Analysis of the most appropriate risk management option (RMOA)

Substance Name: Homosalate

EC Number: 204-260-8

CAS Number: 118-56-9

Authority: France

Date: January 2018

Cover Note

In the framework on the French National Strategy on Endocrine Disruptors in 2017, the French Competent Authority requested ANSES to evaluate the ED properties of homosalate and verify whether risk management measures should be necessary for this substance. ANSES concludes that further investigations are needed to clarify toxicological and environmental concerns, including endocrine disruptive potential. In addition to this work, it should be noted that Germany assessed this substance in the framework of manual screening in 2016 concluding that a compliance check (CCH) is recommended. In the framework of CCH process, a request of a sub-chronic toxicity study, a pre-natal developmental toxicity study, an extended one-generation reproductive toxicity study and the identification of degradation products was agreed in MSC-57. This substance has not been discussed at the ED-EG level in November 2017 as initially planned as ED-EG meeting was scheduled just before the decision making process of the CCH.

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1 IDENTITY OF THE SUBSTANCE

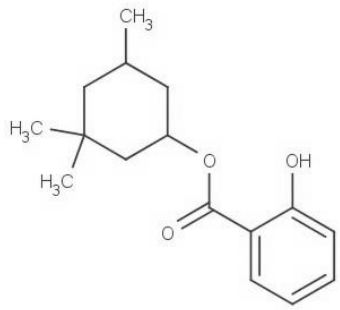
1.1 Other identifiers of the substance

Table 1: Other Substance identifiers

EC name (public):	Homosalate
IUPAC name (public):	3,3,5-trimethylcyclohexyl salicylate
Index number in Annex VI of the CLP Regulation:	Not listed in Annex VI
Molecular formula:	C16H22O3
Molecular weight or molecular weight range:	262.3441
Synonyms:	Homomenthylsalicylate Homosalate Sunobel®HMS

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

Structural formula:



1.2 Similar substances/grouping possibilities

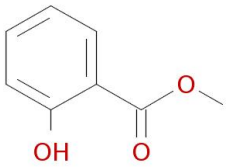
The registrant proposed in the registration dossier a read across of homosalate with the substances methyl salicylate for long-term repeat dose toxicity, reproductive and developmental toxicities and the substance 2-ethylhexyl salicylate for eye irritation and for the short term with fish

The following tables present general information of the substances proposed for the read across by the registrant:

Table 3: General information on methyl salicylate

EC number:	204-317-7
EC name (public):	Methyl salicylate
CAS number:	119-36-8
IUPAC name (public):	Methyl salicylate Methyl 2-hydroxybenzoate Methyl 2-hydroxybenzoate Methyl-2-hydroxybenzoate Metil szalicilát Salicylic acid, methyl ester
Index number in Annex VI of the CLP Regulation:	Not listed in Annex VI
Molecular formula:	C8H8O3
Molecular weight or molecular weight range:	152.1473 g/mol
Synonyms:	2-HYDROXYBENZOATE DE METHYLE 2-Hydroxybenzoic acid methyl ester Benzoic acid, 2-hydroxy-, methyl ester HYDROXY-2 BENZOATE DE METHYLE Methyl 2-hydroxybenzoate Methyl salicylate SALICYLATE DE METHYLE Salicylic acid, methyl ester Wintergreen oil

Structural formula:



According to ECHA disseminate website, the substance is used in the following products: perfumes and flagrances, fuels, air care products, washing and cleaning products, cosmetics and personal care products, biocides (e.g. disinfectants, pest control products), polishes and waxes.

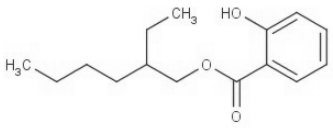
The substance was on the CoRAP list for substance evaluation in 2015 by France. This evaluation was based on the following concerns: suspected CMR (especially reprotoxicity), consumer use and high aggregated tonnage. Following the substance evaluation, France produced a draft decision with requests related to human health, ecotoxicological /environmental fate and exposure. At this time, France is currently assessing the new data submitted by the registrants during the period of registrant's comments to conclude if the draft decision should be modified.

Furthermore, the substance is currently enrolled in the PACT list by France for hazard assessment and RMOA activity due to endocrine and CMR properties, respectively. More information about the read-across with methyl salicylate is presented in the 3.2 section.

Table 4: General information on 2-ethylhexyl salicylate

EC number:	204-263-4
EC name (public):	2-ethylhexyl salicylate
CAS number:	118-60-5
IUPAC name (public):	2-ethylhexyl 2-hydroxybenzoate 2-ETHYLHEXYL SALICYLATE 2-Ethylhexylsalicylate Ethylhexyl Salicylate
Index number in Annex VI of the CLP Regulation:	Not listed in Annex VI
Molecular formula:	C15H22O3
Molecular weight or molecular weight range:	250.3
Synonyms:	SOCT Sunobel® OS

Molecular formula:



According to ECHA disseminate website, the substance is used in the following products: cosmetics and personal care products.

3 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table 5: Completed or ongoing processes

RMOA		☐ Risk Management Option Analysis (RMOA) other than this RMOA
REACH Processes	Evaluation	☒ Compliance check, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restri -ction	☐ Annex XVII[1]
Harmonised C&L		☐ Annex VI (CLP) (see section 3.1)
Processes under other EU legislation		☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009
		☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments
Previous legislation		☐ Dangerous substances Directive Directive 67/548/EEC (NONS)
		☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)
(UNEP) Stockholm convention (POPs Protocol)		☐ Assessment
		☐ In relevant Annex

[1] Please specify the relevant entry.

Other processes/ EU legislation	☒ Other (provide further details below) According to regulation (EC) N° 1223/2009, homosalate can be used in cosmetic products (including sun screen) at a maximum concentration at 10% weight/weight (SCCP; 2007). The substance was in the manual screening short list in 2016. Under this process, Germany concluded that a CCH prior to a SEv is required based on data gaps for repeated-dose toxicity, reproductive toxicity, developmental toxicity and additional consumer use. In addition, it was stated that the adequacy of the analogue approach used by the registrant should be evaluated. Finally, further data is necessary to decide about PBT properties (e.g. in a substance evaluation). Following this outcome, a CCH was initiated by ECHA.The final decision contains a request for a 90-day repeated dose toxicity study, a pre-natal developmental toxicity study, a full extended one-generation reproductive toxicity study and a degradation test, identifying the degradation products of the substance. This decision was agreed at MSC-57.

4 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

4.1 Classification

4.1.1 Harmonised Classification in Annex VI of the CLP

Table 6: Harmonised classification

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)		
No harmonized classification							

4.1.2 Self classification

- In the registration: No self-classification

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:
  - Skin Irrit. 2 – H315
  - Eye Irrit 2 – H319
  - STOT SE 3 – H335
  - Aquatic Chronic 4 – H413

4.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

No ongoing activity.

4.1.4 CLP Notification Status

Table 7: CLP Notifications

	CLP Notifications[2]
Number of aggregated notifications	3
Total number of notifiers	113

[2] C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 16 March 2017)

4.2 Additional hazard information

4.2.1 Human health

- Read-across with methyl salicylate

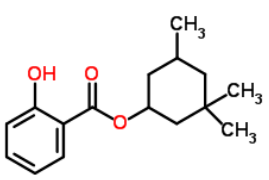
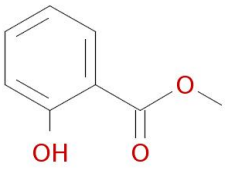
The registrants proposed a read-across with methyl salicylate for long-term repeat dose toxicity, reproductive and developmental toxicities.

The justification provided by the registrant consists on a similar pathway for biotransformation considering that both methyl salicylate and homosalate are metabolized into a common compound: salicylic acid (SA), in addition to an alcohol specific to each parent molecule. In this context, the registrants consider that these substances have comparable mode of action with regard to systemic toxicity. This scenario is consistent with the scenario 1 (analogue approach for which the read-across hypothesis is based on (bio)transformation to common compound) of the Read-across Assessment Framework (RAAF).

Table 8: Scenario corresponding to the proposed read-across according to the RAAF

	Parent substances	**(Bio)transformation**	**Common compound**	**Non-common compound**
Target	Homosalate (HMS)	HMS → SA + 3,3,5-trimethylcyclohexanol	Salicylic acid (SA)	3,3,5-trimethylcyclohexanol
Source	Methyl salicylate (MeS)	MeS → SA + methanol	Salicylic acid (SA)	Methanol

Table 9: Data matrix

	Homosalate	**Methyl salicylate**
Chemical structure		
CAS number	118-56-9	119-36-8
Molecular weight	262.3441 g/mol	152.1473 g/mol
Physicochemical properties		
Water solubility	0.4 mg/L (25 °C) (ECHA website)	0.67 g/L at ambient temperature (Merck Index 14th, 2006)
Log Kow	> 6 at 40°C (ECHA website)	2.55 (Sangster database)
Vapour pressure	0.015 Pa at 15 °C and 0.013 Pa at 20 °C	10 Pa at 22°C and 100 Pa at 51°C

