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Short review

RIFM fragrance ingredient safety assessment, 4-ethylbenzaldehyde, CAS Registry Number 4748-78-1

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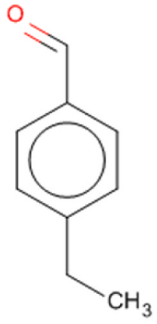
Version: 061019. This version replaces any previous versions.

Name: 4-Ethylbenzaldehyde
CAS Registry Number: 4748-78-1



Abbreviation/Definition List:

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

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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
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

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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 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-ethylbenzaldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data on the read-across analog benzaldehyde (CAS # 100-52-7) show that 4-ethylbenzaldehyde is not expected to be genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog 3,4-dimethylbenzaldehyde (CAS # 5973-71-7) provide a calculated MOE >100 for the developmental and reproductive toxicity endpoints. Data on read-across analog cuminaldehyde (CAS # 122-03-2) provided 4-ethylbenzaldehyde a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm^2. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on data; 4-ethylbenzaldehyde is not phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-ethylbenzaldehyde 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.	(ECHA REACH Dossier: 4-Ethylbenzaldehyde; ECHA, 2019; RIFM, 2009)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	NTP (1990)
Developmental and Reproductive Toxicity: NOAEL = 250 mg/kg/day and 1000 mg/kg/day, respectively.	(ECHA REACH Dossier: 3,4-Dimethylbenzaldehyde; ECHA, 2015)

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Skin Sensitization: Weak sensitizer. NESIL = 1100 μg/cm^2.	RIFM (2012a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	RIFM (1984)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.8 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 30.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 40.29 mg/L	Salvito (2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1	Salvito (2002)
Critical Ecotoxicity Endpoint: LC50: 40.29 mg/L	Salvito (2002)
RIFM PNEC is: 0.040 μg/L	

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

1. Identification

1. **Chemical Name:** 4-Ethylbenzaldehyde
2. **CAS Registry Number:** 4748-78-1
3. **Synonyms:** Benzaldehyde, 4-ethyl; *p*-Ethylbenzaldehyde; Ethyl benzaldehyde; 4-ｴﾁﾙﾍﾞﾝｽﾞｱﾙﾃﾞﾋﾄﾞ; 4-Ethylbenzaldehyde
4. **Molecular Formula:** $C_9H_{10}O$
5. **Molecular Weight:** 134.17
6. **RIFM Number:** 6278

2. Physical data

1. **Boiling Point:** 220.89 °C (EPI Suite)
2. **Flash Point:** 198.00 °F TCC (92.22 °C)*
3. **Log K_{OW}:** 2.75 (EPI Suite)
4. **Melting Point**: 7.14 °C (EPI Suite)
5. **Water Solubility:** 397.7 mg/L (EPI Suite)
6. **Specific Gravity:** 0.98000 to 1.00000 @ 25.00 °C*
7. **Vapor Pressure:** 0.0824 mm Hg @ 20 °C (EPI Suite v4.0), 0.1 mm Hg 20 °C (Fragrance Materials Association Database), 0.125 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with a peak at 250 nm and returning to baseline by 330 nm; molar absorption coefficient above the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic**: A colorless to pale-yellow, clear liquid with a medium, fruity, bitter, almond, sweet anise odor in a 10% or less solution of dipropylene glycol*.*http://www.thegoodscentscompany.com/data/rw1038111.html, retrieved 03/10/15.

