SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2-ethylhexyl acetate

EC No 203-079-1

CAS No 103-09-3

Evaluating Member State(s): Belgium

Dated: March, 2016

Evaluating Member State Competent Authority

Belgian Federal Public Service Health, Food Chain Safety and Environment, Risk Management service
Adress : Eurostation
Victor Horta plein 40/10
1060 Brussels
Belgium
Tel: /
Fax: + 32 2 524 96 03
Email: evaluation.reach@environment.belgium.be

Year of evaluation in CoRAP: 2015

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

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

DISCLAIMER

Foreword

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

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

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

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

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

2-ethylhexyl acetate was originally selected for substance evaluation in order to clarify concerns about:

- Exposure/wide dispersive use

- Consumer use

- Reprotoxicity

During the evaluation no other concerns were identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A final compliance check decision was issued on 17-09-2014:

CCH-D-0000005118-76-02/F
This decision is under Appeal (Appeal Case No. A-015-2014)

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 below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
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

4.1.1. Harmonised Classification and Labelling

NA

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

NA

4.1.3. Restriction

NA

4.1.4. Other EU-wide regulatory risk management measures

NA

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/exposure	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers(e.g. change in supported uses, applied risk management measures, etc.)	

The initial grounds for concern were clarified after in depth evaluation of the data available in the registration dossier and after evaluation of the full study reports.

Reprotoxicity:

On 16 March 2015, the registration dossier was updated. Amongst others, a 2-generation reproductive toxicity study with Di(2-ethylhexyl)terephthalate (read-across) was added to the dossier.

In a first step the eMSCA could conclude that the read-across approach with 2-ethylhexan-1-ol (used for multiple endpoints) applied by the registrant seemed plausible. It should be noted that a substance evaluation for this substance was performed by Poland and the conclusions regarding this evaluation are available on the ECHA website.

In a second step, the data in the registration dossier were analysed (as well as some of the full study reports).

After evaluation of all available information, no concern was identified for reproductive toxicity justifying the request for further information under the substance evaluation process or regulatory action. The registration dossier however lacked data on the reproductive toxicity enpoints with the registered substance itself or even with the acceptable read-across substance 2-ethylhexanol. Only tests with Di(2-ethylhexyl)terephthalate (2-generation study) and 2-ethylhexanoic acid (OECD 422) were

available. There is remaining uncertainty about the acceptability of the read-across with these substances as explained further in this document.

Other parts of the dossier (like environment) were also briefly analysed and no additional concern was identified.

Exposure/wide dispersive use and professional/consumer use:

On 16 March 2015, the registration dossier was updated with a thorough risk assessment (including RCR values).

No further concern was identified.

5.2. Other actions

NA

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

Not applicable, see section 5.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

2-ethylhexyl acetate was originally selected for substance evaluation in order to clarify concerns about:

- Exposure/wide dispersive use :
The substance is used by professionals and by consumers. The CSR however doesn't contain any calculated RCR values.

For workers it is stated by the registrant that the hazard skin irritation is not quantifiable with the available data and that therefore a qualitative assessment for a low hazard substance was performed based on the REACH guidance document for a low hazard substance. The registrant states that by the implementation of all the given risk management measures (RMMs) and operation conditions (OCs), all identified uses for workers are considered as safe.

- Consumer use :
For consumers the registrant states that product mixtures which do not fulfill the requirements for a classification as skin irritating item (R38/ skin irritation Cat. 2) as described in Regulation (EC) No 1272/2008, chapter 3.2.3, represent no hazard which is

relevant for classification and were therefore considered as safe for use of consumers. Additionally, dermal contact to consumer products has to be minimized by appropriate article design.

- Reprotoxicity :
A study according to OECD 414 performed with 2-ethylhexan-1-ol shows potential concern for developmental toxicity.
There are no tests on reproductive toxicity available in the dossier with the registered substance.

During the evaluation no other concerns were identified.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Exposure/wide dispersive use	Concern not substantiated. No further action
Consumer use	Concern not substantiated. No further action
Reprotoxicity	Read-across with 2-ethylhexan-1-ol seems plausible. This substance was evaluated by Poland (CoRAP 2014) and the conclusion document is available on the ECHA website. Read-across with 2-ethylhexanoic acid and Di(2-ethylhexyl)terephthalate however were only considered as indicative information. Based on the information provided by the registrant, no concern for reprotoxicity could be identified that would merit a request for further information under the substance evaluation process or risk management measures.

7.2. Procedure

On 10 March 2015 the registrant was contacted and full study reports were requested.

On 17 March 2015 the evaluation officially started.

The lead registration dossier was updated on 16 March 2015.

Most full study reports were received in April 2015.

The initial evaluation concentrated on the acceptability of the read-across. The read-across applied with 2-ethylhexan-1-ol seemed plausible, while the read-across with 2-ethylhexanoic acid and Di(2-ethylhexyl)terephthalate was was only considered as indicative information.

The available data were evaluated for human health and environment although the main focus was on the human health part, while the environment part was only briefly analysed. After evaluation, there was no remaining concern for human health and no additional concern was identified for the environment.

Furthermore, no further concern regarding the exposure or risk assessment was identified.

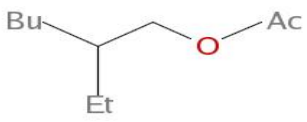
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	2-ethylhexyl acetate
EC number:	203-079-1
CAS number:	103-09-3
Index number in Annex VI of the CLP Regulation:	NA
Molecular formula:	$C_{10}H_{20}O_2$
Molecular weight range:	172.2646
Synonyms:	Trade names on dissemination website : Acetic acid, 2-ethylhexyl ester (7CI, 8CI, 9CI) 1-Hexanol, 2-ethyl-, acetate (6CI) .beta.-Ethylhexyl acetate 2-Ethyl-1-hexanol acetate 2-Ethyl-1-hexyl acetate 2-Ethylhexyl acetate Octyl acetate

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

Structural formula:



Read-across was applied with the following three substances:

SUBSTANCE IDENTITY

Public name:	2-ethylhexan-1-ol
EC number:	203-234-3
CAS number:	104-76-7
Index number in Annex VI of the CLP Regulation:	NA
Molecular formula:	$C_8H_{18}O$

SUBSTANCE IDENTITY	
Public name:	2-ethylhexanoic acid
EC number:	205-743-6
CAS number:	149-57-5
Index number in Annex VI of the CLP Regulation:	Repr. 2; H361d: Suspected of damaging fertility or the unborn child.
Molecular formula:	$C_8H_{16}O_2$

SUBSTANCE IDENTITY	
Public name:	Di(2-ethylhexyl)terephthalate (DEHT)
EC number:	229-176-9
CAS number:	6422-86-2
Index number in Annex VI of the CLP Regulation:	NA
Molecular formula:	$C_{24}H_{38}O_4$

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid at 20°C and 101.3kPa
Vapour pressure	0.31 hPa at 25°C (the lowest value from selected data for this endpoint in the registration dossier) EPI Suite estimation: 2.30E-01 mmHg at 25°C
Water solubility	3.9 mg/L at 20°C and pH 6.1 EPI Suite estimation: 38.59 mg/L at 25°C EU Method A.6: column elution method

	Conclusion: substance is slightly soluble (0.1-100 mg/L)
Partition coefficient n-octanol/water (Log Kow)	Log Kow = 4.3 at 25° C OECD 107 (shake-flask method) EPI Suite estimation value of 3.74 (no data available on pH)
Flash point	71°C at 1013 hPa
Auto-flammability	268°C at 1013 hPa
Flammability	Not flammable
Explosive properties	Non-explosive
Oxidising properties	Non-oxidising
Granulometry	NA: non solid or granular form
Dissociation constant	NA: No ionic structure
Viscosity	1.3 mPa·s (dynamic) at 20°C

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

Table 7

USES

Use(s)	
Uses as intermediate	/
Formulation	Formulation and (re)packaging of substances and mixtures, distribution of substance, formulation, transfer of substance or preparations
Uses at industrial sites	Use in coatings (paints, lacquers, inks, adhesives), use as laboratory reagent, use as solvent and cleaning agents, use as intermediate, use in oil and gas field and production operations
Uses by professional workers	Use as solvent and in cleaning agents, use in coatings (paints, inks, lacquers, adhesives) , use as laboratory reagent, use as co-formulant in plant protection products
Consumer Uses	Use in coatings (paints, lacquers, inks, adhesives), solvents and cleaning agents, lubricants, consumer care products, co-formulant in plant production products
Article service life	/

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

NA

7.6.2. Self-classification

- In the registration(s):

Skin irrit. 2; H315: Causes skin irritation

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

Not classified

Eye irrit. 2; H319: Causes serious eye irritation

Aquatic chronic 2; H411: Toxic to aquatic life with long lasting effects

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Abiotic degradation

7.7.1.1.1. Phototransformation in air

Table 8. Studies on phototransformation in air

Method	Results	Remarks	Reference
EPIWIN SRC AOP v1.91 PHOTOCHEMICAL REACTION WITH OH RADICALS - Concentration of OH radicals: 500000 molecule/cm³ - Degradation rate constant: 0.000000000010948 cm³/molecule-sec - Temperature for which rate constant was calculated: 25 °C - Calculated t 1/2 is based on a 24 h day	Half-life (DT50): 35h	2 (reliable with restrictions) key study estimated by calculation **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

Based on calculations with AOPWIN v1.91, the substance is photodegradable in air with a half-life of 35 hours.

