systemic DNELs were derived from the NOAEC obtained in a long-term 2-species (Fischer 344 rat and B6C3F1 mouse) inhalation bioassay with tetrahydrofuran by the US National Toxicology Program (NTP, 1998) (Table 21 and

Table **22**). The acute narcotic effects in mice were proven to be the most critical systemic effect. These derived DNELs were considered to be sufficiently protective also for chronic effects.

For the dermal route no data are available, hence the starting point for long-term dermal DNEL calculations is also the NOAEC obtained in the inhalation study.

In 2010 RAC evaluated the carcinogenic properties of tetrahydrofuran. Tetrahydrofuran was classified for carcinogenicity in category 2 due to significant doubts about the relevance to humans of all the experimental tumour findings and furthermore Tetrahydrofuran is non-genotoxic (RAC, 2010). Due to these uncertainties the DNEL derivation was not based on possible carcinogenic properties of THF. However, if the experimental tumour findings would be taken into account it would not lead to a lower DNEL.

Table 21

DNELlong-term CALCULATION – WORKER – INHALATION, SYSTEMIC EFFECT				
Exposure pattern	**Route**	**Descriptor**	**Value**	**Remarks**
Long-term systemic effect	Inhalation	Relevant dose descriptor	NOAEC: 1795 mg/m³	The NOAEC is based on a long-term inhalation bioassay in mice. The critical systemic effect appears to be narcosis at 600 ppm (= 1795 mg/m³).
		Modification of the relevant dose descriptor	$NOAEC_{worker}$= $NOAEC_{mouse}$ x 6/8 x 5/5 x 6.7/10	From study (mouse) to human (worker): hours per day (6 h → 8 h) and days per week (5 days → 5 days); Respiratory volume (8 h) normal (6.7 m³) to light activity (10 m³)
		Corrected dose descriptor	$NOAEC_{worker}$= 902 mg/m³	
		Assessment factor (AF)	**AF Value**	**Remarks**
		Dose response	1	
		Interspecies	2.5	Remaining differences
		Intraspecies	5	worker
		Exposure duration	1	
		Quality of database	1	
		DNEL	902 mg/m³ / (1 x 2.5 x 5 x 1 x 1) = **72 mg/m³**	

Table 22

DNELlong-term CALCULATION – WORKER – DERMAL, SYSTEMIC EFFECT				
Exposure pattern	**Route**	**Descriptor**	**Value**	**Remarks**
Long-term systemic effect	Dermal	Relevant dose descriptor	NOAEC: 1795 mg/m³	The NOAEC is based on a long-term inhalation bioassay in mice. The critical systemic effect appears to be narcosis at 600 ppm (= 1795 mg/m³).
		Modification of the relevant dose descriptor	$NOAEL_{worker}$ = $NOAEC_{mouse}$ x 6/8 x 5/5 x 6.7/10 x 10 / 70	From study (mouse) to human (worker): hours per day (6 h → 8 h) and days per week (5 days → 5 days); Respiratory volume (8 h) normal (6.7 m³) to light activity (10 m³) Bw (worker): 70 kg; Respiratory volume light activity (8 h): 10 m³
		Corrected dose descriptor	$NOAEL_{worker}$ = 129 mg/kg bw/day	
		Assessment factor (AF)	**AF Value**	**Remarks**
		Absorption	1	Inhalation-to-dermal extrapolation[a]
		Dose response	1	
		Interspecies	2.5	Remaining differences
		Intraspecies	5	worker
		Exposure duration	1	
		Quality of database	1	
		DNEL	129 mg/kg bw/day / (1 x 1 x 2.5 x 5 x 1 x 1) = **10 mg/kg bw/day**	

a: The results of experimental studies indicate a high absorption of Tetrahydrofuran for oral and dermal route. There are no reliable data for the inhalation route. For route-to-route extrapolation high absorption rates of all routes is to be expected. In the absence of more specific data it is assumed that both percentage and speed of absorption are identical for uptake via skin and inhalation. Therefore, a factor 1 was applied for the inhalation-to-dermal extrapolation.

DNELs used for risk characterisation:

$DNEL_{systemic\ long\ term}$ inhalation: 72 mg/m³ (corresponds to 24 ppm)

$DNEL_{systemic\ long\ term}$ dermal: 10 mg/kg/day

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

The outcome of human hazard characterisation of THF can be summarised as follows:

- The current harmonised classification and labelling is basically supported. Classification for eye irritation should be changed from Eye Irrit. 2 to Eye Dam. 1. Additional classification for acute oral toxicity (Acute Tox 4), narcosis (STOT SE 3/H336) and defatting properties (EUH066) should be considered, in line with the opinion of the Lead Registrant (except EUH066).
- The predominant effect at lower doses in acute and repeat-dose studies is sedation/narcosis.
- In rats and mice, pre-neoplastic and neoplastic lesions were found upon chronic exposure to THF via inhalation leading to classification as Carc. Cat. 2. Although several recent publications were evaluated, still no final conclusion on the mode of action and its relevance for humans is possible, i.e. there is still considerable uncertainty whether these tumours are relevant for humans. However, based on the absence of positive test results in the available genotoxicity tests and on results from mechanistic studies it appears plausible that carcinogenicity is taking place via a non-genotoxic mechanism, involving stimulation of cell proliferation. Therefore, a threshold for these effects can be set.

