Food and Chemical Toxicology 183 (2024) 114265

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

# RIFM fragrance ingredient safety assessment, anisyl formate, CAS registry number 122-91-8

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] *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, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *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*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member 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] *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

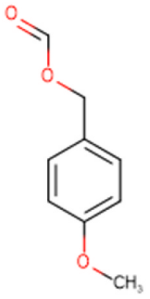
Handling Editor: Dr. Bryan Delaney

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

https://doi.org/10.1016/j.fct.2023.114265
Received 8 June 2023; Received in revised form 8 November 2023; Accepted 22 November 2023
Available online 30 November 2023

Version: 060723. 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: Anisyl formate
CAS Registry Number: 122-91-8



**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 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

(*continued on next column*)

(*continued*)

**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.**

Anisyl formate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that anisyl formate is not genotoxic. Data on read-across analog *p*-anisyl acetate (*p*-methoxybenzyl acetate; CAS # 104-21-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog anisyl alcohol (CAS # 105-13-5) provide anisyl formate a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm$^2$ for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; anisyl formate 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 to anisyl formate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; anisyl formate 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, 2016b; RIFM, 2016a; RIFM, 2016c) |
| **Repeated Dose Toxicity:** NOAEL = 133 mg/kg/day. | (ECHA REACH Dossier: p-Methoxybenzyl Acetate; ECHA, 2016) |
| **Reproductive Toxicity:** Developmental NOAEL = 100 mg/kg/day. Fertility NOAEL = 400 mg/kg/day. | (ECHA REACH Dossier: p-Methoxybenzyl Acetate; ECHA, 2016) |
| **Skin Sensitization:** NESIL = 1700 μg/cm$^2$. | RIFM (2017) |
| **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:** | |
| Critical Measured Value: 87% (OECD 301F) | (RIFM, 2014a) |
| **Bioaccumulation:** | |
| Screening-level: 5.398 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Screening-level: Fish LC50: 2481 mg/L | (RIFM Framework; Salvito, 2002) |

**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

| | |
|---|---|
| **Risk Assessment:** | |
| **Screening-level:** PEC/PNEC (North America and Europe) < 1 | (RIFM Framework; Salvito, 2002) |
| **Critical Ecotoxicity Endpoint:** Fish LC50: 2481 mg/L | (RIFM Framework; Salvito, 2002) |

**RIFM PNEC is:** 2.481 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

## 1. Identification

1. **Chemical Name:** Anisyl formate

2. **CAS Registry Number:** 122-91-8
3. **Synonyms:** Anisyl methanoate; Benzenemethanol, 4-methoxy-, formate; p-Methoxybenzyl methanoate; 4-Methoxybenzyl formate; p-Methoxybenzyl formate; ｷﾞ酸 = p-ﾒﾄｷｼﾍﾞﾝｼﾞﾙ; Anisyl formate
4. **Molecular Formula:** $C_9H_{10}O_3$
5. **Molecular Weight:** 166.17 g/mol
6. **RIFM Number:** 656
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

## 2. Physical data

1. **Boiling Point:** 236.7 °C (EPI Suite v4.11)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log $K_{OW}$:** 0.8 (RIFM, 2014b), 1.61 (EPI Suite v4.11)
4. **Melting Point**: 31.22 °C (EPI Suite v4.11)
5. **Water Solubility:** 2679 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 1.14 (FMA)
7. **Vapor Pressure:** 0.027 mm Hg at 20 °C (EPI Suite v4.0), 0.03 mm Hg at 20 °C (FMA), 0.0462 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm under the acidic condition; no absorbance under neutral or basic conditions. Molar absorption coefficient (435 L $mol^{-1}$ • $cm^{-1}$ under acidic conditions) is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless liquid. Sweet herbaceous-green, yet somewhat dry odor with a faintly musty but not unpleasant undertone. Sweet and slightly spicy-green taste.

## 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 v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.000028% (RIFM, 2020)
2. **Inhalation Exposure*:** 0.00017 mg/kg/day or 0.012 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.00035 mg/kg/day (RIFM, 2020)

*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

### *6.1. Cramer Classification: Class I, Low*

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.5 |
|---|---|---|
| I | I | I |

### *6.2. Analogs Selected*

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** *p*-Anisyl acetate (CAS # 104-21-2)
c. **Reproductive Toxicity:** *p*-Anisyl acetate (CAS # 104-21-2)
d. **Skin Sensitization:** Read-across - anisyl alcohol (CAS # 105-13-5); Weight of evidence (WoE) - acetic acid (CAS # 64-19-7)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

