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# RIFM fragrance ingredient safety assessment, 4-methoxy-α-methylbenzenepropanal, CAS Registry Number 5462-06-6

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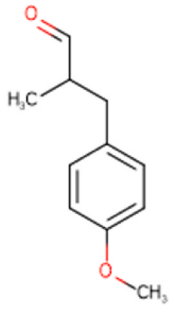
Name: 4-Methoxy-α-methylbenzenepropanal

CAS Registry Number: 5462-06-6



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

(*continued on next column*)

(*continued*)

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.**

4-Methoxy-α-methylbenzenepropanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4-methoxy-α-methylbenzenepropanal is not genotoxic. Data on 4-methoxy-α-methylbenzenepropanal provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provide 4-methoxy-α-methylbenzenepropanal a No Expected Sensitization Induction Level (NESIL) of 5900 μg/cm$^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 4-methoxy-α-methylbenzenepropanal is not phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 4-methoxy-α-methylbenzenepropanal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 4-methoxy-α-methylbenzenepropanal 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 genotoxic. | (RIFM, 2015c; RIFM, 2015g) |
| **Repeated Dose Toxicity:** NOAEL = 43 mg/kg/day. | RIFM, (2018b) |
| **Reproductive Toxicity:** Developmental toxicity: NOAEL = 289.5 mg/kg/day. Fertility: NOAEL = 389.9 mg/kg/day. | RIFM, (2018b) |
| **Skin Sensitization:** NESIL = 5900 μg/cm$^2$. | RIFM, (2008a) |
| **Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic. | (UV/Vis Spectra; RIFM Database; RIFM, 1979b) |

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

**Environmental Safety Assessment**

**Hazard Assessment:**

| | |
|---|---|
| **Persistence:** | |
| Critical Measured Value: 81% (OECD 301F) | RIFM, (2013b) |
| **Bioaccumulation:** | |
| Screening-level: 21.74 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Screening-level: Fish LC50: 404.7 mg/L | (EPI Suite v4.11; US EPA, 2012a) |

**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: 404.7 mg/L | (RIFM Framework; Salvito, 2002) |

**RIFM PNEC is:** 0.4047 μg/L

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

## 1. Identification

1. **Chemical Name:** 4-Methoxy-α-methylbenzenepropanal
2. **CAS Registry Number:** 5462-06-6
3. **Synonyms:** Benzenepropanal, 4-methoxy-α-methyl-; Canthoxal; p-Methoxy-α-methylhydrocinnamaldehyde; 3-(p-Methoxyphenyl)-2-methylpropionaldehyde; 2-Methyl-3-(p-methoxyphenyl)propanal; Fennaldehyde; 2-(p-Anisyl)propanal; 2-Anisylpropional; 2-Methyl-3-(4-methoxyphenyl)propionaldehyde; 3-(4-Methoxyphenyl)-2-methylpropanal; Hydrocinnamaldehyde, p-methoxy-a-methyl-; Foliaver; p-Methoxyhydratropaldehyde; 3 - ( 4 - メトキシフェニ

ル）- 2 - メチルプロパナール; 4-Methoxy-α-methylbenzenepropanal
4. **Molecular Formula:** $C_{11}H_{14}O_2$
5. **Molecular Weight:** 178.23 g/mol
6. **RIFM Number:** 1133
7. **Stereochemistry:** Stereoisomer not specified. One chiral center present, and 2 total enantiomers possible.