7.10. Assessment of endocrine disrupting (ED) properties

No initial or additional concern.

7.11. PBT and VPVB assessment

No initial or additional concern.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Workers

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

On request of the evaluating member state the Lead Registrants provided the missing Appendix 1 of the CSR where the exposure assessments for workers and consumers are described. In the updated CSR (June 2016), the Registrant(s) presented new exposure assessments using the ECETOC TRA V3 tool.

The outcome of the assessment is recorded in the confidential Annex. All in all it can be seen, that worker contributing scenarios (WCSs) with manual handling and using the pure substance or preparations with high concentrations > 25% and/or spray applications and/or no gloves for dermal protection result in highest exposure.

7.12.1.2. Consumers

First of all it was checked whether all identified uses in the technical dossier were covered by exposure scenarios in the CSR (see Table 23). Identified consumer uses in the technical dossier without any further information led to require information via a draft decision allowing the assessment of risks resulting from these uses (request 9).

Table 23

RELATION OF IDENTIFIED CONSUMER USES IN IUCLID AND THE CSR WITH AVAILABLE EXPOSURE SCENARIOS IN THE CSR		
	Identified consumer uses	**ES in the CSR**
PC1	Adhesives, sealants	ES 13-1 (inhalation & dermal route) ES 13-2 (inhalation & dermal route)
PC3	Air care products	No ES is provided in the CSR
PC4	Anti-Freeze and de-icing products	No ES is provided in the CSR
PC9a	Coatings and paints, thinners, paint removers	ES 13-3 (inhalation & dermal route) ES 13-4 (inhalation & dermal route)
PC9b	Fillers, putties, plasters, modelling clay	No ES is provided in the CSR
PC9c	Finger paints	No ES is provided in the CSR
PC13	Fuels	No ES is provided in the CSR
PC18	Ink and toners	No ES is provided in the CSR
PC23	Leather tanning, dye, finishing, impregnation and care products	No ES is provided in the CSR
PC24	Lubricants, greases, release products	No ES is provided in the CSR
PC31	Polishes and wax blends	No ES is provided in the CSR
PC35	Washing and cleaning products (including solvent based products)	ES 12-1 (inhalation & dermal route) ES 12-2 (inhalation & dermal route) ES 12-3 (inhalation & dermal route)

In order to identify possible risks, the CSRs were checked whether the available 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 to clarify whether further risk management options are needed.

The outcome of the assessment is recorded in the confidential Annex of this report as summarized below.

Inconsistencies and data gaps in the CSR regarding consumer exposure scenarios led the eMSCA to consider that risks could be expected for consumer applications of THF. To clarify this concern, product information (e.g. intended purpose of the product, maximum THF concentrations and packaging size) which allows a proper exposure assessment for the intended and reasonable foreseeable uses were requested from the Registrant(s) in the substance evaluation decision for PC 1, PC 9a, and PC 35. Furthermore the missing

exposure scenarios for PC 3, 4, 9b, 9c, 13, 18, 23, 24, 31 & PC 0 (others: PC 5 & 10) by one Registrant were also requested.

Regarding requests 5–9 of the decision, the Registrant(s) commented that these might require extensive information from the downstream users. They assume that default/worst-case value databases might not be readily available for these endpoints. This would require communication with the downstream users, potentially involving a third party agency to maintain confidentiality of the values.

For this reason a questionnaire was sent to the Downstream User Associations (see Appendix IV of the confidential Annex). Upon further consideration, the active Registrant(s) updated their registration dossiers and removed the identified consumer uses PC 9a and 35 in the technical IUCLID as well as in the CSR. The Registrant of the various consumer uses (see above) also updated his registration dossier in line with the joint submission.

The Registrant(s) also added the following recommendations in the CSR: "Product integrated RMM which may be applied in products contain THF are not standardised. As a result of the qualitative risk assessment as a minimum the following RMM are recommended to duly control risk:

- Only use THF which contains stabilisers to prevent peroxide formation
- Max. size packaging = 1 Litre (1000 mL)
- Opening limited to max. 42 mm for packaging over 500 mL (with screw top lid closure) unless packaging contains a lid with built-in applicator where opening should be restricted to a size appropriate for the applicator."

In consequence, the Registrant(s) support PC 1 (adhesives, glues) for consumer uses only and provide new exposure scenarios for PVC primer, PVC cement and universal glues. Based on the information in the CSR, the eMSCA assumes that PVC primer and PVC cement are two different product types which can be used in combination to stick PVC together: the primer to prepare the surface and the cement for glueing the PVC, for instance fitting PVC tubes. In this case the PVC primer should be registered according the ECHA-GD R.12 (ECHA, 2010b) as an identified consumer use PC 9a (primer) with an additional exposure scenario.

