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

Reaction mass of (1S,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate, (1R,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate and 2-methyl-2-{[(1R*,2R*)-2,6,6-trimethylcycloheptyl]oxy}propyl propanoate, and 2-(1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy)-2-methyl propyl propanoate

EC No 604-250-7 and 415-490-5, CAS No 141773-73-1

Evaluating Member State(s): Germany

Dated: 03 August 2017

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Evaluating Member State Competent Authority

BAuA
Federal Institute for Occupational Safety and Health
Division 5 - Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund, Germany

Year of evaluation in CoRAP: 2016

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

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

Foreword

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

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

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

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

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Reaction mass of (1S,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate, (1R,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate and 2-methyl-2-{[(1R*,2R*)-2,6,6-trimethylcycloheptyl]oxy}propyl propanoate, and 2-(1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy)-2-methyl propyl propanoate (Helvetolide) was originally selected for substance evaluation in order to clarify concerns about:

- suspected PBT/vPvB

- exposure concern (wide dispersive use, exposure of environment)

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

- For CAS No. 141773-73-1 a NONS registration with EC No. 415-490-5 exists.

- A Compliance check was performed by ECHA on the registration dossier for EC 604-250-7 in 2015.

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 *[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

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

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 registrant(s) to ensure safety, as reflected in the registration dossiers(e.g. change in supported uses, applied risk management measures, etc.)	

After finalising the substance evaluation, the evaluating Member State Competent Authority (eMSCA) concluded that Helvetolide is not persistent due to primary degradation, potentially bioaccumulative and not toxic. The degradation product Helvetol is potentially persistent but not bioaccumulative. Consequently, the evaluating MSCA overall concludes that Helvetolide is not PBT/vPvB.

The exposure concern could be clarified with the conclusion that due to the use information provided in the registration dossier the exposure data did not suggest any indications for a high risk for the environment. These conclusions were based on the originally available and updated registration dossiers.

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

Reaction mass of (1S,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate, (1R,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate and 2-methyl-2-{[(1R*,2R*)-2,6,6-trimethylcycloheptyl]oxy}propyl propanoate, and 2-(1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy)-2-methyl propyl propanoate (Helvetolide) was originally selected for substance evaluation in order to clarify concerns about:

- suspected PBT/vPvB

- exposure concern (wide dispersive use, exposure of environment)

Table 4

EVALUATED ENDPOINTS **Endpoint evaluated**	**Outcome/conclusion**
Endpoint 1 - Degradation	- Not P/vP due to primary degradation - Metabolite is pot. P/vP
Endpoint 2 - Bioaccumulation	- pot. B/vB - Metabolite not B/vB
Endpoint 3 – Environmental toxicity	- not T
Endpoint 4 – PBT Assessment	- Concern not substantiated - Not PBT - Metabolite not PBT
Endpoint 5 – Exposure	- Releases into the environment may be expected to water, soil and air from wide dispersive uses in fragances and products containing fragances
Endpoint 6 – Risk	- According to the information submitted with the registration dossier, no unacceptable risk in any environmental compartment could be identified.

7.2. Procedure

Manual screening of the PBT properties of Helvetolide was carried out in 2014. Based on the findings of the manual screening the substance evaluation was justified (Justification for the selection of a candidate CoRAP substance). Substance evaluation started in March 2016 based on the data set updated by the Registrant(s) in November 2015. Referred to the screening, Helvetolide fulfils the screening levels of the PBT criteria as defined in Annex XIII. Accordingly, the evaluation is targeted to the persistency, the bioaccumulation potential and toxicity. In Addition to the hazard concern, environmental exposure was evaluated. The conclusions of the evaluation are documented in the technical SEV dossier for every endpoint of the section tree by means of annotations and endpoint summaries. The evaluating MSCA concluded that Helvetolide is not fulfilling the PBT/vPvB criteria of Annex XIII and exposure data show no unacceptable risk for the environment.