## 2. Physical data

1. **Boiling Point:** 533 K (260 °C) (RIFM, 2013c), 535±2 K (262±2 C) at 97.6 kPa (RIFM, 2005b), 199 °C (Fragrance Materials Association [FMA]), 264.35 °C (EPI Suite), 275 °C (548 K) at 1031 ± 1 hPa (RIFM, 2015f)
2. **Flash Point:** 134±2 °C (RIFM, 2005b), >93 °C (Globally Harmonized System), >200 °F; CC (FMA), 85 °C (RIFM, 2015f)
3. **Log $K_{OW}$:** 1.74 (RIFM, 2007), 2.5 at 25 °C (RIFM, 1996), 2.53 (EPI Suite)
4. **Melting Point**: less than 253±0.5 K (<-20±0.5 °C) (RIFM, 2005b), 34.71 °C (EPI Suite), less than −80 °C (<193K) (RIFM, 2015f)
5. **Water Solubility:** 1.08 g/L of solution at 20.0±0.5 °C (RIFM, 2007), 386.9 mg/L (EPI Suite)
6. **Specific Gravity:** 1.040 (FMA), 1.046 at 25 °C (RIFM)
7. **Vapor Pressure:** 0.00587 mm Hg at 20 °C (EPI Suite v4.0), 0.006 mm Hg at 20 °C (FMA), 0.0104 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** A clear liquid

## 3. Volume of use (Worldwide band)

1. 10–100 metric tons (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.29% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00039 mg/kg/day or 0.028 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0046 mg/kg/day (RIFM, 2019)

*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

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

## 7. Metabolism

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

## 8. Natural occurrence

4-Methoxy-α-methylbenzenepropanal 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

Available; accessed 11/01/21.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4-methoxy-α-methylbenzenepropanal 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) | 0.11 |
| 2 | Products applied to the axillae | 0.14 |
| 3 | Products applied to the face/body using fingertips | 0.75 |
| 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 | 0.11 |
| 7 | Products applied to the hair with some hand contact | 0.86 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.21 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 2.7 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 0.75 |
| 10B | Aerosol air freshener | 4.1 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to | 0.21 |

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(*continued*)

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| | skin from inert substrate (feminine hygiene pad) | |
| 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 4-methoxy-α-methylbenzenepropanal, the basis was the reference dose of 0.43 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, 4-methoxy-α-methylbenzenepropanal does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* 4-Methoxy-α-methylbenzenepropanal was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 4-methoxy-α-methylbenzenepropanal 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, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with 4-methoxy-α-methylbenzenepropanal 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, 2015c). Under the conditions of the study, 4-methoxy-α-methylbenzenepropanal was not mutagenic in the Ames test.

The clastogenic activity of 4-methoxy-α-methylbenzenepropanal 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 4-methoxy-α-methylbenzenepropanal in DMSO at concentrations up to 1600 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 450 μg/mL in the presence and absence of metabolic activation. 4-methoxy-α-methylbenzenepropanal 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, 2015g). Under the conditions of the study, 4-methoxy-α-methylbenzenepropanal was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 4-methoxy-α-methylbenzenepropanal does not present a concern for genotoxic potential.

**Additional References:** RIFM, 2017a.

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

#### 11.1.2. Repeated dose toxicity

The MOE for 4-methoxy-α-methylbenzenepropanal is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are sufficient repeated dose toxicity data on 4-methoxy-α-methylbenzenepropanal. In a GLP and OECD 422-compliant study, 12 Wistar Han rats/sex/dose were administered 4-methoxy-α-methylbenzenepropanal via diet at concentrations of 0, 600, 2000, and 6000 ppm (equivalent to doses of 0, 39.6, 129.7, and 389.9 mg/kg/day in males; and 0, 47.1, 161.4, and 451.3 mg/kg/day in females; according to the study report). Males were treated for approximately 6 weeks and females were treated for approximately 8 weeks. No mortality occurred throughout the study period. There were no treatment-related effects detected in clinical signs, behavioral assessment, functional performance, sensory reactivity, food consumption, water consumption, hematology, blood chemistry, or necropsy. Bodyweight gain and food conversion efficiency was reduced in males at the high dose; these effects were not related to palatability issues and thus were considered adverse. Absolute and relative spleen weights, as well as hematopoiesis in the spleen, were reduced in females at the high dose. Based on reduced body weight and food efficiency in males at 6000 ppm, as well as reduced spleen weights and hematopoiesis in females at 6000 ppm, the NOAEL for this study was considered to be 2000 ppm (equivalent to 129.7 mg/kg/day) (RIFM, 2018b).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 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 129.7/3 or 43 mg/kg/day.