Read-across Justification: See Appendix below

## 7. Metabolism

Metabolism of the target material anisyl formate (CAS # 122-91-8) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.5). The target material is predicted to be metabolized to anisyl alcohol (CAS # 105-13-5) and formic acid (CAS # 64-18-6) in the first step with 0.95 pre-calculated and 0.95 intrinsic probability. Hence, anisyl alcohol (CAS # 105-13-5) and formic acid (CAS # 64-18-6) can be used as read-across analogs for the target materials. Due to a lack of data on formic acid, the metabolite analog acetic acid (CAS # 64-19-7) was used. Read-across analog anisyl alcohol (CAS # 105-13-5) and formic acid (CAS # 64-18-6) were out of domain for the *in vivo* rat and the *in vitro* rat S9 simulators (OASIS TIMES v2.3.1.11). However, based on expert judgment, the model's domain exclusion was overridden, and a justification was provided.

**Additional References:** None.

## 8. Natural occurrence

Anisyl formate is reported to occur in the following foods by the VCF*:

Vanilla.

Wine.

*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 (ECHA, 2017a); accessed on 06/07/23.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for anisyl formate 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) | 0.12 |
| 2 | Products applied to the axillae | 0.039 |
| 3 | Products applied to the face/body using fingertips | 0.060 |
| 4 | Products related to fine fragrances | 0.73 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.18 |

(*continued on next page*)

(*continued*)

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.043 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.00017 |
| 5D | Baby cream, oil, talc | 0.000057 |
| 6 | Products with oral and lip exposure | 0.43 |
| 7 | Products applied to the hair with some hand contact | 0.11 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.000057 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 1.4 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 1.1 |
| 10B | Aerosol air freshener | 0.00017 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.000057 |
| 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 anisyl formate, the basis was the subchronic reference dose of 1 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 1700 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 and use levels, anisyl formate does not present a concern for genetic toxicity.

*11.1.1.1. Risk assessment.* Anisyl formate 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, 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 anisyl formate (CAS # 122-91-8) 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 TA1535, TA1537, TA98, TA100, and *Escherichia coli* strains WP2uvrA were treated with anisyl formate 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 dose in the presence or absence of S9 in *Salmonella typhimurium* strains TA1535, TA1537, TA98, and *Escherichia coli* strains WP2uvrA and in the presence of S9 in *S. typhimurium* TA100 strain (RIFM, 2016b). However, in the absence of S9, the *S. typhimurium* TA100 strain was concluded to be positive in the initial as well as confirmatory assay due to an increase in the mean number of revertant colonies observed at ≥1600 and ≥ 3000 μg/plate in the initial and confirmatory mutagenicity assays, respectively. Since increases in revertant colonies for the TA100 strain were very weak, and OASIS times (v2.27.19.13) predicted anisyl formate to be negative in the *in vitro* Ames assay as well as the *in vivo* micronucleus assay simulator, a follow-up mammalian cell gene mutation assay (HPRT/mouse lymphoma assay) was conducted according to OECD TG 476/GLP guidelines. Human lymphocytes were treated with anisyl formate in DMSO at doses equivalent to up to 10 mM (as determined in a preliminary toxicity assay) for 3 h. Effects were evaluated both with and without metabolic activation. No toxicologically significant increases in the frequency of mutant colonies were observed with any dose of the test material, either with or without metabolic activation (RIFM, 2016a). Under the conditions of the study, anisyl formate was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of anisyl formate 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 anisyl formate in solvent DMSO at concentrations up to 1300 μg/mL in the presence and absence of S9 at the 3- and 24-h time points. Anisyl formate did not induce binucleated cells with micronuclei when tested up to the solubility limit in either non-activated or S9-activated test systems (RIFM, 2016c). Under the conditions of the study, anisyl formate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, read anisyl formate does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 05/20/22.

#### 11.1.2. Repeated dose toxicity

The MOE for anisyl formate 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 anisyl formate. Read-across material *p*-anisyl acetate (CAS # 104-21-2; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In a GLP and OECD 422 compliant study, groups of 12 Sprague Dawley rats/sex/dose were administered p-anisyl acetate via gavage (vehicle: corn oil) at doses of 0, 25, 100, and 400 mg/kg/day. Males were treated for a total of 50 days (prior to mating for 2 weeks, during 2 weeks of mating, and 22 days of post-mating). Females were treated for 2 weeks prior to mating until postpartum day 13. An additional 6 Sprague Dawley rats/sex/dose were treated for 50 days and maintained for 2 weeks after treatment as recovery groups. No treatment-related mortality was observed throughout the study period. No treatment-related adverse effects were observed in clinical signs, body weights, bodyweight gains, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, behavior, immunology, organ weights, gross pathology, or histopathology. Based on a lack of adverse findings seen up to the highest dose, the repeated dose NOAEL for this study was considered to be 400 mg/kg/day (ECHA, 2016).

