Food and Chemical Toxicology 189 (2024) 114704

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, cyclohexyl salicylate, CAS registry number 25485-88-5

A.M. Api [a], A. Bartlett [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], A. Bryant-Freidrich [d], G.A. Burton Jr. [e], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [f], W. Dekant [g], C. Deodhar [a], K. Farrell [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], H. Moustakas [a], J. Muldoon [a], T.M. Penning [i], G. Ritacco [a], N. Sadekar [a], I. Schember [a], T.W. Schultz [j], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, Pharmaceutical Sciences, Wayne State University, 42 W. Warren Ave., Detroit, MI, 48202, USA*
[e] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[f] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

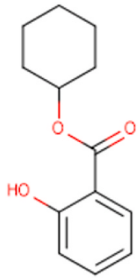
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2024.114704
Received 22 April 2024; Accepted 29 April 2024
Available online 3 May 2024
0278-6915/© 2024 Elsevier Ltd. All rights reserved.

Version: 040424. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: Cyclohexyl salicylate
CAS Registry Number: 25485-88-5

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative

(*continued on next column*)

(*continued*)

WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Cyclohexyl salicylate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclohexyl salicylate is not genotoxic. Data on cyclohexyl salicylate provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog hexyl salicylate (CAS # 6259-76-3) provided cyclohexyl salicylate a No Expected Sensitization Induction Level (NESIL) of 35,000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on data from the target material and the read-across analog benzyl salicylate (CAS # 118-58-1); cyclohexyl salicylate is not expected to be photoirritating/photoallergenic. Data on read-across analog hexyl salicylate (CAS # 6259-76-3) provide a calculated MOE >100 for the local respiratory endpoint. The environmental endpoints were evaluated; cyclohexyl salicylate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1984b; RIFM, 1995a)
Repeated Dose Toxicity: NOAEL = 360 mg/kg/day.	RIFM (1995b)
Reproductive Toxicity: Developmental toxicity: NOAEL = 360 mg/kg/day. Fertility: NOAEL = 180 mg/kg/day.	(ECHA, 2012)
Skin Sensitization: NESIL = 35,000 μg/cm^2.	RIFM (2004)
Photoirritation/Photoallergenicity: Not photoirritating/photoallergenic.	(RIFM, 2021; RIFM, 1983)
Local Respiratory Toxicity: NOAEC = 249 mg/m^3.	ECHA (2011)

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 87% (OECD 301F)	ECHA (2012)
Bioaccumulation:	
Critical Measured Value: 600–900 L/kg (OECD 305E)	RIFM (1993b)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.18 mg/L	RIFM (1985b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	Salvito et al. (2002)
Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.18 mg/L	RIFM (1985b)
RIFM PNEC is: 18 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** Cyclohexyl salicylate
2. **CAS Registry Number:** 25485-88-5

3. **Synonyms:** 2-ﾋﾄﾞﾛｷｼ安息香酸 = ｼｸﾛﾍｷｼﾙ/ｼｸﾛﾍｷｼﾙ = ｻﾘﾁﾗｰﾄ; Salicylic acid, cyclohexyl ester; Cyclohexyl 2-hydroxybenzoate; Cyclohexyl salicylate
4. **Molecular Formula:** $C_{13}H_{16}O_3$
5. **Molecular Weight:** 220.26 g/mol
6. **RIFM Number:** 6533
7. **Stereochemistry:** Stereoisomer not specified. One chiral center is present, and a total of 2 enantiomers are possible.

2. Physical data

1. **Boiling Point:** 333.43 °C (EPI Suite v4.11), 565 K (292 °C) (RIFM, 2011a)
2. **Flash Point:** 150 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.87 (EPI Suite v4.11), 4.7 (RIFM, 2011b)
4. **Melting Point**: 104.34 °C (EPI Suite v4.11)
5. **Water Solubility:** 8.988 mg/L at 25 °C (EPI Suite v4.11), 5.3 mg/L at 20 °C (solution in H_2O) (RIFM, 2011c)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.57e-005 mm Hg (EPI Suite v4.11), 0.055 Pa at 20 °C (RIFM, 2011d)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with peak absorbance at 306 nm and returning to baseline by 330 nm. Molar absorption coefficient (4490 L mol^{-1} • cm^{-1}, condition not specified) is above the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 100–1000 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.25% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00088 mg/kg/day or 0.066 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.007 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Hexyl salicylate (CAS # 6259-76-3)
   e. **Photoirritation/Photoallergenicity:** Benzyl salicylate (CAS # 118-58-1)
   f. **Local Respiratory Toxicity:** Hexyl salicylate (CAS # 6259-76-3)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

