Food and Chemical Toxicology 183 (2024) 114243

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, butyl salicylate, CAS Registry Number 2052-14-4

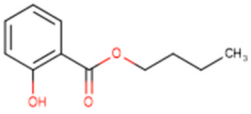
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], J. Muldoon [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], 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] *Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *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*
[f] *Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *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] *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] *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] *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

Version: 060823. 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.



(*continued on next column*)

(*continued*)

Name: Butyl salicylate
CAS Registry Number: 2052-14-4

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2023.114243
Received 8 June 2023; Received in revised form 30 October 2023; Accepted 20 November 2023
Available online 29 November 2023

(*continued*)

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, 2017; Safford et al., 2015a, 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
IFRA - The International Fragrance Association
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
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
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
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, 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.

Butyl salicylate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl salicylate (CAS # 118-61-6) show that butyl salicylate is not expected to be genotoxic. Data on read-across analog amyl salicylate (CAS # 2050-08-0) 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 butyl salicylate a No Expected Sensitization Induction Level (NESIL) of 35000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; butyl salicylate is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure is below the TTC (1.4 mg/day). For the hazard assessment based on the screening data, butyl salicylate is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, butyl salicylate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2019 IFRA Survey.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 2016; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 281 mg/kg/day.	RIFM (2020a)
Reproductive Toxicity: Developmental Toxicity and Fertility NOAEL = 333 mg/kg/day.	RIFM (2020b)
Skin Sensitization: NESIL = 35000 μg/cm^2.	(RIFM, 2004)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 3.2 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 527 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Not applicable	
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment: Not applicable; no 2019 VoU reported for EU and NA	

1. Identification

1. **Chemical Name:** Butyl salicylate
2. **CAS Registry Number:** 2052-14-4
3. **Synonyms:** Benzoic acid, 2-hydroxy-, butyl ester; n-Butyl o-hydroxybenzoate; n-Butyl salicylate; Butyl salicylate
4. **Molecular Formula:** $C_{11}H_{14}O_3$
5. **Molecular Weight:** 194.23 g/mol
6. **RIFM Number:** 614
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 268 °C (Fragrance Materials Association [FMA]), 300.26 °C (EPI Suite v4.11)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F (closed cup) (FMA)
3. **Log K_{OW}:** 4.08 (EPI Suite v4.11)
4. **Melting Point**: 6 °C (FMA), 81.45 °C (EPI Suite v4.11)
5. **Water Solubility:** 19.78 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 1.080 (FMA)
7. **Vapor Pressure:** 0.00196 mm Hg at 20 °C (EPI Suite v4.0), 0.00333 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficients (122, 116, and 133 L mol^{-1} • cm^{-1} for neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid that has a somewhat rough-herbaceous-chemical-odor.

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v.3.2.10)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0010% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00038 mg/kg/day or 0.027 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00055 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford, 2015; Safford, 2017; Comiskey, 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, 2015; Safford, 2015; Safford, 2017; Comiskey, 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 v4.5 (OECD, 2021b)
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl salicylate (CAS # 118-61-6)
   b. **Repeated Dose Toxicity:** Amyl salicylate (CAS # 2050-08-0)
   c. **Reproductive Toxicity:** Amyl salicylate (CAS # 2050-08-0)
   d. **Skin Sensitization:** Hexyl salicylate (CAS # 6259-76-3)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   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

Butyl salicylate is reported to occur in the following foods by the VCF*:

Mountain papaya (*C. candamarcensis*, *C. pubescens*).

*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

Butyl salicylate has been pre-registered for 2010; no dossier available as of 04/19/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for butyl 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)	0.95
2	Products applied to the axillae	0.80
3	Products applied to the face/body using fingertips	0.95
4	Products related to fine fragrances	0.95
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.95
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.95
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	2.8
5D	Baby cream, oil, talc	0.32
6	Products with oral and lip exposure	0.95
7	Products applied to the hair with some hand contact	0.95
8	Products with significant ano-genital exposure (tampon)	0.32
9	Products with body and hand exposure, primarily rinse-off (bar soap)	26
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.95
10B	Aerosol air freshener	100
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.32
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	0.95

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 butyl salicylate, the basis was the subchronic reference dose of 2.81 mg/kg/day, a skin absorption value of 17.1%, and a skin sensitization NESIL of 35000 μg/cm^2.
[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 v3.2.10.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Butyl salicylate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014a). BlueScreen is a human cell-based assay for

measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of butyl salicylate; however, read-across can be made to ethyl salicylate (CAS # 118-61-6; see Section VI).

