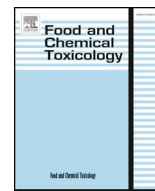




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Short Review

RIFM fragrance ingredient safety assessment, benzaldehyde, CAS Registry Number 100-52-7



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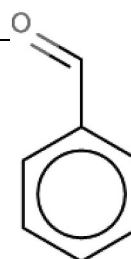
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Version: 031819. This version replaces any previous versions.

Name: Benzaldehyde

CAS Registry Number: 100-52-7

**Abbreviation/Definition List:**

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

AF - Assessment Factor

BCF - Bioconcentration Factor

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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; Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach **DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts

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
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015; #68218), 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.

Benzaldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, and environmental safety. Data show that benzaldehyde is not genotoxic. The repeated dose and local respiratory toxicity endpoints were evaluated using data on benzaldehyde, which provided an MOE > 100. The developmental and reproductive toxicity endpoint was completed using data on read-across analogs benzyl alcohol (CAS # 100-51-6) and benzoic acid (CAS # 65-85-0), which provided an MOE > 100. Data on benzaldehyde provided a NESIL of 590 µg/cm² for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; benzaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; benzaldehyde was found not 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 genotoxic.

(NTP, 1990; RIFM, 2009a)

Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.

NTP (1990)

Developmental and Reproductive Toxicity: NOAEL = 550 mg/kg/day and 500 mg/kg/day, respectively.

(Hardin et al., 1987; Kieckebusch and Lang, 1960)

Skin Sensitization: NESIL = 590 µg/cm².

RIFM (2009b)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.

(UV Spectra, RIFM Database)

Local Respiratory Toxicity: NOAEC = 217 mg/m³.

(ECHA Dossier: Benzaldehyde; ECHA, 2011a; Laham et al., 1991a)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.01 (BIOWIN 3)

(EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 4.4 L/kg

(EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: 96-h Fish LC50: 8.6 mg/L

(ECOSAR; US EPA, 2012b)

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: 96-h Fish LC50: 8.6 mg/L

(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.86 µg/L

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

1. Identification

- Chemical Name:** Benzaldehyde
- CAS Registry Number:** 100-52-7
- Synonyms:** Benzaldehyde; Benzene carboxaldehyde; Benzenecarbal; Benzenemethylal; Benzoic aldehyde; Bitter almond oil, synthetic; Phenylmethanol aldehyde; Benzenecarboxaldehyde; Phenylformaldehyde; Artificial almond oil; アンズ アルデヒド
- Molecular Formula:** C₇H₆O
- Molecular Weight:** 106.13
- RIFM Number:** 155

2. Physical data

- Boiling Point:** ~178°C–179 °C (Bowles and Juneja, 1998), 179 °C (FMA Database), 181.22 °C (US ECHA, 2012)
- Flash Point:** 62 °C (GHS), 145 °F; CC (FMA Database)
- Log K_{ow}:** 1.48 (Patel et al., 2002), 1.50 (Wenzel et al., 1997), 1.71 (US ECHA, 2012)

- Melting Point:** –21.97 °C (US ECHA, 2012)
- Water Solubility:** 6100 mg/L (US ECHA, 2012)
- Specific Gravity:** 1.041–1.046 (FMA Database), 1.043–1.048 (FMA Database)
- Vapor Pressure:** 0.705 mm Hg @ 20 °C (US ECHA, 2012), 0.9 mm Hg 20 °C (FMA Database), 1.01 mm Hg @ 25 °C (US ECHA, 2012)
- UV Spectra:** Minor absorbance within the range of 290–700 nm; molar absorption is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
- Appearance/Organoleptic:** Colorless to yellowish liquid, turns to brown on exposure to air, volatile liquid with odor of bitter almonds with burning aromatic taste

3. Exposure

- Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
- 95th Percentile Concentration in Hydroalcoholics:** 0.0077% (RIFM, 2013c)
- Inhalation Exposure*:** 0.00027 mg/kg/day or 0.021 mg/day (RIFM, 2013c)

