Food and Chemical Toxicology 163 (2022) 112958

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, 2-decenal, CAS registry number 3913-71-1

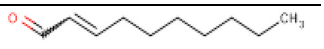
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M.A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[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, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member 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*
[j] *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*
[k] *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*
[l] *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*
[m] *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. Jose Luis Domingo

Version: 111121. 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: fragrance materialsafetyresource.elsevier.com.



(*continued on next column*)

(*continued*)

Name: 2-Decenal CAS Registry Number: 3913-71-1
Additional CAS Numbers*: 3913-81-3 *trans*-2-Decenal
*This material was included in this assessment because they are a mixture of isomers.

Abbreviation/Definition List:

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.112958
Received 15 November 2021; Received in revised form 15 March 2022; Accepted 21 March 2022
Available online 25 March 2022

(*continued*)

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., 2017; Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable 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
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 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.

2-Decenal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analog *trans*-2-dodecenal (CAS # 20407-84-5) show that 2-decenal is not expected to be genotoxic. Data on read-across material hexen-2-al (CAS # 6728-26-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold for Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2-decenal is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data provided 2-decenal a No Expected Sensitization Induction Level (NESIL) of 230 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoint was evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-decenal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-decenal 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2018b; RIFM, 2007)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day. (Gaunt et al., 1971)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 230 μg/cm^2. RIFM (2017)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/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: 3.17 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 101.8 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 8.43 mg/L (RIFM Framework; Salvito et al., 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 et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 8.43 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00843 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

Chemical Name: 2-Decenal	Chemical Name: *trans*-2-Decenal
CAS Registry Number: 3913-71-1	**CAS Registry Number:** 3913-81-3
Synonyms: 2-Decen-1-al; Decenaldehyde; Decylenic aldehyde; 3-Heptylacrolein; Dec-2-enal; 2-Decenal	**Synonyms:** (E)-2-Decenal; 2-Decenal, (E)-; Dec-2-enal; *trans*-2-Decenal
Molecular Formula: $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$
Molecular Weight: 154.25 g/mol	**Molecular Weight:** 154.53 g/mol
RIFM Number: 888	**RIFM Number:** 5306

2. Physical data*

1. **Boiling Point:** 117 °C at 26 mm Hg (Fragrance Materials Association [FMA]), 221.95 °C (EPI Suite)
2. **Flash Point:** 190 °F; CC (FMA)
3. **Log K_{ow}:** 3.6 (RIFM, 2013b), 3.69 (Biobyte Corp.), 3.55 (EPI Suite)
4. **Melting Point**: −8.92 °C (EPI Suite)
5. **Water Solubility:** 67.82 mg/L (EPI Suite); insoluble in water (Food and Agriculture Organisation [FAO])**
6. **Specific Gravity:** 0.840 (FMA); 0.836–0.846 (FAO)**
7. **Vapor Pressure:** 0.0508 mm Hg at 20 °C (EPI Suite v4.0), 0.05 mm Hg at 20 °C (FMA), 0.0782 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L • mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless to slightly yellow liquid

*Physical data for both materials included in this assessment are identical.

**https://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-flav/details/en/c/1348/

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient*** (Creme RIFM aggregate exposure model v2.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00023% (RIFM, 2018a)
2. **Inhalation Exposure**:** 0.000010 mg/kg/day or 0.00064 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure***:** 0.00076 mg/kg/day (RIFM, 2018a)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

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

6.2. Analogs selected

a. **Genotoxicity:** *trans*-2-Dodecenal (CAS # 20407-84-5)
b. **Repeated Dose Toxicity:** Hexen-2-al (CAS # 6728-26-3)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below

7. Metabolism

Not considered for this risk assessment.

8. Natural occurrence

2-Decenal is reported to occur in the following foods*:

Beef	Milk and milk products
Carrot (*Daucus carota* L.)	Olive (*Olea europaea)*
Coriander leaf (*Coriandrum sativum* L.)	Peanut (*Arachis hypogaea* L.)
Coriander seed (*Coriandrum sativum* L.)	Potato (*Solanum tuberosum* L.)
Lamb and mutton	Potato chips (American)

trans-2-Decenal is reported to occur in the following foods:

Chicken	Guinea hen
Citrus fruits	Milk and milk products
Fig (*Ficus carica* L.)	Pecan (*Carya illinoensis Koch*)
Fish	Rapeseed
Guava and feyoa	Vanilla

*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 which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

