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RIFM fragrance ingredient safety assessment, 8-nonenal, CAS Registry number 39770-04-2

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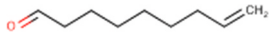

Name: 8-Nonenal

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CAS Registry Number: 39770-04-2

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

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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.

8-Nonenal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 10-undecenal (CAS # 112-45-8) show that 8-nonenal is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. The developmental toxicity and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; the exposure to 8-nonenal is below the TTC (0.03 mg/kg/day and 1.4 mg/kg/day, respectively). Data from analog 10-undecenal (CAS # 112-45-8) provided a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 8-nonenal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 8-nonenal 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.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2007a; RIFM, 2007b)
Repeated Dose Toxicity: NOAEL = 138.6 mg/kg/day.	RIFM (2012)
Reproductive Toxicity: Developmental toxicity: No NOAEL available. Exposure is below the TTC. Fertility: NOAEL = 1135.9 mg/kg/day.	RIFM (2012)
Skin Sensitization: NESIL = 1700 μg/cm^2.	RIFM (2016)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1979)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.91 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 54.42 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 19.27 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: 19.27 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.01927 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 8-Nonenal
2. **CAS Registry Number:** 39770-04-2
3. **Synonyms:** Non-8-enal; 8-Nonenal
4. **Molecular Formula:** $C_9H_{16}O$
5. **Molecular Weight:** 140.22 g/mol
6. **RIFM Number:** 6372
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 194.97 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.14 (EPI Suite)
4. **Melting Point**: −20.77 °C (EPI Suite)
5. **Water Solubility:** 175.5 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.316 mm Hg at 20 °C (EPI Suite v4.0), 0.463 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.2)

1. **95th Percentile Concentration in Fine Fragrance:** 0.000000075% (RIFM, 2020)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or 0.0000001 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.0000006 mg/kg/day (RIFM, 2020)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** 10-Undecenal (CAS # 112-45-8)
   b. **Repeated Dose Toxicity:** 10-Undecenal (CAS # 112-45-8)
   c. **Reproductive Toxicity:** 10-Undecenal (CAS # 112-45-8)
   d. **Skin Sensitization:** 10-Undecenal (CAS # 112-45-8)
   e. **Phototoxicity/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

8-Nonenal is not reported to occur in foods by the VCF*.

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

9. REACH dossier

8-Nonenal has been pre-registered for 2010; no dossier available as of 12/09/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 8-nonenal 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)	0.13
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.78
4	Products related to fine fragrances	0.73
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.18
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.18
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.18
5D	Baby cream, oil, talc	0.060
6	Products with oral and lip exposure	0.43
7	Products applied to the hair with some hand contact	1.5
8	Products with significant ano-genital exposure (tampon)	0.060
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.1
10B	Aerosol air freshener	5.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.060
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 8-nonenal, the basis was the subchronic reference dose of 1.39 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 1700 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
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, 8-nonenal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 8-Nonenal 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, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical

compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of 8-nonenal. The mutagenicity of read-across material 10-undecenal (CAS # 112-45-8; see Section VI) was assessed in a GLP-compliant Ames study conducted in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with 10-undecenal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was observed in any of the strains at any concentration (RIFM, 2007a). Under the conditions of the study, 10-undecenal was considered not mutagenic in bacteria.

There are no studies assessing the clastogenicity of 8-nonenal. The clastogenic activity of read-across material 10-undecenal was assessed in an *in vivo* mouse micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 474. Male and female NMRI mice were treated with 10-undecenal in corn oil via oral gavage at doses of 500, 1000, and 2000 mg/kg body weight. Mice from each dose level were euthanized at 24 h or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce an increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007b). Under the conditions of the study, 10-undecenal was considered not clastogenic *in vivo*. Based on the available data, 10-undecenal does not present a concern for genotoxic potential, and this can be applied to 8-nonenal.

Additional References: RIFM, 2010; RIFM, 2013a.

Literature Search and Risk Assessment Completed On: 04/23/21.

11.1.2. Repeated dose toxicity

The MOE for 8-nonenal is adequate for the repeated dose toxicity endpoint at the current levels of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 8-nonenal. Read-across material, 10-undecenal (CAS # 112-45-8; see Section VI), has sufficient repeated dose toxicity data to support the toxicological evaluation. A GLP/OECD 408 dietary 90-day subchronic toxicity study was conducted in Sprague Dawley Crl:CD BR rats. Groups of 10 rats/sex/dose were fed diets containing 0, 200, 2000, 6000, or 20000 ppm of test material, 10-undecenal (equivalent to doses of 0, 14.3, 138.6, 382.3, or 1135.9 mg/kg/day, respectively) for 90 days. There was a dose-related reduction in body weights among males of the 2000-, 6000-, and 20000-ppm dose groups and females of the 6000- and 20000-ppm dose groups. Bodyweight gains were reduced among males of the 6000- and 20000-ppm dose groups throughout the study and the high-dose females during Week 1. Overall, food consumption was reduced in the animals of both sexes treated at 2000, 6000, and 20000 ppm. Food efficiency was also reduced among the high-dose group animals during the first week of the study. Microscopic examinations showed epithelial acanthosis of the limiting ridge of the stomach among male and female animals in the 2000- and 20000-ppm dose groups, and this extended to the females only of the 6000-ppm dose group. This finding was considered to be indicative of local irritation potential of the test material and may be associated with the route of administration; therefore, it was not considered to be related to systemic toxicity. Since most alterations reported were not considered to be of toxic potential; thus the NOAEL was considered to be 2000 ppm or 138.6 mg/kg/day, based on reduction in food consumption and body weights among the higher dose group animals (RIFM, 2012).

