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RIFM fragrance ingredient safety assessment, 2,6,10-trimethyl-9-undecenal, CAS Registry Number 141-13-9

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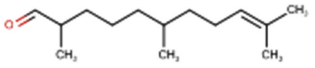

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Name: 2,6,10-Trimethyl-9-undecenal

CAS Registry Number: 141-13-9

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

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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 (Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
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.

2,6,10-Trimethyl-9-undecenal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog citronellal (CAS # 106-23-0) show that 2,6,10-trimethyl-9-undecenal is not expected to be genotoxic. Data on read-across analog citral (CAS # 5392-40-5) provide a calculated Margin of Exposure (MOE) > 100 for repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog 2,6,10-trimethylundeca-5,9-dienal (CAS # 54082-68-7) provided 2,6,10-trimethyl-9-undecenal a No Expected Sensitization Induction Level (NESIL) of 10000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 2,6,10-trimethyl-9-undecenal is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to 2,6,10-trimethyl-9-undecenal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2,6,10-trimethyl-9-undecenal 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, 2003; RIFM, 2016a)

Repeated Dose Toxicity: NOAEL = 60 mg/kg/day. (Ress et al., 2003)

Reproductive Toxicity: Developmental toxicity: NOAEL = 60 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day. (Nogueira et al., 1995; MHW, 1996)

Skin Sensitization: NESIL = 10000 μg/cm^2. RIFM (2017)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 84% (OECD 301F) RIFM (1997b)

Bioaccumulation: Screening-level: 1754 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 72-h Algae EbC50: 0.079 mg/L RIFM (2015c)

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: 72-h Algae EbC50: 0.079 mg/L RIFM (2015c)

RIFM PNEC is: 0.079 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** 2,6,10-Trimethyl-9-undecenal
2. **CAS Registry Number:** 141-13-9
3. **Synonyms:** Adoxal; Farenal; Trimethyl undecylenic aldehyde; 9-Undecenal, 2,6,10-trimethyl-; 2,6,10-Trimethylundec-9-enal; 2,6,10-Trimethyl-9-undecenal
4. **Molecular Formula:** $C_{14}H_{26}O$
5. **Molecular Weight:** 210.36 g/mol
6. **RIFM Number:** 858
7. **Stereochemistry:** Stereocenter not present. Stereoisomerism is not possible.

2. Physical data

1. **Boiling Point:** 266.71 °C (EPI Suite), 260 °C (decomposition at 124 °C) (RIFM, 2015d)
2. **Flash Point:** >100 °C (Globally Harmonized System), >100 °C/212 °F (Givaudan), >200 °F; CC (Fragrance Materials Association [FMA]), >110 °C (mean value) (RIFM, 2015d)
3. **Log K_{OW}:** >6.0 (RIFM, 1997a), 5.42 (EPI Suite)
4. **Melting Point**: 4.7 °C (EPI Suite), less than −60 °C (RIFM, 2015d)
5. **Water Solubility:** 0.9069 mg/L (EPI Suite)

6. **Specific Gravity:** 0.849 (FMA), 0.848–0.854 at 25 °C (Givaudan), 0.8480 (RIFM)
7. **Vapor Pressure:** 0.00682 mm Hg at 20 °C (EPI Suite v4.0), 0.003 mm Hg at 20 °C (FMA), 0.0111 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Arctander, Volume II, 1969: Colorless or very pale straw-colored, slightly viscous liquid. It tends to increase viscosity upon standing and will polymerize if exposed to air. Very powerful and very tenacious, sweet-floral, waxy-rosy odor, sometimes referred to as “ozone-like."

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 v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.021% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.00010 mg/kg/day or 0.0076 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.0013 mg/kg/day (RIFM, 2020b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (RIFM, 2015a; 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, 2015a; 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

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
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2. Analogs Selected:
   a. **Genotoxicity:** Citronellal (CAS # 106-23-0)
   b. **Repeated Dose Toxicity:** Citral (CAS # 5392-40-5)
   c. **Reproductive Toxicity:** Citral (CAS # 5392-40-5)
   d. **Skin Sensitization:** 2,6,10-Trimethylundeca-5,9-dienal (CAS # 54082-68-7)
   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.

7.1. Additional References

None.