	(ECHA website)	(Lide, 2005-2006)
Toxicological properties		
Toxicokinetics	Oral absorption: 100% (default value; Danish QSAR database) Dermal absorption: < 10% (*in vitro* rat and human skin; ECHA website) Metabolized into SA + trimethylcyclohexanol (hypothesis; no experimental data)	Oral absorption: 100% (ECHA website) Dermal absorption: 1-93% (animal and human data) (Yano, 1986; CIR, 2003; RIFM, 2007; Lapczynski, 2007) Metabolized into SA + methanol (no experimental data giving a clear overview of all metabolites and kinetics)
Acute toxicity	LD_{50} oral > 5000 mg/kg bw (SCCP, 2007; ECHA website)	LD_{50} oral = 580 to >2000 mg/kg bw →Acute Tox 4 (self-classification) (Lapczynski, 2007; CIR, 2003; EPA, 2005)
	LD_{50} dermal > 5000 mg/kg bw (SCCP, 2007; ECHA website)	LD_{50} dermal > 2000 mg/kg bw (Lapczynski, 2007)
Irritation	No dermal irritation (*in vitro* and *in vivo*) (SCCP, 2007; ECHA website)	No dermal irritation (ECHA website)
	Not irritant to eye at 12% (ECHA website) Read-across with 2-ethyl-hexyl salicylate (ECHA website).	Contradictory data for eye irritation (CIR, 2003; ECHA website)
Sensitisation	Negative in photoallergy tests in animals and in clinical studies in volunteers (SCCP, 2007; ECHA website) Weak to moderate sensitizer estimated by QSTR (Einslein *et al*. 1997)	Negative in Maximisation assays (Kimber *et al.* 1991; ECHA website ; Lapczynski, 2007) Contradictory results in LLNA (Kimber *et al.* 1991; ECHA website; Lapczynski, 2007; Kimber *et al.* 1998; Gerberick *et al.* 1992; Ashby *et al.* 1995; Basketter *et al.* 1992, 1994, 1998; Montelius *et al.* 1994, 1998; Picotti *et al.* 2006; Adenuga *et al.* 2012; Hou *et al.* 2015) Low incidence of reactions in humans (ECHA website; Lapczynski)
	2-week study in rats by gavage up to 1000 mg/kg	Study in dogs up to 1200 mg/kg bw/day in capsule

Repeated-dose toxicity after oral exposure	bw/day: biochemical changes from 100 mg/kg bw/day (SCCP, 2007).	up to 59 days: weight loss and mortality from 500 mg/kg bw/day and liver effect from 800 mg/kg bw/day. (Webb & Hansen, 1963)
	Combined repeated dose and reproductive/developmental screening study in rats by gavage up to 750 mg/kg bw/day: constant light is expected to have affected the reliability of the study. Target organ at all doses (from 60 mg/kg bw/day): kidney Target organ from 120 mg/kg bw/day: liver Target organs from 300 mg/kg bw/day: thyroid and spleen (ECHA website)	17-week study in rats in the diet up to 500 mg/kg bw/day: reduced body weight gain at 500 mg/kg bw/day. (Webb & Hansen, 1963) Mechanistic studies from 6 to 12 week duration on bone metabolism and growth up to 1000 mg/kg bw/day in rats in the diet: bone lesions from 560 mg/kg bw/day and growth retardation from 320 mg/kg bw/day. (ECHA website)
	No chronic study available	2-year study in rats in the diet up to 1000 mg/kg bw/day: cancellous bone from 250 mg/kg bw/day, high mortality at 1000 mg/kg bw/day. (Webb & Hansen, 1963) 2-year study in dogs in capsule up to 300 mg/kg bw/day: liver effect from 150 mg/kg bw/day. (Webb & Hansen, 1963)
Mutagenicity	Negative *in vitro* in Ames tests, in a HPRT gene mutation study and in chromosomal aberration studies. (Zeiger et al. 1987; ECHA website; SCCP, 2007).	Negative *in vitro* and *in vivo* (ECHA website; FDA, 2006)
Carcinogenicity	No data	Not carcinogenic in rats by gavage up to 500 mg/kg bw/day. All animals died at 1000 mg/kg bw/day. (Webb & Hansen, 1963)
Toxicity on the reproduction	Combined repeated dose and reproductive/developmental screening study in rats by gavage up to 750 mg/kg bw/day: constant light is expected to have affected the reliability of the study. Increased infertility (not dose-related)	Study on fertility and early embryonic development to implantation up to 300 mg/kg/day by subcutaneous injection: no effect on fertility (FDA, 2006) Study on reproductive and developmental toxicity

	From 300 mg/kg bw/day: increased post-implantation loss, lower birth index. At 750 mg/kg bw/day: sperm alteration, low number of corporea lutea. (ECHA website)	(including pre and post-natal development) up to 200 mg/kg/day by subcutaneous injection: no effect on gestation (FDA, 2006) Other studies of lower quality bring unconclusive result on reproductive toxicity (NTP, 1984; Collins, 1971; ECHA website)
Toxicity on the development	Combined repeated dose and reproductive/developmental screening study in rats by gavage up to 750 mg/kg bw/day: constant light is expected to have affected the reliability of the study. From 300 mg/kg bw/day: increased post-implantation loss, lower birth index. (ECHA website)	Study on reproductive and developmental toxicity (including pre and post-natal development) up to 200 mg/kg/day by subcutaneous injection: decreased birth index, delayed balanopreputial separation, delayed incisor eruption, skeletal anomalies and variations at 200 mg/kg/day (FDA, 2006) Other reproductive toxicity studies of lower quality reported reduced viability and decreased pup weight (Collins, 1971; ECHA website)
	No prenatal toxicity study available.	Prenatal toxicity study in rats up to 200 mg/kg/day by subcutaneous injection: decreased foetal body weight, external and skeletal anomalies at 200 mg/kg/day (FDA, 2006) Prenatal toxicity study in rabbits up to 300 mg/kg/day by subcutaneous injection: no effect (FDA, 2006) Other studies of lower quality reported resorption, neural tube defect, malformations and decreased foetal weight (ECHA website; Overman & White, 1983; RIFM, 2007; Lapczynski, 2007; CIR, 2003)
Phototoxicity	No phototoxic, no photoallergy *in vitro* and *in vivo* (SCCP, 2007).	No data

	No photo-genotoxicity in Ames test (SCCP, 2007).	
Endocrine disruption properties	Anti-androgenic *in vitro* (Schlumpf *et al.* 2004; Jimenez-Diaz *et al.* 2013 ; Schreurs *et al.* 2005 ; Kunz *et al.* 2006b) Not androgenic *in vitro* (Ma *et al.* 2003; Jimenez-Diaz *et al.* 2013; Schreurs *et al.* 2005)	No data
	Oestrogenic *in vitro* but not *in vivo* (Schlumpf *et al.* 2004; Jimenez-Diaz *et al.* 2013 ; Schreurs *et al.* 2002; Gomez *et al.* 2005 ; SCCP, 2007; Schlumpf *et al.* 2004) Not anti-oestrogenic *in vitro* (Schlumpf *et al.* 2004; Jimenez-Diaz *et al.* 2013 ; Schreurs *et al.* 2002)	Not oestrogenic *in vitro* and *in vivo* (Miller *et al.* 2001; Zhang *et al.* 2012) Low activity on ERRɣ (human oestrogen-related receptor) (Zhang *et al.* 2013)
	Slight anti-progesterone activity (Schreurs *et al.* 2005)	No data

Comparison of structure:
The source and the target substances both contain a salicylic acid group. In addition, methyl salicylate contains a methyl chain on the carboxyl group although homosalate is an alkyl ester of salicylic acid with a branched substituted cyclohexane (3,3,5-trimethylcyclohexanol group).

Comparison of physicochemical properties:
Homosalate and methyl salicylate are both clear, colourless to pale yellow liquids, with a density close to 1 g/cm^3 (1.05 and 1.17 respectively). Due to the cycloalkane group of the homosalate compared to the methyl group of methyl salicylate, the substances significantly differ in terms of molecular weight, lipophily, water solubility and vapour pressure. Therefore, the comparison of physicochemical properties does not allow to accept the read-across between homosalate and methyl salicylate.

Comparison of toxicological properties:
Homosalate and methyl salicylate are expected to be metabolized into salicylic acid and an alcohol, trimethylcyclohexanol or methanol, respectively. However, there is no adequate experimental data allowing a clear overview of their toxicokinetics (such as exhaustive list of metabolites, percentage of metabolites formed, half-time etc.). This lack of data do not allow an appropriate comparison of their metabolism to support the proposed read-across.

Regarding their acute toxicity, methyl salicylate present a higher oral acute toxicity than homosalate with the lowest LD_{50} in rats of 887 mg/kg bw compared to a LD_{50} > 2000 mg/kg bw for homosalate.

Both substances are not considered as dermal irritant. Homosalate is not irritant to eyes in a non-guideline study at a concentration of 12%. There are contradictory

findings for methyl salicylate. For skin sensitization, contradictory results are reported with methyl salicylate, with positive results obtained in various LLNA performed at rather high doses. Thus, methyl salicylate can be considered as a weak/moderate sensitizer. No experimental guideline study is available for homosalate. Instead, human data using end-use products and photoallergy assays in rodents do not show sensitization concern. However, these studies may be not sensitive enough to detect a weak/moderate sensitizing potential.

Only two repeated-dose toxicity studies are available with homosalate. Only biochemical changes were reported from 100 mg/kg bw/day in a 2-week study in rats exposed by gavage. No subacute study with comparable protocol has been found with methyl salicylate. Homosalate was also tested in a combined repeated dose and reproduction / developmental screening test. The occurrence of a constant lighting during the conduct of the study can significantly affect the reliability of this study. However, it should be noted that several target organs were identified (including kidney, liver, thyroid and spleen) with increasing doses of homosalate. For methyl salicylate, there are several repeated dose toxicity studies. The target organs are the bone in rats and the liver in dogs. However, these studies are limited in terms of endpoints evaluated (no biochemical, urinalysis and ophthalmological examination, limited histopathological examination on few animals). In summary, different target organs were identified after repeated exposure to homosalate and methyl salicylate. However, it cannot be adequately assessed if these differences are linked to a different toxicity, and/or due to the different methodological protocols and/or due to deficiencies of the available studies (in particular constant light in one of the protocol with homosalate).