7.7.1.1.2. Hydrolysis
NA

7.7.1.1.3. Phototransformation in water
NA

7.7.1.1.4. Phototransformation in soil
NA

7.7.1.2. Biodegradation

7.7.1.2.1. Biodegradtion in water

Table 9. Screening tests for biodegradation in water

Method	Results	Remarks	Reference
OECD Guideline 301 B (Ready Biodegradability: CO_2 Evolution Test) GLP	readily biodegradable 70 % Degradation after 28 d	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

The registrant(s) concluded the substance is readily biodegradable, and based on the available information, the eMSCA can support this conclusion.

7.7.1.2.2. Biodegradation in soil

NA

7.7.2. Environmental distribution

7.7.2.1. Adsorption/desorption

Table 10. Studies on adsorption/desorption

Method	Results	Remarks	Reference
adsorption (soil) SRC PCKOCWIN v1.66 calculation	Koc: 222 log Koc: 2.35	2 (reliable with restrictions) key study estimated by calculation **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier
EPISUITE 4.1 KOCWIN v2.00	Koc : 188.5 L/kg (MCI method) Log Koc: 2.275 (MCI method) Koc : 847.6 L/kg (Kow method) Log Koc: 2.928 (Kow method)	2 (reliable with restrictions) estimated by calculation Test material (EC name): 2-ethylhexyl acetate	eMSCA

The Log Koc was calculated with PCKOCWIN v1.66 and resulted in a log Koc value of 2.35. A calculation with EPISUITE resulted in similar results with values of 2.275 (MCI method) and 2.928 (Kow method).

7.7.2.2. Volatilisation

Table 11. Studies on volatilisation

Method	Results	Remarks	Reference
Henry's Law constant SRC HENRYWIN v3.10	H =128.7 Pa m³/mol at 25 °C	2 (reliable with restrictions) key study estimated by calculation **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

Henry´s law constant at 25°C was estimated to be 128,7 Pa m3/mole by SRC HENRYWIN v3.10.

7.7.2.3. Distribution modelling

Calculated by the registrant(s) according to Mackay, Level I (2007) :
Air : 71.6%
Water : 15.4%
Soil : 6.57%
Sediment : 6.64%
Biota : 0%

7.7.3. Bioaccumulation

7.7.3.1. Aquatic bioaccumulation

Table 12. Studies on aquatic bioaccumulation

Method	Results	Remarks	Reference
Estimation of bioconcentration: * BASIS FOR CALCULATION OF BCF - Estimation software: BCF base-line model v02.08 of OASIS CATALOGIC v5.11.15	BCF: 7.08 logBCF corrected 0.85 ±0.90	2 (reliable with restrictions) weight of evidence estimated by calculation **Test material (EC name): 2-**	Registration dossier

Method	Results	Remarks	Reference
- SMILES codes used for calculation O=C(OCC(CCCC)CC)C		**ethylhexyl acetate**	
Estimation of bioconcentration: * BASIS FOR CALCULATION OF BCF - Estimation software: US EPA T.E.S.T. v4.1 * Applied QSAR estimation methods: - Hierarchical method : - FDA method - Single model method : - Group contribution method - Nearest neighbor method - Consensus method = average of the predicted toxicities from the above QSAR methods	BCF: 57.34 (method: consensus) log BCF: 1.76 (method: consensus)	2 (reliable with restrictions) weight of evidence (Q)SAR **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier
Estimation of bioconcentration: * BASIS INFORMATION - Measured logKow of 4.2 * BASIS FOR CALCULATION OF BCF - Estimation software: BCFBAF Program (v3.01) (part of EPI Suite v4.11)	BCF: 202.4 L/kg log BCF: 2.1306	2 (reliable with restrictions) weight of evidence (Q)SAR **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier
Estimation of bioconcentration: * BASIS INFORMATION :	log BCF: 1.42 (CAESAR) BCF: 26 L/kg (CAESAR) log BCF: 2.13 (MEYLAN)	2 (reliable with restrictions) weight of evidence	Registration dossier

Method	Results	Remarks	Reference
- Measured/calculated logPow: measured (4.2) * BASIS FOR CALCULATION OF BCF : - BCF model (CAESAR) (version 2.1.13) - BCF model (Meylan) (version 1.0.2) - BCF Read-Across (version 1.0.2) Calculated using VEGA software	BCF: 136 (MEYLAN) log BCF: 2.47 (Read-across) BCF: 292 (Read-across)	estimated by calculation **Test material (EC name): 2-ethylhexyl acetate**	

The measured log Kow of the substance was 4.2, which would indicate that the substance has a potential to bioaccumulate.

Predictions of the BCF value using different QSAR models result in values ranging from 26 to 292. These values are relatively low and would indicate that the substance has a limited bioaccumulation potential.

The registrant(s) concluded that based on all available data in a weight-of-evidence approach, significant accumulation of 2-ethylhexyl acetate in organisms is not expected, and based on the available information, the eMSCA can support this conclusion.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

7.8.1.1.1. Short term toxicity in fish

Table 13. Short-term effects on fish

Method	Results	Remarks	Reference
Oncorhynchus mykiss freshwater semi-static OECD Guideline 203 (Fish, Acute Toxicity Test) GLP	LC50 (96 h): 8.27 mg/L test mat. (meas. (arithm. mean))	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-**	Registration dossier

Method	Results	Remarks	Reference
		ethylhexyl acetate	
Oncorhynchus mykiss freshwater flow-through OECD Guideline 203 (Fish, Acute Toxicity Test) GLP	LC50 (96 h): > 4.5 mg/L test mat. (nominal)	1 (reliable without restriction) supporting study experimental result **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

The registrant(s) concluded that fish are the most sensitive species revealing a LC50(96h) of 8.27 mg/L and that 2-ethylhexylacetate can be considered acutely toxic to aquatic organisms. The eMSCA can support this conclusion.

7.8.1.1.2. Long term toxicity to fish

NA

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short term toxicity to aquatic invertabrates

Table 14. Short-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater semi-static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) GLP	EC50 (48 h): 22.9 mg/L test mat. (meas. (arithm. mean))	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

7.8.1.2.2. Long term toxicity to aquatic invertebrates

NA

7.8.1.3. Algae and aquatic plants

Table 15. Effects on algae and aquatic plants

Method	Results	Remarks	Reference
Selenastrum capricornutum (new name: Pseudokirchnerella subcapitata) (algae) freshwater static OECD Guideline 201 (Alga, Growth Inhibition Test) GLP	ErC50 (72 h): > 21.9 mg/L test mat. (meas. (arithm. mean)) NOErC (72 h): 10.3 mg/L test mat. (meas. (arithm. mean))	2 (reliable with restrictions) key study experimental result **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

7.8.2. Terrestrial compartment

No information available.

7.8.3. Microbiological activity in sewage treatment systems

Table 16. Effects on micro-organisms

Method	Results	Remarks	Reference
activated sludge, domestic freshwater static OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test) GLP	EC50 (180 min): > 1000 mg/L test mat. (nominal)	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

7.8.4. PNEC derivation and other hazard conclusions

Table 17. Hazard assessment conclusion for the environment

Compartment	Hazard conclusion	Remarks/Justification
Freshwater	PNEC aqua (freshwater): 0.00827 mg/L	Assessment factor: 1000 Extrapolation method: assessment factor Acute tests for all three trophic levels are available. The justification based on the LC50 (96h) of fish (8.27 mg/L).
Marine water	PNEC aqua (marine water): 0.000827 mg/L	Assessment factor: 10000 Extrapolation method: assessment factor The justification based on the freshwater data.
Sediments (freshwater)	PNEC sediment (freshwater): 0.213 mg/kg sediment dw	Extrapolation method: partition coefficient PNEC sediment was derived using the equilibrium partitioning method (input data: Koc = 222 and PNECaqua = 0.00827 mg/L).
Sediments (marine water)	PNEC sediment (marine water): 0.0213 mg/kg sediment dw	Extrapolation method: partition coefficient PNEC sediment marine was derived using the equilibrium partitioning method (input data: Koc = 222 and PNECaqua marine = 0.000827 mg/L).
Sewage treatment plant	PNEC STP: 10 mg/L	Assessment factor: 100 Extrapolation method: assessment factor No effect of respiration inhibition observed up to 1000 mg/L.
Soil	PNEC soil: 0.0377 mg/kg soil dw	Extrapolation method: partition coefficient PNEC soil was derived using the equilibrium partitioning method (input data: Koc = 222, PNECaqua = 0.00827 mg/L and Henry`s Law constant =128.7 Pa m3/mol).