In another study, a group of 5 rats/sex/dose were administered via gavage test material, aldehyde C-11 undecylenic (10-undecenal), at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil for 28 days. The study was conducted according to OECD 407 guidelines with additional 14-day control and high-dose recovery groups included. Alterations in hematological and urine parameters reported were considered to be incidental and not adverse. The absolute and relative weight of the spleen was significantly increased for females of the higher dose group when compared to the control group. In male rats, a statistically significant decrease in the relative thymus weight was observed in the recovery group. The observed variations in the weight of the spleen and thymus were considered to be of no toxicological significance since these changes were only observed in 1 sex and were not confirmed by histopathology. There were no treatment-related external and internal gross pathological changes observed in any treated rats. Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). The most conservative NOAEL of 138.6 mg/kg/day was considered from the 13-week dietary study conducted on 10-undecenal for the repeated dose toxicity endpoint. **Therefore, the 8-nonenal MOE for repeated dose toxicity can be calculated by dividing the 10-undecenal NOAEL in mg/kg/day by the total systemic exposure to 8-nonenal, 138.6/0.0000006, or 231000000.**

In addition, the total systemic exposure to 8-nonenal (0.0006 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.

Derivation of subchronic reference dose (RfD):

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 1.39 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 8-nonenal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 138.6 mg/kg/day by the uncertainty factor, 100 = 1.39 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/21.

11.1.3. Reproductive toxicity

There are insufficient developmental toxicity data on 8-nonenal or any read-across materials. The total systemic exposure to 8-nonenal is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

The MOE for 8-nonenal is adequate for the fertility endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on 8-nonenal or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 8-nonenal (0.0006 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on 8-nonenal. The read-across material, 10-undecenal (CAS # 112-45-8; see Section VI), has sufficient data to support the fertility endpoint. A GLP/OECD 408 dietary 90-day subchronic toxicity study was conducted in Sprague Dawley Crl:CD BR rats. Groups of 10 rats/sex/dose were fed diets containing 0, 200, 2000, 6000 or 20000 ppm of test material, 10-undecenal (equivalent to doses of 0, 14.3, 138.6, 382.3 or 1135.9 mg/kg/day, respectively) for 90 days. In addition to systemic toxicity, estrous cycling, sperm analysis, and reproductive organs were also analyzed. There were no treatment-related effects on the reproductive organs up to the highest dose tested, 20000 ppm, or 1135.9 mg/kg/day (RIFM, 2012). **Therefore, the 8-nonenal MOE for the fertility endpoint can be calculated by dividing the 10-undecenal NOAEL in mg/kg/day by the total systemic exposure to 8-nonenal, 1135.9/0.0000006, or 1893166667.**

In addition, the total systemic exposure to 8-nonenal (0.0006 μg/kg/

day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/21.

11.1.4. Skin sensitization

Based on the existing data on the read-across analog 10-undecenal, 8-nonenal is a skin sensitizer with a defined NESIL of 1700 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 8-nonenal. Based on the read-across material 10-undecenal (CAS # 112-45-8; see Section VI), 8-nonenal is a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, 10-undecenal, was not predicted to be a sensitizer in an *in vitro* direct peptide reactivity assay (DPRA) and human cell line activation test (h-CLAT), whereas it was predicted to be a sensitizer in KeratinoSens and U-SENS tests (Urbisch et al., 2015; Piroird et al., 2015). In a murine local lymph node assay (LLNA), 10-undecenal was found to be sensitizing with an EC3 value of 6.8% (1700 μg/cm^2) (Patlewicz et al., 2003; Roberts et al., 2007; Gerberick et al., 2005). However, this chemical was not found to be sensitizing when tested up to 25% (6250 μg/cm^2) in another LLNA (RIFM, 2001). In a Draize guinea pig test, 8-nonenal was not found to be sensitizing at 10% in diethyl phthalate (RIFM, 1972). The read-across material 10-undecenal was predicted to be a sensitizer in 1 guinea pig open epicutaneous test (OET), where was it was predicted to be a non-sensitizer in another OET (Klecak et al., 1977; Klecak, 1985). The read-across material, 10-undecenal, was predicted to be a sensitizer in a guinea pig Freund's Complete Adjuvant test (FCAT), whereas it was not predicted to be a sensitizer in a guinea pig Draize test (Klecak et al., 1977). Due to the presence of positive data in the existing animal studies, 10-undecenal is determined to be a sensitizer. In human maximization studies on 25 subjects, no reactions indicative of sensitization were observed up to 3450 μg/cm^2 10-undecenal (RIFM, 1971; RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH) conducted with the target material, no sensitization reactions were observed in 50 volunteers when 1% 8-nonenal in dipropylene glycol (RIFM, 1979). Due to limited information provided in this study, the dose per unit area could not be calculated. In a CNIH conducted with the read-across material, no skin sensitization reactions were observed in 40 subjects, when 0.5% (388 μg/cm^2) 10-undecenal in ethanol was used for induction and challenge (RIFM, 1964). In another CNIH, no skin sensitization reactions were observed when 1.5% (1772 μg/cm^2) 10-undecenal in 1:3 diethyl phthalate: ethanol was used for induction and challenge (RIFM, 2016).

