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Short Review

RIFM fragrance ingredient safety assessment, cuminic aldehyde, CAS Registry Number 122-03-2

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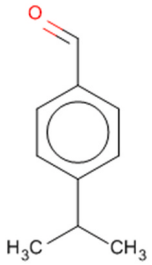
Version: 033020. This version replaces any previous versions

Name: Cuminic aldehyde CAS
Registry Number: 122-03-2



Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding

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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 Observable 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 RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 (*i.e.,* SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria such as, acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, *etc.* A key study for each endpoint was selected based on the most conservative endpoint value (*e.g.,* PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
Cuminic aldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog benzaldehyde (CAS # 100-52-7) show that cuminic aldehyde is not expected to be genotoxic. The repeated dose toxicity and developmental and reproductive toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to cuminic aldehyde is below the TTC (0.03 mg/kg/day and 0.03 mg/kg/day, respectively). Data on cuminic aldehyde provided a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm^2 for the skin sensitization endpoint. For the local respiratory endpoint, a calculated MOE > 100 was provided by the read-across analog benzaldehyde (CAS # 100-52-7). The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; cuminic aldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cuminic aldehyde was not found to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Cuminaldehyde; ECHA, 2017; RIFM, 2009)
Repeated Dose Toxicity: Exposure is below the TTC.	
Developmental and Reproductive Toxicity: Exposure is below the TTC.	
Skin Sensitization: NESIL = 1100 μg/cm^2.	RIFM (2012a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database; Forbes et al., 1977; RIFM, 1972a)
Local Respiratory Toxicity: NOAEC = 217 mg/m^3.	(ECHA REACH Dossier: Cuminaldehyde; ECHA, 2017; Laham et al., 1991)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Data: 86% (OECD 301F)	(ECHA REACH Dossier: Cuminaldehyde; ECHA, 2017)
Bioaccumulation: Screening-level: 57.02 L/kg	(ECOSAR; US EPA, 2012b)
Ecotoxicity: Screening-level: Fish LC50: 40.2 mg/L	Salvito et al. (2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1	Salvito et al. (2002)
Critical Ecotoxicity Endpoint: Fish LC50: 40.2 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0402 μg/L	

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

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1. Identification

1. **Chemical Name:** Cuminic aldehyde
2. **CAS Registry Number:** 122-03-2
3. **Synonyms:** Benzaldehyde, 4-(1-methylethyl)-; Cumaldehyde; Cuminal; Cuminaldehyde; Cuminic aldehyde; 4-Isopropylbenzenecarboxaldehyde; *p*-Isopropylbenzaldehyde; ｸﾐﾝｱﾙﾃﾞﾋﾄﾞ; 4-Isopropylbenzaldehyde
4. **Molecular Formula:** $C_{10}H_{12}O$
5. **Molecular Weight:** 148.2
6. **RIFM Number:** 355

2. Physical data

1. **Boiling Point:** 236 °C (FMA), 228.34 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA)
3. **Log K_{OW}:** 3.17 (EPI Suite)
4. **Melting Point**: 7.45 °C (EPI Suite)
5. **Water Solubility:** 152.8 mg/L (EPI Suite)
6. **Specific Gravity:** 0.978 (FMA)
7. **Vapor Pressure:** 0.0379 mm Hg @ 20 °C (EPI Suite v4.0), 0.07 mm Hg 20 °C (FMA), 0.0587 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid which has a pungent, green-herbaceous odor with notes of animal and vegetable character at the same time

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0023% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000020 mg/kg/day or 0.0014 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015, 2017; Safford et al., 2015, 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 v2.6	OECD QSAR Toolbox v3.2
I	I	I

2 .Analogs Selected:
   a. **Genotoxicity:** Benzaldehyde (CAS # 100-52-7)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Benzaldehyde (CAS # 100-52-7)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment.

8. Natural occurrence (discrete chemical) or composition (NCS)

Cuminic aldehyde is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Angelica (*Angelica archangelica* L.)