7.8.5. Conclusions for classification and labelling

The registrant(s) proposed no self classification for environment. The eMSCA agrees to this.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Absorption:

The experts of the Scientific Panel on Food Additives, Flavourings, processing Aids and materials in Contact with Food state that 2-ethylhexyl acetate is hydrolysed in the GI tract prior to absorption but that there is no experimental evidence of this.

COSMOS-SkinPermPred model predicts the skin permeability coefficient (Kp) for organic compounds, based on the calculated molecular volume and octanol-water partition coefficient (Kow). The predicted Kp of 2-EHAc is 0.0206 cm/hr. The Derwim model uses the molecular weight and the log Kow to estimate the Kp for compounds in water. The estimated kp is 0.0515 cm/hr (Derwim v.2.02)

Metabolism:

Experts within various fora state that in general, aliphatic linear and branched-chain esters of aliphatic linear satured carboxylic acids are anticipated to be readily hydrolysed in humans to their component alcohols and carboxylic acids (IPCS 1998; JECFA, 1998)

The rat liver S9 simulator in the OECD (Q)SAR Toolbox (v.3.3) gives 4 potential metabolites for 2-EHAc : 2-ethylhexan-1-ol, acetic acid, 2-ethylhexanal and 2-ethylhexanoic acid. The estimated toxic hazard classification of the four substances is low (Cramer class I). The HSDB database states that ethylhexanol has the same relative low degree of toxicity as 2-ethylhexyl acetate (HSDB, 1995).

The OECD SIAM task force who evaluated 2-ethylhexyl acetate states that acetate esters of primary alcohols undergo rapid hydrolysis. The reaction is catalysed by esterases and proteases found in mammalian tissue and gastric fluids (SIAM, 2010). The rapid and complete hydrolysis of 2-EHAc to 2-ethylhexan-1-ol as primary metabolite has been demonstrated to occur *in vitro* within blood (half-life 2.3 minutes) and *in vivo* (no more information available). Metabolism data in humans for 2-ethylhexyl acetate are not available (SIAM, 2010).

Excretion:

When acetate is administered to animals, only a small amount can be recovered from the urine (Smyth D.H., 1946).

7.9.2. Justification for read-across

Toxicokinetics of 2-ethylhexan-1-ol:

Absorption: The hydrolysis products acetic acid and 2-ethylhexan-1-ol of 2-ethylhexyl acetate are rapidly absorbed in the GI tract (EFSA, 2008; IPCS, 1998). *In vitro* percutaneous adsorption of 2-ethylhexan-1-ol was measured using full thickness rat skin and human stratum corneum (Barber, 1992). The absorption rates were 0.22±0.09 mg/cm²/hr for rat skin and 0.038±0.014 mg/cm²/hr for human skin. So the ratio rat/human was 5.78, indicating that the human skin is less permeable for the 2-ethylhexan-1-ol than the rat skin. The measured permeability constant (Kp) was 2.59 10^{-4} cm/hr for rat skin and 4.54 10^{-5} cm/hr for human skin. The predicted Kp is higher : 0.01525 cm/hr in COSMOS-SkinPermPred and 0.019 cm/hr in Dermwin v2.02 (In comparison the predicted Kp of 2-EHAc is 0.0206 cm/hr and the estimated kp by Derwim v.2.02 is 0.0515 cm/hr).

Metabolism: The hydrolysis of 2-ethylhexyl acetate to 2-ethylhexan-1-ol is rapid. The subsequent metabolism of 2-ethylhexan-1-ol to 2-ethylhexaldehyde is presumed to occur with subsequent oxidation of the aldehyde intermediate to 2-ethylhexanoic acid. Metabolism and toxicokinetics studies with 2-ethylhexan-1-ol have demonstrated the presence of 2-ethylhexanoic acid in the plasma as well as glucuronide conjugates and oxidation products of 2-ethylhexanoic acid metabolism in the urine (SIAM, 2010).

Excretion: Deisinger (1994) evaluated the excretion following oral, dermal and intravenous application (oral: single dose: 50 and 500mg/kg, repeated dose: 50mg/kg; dermal 1g/kg; intravenous application 1mg/kg) and revealed that all of the oral doses were eliminated rapidly, predominantly in the urine during the first 24h following dosing. The dermal dosing resulted in only about 5% absorption of the 1g/kg dose, with the major portion of the dose recovered unabsorbed from the dermal exposure cell at 6h. The available data show that excretion of 2-ethylhexyl metabolites is almost complete within 24-48hours.

Read across:

Taking the above described toxicokinetics based arguments the use of 2-ethylhexan-1-ol studies for the evaluation of potential systemic toxicity of 2-ethylhexyl acetate is overall accepted and applied in the report.

Additionally general knowledge on the indications for rapid hydrolysis of primary alcohols in acetate esters of primary alcohols, supported by short time measured hydrolysis rates in vitro, read across from 2-ethylhexan-1-ol to 2-ethylhexyl acetate can be accepted for the evaluation of systemic effects from exposure to 2-ethylhexyl acetate.

Moreover the European Commission's joint Research Center (DG JRC) has published a report on the list of compounds and their associated LCI (lowest concentration of interest) (JRC, 2013) and for the determination of the LCI of 2-ethylhexyl acetate the report states that read across from 2-ethylhexan-1-ol has to be applied. The task Force of the OECD-SIAM (2010) is under the impression that the toxicity information of 2-ethylhexan-1-ol is an appropriate surrogate for identifying hazards associated with systemic exposures to 2-ethylhexyl acetate. Also EFSA and IPCS accept that 2-ethylhexyl acetate is rapidly hydrolysed and that its hydrolysis products acetic acid and 2-ethylhexan-1-ol are rapidly absorbed by the GI tract where they may exert toxicity.

Read across with 2-ethylhexan-1-ol is therefore accepted by the eMSCA for the evaluation of 2-ethylhexyl acetate. For the evaluation of local effects, data on 2-ethylhexyl acetate were available.

di-(2-ethylhexyl)terephthalate (DEHT)

Read-across to DEHT is applied by the registrant(s) to fill the information requirement for the 2-generation reproductive toxicity study.

Barber *et al.,* 1994 analysed the hydrolysis of di(2-ethylhexyl)terephthalate (DEHT) using rat gut homogenate fractions in vitro. DEHT was hydrolysed by the intestinal fraction to 2-ethylhexan-1-ol and terephtalic acid. The half-life for DEHT was 53.3 minutes.

The systemic absorption and metabolism of DEHT was also studied in vivo by administration of [^{14}C]-DEHT in corn oil by oral gavage (Barber *et al.,* 1994). In the study radioactivity was eliminated in faeces (around 57%), excreted in urine (around 32%) and expired as $^{14}CO_2$ (around 4%). The majority of the material in the faeces was unchanged DEHT (36.6% of the total dose) and 50.5% of the dose was detected as teraphtalic acid in the urine. Excretion was very rapid (peak 10h after administration >95%).

Based on this toxicokinetics information on DEHT, the eMSCA agrees that 2-ethylhexan-1-ol is available in the body after DEHT application, but the quantity of 2-ethylhexan-1-ol formed from DEHT might not be sufficient to apply a read-across. In addition the half-time of 53.3 minutes is not sufficiently rapid.

Therefore, during the substance evalution the result of the 2-generation study with DEHT was only considered as indicative information to see whether a concern for reproductive toxicity could be identified for 2–ethylhexyl acetate.

2-ethylhexanoic acid

2-ethylhexanoic acid is one of the major metabolites of 2-ethylhexan-1-ol (Deisinger et al., 1994). Information on the quantity of 2-ethylhexanoic acid formed from 2-ethylhexan-1-ol or the half-time however is not provided.

Therefore, during the substance evaluation the result of the OECD 422 study with 2-ethylhexanoic acid was only considered as indicative information to see whether a concern for reproductive toxicity could be identified for 2-ethylhexyl acetate.

7.9.3. Acute toxicity and Corrosion/irritation

Acute toxicity : oral

Table 18 : summary of acute toxicity studies via oral route

Methods	LD50	Remarks	Reference
10 female rats/group By gavage 4 doses (unspecified) No GLP compliance	5140 mg/kg Death occurred predominantly within the first 24h Necropsy : unspecific blood congestion in the organs No macroscopic changes	2 (reliable with restrictions) Key study **Test material (EC name): 2-ethylhexyl acetate**	Schmidt P, Bachmann W (1969)
6 male rats/group no control group By gavage	Ca. 3000mg/kg	4 (not assignable) Supporting study **Test material (EC name): 2-ethylhexyl acetate**	Smyth Jr HF, Carpenter CP (1944)

The registrant concludes that the substance is not acutely toxic via the oral route (LD50 of 5140), and based on the available information, the eMSCA can support this conclusion.