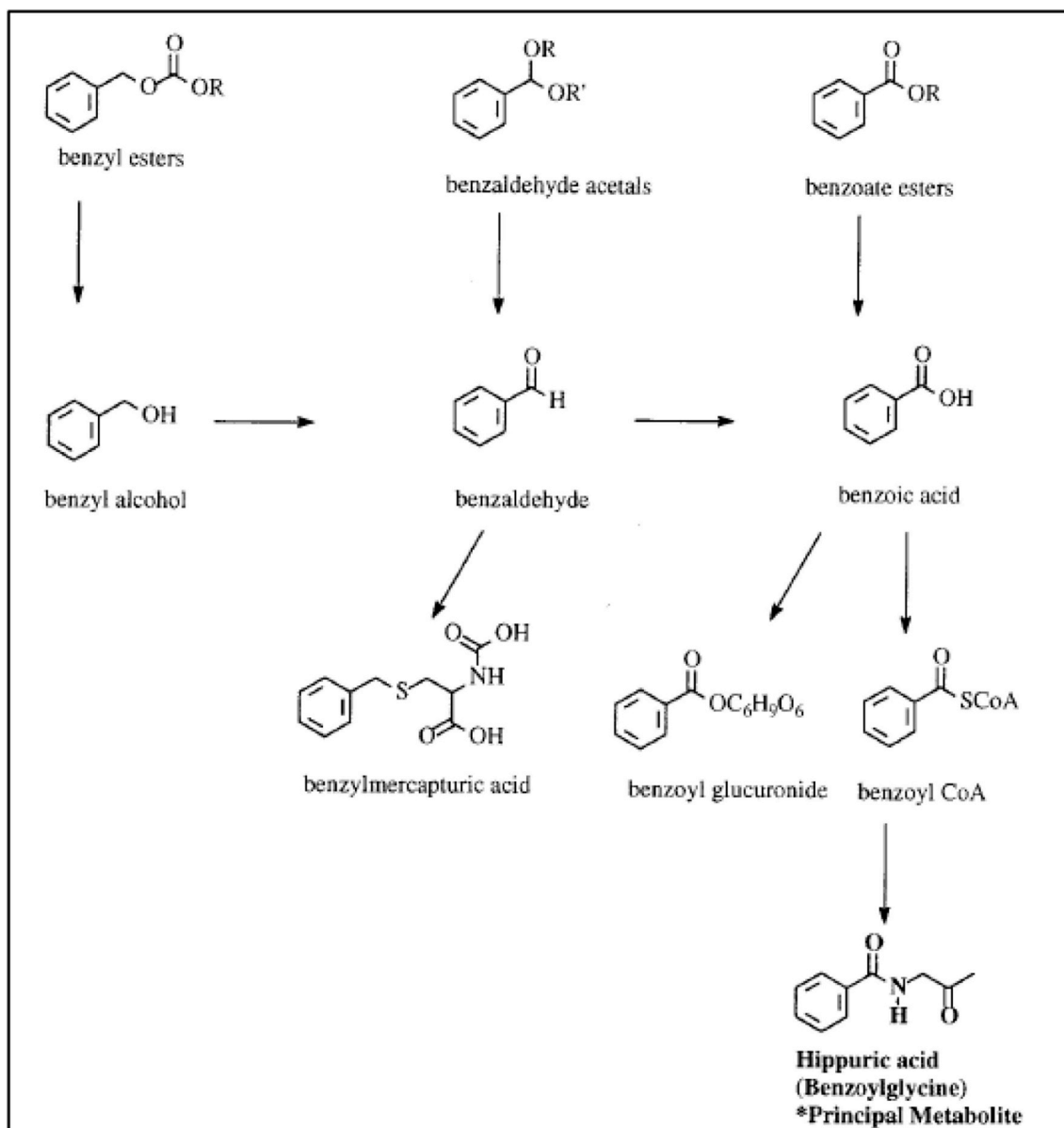


Fig. 1. (Adapted from Adams et al., 2005).

4. Total Systemic Exposure^{**}: 0.0024 mg/kg/day (RIFM, 2013c)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:

- a. **Genotoxicity:** None
 - b. **Repeated Dose Toxicity:** None
 - c. **Developmental and Reproductive Toxicity:** Benzyl alcohol (CAS # 100-51-6); benzoic acid (CAS # 65-85-0)
 - d. **Skin Sensitization:** None
 - e. **Phototoxicity/Photoallergenicity:** None
 - f. **Local Respiratory Toxicity:** None
 - g. **Environmental Toxicity:** None
3. **Read-across Justification:** See [Appendix](#) below

6. Metabolism

Laham et al., 1988 (Data also available in ECHA Dossier: Benzaldehyde [Basic Toxicokinetics: Key experimental results 2]; ECHA, 2011a; accessed December 8, 2017): Benzaldehyde was administered to 2 groups (high-dose: 750 mg/kg/rabbit and low-dose: 350 mg/kg/rabbit) of 3 male New Zealand White rabbits by gavage, whereas water was given orally to the third group. 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 (BMA, present in trace amounts). No free benzyl alcohol was reported in urine of treated or control animals.

Chidgey et al., 1986a: 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 et al., 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 et al., 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 (Fig. 1).

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

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

Capers (<i>Capparis spinosa</i>)	Maize (<i>Zea mays</i> L.)
Cinnamomum species	Ocimum species
Curry (<i>Bergera koenigii</i> L.)	Plum (<i>Prunus</i> species)
Indian cress absolute (<i>Tropaeolum majus</i> L.)	Salvia species
Lemon balm (<i>Melissa officinalis</i> L.)	Vanilla

*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. This is a partial list.