Homosalate is not mutagenic *in vitro*. Methyl salicylate is neither considered mutagenic *in vitro* (gene mutation and chromosomal aberrations assays) or *in vivo* (micronucleus assay in rats).

There is no carcinogenicity data on homosalate. No full carcinogenicity study according to current guidelines is available for methyl salicylate neither. However, the 2-year study in rats treated with methyl salicylate with limited endpoints evaluated (no biochemical, urinalysis and ophthalmological examination, limited histopathological examination on few animals) displayed no increase of tumours.

Toxicity on reproduction and development was assessed in a screening test with homosalate. Infertility, effects on sperm morphology and motility and foetal mortality (evidenced by post-implantation loss and low birth index) were reported. However, the fact that the animals were under constant light can significanty affect the reliability of this study even it should be noted that effect on sperm and on foetal mortality seems to occur with a dose-response relationship. For methyl salicylate, adequate reproductive and developmental studies according to ICH guidelines are available. Methyl salicylate had no effect on fertility but development was significantly affected as evidenced by decreased birth index, delayed balanopreputial separation, delayed incisor eruption and skeletal abnormalities and variations.

Several studies have assessed the endocrine disruption potential of homosalate. The substance presents oestrogenic and anti-androgenic properties *in vitro*. A slight anti-progesterone activity was also found *in vitro*. *In vivo*, no effect was reported in an uterotrophic assay. Methyl salicylate was only evaluated for effects on oestrogenic pathway: it was not oestrogenic *in vitro* and *in vivo*. Only a slight effect on ERRɣ was reported.

Conclusion: differences of toxicity are reported between homosalate and methyl salicylate, especially in acute and repeated-dose toxicity studies. Methodological deficiencies reported in repeated-dose toxicity studies do not allow an adequate

comparison of their toxicity. Therefore, the comparison of toxicological properties does not allow to accept the read-across between homosalate and methyl salicylate.

Toxicity of the hydrolysis products:
The common metabolite between homosalate and methyl salicylate is **salicylic acid**. There is no current harmonized classification for this substance. However, a CLH report was submitted by Novacyl SAS in 2014 who proposed that salicylic acid should be classified Acute Tox. 4 – H302 (harmful if swallowed) and Eye Damage 1 – H318 (cause serious eye damage). On 10 March 2016, the RAC adopted this proposed classification and added Repr. 2 – H361d. This latter classification was based on growth delays, foetal death and malformations in rats. At this time, the classification agreed by the RAC is not included in an ATP yet.

In addition to salicylic acid, the second hydrolysis product is methanol (CAS 67-56-1) for methyl salicylate and 3,3,5-trimethylcyclohexanol (CAS 116-02-9) for homosalate.

Methanol is currently classified as Flam. Liq. 2 – H225, Acute Tox. 3* – H301/311/331, STOT SE 1 – H370** (STOT SE 1; H370: C ≥ 10 % STOT SE 2; H371: 3 % ≤ C < 10 %). In 2013, Italy submitted a CLH report for this substance proposing a classification Repr. 1B – H360D in addition to the current classification. This proposal was not agreed by the RAC on 12 September 2014 considering that methanol blood levels causing clear developmental toxicity in rodents would be acutely toxic or even lethal to humans. A toxicological profile is available within the OECD HPV program which concluded on October 2004 that methanol exhibits potential hazardous properties for human health (neurological effects, central nervous system depression, ocular effects, reproductive and developmental effects and other organ toxicity including changes in the brain, liver, kidney and lungs reported after repeated-dose exposure in animals) (OECD; 2004).

3,3,5-trimethylcyclohexanol was not registered under Reach regulation. There is no harmonized classification. Very little toxicological information is available with this substance. Severe injury on rabbit eyes is reported by HSDB. According to the EDSP (Endocrine Disruptor Screening Program) from EPA, 3,3,5-trimethylcyclohexanol is not an agonist / antagonist of estrogen receptor based on ToxCast model (2015). The 3,3,5-trimethylcyclohexanol can be considered as structurally similar to l-menthol. These two substances contain an hydroxyle group, responsible of their reactivity. However, due to the sterically hindered of the isopropyl group, the hydroxyle group of the l-menthol is less accessible than that of 3,3,5-trimethylcyclhexanol, leading to a higher expected toxicity of this molecule. In addition, 3,3,5-trimethylcyclhexanol is considered to be one of the metabolites of isophorone (without any further information). Intrinsic toxicity specific to trimethylcyclohexanol cannot be ruled out in the absence of adequate data.

Conclusion of the proposed read-across:
The read-across between homosalate and methyl salicylate as proposed by the registrants is not considered acceptable based on differences in structure, physicochemical and toxicological properties.

- Toxicokinetics (absorption, distribution, metabolism and elimination).

No experimental toxicokinetics data is available with homosalate after oral and inhalation routes.

According to the ECHA guidance on information requirements and chemical safety assessment (Chapter R.7c: endpoint specific guidance; version 2.0 of November 2014), a poor oral absorption is expected for homosalate considering its physicochemical properties (low water solubility and log Pow > 5). In contrast, the Danish QSAR database predicted an oral absorption almost complete, comprised between 95 and 100%. Overall, the registrants considered a 100% oral absorption.

Similarly, according to R.7c guidance document, the absorption after inhalation is expected to be low based on physicochemical properties (vapour pressure < 25 kPa and log Pow > 5).

Based on an *in vitro* dermal absorption study performed with a standard sunscreen formulation containing 10.1% of homosalate in human and rat skins, the registrants concluded that homosalate has a dermal absorption below 10 % (1.1 % for human skin and 8.7 % for rat skin) (disseminated ECHA database: study report, 2005). There is no valid *in vivo* skin penetration study, nevetherless, tape stripping methodology in human volunteers showed that small amounts can be considered as absorbed and systemically available (Sarveiya *et al*., 2004). In addition the type of preparation/formulation can have an influence on the proportion of the absorption. Considering all these data, the Scientific Committee on Consumer Products (SCCP; 2007) considered a 2.0% value for dermal absorption.

Following absorption, homosalate is expected to be metabolized to salicylic acid and trimethylcyclohexanol. Reference was made in the SCCP (2007) opinion to an evaluation made by Roberts (2005) (not publicly available) who assumed rapid and complete metabolism of homosalate by esterases in the skin, plasma, liver and other body tissues. In addition, the Danish QSAR database does not predict homosalate as a CYP2C9 or CYP2D6 substrate.

- Acute toxicity

Homosalate is of low acute toxicity by oral and dermal routes (disseminated ECHA database: study reports, 1978; SCCP, 2007). No data is available after inhalation route but considering the low vapour pressure and the low acute toxicity reported by oral and dermal routes, homosalate is not of concern for acute inhalation toxicity.

- Irritation and corrosivity

Homosalate is not a dermal irritant based on an *in vitro* EPISKIN assay (disseminated ECHA database: study report, 2012) and on *in vivo* studies on animals and humans (disseminated ECHA database: study report, 2005; SCCP, 2007).

Limited data are available to assess irritative properties of homosalate on eye. A sunscreen containing 12% homosalate was not irritant to rabbit's eyes (disseminated ECHA database: Springborn laboratories Inc, 2001). A read-across with 2-ethyl-hexyl salicylate was proposed by the registrants without scientific justification. The substance has no harmonized classification. Regarding eye irritation, there are 2 self-classifications as Eye Irrit. 2 – H319 in ECHA website. It is generally recognized that for local targets, the exposure to the parent compounds at the site of contact has to be considered. In this context, the read-across is not considered acceptable.

No data is available regarding respiratory irritation. However, considering its low vapour pressure and low irritative potential, homosalate is not of concern for respiratory irritation.

- Sensitisation

There is no experimental guideline study available to assess sensitisation properties of homosalate. However, photoallergy studies in guinea pigs exposed to 1% homosalate for induction and challenge phases and in mice exposed to 10% and 5% homosalate for induction and challenge phases, respectively, support the lack of sensitization potential of homosalate (disseminated ECHA database: publication unnamed, 1989; Gerberick, 1990; SCCP, 2007) (see further details below in Phototoxicity section).

Clinical studies in humans (including repeated insult patch test and cumulative irritation test) with different types of sunscreens or other cosmetic products containing homosalate up to 15% revealed no skin sensitizing potential (disseminated ECHA database: study report, 2005; SCCP, 2007). However, the use of end-use products containing up to 15% of homosalate make any conclusion on skin sensitisation of homosalate uncertain.

Overall, homosalate does not present any concern for skin sensitization considering the above data. However, according to a QSTR "quantitative structure-toxicity relationship" model (TOPKAT 3.0), homosalate has a weak/moderate sensitizing potential (Einslein *et al.* 1997). In addition, Rietschel (1978) described the case of two patients with follicular dermatitis after being in contact to a commercially available suntan lotion containing homosalate. Contact sensitivity to homosalate was confirmed with patch test. Furthermore, other salicylates, such as methyl salicylate and 3-hexenyl salicylate, present weak to moderate sensitisation potential in LLNA assays. Therefore, in the absence of appropriate LLNA assay with homosalate and considering that all studies available were performed with concentrations of homosalate below 15%, no firm conclusion can be made if this substance is a weak/moderate sensitizer or not.