A default safety factor of 3 was used when deriving a NOAEL from OECD 422 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 400/3 or 133 mg/kg/day.

Therefore, the anisyl formate MOE for the repeated dose toxicity endpoint can be calculated by dividing the p-anisyl acetate NOAEL in mg/kg/day by the total systemic exposure to anisyl formate, 133/0.00035, or 380000.

Additionally, the total systemic exposure to anisyl formate (0.35 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:** 04/12/22.

*11.1.3. Reproductive toxicity*

The MOE for anisyl formate 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 anisyl formate. Read-across material *p*-anisyl acetate (CAS # 104-21-2; see Section VI) has sufficient data to support the reproductive toxicity endpoint.

In a GLP- and OECD 422-compliant study, groups of 12 Sprague Dawley rats/sex/dose were administered p-anisyl acetate via gavage (vehicle: corn oil) at doses of 0, 25, 100, and 400 mg/kg/day. Males were treated for a total of 50 days (prior to mating for 2 weeks, during 2 weeks of mating, and 22 days of post-mating). Females were treated for 2 weeks prior to mating until postpartum day 13. An additional 6 Sprague Dawley rats/sex/dose were treated for 50 days and maintained for 2 weeks after treatment as recovery groups. No treatment-related mortality was observed throughout the study period. No treatment-related adverse effects were observed in the estrous cycle, sperm parameters, or reproductive performance. No treatment-related adverse effects were observed in pup histopathology, anogenital distance, or immunotoxicity. The pup viability index was decreased at the high dose (no statistical significance). Body weights were significantly decreased in pups at the high dose. Based on reduced survival and body weights of pups at the high dose, the developmental toxicity NOAEL for this study was considered to be 100 mg/kg/day. Based on no adverse effects on reproductive performance seen up to the highest dose, the fertility NOAEL for this study was considered to be 400 mg/kg/day (ECHA, 2016).

Therefore, the anisyl formate MOE for the developmental toxicity endpoint can be calculated by dividing the *p*-anisyl acetate NOAEL in mg/kg/day by the total systemic exposure to anisyl formate, 100/0.00035, or 285714.

Therefore, the anisyl formate MOE for the fertility endpoint can be calculated by dividing the *p*-anisyl acetate NOAEL in mg/kg/day by the total systemic exposure to anisyl formate, 400/0.00035, or 1142857.

In addition, the total systemic exposure to anisyl formate (0.35 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.

*11.1.3.1.1. Derivation of 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 an RfD of 1 mg/kg/day.

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 anisyl formate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 100 mg/kg/day by the uncertainty factor, 100 = 1 mg/kg/day.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/12/22.

*11.1.4. Skin sensitization*

Based on the available data, read-across material anisyl alcohol (CAS # 105-13-5) and WoE material acetic acid (CAS # 64-19-7), anisyl formate is a skin sensitizer with a defined NESIL of 1700 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Limited skin sensitization data are available for anisyl formate. Therefore, read-across material anisyl alcohol (CAS # 105-13-5; see Section VI) and WoE material acetic acid (CAS # 64-19-7; see Section VI) were used for the risk assessment of anisyl formate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, anisyl formate is a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly, while the WoE material is not expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across analog anisyl alcohol was found to be borderline and positive in 2 *in vitro* direct peptide reactivity assays (DPRAs), negative in the KeratinoSens assay, and positive in the h-CLAT assay, but negative in the U-SENS test (RIFM, 2014c; RIFM, 2015; Piroird et al., 2015; RIFM, 2018). Read-across material anisyl alcohol was also found to be positive in the murine local lymph node assay (LLNA) with an EC3 value of 5.9% (1475 μg/cm$^2$) (RIFM, 2005). However, In the human maximization test, no reactions indicative of skin sensitization were observed to anisyl formate or anisyl alcohol (RIFM, 1975; RIFM, 1971). Additionally, in a confirmation of no induction in humans test (CNIH) with 1771 μg/cm$^2$ of read-across material anisyl alcohol in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2017).

Based on WoE from structural analysis and *in vitro*, animal, and human studies on the read-across material, WoE material, and the target material, anisyl formate is a sensitizer with a WoE NESIL of 1700 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 an RfD of 1 mg/kg/day.

**Additional References:** Gauggel et al., 1993.

**Literature Search and Risk Assessment Completed On:** 05/22/22.

*11.1.5. Photoirritation/photoallergenicity*

Based on the available UV/Vis absorption spectra, anisyl formate would not be expected to present a concern for photoirritation or photoallergenicity.