Acute toxicity : inhalation

Table 19 : summary of acute toxicity studies via inhalation route

Methods	Results	Remarks	Reference
Inhalation hazard test (vapour) 0 and 7,5 mg/l in 20 female rats /group	0/20 died Slight irritation	3 (not reliable) (inconsistency of information about the concentration of the satured vapour atmosphere) **Test material (EC name): 2-ethylhexyl acetate**	Schmidt P, Bachmann W (1969)

Inhalation hazard test (vapour) Satured vapor 6 male rats No more information available	0/6 died after 15 min exposure 6/6 died after 30 min exposure	3 (not reliable) **Test material (EC name): 2-ethylhexyl acetate**	Smyth Jr HF, Carpenter CP (1944)
Inhalation hazard test (vapour) 0 and 7,5 mg/l in 5 male Guinea pigs/group	0/5 animal died Slight irritation	3 (not reliable) (inconsistency of information about the concentration of the satured vapour atmosphere) **Test material (EC name): 2-ethylhexyl acetate**	Schmidt P, Bachmann W (1969)

3 studies with minimal description of methods and results (reliability 3) and not following a guidance were presented. Two reported no mortality and one indicated the dead of all the tested animals after an exposure period of 30min.

The registrant concludes that the substance is not acutely toxic via the inhalation route. Based on the available information, the eMSCA can support this conclusion.

Acute toxicity : dermal

Table 20 : summary of acute toxicity studies via dermal route

Methods	Results	Remarks	Reference
In guinea pigs (6 per group) No information on the used concentration Type of coverage : occlusive (4 days)	LD50 >17400 mg/kg	4 (not assignable) Experimental result **Test material (EC name): 2-ethylhexyl acetate**	Smyth Jr HF, Carpenter CP (1944)
In rabbits No information on the dose groups used.	LD50 >5000 mg/kg	4 (not assignable) Experimental result **Test material (EC name): 2-ethylhexyl acetate**	Opdyke D.L. (1979)

The registrant concludes that the substance is not acutely toxic via the dermal route. Based on the available information, the eMSCA can support this conclusion.

Skin irritation/corrosion

Table 21 : summary of skin irritation studies

Methods	Results	Remarks	Reference
Non-human information			
0.5 ml in 3 rabbits Type of coverage: semi-occlusive (4 hours) OECD 404	Erythema score : mean 2,11 of max. 4 (time point 24, 48, 72h) (erythema score was in mean 2,33 in 2/3 animals and 1,67 in 1/3; erythema in 2/3 animals and scaling in 1/3 extending beyond the area exposure) Not fully reversible within 14 days (score of 1 in 2 animals at day 14) Edema score : 0 of max.4 (time point 24, 48, 72h) (no effects) Category 2 (irritant)	1 (reliable without restriction) Key study **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier
In rabbits Type of coverage : occlusive	Moderately irritant	4 (not assignable) **Test material (EC name): 2-ethylhexyl acetate**	Opdyke D.L. (1979)
Human information			
Human patch test 2-ethylhexyl acetate	No irrtitation effect	4	Registration dossier

Based on the results of the key study (Registration dossier) following OECD Guidance 404 which revealed an erythema score of 2.33 in 2/3 animals and for which the lesions were not fully reversible within 14 days, the test substance fullfills the requirements to be classified as **skin irritant Cat. 2** following CLP Guidance (EC No 1272/2008) (mean value of ≥2,3 - ≤4 for erythema or for edema in at least 2 of 3 tested animals from gradings at 24, 48 and 72hours after patch removal or inflammation that persists to the end of the observation period normally 14 days in at least 2 animals).

A self classification is proposed by the registrant (**skin irritation Cat. 2 H315 : Causes skin irritation)** and based on the available information, the eMSCA can support this conclusion.

Eye irritation :

Table 22 : summary of eye irritation studies

Methods	Results	Remarks	Reference

In 3 rabbits Dose : 0.1 ml during 24 hours OECD 405	Time point 24, 48, 72h Cornea score : 0 of max. 4 Iris score : 0 of max. 2 Conjunctivae score : 0,67 of max. 3 (fully reversible within 72h) Chemosis score : 0 of max. 4	1 (reliable without restriction) Key study **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier
In vitro study Hen eggs HET-CAM test according to Luepke N.P. (1985) : Hen's Egg Chorio allantoic membrane test for irritation potential	No severe eye irritation Time until appearance of haemorrhagia and coagulation : Mean undiluted test substance : 153 and 235 seconds (respectively) Mean 10% in olive oil : > 300 seconds	2 (reliable with restrictions) Supporting study **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier

The eMSCA concludes that based on the available information there is no concern for eye irritation.

7.9.4. Sensitisation

Skin :

Non-human information :

Table 23 : summary of skin sensitisation studies

Methods	Results	Remarks	Reference
QSAR calculation	The QSAR program calculated a negative sensitisation potential of the test substance.	2 (reliable with restrictions) Key study **Test material (EC name): 2-ethylhexyl acetate**	Registration dossier
QSAR calculation	The QSAR program calculated a negative sensitisation potential of the test substance	2 (reliable with restrictions) Supporting study	Registration dossier

		Test material (EC name): 2-ethylhexyl acetate	
Open epicutaneous test in guinea pigs (6-20 animals/dose) Induction (0.1 ml) and challenge : epicutaneous	No. with positive reactions : 1st reading (after 24h challenge) : 0/24 for test group and 0/10 for control 2nd reading (after 48h challenge) : 0/24 for test group and 0/10 for control Rechallenge : 0/24 for test group and 0/10 for control group Not sensitising	2 (reliable with restrictions) Key study Read-across **Test material (EC name): octyl acetate (CAS number : 112-14-1)**	Klecak G, 1985
Draize test in 10 guinea pigs Induction : intradermal (0.5%) Challenge : intradermal (0.2%) and epicutaneous (20%) OECD 406	No. with positive reactions : 0.2% : 1st reading : 0/10 24h after challenge Rechallenge : 0/10 168h after challenge 20% : 1st reading : 0/10 24h after challenge Rechallenge : 0/10 168h after challenge Not sensitising	2 (reliable with retsrictions) Key study Read-across **Test material (EC name): 3,5,5-trimethylhexyl acetate (CAS number : 58430-94-7)**	Sharp, DW, 1978
Open epicutaneous test in guinea pigs (6-20 animals/dose) Induction and challenge : epicutaneous	No. with positive reactions : 1st reading (after 24h challenge) : 0/24 for test group and 0/10 for control group 2nd reading (after 48h challenge) : 0/24 for test group and 0/10 for control group Rechallenge : 0/24 for test group and 0/10 for control group Not sensitising	2 (reliable with restrictions) Supporting study Read across **Test material (EC name): hexyl acetate (CAS number : 142-92-7)**	Klecak G, 1985
Open epicutaneous test in guinea pigs (6-20 animals/dose) Induction and challenge : epicutaneous	No. with positive reactions : 1st reading (after 24h challenge) : 0/24 for test group and 0/10 for control group 2nd reading (after 48h challenge) : 0/24 for test group and 0/10 for control group	2 (reliable with restrictions) Supporting study Read-across **Test material (EC name):**	Klecak G, 1985

	Rechallenge : 0/24 for test group and 0/10 for control group Not sensitising	**nonyl acetate (CAS number : 143-13-5)**	
Open epicutaneous test in guinea pigs (6-20 animals/dose) Induction and challenge : epicutaneous	No. with positive reactions : 1st reading (after 24h challenge) : 0/24 for test group and 0/10 for control group 2nd reading (after 48h challenge) : 0/24 for test group and 0/10 for control group Rechallenge : 0/24 for test group and 0/10 for control group Not sensitising	2 (reliable with restrictions) Supporting study Read-across **Test material (EC name): heptyl acetate (CAS number : 112-06-1)**	Klecak G, 1985

Human information :