- Repeated-dose toxicity

A range-finding study in rats is described in the SCCP (2007). Only a short summary is available. In this study, 5 animals/sex/group received homosalate at dose levels of 0, 100, 300 and 1000 mg/kg bw/day orally by gavage for 2 weeks. Wet fur and/or salivation were reported in all tested groups. There was only a slight retarded body weight gain in males animals and a corresponding reduction of food efficiency at 1000 mg/kg bw/day. Increases in APTT (activated partial thromboplastin time) and/or PT (prothrombin time) were observed in males from 300 mg/kg bw/day and in females at 1000 mg/kg bw/day. Bilirubin was reduced from 100 mg/kg bw/day in males and from 300 mg/kg bw/day in females, while triglycerides were increased in both sexes at 1000 mg/kg bw/day. These effects were considered as not adverse (bilirubin) or only potentially adverse (triglycerides) by the authors (no data or further information reported).

One combined repeated dose and reproduction / developmental screening test performed in Wistar rats is available with homosalate (disseminated ECHA database: study report unnamed, 2013). Males (10/group) were treated with 0, 60, 120, 300 or 750 mg/kg bw/day of homosalate by gavage once daily from 14 days pre-pairing and for a total of 47 days. Females (10/group) were treated with 0, 60, 120, 300 or 750 mg/kg bw/day homosalate by gavage once daily from 14 days pre-pairing and sacrificed on day 4 post-partum. Pups were sacrificed on day 4 post-partum. This study follows the OECD guideline 422 (1996) except the occurrence of constant lighting during the conduct of the study. This has been

considered as a major deviation from OECD guideline that affect the adequate assessment of the effects observed, in particular on fertility.

One female died and one female was sacrificed during prepairing period at the highest dose of 750 mg/kg bw/day. Decreased body weight and food consumption were reported in both males and females at 750 mg/kg bw/day from pre-pairing period. In males, higher concentration of albumin with lower concentration of globulin was observed at 750 mg/kg bw/day. This effect was also found at 300 mg/kg bw/day but remained within historical control values. Several changes in organ weights were reported: increased liver weight in both sexes from 300 mg/kg bw/day, increased kidney weights in females from 300 mg/kg bw/day, decreased thymus weight in both sexes at 750 mg/kg bw/day and reduced prostate and seminal vesicles weights at 750 mg/kg bw/day.

Histopathologically, minimal to moderate increase in intra-epithelial hyaline droplets in the kidneys was found in all the male groups given homosalate. In a few of the affected animals, the finding was associated with an increase in foci of basophilic (regenerating) tubules, single cell death and/or the presence of granular casts. The registrants consider that these findings are the manifestation of hyaline droplet nephropathy without human relevance. However, there is no data to confirm the suspected origin of the pathogenesis observed in rodents. Minimal or mild centrilobular hypertrophy of hepatocytes was reported in 1/5 males given 120 mg/kg bw/day, in all males and 4/5 females given 300 mg/kg bw/day and in all males and 6/7 females given 750 mg/kg bw/day. The registrants considered this finding as an adaptative reaction to increased metabolic burden caused by the treatment with homosalate. Since only a summary of this study is available and considering the lack of scientific justification provided by the registrants, this statement cannot be confirmed. In thyroid gland, there was a higher incidence and/or severity of diffuse hypertrophy of the follicular epithelium in males at 750 mg/kg bw/day and in females from 300 mg/kg bw/day. This effect was judged by the registrant as most probably associated with the presence of enzyme induction in the liver and consequent increased hepatic clearance of thyroid hormone. However, it is unknown if thyroid hormones were actually dosed in this study. Anyway, effect on thyroid should be presumed to be relevant to human in the absence of mechanistic data indicating the opposite. Finally, a greater incidence and severity of decreased cortical lymphocytes was noted in males from 300 mg/kg bw/day and in females at 750 mg/kg bw/day. The registrants consider this effect as a nonspecific response to stress rather than an effect on immunosuppression. In the absence of further data, this statement cannot be confirmed. Based on this study, the registrants concluded on a NOAEL of 300 mg/kg bw/day based on mortality and decreased food consumption. However, it should be noted that at this dose, effects on liver, thyroid and thymus had already occurred. Reproductive data have been reported under the section "toxicity for the reproduction". Overall, the fact that the animals were under constant light can affect the reliability of this study and the reported effects. In particular, constant light is known to affect fertility and behaviour of rats (Hardy *et al.,* 1969; Fantie *et al*., 1984). However, it should be noted that the effects reported in this study seems to follow a dose-response relationship suggesting that they can actually be treatment-related. In conclusion, due to the major deviation identified, no adequate conclusion can be made from this study. However, the findings should not be disregarded. They lead to concerns that need to be clarified with appropriate data.

No repeated-dose toxicity by inhalation and by dermal route is available with homosalate.

Read-across to methyl salicylate has been proposed by the registrants to fulfil this endpoint. As described above, this read-across has not been considered valid.

- Genotoxicity

Homosalate was not mutagenic in an Ames test performed with *Salmonella typhimurium strains* TA98, 100, 102, 1535 and 1537 at concentrations up to 5000 µg/plate in the absence and in the presence of metabolic activation (disseminated ECHA database: study report unnamed, 2005; SCCP, 2007). Similar results were reported in another Ames test performed with various substances including homosalate in *Salmonella typhimurium strains* TA97, 98, 100, 1535 and 1537 (Zeiger *et al.* 1987).

Homosalate did not induce gene mutations in an *in vitro* HPRT gene mutation study in V79 cells with and without metabolic activation (disseminated ECHA database: study report unnamed, 2013; SCCP, 2007).

In *in vitro* chromosomal aberration studies in V79 cells, homosalate was not clastogenic with and without metabolic activation (disseminated ECHA database: study reports unnamed, 2005 & 2006; SCCP, 2007).

- Carcinogenicity

There is no data with homosalate. Read-across to methyl salicylate has been proposed by the registrants to fulfil this endpoint. As described above, this read-across has not been considered valid.

- Toxicity for the reproduction

One combined repeated dose and reproduction / developmental screening test is available with homosalate (disseminated ECHA database: study report unnamed, 2013). This study is described above under Repeated-dose toxicity. It follows the OECD guideline 422 (1996) except the occurrence of constant lighting during the conduct of the study. This has been considered as a major deviation from OECD guideline that affect the adequate assessment of the effects observed. In particular, constant light is known to affect fertility and behaviour of rats (Hardy *et al.,* 1969; Fantie *et al*., 1984).

In addition to general toxicity reported under the section "repeated-dose toxicity", significant changes in sperm morphology (reduced number of normal complet sperm, increased number of sperms with normal head only and detached tail and of sperms with abnormal head and normal tail) and reduction in sperm motility were noted at 750 mg/kg bw/day. Increased infertility was reported without dose-response relationship at 60, 120 and 750 mg/kg bw/day with 4, 5 and 3 pregnant females in each group (compared to 8 pregnant females in controls and 7 in the 300 mg/kg bw/day group). According to the registrant, this was linked to the constant lighting during the study. At the highest dose, the three pregnant females presented a low number of corporea lutea and higher post-implantation loss. Only one female had living pup at first litter check (but missing on day 2 of lactation period). No birth was recorded in the 2 remaining pregnant females. At 300 mg/kg bw/day, higher incidence of post-implantation loss was noted leading to a lower birth index but without any effect on litter size. There was no effect recorded on pups body weight, sex ratio, post-natal loss and at macroscopical examination at all relevant doses up to 300 mg/kg bw/day. However, the low numbers of pregnancies per group question the validity of data on development of offsprings in this study. Based on this study, the registrants concluded that no NOAEL can be stated for reproduction considering the low number of pregnant females. Overall, the fact that the animals were under constant light is considered to affect the

reliability of this study and the reported effects. Therefore, no adequate conclusion can be made from this study. However, the findings should not be disregarded. They lead to concerns that need to be clarified with appropriate data.

Read-across to methyl salicylate has been proposed by the registrants to fulfil this endpoint. As described above, this read-across has not been considered valid.

- Neurotoxicity

There is no information found related to possible neurotoxicity of homosalate. No effect on brain (weight and histopathology) was reported in the combined repeated dose and reproduction / developmental screening test performed with homosalate (disseminated ECHA database: study report unnamed, 2013).

- Immunotoxicity

No firm conclusion can be made if this substance is a weak/moderate sensitizer or not in the absence of appropriate LLNA assay with homosalate, considering that all studies available were performed with concentrations of homosalate below 15% and taking into account the sensitization potential reported with other salicylates.

In the the combined repeated dose and reproduction / developmental screening test performed with homosalate, a decreased thymus weight was reported in both sexes at 750 mg/kg bw/day and a greater incidence and severity of decreased cortical lymphocytes was noted in males from 300 mg/kg bw/day and in females at 750 mg/kg bw/day (disseminated ECHA database: study report unnamed, 2013).

O'Keefe *et al.* (2016) exposed human THP-1 monocytes and THP-1 derived macrophages *in vitro* to various UV filters, including homosalate, in order to assess the cytotoxicity, ROS generation, immune modulation via cytokine release profiling and cell death pathway. The EC_{50} for cytotoxicity in monocyte and macrophage cultures after 24 hours was about 50-60 µg/mL. Co-exposure with UVA did not alter the cytotoxicity profile. Releases of interleukin-8 (IL-8) and IL-1β were increased (5.5-fold and 12-fold, respectively) by exposure to homosalate. Both interleukines are general inflammatory mediators, involved in the recruitement and proliferation of immune cells. These results suggest some immune-related responses in monocytes and macrophages after *in vitro* exposure to homosalate.

- Phototoxicity

The SCCP (2007) described the following studies assessing the photo-induced toxicity of homosalate.