*11.1.5.1. Risk assessment.* There are no photoirritation studies available for anisyl formate in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm under acidic conditions. 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, anisyl formate 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 between 290 and 700 nm under the acidic condition; no absorbance was found under neutral or basic conditions. The molar absorption coefficient (435 L mol$^{-1}$ • cm$^{-1}$ under acidic conditions) is below 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:** 04/13/22.

*11.1.6. Local Respiratory Toxicity*

The MOE could not be calculated due to a lack of appropriate data. The exposure level for anisyl formate 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 anisyl formate. Based on the Creme RIFM Model, the inhalation

**Table 1**
Summary of existing data on anisyl alcohol as a read-across for anisyl formate.

| WoE Skin Sensitization Potency Category[1] | Human Data | | | | Animal Data | | |
|---|---|---|---|---|---|---|---|
| | NOEL-CNIH (induction) µg/cm² | NOEL-HMT (induction) µg/cm² | LOEL[2] (induction) µg/cm² | WoE NESIL[3] µg/cm² | LLNA Weighted Mean EC3 Value µg/cm² | GPMT[4] | Buehler[4] |
| Moderate | 1771 | 3450 | NA | 1700 | 1475 | NA | 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 |
| | Borderline Positive | Negative | Negative (U-SENS) Positive (h-CLAT) | | No alert found | Schiff base formation | 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.

exposure is 0.012 mg/day. This exposure is 116.7 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:** 05/19/22.

### *11.2. Environmental endpoint summary*

#### *11.2.1. Screening-level assessment*

A screening-level risk assessment of anisyl formate 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, anisyl formate was identified as a fragrance material with no 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,

| | LC50 (Fish) | EC50 (*Daphnia*) | EC50 (Algae) | AF | PNEC | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 2481 | | | 1000000 | 2.481 | |

2012a) did not identify anisyl formate 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, 2017b). 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

*11.2.2. Risk assessment*

Based on the current VoU (2019), anisyl formate does not present a risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies.* Biodegradation

**RIFM, 2014a:** The ready biodegradability of anisyl formate was evaluated in a manometric respirometry test according to the OECD 301F method. Biodegradation of 87% was observed after 28 days.

Ecotoxicity

No data available.

Other available data

Anisyl formate has been pre-registered for REACH with no additional data at this time.

*11.2.3. 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.

Exposure information and PEC calculation (following RIFM Framework: Salvito, 2002)

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 0.8 | 0.8 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional VoU Tonnage Band | <1 | <1 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

Based on the available data, the RQ for this material is $< 1$. No further assessment is necessary.

The RIFM PNEC is 2.481 µg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 05/18/22.

## 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 06/07/23.

## 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.2023.114265.

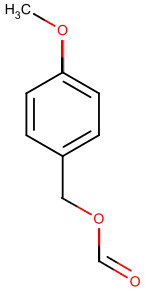
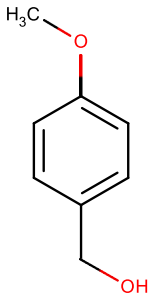
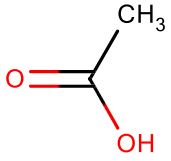
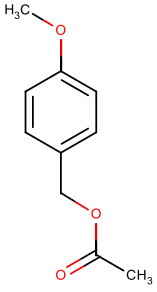
## Appendix

*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, 2017c).

- 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, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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 | WoE Material | Read-across Material |
|---|---|---|---|---|
| | Anisyl formate | Anisyl alcohol | Acetic acid | *p*-Anisyl acetate |
| **CAS No.** | 122-91-8 | 105-13-5 | 64-19-7 | 104-21-2 |
| **Structure** |  |  |  |  |
| **Similarity (Tanimoto Score)** | | Not applicable* | Not applicable* | 0.87 |
| **SMILES** | COc1ccc(COC═O)cc1 | COc1ccc(CO)cc1 | CC(O)═O | COc1ccc(COC(C)═O)cc1 |
| **Endpoint** | | Skin sensitization | Skin sensitization | Repeated dose toxicity<br>Reproductive toxicity |
| **Molecular Formula** | $C_9H_{10}O_3$ | $C_8H_{10}O_2$ | $C_2H_4O_2$ | $C_{10}H_{12}O_3$ |
| **Molecular Weight (g/mol)** | 166.176 | 138.166 | 60.052 | 180.203 |
| **Melting Point (°C, EPI Suite)** | 31.22 | 25.00 | 16.64 | 84.00 |
| **Boiling Point (°C, EPI Suite)** | 236.70 | 259.10 | 117.90 | 270.00 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 6.16E+00 | 2.40E-01 | 2.09E+03 | 3.44E-01 |
| **Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)** | 2.68E+03 | 2.00E+03 | 1.00E+06 | 7.83E+02 |
| **Log KOW** | 1.61 | 1.1 | −0.17 | 2.16 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 20.71 | 13.68 | 6282.71 | 10.46 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 1.17E-01 | 1.31E-03 | 1.45E-02 | 8.48E-02 |
| ***Repeated Dose Toxicity*** | | | | |