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00027% (RIFM, 2017b)
2. **Inhalation Exposure*:** 0.0000055 mg/kg/day or 0.00039 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.00038 mg/kg/day (RIFM, 2017b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 5. 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, 2015, 2017; Safford, 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:** Benzaldehyde (CAS # 100-52-7)
   c. **Developmental and Reproductive Toxicity:** 3,4-Dimethylbenzaldehyde (CAS # 5973-71-7)
   d. **Skin Sensitization:** Cuminaldehyde (CAS # 122-03-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Laham et al., (1988): Data also available in ECHA REACH Dossier: Benzaldehyde key experimental results 2 (ECHA, 2011; accessed 08/12/17): Benzaldehyde was administered to 2 groups (high dose: 750 mg/kg/rabbit; low dose: 350 mg/kg/rabbit) of 3 male New Zealand White rabbits by gavage. Water was given orally to a third group. The urine of all groups was collected daily for 15 consecutive days. The quantitative metabolism of benzaldehyde was reported. Urinary metabolites were identified by GC-MS. Metabolites identified included hippuric acid (HA, 69.9% in the low-dose group vs. 66.7% in the high-dose group), free benzoic acid (FBA, 1.6% in the low-dose group vs. 1.4% in the high-dose group), and conjugated benzoic acid (benzoylglucuronic acid) (BGA, 8.8% in the low-dose group vs. 11.2% in the high-dose group), benzyl glucuronide (BG, 2.9% in the low-dose group vs. 3.0% in the high-dose group), and benzyl mercapturic acid (present in trace amounts). No free benzyl alcohol was reported in the urine of treated or control animals.

Chidgey (1986): The metabolism of benzyl acetate was investigated in male Fischer 344 rats. Rats were dosed by gavage with [methylene-(14)C] benzyl acetate (500 mg/kg) alone or together with metabolic inhibitors. Benzyl acetate is rapidly hydrolyzed to benzyl alcohol, which is oxidized to benzaldehyde and then further oxidized to benzoic acid. Benzoic acid is conjugated with glycine to yield the major urinary excretion product of hippuric acid, or it is conjugated with glucuronic acid to yield benzoyl glucuronide.

Yuan (1995): The effects of gavage versus dosed feed administration on the toxicokinetics of benzyl acetate were studied in male rats and mice. Benzyl acetate was rapidly hydrolyzed to benzyl alcohol and then oxidized to benzoic acid.

Adams (2005): The FEMA panel conducted a safety evaluation of benzyl derivatives as flavoring ingredients which included metabolism among other endpoints. In summary, the panel concluded that benzyl and benzoate esters and benzaldehyde acetals will be readily hydrolyzed to the corresponding parent alcohol, aldehyde, or acid. Following hydrolysis, benzyl alcohol will be sequentially oxidized to benzaldehyde and then benzoic acid. To a minor extent, benzyl alcohol may conjugate with glutathione, benzaldehyde may be reduced to benzyl alcohol, and benzoic acid may conjugate with glucuronic acid. At very high concentrations, benzoic acid may sequester significant quantities of acetyl CoA to form hippuric acid (see Fig. 1).

The QSAR rat liver metabolism simulator showed that 4-ethylbenzaldehyde and benzaldehyde are expected to be metabolized similarly (see the Appendix below and the supplemental data sheets).

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

4-Ethylbenzaldehyde is reported to occur in the following foods*:

- Capers (*Capparis spinoza*)
- Cashew apple (*Anacardium occidentale*)
- Chicken
- Cider (apple wine)
- Fish
- Honey
- Milk and milk products
- Peanut (*Arachis hypogaea* L.)
- Tea
- Trassi (cooked)
- Turkey

*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

https://echa.europa.eu/registration-dossier/-/registered-dossier/27052/1 Available; accessed 06/06/19.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4-ethylbenzaldehyde 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	0.040
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)	0.040