Table 24 : summary of human information for skin sensitisation

Method	Results	Remarks	Reference
Maximization test with human volunteers General population (29 healthy subjects) Patch site pre-tested (5% aqueous sodium lauryl sulphate) Following 10-14d rest period, challenge patches applied for 48 hours	2-ethylhexyl acetate (4%) in petrolatum did not produce any skin sensitisation reaction	4 (not assignable) Key study Experimental result **Test material (EC name): 2-ethylhexyl acetate**	Opdyke DL, 1979
Survey in occupational population (7 male and female dental technicians) Patch tests applied for 24hours Observations directly, 48, 78 and 144 hours after removal	2-ethymhexyl acetate (1%) in petrolatum did not produce any reaction	4 (not assignable) Supporting study Experimental result **Test material (EC name): 2-ethylhexyl acetate**	Estlander T et al, 1984
Survey in occupational population (7 patients sensitized to dental composite resin	Exposure to 2-ethylhexyl acetate (0.5%) caused no effect in 5 subjects	4 (not assignable) Supporting study	Karneva L et al, 1989

products) Patch tests for 24 hours		Experimental result **Test material (EC name): 2-ethylhexyl acetate**	
3 Maximization test with human volunteers General population (25, 4 and 26 volunteers)	First test : exposure to 4% of tested substance in petrolatum produced one sensitisation reaction among the 25 subjects Second test : the same exposure produced no sensitisation reaction among 24 volunteers Thirth test : the same exposure did not produce any sensitisation reaction	4 (not assignable) Supporting study Read-across **Test material (EC name): 3,5,5-trimethylhexyl acetate (CAS number : 58430-94-7)**	Registration dossier
Maximization test with human volunteers Patch tests under occlusion for 48 hours General population (29 healthy subjects)	2-ethylhexan-1-ol (4%) in petrolatum did not produce any skin sensitisation reaction	4 (not assignable) Supporting study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Opdyke L 1979
Study with vonlunteers Test substances were tested either in human maximization test or human repeat insult patch test General population	4% Hexyl acetate : not a skin sensitiser 2% heptyl acetate : not a skin sensitiser 8% octyl acetate : not a skin sensitiser 2% nonnyl acetate : not a skin sensitiser	4 (not assignable) Supporting study Read-across **Test material (EC name): Hexyl acetate, heptyl acetate, octyl acetate, nonyl acetate**	Klecak G, 1985

There were no OECD Guideline study available with 2-ethylhexyl acetate or 2-ethylhexan-1-ol. However, there was human information which revealed that 2-ethylhexyl acetate and 2-ethylhexan-1-ol did not produce skin sensitisation reactions. Some studies conducted with similar substances (hexyl acetate, heptyl acetate, ...) did not show a skin sensitisation effect either.

The eMSCA concludes that based on the available information and weight of evidence there is no concern for skin sensitization nor does the assessment warrant classification as skin sensitiser.

7.9.5. Repeated dose toxicity

Oral :

Table 25 : summary of repeated dose toxicity studies via oral route

Methods	Results	Remarks	Reference
Rat (10/sexe/group) Subchronic (90D) 0, 25, 125, 250, 500 mg/kg by gavage OECD 408	No clinical signs or mortality Bw gain : decrease ($p<0.01$) in both sexes at 500 mg/kg (6-7%) Haematology : increase in reticulocyte numbers at 500 mg/kg (25%) Clinical chemistry : in males at 500 mg/kg : decrease protein and albumin concentration (13%). In females at 500 mg/kg : decrease serum cholesterol (16%) Relative organ weight : Brain : significant increase in males at 500 mg/kg Kidneys : significant increase in both sexes at 250 and 500 mg/kg Liver : significant increase in both sexes at 250 and 500 mg/kg Stomach : significant increase in both sexes at 500mg/kg (and also at 250 mg/kg in females) Testes : significant increase at 500 mg/kg	1 (reliable without restriction) Key study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Astill BD. Et al. (1996)

<table>
<tr>
<td></td>
<td>
Ovaries : significant decrease at 250 mg/kg
<table>
<tr><td></td><td>Males</td><td></td><td></td><td>Females</td><td></td><td></td></tr>
<tr><td>Mg/kg</td><td>0</td><td>250</td><td>500</td><td>0</td><td>250</td><td>500</td></tr>
<tr><td>Brain</td><td>0.68</td><td>0.7</td><td>0.72**</td><td>1.07</td><td>1.1</td><td>1.1</td></tr>
<tr><td>kidneys</td><td>0.69</td><td>0.75**</td><td>0.81**</td><td>0.77</td><td>0.81*</td><td>0.82**</td></tr>
<tr><td>liver</td><td>2.77</td><td>2.98**</td><td>3.57**</td><td>2.67</td><td>2.88**</td><td>3.07**</td></tr>
<tr><td>Stomach</td><td>0.57</td><td>0.58</td><td>0.63**</td><td>0.71</td><td>0.75*</td><td>0.82**</td></tr>
<tr><td>Testes</td><td>1.11</td><td>1.16</td><td>1.17*</td><td></td><td></td><td></td></tr>
<tr><td>Ovaries</td><td></td><td></td><td></td><td>0.041</td><td>0.037*</td><td>0.039</td></tr>
</table>
* p0.05; ** p0.01

<u>Histopathology :</u> forestomach : 500 mg/kg : inflammatory changes (attributable to the irritation properties of 2-EH)

Liver : 500 mg/kg : statistically significant increase of the hepatic cyanide-insensitive palmitoyl coenzyme A activity (peroxisome proliferation)

NOAEL : 250 mg/kg bw/d
</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse (10/sexe/group)

Subchronic (90D)</td>
<td><u>Mortality :</u> 1 female died at 250mg/kg

<u>BW :</u> no difference

<u>Hematology and clinical chemistry :</u> no difference</td>
<td>1 (reliable without restriction)

Key study

Read-across</td>
<td>Astill BD. Et al. (1996)</td>
</tr>
</table>

0, 25, 125, 250 and 500mg/kg OECD 408	Relative organ weight : Stomach : increase in both sexes at 500 mg/kg (males : 1.03** vs 0.76; females : 1.12** vs 0.87) (already at 250 mg in females (1.03**) Liver : increase in both sexes at 500 mg/kg (males : 4.23** vs 3.43; females : 4.16** vs 3.48) (and in males at 250 mg/kg 3.82*) Histopathology : forestomach : 500 mg/kg : moderate focal or multifocal acanthosis (in 2 males and 1 females) NOAEL : 250 mg/kg	**Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	

The eMSCA concludes that based on the available information there is no concern for repeated dose toxicity via oral route.

Inhalation :

Table 26 : summary of repeated dose toxicity studies via inhalation route

Method	Results	Remarks	Reference
Rat (10/sexe/dose) Subchronic (90D) 0, 15, 40 and 120 ppm (0, 0.08, 0.213, 0.640 mg/l) OECD 413	No treatment related effects NOAEC : 120 ppm	1 (reliable without restriction) Key study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Klimisch H-J. et al. (1998)
Rat (30 females treated and 20 males for control)	Hematology : decrease number of leucocytes ($p<0.002$) and number of lymphocytes ($p<0.01$) directly after the last exposure but not 4 weeks post-exposure	3 (not reliable) Experimental result	Schmidt P and Bachmann W, 1969

Subacute (20 days) 0, 75 mg/l	Organ weight : weight of spleen and ovaries were lowered in treated animals (respectively : $p<0.05$ and $p<0.01$) LOAEL 7.5 mg/l	**Test material (EC name): 2-ethylhexyl acetate**	

The eMSCA concludes that based on the available information there is no concern for repeated dose toxicity via inhalation route.

Dermal :

Table 27 : summary of repeated dose toxicity studies via dermal route

Method	Results	Remarks	Reference
Rat (females : 6 controls and 12 treated) Subacute (12D) 0, ca 1070 mg/kg bw/d Type of coverage : open	NOAEL ≥1070 mg/kg (local and systemic) No significant differences were observed between treated and control animals	2 (reliable with restrictions) Weight of evidence Experimental result **Test material (EC name): 2-ethylhexyl acetate**	Schmidt P and Bachmann W, 1969

The eMSCA concludes that there is no concern for repeated dose toxicity via dermal route.

7.9.6. Mutagenicity

In vitro data :

Table 28 : summary of *in vitro* mutagenicity studies

Method	Test results	Remarks	Reference
Bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. typhimurium TA 1535, TA1537, TA98 and TA 100 (met. act. : with and without) S. typhimurium TA 1538 (met. act. : with and without) Doses : 10, 100, 500, 1000 and 5000 µg/plate Comparable to OECD 471	Negative for S. typhimurium TA1535, TA1537, TA98 and TA100 with and without met. act. (cytotoxicity : yes (5000 µg/plate; 1000 µg/plate w/o S-9 in TA1535)	2 (reliable with restrictions) Key study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Registration dossier

Mammalian cell gene mutation assay (gene mutation) Chinese hamster ovary (CHO) (with and without met. act.) Doses : without met. act. : 20, 50, 100, 200, 250 and 300 nl/ml With met. act. : 100, 200, 250, 300, 350 and 400 nl/ml Comparable to OECD 476	Negative for Chinese hamster ovary with and without met. act. Cytotoxicity : 400 nl/ml	1 (reliable without restriction) Key study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Registration dossier
DNA damage and repair assay, unscheduled DNA synthesis in mammalian cells *in vitro* (DNA damage and/or repair) Hepatocytes from fisher rats without met. act. Doses : 2.5, 5, 10, 25, 50, 100, 250, 500 and 1000 nl/ml Comparable to OECD 486	Negative for hepatocytes Cytotoxicity : 500 nl/ml	1 (reliable without restriction) Key study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	US EPA (1987)

Gene mutation in bacteria: A GLP conform Ames test was performed with S. typhimurium TA1535, TA1537, TA98 and TA100. 2-ethylhexan-1-ol did not increase the number of revertants in any strain and was therefore not mutagenic in the Ames test. Cytotoxicity was observed generally in the highest dose.