Cyclohexyl salicylate is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 04/04/24 (ECHA, 2012).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for cyclohexyl salicylate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.11
2	Products applied to the axillae	0.80
3	Products applied to the face/body using fingertips	0.85
4	Products related to fine fragrances	15
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	3.8
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	1.5
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	1.1
5D	Baby cream, oil, talc	0.35
6	Products with oral and lip exposure	0.11
7	Products applied to the hair with some hand contact	1.3
8	Products with significant ano-genital exposure (tampon)	0.35
9	Products with body and hand exposure, primarily rinse-off (bar soap)	8.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	4.5
10B	Aerosol air freshener	5.5
11	Products with intended skin contact but minimal transfer of fragrance to	0.35

(continued on next page)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	skin from inert substrate (feminine hygiene pad)	
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For cyclohexyl salicylate, the basis was the reference dose of 1.80 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 35,000 μg/cm^2.

As a conservative approach, we assumed that 100% of the material exposed via the skin is bioavailable (see Section V), thereby deriving the most stringent MOE. Since the MOE is > 100 (see the repeated dose and reproductive toxicity sections), we then refined the exposure to 40% using an *in silico* Skin Absorption Model (SAM) to determine the Maximum Allowable Concentrations for each category listed in Section X.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, cyclohexyl salicylate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Cyclohexyl salicylate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of cyclohexyl salicylate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with cyclohexyl salicylate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1984b). Under the conditions of the study, cyclohexyl salicylate was not mutagenic in the Ames test.

The clastogenicity of cyclohexyl salicylate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung (V79) cells were treated with cyclohexyl salicylate in DMSO at concentrations up to 60 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 1995a). Under the conditions of the study, cyclohexyl salicylate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, cyclohexyl salicylate does not present a concern for genotoxic potential.

Additional References: RIFM, 1984c.

Literature Search and Risk Assessment Completed On: 03/28/24.

11.1.2. Repeated dose toxicity

The MOE for cyclohexyl salicylate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on cyclohexyl salicylate. In an OECD 408-compliant study, 10 Hsd/Win:Wu rats/sex/dose were administered cyclohexyl salicylate via gavage at doses of 0, 40, 120, and 360 mg/kg/day for 90 days. An additional 5 Hsd/Win:Wu rats/sex/dose at 0 and 360 mg/kg/day were maintained after treatment to check for recovery. No mortality occurred throughout the study period. There were no effects on food consumption, food conversion, bodyweight gain, hematology, clinical chemistry, ophthalmology, organ weights, macroscopic examinations, or histopathology. Based on no adverse effects seen up to the highest dose, the NOAEL for this study was considered to be 360 mg/kg/day (RIFM, 1995b).

Therefore, the cyclohexyl salicylate MOE for the repeated dose toxicity endpoint can be calculated by dividing the cyclohexyl salicylate NOAEL in mg/kg/day by the total systemic exposure to cyclohexyl salicylate, 360/0.007, or 51,428.

In addition, the total systemic exposure to cyclohexyl salicylate (7 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/24.

11.1.3. Reproductive toxicity

The MOE for cyclohexyl salicylate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity and fertility data on cyclohexyl salicylate.

In an OECD 415-compliant study, 24 Wistar rats/sex/dose were administered cyclohexyl salicylate via gavage at doses of 0, 60, 180, and 540 mg/kg. Males were treated for 10 weeks before mating and throughout mating, up to euthanasia (a total of 14 weeks). Females were treated for 2 weeks before mating and throughout mating, gestation, and lactation, up to weaning on, or shortly after, 21 days postpartum. Weight gain and food consumption were significantly reduced in both sexes at the high dose. Dystocia in pre-birth dams and increased pre-birth loss were observed at the high dose. Thus, the fertility NOAEL for this study was considered to be 180 mg/kg/day (ECHA, 2012).