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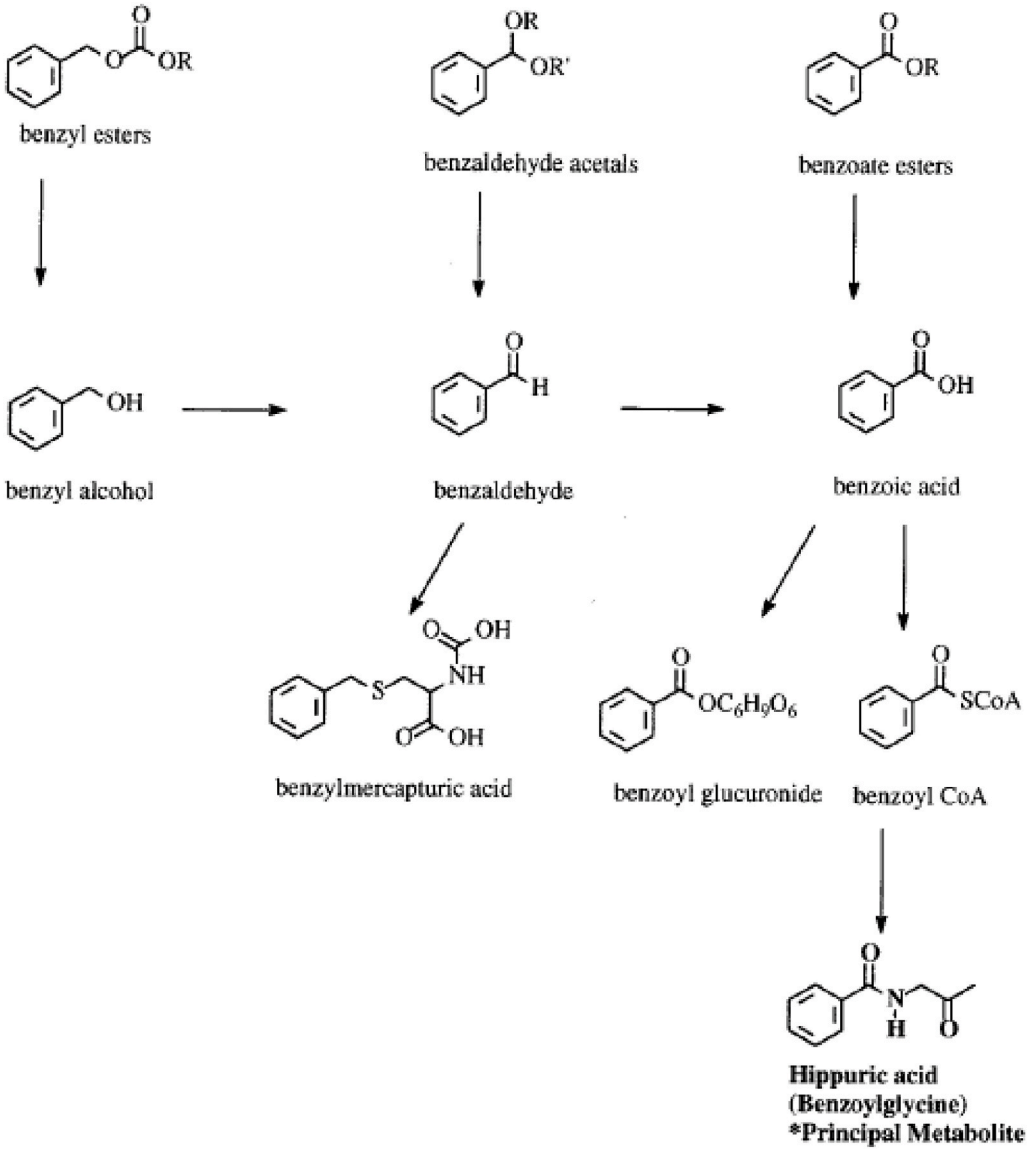


Fig. 1. (Adapted from Adams, 2005).

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
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)	0.92
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)	0.040
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-ethylbenzaldehyde, the basis was the reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 80%, and 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, 4-ethylbenzaldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 4-Ethylbenzaldehyde was assessed in the BlueScreen assay and found negative for cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013a).

The mutagenic activity of 4-ethylbenzaldehyde 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 4-ethylbenzaldehyde 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 (https://echa.europa.eu/registration-dossier/-/registered-dossier/27052/7/7/2 ECHA, 2019). Under the conditions of the study, 4-ethylbenzaldehyde was not mutagenic in the Ames test.

