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# RIFM fragrance ingredient safety assessment, methoxycitronellal, CAS Registry Number 3613-30-7

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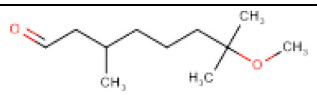

Name: Methoxycitronellal
CAS Registry Number: 3613-30-7

**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**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 (RIFM, 2015a; 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, 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

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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.**

Methoxycitronellal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2) show that methoxycitronellal is not expected to be genotoxic and provided a No Expected Sensitization Induction Level (NESIL) of 5900 μg/cm$^2$ for the skin sensitization endpoint. Data on read-across analog trimethylhexanal (CAS # 5435-54-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog 2-methylundecanal (CAS # 110-41-8) provide a calculated MOE >100 for the reproductive toxicity endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methoxycitronellal is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog hydroxycitronellal (CAS # 107-75-5). The environmental endpoints were evaluated; methoxycitronellal 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.

**Human Health Safety Assessment**

| | |
|---|---|
| **Genotoxicity:** Not expected to be genotoxic. | (RIFM, 2014b; RIFM, 2016b; RIFM, 2016c; RIFM, 2016a) |
| **Repeated Dose Toxicity:** NOAEL = 83 mg/kg/day. | (ECHA REACH Dossier: 3,5,5-Trimethylhexanal; ECHA, 2011) |
| **Reproductive Toxicity:** Developmental toxicity NOAEL: 1350 mg/kg/day. Fertility NOAEL: 991 mg/kg/day. | (RIFM, 2019a; RIFM, 2019b) |
| **Skin Sensitization:** NESIL = 5900 μg/cm$^2$. | RIFM (2015b) |
| **Phototoxicity/ Photoallergenicity:** Not expected to be phototoxic/ photoallergenic. | (UV/Vis Spectra; RIFM Database) |
| **Local Respiratory Toxicity:** NOAEC = 70 mg/m$^3$. | RIFM (2013a) |

**Environmental Safety Assessment**

| | |
|---|---|
| **Hazard Assessment:** | |
| **Persistence:** Screening-level: 2.58 (BIOWIN 3) | (EPI Suite v4.11; US EPA, 2012a) |
| **Bioaccumulation:** Screening-level: 33.33 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** Screening-level: Fish LC50: 49.6 mg/L | (RIFM Framework; Salvito, 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, 2002) |
| **Critical Ecotoxicity Endpoint:** Fish LC50: 49.6 mg/L | (RIFM Framework; Salvito, 2002) |

**RIFM PNEC is:** 0.0496 μg/L

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

## 1. Identification

1. **Chemical Name:** Methoxycitronellal
2. **CAS Registry Number:** 3613-30-7
3. **Synonyms:** 3,7-Dimethyl-7-methoxy-1-octanal; Hydroxycitronellal methyl ether; Methoxydihydrocitronellal; 7-methoxy-3,7-dimethyloctanal; Octanal, 7-methoxy-3,7-dimethyl-; ﾒﾄｷｼｼﾄﾛﾈﾗｰﾙ; Methoxycitronellal

4. **Molecular Formula:** $C_{11}H_{22}O_2$
5. **Molecular Weight:** 186.29 g/mol
6. **RIFM Number:** 639
7. **Stereochemistry:** Isomer not specified. One chiral center present, and a total of 2 enantiomers possible.

## 2. Physical data

1. **Boiling Point:** 111 °C at 10 mm Hg (Fragrance Materials Association [FMA]), 224.38 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA), >93 °C (Globally Harmonized System)
3. **Log $K_{OW}$:** 2.81 (EPI Suite)
4. **Melting Point**: 4.79 °C (EPI Suite)
5. **Water Solubility:** 203.2 mg/L (EPI Suite)
6. **Specific Gravity:** 0.890 (FMA)
7. **Vapor Pressure:** 0.0686 mm Hg at 20 °C (EPI Suite v4.0), 0.105 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 $mol^{-1} \bullet cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless slightly oily liquid with a fresh lily-like odor, faintly herbaceous, sweet, and very tenacious odor, but overall, disappointingly weak (Arctander, Volume II, 1969)

## 3. Volume of use (Worldwide band)

1. 0.1–1 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.19% (RIFM, 2019c)
2. **Inhalation Exposure*:** 0.00034 mg/kg/day or 0.024 mg/day (RIFM, 2019c)
3. **Total Systemic Exposure**:** 0.0051 mg/kg/day (RIFM, 2019c)

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

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

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| III* | III | I |

*See the Appendix below for further details.