In an OECD 414-compliant study, 22 pregnant CD-1 rats/dose were administered cyclohexyl salicylate via gavage at doses of 0, 40, 120, and 360 mg/kg/day from days 6–15 post-coitum. No signs of toxicity nor embryotoxic or teratogenic potential were observed up to the highest dose. Thus, the developmental toxicity NOAEL for this study was considered to be 360 mg/kg/day (ECHA, 2012).

Therefore, the cyclohexyl salicylate MOE for the developmental toxicity endpoint can be calculated by dividing the cyclohexyl salicylate NOAEL in mg/kg/day by the total systemic exposure to cyclohexyl salicylate, 360/0.007, or 51,428.

Therefore, the cyclohexyl salicylate MOE for the fertility endpoint can be calculated by dividing the cyclohexyl salicylate NOAEL in mg/kg/day by the total systemic exposure to cyclohexyl salicylate, 180/0.007, or 337,837.

In addition, the total systemic exposure to cyclohexyl salicylate (7 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in

finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a reference dose (RfD) of 1.80 mg/kg/day.

11.1.3.1.1. Derivation of RfD. The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for cyclohexyl salicylate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 180 mg/kg/day by the uncertainty factor, 100 = 1.80 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/24.

11.1.4. Skin sensitization

Based on the existing data and read-across to hexyl salicylate (CAS # 6259-76-3), cyclohexyl salicylate is considered a skin sensitizer with a defined NESIL of 35,000 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for cyclohexyl salicylate. Based on the existing data and read-across material hexyl salicylate (CAS # 6259-76-3; see Section VI), cyclohexyl salicylate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, hexyl salicylate, was found to be negative in an *in vitro* Direct Peptide Reactivity Assay (DPRA), both negative and positive in a KeratinoSens assay (RIFM, 2014; Urbisch, 2015; RIFM, 2015a; RIFM, 2015b), and positive in human cell line activation test (h-CLAT) and U-SENS tests (Urbisch, 2015; Piroird et al., 2015). In a murine local lymph node assay (LLNA), read-across material hexyl salicylate was found to be sensitizing with an EC3 value of 0.18% (45 μg/cm^2) (RIFM, 2006a). In a guinea pig maximization test, cyclohexyl salicylate did not present reactions indicative of sensitization (RIFM, 1984a). In a human maximization test, no skin sensitization reactions were observed with read-across material hexyl salicylate (RIFM, 1975). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 35,000 μg/cm^2 of read-across material hexyl salicylate in 3:1 diethyl phthalate: ethanol, no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2004).

Based on the weight of evidence (WoE) from structural analysis, the animal study, and data for read-across material hexyl salicylate, cyclohexyl salicylate is a sensitizer with a WoE NESIL of 35,000 μg/cm^2 (see Table 1 below). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and an RfD of 1.80 mg/kg/day.

Additional References: RIFM, 1968; Sharp (1978); RIFM, 2003; RIFM, 1981; RIFM, 1967.

Literature Search and Risk Assessment Completed On: 03/28/24.

Table 1
Data summary for hexyl salicylate as read-across material for cyclohexyl salicylate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[a] (Induction) μg/cm^2	WoE NESIL[b] μg/cm^2
45 [1]	Weak	35,433	2069	NA	35,000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Data derived from CNIH or HMT.

[b] WoE NESIL limited to 2 significant figures.

