Food and Chemical Toxicology 167 (2022) 113356

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 2-dodecenal, CAS registry number 4826-62-4

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], 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], M. Na [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), Editor-in-Chief, Professor and Chairman, 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: 111821. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

(*continued on next column*)

(*continued*)

Name: 2-Dodecenal CAS Registry Number: 4826-62-4
Additional CAS Numbers*:20407-84-5 2-*trans*-Dodecenal
*This material is 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.2022.113356
Received 19 November 2021; Received in revised form 15 July 2022; Accepted 3 August 2022
Available online 8 August 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., 2015; 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
DRF - Dose Range Finding
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 Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api 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-Dodecenal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-dodecenal is not genotoxic. Data on read-across analog 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 of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2-dodecenal is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from 2-dodecenal and read-across analog 2-decenal (CAS # 3913-71-1) provided 2-dodecenal a No Expected Sensitization Induction Level (NESIL) of 230 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-dodecenal is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; 2-Dodecenal 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.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2007a; RIFM, 2007b)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day. (Gaunt et al., 1971)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 230 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: 80% (OECD 301F) for CAS # 20407-84-5 RIFM (2013c)
Bioaccumulation:
Screening-level: 19.13 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 96-h fish LC50: 0.152 mg/L (ECOSAR v2.0; US EPA, 2012b)
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: 96-h fish LC50: 0.152 mg/L (ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 0.0152 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

Chemical Name: 2-Dodecenal	Chemical Name: 2-*trans*-Dodecenal
CAS Registry Number: 4826-62-4	**CAS Registry Number:** 20407-84-5
Synonyms: 3-Nonylacrolein; Dodec-2-enal; 2-Dodecenal	**Synonyms:** (2E)-2-Dodecenal; (E)-2-Dodecen-1-al; (E)-Dodec-2-en-al; *trans*-2-Dodecen-1-al; 2-Dodecenal; 2-Dodecenal, (2E)-; 2-*trans*-Dodecenal; Dodec-2-enal; Dodecenal; Mandarine Aldehyd HM
Molecular Formula: $C_{12}H_{22}O$	**Molecular Formula:** $C_{12}H_{22}O$
Molecular Weight: 182.3 g/mol	**Molecular Weight:** 182.3 g/mol
RIFM Number: 1112	**RIFM Number:** 5885

2. Physical data*

1. **Boiling Point:** 272 °C (Fragrance Materials Association [FMA]), 257.92 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; closed cup (FMA)
3. **Log K_{OW}:** 4.7 (RIFM, 2013b), 4.53 (EPI Suite)

4. **Melting Point**: 12.85 °C (EPI Suite)
5. **Water Solubility:** 7.259 mg/L (EPI Suite)
6. **Specific Gravity:** 0.85 (FMA)
7. **Vapor Pressure:** 0.0111 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg 20 °C (FMA), 0.0178 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (75 L mol^{-1} • cm^{-1}, condition unspecified) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless, oily liquid with a powerful, citrus-like odor

3. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2015).

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0053% (RIFM, 2018)
2. **Inhalation Exposure**:** 0.000021 mg/kg/day or 0.0015 mg/day (RIFM, 2018)
3. **Total Systemic Exposure***:** 0.00057 mg/kg/day (RIFM, 2018)

*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, 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 (RIFM, 2015; Safford et al., 2015; Safford, 2017; Comiskey, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Hexen-2-al (CAS # 6728-26-3)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Decenal (CAS # 3913-71-1)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

2-Dodecenal is reported to occur in the following foods by the VCF*:
Beef.
Citrus fruits.
Coriander leaf (*Coriandrum sativum* L.)
Milk and milk products.
Peanut (*Arachis hypogaea* L.)
Pork Rice (*Oryza sativa* l.)
2-*trans*-Dodecenal is reported to occur in the following foods by the VCF*:
Chicken.
Citrus fruits.
Coriander leaf (*Coriandrum sativum* L.)
Coriander seed (*Coriandrum sativum* L.)
Milk and milk products.
Mushroom.
Olive (*Olea europaea*).
*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

2-Dodecenal is pre-registered for 2010; no dossier available as of 11/12/21. Available for 2-trans-Dodecenal; accessed 03/23/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-dodecenal are detailed below.

IFRA Category[b]	Description of Product Type	Maximu[c] 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

(*continued on next page*)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximu[c] Acceptable Concentrations[a] in Finished Products (%)[c]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0083
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-dodecenal, the basis was the subchronic reference dose of 2 mg/kg/day, 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).