As a result of the Downstream User Association's survey, glue packaging varies from 125 mL tube glues to 5 L cans. Although the Registrants recommend in their updated CSRs a maximum packaging size of 1 L, this information is not in line with the chosen exposure scenarios "tube glue" and "bottle glue". These application forms differ from the use of glues which are stored in a can. Therefore, the scenarios do not cover consumer applications adequately, and their exposure levels could be underestimated. Furthermore the recorded model and operational conditions do not seem plausible.

Some more clarifying information with regard to consumer uses PC 1 and PC 9a (PVC cement, PVC primer) were asked from Registrant(s) but not obtained within the timeframe of finalizing the evaluation (see confidential Annex). The Registrant(s) would still need to address these discrepancies in their dossiers.

7.12.2. Combined exposure assessment

Not applicable.

7.13. Risk characterisation

7.13.1. Human health

7.13.1.1. Workers

For the calculation of the RCRs the DNELs derived from the NOAEC obtained in a long-term 2-species (Fischer 344 rat and B6C3F1 mouse) inhalation bioassay with THF by the US National Toxicology Program (NTP, 1998) were used: $DNEL_{worker,\ inhalation}$ = 72 mg/m³ (corresponds to 24 ppm) and $DNEL_{worker,\ dermal}$ = 10 mg/kg bw/day. The calculated RCRs are listed in the confidential part.

Inhalation route

For inhalation route the systemic risk assessment for each scenario yields a RCR of less than 1 when risk reduction measures described in chapter 9.1.1 (confidential part) are implemented.

Dermal route

For dermal route the systemic risk assessment for each scenario yields a RCR of less than 1 when risk reduction measures described in chapter 9.1.1 (confidential part) are implemented.

Combined routes (inhalation and dermal)

Combined risk characterisation via inhalation and dermal route is performed by summation of the respective RCRs. The combined RCR of some scenarios slightly exceeds the value of 1 (maximum 1.17) especially where manual handling and using the pure substance or preparations with high concentrations (> 25%) and/or spray applications and/or no gloves for dermal protection occurs. However, the implementation of additional risk reduction measures would result in a combined RCR less than 1. Therefore, this slight exceedance does not raise concern.

7.13.1.2. Consumers

Acute exposure

Relevant scenarios for consumers for which calculations can be performed: ES 12.1-12.3 (PC 35), ES 13.1-13.2 (PC 1), and ES 13.3-13.4 (PC 9a), cf. section 7.12.1.

Inhalation only

The critical endpoint for acute exposure is sedation/narcosis. The relevant dose descriptor is the external THF concentration in air. The relevant DNEL is 24 ppm or 72 mg/m³ (cf. section 7.9.12.). Comparing this value with consumer exposure as calculated by the eMSCA in the confidential annex results in the RCRs presented in Table 24 for which the ES and external concentration cannot be linked to a specific Registrant.

Table 24

RCRs FOR EXPOSURE SCENARIOS (ES) WITH ACUTE INHALATION EXPOSURE. RCRs>1 ARE HIGHLIGHTED.			
ES	**External Concentration (mg/m³)**	**DNEL (mg/m³)**	**RCR**
12.1	25	72	0.3
12.2	36	72	0.5
12.3	225	72	**3.1**
13.1	136	72	**1.9**
13.2	1700	72	**23.6**

13.3	5550	72	**77.1**
13.4	4130	72	**57.4**

Dermal only

The relevant methodology has been explained in the confidential part. RCRs resulting from a comparison of the estimated dermal uptake with the DNEL of 1.6 mg/kg bw/h are given in Table 25.

Table 25

RCRs FOR EXPOSURE SCENARIOS (ES) WITH ACUTE DERMAL EXPOSURE. RCRs>1 ARE HIGHLIGHTED.				
ES	**Dermal uptake (mg/kg bw/event)**	**Exposure time (h)**	**Dermal uptake* (mg/kg bw/h)**	**RCR**
12.1	3.47	0.5	7	**4.4**
12.2	1.72	0.333	1.72	**1.1**
12.3	12.00	0.16	75	**47**
13.1	1.07	4	0.3	0.19
13.2	0.1	4	0.03	0.019
13.3	6.43	2	12.0	**7.5**
13.4	0.36	1	1.7	**1.1**

* Rounded to the last significant figure to reflect uncertainty

Uncertainties:

- In the absence of more specific data, this approximation includes the assumption that both percentage and speed of absorption are identical for uptake via skin and inhalation. This might be an overestimation regarding the dermal part. Uncertainty increases with decreasing exposure duration as, at a certain point, exposure might be too short to cause a significant amount of sedation.
- Moreover, the above calculations assume that the complete dermal load is already absorbed during the exposure event. This might be an overestimation, in particular for short event durations. On the other hand, in order to reduce the dermal RCR for ES 12.3 to below 1, a time for absorption of 470 min (i.e. almost eight hours) would have to be assumed instead of the 10 min used for calculation of the above value of 47 in Table 25.

Chronic exposure:

Relevant scenarios for consumers: ES 12.1-12.3 (PC 35).