11.1.5. Photoirritation/photoallergenicity

Based on *in vitro* study data, cyclohexyl salicylate would not be expected to present a concern for photoirritation. Based on *in vivo* study data for the read-across analog benzyl salicylate (CAS # 118-58-1), cyclohexyl salicylate does not present a concern for photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm, with peak absorbance at 306 nm and a return to baseline by 330 nm. The corresponding molar absorption coefficient is above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In an *in vitro* 3T3-Neutral Red uptake phototoxicity assay (OECD TG 432), cyclohexyl salicylate was not found to be photoirritating (RIFM, 2021). Photoallergy data are not available for cyclohexyl salicylate. Benzyl salicylate (CAS # 118-58-1) is structurally similar to the target material, demonstrates even greater UV absorbance, and has available *in vivo* photoallergy study data. As such, it is a read-across analog for the photoallergy endpoint for cyclohexyl salicylate. In the *in vivo* photoallergy study, 10% benzyl salicylate did not result in any skin reactions and was concluded to be both non-photoirritating and non-photoallergenic in the test system (RIFM, 1983). Based on *in vitro* study data, cyclohexyl salicylate would not be expected to present a concern for photoirritation. Based on *in vivo* study data on the read-across analog, benzyl salicylate (CAS # 118-58-1), cyclohexyl salicylate does not present a concern for photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate significant absorbance in the range of 290–700 nm, with peak absorbance at 306 nm and a return to baseline by 330 nm. The molar absorption coefficient (4490 L mol^{-1} • cm^{-1}, condition not specified) is above the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/24.

11.1.6. Local respiratory toxicity

There are no inhalation data available on cyclohexyl salicylate; however, in a 28-day inhalation exposure study for the read-across analog hexyl salicylate (CAS # 6259-76-3; see Section VI), a NOAEC 249 mg/m^3 was reported in the ECHA dossier for hexyl salicylate (ECHA, 2011).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 28-day, repeat dose inhalation study conducted in male and female Wistar rats (5/sex/dose), a NOAEC of 249 mg/m^3 was reported for hexyl salicylate (ECHA, 2011). The animals were exposed via nose-only inhalation exposure to hexyl salicylate at 0, 10.9, 52.3, and 249 mg/m^3 6 h a day and 5 days per week. Detailed clinical observations, body and organ weights, food consumption, hematology, clinical chemistry, gross pathology, and histopathology (adrenals, lungs with trachea and larynx, brain, spleen, heart, testes, kidneys, thymus, and liver) were all recorded. There were no treatment-related effects observed at any test concentration. The local respiratory NOAEC was determined to be 249 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (249 mg/m^3) × (1 m^3/1000 L) = 0.249 mg/L

- Minute ventilation of 0.17 L/min for a rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.249 mg/L) × (61.2 L/d) = 15.24 mg/day
- (15.24 mg/day)/(0.0016 kg lung weight of rat*) = 9524.25 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.066 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.102 mg/kg lung weight/day, resulting in a MOE of 93375 (i.e., [9524.25 mg/kg lung weight/-day]/[0.102 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.066 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/24.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cyclohexyl salicylate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, cyclohexyl salicylate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify cyclohexyl salicylate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

11.2.1.1. Risk assessment. Based on the current VoU (2019), cyclohexyl salicylate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 1997**: The inherent biodegradability of the test material was evaluated in a sealed vessel test using a modified SCAS test according to the OECD 301B guideline. The average extent of mineralization of the test material was 77.3% after 28 days.

RIFM, 1996: The ultimate biodegradability of the test material was evaluated using the sealed vessel test according to the OECD 301B guideline. Biodegradation of 58% was observed after 28 days.

RIFM, 1993a: The inherent biodegradability of the test material was evaluated using the sealed vessel test according to the OECD 301B guideline. Biodegradation of 55.7% was observed after 56 days.

RIFM, 1984d: Biodegradation of the test material was determined using the closed bottle test according to the EEC Directive 79/831 Annex V. Biodegradation of 81% was observed after 30 days at a test concentration of 2 mg/L.

RIFM, 1993b: The potential of the test material to bioaccumulate in fish was studied using C-14 (carboxyl)-labeled test material at 2 test concentrations (1 mg/L and 10 mg/L) using zebrafish (*Brachydanio rerio*), according to the OECD 305E guidelines under flow-through conditions. The BCF was calculated to be between 600 and 900 L/kg (wet wt.) at both concentrations. A steady state was attained within the first 2 days of exposure.

RIFM, 2012: The *in vitro* stability of the test material was evaluated in fish S9 liver fractions by monitoring the disappearance as a function of incubation time. Rapid enzymatic degradation by trout liver S9 fractions was observed for the test material.

11.2.1.2.2. Ecotoxicity. **RIFM, 1989:** An acute toxicity test was conducted with zebrafish in a semi-static system for 96 h. The LC0 and LC100 values were reported to be 2.1 and 6.1 mg/L, respectively.