Homosalate was shown to have no phototoxic potential in the presence of artificial sunlight in murine Balb/c 3T3 fibroblasts according to OECD guideline 432. Homosalate did not show photoallergic, contact allergic, phototoxic or irritant potential in guinea pigs after 6 occlusive inductions of 1% homosalate in methanol under UV-A followed by an occlusive challenge of 1% of homosalate in acetone (with or without irradiation). Similar results were obtained in a mouse ear-swelling photoallergy test after an induction with a 10% preparation and challenge with a 5% preparation. No phototoxicity / photoallergy was reported in several humans studies where volunteers were exposed to sunscreen products containing 10 or 15% homosalate.

Homosalate was negative in an Ames test in *Salmonella typhimurium* strains TA1537, TA98, TA100 and TA102 up to 5000 µg/plate with and without metabolic

activation under irradiation with artificial sunlight. In *in vitro* chromosomal aberration studies in V79 cells, homosalate was not clastogenic with and without metabolic activation in the absence and in the presence of artificial sunlight.

4.2.2 Environment

Environmental hazards properties presented are based on available data from the chemical safety report (CSR) of Homosalate. Scientific public papers available dealing on e-fate and ecotoxicity were also considered in the evaluation of the substance.

- E-fate and Ecotoxicity of Homosalate

Homosalate is a liquid substance with a melting point of -20°C at an atmospheric pressure of 101.3 kPa and a boiling point of 295.1°C. According to data, homosalate exhibits a water solubility of 0.4 mg/L at 25°C, and has a low volatility vapour pressure of 0.015 Pa at 25°C. According to the estimated Henry's Law Constant value of 1.96 Pa m^3/mol, the substance could exhibit a partition from aqueous systems to the atmosphere.

If the substance is released to air, according to AOP win[3] (EPIsuite), homosalate is expected to undergo atmospheric oxidation in air with an estimated half-life of 0.25 days. Homosalate absorbs ultraviolet rays with a wavelength from 295 nm to 315 nm, and therefore may be susceptible to direct photolysis by sunlight.

If released into water, Homosalate could volatilize from water surfaces. According to the CSR, results of an hydrolysis test (EU Method C.7) performed at pH 4, 7, 9 and temperatures 20.3°C, 25°C, 30.7°C, the substance presents a half-life value of 215 hours (25°C) indicating a moderate stability to hydrolysis in the environment. No transformation products were measured in the test. However, the registrant highlights that as Homosalate contains an ester group, the substance hydrolysis into its associated acid and alcohol is expected. This is in accordance with results obtained from the prediction tool EAWAG-BBD: Pathway prediction systems (PPS), which shows the first degradation products of Homosalate in salicylic acid (CAS number: 69-72-7) and 3,3,5-trimethylcyclohexanol (CAS number: 116-02-9).

Concerning biodegradation, screening tests are presented in the CSR. Results from a ready biodegradation test (OECD 301F, oxygen consumption) show that homosalate exhibits a degradation rate of 21% after 28 days, resulting the substance as not-readily biodegradable. However, in an inherent biodegradation test (OECD 302C), homosalate exhibited a degradation rate of 72% after 28 days but no information about degradation within 7 days, as expected from the REACH guideline R7 to validate the test, is presented in the CSR. Moreover, according to EPIsuite (MCI method) the substance presents an estimated log Koc of 3.83 at 20°C, but considering the log Kow of 6.63, the log Koc is estimated to 4.43. Thus, it is expected a tendency of adsorption of homosalate onto suspended solids and sediments.

[3] The Atmospheric Oxidation Program for Microsoft Windows;

The BIOWIN[4] biodegradation models were evaluated in order to predict not-readily biodegradable properties. The results obtained do not allow to establish definitive conclusions. According to Biowin 2 (non-linear model prediction), the substance presents fast biodegradation (p=0.92), for Biowin 3 (ultimate degradation timeframe) a value of 2.63 was recorded, which means that no conclusion can be made and more relevant degradation information is needed. Biowin 6 (MITI non-linear model prediction) shows that homosalate does not biodegrade fast (p=0.32).

Modelisation half-lives for environmental compartments were calculated from PBT profiler[5]. According to these results, Homosalate would exhibit a half-life in water of 38 days, 75 days in soil and 340 days in the sediments. Comparing these values with the criteria fixed in annex XIII of REACH regulation concerning P/vP properties, homosalate could be considered as P/vP (persistence and very persistent) for the sediment compartment.

Considering all these information, experimental data is necessary to confirm the P properties of homosalate as well as their associated degradation products.

Concerning bioaccumulation, homosalate exhibits lipophilic properties, the log Kow of 6.63 allow to consider the substance as potential B/vB by screening criteria (log Kow>4.3). Furthermore, a BCF value of 244.4 L/Kg estimated by QSAR (BCFBAF v3.01) considering biotransformation of the substance is presented in the CSR. However, taking account a worst case scenario in which the substance does not biotransformate, homosalate exhibits a BCF value of 20150 L/kg. Another estimation, using the experimental log Kow value of 6.34, allows to obtain a BCF of 7080 L/kg. Moreover, concentrations of homosalate were found in muscle fish (*Perca fluviatilis*) up to 3.1 mg/kg lipids (*Nagtegaal and al. 1997*). These data could give an indication that the substance is not completely metabolized by fish and stored in the lipids.

In summary, whereas the lipophilic properties of homosalate is estimated via BCF values (worst case) or monitoring data from fish, it is not possible to exclude a bioaccumulation concern. Further information from experimental data is thus necessary.

For toxicity assessment, no long term toxicity data is available in both CSR and literature. Ecotoxicity data in the registration dossier is fully based in short term tests with fish, invertebrates (*Daphnia magna*) and algae (*Pseudokirchnerella supcapitata)*. No other information from external sources was identified. For the short term test with fish, the registration dossier presents three different experimental data with *Danio rerio* from a read across with the substance 2-ethylhexyl salicylate (CAS no. 118-60-5). According to the conclusions of registration dossier, no mortality was observed in all three fish studies with 2-ethylhexyl salicylate within the limits of water solubility. However, in the frame of this RMOA the read across has been judged not acceptable by Anses. Short term aquatic toxicity of homosalate could be requested in relation to Annex X of REACH regulation.

Furthermore, it is important to mention that 2-ethylhexyl salicylate is listed in the TEDX list of potential endocrine disruptors. *In vitro* data (Kunz and Fent, 2006) reveals that the substance exhibits multiple hormonal activities (anti-estrogenic,

[4] BIOWIN estimates the probability of rapid aerobic and anaerobic biodegradation of an organic compound in the presence of mixed populations of environmental microorganisms.

[5] PBT Profiler is a screening level predictive tool.

androgenic and anti-androgenic activities). Thus, a thorough assessment concerning long term ecotoxicity and ED properties is needed.

Concerning the others taxa, the reliability of data for the test with *D. magna* and *P. supcapitata* is questionable due to some inconsistencies in the performance of the tests. No information about toxicity for others environmental organisms is neither presented in the registration dossier nor reported in the literature.

In conclusion, the available data from short term test do not allow to conclude on the toxicity of the substance on aquatic organisms. Further data, especially from long term tests are needed to assess the environmental risk of homosalate in aquatic organisms.

- Occurrence of homosalate in aquatic ecosystems

Despite the fact that the homosalate is expected to hydrolise into salycilic acid and 3,3,5-trimethylcyclohexanol in the environment, monitoring data reports the presence of homosalate in aquatic systems. The following scientific studies show the presence of homosalate in aquatic ecosystems:

- Sanchez-Rodriguez et al. 2015, detected the presence of homosolate in the coastal waters of six beaches around Gran Canaria Island as consequence of recreational seaside activities. Homosalate was detected with a frequency of 100% especially for the semi closed beaches with concentrations reaching 536.2 ng/L. In the case of open beaches the frequency of detection was between 22-39% with concentrations arriving until 102.2 ng/L.
- Bargar et al. 2015, detected concentrations of homosalate in frequented beaches located in the island of St. John of the US Virgin Islands, arriving until 633 ng/L.
- Tashiro and Kameda 2013, reported concentrations of homosalate up to 214 ng/L in seawater samples from a commonly visited beach in Okinawa island of Japan.
- Cuderman and Heath 2007, detected concentrations of homosalate of 345 ng/L and 165 ng/L in river samples from the Slovene recreational sites of Nadiža-Soča and Kolpa respectively.

According to these information, a continuous exposure to homosalate into the environment occurs directly as a result of recreational activities when it washed off from the skin. Furthermore, it has been also reported that indirect exposure to the environment can also occur via wastewater-treatment plants (Silvia Cruz and Barcelo, 2009).

In summary concerning environmental issues, the available data does not allow to draw definitive conclusions about the persistence, bioaccumulation and long term toxicity also strong alerts exist. More experimental data are needed in order to clarify the uncertainties concerning the long-term risk associated of homosalate in the environment.

4.2.3 Endocrine disruption properties

Homosalate is reported in the TEDX List of Potential Endocrine Disruptors based in the results of publications of Kunz & Fent (2006) and Schlumpf *et al.* (2001).

In the context of the Endocrine Disruptor Screening Program (EDSP), the US-EPA screened bioactivity of various substances on estrogen receptor based on

ToxCastTM "ER model" (June 2015). The ER bioactivity of homosalate was estimated at 0.0217.

According to Danish QSAR database, homosalate is predicted to activate the estrogen receptor α (based in positive predictions in Battery, Leadscope and SciQSAR models) and to act as an antagonist of androgen receptor (AR) (based in positive experimental results and predictions in Battery, CASE Ultra and Leadscope models).