Inhalation only

The relevant DNEL for chronic exposure is 7 mg/kg bw/d (cf. section 7.9.12). Comparing this value with consumer exposure as calculated by the eMSCA in section 7.9.12. results in RCRs presented in Table 26:

Table 26

RCRs FOR EXPOSURE SCENARIOS (ES) WITH CHRONIC INHALATION EXPOSURE. RCRs>1 ARE HIGHLIGHTED.			
ES	**Inhalation burden (mg/kg bw/d)**	**DNEL (mg/kg bw/d)**	**RCR**
12.1	0.57	7	0.08
12.2	0.27	7	0.04

12.3	0.82	7	0.12

All calculated RCRs are below 1, if only inhalation exposure is considered.

Dermal only

The RCRs obtained by using the same methodology as for inhalation exposure alone, i.e. comparing estimated consumer exposure with the 'safe' daily body burden of 7 mg/kg bw/d, are given in Table 27.

Table 27

RCRs FOR EXPOSURE SCENARIOS (ES) WITH CHRONIC DERMAL EXPOSURE. RCRs>1 ARE HIGHLIGHTED.			
ES	**Dermal burden (mg/kg bw/d)**	**DNEL (mg/kg bw/d)**	**RCR**
12.1	6.94	7	0.99
12.2	1.72	7	0.25
12.3	12	7	**1.71**

The RCR for scenario 12.1 is close to 1, while for scenario 12.3, an RCR > 1 is calculated.

7.13.2. Overall risk characterisation (consumers)

7.13.2.1. Acute exposure

Combined routes (inhalation and dermal exposure)

Combined risk characterisation via inhalation and the dermal route is performed by summation of the respective RCRs given above in Table 26 and Table 27 (section 7.13.1.). The results are presented in Table 28.

Table 28

COMBINED RCRs FOR EXPOSURE SCENARIOS (ES) WITH ACUTE EXPOSURE. RCRs_1 ARE HIGHLIGHTED.			
ES	**RCR (inhalation)***	**RCR (dermal)****	**RCR (combined)**
12.1	0.3	4.4	**4.7**
12.2	0.5	1.1	**1.6**
12.3	3.1	47	**50.1**
13.1	1.9	0.19	**2.09**
13.2	23.6	0.019	**23.8**
13.3	77.1	No data	**> 77.1**
13.4	57.4	1.1	**58.5**

*cf. Table 26; ** cf. Table 27

With current assumptions, including low-level tier exposure assessment, RCRs > 1 are calculated for all relevant scenarios.

It could not be sufficiently clarified whether the exposure scenarios in the CSR cover consumer applications adequately. Their exposure levels could be underestimated especially for the event exposure. Therefore, narcotic effects (drowsiness or dizziness) cannot be excluded during use.

Aggregate (combined use, combined routes)

Theoretically, for scenarios ES 12.1-12.3, all of which result in combined RCRs > 1 individually, aggregate risk characterisation for acute exposure (which is performed by adding up the respective RCRs in the rightmost column of Table 28) results in an **aggregated RCR of 4.7 + 1.6 + 50.1 = 56.4**. It is however unclear whether the respective scenarios will take place in such close temporal proximity that external THF concentrations will add up with the result of even higher substance intake per unit time (and thus, higher probability of sedative effects).

7.13.2.2. Chronic exposure

Combined inhalation and dermal exposure

Combined risk characterisation via inhalation and the dermal route is performed by summation of the respective RCRs given above in Table 26 and Table 27 (section 7.13.1.). The results are presented in Table 29.

Table 29

COMBINED RCRs FOR EXPOSURE SCENARIOS (ES) WITH CHRONIC EXPOSURE. RCRs>1 ARE HIGHLIGHTED.			
ES	**RCR (inhalation)***	**RCR (dermal)****	**RCR (combined)**
12.1	0.08	0.99	**1.07**
12.2	0.04	0.25	0.29
12.3	0.12	1.71	**1.83**

*cf. Table 26; ** cf. Table 27

Scenarios 12.1 and 12.3 result in RCRs > 1.

Aggregate (combined use, combined routes)

Aggregation of scenarios 12.1-12.3 for chronic exposure is meaningful because these scenarios are assumed to apply to the same person on the same day (and on a daily basis). Therefore, the individual scenarios all contribute to the total daily THF burden. By adding up the RCRs in the rightmost column of Table 29, an **aggregated RCR of 1.07 + 0.29 + 1.83 = 3.19** is obtained.

Summary of combined and aggregate risk characterisation

Currently all scenarios for which a calculation is possible have combined RCRs > 1 for acute exposure with RCRs ranging from 2 to > 77. For chronic exposure, risk characterisation results in combined RCRs > 1 for two out of three scenarios, but exceedance was less dramatic (RCRs = 1.07 or 1.83, respectively).

With the withdrawal of consumer uses, aggregated exposure is no longer a subject of further evaluation in this SEv.