[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-dodecenal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Dodecenal was tested in the BlueScreen assay and was found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity in the presence and the absence of metabolic activation (RIFM, 2013a). 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 mutagenicity of 2-dodecenal was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the standard plate incorporation and modified preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with 2-dodecenal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate with and without metabolic activation. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2007a). Under the conditions of the study, 2-dodecenal was not mutagenic in the Ames test.

The clastogenicity of 2-*trans*-dodecenal was assessed 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 2-*trans*-dodecenal in corn oil via a single oral dose at the concentrations of 500, 1000, and 2000 mg/kg. 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, 2007b). Under the conditions of the study, 2-*trans*-dodecenal was considered not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 2-dodecenal does not present a concern for genotoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.1.2. Repeated dose toxicity

The MOE for 2-dodecenal 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-dodecenal. Read-across material hexen-2-al (CAS # 6728-26-3; see Section VI) 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 study data are shown below in Table 1. However, these data were insufficient to derive a NOAEL.

Therefore, the 2-dodecenal MOE can be calculated by dividing the hexen-2-al NOAEL in mg/kg/day by the total systemic exposure to 2-dodecenal, 200/0.00057, or 350877.

In addition, the total systemic exposure to 2-dodecenal (0.57 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. (2020) and a subchronic reference dose (RfD) of 2 mg/kg/day.

11.1.2.2. 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-dodecenal 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-dodecenal or any read-across materials. The total systemic exposure to 2-dodecenal 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-dodecenal or any read-across materials that can be used to support the reproductive toxicity endpoints. The total systemic exposure to 2-dodecenal (0.57 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints 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.

11.1.4. Skin sensitization

Based on data from 2-dodecenal and read-across analog 2-decenal (CAS # 3913-71-1), 2-dodecenal is considered a skin sensitizer with a defined NESIL of 230 μg/cm^2.

Table 1
Available additional studies within inadequate study design for the treatment material.

Duration	Animals/Sex/Dose	GLP/Guidelines	Route	Doses	Adverse effects	NOAEL	Ref
28 days	5 male F344 rats/dose	OECD 407	Oral gavage	0, 10, 30, 100 mg/kg/day	None	100	ECHA (2018)

11.1.4.1. Risk assessment. Limited skin sensitization data exist on 2-dodecenal. Based on the existing data and read-across to 2-decenal (CAS # 3913-71-1; see Section VI), 2-dodecenal is considered a skin sensitizer. 2-Dodecenal and read-across 2-decenal are predicted to be directly reactive to skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across 2-decenal was found to be positive in the *in vitro* direct peptide reactivity assay, KeratinoSens test, and U-SENS test (Natsch et al., 2013). In a local lymph node assay (LLNA), 2-dodecenal was found to be sensitizing with an EC3 value of 2.2% (550 μg/cm^2) (RIFM, 2012). In an LLNA with the read-across material 2-decenal, the EC3 value was reported as 2.5% (625 μg/cm^2) (Roberts et al., 2007; Gerberick et al., 2005). In a human maximization test conducted on 25 subjects, no reactions indicative of sensitization were observed with 1% (690 μg/cm^2) 2-dodecenal (RIFM, 1980). Similarly, in human maximization tests with read-across 2-decenal at 4% or 2760 μg/cm^2 in petrolatum, no reactions were observed when it was used for induction and challenge (RIFM, 1973a; RIFM, 1977). In a Confirmation of No Induction in Humans test (CNIH), no reactions indicative of sensitization were observed when read-across 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, 1973b; RIFM, 1970). In a CNIH conducted according to the methodology of Politano and Api (Politano, 2008) with 0.2% w/v or 236 μg/cm^2 read-across *trans*-2-decenal in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2017).

Based on the weight of evidence (WoE) from the available data from 2-dodecenal and read-across analog 2-decenal, 2-dodecenal is considered a skin sensitizer with a 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. (2020)[a] and a subchronic RfD of 2 mg/kg/day.

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

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

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, 2-dodecenal 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 2-dodecenal in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-dodecenal does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient (75 L mol^{-1} • cm^{-1}, unspecified condition) 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: 03/02/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-dodecenal 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-dodecenal. Based on the Creme RIFM Model, the inhalation exposure is 0.0015 mg/day. This exposure is 933.4 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-dodecenal 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

Table 2
Data summary for 2-decenal as read-across for 2-dodecenal.

LLNA Weighted Mean EC3 Value [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; N/A = 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.

