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RIFM fragrance ingredient safety assessment, nonanal, 5-ethyl-2-methyl-, CAS Registry Number 68141-14-0

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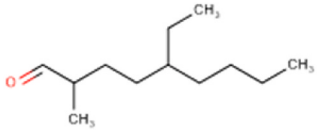

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Name: Nonanal, 5-ethyl-2-methy
CAS Registry Number: 68141-14-0

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

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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., 2020)
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.

Nonanal, 5-ethyl-2-methyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on the read-across analog 3,5,5-trimethylhexanal (CAS # 5435-64-3) show that nonanal, 5-ethyl-2-methyl- is not expected to be genotoxic. Data on analog 2-ethylhexanal (CAS # 123-05-7) provided a Margin of Exposure (MOE) < 100 for the repeated dose toxicity endpoint. Data on analog 2-methylundecanal (CAS # 110-41-8) provided an MOE <100 for the reproductive toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 2900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; nonanal, 5-ethyl-2-methyl- is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material (1.4 mg/day). The environmental endpoints were evaluated; nonanal, 5-ethyl-2-methyl- 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.	ECHA REACH Dossier: 3,5,5-Trimethylhexanal; ECHA (2011b)
Repeated Dose Toxicity: NOAEL = 51 mg/kg/day.	ECHA REACH Dossier: 2-Ethylhexanal; ECHA (2011a)
Reproductive Toxicity: Developmental toxicity NOAEL: 1350 mg/kg/day. Fertility NOAEL: 991 mg/kg/day.	(RIFM, 2019a; RIFM, 2019b)
Skin Sensitization: NESIL = 2900 μg/cm^2.	RIFM (2016)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)	
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening-level: 3.11 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 502 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1.360 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: 1.360 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00136 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Nonanal, 5-ethyl-2-methyl-
2. **CAS Registry Number:** 68141-14-0
3. **Synonyms:** Nonanal, 5-ethyl-2-methyl-
4. **Molecular Formula:** $C_{12}H_{24}O$
5. **Molecular Weight:** 184.32
6. **RIFM Number:** 7012
7. **Stereochemistry:** Isomer not specified. Two chiral centers present and a total of 4 enantiomers (2 distereoisomers) possible.

2. Physical data

1. **Boiling Point:** 231.03 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.6 (EPI Suite)
4. **Melting Point**: −7.46 °C (EPI Suite)
5. **Water Solubility:** 6.208 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0481 mm Hg at 20 °C (EPI Suite v4.0), 0.0741 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 tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00026% (RIFM, 2017)
2. **Inhalation Exposure*:** <0.00010 mg/kg/day or 0.00000060 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0000019 mg/kg/day (RIFM, 2017)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

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

6.2. Analogs selected

a. **Genotoxicity:** 3,5,5-Trimethylhexanal (CAS # 5435-64-3)
b. **Repeated Dose Toxicity:** 2-Ethylhexanal (CAS # 123-05-7)
c. **Reproductive Toxicity:** 2-Methylundecanal (CAS # 110-41-8)
d. **Skin Sensitization:** 2-Methylundecanal (CAS # 110-41-8)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

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

8. Natural occurrence

Nonanal, 5-ethyl-2-methyl- 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

Nonanal, 5-ethyl-2-methyl- has been pre-registered for 2010; no dossier available as of 11/10/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for nonanal, 5-ethyl-2-methyl- 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)	0.22
2	Products applied to the axillae	0.066
3	Products applied to the face/body using fingertips	1.3
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.32
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.32
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.32
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.73
7	Products applied to the hair with some hand contact	2.5
8	Products with significant ano-genital exposure (tampon)	0.11
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	8.7
10B	Aerosol air freshener	8.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.11
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	84

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 nonanal, 5-ethyl-2-methyl-, the basis was the reference dose of 0.51 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2900 μg/cm^2.
[b] For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c] Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, nonanal, 5-ethyl-2-methyl- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Nonanal, 5-ethyl-2-methyl- was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. 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 nonanal, 5-ethyl-2-methyl-; however, read-across can be made to 3,5,5-trimethylhexanal (CAS # 5435-64-3; see Section VI). The mutagenic activity of 3,5,5-trimethylhexanal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with 3,5,5-trimethylhexanal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA, 2011b). Under the conditions of the study, 3,5,5-trimethylhexanal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of nonanal, 5-ethyl-2-methyl-; however, read-across can be made to 3,5,5-trimethylhexanal (CAS # 5435-64-3; see Section VI). The clastogenic activity of 3,5,5-trimethylhexanal was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage, to groups of male and female NMRI mice. Doses of 0 or 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h; 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 (ECHA, 2011b). Under the conditions of the study, 3,5,5-trimethylhexanal was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 3,5,5-trimethylhexanal does not present a concern for genotoxic potential, and this can be extended to nonanal, 5-ethyl-2-methyl-.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.2. Repeated dose toxicity