9. REACH dossier

Both materials are pre-registered for 2010; no dossier available as of 11/11/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-decenal 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)	0.018
2	Products applied to the axillae	0.0053
3	Products applied to the face/body using fingertips	0.11
4	Products related to fine fragrances	0.099
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.025
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.025
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.025
5D	Baby cream, oil, talc	0.0083
6	Products with oral and lip exposure	0.058
7	Products applied to the hair with some hand contact	0.20
8	Products with significant ano-genital exposure (tampon)	0.0083
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.19
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.69
10B	Aerosol air freshener	0.69
11	Products with intended skin contact but minimal transfer of fragrance to	0.0083

(*continued on next page*)

(*continued*)

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

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 2-decenal, the basis was the subchronic reference dose of 2.0 mg/kg/day (see the Repeated Dose Toxicity Section below), a predicted skin absorption value of 40%, and a skin sensitization NESIL of 230 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 v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-decenal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Decenal was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an isomer of the target material (*trans*-2-decenal) and an equi-reactive read-across material (*trans*-2-dodecenal) were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of additional material and isomer *trans*-2-decenal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with *trans*-2-decenal 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, 2018b). Under the conditions of the study, *trans*-2-decenal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2-decenal; however, read-across can be made to *trans*-2-dodecenal (CAS # 20407-84-5; see Section VI and Appendix).

The clastogenic activity of *trans*-2-dodecenal was evaluated in an *in vivo* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 474. Groups of male and female NMRI mice were treated with *trans*-2-dodecenal in corn oil via a single oral dose at the concentrations of 500, 1000, and 2000 mg/kg body weight. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007). Under the conditions of the study, *trans*-2--dodecenal was considered not clastogenic in the *in vivo* micronucleus test. Based on all the data, 2-dodecenal does not present a concern for genotoxicity, and this may be extended to 2-decenal.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/15/21.

11.1.2. Repeated dose toxicity

The MOE for 2-decenal is sufficient for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 2-decenal. Read-across material hexen-2-al (CAS # 6728-26-3; see Section VI and Appendix) has sufficient data to support the repeated dose toxicity endpoint. In a non-GLP and non-guideline subchronic study, 15 CFE rats/sex/dose were fed diets containing 0, 260, 640, 1600, or 4000 ppm *hexen-2-al* for 13 weeks (equivalent to 0, 13, 32, 80, or 200 mg/kg/day, respectively). No treatment-related mortality was reported for any dose group. No treatment-related changes in food consumption, body weight parameter, hematology, clinical chemistry, organ weights, and histopathology were reported. There was a slight increase in male urine volume with a concurrent decrease in the specific gravity of urine at the highest dose, but there were no alterations in kidney weight or histopathology. In the high-dose group females, ovary weight was significantly increased but without any correlating histopathological changes. Hence, these effects were not considered to be treatment-related adverse effects. Based on the lack of any treatment-related adverse effects at the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 4000 ppm or 200 mg/kg/day (Gaunt et al., 1971).

Additional data are provided in Table 1 below. However, the data were insufficient to derive a NOAEL.

Therefore, the 2-decenal MOE can be calculated by dividing the hexen-2-al NOAEL in mg/kg/day by the total systemic exposure to 2-decenal, 200/0.00076, or 263157.

In addition, the total systemic exposure to 2-decenal (0.76 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.

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. (RIFM, 2020b) and a subchronic reference dose (RfD) of 2 mg/kg/day.

Derivation of subchronic RfD

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 2-decenal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 2 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-decenal or any read-across materials evaluated. The total systemic exposure to 2-decenal is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-decenal or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-decenal (0.76 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: 03/03/21.

Table 1
Additional data with inadequate study design for the treatment material.

Duration	Animals/Sex/Dose	GLP/Guidelines	Route	Doses	Adverse effects	NOAEL	Ref
28 days	5 male F344rats/dose	OECD 407	Oral gavage	0, 10, 30, 100 mg/kg/day	None	100	ECHA, 2012

11.1.4. Skin sensitization

Based on existing data, 2-decenal is considered a skin sensitizer with a defined NESIL of 230 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 2-decenal is considered a moderate skin sensitizer. 2-Decenal is predicted to be directly reactive to skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Furthermore, 2-decenal has been demonstrated to react with cysteine- and lysine-based peptides in Direct Peptide Reactivity Assay (DPRA), induce luciferase activity in KeratinoSens and CD86 expression in the U937-CD86 test (Natsch et al., 2013). 2-decenal has been found to be positive in the murine local lymph node assay (LLNA) with a reported EC3 value of 2.5% (625 μg/cm^2) (Roberts et al., 2007; Gerberick et al., 2005). In human maximization tests, no reactions were observed when 4% or 2760 μg/cm^2 2-decenal in petrolatum was used for induction and challenge (RIFM, 1977a; RIFM, 1977b). In a Confirmation of No Induction in Humans test (CNIH), no reactions indicative of sensitization were observed when 2-decenal at 0.125% in alcohol SDA 39C (97 μg/cm^2) and 2% in dimethyl phthalate (unknown patch size) was used for induction and challenge (RIFM, 1973; RIFM, 1970). In a CNIH conducted according to Politano and Api (Politano and Api, 2008) with 0.2% w/v or 236 μg/cm^2 *trans*-2-decenal in 1:3 ethanol: DEP, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2017).