7.14. References

Abbott M.G., McFee A.F., and Tice R.R. (1991): Genotoxicity of four furan compounds tested in vivo. Environmental and Molecular Mutagenesis 17 (Suppl. 19), 5

Alden C.L. (1986): A review of unique male rat hydrocarbon nephropathy. Toxicologic Pathology 14 (109), 111

Bahnemann R. (2000): Cell proliferation in the liver: A malpractice not to measure the zonal distribution? Comparison of the lobule-dependent zonal measurement method with the common method of randomly distributed measurement fields. Toxicology Methods 10 (2), 81-97

[redacted]

Brooke I., Cocker J., Delic J.I., Payne M., Jones K., Gregg N.C., and Dyne D. (1998): Dermal uptake of solvents from the vapour phase: An experimental study in humans. Annals of Occupational Hygiene 42 (8), 531-540

[redacted]

Bruner R.H., Greaves P., Hard G.C., Regan K.S., Ward J.M., and David R.M. (2010): Histopathologic changes in the kidneys of male F344 rats from a 2-year inhalation carcinogenicity study of tetrahydrofuran: A pathology working group review and re-evaluation. Regulatory Toxicology and Pharmacology 58 (1), 100-105

Cartigny B., Azaroual N., Imbenotte M., Sadeg N., Testart F., Richecoeur J., Vermeersch G., and Lhermitte M. (2001): H-1 NMR spectroscopic investigation of serum and urine in a case of acute tetrahydrofuran poisoning. Journal of Analytical Toxicology 25 (4), 270-274

Chhabra R.S., Elwell M.R., Chou B., Miller R.A., and Renne R.A. (1990): Subchronic toxicity of tetrahydrofuran vapors in rats and mice. Fundamental and Applied Toxicology 14 (2), 338-345

Chhabra R.S., Herbert R.A., Roycroft J.H., Chou B., Miller R.A., and Renne R.A. (1998): Carcinogenesis studies of tetrahydrofuran vapors in rats and mice. Toxicological Sciences 41 (2), 183-188

[redacted]

Droz P.O., Berode M., and Jang J.Y. (1999): Biological monitoring of tetrahydrofuran: Contribution of a physiologically based pharmacokinetic model. American Industrial Hygiene Association Journal 60 (2), 243-248

[redacted]

ECHA (2010a): Annex 1. Background document to the opinion proposing harmonised classification and labelling at Community level of tetrahydrofuran. ECHA/RAC/DOC no CLH-O-0000000954-69-03/A1, date: 2010-05-25. European Chemicals Agency, Helsinki

ECHA (2010b): Guidance on information requirements and chemical safety assessment . Chapter R.12: Use descriptor system. Version 2, date: 2010-03. European Chemicals Agency, Helsinki (last accessed 2015-04-24)

ECHA (2012): Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1, date: 2012-11. European Chemicals Agency, Helsinki

Elovaara E., Pfaffli P., and Savolainen H. (1984): Burden and biochemical effects of extended tetrahydrofuran vapour inhalation of three concentration levels. Acta Pharmacologica et Toxicologica 54 (3), 221-226

Fenner-Crisp P.A., Mayyes E.M., and David R.M. (2011): Assessing the human carcinogenic potential of tetrahydrofuran: I. Mode of action and human relevance analysis of the male rat kidney tumor. II. Mode of action and human relevance analysis of the female mouse liver tumor. Regulatory Toxicology and Pharmacology 60 (1), 20-39

Fowles J., Boatman R., Bootman J., Lewis C., Morgott D., Rushton E., van Rooij J., and Banton M. (2013): A review of the toxicological and environmental hazards and risks of tetrahydrofuran. Critical Reviews in Toxicology, 811-828. Informa Healthcare, 10/22/2013 (last accessed 11/28/2013)

French MSCA (2009): Annex VI report - proposal for harmonised classification and labelling - tetrahydrofuran, date: 6/2009

Galloway S.M., Armstrong M.J., Reuben C., Colman S., Brown B., Cannon C., Bloom A.D., Nakamura F., Ahmed M., Duk S., Rimpo J., Margolin B.H., Resnick M.A., Anderson B., and Zeiger E. (1987): Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environmental and Molecular Mutagenesis 10 (Suppl. 10), 1-175

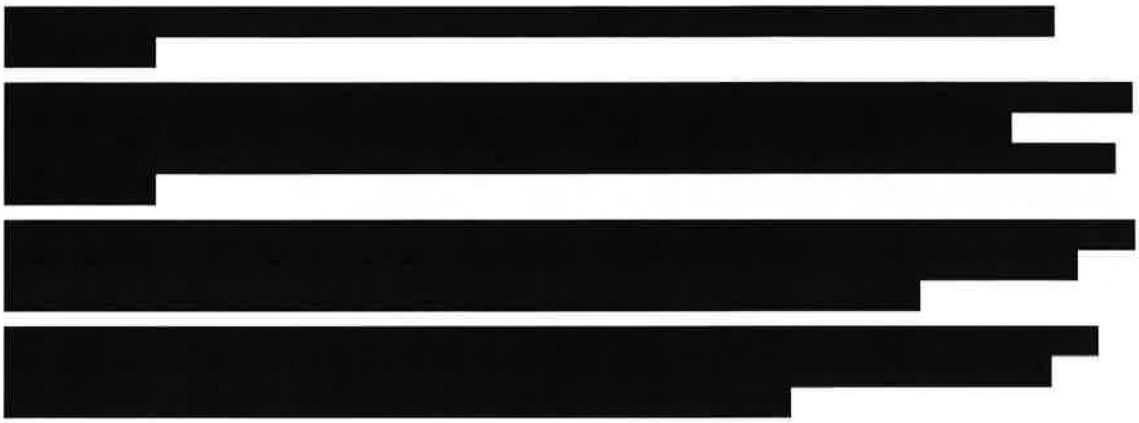
Gamer A.O., Jaeckh R., Leibold E., Kaufmann W., Gembardt C., Bahnemann R., and Van Ravenzwaay B. (2002): Investigations on cell proliferation and enzyme induction in male rat kidney and female mouse liver caused by tetrahydrofuran. Toxicological Sciences 70 (1), 140-149