There are no studies assessing the clastogenic potential of 4-ethylbenzaldehyde. The read-across material benzaldehyde (CAS # 100-52-7; see Section 6) has been extensively studied in *in vitro* assays with varying results. Benzaldehyde was found to be positive in 2 sister chromatid exchange studies (Galloway, 1987; Jansson, 1988). Benzaldehyde was considered to be negative in 1 chromosomal aberration study (Galloway, 1987), while it produced a positive result in another chromosomal aberration study (Matsuoka, 1998). In a report by McGregor et al., benzaldehyde induced significant increases in mutation frequency in mouse lymphoma LY5178Y cells without S9 mix only at doses close to toxic levels (McGregor, 1991). Benzaldehyde also was found to give a positive result when tested in an *in vitro* COMET assay (Demir, 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 (PCEs). 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 PCEs 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.

Based on the available data, benzaldehyde does not present a concern for genotoxic potential, and this can be extended to 4-ethylbenzaldehyde.

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

Literature Search and Risk Assessment Completed On: 05/26/19.

11.1.2. Repeated dose toxicity

The MOE for 4-ethylbenzaldehyde 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 4-ethylbenzaldehyde.

The repeated dose toxicity of read-across material benzaldehyde (CAS # 100-52-7; see Section 6) has been extensively tested in rats and mice. In a 2-year carcinogenicity study, the NOAEL for repeated dose toxicity following daily oral gavage of the test material was determined to be 200 mg/kg/day, based on decreased survival of male rats (NTP, 1990). Therefore, the benzaldehyde MOE is equal to the benzaldehyde NOAEL in mg/kg/day divided by the total systemic exposure to benzaldehyde, 200/0.00038 or 526316.

In addition, the total systemic exposure to 4-ethylbenzaldehyde (0.38 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.

In the carcinogenicity study conducted by the US NTP with benzaldehyde, it was concluded that there was no evidence of carcinogenic activity in rats and some evidence of carcinogenic activity in mice, due to increased incidences of squamous cell papillomas and hyperplasia of the forestomach (NTP, 1990). These carcinogenicity data on benzaldehyde were thoroughly reviewed and determined to be not relevant to human health (FFHPVC, 2001). The occurrence of squamous cell papillomas and forestomach hyperplasia in rodents is common in gavage studies in which a high concentration of an irritating material in corn oil is delivered daily by needle into the forestomach for 2 years. Squamous cell papillomas are benign neoplasms of squamous epithelium, arise as a result of chronic irritation, and do not progress to squamous cell carcinomas. Additionally, this effect is not a concern for human health because the target organ is species-specific and arises via a non-genotoxic mechanism. The International Agency for Research on Cancer concluded that for carcinogens targeting the forestomach in rodents, "the relevance for humans is probably limited for agents that have no demonstrable genotoxicity and that are solely carcinogenic for the forestomach squamous epithelium in rodents after oral administration since the exposure conditions are quite different between the experimental animals and humans. Consequently, for these agents, the mode of carcinogenic action could be specific to the experimental animals" (https://pdfs.semanticscholar.org/185c/b541536aa4edb2c3e52ae1afd6be3c722d97.pdf IARC, 1999).

Derivation of reference dose (RfD)

Section 10 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, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 2.0 mg/kg/day.

The reference dose for 4-ethylbenzaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 2.0 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/01/17.