8. Natural occurrence

2,6,10-Trimethyl-9-undecenal 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

HYPERLINK “https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/18713/1/2" \o “https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/18713/1/2″Available; accessed 11/11/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,6,10-trimethyl-9-undecenal 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)	0.38
2	Products applied to the axillae	0.23
3	Products applied to the face/body using fingertips	0.15
4	Products related to fine fragrances	2.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.53
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.076
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.15
5D	Baby cream, oil, talc	0.025
6	Products with oral and lip exposure	1.4
7	Products applied to the hair with some hand contact	0.15
8	Products with significant ano-genital exposure (tampon)	0.025
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.23
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.15
10B	Aerosol air freshener	1.2
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.025
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	38

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 2,6,10-trimethyl-9-undecenal, the basis was the subchronic reference dose of 0.60 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 10000 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-I

FRA-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 and use levels, 2,6,10-trimethyl-9-undecenal does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2,6,10-trimethyl-9-undecenal 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 2,6,10-trimethyl-9-undecenal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2003). Under the conditions of the study, 2,6,10-trimethyl-9-undecenal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2,6,10-trimethyl-9-undecenal; however, read-across can be made to citronellal (CAS # 106-23-0; see Section VI).

The clastogenic activity of citronellal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with citronellal in DMSO at concentrations up to 1540 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of metabolic activation. Citronellal did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2016a). Under the conditions of the study, citronellal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2,6,10-trimethyl-9-undecenal.

Based on the data available, citronellal does not present a concern for genotoxic potential, and this can be extended to 2,6,10-trimethyl-9-undecenal.

Additional References: RIFM, 2000; Heck et al., 1989; RIFM, 2006.

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.2. Repeated dose toxicity

The MOE for 2,6,10-trimethyl-9-undecenal 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 2,6,10-trimethyl-9-undecenal. Read-across material citral (CAS # 5392-40-5; see Section VI) has been extensively studied in several species and has sufficient repeated dose toxicity data via several routes of exposure. An NTP-sponsored chronic diet study was conducted in compliance with GLP on groups of 50 F344/N rats/sex/group. The animals were administered test material, citral (microencapsulated), at concentrations of 1000, 2000, or 4000 ppm for 104–105 weeks. Additional groups of 50 male and 50 female rats received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). The concentrations are equivalent to approximately 50, 100, and 210 mg/kg/day. The NOAEL for treatment-related non-neoplastic effects was 100 mg/kg/day, based on decreased body weight among the animals in the high-dose group (Ress et al., 2003). In another GLP study, a group of 50 B6C3F1 mice/sex/group were fed diets containing citral at concentrations of 500, 1000, or 2000 ppm for 104–105 weeks. Additional groups of 50 male and 50 female mice received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). The concentrations are equivalent to approximately 60, 120, and 260 mg/kg/day. There was an increase in the incidences of malignant lymphoma in females with a positive trend. The incidence in 2000 ppm females was significantly greater than that in the vehicle control group but was within the historical ranges in controls (all routes). Immunostaining of the lymphomas did not reveal any differences in the origin of the lymphomas in the vehicle control and the treatment group animals. Incidences of hepatomas (hepatocellular adenoma or carcinoma), inflammation, and ulceration among the 2000 ppm group males and all treated females, adrenal cortical focal hyperplasia in high-dose group males, nephropathy among high-dose group females, and minimal tubule mineralization among the 500 and 1000 ppm group females was reported. However, the incidences were either within the historical control range, or the toxicological significance of such occurrences remained unknown. The NOAEL for treatment-related non-neoplastic effects was 60 mg/kg/day (Ress et al., 2003; NTP, 2003).