RIFM, 1984d: An acute fish toxicity test was conducted using zebrafish in a continuous flow system. The LC50 value was calculated to be 3.78 mg/L at 48 and 96 h based on nominal concentrations.

RIFM, 1984d: An acute toxicity study with *Daphnia magna* was conducted using a semi-static system for 48 h. The LC50 value at 24 h was reported to be 2.16 mg/L. No 48-h LC50 was determined.

RIFM, 1985b: An acute toxicity study with algae was conducted under static conditions according to the Umweltbundesamt (The Federal Environmental Agency) "Inhibition of Cell Growth in the Green Algae *Scenedesmus subspicatus*." The EbC50 and ErC50 values at 72 h for the test material were determined to be 0.78 mg/L and 1.2 mg/L, respectively. The 72-h NOEC value based on nominal test concentration for growth rate was reported to be 0.5 mg/L.

RIFM, 2006b: A fish early-life stage toxicity test was conducted using fathead minnows according to the OECD 210 guidelines under dynamic test conditions. The 28-day NOEC value based on the mean measured concentration was reported to be 0.0019 mg/L based on weight. (Note: This study is disregarded and not considered for PNEC calculations due to major methodological deficiencies).

RIFM, 1985a: The subchronic toxicity of test material to zebrafish

(*Brachydanio rerio*) was studied over a 28-day period under semi-static conditions (renewal every 48 or 72 h) according to the UBA Guideline – "Sublethal effects on zebrafish – *Brachydanio rerio*." The 28-day NOEC value based on the mean measured concentration was reported to be 0.48 mg/L for mortality.

RIFM, 1985b: The long-term toxicity of the test material to *Daphnia magna* was studied for 21-Days under semi-static renewal conditions according to the Umweltbundesamt (The Federal Environmental Agency) "Extended Toxicity Test in *Daphnia Magna*" guideline. The concentration was reported to be 2.07 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 and NOEC values based on time-weighted average concentration for growth rate were reported to be 2.2 mg/L and 0.69 mg/L, respectively.

11.2.1.3. Risk assessment refinement. Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.33			1000000	0.00133	
ECOSAR Acute Endpoints **(Tier 2)** v2.0	0.618	0.945	0.255			Esters
ECOSAR Acute Endpoints **(Tier 2)** v2.0	0.251	0.271	0.943	10000	0.0251	Phenols
ECOSAR Acute Endpoints **(Tier 2)** v2.0	0.475	0.352	0.785			Neutral Organic SAR
Tier 3: Measured Data (including REACH)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	2.07		0.48			
Daphnia		2.16	0.18	10	18	
Algae		2.2	0.69			

21-day NOEC value based on the mean measured concentration was reported to be 0.18 mg/L for reproduction.

11.2.1.2.3. Other available data. Cyclohexyl salicylate has been registered for REACH with the following additional information available at this time (ECHA, 2012):

The ready biodegradability of the test material was evaluated using a closed bottle test according to the OECD 301D guideline. Biodegradation of 76% was observed after 28 days.

The ready biodegradability of the test material was evaluated using a manometric respirometry test according to the OECD 301F guideline. Biodegradation of 87% was observed after 28 days.

An acute fish (*Danio rerio*) toxicity test was conducted under flow-through conditions. The 96-h LC50 value based on the mean measured

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.7	4.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	100–1000	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for these materials is < 1. No further assessment is necessary.

The RIFM PNEC is 18 µg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic

environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 04/01/24.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/04/24.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.114704.

Appendix

Read-across Justification

Methods

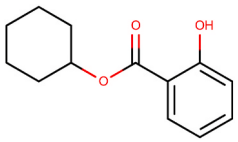
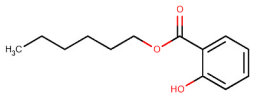
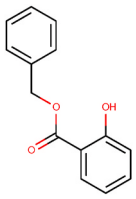
The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Cyclohexyl salicylate	Hexyl salicylate	Benzyl salicylate
CAS No.	25485-88-5	6259-76-3	118-58-1