The mutagenic activity of ethyl 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 and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with ethyl 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, 2016). Under the conditions of the study, ethyl salicylate was not mutagenic in the Ames test, and this can be extended to butyl salicylate.

The clastogenic activity of ethyl salicylate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with ethyl salicylate in DMSO. The micronuclei analysis was conducted at concentrations up to 1662 μg/mL in the presence and absence of metabolic activation. Ethyl salicylate did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, ethyl salicylate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to butyl salicylate.

Based on the data available, ethyl salicylate does not present a concern for genotoxic potential, and this can be extended to butyl salicylate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/22.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on butyl salicylate. Read-across material amyl salicylate (CAS # 2050-08-0; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a GLP- and OECD 408-compliant study, 10 Wistar Han rats/sex/dose were administered amyl salicylate via diet at concentrations of 0, 750, 3750, and 7500 ppm (equivalent to doses of 0, 55, 281, and 569 mg/kg/day in males, and 0, 67, 329, and 607 mg/kg/day in females, according to the study report) for 90 days. No mortality was observed throughout the study. No treatment-related adverse effects were observed in clinical signs, hematology, clinical chemistry, gross necropsy, organ weights, or histopathology. Reduced body weights and bodyweight gains, reflective of undernutrition, were observed in both sexes at the high dose. Based on reduced body weights and bodyweight gains observed in both sexes at 7500 ppm, the repeated dose toxicity NOAEL for this study was determined to be 3750 ppm (equivalent to 281 mg/kg/day in males and 329 mg/kg/day in females) (RIFM, 2020a).

In a GLP- and OECD 421-compliant study, 10 Wistar Han rats/sex/dose were administered amyl salicylate via diet at concentrations of 0, 500, 1500, and 5000 ppm (equivalent to doses of 0, 33, 100, and 333 mg/kg/day, according to the study report) for a minimum of 28 days. No mortality was observed throughout the study. No treatment-related adverse effects were observed in clinical signs, macroscopic examination, organ weights, or macroscopic examination. Reduced body weights and bodyweight gains were observed in females at 5000 ppm during premating but recovered during the remainder of the study period and, thus, were not considered adverse. Based on no treatment-related adverse effects up to the highest dose, the repeated dose toxicity NOAEL for this study was determined to be 5000 ppm (equivalent to 333 mg/kg/day) (RIFM, 2020b).

The more conservative NOAEL was derived from the OECD 408 study at 281 mg/kg/day.

Therefore, the butyl salicylate MOE is equal to the amyl salicylate NOAEL (mg/kg/day) divided by the total systemic exposure (mg/kg/day) to butyl salicylate, 281/0.00055, or 510909.

In addition, the total systemic exposure to butyl salicylate (0.55 μg/kg/day) is below the TTC of a Cramer Class I material (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1.1. Derivation of subchronic reference dose (RfD). 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 subchronic RfD of 2.81 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for butyl salicylate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 281 mg/kg/day by the uncertainty factor, 100 = 2.81 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/31/22.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on butyl salicylate. Read-across material amyl salicylate (CAS # 2050-08-0; see Section VI) has sufficient data to support the reproductive toxicity endpoint. In a GLP- and OECD 421-compliant study, 10 Wistar Han rats/sex/dose were administered amyl salicylate via diet at concentrations of 0, 500, 1500, and 5000 ppm (equivalent to doses of 0, 33, 100, and 333 mg/kg/day, according to the study report) for a minimum of 28 days. Males were exposed for 29 days (from 14 days prior to mating and during the mating period), and females were exposed from 51 to 61 days (which includes 14 days prior to mating, variable time to conception, the duration of pregnancy, and at least 13 days after delivery, up to and including the day of scheduled necropsy). No treatment-related adverse effects were observed on mating and fertility indices, precoital time, number of implantations, estrous cycle, or histopathology of reproductive organs. No treatment-related adverse effects were observed on gestation, viability and lactation indices, gestation duration, parturition, maternal care, litter size, sex ratio, pup mortality, pup clinical signs, pup body weights, pup anogenital distance, pup areola/nipple retention, T4 thyroid hormone levels, or macroscopic examination. Based on no treatment-related adverse effects up to the highest dose, the developmental toxicity and fertility NOAEL for this study were determined to be 5000 ppm (equivalent to 333 mg/kg/day) (RIFM, 2020b).