The MOE for nonanal, 5-ethyl-2-methyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on nonanal, 5-ethyl-2-methyl-. Read-across material 2-ethylhexanal (CAS # 123-05-7; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a good laboratory practice (GLP) (OECD 412) compliant study, groups of 5 male and 5 female Fischer-344 rats were exposed to 2-ethylhexanal (97.3% pure) through head-nose inhalation (6 h/day) at concentrations of 0, 25, 100, and 250 ppm (analytical concentration 0, 25.5, 102.2, and 250.7 parts per million [ppm]) corresponding to 0, 0.14, 0.54, and 1.34 mg per liter (mg/L) for 28 days. No mortality was reported during the study. The effects seen at 250 ppm included a statistically significant decrease in body weight among males, a minimal decrease in food consumption, a decrease in lymphocytes and increase in the neutrophil counts (both sexes), changes in clinical chemistry parameters (decreased glucose level, increased triglyceride and decreased cholesterol), increase in the adrenal weights (males and females), increase in liver weight (males and females), increase in lung weight (males and females) and decrease in thymus weight (males and females). At 25 and 100 ppm, the effects were limited to hematology parameters (decreased percentage of lymphocytes and increased percentage of neutrophils), clinical chemistry (increase in alkaline phosphatase), and increase in the adrenal weights. No treatment-related macroscopic or histopathological changes were noted. 2-Ethylhexanal was reported to modulate the activity of hepatic peroxisomal proliferation. Administration of 2-ethylhexanal to Fischer-344 rats resulted in minor effects on biochemical markers of peroxisomal proliferation at 250 ppm. However, confirmatory qualitative structural analysis during histopathological examination revealed no changes at 250 ppm. Additionally, liver weight (a sensitive marker for peroxisome proliferation) was not increased. Because peroxisomal proliferators are known to generally produce a more marked effect, the results showed that 2-ethylhexanal is only a very weak peroxisome proliferator in this species. The relevance is questionable because such findings on peroxisome proliferation are usually restricted to rodents and are not important for human toxicity. Overall, the exposure of 2-ethylhexanal was reported to be a weak peroxisomal proliferator in rats with an overall NOAEL of 102 ppm (ECHA, 2011a). Thus, the NOAEL was considered to be 102.2 ppm (0.54 mg/mL) or 153 mg/kg/day for systemic toxicity.

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 153/3 or 51 mg/kg/day.

Therefore, the nonanal, 5-ethyl-2-methyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-ethylhexanal NOAEL in mg/kg/day by the total systemic exposure to nonanal, 5-ethyl-2-methyl-, 51/0.0000019 or 26842105.

In addition, the total systemic exposure to nonanal, 5-ethyl-2-methyl- (0.0019 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose (RfD) of 0.51 mg/kg/day.

Derivation of 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 RfD for nonanal, 5-ethyl-2-methyl- was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 51 mg/kg/day by the uncertainty factor, 100 = 0.51 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/08/21.

11.1.3. Reproductive toxicity

The MOE for 5-ethyl-2-methyl- is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on nonanal, 5-ethyl-2-methyl-. Read-across material 2-methylundecanal (CAS # 110-41-8; see Section VI) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint.

In an OECD 414/GLP prenatal developmental toxicity study, 22 female Wistar Han rats/group were administered dose levels of 0, 1500, 5000, and 15000 ppm (equivalent to 147, 477, and 1350 mg/kg/day) in diet from gestation days (GDs) 6–21. No mortality was observed. No treatment-related clinical signs of toxicity were observed in any dose groups. A lower test-diet consumption at the start of treatment was observed in mid- and high-dose groups compared to the control. However, the food consumption in mid- and high-dose groups over the remaining treatment period and the overall mean was similar to the

control. Histopathological examination at the end of the administration period showed no abnormalities due to the test material. Furthermore, the numbers of pregnant females, corpora lutea and implantation sites, and pre-implantation loss were comparable in the control and test groups. Thus, the NOAEL for developmental toxicity was considered to be 15000 ppm (equivalent to 1350 mg/kg/day), the highest dose tested (RIFM, 2019a).