RIFM Environmental Framework, 2-dodecenal was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

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

11.2.2. Risk assessment

Based on the current VoU (2015), 2-dodecenal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. For CAS # 20407-84-5.

RIFM, 2013c: The ready biodegradability of the test material was evaluated using the OECD 301F guideline. Biodegradation of 80% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. For CAS # 20407-84-5.

RIFM, 2014: A fish (*Oryzias latipes*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 value based on the arithmetic mean measured concentration was reported to be 0.718 mg/L (95% CI: 0.6473–0.7964 mg/L).

RIFM, 2016a: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The study was conducted with a saturated solution with a nominal loading of 10 mg/L of the test material and further 4 dilution levels in a geometric series with a separation factor of 2.2 (nominal loading rates of 4.27%–45.5%). The 48-h EL50 based on nominal loading levels was reported to be 4.76 mg/L.

RIFM, 2016b: The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. Five loading levels of the test item in a geometric series with a separation factor of 3.16, prepared by diluting the saturated solution with dilution water, were tested as follows: 0.316–1.00 – 3.16–10.0 – 31.6–100% of the saturated solution. The 72-h EL50 values based on nominal loading levels for growth rate and yield were reported to be >100% of the test item.

11.2.2.1.3. Other available data. 2-Dodecenal has been 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, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.5	5.5
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band*	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional volumes for both CAS #.

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

The RIFM PNEC is 0.0152 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.22			1000000	0.00022	
ECOSAR Acute Endpoints **(Tier 2)** v2.0	0.152	0.904	1.176	10000	0.0152	Vinyl/Allyl Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** v2.0	0.800	0.574	1.123			Neutral Organics SAR

Literature Search and Risk Assessment Completed On: 03/11/21.

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 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://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 11/16/21.

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. 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.2022.113356.

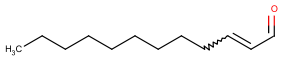
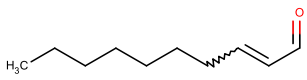
Appendix

Read-across Justification

Methods

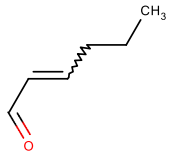
The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015)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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite 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-Dodecenal	2-Decenal	Hexen-2-al
CAS No.	4826-62-4	3913-71-1	6728-26-3
Structure			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
			
Similarity (Tanimoto Score)		0.93	0.64
Endpoint		Skin sensitization	Repeated dose toxicity
Molecular Formula	$C_{12}H_{22}O$	$C_{10}H_{18}O$	$C_6H_{10}O$
Molecular Weight (g/mol)	182.31	154.25	98.14
Melting Point (°C, EPI Suite)	12.85	−8.92	−55.63
Boiling Point (°C, EPI Suite)	257.92	230.00	146.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.37	10.43	629.28
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.26	67.82	5261.00
Log K_{OW}	4.53	3.55	1.58
J_{max} (μg/cm^2/h, SAM)	1.14	8.68	215.10
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	54.82	31.11	4.95
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized		Not categorized
Skin Sensitization			
Protein Binding (OASIS v1.1)	Michael addition|Michael addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds|Michael addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes |Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Michael addition|Michael addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds|Michael addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes |Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	
Protein Binding (OECD)	Michael addition|Michael addition ≫ Polarised Alkenes|Michael addition ≫ Polarised Alkenes ≫ Polarised alkene - aldehydes|Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Michael addition|Michael addition ≫ Polarised Alkenes|Michael addition ≫ Polarised Alkenes ≫ Polarised alkene - aldehydes|Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	
Protein Binding Potency	Highly reactive (GSH)|Highly reactive (GSH) ≫ 2-Alken-1-als (MA)	Highly reactive (GSH)|Highly reactive (GSH) ≫ 2-Alken-1-als (MA)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1	Michael Addition|Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds|Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes	Michael Addition|Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds|Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Michael Acceptor identified.	Alert for Michael Acceptor identified.	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on the target material, 2-dodecenal (CAS # 4826-62-4). 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-decenal (CAS # 3913-71-1) and hexen-2-al (CAS # 6728-26-3) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusion

- 2-Decenal (CAS # 3913-71-1) was used as a read-across analog for target material 2-dodecenal (CAS # 4826-62-4) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the structural class of aliphatic aldehydes.
  - o The target material and the read-across analog share an aldehyde functional group with α,β-unsaturation.