Beans	Ginger (*Zingiber* species)
Beef	Grape brandy
Calabash nutmeg (*Monodora myristica* Dunal)	Honey
Calamus (sweet flag) (*Acorus calamus* L.)	Katsuobushi (dried bonito)
Cardamom (*Ellettaria cardamomum* Maton.)	Lemon balm (*Melissa officinalis* L.)
Cinnamomum species	Lovage (*Levisticum officinale* Koch)
Citrus fruits	Macadamia nut (*Macadamia integrifolia*)
Cloves (*Eugenia caryophyllata Thunberg*)	*Mangifera* species
Cumin seed (*Cuminum cyminum* L.)	Mastic (*Pistacia lentiscus*)
Curcuma species	Nutmeg (*Myristica fragrans* Houttuyn)
Dill (*Anethum* species)	Origanum (Spanish) (*Coridothymus cap.* (L.) Rchb.)
Eucalyptus oil (*Eucalyptus globulus Labill*)	Parsley (*Petroselium* species)
Pistacia atlantica	Turpentine oil (*Pistacia terebinthus*)
Sweet marjoram (*Origanum majorana* L.)	Wild marjoram (*Origanum vulgare* L.)
Thyme (*Thymus* species)	Wormwood oil (*Artemisia absinthium* L.)

* 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 04/05/19.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for cuminic aldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.085
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.51
4	Products related to fine fragrances	0.47
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.12
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.12
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.12
6	Products with oral and lip exposure	0.28
7	Products applied to the hair with some hand contact	0.96
8	Products with significant ano-genital exposure (tampon)	0.05
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.92
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.3
10B	Aerosol air freshener	3.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.8
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted

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 cuminic aldehyde, the basis a skin sensitization NESIL of 1100 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).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current data, cuminic aldehyde does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of cuminic aldehyde was assessed in an Ames study 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 cuminic aldehyde at 0, 50, 150, 500, 1500, and 5000 μg/plate in the presence and absence of an exogenous metabolically active mixture (S9). No increase in the number of revertant colonies was observed in the tester strains at any concentration (ECHA, 2017). Under the conditions of the study, cuminic aldehyde is not mutagenic in bacteria.

There are no studies assessing the clastogenic potential of cuminic aldehyde. The read-across material benzaldehyde (CAS # 100-52-7; see Section VI) has been extensively studied in *in vitro* assays with varying results. Benzaldehyde was found to be positive in 2 sister chromatid exchange studies (Galloway et al., 1987; Jansson et al., 1988). Benzaldehyde was considered to be negative in one chromosomal aberration study (Galloway et al., 1987), while it produced a positive result in another chromosomal aberration study (Matsuoka et al., 1998). In a report by McGregor et al., benzaldehyde induced significant increases in mutation frequency in mouse lymphoma LY5178Y cells without S9 only at doses close to toxic levels (McGregor et al., 1991). Benzaldehyde was also found to give a positive result when tested in an *in vitro* COMET assay (Demir et al., 2010). To clarify the mixed *in vitro* results, benzaldehyde was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female NMRI mice. Doses of 200, 500, and 1000 mg/kg were administered. Mice from each dose level were euthanized at 24 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. Additionally, bone marrow was assessed at 48 h at the highest dose of 1000 mg/kg. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2009). Under the conditions of the study, benzaldehyde was considered to be not clastogenic in the *in vivo* micronucleus test.

In the FEMA GRAS assessment of benzyl derivatives used as flavor ingredients, benzaldehyde and 34 structurally-related substances were evaluated for safety. It was concluded that the group of benzyl derivatives is not genotoxic *in vivo* (Adams et al., 2005).

Based on the available data, benzaldehyde does not present a concern for genotoxic potential, and this can be extended to cuminic aldehyde.

Additional References: NTP, 1990; Kasamaki et al. (1982); Rockwell and Raw, (1979); Florin et al. (1980); Rapson et al. (1980); Haworth et al. (1983); Woodruff et al. (1985); Sofuni et al. (1985); Sasaki and Endo, (1978); Heck et al. (1989); Galloway et al. (1987); Jansson et al. (1988); Nohmi et al. (1985); Vamvakas et al. (1989); Matsui et al. (1989); Sasaki et al. (1989); McGregor et al. (1991); Dillon et al. (1992a); Dillon et al. (1998); Gee et al. (1998); Becker et al. (1996); Ono et al. (1991); Dillon et al. (1992b); RIFM, 1982; RIFM, 1983; Zeiger and Margolin, (2000); Kubo et al. (2002); Nambata et al. (1980); Miller et al. (2005); Pettersen et al. (1983); Matsuoka et al. (1998); RIFM, 2010; Demir et al. (2010); RIFM, 2012c; RIFM, 2013; Rockwell and Raw, (1979); Sasaki et al. (1989).