Another OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were exposed to the test material 2-methylundecanal at dose levels of 0, 1500, 5000, and 15000 ppm (mg/kg/day equivalency in males: 0, 96–108, 313–360, and 991–1093, respectively; in females: 0, 97–292, 339–995, and 1005–2527, respectively) in diet. Males were treated for 29 days (up to and including the day before scheduled necropsy) and females were treated for 51–63 days (2 weeks prior to mating, during mating, and 14–16 days after delivery, up to and including the day of scheduled necropsy). No parental toxicity was observed up to the highest dose. There were no treatment-related developmental toxicity effects seen at any dose levels. Thus, the NOAEL for developmental toxicity was considered to be 15000 ppm (equivalent to 991 mg/kg/day), the highest dose tested (RIFM, 2019b).

The NOAEL for developmental toxicity was derived from the more robust OECD 414 study and was considered to be 1350 mg/kg/day.

Therefore, the nonanal, 5-ethyl-2-methyl-MOE for the developmental toxicity endpoint can be calculated by dividing the 2-methylundecanal NOAEL in mg/kg/day by the total systemic exposure for nonanal, 5-ethyl-2-methyl-, 1350/0.0000019 or 710526316.

There are sufficient fertility data on 2-methylundecanal. An OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were exposed to the test material 2-methylundecanal at dose levels of 0, 1500, 5000, and 15000 ppm (mg/kg/day equivalency in males: 0, 96–108, 313–360, and 991–1093, respectively; in females: 0, 97–292, 339–995, and 1005–2527, respectively) in diet. Males were treated for 29 days (up to and including the day before scheduled necropsy) and females were treated for 51–63 days (2 weeks prior to mating, during mating, and 14–16 days after delivery, up to and including the day of scheduled necropsy). No treatment-related effects were seen for gestation, viability and lactation indices, duration of gestation, parturition, sex ratio, live litter size, maternal care, clinical signs, body weight, anogenital distance, areola/nipple retention, serum level of T4 thyroid hormone, and macroscopic examination. Thus, the NOAEL for fertility was considered to be 15000 ppm (equivalent to 991 mg/kg/day), the highest dose tested (RIFM, 2019b).

Therefore, the nonanal, 5-ethyl-2-methyl-MOE for the fertility endpoint can be calculated by dividing the 2-methylundecanal NOAEL in mg/kg/day by the total systemic exposure for nonanal, 5-ethyl-2-methyl-, 991/0.0000019 or 521578947.

In addition, the total systemic exposure to nonanal, 5-ethyl-2-methyl- (0.00019 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/05/21.

11.1.4. Skin sensitization

Based on read-across material 2-methylundecanal (CAS # 110-41-8), nonanal, 5-ethyl-2-methyl- is considered a skin sensitizer with a defined NESIL of 2900 μg/cm^2.

11.1.4.1. Risk assessment. No skin sensitization studies are available for nonanal, 5-ethyl-2-methyl-. Based on the read-across material 2-methylundecanal (CAS # 110-41-8; see Section VI), nonanal, 5-ethyl-2-methyl- is considered a skin sensitizer with a defined NESIL of 2900 μg/cm^2. The chemical structure of these materials indicates that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material, 2-methylundecanal was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens test, and U-SENS test (Natsch et al., 2013). In a murine local lymph node assay (LLNA), read-across 2-methylundecanal was found to be sensitizing with an EC3 value of 10% (2500 μg/cm^2) (Patlewicz et al., 2003; Gerberick et al., 2005; Roberts et al., 2007). In a human maximization test, no skin sensitization reactions were observed with read-across 2-methylundecanal (RIFM, 1971). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2953 μg/cm^2 of read-across 2-methylundecanal in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2016). In 2 other CNIHs with 969 μg/cm^2 of read-across 2-methylundecanal in ethanol, no reactions indicative of sensitization were observed in any of the 40 volunteers (EPA, 1991; RIFM, 1964).

Based on weight of evidence (WoE) from structural analysis and data on read-across material 2-methylundecanal, nonanal, 5-ethyl-2-methyl- is a weak sensitizer with a WoE NESIL of 2900 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. (RIFM, 2020b) and a reference dose of 0.51 mg/kg/day.

Additional References: Klecak (1979); Klecak (1985).