Based on the weight of evidence (WoE) from structural analysis, animal studies, and human studies on the read-across material 10-undecenal, 8-nonenal is a sensitizer with a WoE NESIL of 1700 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 1.39 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/12/21.

Table 1
Data summary for 10-undecenal as read-across material for 8-nonenal

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Sensitization Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
1700 [1]	Moderate	1772	3450	NA	1700

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

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra and the available human study data, 8-nonenal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In a human photoallergy study, 1% 8-nonenal did not induce phototoxic or photoallergenic reactions in any of the subjects tested (RIFM, 1979). Based on the available human study data and the lack of absorbance, 8-nonenal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 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: 04/13/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 8-nonenal 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 8-nonenal. Based on the Creme RIFM Model, the inhalation exposure is 0.0000001 mg/day. This exposure is 14000000 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: 04/16/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 8-nonenal 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, 8-nonenal was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (*i.e.*, its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 8-nonenal 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 ≥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 Volume of Use (2015), 8-nonenal does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.3.3. Other available data. 8-Nonenal has been pre-registered for REACH with no additional data at this time.

11.2.4. 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	3.14	3.14
Biodegradation Factor Used	0	0

(*continued on next column*)

(*continued*)

Exposure	Europe (EU)	North America (NA)
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.01927 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: 03/29/21.

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 12/09/21.

Declaration of competing interest

The authors declare that they have no known competing financial

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>19.27</u>			1000000	0.01927	

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.2022.113175.

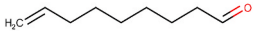
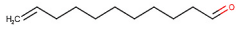
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European 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 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	8-Nonenal	10-Undecenal
CAS No.	39770-04-2	112-45-8
Structure		
Similarity (Tanimoto Score)		1.00
SMILES	C=CCCCCCCC=O	C=CCCCCCCCCC=O
Endpoint		Genotoxicity Skin sensitization Repeated dose toxicity Fertility
Molecular Formula	$C_9H_{16}O$	$C_{11}H_{20}O$
Molecular Weight (g/mol)	140.226	168.28
Melting Point (°C, EPI Suite)	−20.77	1.73
Boiling Point (°C, EPI Suite)	194.97	233.44
Vapor Pressure (Pa @ 25 °C, EPI Suite)	6.17E+01	8.71E+00
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1.76E+02	113[2]
Log K_{OW}	3.14	3.7[1]
J_{max} (μg/cm^2/h, SAM)	19.95	2.88
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.72E+01	6.56E+01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
In Vitro Mutagenicity (Ames, ISS)	Simple aldehyde	Simple aldehyde
In Vivo Mutagenicity (Micronucleus, ISS)	Simple aldehyde	Simple aldehyde
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Skin Sensitization		
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ 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)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation 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

Summary

There are insufficient toxicity data on the 8-nonenal (CAS # 39770-04-2). 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, 10-undecenal (CAS # 112-45-8) was identified as a read-across material with data for the respective toxicity endpoints.

Conclusion

- 10-undecenal (CAS # 112-45-8) was used as a read-across analog for the target material, 8-nonenal (CAS # 39770-04-2), for the skin sensitization, genotoxicity, fertility, and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target material and the read-across analog share a nonenal fragment.
  - o The key difference between the target material and the read-across analog is that the target has a 9-membered aliphatic chain, whereas the read-across analog has an 11-membered aliphatic chain. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog and the target material are predicted to be a carcinogen by the ISS model and Schiff base formers for genotoxicity. The data described in the genotoxicity section above shows that the read-across analog does not pose a concern for genotoxicity. Therefore, the alert was superseded by the availability of the data.
  - o The read-across analog and the target material were predicted to be sensitizers by the CAESAR model and Schiff base formers by OECD for the skin sensitization endpoint. The data for the read-across analog confirms that it is a sensitizer. The alert is concordant with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the skin sensitization, genotoxicity, and repeated dose toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog are not toxicologically significant.

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