The available data demonstrate that 2-decenal is a moderate skin sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 230 μg/cm^2 (see Table 2). 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. (RIFM, 2020b) and a subchronic RfD of 2 mg/kg/day.

Additional References: Natsch et al., 2007; Natsch and Gfeller, 2008; McKim et al., 2010.

Literature Search and Risk Assessment Completed On: 02/26/21.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 2-decenal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-decenal in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-decenal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD test guideline 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/02/21.

11.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-decenal 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 2-decenal. Based on the Creme RIFM Model, the inhalation exposure is 0.00064 mg/day. This exposure is 2187.5 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: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

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

Table 2
Data summary for 2-decenal.

LLNA Weighted Mean EC3 [No. Studies] μg/cm^2	Potency Classification[1]	Human 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
625[1]	Moderate	236	2760	N/A	230

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2] Data derived from CNIH or HMT.
[3] WoE NESIL limited to 2 significant figures.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-decenal 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, 2012). 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).

11.2.2. Risk assessment

Based on the current VoU (2015), 2-decenal does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 2-decenal 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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.6	3.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional volumes for both CAS Numbers.

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

The RIFM PNEC is 0.00843 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 volumes of use.

Literature Search and Risk Assessment Completed On: 03/09/21.

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
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **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 HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **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://chem.nlm.nih.gov/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 11/11/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112958.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	8.43			1,000,000	0.00843	

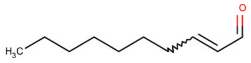
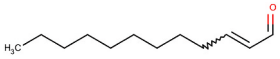
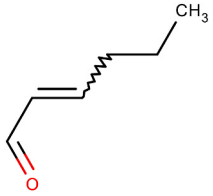
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (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, 2017).

- 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	2-Decenal	2-*trans*-Dodecenal	Hexen-2-al
CAS No.	3913-71-1	20407-84-5	6728-26-3
Structure			
Similarity (Tanimoto Score)		0.93	0.63
Endpoint		Genotoxicity	Repeated dose toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{12}H_{22}O$	$C_6H_{10}O$
Molecular Weight (g/mol)	154.25	182.31	98.14
Melting Point (°C, EPI Suite)	−8.92	12.85	−55.63
Boiling Point (°C, EPI Suite)	230.00	257.92	146.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	10.43	2.37	629.28
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	67.82	7.26	5261.00
Log K_{OW}	3.55	4.53	1.58
J_{max} (μg/cm^2/h, SAM)	8.68	1.14	215.10
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	31.11	54.82	4.95
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	AN2|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ α,β-unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ α,β-unsaturated Aldehydes	AN2|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ α,β-unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ α,β-unsaturated Aldehydes	
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition ≫ α,β-unsaturated aldehydes	Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition ≫ α,β-unsaturated aldehydes	
Carcinogenicity (ISS)	α,β-unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity	α,β-unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	α,β-unsaturated carbonyls	α,β-unsaturated carbonyls	

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
***In Vivo* Mutagenicity (Micronucleus, ISS)**	α,β-unsaturated carbonyls	α,β-unsaturated carbonyls	
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized		Not categorized
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on the target material 2-decenal (CAS # 3913-71-1). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 2-dodecenal (E)- (CAS # 20407-84-5) and hexen-2-al (CAS # 6728-26-3) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusion