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, nonanal, 5-ethyl-2-methyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for nonanal, 5-ethyl-2-methyl- in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, nonanal, 5-ethyl-2-methyl- 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.

Table 1
Data summary for 2-methylundecanal as read-across material for nonanal, 5-ethyl-2-methyl-.

LLNA weighted mean EC3 value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) g/cm^2	WoE NESIL[3] μg/cm^2
2500 [1	Weak	2953	2760	N/A	2900

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.

Literature Search and Risk Assessment Completed On: 02/18/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for nonanal, 5-ethyl-2-methyl- 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 nonanal, 5-ethyl-2-methyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.00000060 mg/day. This exposure is 2333333 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 nonanal, 5-ethyl-2-methyl- 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, nonanal, 5-ethyl-2-methyl- 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 nonanal, 5-ethyl-2-methyl- as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), nonanal, 5-ethyl-2-methyl- does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Nonanal, 5-ethyl-2-methyl- has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.6	4.6
Biodegradation Factor Used	0	0
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 0.00136 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/08/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 11/10/21.

	(mg/L)	(*Daphnia*) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level **(Tier 1)**	1.360			1000000	0.00136	

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.2022.112858.

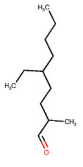
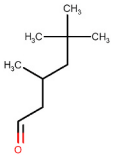
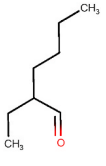
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow 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 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, oncologic classification, ER binding, and repeat dose categorization predictions 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	Read-across Material
Principal Name	Nonanal, 5-ethyl-2-methyl-	3,5,5-Trimethylhexanal	2-Methylundecanal	2-Ethylhexanal
CAS No.	68141-14-0	5435-64-3	110-41-8	123-05-7
Structure				
Similarity (Tanimoto Score)		0.75	0.96	0.83

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Endpoint		• Genotoxicity	• Skin sensitization • Reproductive toxicity	• Repeated dose toxicity
Molecular Formula	$C_{12}H_{24}O$	$C_9H_{18}O$	$C_{12}H_{24}O$	$C_8H_{16}O$
Molecular Weight	184.323	142.242	184.323	128.215
Melting Point (°C, EPI Suite)	−7.46	−35.47	3.24	−42.32
Boiling Point (°C, EPI Suite)	231.03	173.00	171.00	163.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	9.88E+00	1.07E+01	1.99E+02	2.67E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6.21E+00	1.89E+02	5.37E+00	4.00E+02
Log K_{OW}	4.6	3.09	4.67	3.07
J_{max} (μg/cm^2/h, SAM)	0.98	19.97	0.87	51.20
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.17E+02	5.00E+01	1.17E+02	8.51E+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		
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
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (moderate reliability)		Non-toxicant (low reliability)	
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	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on nonanal, 5-ethyl-2-methyl- (CAS # 68141-14-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 3,5,5-trimethylhexanal (CAS # 5435-64-3), 2-methylundecanal (CAS # 110-41-8), and 2-ethylhexanal (CAS # 123-05-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 3,5,5-Trimethylhexanal (CAS # 5435-64-3) was used as a read-across analog for the target nonanal, 5-ethyl-2-methyl- (CAS # 68141-14-0) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of aliphatic aldehydes.
  - o The key difference between the target material and the read-across analog is in the chain length and branching of the aliphatic portion of aldehydes. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have 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 target material and the read-across analog have Schiff base formation alerts. The data described for the read-across analog confirms that the analog does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog, and data on the read-across analog, *in silico* alerts are superseded.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Methylundecanal (CAS # 110-41-8) was used as a read-across analog for the target nonanal, 5-ethyl-2-methyl- (CAS # 68141-14-0) for the skin sensitization and reproductive toxicity endpoints.
  - o The target material and the read-across analog belong to a class of aliphatic aldehydes.
  - o The key difference between the target material and the read-across analog is in the chain length and branching of the aliphatic portion of aldehydes. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have 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 target material and the read-across analog have Schiff base formation alerts. The data described for the read-across analog in the skin sensitization section confirms that the analog is a sensitizer. Therefore, *in silico* alerts are consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Ethylhexanal (CAS # 123-05-7) was used as a read-across analog for the target nonanal, 5-ethyl-2-methyl- (CAS # 68141-14-0) for the repeated dose toxicity endpoint.
  - o The target material and the read-across analog belong to a class of aliphatic aldehydes.
  - o The key difference between the target material and the read-across analog is in the chain length and branching of the aliphatic portion of aldehydes. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have 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 target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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