In another study, a group of Fischer 344 rats (number not reported) were treated with test material, citral (vapor/aerosol), at concentrations of 10, 34, or 68 ppm for 6 h/day for 21 consecutive days. No mortality was reported. At 68 ppm, effects included severe ocular, oral, and nasal irritation, reduced weight gains, dose-related chronic active inflammation, hyperplasia, squamous metaplasia, and goblet cell atrophy of the nasal respiratory epithelium, irritation of the trachea and lungs, and corneal ulceration (Gaworski et al., 1993). The same group conducted another study where rats were exposed to citral via inhalation at concentrations of 1, 3, or 10 ppm. Rats exposed to 10 ppm citral developed minimal hyperplasia and squamous metaplasia of the laryngeal epithelium, but these changes were completely reversed during a 5-week recovery period. The LOAEC was determined to be 68 ppm (430 mg/m^3). The NOAEC was determined to be 34 ppm (212 mg/m^3). Using standard minute volume and body weight values for male and female Fischer 344 rats, the calculated NOAEL for repeated dose toxicity is 60 mg/kg/day (Gaworski et al., 1993). The most conservative NOAEL for repeated dose toxicity was determined from a dietary 104–105 week carcinogenicity study in mice to be 500 ppm, or 60 mg/kg/day, based on reduced body weights.

Therefore, the 2,6,10-trimethyl-9-undecenal MOE for the repeated dose toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure for 2,6,10-trimethyl-9-undecenal, 60/0.0013, or 46153.

In addition, the total systemic exposure to 2,6,10-trimethyl-9-undecenal (1.3 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, 2020c) and a subchronic reference dose (RfD) of 0.60 mg/kg/day.

Derivation of subchronic RfD:

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 2,6,10-trimethyl-9-undecenal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 60 mg/kg/day by the uncertainty factor, 100 = 0.60 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.3. Reproductive toxicity

The MOE for 2,6,10-trimethyl-9-undecenal is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on

2,6,10-trimethyl-9-undecenal. Read-across material citral (CAS # 5392-40-5; see Section VI) has sufficient developmental toxicity and fertility data. Citral has been extensively studied via several routes of exposure. An OECD 421 gavage reproduction toxicity screening test was conducted in Crj:CD (SD) rats. Citral was administered to rats via gavage at dose levels of 0, 40, 200, and 1000 mg/kg/day in males for 46 days and in females for 39–50 days, including before and through mating and gestation periods and until day 3 of lactation. Body weights of pups were reduced at 1000 mg/kg/day, though there was no effect on viability or morphogenesis. The NOAEL for developmental toxicity was determined to be 200 mg/kg/day due to a decrease in body weights among the high-dose group pups (MHW, 1996). A gavage developmental toxicity study was conducted on groups of 20 Wistar rats. The pregnant animals were treated with test material, citral, at dose levels of 0 (corn oil), 60, 125, 250, 500, or 1000 mg/kg/day on gestation days 6–15. The study was terminated on gestation day 21. The protocol followed was similar to the OECD 414 developmental toxicity study. Administration of citral seemed to induce whole-litter loss at doses that were deemed to be maternally toxic (125–1000 mg/kg/day), suggesting that treatment-induced prenatal loss was a maternally mediated effect. No increase in visceral anomalies was found at any dose. The LOAEL for both maternal and developmental toxicity was determined to be 60 mg/kg/day, based on maternal body weights and an increased ratio of resorptions per implantations (Nogueira et al., 1995). An inhalation developmental toxicity study was conducted on groups of 25 Sprague Dawley rats. The pregnant animals were treated with test material, citral, by whole-body inhalation for 6 h per day on gestation days 6 through 15 at target doses of 0, 10, or 35 ppm vapor or 85 ppm aerosol/vapor (actual doses of 0, 10, 34, or 68 ppm). There was no effect on pre-implantation or post-implantation death, litter size, or sex ratio at any exposure level. There were no statistically significant differences between treated and control animals in number or percentage of males, females, or live fetuses with malformations, nor were there significant differences in the number of litters with fetal malformations. A slight reduction in mean fetal body weight and a slight increase in the incidence of hypoplastic bones were observed at 68 ppm, a maternally toxic exposure level. The NOAEC for developmental toxicity was determined to be 68 ppm (423 mg/m^3). Using standard minute volume and body weight values for female Sprague Dawley rats, the calculated NOAELs for maternal and developmental toxicity are 56 and 112 mg/kg/day, respectively (Gaworski et al., 1992). A reproductive toxicity screening study was conducted on 30 female Sprague Dawley rats/group, which were administered citral via gavage at dose levels of 0 (corn oil), 50, 160, and 500 mg/kg/day for 2 weeks prior to mating through gestation day 20. Subsequently, the effects of citral on the development of the offspring in utero and through lactation were also reported. There was no gross external alteration attributed to the test material in the fetuses up to the highest dose tested. There was, however, a significant decrease in the average pup body weight at birth among the high-dose group animals as compared to control. Thus, the NOAEL for the developmental toxicity was determined to be 160 mg/kg/day, based on reduced fetal weights among the high-dose group animals (Hoberman et al., 1989). Another OECD 414 GLP gavage prenatal developmental toxicity study was conducted on groups of 25 pregnant female New Zealand White rabbits/group. The animals were administered test material, citral extra via gavage at dose levels of 0 (0.5% carboxymethylcellulose suspension in drinking water [with 0.5 mg Tween 80/100 mL]), 20, 60, or 200 mg/kg/day on GDs 6–28. At terminal sacrifice on GD 29, 17–24 females per group had implantation sites. Mortality was reported among the high-dose group does. Gross pathological examination revealed reddening of the stomach mucosa and multiple ulcerations. Clinical observations in the high-dose group animals included reduced average food consumption and net bodyweight loss. One high-dose female had 4 dead fetuses at termination, which was considered an expression of maternal toxicity in rabbits. This was related to the local irritating potential of the test material on the gastrointestinal tract. One high-dose group doe was reported to have litters having malrotated limbs. However, this was considered to be secondary to maternal toxicity since the doe was reported to have a significant bodyweight loss and reduced food consumption. There were no other reported effects of treatment on the developing fetus. Considering this, there was sufficient evidence that these fetal findings were a direct consequence of severe maternal toxicity. Therefore, the NOAEL for maternal toxicity was determined to be 60 mg/kg/day based on reduced food consumption, distinct bodyweight loss, mortality, and abortion in the most sensitive individuals in the 200 mg/kg/day group. The NOAEL for prenatal developmental toxicity was determined to be 60 mg/kg/day, based on fetal mortality and limb malrotations in the 200 mg/kg/day group (RIFM, 2016c). Citral did not affect the reproductive performance or the development of the offspring up to the highest dose tested.