Gene mutation in mammalian cells : a GLP conform HGPRT test was performed with Chinese hamster ovary cells. 2-ethylhexan-1-ol did not increase the mutant frequencies at the HGPRT test and was therefore considered as inactive in this test. Cytotoxicity was observed at 400 nl/ml.

Cytogenicity in mammalian cells: a GLP conform UDS study was performed with rat hepatocytes. 2-ethylhexan-1-ol did not increase the levels of unscheduled DNA synthesis in rat hepatocytes and was therefore considered as inactive in the UDS test. Cytotoxicity was observed at ≥500 nl/ml.

In vivo data :

Table 29 : summary of *in vivo* mutagenicity studies

Method	Test results	Remarks	Reference
Micronucleus assay (chromosome aberration)	Genotoxicity : negative	1 (reliable without restriction)	Registration dossier

Mouse male/female 456 mg/kg bw (acute treatment); 2 X 456 mg/kg bw/d (multiple treatment) Comparable to OECD 474		Key study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	
Chromosome aberration assay (chromosome aberration) Rat male Oral : gavage 0.02, 0.07 and 0.21 ml/kg bw/d (corresponding to 16.6, 58.1 and 174.3 mg/kg bw/d) Examination of bone marrow arrested in C-metaphase Comparable to OECD 475	Genotoxicity : negative Toxicity : no effects	1 (reliable without restriction) Key study Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Registration dossier

Cytogenicity : a GLP conform micronucleus test was performed in B6C3F1 mice. With one exception (multiple treatment males), there was no significant difference in percentage micronucleated polychromatic erythrocytes between animals dosed with the substance and the control animals. 2-ethylhexan-1-ol was not considered to be clastogenic in this study.

A GLP conform chromosome aberration assay was performed in rats. 2-ehtylhexan-1-ol did not cause aberrations in rat bone marrow cells and was therefore considered as inactive under the conditions of this assay.

The eMSCA concludes that based on the available information there is no concern for mutagenicity.

7.9.7. Carcinogenicity

Oral :

Table 30 : summary of *carcinogenicity* studies via oral route

Method	Results	Remarks	Reference
Mouse (50/sexe/dose) Gavage : 0 (vehicle), 0	Mortality : increase at 750 mg/kg (30% at 76 weeks vs 6% in other groups) Bw : statistically significant decrease (in males -5% at 200 mg and -12% at 750 mg and in females -14% at 750 mg)	1 (reliable without restriction) Key study	Astill BD. Et al. (1996)

(water), 50, 200, 750 mg/kg bw/d 18 months OECD 451	Food consumption : statistically significant reduced at 750 mg in both sex Haematology : no treatment related differences Organ weight : 750 mg/kg : Stomach : significantly ($p<0.01$) increase (males +16%, females +19%) Brain : significantly ($p<0.01$) increase (males +7%, females +12%) Liver : significantly ($p<0.01$) increase (females +21%) Kidneys : significantly ($p<0.01$) increase (females +13%) Testis : significantly ($p<0.01$) increase (+13%) (and slightly significantly increase at all other doses) Histopathology : non-neoplastic : 750 mg : significantly increase incidence of changes in lung (congestion +18%** in males and +20%* in females) and in liver (congestion +14%** in males; peripheral fatty infiltration +62%** in males and +44%** in females; basophilic foci +12%* in females) Neoplastic : 750 mg : significantly increase incidence of liver carcinoma in females (10%)(compared with the vehicle control but not with the water control, and this was attributed to the toxicity (fatty infiltration)) NOAEL (carcinogenicity) : 750 mg/kg LOAEL (toxicity) : 750 mg/kg NOAEL (toxicity) : 200 mg/kg	Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	
Rat (50/sexe/dose) Gavage : 0 (water), o (vehicle), 50, 150 and 500 mg/kg bw/d 24 months OECD 451	Mortality : dose related in females (+52% at 500 mg) (in males : not dose related mortality at 500 mg (38%) exceeded by that at 50 mg (46%)) Clinical signs : dose related increase poor general condition (lethargy, labored breathing, …) Bw : statistically significant differences from controls (in males -5%, -11% and -	1 (reliable without restriction) Key study Read-across **Test material (EC name): 2-ethylhexan**	Astill BD. Et al. (1996)

	23% and in females n.a., -9% and -21% respectively at 50, 150 and 500 mg) Haematology : 500 mg : increase incidence of anisocytosis at 12months (in 9 males/46) Relative organ weights : stomach : increase (50 mg : F 6%, 150 mg M 7% and F 9%, 500 mg : M 21% and F 20%) Liver : increase in females (150 mg : 11% and 500 mg 13%) Kidneys : increase (150 mg : M 22% F 7%, 500 mg : M 19% F 14%) Brain : increase (19% at 150 and 500 mg in both sex) Testis : increase at 500 mg (21%) Histopathology : non-neoplastic : significantly increase incidence of changes at high dose group in stomach, liver, lung, spleen, lymph nodes and prostate Neoplastic : no increase incidence of neoplastic lesions NOAEL (carcinogenicity) : 500 mg/kg LOAEL (toxicity) : 500 mg/kg NOAEL (toxicity) : 150 mg/kg	**-1-ol (CAS number : 104-76-7)**	

The eMSCA concludes that based on the available information there is no concern for carcinogenicity via oral route.

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

Effects on fertility :

Table 31 : summary of fertility effects

Method	Results	Remarks	Reference
Rats (30/sexe/dose) Feed : 0, 3000, 6000, 10000 ppm	Parental F0 : Mortality : 10000 ppm : 3 females	2 (reliable with restrictions) Key study	Faber et al. (2007)

in diet equivalent to : In mg DEHT/kg bw/d (males/females) : F0 : 0, 133-182/184-478, 265-367/372-940, 447-614/595-1030 F1 : 0, 159-256/206-516, 320-523/423-1036 and 552-893/697-1549 In mg 2-EH/kg bw/d (males/females) : F0 : 0 44-61/61-159, 88-122/124-313, 14-205/198-450 F1 : 0 53-85/87-172, 104-174/141-345 and 184-298/232-516 Exposure : Parental F0 : 70 consecutive days (for males : before mating, throughout mating until scheduled necropsy (6-10 days after weaning of litter); for females : before mating, throughout mating, gestation and lactation until scheduled necropsy) Parental F1 : according to the treatment of F0 test animals OECD 416 (two-generation reproduction toxicity study)	Body weight : 10000 ppm : slightly reduced at termination (5% in males and 12% during gestation in females) Food consumption : 1000 ppm : stat significantly reduced throughout gestation and lactation Organ weight : ≥6000 ppm : increase relative liver weight in females Somes other statistically significant decrease were observed but disappeared when compared relative to the bw (suggests that the difference were due to the decrease bw) Histopathology : no test substance related changes Parental F1 : Mortality : 10000 ppm : 7 females Body weight : 10000ppm : reduced at termination (-13% and -6%, respectively in males and females) 6000 ppm : decrease at termination (males -6% and -6.5% in females) Food consumption : 10000 ppm : decrease throughout genetration for males and significantly during gestation and lactation for females 6000 ppm : slightly reduced in both sexes Organ weight : ≥6000 ppm : increase relative liver weight in females Somes other statistically significant decrease were observed but disappeared when compared relative to the bw (suggests that the difference were due to the decrease bw) Histopathology : no test substance related changes Offspring F1 Body weight : ≥6000 ppm : decrease postnatal pup bw Relative organ weight : at PND 21 : ≥6000 ppm : increase for brain (+12 and +25 at 6000 (only in females) and 10000 ppm)	Read-across **Test material (EC name): Bis(2-ethylhexyl) terephthalate (DEHT) (CAS number : 6422-86-2)**	