7.3. Identity of the substance

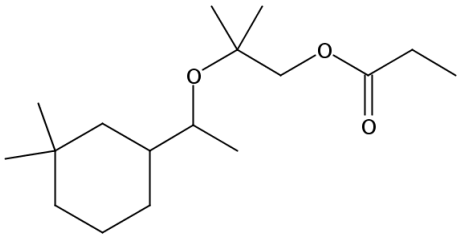
Table 5

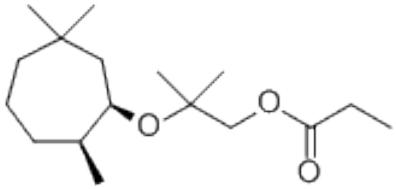
SUBSTANCE IDENTITY	
Public name:	Helvetolide
IUPAC name	Reaction mass of (1S,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate, (1R,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate and 2-methyl-2-{[(1R*,2R*)-2,6,6-trimethylcycloheptyl]oxy}propyl propanoate, and 2-(1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy)-2-methyl propyl propanoate
EC number:	604-250-7 and 415-490-5*
CAS number:	141773-73-1*
Index number in Annex VI of the CLP Regulation:	607-492-00-1*
Molecular formula:	$C_{17}H_{32}O_3$
Molecular weight range:	288.4 g/mol
Synonyms:	reaction mass of (1S,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate, (1R,1'R)-2-[1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy]-2-methylpropyl propanoate and 2-methyl-2-{[(1R,2R)-2,6,6-trimethylcycloheptyl]oxy}propyl propanoate, 1-Propanol, 2-[1-(3,3-dimethylcyclohexyl)ethoxy]-2-methyl-, propanoate

* The names that correspond to stated EC numbers, CAS number and Index number differ from given IUPAC-name of table 5. Nevertheless, the registrations using these numbers are the basis for this substance evaluation and describe substance identities that are identical with the substance identity described in this report.

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

Structural formula:





Multiconstituent/UVCB substance/others

Table 6

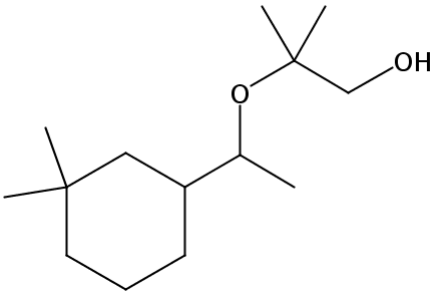
Constituent			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
presented in confidential annex			

7.3.1. Identity of the degradation product (Helvetol)

Table 7SUBSTANCE IDENTITY	
Public name:	Helvetol
IUPAC name	2-[1-(3,3-Dimethylcyclohexyl)ethoxy]-2-methyl-1-propanol
EC number:	-
CAS number:	141773-71-9
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	$C_{14}H_{28}O_2$

Molecular weight range:	228.4 g/mol
Synonyms:	1-Propanol, 2-[1-(3,3-dimethylcyclohexyl) ethoxy]-2-methyl-

Structural formula:



7.4. Physico-chemical properties

Table 8

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES OF THE REGISTERED SUBSTANCE		
Property	**Value**	
Physical state at 20°C and 101.3 kPa	*liquid*	
Melting/freezing point	*< -20 °C*	*according to EU Method A.1 (Melting / Freezing Temperature): method to determine freezing temperature.*
Boiling point	*282 – 303 °C*	*according to EU Method A.2 distillation method; Substance consists of three main constituents*
Density	*0.938 at 20 °C*	*According to EU Method A.3 (Relative Density): pycnometer method*
Vapour pressure	*17.2 Pa at 20 °C (extrapolated)*	*According to EU Method A.4 (Vapour Pressure): isoteniscope (due to the multi-isomers nature of the substance, this result may refer to the most volatile one)*
Water solubility	*4.7 mg/L at 20 °C*	*According to OECD Guideline 105 (Water Solubility): flask modified with slow-stirring*

Partition coefficient n-octanol/water (Log Kow)	*4.68 at 22.5 °C*	*According to EU Method A.8 (Partition Coefficient): shake-flask method*
Granulometry	*Data waiving*	*In accordance with Column 2 of REACH, Annex VII, Section 7.14, the study does not need to be conducted if the substance is marketed or used in a non solid or granular form.*
Stability in organic solvents and identity of relevant degradation products	*Data waiving*	*In accordance with column 2 of REACH Annex IX, the test on stability in organic solvents and identity of relevant degradation products (required in section 7.15) does not need to be conducted as the stability of benzyl alcohol is not considered to be critical.*
Dissociation constant	*Data waiving*	*Based on the chemical structure of the substance, no ionisation is anticipated, in particular under environmentally relevant pH range.*

7.4.1. Physico-chemical properties of the degradation product (Helvetol)

Table 9

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES OF THE REGISTERED SUBSTANCE		
Property	**Value**	
Physical state at 20°C and 101.3 kPa	*liquid*	
Boiling point	*259±8°C*	Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02
Density	*0.911±0.06 g/cm3*	Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02
Vapour pressure	1.98E-3 Torr *at 25 °C*	Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02

7.5. Manufacture and uses

7.5.1. Quantities

Table 10

Tonnage range to be ticked only.