Concerning experimental data with homosalate, several studies are reported in the scientific literature and in the disseminated database from ECHA website. The following table summarised the responses related to endocrine disruption reported in the *in vitro* and *in vivo* tests.

Table 11: Summary of endocrine effects reported with homosalate

Endocrine activity	Results		Method	Reference
	In vitro	***In vivo***		
Androgen	**+ (< 50% at high conc.)**		Rat recombinant AR binding assay	ECHA website (study report unnamed, 2002); SCCP, 2007
	-		MDA-kb2 cell transactivation-activation assay	Ma *et al.,* 2003
	-		AR CALUX assay	Schreurs *et al.,* 2005
	+ (at very high doses)		Yeast hAR transactivation assay	Kunz & Fent, 2006
	-		Gene expression bioassay in PALM cells	Jiménez-Diaz *et al.,* 2013
Anti-androgenic	**+**		MDA-kb2 cell transactivation-activation assay	Ma *et al.,* 2003
	+		AR CALUX Yeast hAR transactivation assay	Schreurs *et al.,* 2005
	+		Yeast hAR transactivation assay	Kunz & Fent, 2006
	+		Gene expression bioassay in PALM cells	Jiménez-Diaz *et al*., 2013
		?	Repeated-dose toxicity study in rats exposed dermally *in utero* or during lactation or during infancy.	Erol *et al.,* 2017
Estrogenic	-		hER α recombinant binding assay	ECHA website (study report unnamed, 2002); SCCP, 2007
		-	Uterotrophic assay	ECHA website (study report unnamed, 2002); SCCP, 2007
	+	-	*In vitro*: gene expression (ER α)	Schreurs *et al.,* 2002 & 2005

			assay in HEK293 reporter cell lines *In vivo*: transgenic zebrafish assay	
	+	-	*In vitro*: E-SCREEN assay in MCF-7 cells *In vivo*: Uterotrophic assay	Schlumpf *et al.,* 2001, 2004
	+ (ERα) (ERβ: only weak response)		Gene expression assay (ER α and ERβ) in HELN cell lines	Gomez *et al.,* 2005
	-		Yeast hER α transactivation assay	Kunz & Fent, 2006
	-		Yeast rtER α transactivation assay	Kunz *et al.,* 2006
	+		E-SCREEN in MCF-7 cells (ER α)	Jiménez-Diaz *et al.,* 2013
		?	Repeated-dose toxicity study in rats exposed dermally *in utero* or during lactation or during infancy.	Erol *et al.,* 2017
Anti-estrogenic	-		Gene expression (ER α) assay in HEK293 reporter cell lines	Schreurs *et al.,* 2002 & 2005
	+ (at very high doses)		Yeast hER α transactivation assay	Kunz & Fent, 2006
	-		E-SCREEN in MCF-7 cells (ER α)	Jiménez-Diaz *et al.,* 2013
		?	Repeated-dose toxicity study in rats exposed dermally *in utero* or during lactation or during infancy.	Erol *et al.,* 2017
Progesterone	-		Calux assay	Schreurs *et al.,* 2005
	?		*In vitro* study in human sperm cells	Rehfeld *et al.*, 2016
Anti-progesterone	**+ (slightly)**		Calux assay	Schreurs *et al.,* 2005
Glucocorticoid	**-**		MDA-kb2 cell transactivation-activation assay	Ma *et al.,* 2003
Thyroid-related activity		?	Repeated-dose toxicity study in rats exposed dermally *in utero* or during lactation or during infancy.	Erol *et al.,* 2017

***In vitro* studies**

Investigation of androgen-pathway:

Binding to androgen receptor was assessed using an *in vitro* rat recombinant fusion protein containing both hinge region and ligand domain of the AR (androgen receptor). Homosalate (purity: 99.6%) moderately displaced the radiolabelled ligand methyltrienolone from the AR in a concentration dependent manner. This displacement only occurred at high concentration, with 32-41% inhibition at the highest concentration of 0.1 mM. In contrast, reference test substances (dihydrotestosterone and androstenedione) can significantly displace the radiolabelled ligand from the AR (disseminated ECHA database: study report unnamed, 2002; SCCP, 2007).

Ma *et al.* (2003) assessed the (anti)androgenic activity of homosalate (purity > 98%) in MDA-kb2 cells, an human breast cancer cells with endogenous androgen and glucocorticoid receptors and stably transfected with luciferase reporter plasmid. Homosalate antagonized dihydrotestosterone (DHT)-induced luciferase activity with an IC_{50} (inhibitory concentration 50%) of 5.57 µM. No androgenic activity was reported in this system. Kunz and Fent (2006) suggest that this negative result could be due to the low endogenous occurrence of hAR in this cell line.

An AR CALUX® bioassay was used to measure the (anti)androgenic effects of homosalate (purity not mentioned) among other substances at the androgen receptor. The bioassay is based on the generation of stable human AR transfectants of U2-OS cells (human osteosarcoma cell line) and contains a pSG5-neo-hAR expression vector in combination with a 3x ARE-TATA-Luc-reporter construct. Dihydrotestosterone was used as a positive control for AR agonism, whereas flutamide and vinclozolin were used as controls for AR antagonism. Although no AR transactivation was reported, homosalate was found to be an AR antagonist (with IC_{50} of 1.7 µM compared to 0.5 and 0.1 µM for flutamide and vinclozolin, respectively). This effect was reversed by coincubation with excess of dihydrotestosterone, showing the specificity of the response (Schreurs *et al.* 2005).

Kunz & Fent (2006) investigated the (anti)androgenic activity of homosalate (> 99% pure) using recombinant yeast systems carrying hAR. Yeast cells contain expression plasmids carrying androgen responsive elements regulating the expression of the reporter gene lacZ, encoding for the enzyme β-galactosidase which is synthesized and excreted into the medium. Chlorophenol red β-D-galactopyranoside is hydrolyzed by this enzyme, changing from yellow to red. Both androgenic (EC_{50} (effective concentration 50%) = 170 µM, compared to 2.07 nM for dihydrotestosterone) and antiandrogenic (IC_{50} = 107 µM, compared to 4.3 µM for flutamide) effects were demonstrated. It should be noted that androgenic activity was only observed at very high concentration (10^{-3}M).

Jimenez-Diaz *et al.* (2013) investigated the activation of hAR using *in vitro* bioassay based on transfected bioluminescent PALM cell line (from human prostate carcinoma). R1881 at 0.2 nM was used as AR agonist. No androgenic effect was observed with homosalate (purity not mentioned) in the concentration range tested (0.01-10 µM) in PALM cells, whereas the substance was found to be hAR antagonist (IC_{50} = 2.66 µM).

Conclusion:
Three studies (Ma *et al.,* 2003; Schreurs *et al.,* 2005; Jimenez-Diaz *et al.,* 2013) suggest that homosalate is not an AR agonist, whereas one study observed a weak

androgenic effect at high concentration (Kunz and Fent, 2006). An efficient anti-androgenic effect was observed in all four studies in which this effect was investigated (Ma *et al.,* 2003; Schreurs *et al.,* 2005; Kunz and Fent, 2006, Jimenez-Diaz *et al.,* 2013). Overall, it is considered that homosalate have anti-androgenic properties *in vitro*.

Investigation of oestrogen-pathway:

The potential interaction of homosalate (purity: 99.6%) with oestrogen receptor (ER) was examined in a receptor binding assay with human recombinant ER of the α-subtype as receptor and radiolabelled estradiol as ligand. No affinity of homosalate to the ER at the maximum tested concentration of 100 000 nM was observed. In contrast, the positive reference substances (oestradiol and genistein) displaced the radiolabelled estradiol from the ER (disseminated ECHA database: study report unnamed, 2002; SCCP, 2007).

The (anti)oestrogenicity of homosalate (purity not mentioned) was also examined by Schreurs *et al.* (2002 & 2005) by using HEK293 cells (human embryonal kidney cells), which lack significant endogenous levels of ER. The cell line was stably transfected with a reporter construct, consisting of 3 estrogen response elements upstream from a TATA box in front of luciferase cDNA and a hERα or hERβ expression plasmid. 17beta-estradiol was used as positive control. Homosalate was able to activate transcription of ERα (EC_{50} of 1.6 µM compared to 2.1 pM for estradiol) and ERβ to a limited extent (dose response reached a plateau level at 32% of estradiol for which EC_{50} = 83 pM). Repression of hERα and hERβ was also tested, but no clear dose-dependent antagonistic effects were observed for either receptors.

Schlumpf *et al.* (2001 & 2004) reported an estrogenic activity of homosalate (purity not mentioned) *in vitro* in MCF-7 cells (E-Screen) with cell proliferation and secretion of the oestrogen-regulated pS2 protein as endpoints. 17beta-estradiol was used as positive control. The EC_{50} was 1.56 µM (compared to 1.22 pM for estradiol). The maximal cell count increase was 79.65 % of estradiol, whereas the maximal proliferative effect was 36.81 % of estradiol. The authors classified the substance as a partial agonist based on its maximum effects on cell proliferation in relation to oestradiol. The antiestrogenic activity of homosalate was not examined.

Gomez *et al.* (2005) tested the estrogenic activity of homosalate (purity not mentioned) using 3 reporter cell lines: HELN (ER negative), HELN hERα (expressing human ERα) and HELN hERβ (expressing human ERβ). HeLa cell lines expressing luciferase constitutively were transfected with the appropriate plasmid to stably express hERα or hERβ. Estradiol was used as positive control. Homosalate was first tested in HELN cell line and a non-specific response was observed (activation of luciferase expression in the absence of ER). Then, homosalate was assayed in HELN ERα and HELN ERβ cell lines. At 1 µM, the substance activated ERα while it had no non-specific response on HELN. A weak estrogenic activity towards ERβ was observed but this response could be due to non-specific induction. These results indicate that homosalate is a clear agonist of ERα but show a much less activation of ERβ, if any.