Garnier R., Rosenberg N., Puissant J.M., Chauvet J.P., and Efthymiou M.L. (1989): Tetrahydrofuran poisoning after occupational exposure. British Journal of Industrial Medicine 46 (9), 677-678

Hara K., Nagata T., and Kimura K. (1987): Forensic toxicological analysis of tetrahydrofuran in body materials. Zeitschrift fur Rechtsmedizin 98 (1), 49-55

Hard G.C., Banton M.I., Bretzlaff R.S., Dekant W., Fowles J.R., Mallett A.K., McGregor D.B., Roberts K.M., Sielken R.L., Valdez-Flores C., and Cohen S.M. (2013): Consideration of rat chronic progressive nephropathy in regulatory evaluations for carcinogenicity. Toxicological Sciences 132 (2), 268-275

Hard G.C., Betz L.J., and Seely J.C. (2012): Association of advanced chronic progressive nephropathy (CPN) with renal tubule tumors and precursor hyperplasia in control F344 rats from two-year carcinogenicity studies. Toxicologic Pathology 40 (3), 473-481



Hatch G., Anderson T., Elmore E., and Nesnow S. (1983): Status of enhancement of DNA viral transformation for determination of mutagenic and carcinogenic potential of gaseous and volatile compounds. Environmental Mutagenesis (5), 422

Hellwig J., Gembardt C., and Jasti S. (2002): Tetrahydrofuran: Two-generation reproduction toxicity in Wistar rats by continuous administration in the drinking water. Food and Chemical Toxicology 40 (10), 1515-1523

Hermida S.A.S., Possari E.P.M., Souza D.B., De Arruda Campos I.P., Gomes O.F., Di Mascio P., Medeiros M.H.G., and Loureiro A.P.M. (2006): 2'-Deoxyguanosine, 2'-deoxycytidine, and 2'-deoxyadenosine adducts resulting from the reaction of tetrahydrofuran with DNA bases. Chemical Research in Toxicology 19 (7), 927-936

Hofmann H.T. and Oettel H. (1954): Zur Frage der Toxizität von Tetrahydrofuran. Naunyn-Schmiedebergs Archiv fur Experimentelle Pathologie und Pharmakologie 222 (1-2), 233-235

Horiguchi S., Teramoto K., and Katahira T. (1984): Acute and repeated inhalation toxicity of tetrahydrofuran in laboratory animals. Studies on the toxicity of an organic solvent, tetrahydrofuran, report 4. Sumitomo Bulletin of Industrial Health 20, 141-157

IARC (1999): Species differences in thyroid, kidney and urinary bladder carcinogenesis, date: 1999. International Agency for Research on Cancer. Organization W.H.

Jochmann W. (1961): Zur Frage der Schädigung von Leber und Niere durch Tetrahydrofuran. Archiv fur Gewerbepathologie und Gewerbehygiene 18, 698-717

Juntunen J., Kaste M., and Harkonen H. (1984): Cerebral convulsion after enfluran anesthesia and occupational exposure to tetrahydrofuran. Journal of Neurology Neurosurgery and Psychiatry 47 (11), 1258-1258

Kageyama M. (1988): Exposure of humans to inhalation of tetrahydrofuran, elimination through expiration and decay in alveolar air and blood. Journal of the Osaka City Medical Center 37 (1), 19-33

Katahira T., Teramoto K., and Horiguchi S. (1982a): Experimental studies on the acute toxicity of tetrahydrofuran in animals. Japanese Journal of Industrial Health 24 (4), 373-378

Katahira T., Teramoto K., and Horiguchi S. (1982b): Experimental studies on the toxicity of tetrahydrofuran administered to animals by repeated inhalation. Japanese Journal of Industrial Health 24 (4), 379-387

Kawata F. and Ito A. (1984): Experimental studies of effects on organic solvents in living body changes of tetrahydrofuran concentration in rat's organs and histological observations after inhalation. Japanese Journal of Legal Medicine 38 (3), 367-375

Kawata F., Shimizu T., and Ozono S. (1986): [Determination and fluorescent-histochemical approach to catecholamines in the rat brain after inhalation of tetrahydrofuran]. Japanese Journal of Legal Medicine 40 (6), 811-820

Kimura E.T., Ebert D.M., and Dodge P.W. (1971): Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicology and Applied Pharmacology 19 (4), 699-704

Komsta E., Chu I., Secours V.E., Valli V.E., and Villeneuve D.C. (1988): Results of a short-term toxicity study for three organic chemicals found in Niagara River drinking water. Bulletin of Environmental Contamination and Toxicology 41 (4), 515-522

Lide D.R. (2005-2006): CRC Handbook of Chemistry and Physics, 86th edition, CRC Press, pp 3-42. ISBN: 978-1482260960.