	10000 ppm : decrease spleen weight in males (13%) Developmental landmarks : 10000 ppm : delay of 2 days of balanopreputial separation Necropsy : no observed changes Reproductive parameters : unaffected Litter parameters : unaffected Sperm parameters : no modification Offspring F2 Body weight : ≥6000 ppm : decrease postnatal pup bw Relative organ weight : 10000 ppm : decrease spleen weight (8% in males and 11% in females), increase brain weight (23-25% in both sexes), decrease thymus weight (only in females, 12%) Necropsy : no observed changes Reproductive parameters : unaffected Litter parameters : unaffected Sperm parameters : no modification NOAEL (parental toxicity) : 3000 ppm NOAEL (reproduction) : 10000 ppm NOAEL (developmental toxicity) : 3000 ppm		
Rats (10/sexe/dose) Feed : 1538, 4615 and 15385 mg/kg diet (corresponding respectively to 82-86, 248-253 and 761-797 mg/kg bw/d in males and 107-116, 308-351 and 809-1146 mg/kg bw/d in females Premating period of 2 weeks, during	Mortality and clinical signs : no effects Bw and food consumption : high dose group : decrease (up to 10% at the end of gestation) Fertility and reproductive performance : no effects on the incidences of liveborn, stillborn pups, viability indices of pups, sex-ratio's and pup observations Weight of pups : high dose group : decrease on PND 4 (14%) considered treatment related Haematology : high dose group : in females : lower values for mean corpuscular volume, mean corpuscular haemoglobin concentration,	1 (reliable without restriction) Supporting study Read-across **Test material (EC name): 2-ethylhexanoic acid (CAS**	Registration dossier

mating, gestation and lactation until PND 4 to 7) OECD 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) 2-ethylhexanoic acid (a potential metabolite of 2-EHAc)	reticulocytes, total white blood cells, monocytes and absolute number of neutrophils NOAEL P (maternal toxicity) : 4615 mg/kg diet NOAEL P (fertility) : 15385 mg/kg diet NOAEL F1 (developmental) : 4615 mg/kg diet	**number : 149-57-5)**	

There is no study available assessing the effect of 2-ethylhexylacetate or 2-ethylhexanol on fertility. The above two studies on DEHT and on 2-ethylhexanoic acid in addition to the results of the 90 day repeated dose toxicity study (see paragraph 7.9.5) were taken into account to verify whether on the basis of the available data a concern for reproductive toxicity could be identified.

Bis(2-ethylhexyl) terephthalate

No effect of DEHT on fertility was seen in the study of Faber et al. (2007).

Based on the toxicokinetics profile of DEHT as clarified under section 7.9.2, the eMSCA agrees that 2-ethylhexan-1-ol is available in the body after DEHT application, but the half-time of 53.3 minutes is not very rapid and the quantity of 2-ethylhexan-1-ol formed from DEHT might not be sufficient to apply read-across.

Therefore, during the substance evalution the result of the 2-generation study with DEHT was only considered as indicative information to see whether a concern for reproductive toxicity could be identified for 2–ethylhexyl acetate.

2-ethylhexanoic acid

No effect of 2-ethylhexanoic acid on fertility was seen in the OECD 422 study.

2-ethylhexanoic acid is one of the major metabolites of 2-ethylhexan-1-ol (Deisinger et al., 1994). No information on the quantity of 2-ethylhexanoic acid formed from 2-ethylhexan-1-ol or on the half-time is provided.

Moreover, it should be noted that 2-ethylhexanoic acid shows effects on development (harmonised classification as Repr. 2, H361d), while no effects on development were observed with 2-ethylhexanol. Therefore, the substances likely don’t have the same toxicity pattern.

Therefore, during the substance evaluation the result of the OECD 422 study with 2-ethylhexanoic acid was only considered as indicative information to see whether a concern for reproductive toxicity could be identified for 2-ethylhexyl acetate.

Additional information: 90-day study on 2-ethylhexan-1-ol

In the 90-day repeated dose toxicity study the relative weight of testes at 500 m/kg/day was increased and that of ovaries decreased at 250 mg/kg/day (but not at 500 mg/kg/day). Due to the lack of a dose response relationship and the lack of histopathological changes in testes or the ovaries, the changes in weight alone are not seen as adverse.

Based on this study, no concern for fertility was detected.

Comment by the evaluating member state:

Based on the available information, no concern for fertility was identified. It should be noted that no studies addressing specifically the fertility of 2-ethylhexyl acetate nor 2-ethylhexan-1-ol were available.

Developmental toxicity :

Table 32 : summary of developmental effects

Method	Result	Remarks	Reference
Rats, Gavage : single application on GD 12 (0, 6.25, 12.5 mmol/kg (833, 1666 mg/kg)	833 mg/kg : slight increase in malformed foetuses (2% vs 0% in control) 1666 mg/kg : decrease mean fetal bodyweight (3.5 g vs 4.1 g in control) and 22% of foetuses showed malformation (hydronephrosis, tail anomalies, anomalies of the extremities) (vs 0% in control) No information on maternal toxicity	3 (not assignable) Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Ritter EJ. Et al. (1987)
Mouse (50 females) Gavage : 0 and 1525 mg/kg Exposure : GD 7 through 14	1525 mg/kg : mortality (17 females died), clinical signs (languidity, ataxia, coldness to touch, wet stains), decrease bodyweight, reproductive index, mean number of live pups per litter, litter weight and mean pup viability per litter. The mean percent of dead pups was greater than in controls.	3 (not reliable) Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number :**	Hardin BD et al, 1987

<table>
<tr><td></td><td></td><td>104-76-7)</td><td></td></tr>
<tr><td>Mouse (28 females/group)

feed

0, 17, 59 and 191 mg/kg bw/d

Exposure : GD 0 through 17

OECD 414 (Prenatal developmental toxicity study)</td><td>No maternal, developmental or teratogenicity toxicity at all doses.

NOAEL (maternal toxicity, developmental toxicity, teratogenicity) : 191 mg/kg bw/d</td><td>1 (reliable without restriction)

Weight of evidence

Read-across

Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)</td><td>Tyl et al. (1991)</td></tr>
<tr><td>Rat (10 females/group)

Gavage : 0 (water), 0 (vehicle), 130, 650 and 1300 mg/kg bw/d

Exposure : GD6 through GD15

OECD 414 (prenatal developmental toxicity study)</td><td><u>Maternal effects :</u>

1300 mg/kg bw/d : 6 females died, significant decrease bodyweight (308.9 g vs 375.0 g in control) and food consumption, pronounced clinical signs (abdominal or lateral position, apathy, CNS depression, nasal discharge, salivation), significant macroscopy modifications (discoloration of liver and lung, lung edema and emphysema, distinctly reduced mean uterus weight (32.9 g vs 77.7 g in controls))

650 mg/kg bw/d : 2 females with piloerection

<u>Embryo and teratogenic effects :</u>

1300 mg/kg bw/d : fetal bodyweight markedly reduced (2.86 g vs 3.8 g), increase early resorptions (7.8 vs 1.0 in controls), high postimplantation loss (54.7% vs 8.2% in controls), increase incidences of skeletal changes (malformations (17.9% vs 1.4%), variations (71% vs 32%) and retardations (54% vs 26%))

650 mg/kg bw/d :
<table>
<tr><td></td><td>0 (water)</td><td>0 (vehicle)</td><td>130</td><td>650</td><td>1300</td></tr>
<tr><td>Fetal weight</td><td>3.8</td><td>3.82</td><td>3.8</td><td>3.44 **</td><td>2.86 **</td></tr>
</table>
</td><td>4 (not assignable)

Weight of evidence

Read-across

Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)</td><td>Hellwig J. and Jäckh R. (1997)</td></tr>
</table>

	No. (and %) of foetuses with malformations	1 (0.8)	2 (1.4)	3 (2.3)	7 (5.5)	5** (17.9)		
	No. (and %) of litters with malformations	1 (11)	2 (20)	3 (30)	4 (44)	2 (100)		
	No. (and %) of foetuses with variations	46 (37)	46 (32)	41 (32)	49 (39)	20 (71) **		
	No. (and %) of litters with variations	8 (89)	10 (100)	9 (90)	8 (89)	2 (100)		
	No. (and %) of foetuses with retardations	28 (23)	38 (26)	31 (24)	51 (40)	15 (54) **		
	No. (and %) of litters with retardations	8 (89)	10 (100)	8 (80)	9 (100)	2 (100)		
	For fetal bowy weight, historical control data (for that strain of rats in this laboratory) a mean fetal body weight was 3.9 ± 0.5. NOAEL (maternal toxicity, embryotoxicity, teratogenicity) : 650 mg/kg bw/d							
Rats (15 females) Inhalation : 850 mg/m3 Exposure : GD 1 through 19 OECD 414 (prenatal developme	No effect except reduced feed consumption (-10%) and reduced bodyweight gain (-20%) during gestation No embryo or teratogenic effects NOAEC : 850 mg/m3						2 (reliable with restriction) Weight of evidence Read-across **Test material (EC name):**	Nelson et al. (1989)

ntal toxicity study)		**2-ethylhexan-1-ol (CAS number : 104-76-7)**	
Rats (8 females/dose group in the preliminary test and 25 females per dose group in the main test) Dermal 0, 0.3, 1.0, 3.0 ml/kg bw/d (0, 252, 840, 2520 mg/kg bw/d) Exposure : GD 6 through 15 OECD 414 (prenatal developmental toxicity study)	Mortality or clinical signs : no effects Body weight gain : 2520 mg : decrease No adverse effect on maternal gestational parameters, maternal organ weight, fetal weight, sex ratio, viability, or the incidence of malformations and variations. NOAEL (maternal toxicity) : 840 mg/kg bw/d NOAEL (developmental and teratogenicity) : 2520 mg/k g bw/d	1 (reliable without restriction) Weight of evidence Read-across **Test material (EC name): 2-ethylhexan-1-ol (CAS number : 104-76-7)**	Tyl et al. (1992)

The different studies with 2-ethylhexan-1-ol reveal evidence of adverse effect of this substance on development at very high doses causing also strong toxic effects in dams and thus these effects can be considered as a consequence of the maternal toxicity. The studies for which there were no maternal effects, no embryotoxicity or teratogenicity were observed.