Therefore, the 4-methoxy-α-methylbenzenepropanal MOE for the repeated dose toxicity endpoint can be calculated by dividing the 4-methoxy-α-methylbenzenepropanal NOAEL in mg/kg/day by the total systemic exposure to 4-methoxy-α-methylbenzenepropanal, 43/0.0046 or 9348.

In addition, the total systemic exposure to 4-methoxy-α-methylbenzenepropanal (4.6 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*11.1.2.1.1. Derivation of subchronic reference dose (RfD).* Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic RfD of 0.43 mg/kg/day.

The RIFM Criteria Document (Api, 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 4-methoxy-α-methylbenzenepropanal was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 43 mg/kg/day by the uncertainty factor, 100 = 0.43 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:** 03/10/21.

#### 11.1.3. Reproductive toxicity

The MOE for 4-methoxy-α-methylbenzenepropanal is adequate for the reproductive toxicity endpoint at the current level of use.

*11.1.3.1. Risk assessment.* There are sufficient reproductive toxicity data on 4-methoxy-α-methylbenzenepropanal. In a GLP and OECD 422-compliant study, 12 Wistar Han rats/sex/dose were administered 4-methoxy-α-methylbenzenepropanal via diet at concentrations of 0, 600,

2000, and 6000 ppm (equivalent to doses of 0, 39.6, 129.7, and 389.9 mg/kg/day in males; and 0, 47.1, 161.4, and 451.3 mg/kg/day in females; according to the study report). These concentrations were equivalent to doses of 0, 96.2, 289.5, and 859.8 mg/kg/day in females during lactation. Males were treated for approximately 6 weeks, and females were treated for approximately 8 weeks. No treatment-related effects were observed on the estrous cycle, mating performance, conception rates, or gestation lengths. There were no treatment-related effects on the mean number of implantations, post-implantation loss, litter size, sex ratio, or subsequent offspring survival. Offspring body weight, offspring bodyweight gain, and litter weights were reduced in females at the high dose. Based on reduced offspring body weights at the high dose, the developmental toxicity NOAEL was considered to be 2000 ppm (equivalent to 289.5 mg/kg/day). Based on no adverse effects on fertility up to the highest dose, the fertility NOAEL was considered to be 6000 ppm (equivalent to 389.9 mg/kg/day) (RIFM, 2018b).

Therefore, the 4-methoxy-α-methylbenzenepropanal MOE for the developmental toxicity endpoint can be calculated by dividing the 4-methoxy-α-methylbenzenepropanal NOAEL in mg/kg/day by the total systemic exposure to 4-methoxy-α-methylbenzenepropanal, 289.5/0.0046, or 62,934.

The 4-methoxy-α-methylbenzenepropanal MOE for the fertility endpoint can be calculated by dividing the 4-methoxy-α-methylbenzenepropanal NOAEL in mg/kg/day by the total systemic exposure to 4-methoxy-α-methylbenzenepropanal, 389.9/0.0046, or 84,760.

In addition, the total systemic exposure to 4-methoxy-α-methylbenzenepropanal (4.6 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

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

### 11.1.4. Skin sensitization

Based on the available data, 4-methoxy-α-methylbenzenepropanal is considered to be a skin sensitizer with a defined NESIL of 5900 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Based on the existing data, 4-methoxy-α-methylbenzenepropanal is considered to be a sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). 4-Methoxy-α-methylbenzenepropanal was found to be negative in an *in vitro* Direct Peptide Reactivity Assay, but positive in KeratinoSens test and h-CLAT as well as U-Sens tests (RIFM, 2015e; RIFM, 2015d; RIFM, 2018a; RIFM, 2015b). In a murine local lymph node assay (LLNA), 4-methoxy-α-methylbenzenepropanal was found to be sensitizing with an EC3 value of 23.6% (5900 μg/cm$^2$) (RIFM, 2004). In guinea pig maximization tests (GMPTs), 4-methoxy-α-methylbenzenepropanal was found to be sensitizing at the high dose, but no reactions were observed at the lower dose (RIFM, 1999; RIFM, 1976). In a confirmatory human maximization test, no skin sensitization reactions were observed (RIFM, 1980a). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 5906 μg/cm$^2$ of 4-methoxy-α-methylbenzenepropanal in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 104 volunteers (RIFM, 2008a). Based on the available data, summarized in Table 1, 4-methoxy-α-methylbenzenepropanal is considered to be a weak skin sensitizer with a defined NESIL of 5900 μg/cm$^2$.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic RfD of 0.43 mg/kg/day.