### 6.2. Analogs selected

a. **Genotoxicity:** 6-Methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2)
b. **Repeated Dose Toxicity:** 3,5,5-Trimethylhexanal (CAS # 5435-64-3)
c. **Reproductive Toxicity:** 2-Methylundecanal (CAS # 110-41-8)
d. **Skin Sensitization:** 6-Methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Hydroxycitronellal (CAS # 107-75-5)
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

Methoxycitronellal is reported to occur in the following foods by the VCF*:

Licorice (*Glycyrrhiza* species)

*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

Available; accessed on 11/10/21.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for methoxycitronellal 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) | 0.45 |
| 2 | Products applied to the axillae | 0.14 |
| 3 | Products applied to the face/body using fingertips | 1.6 |
| 4 | Products related to fine fragrances | 2.5 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.64 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.64 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.64 |
| 5D | Baby cream, oil, talc | 0.21 |
| 6 | Products with oral and lip exposure | 0.52 |
| 7 | | 3.7 |

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(*continued*)

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| | Products applied to the hair with some hand contact | |
| 8 | Products with significant ano-genital exposure (tampon) | 0.21 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 4.9 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 1.0 |
| 10B | Aerosol air freshener | 18 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.21 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | No Restriction |

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For methoxycitronellal, the basis was the subchronic reference dose of 0.83 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 5900 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, methoxycitronellal does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* Methoxycitronellal was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity without metabolic activation, positive for cytotoxicity with metabolic activation, and negative for genotoxicity with metabolic activation (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. While the BlueScreen assay on the target material showed positive results, data from 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 methoxycitronellal; however, read-across can be made to 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2; see Section VI). The mutagenic activity of 6-methoxy-2,6-dimethylheptan-1-al 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 6-methoxy-2,6-dimethylheptan-1-al 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 (RIFM, 2014b). Under the conditions of the study, 6-methoxy-2,6-dimethylheptan-1-al was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of methoxycitronellal; however, read-across can be made to 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2; see Section VI). The clastogenic activity of 6-methoxy-2,6-dimethylheptan-1-al 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 6-methoxy-2,6-dimethylheptan-1-al in DMSO at concentrations of up to 1723 μg/mL in the presence and absence of S9 for 3 h and in the absence of metabolic activation for 24 h. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at all 3 evaluated concentrations of the 3-h treatment without S9 and at the highest evaluated concentration (1723 μg/mL) of the 3-h treatment with S9. No statistically significant increase in the BNMN frequency was observed at any evaluated concentration in the 24-h treatment without S9 (RIFM, 2016b). Under the conditions of the study, 6-methoxy-2,6-dimethylheptan-1-al was considered positive for clastogenic activity in the *in vitro* micronucleus test.

As a follow-up to the positive *in vitro* MNT assay, a GLP-compliant 3D reconstructed skin micronucleus assay (RSMN) was conducted to evaluate the genotoxic potential of 6-methoxy-2,6-dimethylheptan-1-al in EpiDerm. Acetone was used as the vehicle. EpiDerm tissues were treated with 6-methoxy-2,6-dimethylheptan-1-al at 24-h intervals for 48 and 72 h, at concentrations up to 45 mg/mL. No increase in the number of binucleated cells with micronuclei was observed when tested up to the maximum dose (RIFM, 2016c). Under the conditions of the study, 6-methoxy-2,6-dimethylheptan-1-al was concluded to be negative for the induction of micronuclei in the RSMN using the EpiDerm model.

To investigate the biological and systemic relevance of the *in vitro* MNT assay, the clastogenic activity of 6-methoxy-2,6-dimethylheptan-1-al was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. 6-Methoxy-2,6-dimethylheptan-1-al was administered in corn oil to groups of male and female CD-1 mice at doses of 500, 1000, and 2000 mg/kg were. Mice from each dose level were euthanized at both 24- and 48-h time points, at which time the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow compared to vehicle control (RIFM, 2016a). Under the conditions of the study, test 6-methoxy-2,6-dimethylheptan-1-al was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 6-methoxy-2,6-dimethylheptan-1-al does not present a concern for genotoxic potential, and this can be extended to methoxycitronellal.