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

Helvetolide is an odour agent and a basic compound of fragrances and other products which contain fragrances, such as laundry detergents.

Table 11: Uses of Helvetolide, where opportunity for exposure arises, according to the registration documents.

USES Identifiers	Uses where opportunity for exposure arises
Manufacture (M-1)	Use in batch and other processes (synthesis) (PROC 4); Transfer of substance or preparation from/to vessels/large containers at dedicated facilities (PROC 8b); **ERC 1 (manufacture)**; no spERC provided; process and industrial wastewater will occur.
Uses as intermediate	None
Formulation of fragrance compounds (F-1: GES 1) at 10-100 sites	Mixing or blending in batch processes (multistage and/or significant contact) (PROC 5); Transfer of substance or preparation from/to vessels and large/small containers at (non)-dedicated facilities (PROC 8a/b, 9); **ERC 2 (formulation of preparations)**; no spERC provided.
Formulation of fragrance end-products (F-2: GES 2) at 10-100 sites	Mixing or blending in batch processes (multistage and/or significant contact) (PROC 5); Transfer of substance or preparation from/to vessels and large/small containers at (non)-dedicated facilities (PROC 8a/b, 9); **ERC 2 (formulation of preparations)**; no spERC provided.
Uses at industrial sites	None
Professional end-use of washing and cleaning products (PW-1; GES 4)	PROC 4, 8a/b as before; Roller application or brushing (PROC 10); Non-industrial spraying (PROC 11); Treatment of articles by dipping and pouring (PROC 13); **ERC 8a/8d (wide dispersive indoor/outdoor use of processing aids in open systems)**; no speERC provided.

USES	
Identifiers	**Uses where opportunity for exposure arises**
Professional end-use of polishes and wax blends (PW-2; GES 5)	PROC 8b as before; Roller application or brushing (PROC 10); Non-industrial spraying (PROC 11); **ERC 8a (wide dispersive indoor use of processing aids in open systems)**; no speERC provided.
Consumer end-use of washing and cleaning products (C-1; GES 6)	Product Category PC 35; **ERC 8a/8d (wide dispersive indoor/outdoor use of processing aids in open systems)**; no speERC provided.
Consumer end-use of air care products (C-2; GES 7)	Product Category PC 3; **ERC 8a (wide dispersive indoor use of processing aids in open systems)**; no speERC provided.
Consumer end-use of polishes and wax blends (C-3; GES 9)	Product Category PC 31; **ERC 8a (wide dispersive indoor use of processing aids in open systems)**; no speERC provided.
Consumer end-use of cosmetics (C-4; GES 10)	Product Category PC 28, 29; **ERC 8a (wide dispersive indoor use of processing aids in open systems)**; no speERC provided.
Article service life	For the Exposure Scenarios PW-1, PW-2, and C 1-4, the subsequent service life is not relevant for the respective use.

For Helvetolide, relevant releases may be expected to water, soil and air from wide dispersive uses in fragances and products containing fragances.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 12

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)**		
607-492-00-1	2-(1-(3',3'-dimethyl-1'-cyclohexyl)ethoxy)-2-methyl propyl propanoate	415-490-5	141773-73-1	Aquatic Chronic 2	H411		

7.6.2. Self-classification

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

For EC Number 604-250-7:
Aquatic Chronic 1 H410
Skin Irrit. 2 H315

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Abiotic degradation

One valid key study (1995) is available in the registration dossier(s) to assess the abiotic degradation of the test substance Helvetolide. The study was performed according to a method equivalent to OECD Guideline 111 with GLP statement. No major deviation was observed even though some information is lacking such as the repeatability and sensitivity of the analytical method.