**Additional References:** RIFM, 1965; RIFM, 1979a; RIFM, 1979b; RIFM, 1980b; RIFM, 1965.

**Literature Search and Risk Assessment Completed On:** 04/18/21.

**Table 1**
Data summary for 4-methoxy-α-methylbenzenepropanal.

| 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$^2$ |
| 5900 [a] | Weak | 5905 | 1380 | NA | 5900 |

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.

21.

### 11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available human study data, 4-methoxy-α-methylbenzenepropanal would not be expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.1. Risk assessment.* 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). The phototoxic and photoallergenic potential of 4-methoxy-α-methylbenzenepropanal was evaluated in human volunteers at a concentration of 10% (RIFM, 1979b). No phototoxic or photoallergenic reactions were seen in any of the volunteers. Based on the human study data and the lack of absorbance, 4-methoxy-α-methylbenzenepropanal 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:** 04/14/21.

### 11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-methoxy-α-methylbenzenepropanal 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 4-methoxy-α-methylbenzenepropanal. Based on the Creme RIFM Model, the inhalation exposure is 0.028 mg/day. This exposure is 50.0 times lower than the Cramer Class I TTC value of 1.4 mg/day based on human lung weight of 650 g (Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/16/21.

## 11.2. Environmental endpoint summary

### 11.2.1. Screening-level assessment

A screening-level risk assessment of 4-methoxy-α-methylbenzenepropanal 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, 4-methoxy-α-methylbenzenepropanal was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 4-methoxy-α-methylbenzenepropanal 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, 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.

**RIFM, 2013b:** The purpose of this study was to assess the ready biodegradability of the test material with a manometric respirometry test according to the OECD 301F guidelines. Under the conditions of this study, biodegradation of 81% was observed.

**RIFM, 2005a:** The ready biodegradability of the test material was evaluated according to the OECD 301D method. Biodegradation of 50% was observed after 28 days.

**RIFM, 2008b:** The biodegradability of the test material was evaluated in a closed-system oxygen consumption measuring apparatus, and the biochemical oxygen demand (BOD) was measured over a 28-day period. Under the conditions of the study, the average biodegradation by BOD was 80%.

*11.2.2.1.2. Ecotoxicity.* **RIFM, 2017b:** An acute fish (*Oncorhynchus mykiss*) toxicity test was conducted according to the OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on the mean measured concentration was reported to be 5.2 mg/L.

**RIFM, 2016a:** A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 12 mg/L.

**RIFM, 2016b:** An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 based on time-weighted average concentrations was 21 mg/L for growth rate and 7.1 mg/L for yield.

*11.2.2.1.3. Other available data.* 4-Methoxy-α-methylbenzenepropanal has been registered for REACH, with no additional information available at this time.

### 11.2.3. Risk assessment refinement

Since 4-methoxy-α-methylbenzenepropanal has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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>404.7</u> | | | 1000000 | 0.4047 | |

### 11.2.2. Risk assessment

Based on the current Volume of Use (2015), 4-methoxy-α-methylbenzenepropanal presents no risk to the aquatic compartment in the screening-level assessment.

#### 11.2.2.1. Key studies

*11.2.2.1.1. Biodegradation.* **RIFM, 1998:** The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F guidelines. The test material underwent 67% biodegradation in 34 days (47% after 28 days).

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 1.74 | 1.74 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 10–100 | 10–100 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

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

The RIFM PNEC is 0.4047 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:** 04/22/21.

## 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 11/09/21.

## 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.

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