Therefore, the butyl salicylate MOE for the developmental toxicity and fertility endpoints can be calculated by dividing the amyl salicylate NOAEL in mg/kg/day by the total systemic exposure to butyl salicylate, 333/0.00055, or 605455.

In addition, the total systemic exposure to butyl salicylate (0.55 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/31/22.

11.1.4. Skin sensitization

Based on the existing data on the read-across material hexyl salicylate, butyl salicylate is a skin sensitizer with a defined NESIL of 35000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for butyl salicylate. Therefore, read-across material hexyl salicylate (CAS # 6259-76-3; see Section VI) was used for the risk assessment of butyl salicylate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, butyl salicylate is a skin sensitizer. The chemical structure 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 v4.5). Read-across hexyl salicylate was predicted not to be sensitizing based on OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a). Hexyl salicylate was negative in the direct peptide reactivity assay (DPRA) and KeratinoSens, inconclusive in the human cell line activation test (h-CLAT), but positive in the U-SENS test (RIFM, 2014b; Urbisch, 2015; RIFM, 2015a; RIFM, 2015b; Piroird et al., 2015). In a murine local lymph node assay (LLNA), read-across hexyl salicylate was found to be sensitizing with an EC3 value of 0.18% (45 μg/cm^2) (RIFM, 2006). In a guinea pig maximization test, read-across hexyl salicylate did not lead to skin sensitization reactions (RIFM, 1981). In human maximization tests, no skin sensitization reactions were observed when butyl salicylate and read-across material hexyl salicylate were tested at 1380 μg/cm^2 and 2070 μg/cm^2, respectively (RIFM, 1975a; RIFM, 1975b). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 35433 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 103volunteers (RIFM, 2004).

Based on the weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies on the read-across material and the target material, butyl salicylate is a sensitizer with a WoE NESIL of 35000 μg/cm^2 (Table 1). 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 subchronic RfD of 2.81 mg/kg/day.

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

Literature Search and Risk Assessment Completed On: 03/31/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, butyl salicylate would not be expected to present a concern for photoirritation or

Table 1
Summary of existing data on hexyl salicylate as a read-across for butyl salicylate.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) μg/cm^2	WoE NESIL[3] μg/cm^2	LLNA Weighted Mean EC3 Value μg/cm^2	GPMT[4]	Buehler[4]
Very weak	35433	2070	NA	35000	45	Negative	NA
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Negative	Inconclusive		No alert found	No alert found	No alert found

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; KE = Key Event; NA = Not Available

[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[2]Data derived from CNIH or HMT

[3]WoE NESIL limited to 2 significant figures

[4]Studies conducted according to the OECD TG 406 are included in the table.

[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for butyl salicylate in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, butyl salicylate does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficients (122, 116, and 133 L $mol^{-1} \bullet cm^{-1}$ for neutral, acidic, and basic conditions, respectively) are below the benchmark of concern for photoirritating effects, 1000 L $mol^{-1} \bullet cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/21/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for butyl salicylate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on butyl salicylate. Based on the Creme RIFM Model, the inhalation exposure is 0.027 mg/day. This exposure is 51.9 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/23/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of butyl salicylate was performed following the RIFM Environmental Framework (Salvito, 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, butyl salicylate was not assessed as no Volume of Use was reported.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify butyl 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, 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 $\geq$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).

11.2.1.1. Risk assessment. Not applicable.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Butyl salicylate has been pre-registered for REACH with no additional data at this time.

11.2.1.3. Risk assessment refinement. Not applicable.

Literature Search and Risk Assessment Completed On: 03/30/22.

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 06/08/23.

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.2023.114243.

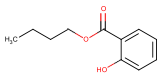
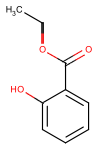
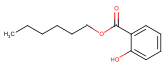
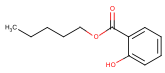
Appendix

Read-across justification

Methods

The read-across analogs were 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 Chemical 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 v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- 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 v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

Principal Name	Target Material	Read-across Material	Read-across Material	Read-across Material
	Butyl salicylate	Ethyl salicylate	Hexyl salicylate	Amyl salicylate
CAS No.	2052-14-4	118-61-6	6259-76-3	2050-08-0
Structure				
Similarity (Tanimoto Score)		0.83	0.92	0.95
Endpoint		• Genotoxicity	• Skin sensitization	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{11}H_{14}O_3$	$C_9H_{10}O_3$	$C_{13}H_{18}O_3$	$C_{12}H_{16}O_3$
Molecular Weight (g/mol)	194.23	166.18	222.28	208.26
Melting Point (°C, EPI Suite)	−5.90	1.00	99.68	90.74
Boiling Point (°C, EPI Suite)	271.00	232.50	327.79	270.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.44	11.28	0.00	0.11
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	19.78	737.10	6.08	18.94
Log K_{OW}	4.63	2.95	5.06	4.57
J_{max} (μg/cm^2/h, SAM)	2.94	43.56	0.86	2.44
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.07	0.61	1.89	1.43
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	No alert found		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found		