Hydrolysis was assessed in a preliminary test and in a main test. In the preliminary test, the substance failed to hydrolyse at pH 4 and pH 7 (at 50 °C). Therefore, the main test was perfomed at pH 9 and directly at 25 °C. The log_{10}-regressions suggest that the reactions are pseudo-first order because log_{10} concentration versus time is linear (r^2 > 0.98). The measurements at pH 9 and 25 °C resulted in a rate constant of 8.60 $*10^{-7}$ [s^{-1}], which corresponds to a half-life of 224 hours or a little over 9 days. The rate constant at pH 9 and 50 °C was derived as 3.58 $*10^{-2}$ [h^{-1}], which corresponds to a half-life of 19.4 hours. The degradation products of Helvetolide were not identified.

Phototransformation of Helvetolide in air, water and soil was not assessed by the registrant(s). A calculation of the phototransformation half-life of Helvetolide by the evaluating MSCA resulted in $DT_{50,air}$ of 4.1 hours (based on 12-hr day; 1.5E6 OH/cm³). This calculation with AOPWin v1.92 is rated Klimisch 4 (not assignable) because it is not validated in this document. A similar calculation for the major (approx. 70-80%) transformation product of Helvetolide (C6 isomer metabolite Helvetol, molecular formular: $C_{14}H_{28}O_2$; molecular weight: 228.38 g/mol; smiles notation: C1(CC(CCC1)C(C)OC(C)(CO[H])C)(C)C resulted in a $DT_{50,air}$ of 3.5 hours (based on 12-h day; 1.5E6 OH/cm³). Therefore, air does not appear to be a significant pathway for distribution of Helvetolide or Helvetol.

The analysis of the possible photodegradation pathway in air indicates that there are no preferred starting points for photodegradation in the Helvetolide molecule. Helvetol may be one among other metabolites, all of which do not appear to be relevant with regard to long-range transport or precipitation (expert judgement).

7.7.1.2. Biodegradation

Screening tests

In total, four biodegradation screening tests are provided in the registration dossier(s); one key study and 3 supporting studies.

The key biodegradation screening study with Helvetolide (2009) was done equivalent or similar to OECD Guideline 301 C, Modified MITI Test (I), and rated Klimisch 2 (reliable with restriction). This test is suitable for volatile substances. Degradation was determined to be 19 % $Th0_2$-consumption based on BOD measurements after 28 days, thus failing the pass-level of 60%.

Nearly all of the parent test substance has disappeared (< 2%) after 28 days and Helvetol was formed as transformation product (M1) at a rate of 79%. The other degradation product propionic acid (M2) is considered to have been mineralised (thus creating the 19% O_2-consumption). The parent substance and M1 (Helvetol) were monitored by GC; propionic acid (M2) was monitored by HPLC.

In conclusion, this screening test shows that primary degradation of Helvetolide takes place, but the ultimate degradation is below the pass level of 60%. Therefore, Helvetolide is considered to be "not readily biodegradable".

The supporting biodegradation screening studies in the registration dossier(s) (CO_2 Evolution Test; Closed Bottle Test; SCAS Removability; all dated 1994/1995) also indicate that Helvetolide is "not readily biodegradable".

Simulation tests

A simulation testing for biodegradation in water and sediment has been waived by the registrant(s). Further degradation studies with Helvetol are not available.

7.7.1.3. Conclusions on degradation

Hydrolysis of Helvetolide seems to be a major pathway of abiotic degradation at higher pH-levels (pH > 9). The major hydrolytic degradation product is Helvetol (CAS 141773-71-9), next to propionic acid (CH_3-CH_2-COOH). The hydrolysis half-life of Helvetolide was determined to be 224 hours or a little over 9 days (at pH 9 and 25 °C).

The calculated phototransformation half-life of Helvetolide in air is 4.1 hours (based on 12-h day; 1.5E6 OH/cm³). A similar calculation for the metabolite Helvetol resulted in a $DT_{50,air}$ of 3.5 hours. Helvetol may be one among other metabolites, all of which do not appear to be relevant with regard to long-range transport or precipitation.Therefore, air does not appear to be a significant pathway for distribution of Helvetolide or Helvetol.

In a screening test (OECD 301 C) Helvetolide is transformed to Helvetol (M1), which does not appear to biodegrade further. O_2-consumption of up to 19% ThOD in this test seems to be caused by mineralisation of the minor transformation product propionic acid (M2). Therefore, Helvetolide is "not readily biodegradable".

Simulation tests for biodegradation are not available.