The developmental toxicity study on rats (Nogueira et al., 1995) was not considered toward determining the NOAEL since the incidences of resorptions without any visceral alterations in fetuses were reported in the presence of maternal toxicity. Similar effects on the developing fetuses were not reported among rabbits treated at comparable doses during the OECD 414 study (RIFM, 2016c) or rats during the OECD 421 study (MHW, 1996). Therefore, the NOAEL for the developmental toxicity endpoint was considered to be 60 mg/kg/day, as determined from the most recent OECD 414/GLP developmental toxicity study on rabbits (RIFM, 2016c; ECHA, 2011).

Therefore, the 2,6,10-trimethyl-9-undecenal MOE for the developmental toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure for to 2,6,10-trimethyl-9-undecenal, 60/0.0013, or 46153.

The OECD 421 (MHW, 1996) and the reproductive toxicity screening study (Hoberman et al., 1989) conducted on citral did not show any adverse effects towards the male or the female reproductive study. Thus, the NOAEL for reproductive toxicity was determined to be 1000 mg/kg/day.

Therefore, the 2,6,10-trimethyl-9-undecenal MOE for the reproductive toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure for 2,6,10-trimethyl-9-undecenal, 1000/0.0013, or 769230.

In addition, the total systemic exposure for to 2,6,10-trimethyl-9-undecenal (1.3 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: 02/09/21.

11.1.4. Skin sensitization

Based on the available data and read-across material 2,6,10-trimethylundeca-5,9-dienal (CAS # 54082-68-7), 2,6,10-trimethyl-9-undecenal is considered a skin sensitizer with a defined NESIL of 10000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the available data, 2,6,10-trimethyl-9-undecenal is a skin sensitizer. However, no sufficient human data are available to confirm the NESIL in humans. Therefore, 2,6,10-trimethylundeca-5,9-dienal was used as a read-across (CAS # 54082-68-7; see Section VI). The chemical structure of these materials indicates that they would be expected to be reactive to skin proteins (Roberts et al., 2007; OECD Toolbox v4.2; Toxtree v3.1.0). In a murine local lymph node assay (LLNA), 2,6,10-trimethyl-9-undecenal was predicted to be sensitizing with an EC3 value of 32% (8000 μg/cm^2) (RIFM, 2016d). In another LLNA with the read-across material, 2,6,10-trimethylundeca-5,9-dienal was found to be sensitizing with an EC3 value of 42.3% (10575 μg/cm^2) (RIFM, 2016b). In a Confirmation of No Induction in Humans test (CNIH), the read-across material did not induce any reactions indicative of sensitization in 108 subjects when 8.5% (10039 μg/cm^2) in