Literature Search and Risk Assessment Completed On: 06/11/17.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on cuminic aldehyde or any of the read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to cuminic aldehyde (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/20/17.

11.1.3. Developmental and reproductive toxicity

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

11.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on cuminic aldehyde or any of the read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to cuminic aldehyde (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/20/17.

11.1.4. Skin sensitization

Based on the available data, cuminic aldehyde is considered to be a weak skin sensitizer with a defined NESIL of 1100 μg/cm^2.

11.1.4.1. Risk assessment. Based on the available data, cuminic aldehyde is considered to be a weak skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD Toolbox v3.4). Cuminic aldehyde was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) and h-CLAT test, but negative in a KeratinoSens test. In 4 different guinea pig tests (open epicutaneous test, guinea pig maximization test, Draize test, and Freund's complete adjuvant test), cuminic aldehyde was found to be sensitizing, although limited study details were provided. Thus, cuminic aldehyde was tested in a murine local lymph node assay (LLNA) but was found to be non-sensitizing up to 10% (2500 μg/cm^2) (RIFM, 2012b). In 2 separate human maximization tests, each conducted on 25 subjects, no reactions indicative of sensitization were observed with 4% cuminic aldehyde (2760 μg/cm^2) (RIFM, 1972b; RIFM, 1975). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 1181 μg/cm^2 of cuminic aldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2012a). Based on the available data, cuminic aldehyde is considered to be a weak skin sensitizer with a defined NESIL of 1100 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. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf).

Table 1
Data Summary for cuminic aldehyde.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
> 2500 [1]	Weak	1181	2760	NA	1100

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

Additional References: Klecak (1985).

Literature Search and Risk Assessment Completed On: 06/09/17.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra and existing data, cuminic aldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV spectra indicate minor absorbance in the critical range of 290–700 nm; the molar absorption coefficient is below the benchmark of concern for phototoxicity (Henry et al., 2009). The phototoxic potential of 100% cuminic aldehyde was evaluated in hairless mice and miniature swine, and there were no observed effects (Forbes et al., 1977; RIFM, 1972a). Based on UV/Vis absorbance and the available *in vivo* studies, cuminic aldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV Spectra Analysis. UV/Vis absorption spectra (OECD TG 101) for cuminic aldehyde were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/15/17.

11.1.6. Local Respiratory Toxicity

There are no inhalation data available on cuminic aldehyde. However, in a 2-week, repeat-dose inhalation study of the read-across analog benzaldehyde (CAS # 100-52-7; see Section VI), a lowest observed adverse effect level (LOAEC) of 2170 mg/m^3 was reported (ECHA, 2011; data also available in Laham et al., 1991).

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. A 2-week, repeat-dose whole-body inhalation study was conducted by exposing male and female rats (14/sex/group) for 6 h/day to 500 ppm, 750 ppm, and 1000 ppm (equivalent to 2170, 3255, and 4340 mg/m^3, respectively) of benzaldehyde (ECHA, 2011; Laham et al., 1991). Observations of clinical signs, body weight, core temperature, necropsy, and histopathology were conducted. Additionally, various hematology and biochemical parameters were evaluated. Histopathological examination of tissues from exposed rats showed goblet cell metaplasia that was largely confined to the respiratory epithelial lining of the nasal septum in male rats. This change was noted in males exposed to 500 or 1000 ppm (equivalent to 2170 or 4340 mg/m^3, respectively) of benzaldehyde (similar incidence and severity at both concentrations). There were no treatment-related changes in females. No other abnormal microscopic changes were observed. A NOAEC was not derived due to the presence of treatment-related effects in all treatment groups.

A LOAEC of 500 ppm (equivalent to 2170 mg/m^3) was reported for benzaldehyde (ECHA, 2011). By applying a safety factor of 10 to the LOAEC, a NOAEC of 50 ppm (217 mg/m^3) has been established.