7.7.2. Environmental distribution

7.7.3. Bioaccumulation

Helvetolide: The experimental log K_{ow} (shake flask method) of 4.68 is above the screening value of 4.5. No experimental BCF value is available. As Helvetolide degrades to Helvetol, the bioaccumulation potential of this metabolite is further evaluated.

Helvetol (hydrolysis metabolite): The experimental log K_{ow} (HPLC method) of 4.33 is close to the screening value of 4.5. BCF values were estimated with EPI Suite (v. 4.1) and ranged between 334 L/kg (regression based using log K_{ow}) and 607 L/kg (Arnot-Gobas Method including biotransformation, lower trophic level). The estimated

biotransformation rate constant kM of 0.72 / day (10 gram fish) corresponds to a relatively short estimated biological half-life of 0.96 days. As the substance is within the domain of the BCF/BAF model and the calculation is documented in QMRF and QPRF by the registrant(s), the estimated BCF values are considered as reliable with restriction.

One valid and reliable experimental BCF study is available on Helvetol in the registration dossier(s) (2013). This study followed the latest OECD 305 Guideline (2012) and was conducted using Helvetol (two isomers, one at 96% and the second at 3%) dissolved in water at two sub-lethal concentrations for a period of 28 days. The test organism was *Cyprinus carpio*. The test conditions were stable throughout the study and well wihin the acceptable limits (pH: 7.7-7.8, dissolved oxygen: 7.20-7.35, DOC < 2 mg/L).

The authors considered that steady-state was reached on day 28 although there was evidence that steady-state had already occurred by day 7 of the study. In both concentrations low BCFs were determined (11 - 25 with a mean of 15 at the highest water concentration of approximately 0.07 mg/L based on the major isomer and <21 - <35 [LOD] at the lowest water concentration of approximately 0.007 mg/L based on the major isomer). Results from the second isomer were almost identical. The measured BCF values are lower than expected from the log K_{ow}. This might be explained by the relatively high water solubility of 37.52 mg/L, which indicates that Helvetol has a high potential for excretion from water breathing organisms. The relatively high estimated biotransformation rate may also explain the low BCF values.

The available estimated and experimental data together lead to the conclusion that Helvetol, the major breakdown product of Helvetolide, has a low potential for bioaccumulation.

The substance is suspected to have higher bioaccumulation potential in air-breathing organisms than in water breathing organisms. The concerns related to the bioaccumulation potential in air-breathing organisms could not be clarified due to current lack of an assessment and testing approach. The approach is under development. This concern may need to be further assessed and potential information requested when the approach becomes available.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Acute toxicity to fish:

An acute test on fish toxicity with the species *O. mykiss* is available with the registered substance Helvetolide (1995). The test was well conducted according OECD Guideline 203 and according to GLP standard. The LC_{50} after 96 h is 3.4 mg/L and the NOEC is 1.7 mg/L; thes values were calculated using the geometric mean of measured concentrations according to OECD TG 23 (Guidance document on aquatic toxicity testing of difficult substances and mixtures).

At the concentration 1.7 mg/L (measured) no effects were seen. It is remarkable that at the concentration 3.4 mg/L non-lethal effects appeared already after a very short time of exposure: After 6 h exposure increased pigmentation was seen in 7 of 10 fish. Later (after 48 h) loss of equilibrium occurred in 2 fish. After 72 h, 3 of 8 fish were moribund.

At the end of study (after 96 h) 50% of fish were surviving, however all these fish showed increased pigmentation. At the next higher concentration of 8.7 mg/L (measured) all fish were dead after 24 h exposure.

As demonstrated above a very steep dose-reponse curve was seen in the acute fish toxicity test, as all sub-lethal effects and also the first lethal effects appeared in one concentration (3.4 mg/L) with no effects in the lower concentration (1.7 mg/L) and with only dead animals in the next higher concentration (8.7 mg/L). That means that a slight increase of the concentration caused a considerable effect.