1:3 EtOH:DEP was used for induction and challenge (RIFM, 2017). Additionally, no reactions indicative of skin sensitization were observed in a human study conducted with the target material 2,6,10-trimethyl-9-undecenal (RIFM, 1976).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and data from read-across analog 2,6,10-trimethylundeca-5,9-dienal (CAS # 54082-68-7), 2,6,10-trimethyl-9-undecenal is a sensitizer with a WoE NESIL of 10000 μg/cm^2 (see Table 1 below). 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, 2020c) and a subchronic RfD of 0.60 mg/kg/day.

Additional References: RIFM, 2014; RIFM, 1978.

Literature Search and Risk Assessment Completed On: 02/07/21.

11.1.4.2. Phototoxicity/photoallergenicity. Based on the UV absorption spectra, 2,6,10-trimethyl-9-undecenal does not present a concern for phototoxicity or photoallergenicity.

11.1.4.3. Risk assessment. There are no phototoxicity studies available for 2,6,10-trimethyl-9-undecenal in experimental models. UV absorption spectra indicate no absorption between 290 and 500 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2,6,10-trimethyl-9-undecenal does not present a concern for phototoxicity or photoallergenicity.

11.1.5. UV spectra analysis

Available UV absorption spectra for 2,6,10-trimethyl-9-undecenal demonstrate no absorbance between 290 and 500 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: 02/09/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2,6,10-trimethyl-9-undecenal 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 2,6,10-trimethyl-9-undecenal. Based on the Creme RIFM Model, the inhalation exposure is 0.0076 mg/day. This exposure is 184.2 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: 02/12/21.

Table 1
Data summary for 2,6,10-trimethylundeca-5,9-dienal as read-across for 2,6,10-trimethyl-9-undecenal.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	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
10575 [1]	Weak	10039	NA	NA	10000

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

[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.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6,10-trimethyl-9-undecenal was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2,6,10-trimethyl-9-undecenal 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 2,6,10-trimethyl-9-undecenal 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). 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 Volume of Use (2015), 2,6,10-trimethyl-9-undecenal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 1997b: A ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. The biodegradation rate was 71% after 10 days and 84% after 28 days.

RIFM, 2001a: A ready biodegradability of 2,6,10-trimethyl-9-undecenal was determined by the closed bottle test according to the OECD

301D method. Under the conditions of the study, 0.42 mg of test material had a mean biodegradation level of 35% after 28 days.

11.2.3.2. Ecotoxicity. RIFM, 2001b: A 48-h *Daphnia magna* acute toxicity test was conducted with 2,6,10-trimethyl-9-undecenal according to the OECD 202 Part I method under static conditions. Because the test material is poorly water-soluble, it was tested using the aqueous extracts from the test material, and the effective-loadings values were calculated on the basis of the nominal concentrations. The 48-h EL50 was reported to be 0.9 mg/L.

RIFM, 2015b: A 96-h fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 guidelines under semi-static conditions. The LC50 value based on the mean measured concentration was reported to be greater than 0.474 mg/L.

RIFM, 2015c: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 based on geometric mean measured concentration was 0.079 mg/L, 0.087 mg/L, and 0.119 mg/L for biomass, yield, and growth rate, respectively.

11.2.4. Other available data

2,6,10-Trimethyl-9-undecenal has been registered for REACH with no additional data at this time.

Risk Assessment Refinement:

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.0	6.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.079 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.

Literature Search and Risk Assessment Completed On: 01/06/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.0939			1000000	9.4E-05	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.194	0.057	0.189	10000	0.0057	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.146	0.114	0.313			Neutral Organics SAR (Baseline Toxicity)
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.473					
Daphnia		0.9				
Algae		0.079		1000	0.079	

- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 11/11/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. 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.2022.113100.