11.1.3. Developmental and reproductive toxicity

The MOE for 4-ethylbenzaldehyde is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 4-ethylbenzaldehyde. Read-across material, 3,4-dimethylbenzaldehyde (CAS # 5973-71-7; see Section 6) has sufficient developmental and reproductive toxicity data. An OECD/GLP 422 study was conducted on groups of 10 Sprague Dawley rats/sex/group. The rats were administered the test material at doses of 0 (polyethylene glycol), 50, 250, and 1000 mg/kg/day for a period of up to 46 consecutive days. High-dose females showed lower live-birth and viability indexes in comparison to controls due to the birth of less offspring per litter and a lower survival rate among offspring during the lactation period. At 1000 mg/kg/day, 14 pups were either missing or found dead at day 1 of lactation. In addition, 9 other pup deaths were observed throughout the remaining days of lactation. Offspring from the 1000 mg/kg/day dose group showed less successful completion of surface righting assessments. In addition, lower total litter weights and lower offspring body weight were reported at this dose level. These effects are thought to be a consequence of the impaired physical health of the females caused by irritation of the stomach. In addition, 3 high-dose litters had distension of the abdomen throughout the lactation period with one of these litters having gaseous distension of the stomach and intestines at necropsy.

Thus, the NOAEL for developmental toxicity was considered to be 250 mg/kg/day due to a reduction in the live-birth and viability indexes, lower offspring and litter weight, and 3 litters at the high-dose level also having gaseous distension of the abdomen. No adverse effect on mating performance, fertility, or gestation lengths was reported among treated animals. Thus, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (https://echa.europa.eu/registration-dossier/-/registered-dossier/12006/1 ECHA, 2015).

The 4-ethylbenzaldehyde MOE for the developmental toxicity endpoint can be calculated by dividing the NOAEL for 3,4-dimethylbenzaldehyde by the total systemic exposure to 4-ethylbenzaldehyde, 250/0.00038 or 657895.

The 4-ethylbenzaldehyde MOE for the reproductive toxicity endpoint can be calculated by dividing the NOAEL for 3,4-dimethylbenzaldehyde by the total systemic exposure to 4-ethylbenzaldehyde, 1000/0.00038 or 2631579.

In addition, the total systemic exposure to 4-ethylbenzaldehyde (0.38 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 11/07/17.

11.1.4. Skin sensitization

Based on the available data summarized for the read-across material cuminaldehyde (CAS # 122-03-2), 4-ethylbenzaldehyde is considered a weak skin sensitizer with a defined NESIL of 1100 μg/cm^2.

11.1.4.1. Risk assessment. Based on the available data and read-across to cuminaldehyde, 4-ethylbenzaldehyde is considered to be a weak skin sensitizer. 4-Ethylbenzaldehyde and cuminaldehyde are predicted to be directly reactive to skin proteins (Roberts, 2007; Toxtree v2.6.13). Cuminaldehyde was found to be positive in the *in vitro* direct peptide reactivity assay (DPRA) and human cell line activation test (h-CLAT) but negative in the KeratinoSens (RIFM, 2016; RIFM, 2017a). In 4 different guinea pig tests (Open Epicutaneous Test [OET], guinea pig maximization test [GPMT], Draize Test, and Freund's Complete Adjuvant Test [FCAT]), cuminaldehyde was found to be sensitizing, although limited study details were provided. Thus, cuminaldehyde 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% cuminaldehyde (2760 μg/cm^2) (RIFM, 1972; RIFM, 1975). In a human repeat insult patch test (HRIPT) with 41 subjects, the target material 4-ethylbenzaldehyde did not induce sensitization reactions at 2.5% or 1938 μg/cm^2 (RIFM, 1965). Additionally, in a confirmatory HRIPT with 1181 μg/cm^2 of the read-across material cuminaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 subjects (RIFM, 2012a).

Based on the available data summarized for the read-across material cuminaldehyde (CAS # 122-03-2; see Section 6) and summarized in the current IFRA Standard for 4-ethylbenzaldehyde, this material is considered to be a weak skin sensitizer with a defined NESIL of 1100 μg/cm^2 (see Table 1 below). Section 10 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, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 2.0 mg/kg/day.

Additional References: RIFM, 1984.

Literature Search and Risk Assessment Completed On: 05/04/17.

Table 1
Data summary for cuminaldehyde as read-across for 4-ethylbenzaldehyde.

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

NOEL = No observed effect level; HRIP = Human Repeat Insult Patch Tes; 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.

17.