Kunz and Fent (2006) investigated the (anti)estrogenic activity of homosalate (> 99% pure) using recombinant yeast systems carrying a hERα. Yeast cells contained expression plasmids carrying estrogen responsive elements regulating the expression of the reporter gene lacZ, encoding for the enzyme β-galactosidase which is synthesized and excreted into the medium. Chlorophenol red β-D-galactopyranoside is hydrolyzed by this enzyme, changing from yellow to red. Estradiol was used as positive controls for ER activation. No estrogenic activity was observed with this system for homosalate. Anti-estrogenic responses were detected

for the highest concentration of homosalate (10^{-2} M and 10^{-3} M), obtaining an IC_{50} of 2.06 mM, compared to 0.5 µM for 4-hydroxytamoxifen. However, the cytotoxicity was not evaluated with these concentrations.

Kunz et al. (2006) evaluated the estrogenic activity of homosalate employing a recombinant yeast carrying the estrogen receptor of rainbow trout (rtER α) and compared the results with yeast carrying the human hER α for receptor specificity. No estrogenic activity was detected with both receptors. The authors reported that the system with the rtER α was 62 times less sensitive than hER α toward E2.

Jimenez-Diaz *et al.* (2013) investigated the activation of hERα in MCF-7 cells using E-screen test. Estradiol was used as positive control for MCF-7 proliferative test. Homosalate (purity not mentioned) increased proliferation in a dose-dependent manner (EC_{50} = 5.53 µM), but failed to antagonize estradiol-induced proliferation in MCF-7 cells up to the concentration of 10 µM.

Conclusion:
Most of the observations suggest that homosalate is estrogenic *in vitro*, the substance being active mainly on ER α. A possible explanation of the negative result reported in yeast could be the limited sensitivity of this system compared to transfected cell lines.

An anti-estrogenic effect was found at high concentrations in yeast system (Kunz and Fent, 2006) but this effect was not observed in other assays in mammalian cells (Schreurs *et al*., 2002 & 2005; Jimenez-Diaz *et al*., 2013). Overall, the evidence is rather limited to conclude that homosalate can have anti-oestrogenic activity *in vitro*.

Investigation of progesterone-pathway:
A PR CALUX® bioassay was used to measure the agonistic and antagonistic effects of homosalate among other substances at the progesterone receptor. This bioassay is based on the generation of stable human PR transfectants of U2-OS cells (human osteosarcoma cell line) and contain a pSG5-neo-hPR expression vector in combination with a 3x ARE-TATA-Luc-reporter construct. ORG2058 was used as a positive control for agonism and RU486 as control for antagonism. No agonist but a slightly antagonist effect (with an IC_{50} of 3.0 µM, compared to 4.9 pM for RU486) was found with homosalate (purity not mentioned). This effect was reversed by coincubation with excess of ORG2058, a PR agonist, showing the specificity of the response (Schreurs *et al*., 2005).

In contrast, Rehfeld *et al.* (2016) found that homosalate induced a Ca^{2+} signal *in vitro* in human sperm cells which ressembled to that induced by progesterone. Specially, this effect would occurred *via* an effect on CatSper (cationic channel of sperm), either acting agonistically on the binding pockets of progesterone or prostaglandin or affecting CatSper through another unknown mechanism independent of changes in pH. Because Ca^{2+} signalling controls important sperm function, the effect of homosalate might interfere with the normal human fertilization process and impair fertility.

Conclusion:
Some effects of unknown biological relevance have been reported *in vitro* regarding possible interaction between homosalate and progesterone signalling pathway.

Investigation of glucocorticoid pathway:
Homosalate (purity > 98%) was tested with respect to possible interaction with glucorticoide receptor activation by Ma *et al.* (2003) in MDA-kb2 cells, an human breast cancer cells with endogenous androgen and glucocorticoid receptors and stably transfected with luciferase reporter plasmid. Homosalate did not change the

effect of 50 nM dexamethasone on luciferase activity suggesting the absence of interaction with glucorticoide receptor (Ma *et al.,* 2003).

Conclusion:
No interaction between homosalate and glucocorticoide receptor was found *in vitro* in MDA-kb2 cells.

***In vivo* studies**

Homosalate (purity: 89.64%) was investigated for its oestrogenic potential in an uterotrophic assay in immature rats (according to OECD guideline 440). Wistar female rats (6/groups) received homosalate at the dose levels of 0, 200 and 1000 mg/kg bw by subcutaneous injections, once a day for 3 consecutive days. Two additional groups were included receiving ethinylestradiol as positive control at the doses of 0.3 and 1.0 µg/kg bw. There was no mortality and no effect on clinical signs, food consumption and body weight. There was no effect on uterus weights (blotted and wet). In comparison, the positive control induced enlarged uterus associated with an increase of uterus weight (disseminated ECHA database: study report unnamed, 2002; SCCP, 2007).

Negative result was also reported in another uterotrophic assay performed in Long Evans immature rats receiving homosalate (purity not mentioned) in the diet at 491 or 892 mg/kg bw/day for 4 days from post-natal day 21. The phytoestrogen levels in the diet were not reported in the publication. Ethynilestradiol was used as positive control (Schlumpf *et al.* (2001 & 2004)).

A recent publication aims to investigate the endocrine-disrupting effects of homosalate in rat pups during the prenatal, lactation and early postnatal periods (Erol *et al.,* 2017). In this study, a 10% homosalate (purity unknown) paraffin solution was used. To determine the effects of homosalate after prenatal exposure, the solution was topically applied to 5 pregnant Wistar Hannover rats at 2 mg/cm^2 (on 9 cm^2) once daily from gestation day 1 until delivery. To determine the effects of homosalate after exposure during lactation, the solution was applied at the same dosage to 5 rat mothers between post-natal day 2 to 21. To determine the effects of homosalate after exposure during infancy period, the solution was applied at 2 mg/cm^2 (on 4 cm^2) for 6 consecutive days between post-natal day 21-26 to 10 pups. The pups issued from the different groups of exposure were examined daily from post-natal day 26 for signs of puberty. Vaginal opening, vaginal smear and preputial separation were examined as sign of puberty onset. Thyroid gland, testes, prostate, seminal vesicles, uterus, bilateral oviduct and ovaries were weighted. Serum thyroid-stimulating hormone (TSH), thyroxine (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone and estradiol levels were measured. Uterus, ovaries and testis were histopathologically examined.

After prenatal exposure and compared to control groups, the average thyroid gland weight, LH and TSH levels were decreased in treated females. In treated males, there was an increase of FSH and LH. Oestradiol levels were higher in treated females and testosterone levels were lower in treated males. No effect was observed histopathologically in the ovaries, uterus and testis. After lactation exposure and compared to control groups, a decrease of oestradiol level was noted in treated females. The number of Graaffian follicles was significantly increased. In treated males, TSH level was decreased, seminal vesicle weight was decreased whereas testis weight was increased. No significant effect was reported in the structure of seminiferous tubules. After exposure during infancy period and compared to control groups, treated females exhibited increased thyroid gland weight and decreased oestradiol levels. Treated males exhibited higher TSH, T4, LH and FSH levels. No effect was observed histopathologically in the ovaries, uterus and testis.

Some inconsistencies in the presentation of results have been noted in the publication challenging the adequate assessment of the reported effects. In addition, as only one dose was tested, dose-response relationship cannot be conducted. Finally, the tested material was not the pure substance but a 10% solution. Therefore, this study is not considered sufficiently robust to properly assess the endocrine-disrupting effects of homosalate.

Schreurs *et al.* (2002) exposed *in vivo* transgenic zebrafish to a single concentration of homosalate (10^{-5} M). Exposure was carried out with juvenile fish of 4-5 weeks of age. The substance was first dissolved in ethanol and then added to water in a 1:10,000 dilution. Fish were fed with live brine shrimp (*Artemia Salinas*) once every day. At the end of exposition the luciferase activity was measured in a scintillation counter. No transcriptional activation was detected for the concentration tested. However, no final conclusion can be attributed from this study due to only one concentration was tested and the low sensitivity of the test.

Overall conclusion on endocrine disruption properties of homosalate:

Level 1: non-testing methods:
QSAR gives some indications that homosalate can activate the estrogen receptor α and act as an antagonist of androgen receptor.

Level 2: *in vitro* assays:
Anti-androgenic and oestrogenic activities are clearly reported in *in vitro* studies. It is known that this mixed activity favours the development of mammary tumours and can affect fertility and development. In addition, there were some contradictory interactions with progesterone signalling pathway of unknown relevance.

Level 3: *in vivo* assays with data regarding MoA:
Negative results were found in uterotrophic assays performed up to high doses. However, it can be noted that this type of assay is only based on an assessment of uterus weight. Thus, this type of test cannot allow a firm conclusion on all possible oestrogenic mode of actions. In addition, although this assay has a good sensitivity for strong oestrogenic compounds, the sensitivity is lower for weaker oestrogenic compounds. Negative result was also reported in transgenic zebrafish but no final conclusion can be made from this study.

Level 4: *in vivo* assays with data regarding adverse effects:
Some variations of hormones were reported when rats were exposed during different sensitive periods. However, no clear trend has been identified in the fluctuations and there was no effect reported at histopathological examination of the reproductive organs. Anyway, this study is not considered sufficiently robust to conclude on the endocrine-disrupting effects of homosalate due to the limitations reported in the section above. In addition, possible effects on fertility (increased infertility, sperm changes), development (higher post-implantation) and thyroid (hypertrophy of the follicular epithelium) were raised in a OECD 422 study but the fact that the animals were under constant light can have affected the reliability of the reported effects.