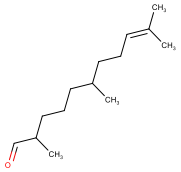
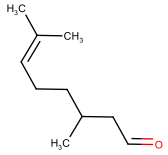
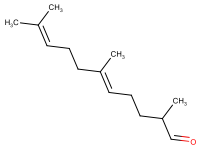
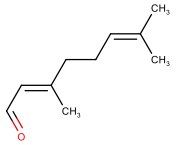
Appendix

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	2,6,10-Trimethyl-9-undecenal	Citronellal	2,6,10-Trimethylundeca-5,9-dienal	Citral
CAS No.	141-13-9	106-23-0	54082-68-7	5392-40-5
Structure				
Similarity (Tanimoto Score)		0.79	0.56	0.42
Endpoint		• Genotoxicity	• Skin sensitization	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{14}H_{26}O$	$C_{10}H_{18}O$	$C_{14}H_{24}O$	$C_{10}H_{16}O$
Molecular Weight (g/mol)	210.361	154.253	208.345	152.237

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Melting Point (°C, EPI Suite)	4.70	−28.33	5.72	−26.74
Boiling Point (°C, EPI Suite)	266.71	207.00	277.12	227.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.48E+00	3.39E+01	8.32E-01	1.22E+01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	9.07E-01	3.89E+01	1.10E+00	1.34E+03
Log K_{OW}	5.42	3.83	5.34	3.45
J_{max} (μg/cm^2/h, SAM)	0.15	5.87	0.18	164.13
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.14E+02	6.88E+01	2.22E+02	3.81E+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)	Non-toxicant (low 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)	No alert found		No alert found	
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 is insufficient toxicity data on 2,6,10-trimethyl-9-undecenal (CAS # 141-13-9). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, citronellal (CAS # 106-23-0), 2,6,10-trimethylundeca-5,9-dienal (CAS # 54082-68-7), and citral (CAS # 5392-40-5) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusions

- Citronellal (CAS # 106-23-0) was used as a read-across analog for the target material 2,6,10-trimethyl-9-undecenal (CAS # 141-13-9) for the genotoxicity endpoint.
  - 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 have the α-substituted aldehyde and unsaturated isopropyl group at the tail end common among them.
  - o The key difference between the target material and the read-across analog is that the target has a longer aliphatic chain than the read-across. 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 material.
  - 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 compare their toxicological properties.
  - o According to the QSAR OECD Toolbox, structural alerts for genotoxicity endpoint are consistent between the target material and the read-across analog. The target material and the read-across analog have an alert for Schiff base formation. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alert is superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the genotoxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
- 2,6,10-Trimethylundeca-5,9-dienal (CAS # 54082-68-7) was used as read-across analog for the target material 2,6,10-trimethyl-9-undecenal (CAS # 141-13-9) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - 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 QSAR OECD Toolbox, structural alerts for skin sensitization endpoint are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have alerts for the read-across analog that confirm that the substance is a sensitizer. Therefore, the alerts are consistent 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 endpoint 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 deemed to be toxicologically insignificant.
- Citral (3,7-dimethyl-2,6-octadienal) (CAS # 5392-40-5) was used as structurally similar read-across analog for the target material 2,6,10-trimethyl-9-undecenal (CAS # 141-13-9) for the repeated dose and reproductive 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 have 1-methyl-hept-1-ene common among them.
  - o The key difference between the target material and the read-across analog is that the read-across is an α,β-unsaturated aldehyde. In contrast, the target does not have α-β unsaturation to the aldehyde group. Because the read-across analog has an activated aldehyde group, it will form a direct-acting Schiff base and be a Michael acceptor, increasing toxicity compared to the target for systemic toxicity endpoints. It will be more reactive for reproductive toxicity. Repeated dose toxicity endpoints The read-across analog contains the structural features of the target material relevant to this endpoint. It is expected to have equal or greater potential for toxicity than the target material.
  - 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 compare their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the respiratory, reproductive toxicity, and repeated dose toxicity endpoints are consistent between the target material and the read-across analog.
  - o According to the metabolic simulator, the read-across is expected to undergo metabolism and form a Schiff base at the activated aldehyde group. The target material will not have similar metabolism as seen for the read-across analog.
  - o The structural alerts for respiratory, reproductive, and developmental toxicity 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 deemed to be toxicologically insignificant.

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