11.1.5. Phototoxicity/photoallergenicity

Based on the existing data from a human study, 4-ethylbenzaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV spectra of 4-ethylbenzaldehyde indicate significant absorbance in the critical range of 290–700 nm, with peak absorbance at 250 nm and returning to baseline by 330 nm. The molar absorption coefficient is above the benchmark of concern for phototoxicity/photoallergenicity. The phototoxic and photoallergenic potential of 4-ethylbenzaldehyde was evaluated in human volunteers at a concentration of 2%, and no phototoxic or photoallergenic reactions were seen in any of the volunteers (RIFM, 1984). Based on data from the human study, 4-ethylbenzaldehyde 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) were generated for 4-ethylbenzaldehyde. The spectra demonstrate that the material absorbs in the range of 290–700 nm, with a peak at 250 nm and returning to baseline by 330 nm. The molar absorption coefficient for λ max within this range is above 1000 L mol^{-1} · cm^{-1}, the benchmark of concern for phototoxic effects (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/17/17.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-ethylbenzaldehyde 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-ethylbenzaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.00039 mg/day. This exposure is 3590 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: 03/28/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-ethylbenzaldehyde 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-ethylbenzaldehyde 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-ethylbenzaldehyde 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).

11.2.2. Risk assessment

Based on current VoU (2015), 4-ethylbenzaldehyde does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

Biodegradation. No data available.

Ecotoxicity. No data available.

Other available data. 4-Ethylbenzaldehyde has been registered under REACH, and the following additional data is available:

A fish (*Brachydanio rerio*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 was reported to be 23.4 mg/L (https://echa.europa.eu/registration-dossier/-/registered-dossier/27052/1 ECHA, 2019).

11.2.3. Risk assessment refinement

Since 4-ethylbenzaldehyde 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.75	2.75
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 the available data, the RQ for this class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.040 μg/L. The revised PEC/PNECs for EU and NA are not applicable and were cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 04/03/19.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	40.29			1000000	0.040	

appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 03/26/20.

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.2020.111700.

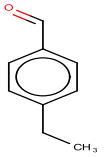
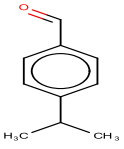
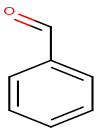
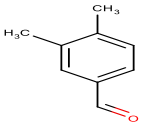
Appendix

Read-across Justification

Methods

The read-across analogs were 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, 2017).

- 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, appropriate read-across analogs from the cluster were 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 (US EPA, 2012a).
- J_{max} values were calculated using the RIFM skin absorption model (SAM), and 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 and skin sensitization were estimated using CAESAR v2.1.7 and 2.1.6, respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2018).

	Target Material	Read-across Material		
Principal Name	Benzaldehyde, 4-ethyl-	Cuminaldehyde	Benzaldehyde	3,4-dimethylbenzaldehyde
CAS No.	4748-78-1	122-03-2	100-52-7	5973-71-7
Structure				
Similarity (Tanimoto score)		0.88	0.71	0.62
Read-across endpoint		• Skin sensitization	• Genotoxicity • Repeated dose toxicity	• Developmental and reproductive toxicity
Molecular Formula	$C_9H_{10}O$	$C_{10}H_{12}O$	C_7H_6O	$C_9H_{10}O$
Molecular Weight	134.17	148.2	106.12	134.18
Melting Point (°C, EPI Suite)	7.14	7.45	−21.97	13.40
Boiling Point (°C, EPI Suite)	220.89	228.34	181.22	220.88
Vapor Pressure (Pa @ 25°C, EPI SUITE)	16.7	7.82	135	16.7
Log K_{ow}(KOWWIN v1.68 in EPI Suite)	2.75	3.17	1.48	2.80
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	397.7	152.8	6950	356.1
J_{max} (μg/cm^2/h, SAM)	74.643	48.066	201.376	32.451
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.99E+000	2.65E+000	1.36E+000	1.66E+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 (genotoxicity and non-genotoxicity) alerts (ISS)	• Carcinogen (moderate reliability)		• Carcinogen (experimental value)	