**Additional References:** RIFM, 2013b.

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

#### *11.1.2. Repeated dose toxicity*

The MOE for methoxycitronellal 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 methoxycitronellal. Read-across material 3,5,5-trimethylhexanal (CAS # 5435-54-3; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. A 28-day OECD/GLP 407 subchronic oral toxicity study was conducted in Wistar rats. Groups of 5 rats/sex/dose were administered the test material 3,5,5-trimethylhexanal via oral gavage at doses of 0, 50, 150, or 500 mg/kg/day for 28 days. Post-exposure satellite groups were also assigned to the control and high-dose groups to serve as the 14-day treatment-free recovery groups.

Treatment-related clinical signs of piloerection and squatting/hunchback position were observed in the male and female high-dose group after the administration of the test material at 500 mg/kg/day. Two female animals of the high-dose groups died overnight and were subsequently replaced by substitutes. The highest dose was reduced to 250 mg/kg/day as a result of mortality and adverse clinical signs. After the reduction of the high dose to 250 mg/kg/day, only animals of this dose group showed clinical signs on the second day. On the third day, one female of the high-dose group died, most likely as a result of the administration of 500 mg/kg/day on the first day of the study. During the recovery period, no clinical signs were observed in the high-dose group (250 mg/kg/day). There was also a statistically significant decrease in body weight and a slightly reduced group mean weekly bodyweight in high-dose females at the end of the treatment period; however, these findings were reversible in the recovery groups. Centrilobular hypertrophy of the liver in correlation with statistically significantly higher relative and absolute liver weights and focal periportal vacuolation in treated females were considered to be treatment-related. However, histopathological examination of the livers did not reveal any signs of degenerative or necrotic changes of hepatocytes. The liver changes observed were considered to be an expression of a reversible adaptive response to the test material and were not deemed as an adverse effect. Thus, the NOAEL for repeated dose toxicity was considered to be 250 mg/kg/day, the highest dose tested (ECHA, 2011).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 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 250/3 or 83 mg/kg/day.

Therefore, the methoxycitronellal MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,5,5-trimethylhexanal NOAEL in mg/kg/day by the total systemic exposure for methoxycitronellal, 83/0.0051, or 16275.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic reference dose (RfD) of 0.83 mg/kg/day.

*11.1.2.2. Derivation of subchronic RfD.* The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 × ) and intra-species (10 × ) differences. The subchronic RfD for methoxycitronellal was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 83 mg/kg/day by the uncertainty factor, 100 = 0.83 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 methoxycitronellal 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 methoxycitronellal. Read-across material 2-methylundecanal (CAS # 110-41-8; see Section VI) has sufficient 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, 15000 ppm (Equivalent to 147, 477, 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 as compared to 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).

In 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, 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 (which was specifically designed to analyze prenatal developmental toxicity) and was considered to be 1350 mg/kg/day.

Therefore, the methoxycitronellal 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 methoxycitronellal, 1350/0.0051 or 264706.

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, 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 methoxycitronellal MOE for the fertility endpoint can be calculated by dividing the 2-methylundecanal NOAEL in mg/kg/day by the total systemic exposure for methoxycitronellal, 991/0.0051 or 194314.

**Additional References:** None.

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

**Table 1**
Data summary for 6-methoxy-2,6-dimethylheptan-1-al as read-across for methoxycitronellal.

| 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$^2$ |
| 6000 [1] | Weak | 5905 | N/A | N/A | 5900 |

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.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

*11.1.4. Skin sensitization*

Based on the existing data and read-across 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2), methoxycitronellal is considered a skin sensitizer with a defined NESIL of 5900 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Limited skin sensitization studies are available for methoxycitronellal. Based on the available data and read-across 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2; see Section VI), methoxycitronellal is considered a sensitizer with a defined NESIL of 5900 μg/cm$^2$. The chemical structure of these materials indicate that they would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across 6-methoxy-2,6-dimethylheptan-1-al was found to be positive in *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and human cell line activation test (h-CLAT) (RIFM, 2016d; RIFM, 2020; RIFM, 2017). In a murine local lymph node assay (LLNA), methoxycitronellal was found not to be sensitizing when tested up to 50% (12500 μg/cm$^2$) (RIFM, 2014c). In another LLNA, read-across 6-methoxy-2,6-dimethylheptan-1-al was not found to be sensitizing when tested up to 50% (12,500 μg/cm$^2$) (RIFM, 2012). However, in an additional LLNA, read-across 6-methoxy-2,6-dimethylheptan-1-al was found to be sensitizing with an EC3 value of 24% (6000 μg/cm$^2$) (RIFM, 2010). A human maximization test was inconclusive with 10% methoxycitronellal (RIFM, 1975a). In a Confirmation of No Induction in Humans test (CNIH) with 5905 μg/cm$^2$ of read-across 6-methoxy-2,6-dimethylheptan-1-al in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 106 volunteers (RIFM, 2015b).