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

- (217 mg/m^3) × (1 m^3/1000L) = 0.217 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

- (0.217 mg/L) × (61.2 L/d) = 13.3 mg/day
- (13.3 mg/day)/(0.0016 kg lung weight of rat*) = 8312.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0014 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015; Safford et al., 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 et al., 2009) to give 0.0022 mg/kg lung weight/day resulting in an MOE of 3778409 (i.e., [8312.5 mg/kg lung weight/day]/[0.0022 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 0.0014 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*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: Steinhagen and Barrow (1984); Babiuk et al. (1985); Price, (1977); Kutzman et al. (1980); Peresedov (1974); Duchamp (1982); Revial et al. (1982); Roth and Tansy (1972); UGCM, 1997; Buchbauer et al. (1993); Silver (1992); Buchbauer et al. (1992); Lacroix et al. (2000); Helmig et al. (1999a); Helmig et al. (1999b); Ferrari et al. (1998); Lacroix et al. (2002); Yang et al. (2005); Kutzman et al. (1978); Johnson et al. (2005); Hummel et al. (2003); Miyoshi et al. (2013); Regnault-Roger and Hamraoui (1995).

Literature Search and Risk Assessment Completed On: 03/19/19.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level Assessment

A screening-level risk assessment of cuminic aldehyde was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's VoU in a region, its log K_{ow}, and molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ration Predicted Environmental Concentration/Predicted No Effect Concentration or 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, cuminic aldehyde 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 cuminic aldehyde as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk Assessment

Based on the current Volume of Use (2015), cuminic aldehyde 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. Cuminic aldehyde has been registered under REACH and the following data is available:

The ready biodegradability of the test material was evaluated according to the OECD 301F method, and biodegradation of 86% was observed after 28 days (ECHA, 2017).

11.2.3. Risk Assessment Refinement

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (mg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>19.18</u>			1000000	0.019	

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.8	2.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.0402 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: 03/13/19

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**
- **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 01/22/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111498.

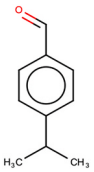
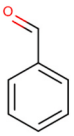
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemicals Agency (ECHA) read-across assessment framework or RAAF (ECHA, 2016).

- The materials were first clustered based on their structural similarity. In the second step, data availability and data quality on the selected cluster were examined. Finally, an appropriate read-across analog from the cluster was confirmed by using 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 analog were calculated using EPI Suite v4.11 developed by US EPA (US EPA, 2012a).
- J_{max} values were calculated using the RIFM skin absorption model (SAM); the parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat-dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental toxicity was estimated using CAESAR v.2.1.7 (Cassano et al., 2010), and skin sensitization was estimated using ToxTree 2.6.13.
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target material and read-across analog were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Cuminic aldehyde	Benzaldehyde
CAS No.	122-03-2	100-52-7
Structure		
Similarity (Tanimoto score)		0.66
Read-across Endpoint		• Genotoxicity • Local respiratory toxicity
Molecular Formula	$C_{10}H_{12}O$	C_7H_6O
Molecular Weight	148.2	106.12
Melting Point (°C, EPI Suite)	7.45	−21.97
Boiling Point (°C, EPI Suite)	228.34	181.22
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.82	135
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.17	1.48
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	152.8	6950
J_{max} (μg/cm^2/h, SAM)	48.066	201.376
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.65E+000	2.71E+000
Genotoxicity		
DNA Binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA Binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (Moderate reliability)	• Carcinogen (experimental value)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames test) Alerts by ISS**	• Simple aldehyde	• Simple aldehyde
***In vivo* Mutagenicity (Micronucleus) Alerts by ISS**	• Simple aldehyde	• Simple aldehyde
Oncologic Classification	• Aldehyde-type compounds	• Aldehyde-type compounds
Respiratory		
Respiratory Sensitization OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Metabolism		
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2
Rat liver S9 metabolism simulator and structural alerts for metabolites		

Summary

There are insufficient toxicity data on the target material cuminic aldehyde (CAS # 122-03-2). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analog benzaldehyde (CAS # 100-52-7) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Benzaldehyde (CAS # 100-52-7) was used as a read-across analog for the target material cuminic aldehyde (CAS # 122-03-2) for the genotoxicity and local respiratory endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aromatic aldehydes.
  - o The target material and the read-across analog share an aldehyde functional group and an aromatic ring.
  - o The key difference between the target material and the read-across analog is that the target material has an isopropyl substitution on the aromatic ring at the para position while the read-across material does not. This structure difference between the target material and the read-across analog does not affect consideration of these toxicity endpoints.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the table above. The Tanimoto score is mainly driven by the aldehyde functional group and aromatic ring fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - 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 QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have a carcinogenicity alert by the ISS model. Both substances also have *in vitro* and *in vivo* mutagenicity alerts and are classified as aldehyde-type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genotoxicity. Therefore, the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.

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