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material		
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	
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Styrene (Renal Toxicity) Alert • Toluene (Renal toxicity) Alert	
Developmental and Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2 group			• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (low reliability)			• Toxicant (low reliability)
Skin Sensitization				
Protein Binding by OASIS v1.1	• No alert found	• No alert found		
Protein Binding by OECD	• No alert found	• No alert found		
Protein Binding Potency	• Not possible to classify (GSH)	• Not possible to classify (GSH)		
Protein Binding Alerts for Skin Sensitization by OASIS v1.1	• No alert found	• No alert found		
Skin Sensitization Model (CAESAR) (v2.1.6)	• Non-sensitizer (good reliability)	• Sensitizer (good reliability)		
Metabolism				
OECD QSAR Toolbox (3.4) Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on the 4-ethylbenzaldehyde (CAS # 4748-78-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, cuminaldehyde (CAS # 122-03-2), benzaldehyde (CAS # 100-52-7), and 3,4-dimethylbenzaldehyde (CAS # 5973-71-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusion

- Cuminaldehyde (CAS 122-03-2) was used as a read-across analog for the target material 4-ethylbenzaldehyde (CAS # 4748-78-1) for the skin sensitization endpoint.
  - 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 a benzaldehyde fragment.
  - o The key difference between the target material and the read-across analog is that the target material has an ethyl substituent on the benzaldehyde fragment, whereas the read-across analog has an isopropyl group. This structural difference between the target material and the read-across analog does not affect consideration of the toxicity endpoint.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog is predicted to be a sensitizer with good reliability by the CAESAR model for skin sensitization, whereas the target material is predicted to be a non-sensitizer. Based on read-across data and structural similarity between the target material and the read-across material, the target material was considered a sensitizer.
  - 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 toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.
  - o Except for skin sensitization, the structural differences between the target material and the read-across analog were not toxicologically significant.
- Benzaldehyde (CAS # 100-52-7) was used as a read-across analog for the target material 4-ethylbenzaldehyde (CAS # 4748-78-1) for the genotoxicity and repeated dose toxicity 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 a benzaldehyde fragment.
  - o The key difference between the target material and the read-across analog is that the target material has an ethyl substituent on the benzaldehyde fragment, while there is no substituent on the read-across analog. This structural difference between the target material and the read-across analog is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.

- According to the QSAR OECD Toolbox (v3.4), structural alerts for the endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog have a carcinogenicity alert by the ISS model. Both substances also have *in vivo* and *in vitro* mutagenicity alerts and are classified as simple 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 shows that the read-across analog does not pose a concern for genotoxicity. Therefore, the alert was superseded by the availability of the data.
- The read-across analog has 2 alerts for the repeated dose toxicity endpoint, which are not present for the target material. These alerts are due to the structural similarity score (Dice) of the read-across analog with styrene and toluene above 0.5. The target material has a structural similarity score <0.5 due to 4-ethyl substitution. The data for the read-across analog confirms that the MOE is adequate at the current level of use. Therefore, the alert can be ignored.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.
- The structural differences between the target material and the read-across analog are toxicologically insignificant.

- 3,4-dimethylbenzaldehyde (CAS # 5973-71-7) was used as a read-across analog for the target material 4-ethylbenzaldehyde (CAS # 4748-78-1) for the developmental and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to the structural class of aromatic aldehydes.
  - The target material and the read-across analog share a benzaldehyde fragment.
  - The key difference between the target material and the read-across analog is that the target material has an ethyl substituent on the benzaldehyde fragment, while the read-across analog has 2 methyl substituents on the benzaldehyde fragment. This structural difference between the target material and the read-across analog is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. 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 a comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for the endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog have a developmental toxicity alert as toxicants. The data described in the developmental and reproductive toxicity section shows that the read-across analog does not pose a concern for reproductive toxicity. Therefore, the alert was superseded by the availability of the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are toxicologically insignificant.

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