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across Material	Read-across Material	Read-across Material
	Butyl salicylate	Ethyl salicylate	Hexyl salicylate	Amyl salicylate
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No skin sensitization reactivity domain alerts were identified.	No skin sensitization reactivity domain alerts were identified.		
Oncologic Classification	Phenol-type Compounds	Phenol-type Compounds		
Repeated Dose Toxicity				
Repeated Dose (HESS)	Not categorized			Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.5)	Moderate binder, OH group			Strong binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)			Non-toxicant (moderate reliability)
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 were identified.		No skin sensitization reactivity domain alerts were identified.	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on butyl salicylate (CAS # 2052-14-4). Hence, *in silico* evaluation was conducted to determine read-across materials. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, ethyl salicylate (CAS # 118-61-6), hexyl salicylate (CAS # 6259-76-3), and amyl salicylate (CAS # 2050-08-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusion

- Ethyl salicylate (CAS # 118-61-6) was used as a read-across analog for the target material, butyl salicylate (CAS # 2052-14-4), for the genotoxicity endpoint.
  - o The target material and the read-across analog are salicylate esters.
  - o The key difference between the target material and the read-across analog is that the target material has an butyl alcohol fragment, while the read-across analog has an ethyl alcohol fragment. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
  - 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - 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.
- Hexyl salicylate (CAS # 6259-76-3) was used as a read-across analog for the target material, butyl salicylate (CAS # 2052-14-4), for the skin sensitization endpoint.
  - o The target material and the read-across analog are salicylate esters.
  - o The key difference between the target material and the read-across analog is that the target material has a butyl alcohol fragment, while the read-across analog has a hexyl alcohol fragment. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
  - 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - 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.
- Amyl salicylate (CAS # 2050-08-0) was used as a read-across analog for the target material, butyl salicylate (CAS # 2052-14-4), for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are salicylate esters.
  - o The key difference between the target material and the read-across analog is that the target material has a butyl alcohol fragment, while the read-across analog has a pentyl alcohol fragment. The differences between structures do not essentially change the physical–chemical properties nor

raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.

- 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The target material and the read-across analog show similar alerts for ER Binding. ER Binding is a molecular initiating event analogous to protein binding. ER Binding is not necessarily predictive of endocrine disruption, given the complex pre- and post-receptor events that determine activity. The data described in the developmental and reproductive toxicity section confirm that the MOE for the target material is adequate under the current usage. Therefore, the alert is superseded by 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.

References

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118, 104805.

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.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718.

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.

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, 2021a. Guideline No. 497: Defined Approaches on Skin Sensitisation, OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. https://doi.org/10.1787/b92879a4-en. Retrieved from.

OECD, 2021b. The OECD QSAR Toolbox, v3.2–4.5. 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 report number 60419 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise.

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

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

RIFM (Research Institute for Fragrance Materials, Inc.), 1975b. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1799 (RIFM, Woodcliff Lake, NJ, USA.

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

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 report number 44882 (RIFM, Woodcliff Lake, NJ, USA.

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.), 2006. Hexyl Salicylate: Local Lymph Node Assay. RIFM report number 51636 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Report on the Testing of Butyl Salicylate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 67245 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. 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.), 2016. Ethyl Salicylate: Salmonella typhimurium and Escherichia coli Reverse Mutation Assay. Unpublished report from RIFM report number 71329 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Ethyl Salicylate: Micronucleus Test in Human Lymphocytes in Vitro. Unpublished report from RIFM report number 72436 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey 24. March 2019.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. Reaction Mass of 2-methylbutyl Salicylate and Pentyl Salicylate (Amyl Salicylate): A 90-day Study by Dietary Administration in Wistar Han Rats. RIFM report number 77769 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. Reaction Mass of 2-methylbutyl Salicylate and Pentyl Salicylate (Amyl Salicylate): Reproduction/Developmental Toxicity Screening Test by Dietary Administration in Rats. RIFM report number 77770 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan.

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., 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.

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.