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Structure			
Similarity (Tanimoto Score)		0.89	0.63
Endpoint		• Skin sensitization • Local respiratory toxicity	• Photoallergenicity
Molecular Formula	$C_{13}H_{16}O_3$	$C_{13}H_{18}O_3$	$C_{14}H_{12}O_3$
Molecular Weight (g/mol)	220.27	222.28	228.25
Melting Point (°C, EPI Suite)	104.34	99.68	130.50
Boiling Point (°C, EPI Suite)	333.43	327.79	320.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.00	0.00	0.00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	8.99	6.08	24.59
Log K_{OW}	4.87	5.06	4.31
J_{max} (μg/cm^2/h, SAM)	1.19	0.86	2.08
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.84	1.89	0.04
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	
Protein Binding (OECD)	No alert found	No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified	No skin sensitization reactivity domain alerts identified	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	N/A*

*Not applicable for the endpoint used.

Summary

There are insufficient toxicity data on cyclohexyl salicylate (CAS # 25485-88-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, hexyl salicylate (CAS # 6259-76-3) and benzyl salicylate (CAS # 118-58-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Hexyl salicylate (CAS # 6259-76-3) was used as a read-across analog for the target material cyclohexyl salicylate (CAS # 25485-88-5) for the local respiratory toxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters of salicylic acid.
  - o The target material and the read-across analog share a salicylic acid structure.
  - o The key difference between the target material and the read-across analog is that the target material is an ester of cyclohexanol, whereas the read-across analog is an ester of n-hexanol. This difference in the alcohol, which is cyclic in the target material compared to the straight chain in the read-across analog, is not expected to show any difference in the reactivity of the molecules. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no *in silico* alerts for the target material and the read-across analog, which is consistent with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Benzyl salicylate (CAS # 118-58-1) was used as a read-across analog for the target material cyclohexyl salicylate (CAS # 25485-88-5) for photoallergenicity.
  - o The target material and the read-across analog are structurally similar and belong to esters of salicylic acid.
  - o The key difference between the target material and the read-across analog is that the target material has a cyclohexyl substituent on the alcohol side, whereas the read-across analog has a benzyl substituent on the alcohol side. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog have a chromophore that is of interest to human health toxicity and is expected to be absorbed in the UV/Vis range of the electromagnetic spectrum. The UV/Vis absorption spectra for the read-across analog indicate significant absorption between 290 and 700 nm, with a peak absorbance at 306 nm and a return to baseline of 330 nm. The corresponding molar absorption coefficient is above the benchmark of concern for photoallergenicity. Therefore, based on the structural similarity between the target material and the read-across analog, the target material is expected to absorb as well and is not expected to pose a concern for photoallergenicity.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECHA, 2011. Hexyl salicylate registration dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/14766/1/2.

ECHA, 2012. Cyclohexyl salicylate registration dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/5340/1/2.

ECHA, 2017a. Guidance on information requirements and chemical safety assessment: chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2019. Volume of Use Survey. January-December 2019.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

Piroird, C., Ovigne, J.-M., Rousset, F., Martinozzi-Teissier, S., Gomes, C., Cotovio, J., Alepee, N., 2015. The Myeloid U937 Skin Sensitization Test (U-SENS) addresses the activation of dendritic cell event in the adverse outcome pathway for skin sensitization. Toxicol. Vitro 29 (5), 901–916.

RIFM (Research Institute for Fragrance Materials, Inc.), 1967. Human Repeated Insult Patch Test; Skin Sensitization Study in guinea Pigs; Acute Eye Irritation in Rabbits with 2-phenoxyethyl Isobutyrate (Phenirat). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 60419.

RIFM (Research Institute for Fragrance Materials, Inc.), 1968. Human Patch Tests with Fragrance Materials and Skin Sensitization Study with Fragrance Materials with guinea Pigs. Unpublished Report from Symrise. RIFM Report Number 60420. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1798. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Guinea Pig Skin Sensitisation Test with Hexyl Salicylate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 46933.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983. Phototoxicity and Photoallergy Tests with Benzyl Salicylate in the guinea Pig Unpublished Report from Rhodia Services - RSP. RIFM Report Number 40988. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1984a. Guinea Pig Sensitization Study Conducted with Cyclohexyl Salicylate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Kao. RIFM report number 55195.

RIFM (Research Institute for Fragrance Materials, Inc.), 1984b. Cyclohexyl Salicylate: Ames Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Kao. RIFM report number 55269.