(*continued on next page*)

(*continued*)

| Principal Name | Target Material | Read-across Material | WoE Material | Read-across Material |
|---|---|---|---|---|
| | Anisyl formate | Anisyl alcohol | Acetic acid | *p*-Anisyl acetate |
| **Repeated Dose (HESS)** | Not categorized | | | Acetaminophen (Hepatotoxicity) Alert\| Acetaminophen (Renal toxicity) Alert\| Phenacetin (Hepatotoxicity) Alert\| Phenacetin (Renal toxicity) Alert |
| ***Reproductive Toxicity*** | | | | |
| **ER Binding (OECD QSAR Toolbox v4.5)** | Non-binder, without OH or $NH_2$ group | | | Non-binder, without OH or $NH_2$ group |
| **Developmental Toxicity (CAESAR v2.1.6)** | Toxicant (low reliability) | | | Toxicant (low reliability) |
| ***Skin Sensitization*** | | | | |
| **Protein Binding (OASIS v1.1)** | No alert found | No alert found | No alert found | |
| **Protein Binding (OECD)** | No alert found | 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) | Not possible to classify according to these rules (GSH) | |
| **Protein Binding Alerts for Skin Sensitization (OASIS v1.1)** | No alert found | No alert found | No alert found | |
| **Skin Sensitization Reactivity Domains (Toxtree v2.6.13)** | Alert for Acyl Transfer agent identified | 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 | No metabolites formed | See Supplemental Data 3 |

*Tanimoto score not reported as the read-across analogs are metabolites of the target material and not structural analogs.

*Summary*

There are insufficient toxicity data on anisyl formate (CAS # 122-91-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, anisyl alcohol (CAS # 105-13-5), acetic acid (CAS # 64-19-7), and *p*-anisyl acetate (CAS # 104-21-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

*Conclusions*

- Read-across alcohol anisyl alcohol (CAS # 105-13-5) and read-across acid acetic acid (CAS # 64-19-7) were used as read-across analogs for the target ester anisyl formate (CAS # 122-91-8) for the skin sensitization endpoint.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.5, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- *p*-Anisyl acetate (CAS # 104-21-2) was used as a read-across analog for the target material anisyl formate (CAS # 122-91-8) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the esters group.
  - o The key difference between the target material and the read-across analog is that the target material is a formate, whereas the read-across analog is an acetate. This structural difference is toxicologically insignificant.
  - 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 read-across analog has alerts for hepatotoxicity and renal toxicity, which are not present in the target material. The predictions are 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, 2012. Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.8: Characterisation of Dose [concentration]-Response for Human Health. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2016. p-Methoxybenzyl Acetate Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/16832/1/2.

ECHA, 2017a. Anisyl Formate Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/19734/1/2.

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

Gauggel, D.L., Sarlo, K., Asquith, T.N., 1993. A proposed screen for evaluating low-molecular-weight chemicals as potential respiratory allergens. J. Appl. Toxicol. 13 (5), 307–313.

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, 2021. 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.), 1971. Appraisal of Sensitizing Powers by Maximization Testing in Humans. Report to RIFM. RIFM report number 1805 (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.), 2005. Anisyl Alcohol Diluted with Vehicle 1:3 EtOH:DEP: Local Lymph Node Assay. RIFM report number 48750 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Anisyl Formate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65344 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Ready Biodegradability of Anisyl Formate. RIFM report number 67203 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. Partition Coefficient N-Octanol/water of Anisyl Formate. RIFM report number 67204 (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014c. 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.), 2015. 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.), 2016a. Anisyl Formate: in Vitro L5178Y Gene Mutation Assay at the Hprt Locus. RIFM report number 69972 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Anisyl Formate: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM report number 70049 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016c. Anisyl Formate: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 70051 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Anisyl Alcohol: Repeated Insult Patch Test (RIPT). RIFM report number 71800 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Non-animal Methods to Predict Skin Sensitization (I): the Cosmetics Europe Database. RIFM report number 73469 (RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020. Exposure Survey 27. May 2020.

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.

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.

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.