Lock E.A. and Hard G.C. (2004): Chemically induced renal tubule tumors in the laboratoryrRat and mouse: Review of the NCI/NTP database and categorization of renal carcinogens based on mechanistic information. Critical Reviews in Toxicology 34 (3), 211-299

Loureiro A.P.M., De Arruda Campos I.P., Gomes O.F., Possari E.P.M., Di Mascio P., and Medeiros M.H.G. (2005): Structural characterization of an etheno-2'-deoxyguanosine adduct modified by tetrahydrofuran. Chemical Research in Toxicology 18 (2), 290-299

Maher T.J., Vo T., Hartman N., Kalaria H., Werawattanachai N., and Quang L.S. (2003): Neurotoxicity of the gamma-hydroxybutyrate precursor, tetrahydrofuran. Faseb Journal 17 (4-5), N. N.

Malley L.A., Christoph G.R., Stadler J.C., Hansen J.F., Biesemeier J.A., and Jasti S.L. (2001): Acute and subchronic neurotoxicological evaluation of tetrahydrofuran by inhalation in rats. Drug and Chemical Toxicology 24 (3), 201-219

Mast T.J., Rommereim R.L., Weigel R.J., Stoney K.H., Schwetz B.A., and Morrissey R.E. (1989): Developmental toxicity of tetrahydrofuran in mice and rats. Toxicologist 9 (1), 274

Mast T.J., Weigel R.J., Westerberg R.B., Schwetz B.A., and Morrissey R.E. (1992): Evaluation of the potential for developmental toxicity in rats and mice following inhalation exposure to tetrahydrofuran. Fundamental and Applied Toxicology 18 (2), 255-265

Matthews E.J., Spalding J.W., and Tennant R.W. (1993): Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in Salmonella and carcinogenicity in rodent bioassays. Environmental Health Perspectives 101 (Suppl. 2), 347-482

McMahon R.E., Cline J.C., and Thompson C.Z. (1979): Assay of 855 test chemicals in ten tester strains using a new modification of the Ames test for bacterial mutagens. Cancer Research 39 (3), 682-693

Melnick R.L., Cohn M.C., and Portier C.J. (1996): Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis. Environmental Health Perspectives 104 (Suppl. 1), 123-134

Mirsalis J., Tyson K., Beck J., Loh E., Steinmetz K., Contreras C., Austere L., Martin S., and Spalding J. (1983): Induction of unscheduled DNA synthesis in hepatocytes following in vitro and in vivo treatment. Environmental Mutagenesis (5), 482

Mortelmans K., Haworth S., Lawlor T., Speck W., Tainer B., and Zeiger E. (1986): Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environmental Mutagenesis 8 (Suppl. 7), 1-119

Mortensen P.B. (2005): Emission and evaluation of chemical substances from selected electrical and electronic products – part 2. Eurofins A/S. Danish Environmental Protection Agency. Danish Ministry of the Environment

Muttray A., Haxel B., Mann W., and Letzel S. (2006): Anosmie und Rhinitis durch eine berufliche Lösungsmittelexposition. HNO 54 (11), 883-887

Nilsson N.H., Malmgren-Hansen B., Bernth N., Pedersen E., and Pommer K. (2006): Survey and health assesment of chemicals substances in sex toys. Danish Technological Institute. Danish Envirionmental Protection Agency. Danish Ministry of the Environment

Nilsson N.H., Pedersen S., Hansen P.L., and Christensen I. (2004): Survey of chemical substances in consumer products. Danish Technological Institute. Danish Envirionmental Protection Agency. Danish Ministry of the Environment

NTP (1998): Toxicology and carcinogenesis studies of tetrahydrofuran (CAS No. 109-99-9) in F344/N rats and B6c3F mice (Inhalation Studies). NIH Publication No. 98-3965/NTP TR 475, date: 1998-06. National Institutes of Health, National Toxicology Program. U.S. Department of Health and Human Services. Public Health Service

Ohashi Y., Nakai Y., and Harada H. (1982a): Effects of short-term exposure to tetrahydrofuran on rabbit nasal mucous membranes. Sumitomo Bulletin of Industrial Health 18, 89-93

Ohashi Y., Nakai Y., Harada H., Horiguchi S., Teramoto K., and Katahira T. (1982b): Experimental studies on the mucosal membrane of respiratory tracts of rats exposed to tetrahydrofuran. Changes in ciliary functions and fine structures with time by electron microscopy. Japanese Journal of Industrial Health 24 (5), 485-497

Ong C.N., Chia S.E., Phoon W.H., and Tan K.T. (1991): Biological monitoring of occupational exposure to tetrahydrofuran. British Journal of Industrial Medicine 48 (9), 616-621

[redacted]

Seely J.C. and Hard G.C. (2008): Chronic progressive nephropathy (CPN) in the rat: Review of pathology and relationship to renal tumorigenesis. Journal of Toxicologic Pathology 21 (4), 199-205

Shelby M.D. and Witt K.L. (1995): Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. Environmental and Molecular Mutagenesis 25 (4), 302-313