In summary, the current available dataset does not allow to conclude on endocrine potential of homosalate considering the effects reported *in vitro* and the absence of adequate studies *in vivo*. Despite the bad quality of the *in vivo* studies, findings that could be linked to an endocrine disruption were identified, in particular fluctuations of hormones, sperm changes and effects on thyroid. These effects raised some concerns regarding ED properties of homosalate.

4.2.4 Overall conclusion on hazard

Data on the toxicity of homosalate for human health is limited. Indeed, only two repeated-dose toxicity studies are available to fulfill the endpoints related to repeated-dose toxicity, carcinogenicity and toxicity on reproduction and development. The first one is a 2-week study, for which only a short summary is available in the SCCP opinion (2007). The second study is a combined repeated dose and reproduction / developmental screening test. Effects on kidney, liver, thyroid and spleen were reported. In addition, fertility and development were impacted by homosalate. The occurrence of constant lighting during the conduct of the study has been considered as a major deviation from OECD guideline 422 since it can impact the adequate assessment of the effects observed, in particular for the fertility part of the study. However, it should be noted that the majority of the effects reported seems to follow a dose-response relationship suggesting that they can be actually treatment-related. In this context, these findings raise concerns that need to be clarified with appropriate data. In addition to these studies, the registrants proposed a read-across with methyl salicylate for long-term, reproductive and developmental toxicities. This read-across has not been judged valid based on differences in structure, physicochemical and toxicological properties. Therefore, considering the reproduction / developmental screening test of questionable reliability and the non-valid read-across, datagaps have been identified for repeated-dose toxicity and reproductive and developmental toxicity endpoints.

Regarding environmental issues, the available information does not allow to draw definitive conclusions about the PBT properties of homosalate. Furthermore, according to modelling estimation, homosalate could exhibit a half life value substantially higher than the threshold value of P/vP criteria for the sediment compartment. The persistence of the substance in the aquatic environments and their associated degration/transformation products must be clarified. Concerning bioaccumulation, the lipophilic properties of homosalate, its estimated BCF values (worst case) and the monitoring data which shows that the substance can reach and accumulate in tissues of fish, provide indications of the potential capacity of homosalate to bioaccumulate in aquatic organisms. Further information from experimental data is thus necessary.

The available information related to aquatic toxicity of homosalate, is mainly based in short term tests. The monitoring data from scientific papers, shows the ocurrence of homosalate in aquatic systems due to direct discharges from recreational activities and indirectly through wastewater. The continuous exposition of homosalate to the environment justify the need to have more information about aquatic toxicity from long term tests.

Finally, concerns about anti-androgenic and estrogenic properties has been raised from *in vitro* studies. Contradictory results were reported for progestative properties. No estrogenic activity was reported in uterotrophic assays or transgenic zebrafish assay. Some variations of hormones were reported when rats were exposed during different sensitive periods; but without a consistent biological trend identified. In addition, possible effects on fertility, development and thyroid were raised in a OECD 422 study but the fact that the animals were under constant light can have affected the reliability of the reported effects. Therefore, at this time, there is no sufficient information to have a firm conclusion on endocrine effects of homosalate as good quality *in vivo* data integrating different endocrine pathways are missing. In this context, further investigations are needed, in particular regarding potential effects on fertility and development of humans and environmental organisms of homosalate.

5 INFORMATION ON (AGGREGATED) TONNAGE AND USES[6]

5.1 Tonnage and registration status

Table 12: Tonnage and registration status

From ECHA dissemination site	
Registrations	☒ Full registration(s) (Art. 10) ☐ Intermediate registration(s) (Art. 17 and/or 18)
Total tonnage band for substance (excluding volume registered under Art 17 or Art 18, or directly exported)	1,000-10,000 tpa

[6] *Please provide here the date when the dissemination site was accessed.*

5.2 Overview of uses

According to ECHA disseminated website, homosalate is used by consumers in the following products: cosmetics and personal care products. The substance is used as UV filter in concentrations of up to 10% in the EU or 15% depending upon where the product is used (e.g. in the USA) in sunscreen products alone or in combination with other UV absorbers to protect the skin against harmful effects of the UV radiation (SCCP; 2007).

Table 13: Uses

	Use(s)
Uses as intermediate	No information
Formulation	Formulation of end-products in Cosmetics, personal care products (PC 39) as UVA and UVB absorber
Uses at industrial sites	ECHA has no public registered data indicating whether or in which chemical products the substance might be used.
Uses by professional workers	ECHA has no public registered data indicating whether or in which chemical products the substance might be used.
Consumer Uses	Consumer end-use of cosmetics Use in perfumes, fragrances (PC 28) and in cosmetics and personal care products (PC 39)
Article service life	ECHA has no public registered data on the routes by which this substance is most likely to be released to the environment. ECHA has no public registered data indicating whether or into which articles the substance might have been processed.

6 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

6.1 Need for (further) risk management

Homosalate, is an ester formed from salicylic acid and 3,3,5-trimethylcyclohexanol. The substance is used as UV filter in concentrations of up to 10% in the European Union, or 15% depending upon where the product is used (e.g. in the USA) in sunscreen products alone or in combination with other UV absorbers (SCCP, 2007). The role of UV filter is to get protection of the skin against harmful effects of the UV sun radiation.

Concerning human health, the evaluation was based on information from the registration dossier of the Lead registrant and from scientific literature (end of bibliographic search on 13 October 2017). In the body, homosalate is expected to be metabolized into salicylic acid and an alcohol (3,3,5-trimethylcyclohexanol). Very limited data is available on the toxicity of homosalate. This substance is not acutely toxic and does not exhibit irritating properties. Despite negative results in available studies regarding skin sensitization, homosalate may be considered as a weak or moderate sensitizer in the absence of more sensitive assays such as LLNA. Only biochemical changes were reported from 100 mg/kg bw/day administered by gavage for 2 weeks. Several target organs (kidney, liver, thyroid, spleen) and effects on fertility (increased infertility) and development (foetus lethality) were identified from a combined repeated dose and reproductive/developmental screening study in rats by gavage. However, the occurrence of constant light during the conduct of this assay does not allow an adequate assessment of the results. Homosalate is not mutagenic *in vitro*. Finally, in order to fulfill the endpoints for long-term repeated-dose toxicity, reproductive and developmental toxicities, the registrants have proposed a read-across with methyl salicylate. Nevertheless, the read-across was not substantiated by metabolic data and a comparison of the available physicochemical and toxicological data showed significant differences. In conclusion, considering the reproduction / developmental screening test of questionable reliability and the non-valid read-across, datagaps have been identified for repeated-dose toxicity and reproductive and developmental toxicity endpoints in regard to the minimum standard information requirement for tonnage band > 1000 tons/year. In this line, a CCH was initiated by ECHA requesting a subchronic toxicity study, an EOGRTS and a prenatal developmental toxicity study. These requests were agreed at MSC-57.

Regarding environmental issues, according to the available information, homosalate could exhibits P/vP properties specially in the aquatic environnement. Furthermore, the substance is potentially B/vB by screening criteria and the toxicity effects in aquatic organism is uncertain. Recently, a CCH was agreed which requests a biodegradation test, identifying the degradation products of the substance. If PBT or vP/vB properties of homosalate and/or degradations producsts are confirmed, this would represents a risk for the environment, specially for the aquatic compartiment due to continuous exposure (direct and indirectly) by their cosmetic uses. In this case, the best risk management option would be the identification of the substance as SVHC.

Regarding endocrine disruptor properties, several *in vitro* studies show that homosalate exhibits estrogenic and anti-androgenic properties. Contradictory results were reported for progestative properties *in vitro*. No adequate *in vivo* study is available to rule out these concerns. Thus, at this time, there is no sufficient information to have a firm conclusion on endocrine effects of homosalate. In this context, further investigations are needed, in particular regarding potential effects on fertility and development of humans and environmental organisms of homosalate. The requests described in the final decision from ECHA in the frame of dossier evaluation (subchronic toxicity study, EOGRTS and prenatal developmental

toxicity study) should help to clarify these concerns. Depending on these results, *in vivo* studies with environmental organisms (e.g. fish) would be considered.

Table: SVHC Roadmap 2020 criteria

	Yes	No
a) Art 57 criteria fulfilled?		x
b) Registrations in accordance with Article 10?	x	
c) Registrations include uses within scope of authorisation?	x	
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?		x

6.2 Conclusions on the most appropriate (combination of) risk management options

Considering the identified datagaps and concerns for human health and PBT properties of homosalate, the recommended management options are the following:

In the framework of dossier evaluation, an ECHA decisition requesting a subchronic toxicity study, an EOGRTS (without extension of cohort 1B and with cohorts 2A, 2B and 3), a prenatal developmental toxicity study and the identification of degradation products was agreed at MSC 57.

Further work within the CoRAP would be necessary to clarify concerns related to PBT properties. In addition, the current available data raise concerns on possible endocrine disrupting properties of homosalate. Depending on the results obtained from the studies requested in the CCH process, further work on human health could also be necessary within the CoRAP.

Anses believes that it is wiser to wait for the outcome of the CCH before putting the substance on the CoRAP and before initiating further evaluation work. Anses will also follow the ongoing activities on other salicylates (such as methyl salicylate, benzyl salicylate or ethylhexyl salicylate) considering the read-across proposed for these substances in each registration dossier. Finally, depending on the outcomes of the CCH and after evaluating the new dataset on the substance, other risk management options could be envisaged.

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