- 2-Dodecenal, (E)- (CAS # 20407-84-5) was used as a read-across analog for target material 2-decenal (CAS # 3913-71-1) for the genotoxicity endpoint.
  - The target substance and the read-across analogs belong to the structural class of alpha, beta-unsaturated straight-chain aldehydes.
  - The target substance and the read-across analogs share an aldehyde moiety with alpha-beta unsaturation.
  - The key difference between the target substance and the read-across analogs is that the target substance is a C10 molecule while the read analogs, 2-dodecenal (CAS # 4826-62-4) and 2-dodecenal, (E)- (CAS # 20407-84-5), are C12 molecules. This structural difference is not toxicologically significant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$80% skin absorption for the target substance and $\leq$40% absorption for the read-across analogs. While percentage skin absorption estimated from J_{max} values indicates exposure to the substance, it does not represent hazard or toxicity parameters. Therefore, the J_{max} of the target substance and the appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicological endpoints are consistent between the target substance and the read-across analogs.
  - The target substance and the read-across analogs have a carcinogenicity alert according to the ISS model. The target and the read-across analogs also have an *in vitro* and *in vivo* mutagenicity alert along with DNA binding alerts and are classified as alpha, beta-unsaturated carbonyls. This shows that the read-across analog is predicted to have comparable reactivity with the target substance. The data described in the genotoxicity section show that the read-across analogs do not pose a concern for genetic toxicity. Therefore, the alerts were superseded by the data.
  - The target substance and the read-across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural differences between the target material and the read-across analogs are toxicologically insignificant.
- Hexen-2-al (CAS # 6728-26-3) was used as a read-across analog for the target material 2-decenal (CAS # 3913-71-1) for the repeated dose toxicity endpoint.
  - The target substance and the read-across analog belong to the structural class of aliphatic aldehydes.
  - The target substance and the read-across analog share an aldehyde moiety with alpha-beta unsaturation.
  - The key difference between the target substance and the read-across analog is that the target substance is a C10 molecule while the read-across analog is a C6 molecule. This structural difference between the target substance and the read-across analog is not toxicologically significant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score are not toxicologically significant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for toxicological endpoints are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are toxicologically insignificant.

References

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

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.
Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., et al., 2010, July. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (S1), S4. Springer International Publishing.
Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.
ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment, November 2012 v1.1. http://echa.europa.eu/.
ECHA, 2017. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.
Gaunt, I.F., Colley, J., Wright, M., Creasey, M., Grasso, P., Gangolli, S.D., 1971. Acute and short-term toxicity studies on trans-2-hexenal. Food Chem. Toxicol. 9 (6), 775–786.
Gerberick, G.F., Ryan, C.A., Kern, P.S., Schlatter, H., Dearman, R.J., Kimber, I., Patlewicz, G.Y., Basketter, D.A., 2005. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis 16 (4), 157–202.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photo safety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.
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.
McKim Jr., J.M., Keller III, D.J., Gorski, J.R., 2010. A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-medicated gene expression in human skin cells. Cutan. Ocul. Toxicol. 29 (3), 171–192.
Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.
Natsch, A., Gfeller, H., 2008. LC-MS-Based characterization of the peptide reactivity of chemicals to improve the in vitro prediction of the skin sensitization potential. Toxicol. Sci. 106 (2), 464–478.
Natsch, A., Gfeller, H., Rothaupt, M., Ellis, G., 2007. Utility and limitations of a peptide reactivity assay to predict fragrance allergens in vitro. Toxicol. Vitro 21 (7), 1220–1226.
Natsch, A., Ryan, C.A., Foertsch, L., Emter, R., Jaworska, J., Gerberick, F., Kern, P., 2013. A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation. J. Appl. Toxicol. 33 (11), 1337–1352.
OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA, p. 7, 2015, Retrieved from. http://www.oecd.org/.
OECD, 2018. The OECD QSAR Toolbox v3.2–4.2. http://www.qsartoolbox.org/.
Politano, V.T., Api, A.M., 2008. The Research Institute of Fragrance Materials' human repeated insult patch test protocol. Regul. Toxicol. Pharmacol. 52 (1), 35–38.
RIFM (Research Institute for Fragrance Materials, Inc), 1970. Sensitization and Irritation Studies of Fragrance Materials. Unpublished Report from Givaudan-Roure Corporation. RIFM Report Number 27952. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1973. Repeated Insult Patch Test with 2-decenal. Unpublished Report from International Flavors and Fragrances. RIFM Report Number 50625. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1977a. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1702. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1977b. Human Maximization Studies. Report to RIFM. RIFM Report Number 1979. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2007. Micronucleus Assay in Bone Marrow Cells of the Mouse with 2-Trans-Dodecenal. RIFM Report Number 54286. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013a. Report on the Testing of 2-decenal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66172. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013b. Partition Coefficient N-Octanol/water of Trans-2-decenal. Unpublished Report from Givaudan. RIFM Report Number 66660. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015. Novel Database for Exposure to Fragrance Ingredients in Cosmetics and Personal Care Products. RIFM Report Number 68681. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017. trans-2-Decenal: Repeated Insult Patch Test. RIFM Report Number 72571. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2018a. Exposure Survey 22, November 2018.
RIFM (Research Institute for Fragrance Materials, Inc), 2018b. trans-2-Decenal: Bacterial Reverse Mutation Test Using Bacterial Strain. Unpublished Report from Takasago International Corporation. RIFM Report Number 73500. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM Report Number 76272. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2020b. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. RIFM, Woodcliff Lake, NJ, USA.
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., et al., 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 (12), 164–176.
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, v1.11. United States Environmental Protection Agency, Washington, DC, USA.