Table 13: Acute toxicity to fish

Species / Test type	Duration / test conditions	Concentrations / Solvent	Effect value / Endpoint	Evaluating MSCA Comments	GLP	Reference
Oncorhynchus mykiss Rainbow trout OECD 203	Semi-static 96 h	1.4 - 2.5 - 4.4 - 7.9 mg/L (n), 0.9 – 1.7 – 3.4 – 8.7 mg/L (m) Concentration loss over test: 26-45 % Solvent: Tween 80-dimethylformamide, solvent control existed.	Mortality: LC_{50} (96h) 3.4 mg/L (m) LC_0: 1.7 mg/L (m)	At 3.4 mg/L: After 6 h exposure increased pigmentation; after 48 h loss of equilibrium and after 72 h presence of moribund fish. After 96 h 5 of 10 fish were dead. All surviving fish had increased pigmentation. No effects observed at 1.7 mg/L (m).	yes	Reg. dossier(s) 1995

Chronic toxicity to fish:

The registrant(s) waived the test on chronic toxicity to fish on the following grounds: "In accordance with column 2 of REACH Annex IX, further testing on the long-term effects on aquatic organisms does not need to be conducted as the chemical safety assessment does not indicate a need for further investigation."

No test on chronic toxicity to fish is requested as result of the substance evaluation for the following reasons:

- ECOSAR assigned Helvetolide to two classes: One class is the neutral organic-class. Neutral organics are considered to have baseline toxicity. They act in a non-polar narcosis mechanism of action. A steep dose-response like it did appear in the acute fish toxicity test can also be connected to the narcotic mode of action.

- Based on the LC_{50} value of 3.4 mg/L the acute to chronic ratio (factor LC_{50}/NOEC) would need to be 340 and based on the LC_0 value of 1.7 mg/L the factor of LC_0/NOEC would need to be 170. It is very unlikely that the ratios would reach these values.

- ECOSAR assigned Helvetolide also to the class esters. The chronic value (ChV) obtained by ECOSAR was 0.044 mg/L for the class esters. There were four substances in the class esters. Two substances were in the the pH-range of Helvetolide: Butylbenzyl phthalate and Dibutyl fumarate.

  Butylbenzyl phthalate had a ChV of 0.2 mg/L in an Early life-stage fish test with duration of 124 d (longer than normal). An existing special endocrine test was not used, because phthalates are endocrine acting substances but not Helvetolide (see below). Butylbenzyl phthalate is also a substance toxic to reproduction.

  Dibutyl fumarate had a ChV of 0.03 mg/L. It is an α,β-unsaturated carbonyl compound and has therefore structural alerts for enhanced toxicity (may cause Michael type addition reaction with unspecific binding to DNA or proteins).

  Helvetolide is an ester compound like the two substances above, but does not have other structures like the two substances (α,β-unsaturated carbonyl compound or substance with one or more aromatic rings) that could be alarming.

  Nevertheless both substances do not fulfill the T-criteria in the chronic fish test. Therefore it would be implausible that Helvetolide would fulfil the T-criteria.

- There is no indication for endocrine activity of Helvetolide as the substance does not contain an aromatic ring in the molecule.

- The results from human health studies (evaluated by the registrant) show, that not enhanced toxicity occured in a test on Repeated dose toxicity (EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral)). The NOAEL was 1000 mg/kg bw/day (nominal). Increased liver and thyroid weights at the doses of 1000 mg/kg bw/day and 500 mg/kg bw/day respectively were not regarded of toxicological significance. Another experiment (OECD Guideline 415, One-Generation Reproduction Toxicity Study) showed a NOAEL of 1000 mg/kg bw/day (toxicity, fertility, growth, development, viability). There were also no effects on estrous cycle, sperm, reproduction.

- The QSAR Toolbox assigned Helvetolide to the Verhaar class 3 (unspecific reactivity). However, all structural alerts that would have led to the allocation of Helvotolide to the Verhaar class 3 were not fulfilled. But due to not fulfilment of the structural alerts for class 2, Helvetolide was assigned to Verhaar class 3 (exclusion principle).

- A test on chronic aquatic toxicity is available (*D. magna*, OECD 211).

- In summary there is no convincing indication to request a test on chronic fish toxicity.

7.8.1.2. Aquatic invertebrates

Acute toxicity to *Daphnia magna*:

A test on acute toxicity on *Daphnia magna* was conducted in 1995 (registration dossier(s)) according to OECD Guideline 202 and GLP-standards. The performance deviated slightly from the guideline, as 2 groups of 10 animals each were exposed instead of 4 groups of 5 animals each. However this deviation in all likelyhood did not affect the results. Apart from that, the test was well conducted.

The EC_{50} after 48 h was 3.3 mg/L, the EC_0 was 1 mg/L. The dose-response curve was normal and not as steep like in the acute fish test.