The weight of evidence (WoE) from the available data and read-across analog 6-methoxy-2,6-dimethylheptan-1-al demonstrate that methoxycitronellal is a weak sensitizer with a WoE NESIL of 5900 μg/cm$^2$ (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 0.83 mg/kg/day.

**Additional References:** RIFM, 1975b; RIFM, 1964.

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

*11.1.5. Phototoxicity/Photoallergenicity*

Based on the available UV/Vis spectra, methoxycitronellal 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 methoxycitronellal 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, 2009). Based on the lack of absorbance, methoxycitronellal 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, 2009).

**Additional References:** None.

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

*11.1.6. Local respiratory toxicity*

There are no inhalation data available on methoxycitronellal; however, in a two-week inhalation study for the analog hydroxycitronellal (CAS # 107-75-5; see Section VI), a NOAEC of 70 mg/m$^3$ was reported (RIFM, 2013a).

*11.1.6.1. Risk assessment.* The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week, nose-only inhalation study conducted in rats, a NOAEC of 70 mg/m$^3$ was reported for hydroxycitronellal (RIFM, 2013a). The target exposure concentrations were 0.70, 7.0, and 70 mg/m$^3$, and the overall mean exposure concentrations were 0.84, 6.4, and 73 mg/m$^3$. Clinical observations were recorded prior to, during, and post-exposure. At necropsy, bronchoalveolar lavage was performed for cytokine analysis, and lung tissue was collected for histopathology (5 animals/sex/group). Additionally, hematology and serum chemistry were considered (5 animals/sex/group). All parameters examined and measured were unaffected by material exposure; however, there was an accumulation of yellow material on the body surface of females in the highest concentration group (70 mg/m$^3$). This was considered a non-adverse clinical observation. Therefore, the NOAEC was determined to be 70 mg/m$^3$, the highest exposure concentration tested.

This NOAEC expressed in mg/kg lung weight/day is:

- (70 mg/m$^3$) × (1 m$^3$/1000 L) = 0.070 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.070 mg/L) × (61.2 L/d) = 4.28 mg/day
- (4.28 mg/day)/(0.0016 kg lung weight of rat**) = 2675 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.024 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (RIFM, 2015a; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.037 mg/kg lung weight/day resulting in a MOE of 72297 (i.e., [2675 mg/kg lung weight/day]/[0.037 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.024 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

**Additional References:** Troy (1977); RIFM, 2003b; RIFM, 2002; RIFM, 2003c; Isola (2002); Rogers (2003a); RIFM, 2003d; RIFM, 2003a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola (2004a); Rogers (2005); RIFM, 1972; Vethanayagam (2013); RIFM, 2014a.

**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 methoxycitronellal was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log $K_{OW}$, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA 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, methoxycitronellal 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) identified methoxycitronellal as possibly being persistent but not 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

#### 11.2.2. Risk assessment

Based on the current Volume of Use (2015), methoxycitronellal 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.* Methoxycitronellal has been registered for REACH, with no additional data available 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.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | <u>49.6</u> | | | 1000000 | 0.0496 | |

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

| Exposure | Europe | North America |
|---|---|---|
| Log $K_{ow}$ Used | 2.81 | 2.81 |
| 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 0.0496 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.

## Declaration of competing interest

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

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113133.

## Appendix

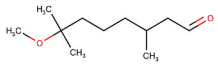
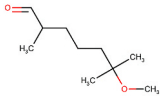
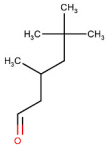
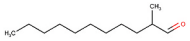
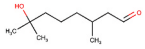
*Read-across Justification*