- The key difference between the target material and the read-across analog is that the target material is a C12 molecule while the read-across analog is a C10 molecule. This structural difference between the target material and the read-across analog is not toxicologically significant.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aldehyde functional group with α,β-unsaturated fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- The read-across analog has a greater water solubility than the target material. This will result in greater bioavailability, which makes the read-across analog more conservative when compared to the target material. Therefore, the read-across analog is an appropriate choice for comparison of toxicological properties with the target material.
- According to the QSAR OECD Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog have a Michael acceptor alert by skin sensitization reactivity domains in Toxtree. The target and the read-across analog also have several protein-binding alerts. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the skin sensitization section show that the read-across analog is considered to be a strong sensitizer, consistent with the *in silico* alerts.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural differences between the target material and the read-across analog are not toxicologically significant.

- Hexen-2-al (CAS # 6728-26-3) was used as a read-across analog for the target material, 2-dodecenal (CAS # 4826-62-4), for the repeated dose toxicity endpoint.
  - The target material and the read-across analog belong to the structural class of aliphatic aldehydes.
  - The target material and the read-across analog share an aldehyde moiety with α,β-unsaturation.
  - The key difference between the target material and the read-across analog is that the target material is a C12 molecule while the read-across analog is a C6 molecule. This structural difference between the target material and the read-across analog is not toxicologically significant.
  - The similarity between the target material 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 material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - The read-across analog has a greater water solubility than the target material. This will result in greater bioavailability, which makes the read-across analog more conservative when compared to the target material. Therefore, the read-across analog is an appropriate choice for comparison of toxicological properties with the target material.
  - Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$40% skin absorption for the target material and $\leq$80% absorption for the read-across analog. 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 material 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 material and the read-across analog.
  - The target material 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., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 2020, 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., 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, 2020.

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

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

ECHA, 2018. *trans*-Hex-2-enal Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/25168/1/2.

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 photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. February 2015. of Use Survey.

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. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. 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), 1973a. Report on human maximization studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM Report Number 1802.

RIFM (Research Institute for Fragrance Materials, Inc), 1973b. Repeated Insult Patch Test with 2-decenal. Unpublished Report from International Flavors and Fragrances. RIFM, Woodcliff Lake, NJ, USA. RIFM Report Number 50625.

RIFM (Research Institute for Fragrance Materials, Inc), 1977. Human Maximization Studies. Report to RIFM. RIFM, Woodcliff Lake, NJ, USA. RIFM Report Number 1979.

RIFM (Research Institute for Fragrance Materials, Inc), 1980. Report on Human Maximization Studies. Report to RIFM. RIFM, Woodcliff Lake, NJ, USA. RIFM Report Number 1790.

RIFM (Research Institute for Fragrance Materials, Inc), 2007a. Salmonella typhimurium reverse mutation with 2-dodecenal. RIFM, Woodcliff Lake, NJ, USA. RIFM Report Number 54281.

RIFM (Research Institute for Fragrance Materials, Inc), 2007b. 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), 2012. Dodecenal: Local Lymph Node Assay. RIFM Report Number 68696. RIFM, Woodcliff Lake, NJ, USA, p. 2.

RIFM (Research Institute for Fragrance Materials, Inc), 2013a. Report on the testing of 2-dodecenal in the BlueScreen HC Assay (-/+ S9 metabolic activation). RIFM, Woodcliff Lake, NJ, USA. RIFM Report Number 65954.

RIFM (Research Institute for Fragrance Materials, Inc), 2013b. Partition Coefficient N-Octanol/water of 2-dodecenal and 2-Trans-Dodecenal (dodecenal). Unpublished report from Givaudan. RIFM report number 66669. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013c. 2-trans-Dodecenal (Dodecenal): Assessment of Ready Biodegradability: Manometric Respirometry Test. Unpublished report from Firmenich. RIFM report number 71421. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2014. Acute Toxicity Test of 2-Trans-Dodecenal (Mandarin Aldehyde) in Fish (Ricefish, Oryzias latipes). Unpublished report from Symrise. RIFM report number 68769. 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), 2016. 2-trans-Dodecenal (Dodecenal): Acute Immobilisation Test to Daphnia Magna, Static, 48 Hours. Unpublished Report from Firmenich. RIFM report number 71420. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016b. 2-trans-Dodecenal: Alga, Growth Inhibition Test with Pseudokirchneriella Subcapitata, 72 Hours. Unpublished report from Firmenich. RIFM report number 74598. 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), 2018. Exposure Survey 21, September 2018.

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, 2022.

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.