Table 14: Acute toxicity to aquatic invertebrates

Species / Test type	Duration / test condition	Concentrations / Solvent	Effect value / Endpoint	Evaluating MSCA Comments	GLP	Reference
Daphnia magna OECD 202	48 h, static	0.1 – 0.18 – 0.32 – 0.56 – 1.0 – 1.8 – 3.2 – 5.6 – 10 mg/L (n), measured concentration were in the range of 80 - 100% of nominal	Mobility: EC_{50}: (48h): 3.3 mg/L (n) EC_0: 1 mg/L (n)	2 groups of 10 animals each were performed instead of 4 groups of 5 animals each.	yes	Reg. dossier(s) 1995

Chronic toxicity to *Daphnia magna*:

A test on chronic toxicity to *Daphnia magna* was conducted in 2003 (registration dossier(s)) according to OECD Guideline 211 and GLP-standards. Also this test was well conducted. The NOEC was 0.18 mg/L and the LOEC 0.61 mg/L (both values are measured concentrations).

For this report the concentrations were calculated using the geometric mean according to OECD Guideline 203 (Guidance document on aquatic toxicity testing of difficult substances and mixtures: "For static and semi-static tests, where the concentrations do not remain within 80-120% of nominal, the effect concentrations could be determined and expressed relative to the geometric mean of the measured concentrations.").

There were some sub-lethal effects: The daphnids at the 2.06 mg/L test concentration were observed in the beginning to be markedly smaller (decreased length) and later smaller and paler than the control animals prior to 100% mortality at this concentration on day 12. At 0.61 mg/L some of the Daphnids were paler prior to 100% mortality on day 16. After 21 days the length of surviving adults was determined. Based on length there were no statistically significant differences between control and the concentrations 0.025, 0.059 and 0.18 mg/L.

Some of the daphnids at the 0.61 mg/l test concentration were observed to be paler than the control animals. All the daphnids in this concentration were dead on day 16.

At the two higher concentrations (2.06 and 0.61 mg/L) all parent animals died. At the next lower concentration (0.18 mg/L) 2 of 10 parent daphnids died (not statistical significant using Cochran-Armitage Test Procedure as statistical calculation). In the control and at the lowest test concentration (0.025 mg/L) 1 of 10 *Daphnia* respectively died, too). **The NOEC for parental mortality is 0.18 mg/L.**

After 21 days there were no statistically significant differences between the control, 0.025, 0.059 and 0.18 mg/I test groups regarding the number of live young produced per adult. Therefore, the **NOEC is 0.18 mg/L for reproduction**.

Table 15: Chronic toxicity to aquatic invertebrates

Species / Test type	Duration / test condition	Concentrations / Solvent	Effect value / Endpoint	Evaluating MSCA Comments	GLP	Reference
Daphnia magna OECD 211	21 d, semi-static, solution renewed 3 times a week	0.03 – 0.095 – 0.30 – 0.95 – 3 mg/L (n); 0.025 – 0.059 – 0.18 – 0.61 – 2.06 mg/L (m, geometric mean); measured values were in the range of 95 and 147% of nominal for freshly prepared samples and between 11 to 59% of nominal for expired media; no solvent	NOEC 0.18 mg/L (m) reproduction NOEC 0.18 mg/L (m) parental mortality LOEC 0.61 (m)	Some parental daphnids at 0.61 mg/L (m) were observed to be paler prior to 100% mortalities on day 16. The parental daphnids at 2.06 mg/L (m) were smaller and paler than the control animals prior to 100% mortalities on day 12.	yes	Reg. dossier(s) 2003

7.8.1.3. Algae and aquatic plants

The registrant(s) provided a test on toxicity to algae with the duration of 96 h (1995). According to OECD TG 201 a test duration of 72 h is specified. However, the longer test duration does not matter.

Two of three validity criteria of the test could not be specified ('mean coefficient of variation for section-by-section specific growth rates in the control' and 'coefficient of variation of average specific growth rate during the whole test period in the control'), no cell density values were given. The validity criteria 'biomass in the control cultures should have increased exponentially by a factor of at least 16' was fulfilled: Biomass in the control cultures increased exponentially by a factor of at least 16 within the test period.

However it is obvious based on the measured absorbance values that no effects appeared. Therefore, a repeat of the test would not reveal new information.