Svendsen N., Pedersen S.F., Hansen O.C., Pedersen E., and Bernth N. (2005): Survey and release of chemical substances in "slimy" toys. Danish Technological Institute. Danish Environmental Protection Institute. Danish Ministry of the Environment

Swenberg J.A. and Lehman-McKeeman L.D. (1999): Alpha2-urinary globulin-associated nephropathy as a mechanism of renal tubule cell carcinogenesis in male rats. In: Species differences in thyroid, kidney and urinary ladder carcinogenesis (Capen C.C., Dybing E., Rice J.M., and Wilbourn J.D., eds.), chapter 147, pp. 95-118. International Agency for Research on Cancer, Lyon, France

US EPA (2012): Toxicological review of tetrahydrofuran - (CAS No. 109-99-9) - In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-11/006F, date: 2/2012. United States Environmental Protection Agency

Valencia R., Mason J.M., Woodruff R.C., and Zimmering S. (1985): Chemical mutagenesis resting in Drosophila .3. Results of 48 coded compounds tested for the national toxicology program. Environmental Mutagenesis 7 (3), 325-348

Van Ravenzwaay B., Gamer A.O., Leibold E., and Kaufmann W. (2003): Effect of cytochrome P-450 inhibition on tetrahydrofuran-induced hepatocellular proliferation in female mice. Archives of Toxicology 77 (8), 459-464

Van Vlierberghe H. (1995): Tetrahydrofuran-hepatitis. Tijdschrift voor Geneeskunde 51 (1), 70-72

Werawattanachai N., Towiwat P., Unchern S., and Maher T.J. (2007): Neuropharmacological profile of tetrahydrofuran in mice. Life Sciences 80 (18), 1656-1663

7.15. Abbreviations

List of abbreviations	
ABT	1-aminobenzotriazole
ADME	Absorption, Distribution, Metabolism, and Excretion
AF	Assessment Factor
AGS	German Committee for Hazardous Substances
AI	Apoptotic Index
ALAT	Alanine-aminotransferase
APF	Assigned Protection Factor
ASAT	Aspartate-aminotransferase
ATH	Atypical Hyperplasia
ATP	Adaptation to Technical Progress
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Health and Safety)
bw	Body weight
CLP	Regulation (EC) 1272/2008 on the Classification, Labelling, and Packaging of dangerous substances and mixtures
C_{max}	Maximum Concentration
CoRAP	Community Rolling Action Plan
CPN	Chronic Progressive Nephropathy
CS	Contributing Scenario (within an ES)
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
CYP450	Cytochrome P450
DA	Dopamine
DMEL	Derived Minimum Effect Level
DNEL	Derived No-Effect Level
EC	Effective Concentration
ECHA	European Chemicals Agency
eMS(CA)	Evaluating Member State (Competent Authority)
EMKG	Easy-to use-workplace control scheme
ENM	Electroneuromyography

EROD	Ethoxyresorufin-O-deethylase
ES	Exposure Scenario
EU	European Union
F	Female
FOPH	Federal Office of Public Health (Switzerland)
GD	Gestational Days
GHB	γ-Hydroxybutyric acid
GOT	Glutamate-oxalacetate-transaminase
GPT	Glutamate-pyruvate-transaminase
IOEL	Indicative Occupational Exposure Limit
IR	Information Requirement(s)
IUCLID	International Uniform Chemical Information Database
i.v.	intravenous
K_p	Permeability constant
LEV	Local Exhaust Ventilation
LI	Labelling Index
LLNA	Local Lymph Node Assay
M	Male
MAP	Motor Nerve Action Potential
MNCV	Motor Nerve Conduction Velocity
MEK	methyl ethyl ketone
MI	Mitotic index
MSDS	Material safety data sheet
NA	Noradrenaline
NO(A)EC/L	No observed (adverse) effect concentration/level
OC	Operational Conditions
OECD	Organisation for Economic Co-Operation and Development
PBTK	Physiology-based Toxicokinetic (Model)
PC	Product category
PCNA	Proliferating Cell Nuclear Antigen
PND	Postnatal Day
PoD	Point of Departure

PPE	Personal Protective Equipment
PROC	Process category
PROD	Propoxyresorufin-O-dealkylase
PVC	Polyvinyl chloride
RAC	Risk Assessment Committee
RCR	Risk Characterisation Ratio
REACH	Regulation (EC) 1907/2006 on the Regulation, Evaluation, Authorisation, and Restriction of Chemical Substances
RMM	Risk Management Measures
RPE	Respiratory Protection Equipment
SCOEL	Scientific Committee on Occupational Exposure Limits
SD	Standard Deviation
SEv	Substance Evaluation
SPIN (database)	Substances in Preparations in Nordic Countries
STOT RE	Specific Target Organ Toxicity, Repeated Exposure
SVHC	Substance of Very High Concern
TD_{50}	Dose causing toxicity in 50% of the exposed population
THF	Tetrahydrofuran
TUNEL	TdT-mediated dUTP-biotin nick end labeling
UVCB	(Substance of) Unknown or Variable Composition or Biological Origin
V	Volume
VOC	Volatile organic compounds
WCS	Worker contributing scenario