Summary of reproductive toxicity :

The eMSCA concludes that based on the currently available information there is no concern for reproductive toxicity (fertility and developmental toxicity).

7.9.9. Hazard assessment of physico-chemical properties

Not evaluated.

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

Not evaluated.

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

Based on the available data, the eMSCA agrees with the self classification:

Skin irrit. 2; H315: Causes skin irritation

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

P: The substance degraded 70% within 28 days in a ready biodegradability test. The substance is not P.

B: With a measured log Kow of 4.2, the substance almost meets the screening criterion for B. However, calculated BCF values are well below 2000. The substance is probably not B.

T: None of the aquatic toxicity tests meet the screening criterion for T. The most sensitive species was fish with a LC50 of 8.27 mg/L. The substance is probably not T.

Based on the available information, the evaluating MSCA agrees with the conclusion of the registrant(s) that 2-ethylhexyl acetate is not PBT.

7.12. Exposure assessment

Not evaluated.

7.13. Risk characterisation

Based on the available information in the registration dossier, no risk for workers, consumers or the environment could be identified for any of the chosen scenarios.

7.14. References

Astill B.D. Et al., *Prechronic toxicity studies on 2-ethylhexan-1-ol in F334 rats and B6C3F1 mice*, Fundam. Appl. Toxicol. 29, 31-39, 1996.

Barber E.D. et al., *A comparative study of the rates of in vitro percutaneous absorption of eight chemicals using rat and human skin*, Fundam. Appl. Toxicol. 19, 493-497, 1992.

Barber E.D. et al., *Hydrolysis, absorption and metabolism of de(2-ethylhexyl) terephthalate in the rat*, Xenobiotica 24(5), 441-450

Deisinger et al., *Metabolism of 2-ethylhexan-1-ol administered orally and dermally to the female Fischer 344 rat*, Xenobiotica 24, 429-440, 1994.

DERMWIN via http://www.epa.gov/oppt/exposure/pubs/episuite.htm

EFSA, *Opinion of the Scientific Panel on Food Additives, Flavourings, processing Aids and Materials in Contact with Food, Flavouring Group Evaluation 4 : 2-ethylhexyl derivatives from chemical group 2*, EFSA Journal 929, 1-46, 2008.

Estlander T. et al., *Hand dermatitis in dental technicians*, Contact Dermatitis 10(4), 201-205, 1984 (cited in RIFM data base 2009-09-08).

Faber et al., *Two generation reproduction study of Di-2-Ethylhexyl Terephtalate in Crl:CD Rats*, Birth Defects Research, 80, 69-81, 2007.

Hardin B.D. et al., *Evaluation of 60 chemicals in a preliminary developmental toxicity test*, Teratogenisis, Carcinogenesis and Mutagenisis 7, 29-48, 1987.

Hellwig J. and Jäckh R., *Differential prenatal toxicity of one straight-chain and five vrnahced-chain primary alcohols in rats*, Food and Chem. Tox. 35, 489-500, 1997.

IPCS-International Programme on Chemical Safety, *WHO Food additives series 40 Esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids*, 1998

JECFA, *Esters of aliphatic acyclic primary alcohols with branched-chain aliphatic acyclic acids,* The forty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives WHO Food additives series 40, World Health Organization, Geneva 1998.

JRC, ECA-IAQ (European Collaborative Action, Urban Air, Indoor Environment and Human Exposure), *Harmonisation framework for health based evaluation of indoor emissions from construction products in the European Union using the EU-LCI concept*, Report No 29. EUR 26168 EN. Luxembourg: Office for Official Publications of the European Communities. 2013

Karneva L. et al., *Allergic contact dermatitis from dental composite resins due to aromatic epoxy acrylates and aliphatic acrylates*, Contact Dermatitis 20, 201-211, 1989 (cited in RIFM data base 2009-09-08)

Klecak G., *The Freund's Complete DAjuvant Test and the Open Epicutaneous Test – A complementary test procedure for realistic assessment of allergenic potential*, Curr. Probl. Derm. 14, 152-171, 1985.

Klimisch H.J. et al., *Subchronic inhalation toxicity study of 2-ethylhexan-1-ol vapour in rats,* Food and Chemical Toxicology 36, 165-168, 1998.

Meylan et al., *Improved method for estimating bioconcentration/bioaccumulation factor from octanol/water partition coefficient*, Environ. Toxicol. Chem. 18(4), 664-672, 1999.

Nelson et al., *Developmental Toxicology of 1-pentanol, 1-hexanol, and 2-ethyl-1-hexanol by inhalation to rats*, J. Am. Coll. Toxicol. 8(2), 405-410, 1989.

Opdyke D.L., *Monographs on fragrance raw materials*, Food Cosmet. Toxicol. 779, 1979.

Ritter E.J. et al., *Teratogenicity of di(2-ethylhexyl) phtalate, 2-ethylhexan-1-ol, 2-ethylhexanoic acid and valporic acid and potential by caffeine*, Teratology 35, 41-46, 1987.

Schmidt P. and Bachmann W., *Zur arbeitshygienisch-toxikologischen Beurteilung volkswirtschaftlich bedeutsamer chemischer Substanzen. 4. Kurzmitteilung: Technisches 2-Aethylhexylacetat (Octylacetat)*, Z Gesamte Hyg. 15(12), 928-929, 1969.

SIAM, SIDS Initial assessment profile of 2-ethylhexyl acetate, 2007. SIAM 31, 20-22 October 2010.

Sharp D.W., *The sensitization potential of some perfume ingredients tested using modified draize procedure*, Toxicology 9, 261-271, 1978.

Smyth D.H., *The rate and site of acetate metabolism in the body*, J. Physiol. 105, 299-315, 1946.

Smyth Jr H.F and Carpenter C.P., *The place of the range finding test in the industrial toxicology laboratory*, J. Ind. Hyg. Toxicol. 26, 269-273, 1944.

Tyl et al., *Final report on the Developmental Toxicity in CD-1-Swiss mice*, NTIS (Springfield), 1991.

Tyl et al., *The developmental toxicity of 2-ethylhexan-1-ol applied dermally to pregnant Fischer 344 rats*, Fund. Appl. Toxicol. 19, 176-185, 1992.

US EPA, *Eight toxicological studies of 2-ethylhexan-1-ol*. TSCATS/OTS0515130, report no. 20991, 1987.

7.15. Abbreviations

2-EH : 2-ethylhexan-1-ol

2-EHAc : 2-ethylhexyl acetate

BE CA : Belgian Competent Authority

Bw : body weight

CORAP : community Rolling Action plan

CSR : Chemical safety Report

DEHT : di (2-ethylhexyl) terephthalate

DNEL : derived No Effect Level

ECHA : The European Chemicals Agency

ED : Endocrine Disruptor

EFSA : The European Food Safety Authority

eMSCA : The Evaluating Member State Competent Authority

GI : gastro-intestinal

GLP : Good Laboratory Practice

IPCS : International Programme on Chemical Safety

Kow : octanol-water partition coefficient

Kp : skin permeability coefficient

LCI : Lowest Concentration of Interest

LD50 : Lethal Dose 50

LOAEC : Lowest Observed Adverse Effect Concentration

LO(A)EL : Lowest Observed (Adverse) Effect Level

NA : Not applicable

NOAEC : No Observed Adverse Effect Concentration

NO(A)EL : No Observed (Adverse) Effect Level

OECD : Organisation for Economic Co-operation and Development

Ppm : Parts Per Million

QSAR : Quantitative Structure-Activity Relationship

RCR : Risk Characterisation Ratio

Rel. : Reliability

RSSs : Robuste Study Summaries

SVHC : Substance of Very high Concern

UDS : Unscheduled DNA Synthesis

US EPA : the United States Environmental Protection Agency