Table 16: Toxicity to algae

Species / Test type	Duration / test condition	Concentrations / Solvent	Effect value / Endpoint	Evaluating MSCA comments	GLP	Reference
Pseudokirchneriella	96 h,	14 mg/L (n); 1.1 mg/L (m, at	NOEC >= 1.1 mg/L (m);	The registrant(s)	yes	Reg. dossier(s)

subcapitata OECD 201	static	the end of the test) At 0 h 97% of nominal (equates to 13.6 mg/L), at 96 h 8-9 % of nominal (equates to 1.06 to 1.21 mg/L); Solvent: Tween 80-di-methylformamide	E_rC_{50} > 1.1 mg/L (m)	used the concentration of 1.1 mg/L. That means a worst case scenario as it is the concentration only measured at the end of the test. However it does not matter, as no effects appeared.		1995

7.8.1.4. Sediment organisms

Not assessed

7.8.1.5. Other aquatic organisms

7.8.2. Terrestrial compartment

7.8.3. Microbiological activity in sewage treatment systems

7.8.4. PNEC derivation and other hazard conclusions

PNEC values derived in the registration dossier(s) are acceptable; there were no deviations found during the substance evaluation which required clarification or further action.

7.8.5. Conclusions for classification and labelling

The existing Annex VI entry for Helvetolide is considered appropriate (Aquatic Chron. 2).

7.9. Human Health hazard assessment

Not assessed, however, the existing data does not indicate that the T-criteria is fulfilled (using human health hazard evaluation from the registrant(s)).

7.10. Assessment of endocrine disrupting (ED) properties

Not assessed

7.11. PBT and VPVB assessment

1) Persistence:

Helvetolide is not ready biodegradable but shows primary degradation to Helvetol in screening tests. Due to this primary degradation of Helvetolide (biotically driven hydrolysis), the substance is not considered to be persistent. The metabolite Helvetol is regarded as potentially persistent/very persitent ("P/vP") based on the available screening data.

2) Bioaccumulation:

Based on the available screening data (log K_{ow} 4.68), Helvetolide is potentially B. No experimental BCF data are available. As Helvetolide degrades to Helvetol, the bioaccumulation potential of this metabolite is further evaluated.

The log K_{ow} of the metabolite Helvetol is 4.33 and is close to the screening trigger of 4.5. Estimated BCF values range between 334 and 607 L/kg and the available experimental BCF values are very low (0.07 mg/L: BCF 11 - 25 based on the major isomer, 0.007 mg/L: BCF <21 - <35 [LOD] based on the major isomer). The measured BCF values are lower than expected from the log K_{ow}. That might be explained by the relatively high water solubility, which indicates that Helvetol has a high potential for excretion from water breathing organisms. The relatively high estimated biotransformation rate may also be an explanation for the low BCF values.

Taking all this information into account, Helvetol, the major breakdown product of Helvetolide, is considered as not bioaccumulative.

3) Toxicity:

The acute toxicity data for fish, *Daphnia* and algae do not reach the T-screening value of 0.1 mg/L. Also the NOEC from the chronic *Daphnia* test and the NOEC from the algae test do not fulfill the T-criteria of 0.01 mg/L. A chronic fish test is not available but chronic toxicity to fish that would fulfill the T-criteria is not suspected. In summary, Helvetolide does not fulfill the T-criterion.

4) Overall conclusion on the PBT/vPvB assessment:

The evaluating MSCA considers Helvetolide as not persistant due to primary degradation, potentially bioaccumulative and not toxic. The major metabolite Helvetol is potentially persistant but not bioaccumulative. The evaluating MSCA overall concludes that Helvetolide is not PBT/vPvB.

7.12. Exposure assessment

Helvetolide is an odour agent and a basic compound of fragrances and other products which contain fragrances, such as laundry detergents.

For Helvetolide, relevant releases may be expected to water, soil and air from wide dispersive uses in fragances and products containing fragances.

The evaluating MSCA has not performed its own exposure modelling and finds the exposure assessment provided by the registrant(s) to be acceptable.

7.13. Risk characterisation

The environmental RCR values provided by the registrant(s) related to combined exposure based on EUSES are all below 1, and thus do not express an unacceptable risk.

7.14. References

Aside from the registration dossier(s), no other additional sources were used.

7.15. Abbreviations

There are no substance-specific abbreviations.