RIFM (Research Institute for Fragrance Materials, Inc.), 1984c. Cyclohexyl Salicylate: Micronucleus Test. Unpublished Report from Kao. RIFM Report Number 55271. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1984d. Toxicity Studies with Cyclohexyl Salicylate in Fish and Daphnia Magna. Biodegradation Study with Cyclohexyl Salicylate. Unpublished Report from Kao. RIFM Report Number 55412. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1985a. Toxicity of Cyclohexyl Salicylate in 14-day Fish Study. Unpublished Report from Kao. RIFM Report Number 55184. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1985b. Toxicity of Cyclohexyl Salicylate in Daphnia Magna and Algae. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Kao. RIFM report number 55190.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989. Acute Toxicity of Cyclohexyl Salicylate. Unpublished Report from Kao. RIFM Report Number 55186. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1993a. The Inherent Biodegradability of Base Perfumes in the Sealed Vessel Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 49591.

RIFM (Research Institute for Fragrance Materials, Inc.), 1993b. Bioaccumulation Test on Fish with Cyclohexyl Salicylate. Unpublished Report from Kao. RIFM Report Number 55410. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995a. Cyclohexyl Salicylate: in Vitro Mammalian Cytogenetic Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Kao. RIFM report number 55270.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995b. Cyclohexyl Salicylate: 90 Day Oral Subchronic Toxicity Study in the Rat. Unpublished Report from Kao. RIFM Report Number 55275. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1996. The Ultimate Biodegradability of Base Perfumes in the Sealed Vessel Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 49461.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997. Assessment of the Inherent Biodegradability of Cyclohexyl Salicylate in a Sealed Vessel CO2 Production Test Using Acclimatised Effluent from a Modified Semi-continuous Activated Sludge Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 45860.

RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Topical Photoallergy Screening Test of Hexyl Salicylate and Beta-Methyl Naphthyl Ketone in Male Albino Hairless guinea Pigs [CRL: IAF(HA)-hrBR (Outbred)], Including Primary Irritation, Phototoxicity and Contact Hypersensitivity Evaluations. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 44882.

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test with Fragrance Materials. RIFM Report Number 45130. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2006a. Hexyl Salicylate: Local Lymph Node Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 51636.

RIFM (Research Institute for Fragrance Materials, Inc.), 2006b. Cyclohexyl Salicylate: Fish, Early-Life Stage Toxicity Test. Unpublished Report from Kao. RIFM Report Number 55013. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011a. Boiling Point of Cyclohexyl Salicylate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 62970.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011b. Partition Coefficient N-Octanol/water of Cyclohexyl Salicylate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 62971.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011c. Water Solubility of Cyclohexyl Salicylate. Unpublished Report from Givaudan. RIFM Report Number 62972. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011d. Vapour Pressure of Cyclohexyl Salicylate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 62973.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. In Vitro Metabolic Stability of Cyclohexyl Salicylate in Fish Liver S9 Fractions. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 65612.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Cyclohexyl Salicylate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 66004.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Fragrance Material in Vitro Sensitization: Direct Peptide Reactivity Assay (DPRA). RIFM Report Number 68623. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Induction of Antioxidant-Response Element Dependent Gene Activity Cytotoxicity (Using MTT) in the Keratinocyte ARE- Reporter Cell Line Keratinosens. RIFM Report Number 69647. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015b. Induction of Antioxidant-Response Element Dependent Gene Activity and Cytotoxicity (Using MTT) in the Keratinocyte ARE Reporter Cell Line KeratinoSens. RIFM Report Number 69648. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey 25. October 2019.
RIFM (Research Institute for Fragrance Materials, Inc.), 2021. Cyclohexyl Salicylate: Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 78033.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2024. Corrigendum to "Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products". Regul. Toxicol. Pharmacol. 72 (3), 105545, 673-68]. Regul Toxicol Pharmacol.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. Mutagenesis 37 (1), 13–23.
Urbisch, D., Mehling, A., Guth, K., Ramirez, T., Honarvar, N., et al., 2015. Assessing skin sensitization hazard in mice and men using non-animal test methods. Regul. Toxicol. Pharmacol. 71 (2), 337–351.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.