*Methods*

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). 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 | Read-across Material |
|---|---|---|---|---|---|
| **Principal Name** | Methoxycitronellal | 6-Methoxy-2,6-dimethylheptan-1-al | 3,5,5-Trimethylhexanal | 2-Methylundecanal | Hydroxycitronellal |
| **CAS No.** | 3613-30-7 | 62439-41-2 | 5435-64-3 | 110-41-8 | 107-75-5 |
| **Structure** |  |  |  |  |  |
| **Similarity (Tanimoto Score)** | | 0.89 | 0.42 | 0.49 | 0.83 |
| **Endpoint** | | • Genotoxicity<br>• Skin sensitization | • Repeated dose toxicity | • Reproductive toxicity | • Local respiratory toxicity |
| **Molecular Formula** | $C_{11}H_{22}O_2$ | $C_{10}H_{20}O_2$ | $C_9H_{18}O$ | $C_{12}H_{24}O$ | $C_{10}H_{20}O_2$ |
| **Molecular Weight (g/mol)** | 186.295 | 172.268 | 142.242 | 184.323 | 172.268 |
| **Melting Point (°C, EPI Suite)** | 4.79 | −6.46 | −35.47 | 3.24 | 23.36 |
| **Boiling Point (°C, EPI Suite)** | 224.38 | 205.16 | 173.00 | 171.00 | 241.00 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 1.40E+01 | 3.72E+01 | 1.07E+01 | 1.99E+02 | 7.73E-01 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 2.03E+02 | 6.24E+02 | 1.89E+02 | 5.37E+00 | 3.04E+03 |
| **Log KOW** | 2.81 | 2.32 | 3.09 | 4.67 | 2.11 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 6.42 | 13.14 | 19.97 | 0.87 | 45.87 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 7.76E-01 | 5.85E-01 | 5.00E+01 | 1.17E+02 | 2.42E-03 |
| ***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 | Schiff Base Formers\|Schiff Base Formers ≫ Direct Acting Schiff Base Formers\|Schiff Base | | | |

(*continued on next page*)

(*continued*)

| | Target Material | Read-across Material | Read-across Material | Read-across Material | Read-across Material |
|---|---|---|---|---|---|
| | Acting Schiff Base Formers ≫ Mono-carbonyls | 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 | See Supplemental Data 5 |

*Summary*

There are insufficient toxicity data on methoxycitronellal (CAS # 3613-30-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 6-methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2), 3,5,5-trimethylhexanal (CAS # 5435-64-3), 2-methylundecanal (CAS # 110-41-8), and hydroxycitronellal (CAS # 107-75-5) were identified as read-across material with sufficient data for toxicological evaluation.

*Conclusions*

- 6-Methoxy-2,6-dimethylheptan-1-al (CAS # 62439-41-2) was used as a read-across analog for the target material methoxycitronellal (CAS # 3613-30-7) for the genotoxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the class of aldehydes.
  - o The target material and the read-across analog share a common aliphatic branched aldehyde fragment.
  - o The key difference between the target material and the read-across analog is that the target has an octane fragment while the read-across has a heptane fragment. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by an aliphatic branched aldehyde fragment. 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 comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog and target material are predicted to have DNA binding alerts by OECD for genotoxicity, carcinogen alerts by ISS, and are classified as aldehydes. All the other alerts are negative. Data superseded predictions in this case.
  - o In addition, the read-across analog and the target material are also predicted to have positive protein binding alerts by OASIS and OECD model for skin sensitization. All the other alerts for skin sensitization were predicted to be negative. Data superseded predictions in this case.
  - 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.
- 3,5,5-Trimethylhexanal (CAS # 5435-64-3) was used as a read-across analog for the target material methoxycitronellal (CAS # 3613-30-7) for the repeated dose toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of aldehydes.
  - o The target material and the read-across analog share a common aliphatic branched aldehyde fragment.
  - o The key difference between the target material and the read-across analog is that the target has a methoxy group attached which is absent in the read-across analog. 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. The Tanimoto score is mainly driven by an aliphatic branched aldehyde fragment. 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 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.
- 2-Methylundecanal (CAS # 110-41-8) was used as a read-across analog for the target material methoxycitronellal (CAS # 3613-30-7) for the reproductive toxicity endpoint.

- The target material and the read-across analog are structurally similar and belong to the class of aldehydes.
- The target material and the read-across analog share a common aliphatic branched aldehyde fragment.
- The key difference between the target material and the read-across analog is that the target material has a methoxy group attached which is absent in the read-across analog. 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.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by an aliphatic branched aldehyde fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Hydroxycitronellal (CAS # 107-75-5) was used as a read-across analog for the target material methoxycitronellal (CAS # 3613-30-7) for the local respiratory toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the class of aldehydes.
  - The target material and the read-across analog share a common aliphatic branched aldehyde fragment.
  - The key difference between the target material and the read-across analog is that the target has an additional ether functional group while the read-across has a tertiary hydroxy group in the structure. 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.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by an aliphatic branched aldehyde fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

*Explanation of Cramer Class*

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree.

Q1. Normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, divalent S? **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene (see explanation in Cramer et al., 1978)? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **Yes**
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? **No**
Q22. A common component of food? **No**
Q33. Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? **No, High (Class III)**

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