8. REACH dossier

Available; accessed 06/26/17.

9. Conclusion

The maximum acceptable concentrations^a in finished products for benzaldehyde are detailed below.

IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%)
1	Products applied to the lips (lipstick)	0.045
2	Products applied to the axillae	0.014
3	Products applied to the face/body using fingertips	0.27
4	Products related to fine fragrances	0.25
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.064
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.064
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.064
5D	Baby cream, oil, talc	0.021
6	Products with oral and lip exposure	0.15
7	Products applied to the hair with some hand contact	0.52
8	Products with significant ano-genital exposure (tampon)	0.021
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.49

10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.49
10B	Aerosol air freshener	1.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.021
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	100

Note: ^aMaximum 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 benzaldehyde, 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 590 µg/cm².

^bFor a description of the categories, refer to the IFRA RIFM Information Booklet. (<http://www.rifm.org/doc>).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, benzaldehyde does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Benzaldehyde was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013a). The mutagenic activity of benzaldehyde has been assessed in an Ames study conducted by the National Toxicology Program (NTP) according to a protocol similar to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA100, and TA98 were treated with benzaldehyde in DMSO at concentrations up to 1000 µg/plate and in a second study using strains TA100, TA102, and TA104 at concentrations up to 3333 µg/plate in the presence and absence of exogenous metabolic activation (S9). No increase in the number of revertant colonies was observed in the tester strains at the concentrations tested (NTP, 1990). Based on the available data, benzaldehyde was considered to be non-mutagenic.

The clastogenic activity of benzaldehyde 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 a chromosomal aberration study (Galloway et al., 1987), while it produced positive result in another chromosomal aberration study (Matsuoka et al., 1998). In a report by McGregor, benzaldehyde induced significant increases in mutation frequency in mouse lymphoma LY5178Y cells without S9 mix only at doses close to toxic levels (McGregor et al., 1991). Benzaldehyde was found to give 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 corn oil via oral gavage to groups of male and female NMRI mice. Doses of 200, 500, and 1000 mg/kg body weight 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 bodyweight. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2009a). 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* (Adam, 2005).

Based on the available data, benzaldehyde does not present a concern for genotoxic potential.

Additional References: 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, 2012a; RIFM, 2013a.

Literature Search and Risk Assessment Completed On: 05/07/17.

10.1.2. Repeated dose toxicity

The margin of exposure for benzaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. The repeated dose toxicity of benzaldehyde has been extensively tested in rats and mice. The NOAEL for repeated dose toxicity following daily oral gavage was determined to be 200 mg/kg/day, based on decreased survival of male rats in a 2-year carcinogenicity study (NTP, 1990). Therefore, the benzaldehyde MOE is equal to the benzaldehyde NOAEL in mg/kg/day divided by the total systemic exposure to benzaldehyde, 200/0.0024 or 83333.

In addition, the total systemic exposure to benzaldehyde (2.4 µg/mg/day) is below the TTC (30 µg/mg bw/day) 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 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 by the Flavor and Fragrance High Production Volume Consortia (FFHPVC: Benzyl Derivatives) and determined to be not relevant to human health. 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 it 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.” (IARC Technical Publication No. 39, 1999).

The RIFM Criteria Document (Api et al., 2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. These factors can be refined based on availability of data. Due to insufficient intraspecies susceptibility data for benzaldehyde, the factor of 10 remains unchanged. For interspecies variability, the factor of 10 can be further sub-divided into 4 and 2.5 based on toxicokinetic and toxicodynamic differences respectively (Renwick, 1993).

Section IX 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, 2008a; 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>) and a reference dose 2.0 mg/kg/day.

The RfD for benzaldehyde was calculated by dividing the NOAEL of 200 mg/kg/day by the uncertainty factor, 100 = 2.0 mg/kg/day.

Additional References: OECD SIDS, 1994: benzaldehyde; CIR, 2006; WHO, 1996; Laham et al., 1991a; Hruban et al., 1966; Taylor et al., 1964; Kluwe et al., 1983; Hoshino (1940); Sporn et al., 1967; Peresedov (1974); Hagan et al., 1967; Bar and Griepentrog, 1967; Lacroix et al., 2002; Schafer and Bowles, 1985; Schweinsberg et al., 1986; MacEwen (1986); Abramovici and Rachmuth-Roizman, 1983; Nishihara et al., 2000; Kutzman et al., 1980; Kutzman et al., 1978; Bray et al., 1951; Laham et al., 1988; Laham and Potvin, 1987; Teuchy et al., 1971; Smith and Packer, 1972; Walkenstein and Weinhouse, 1953; Sherwin and Crowdle, 1922; NTP, 1993; Ishiguro et al., 1993; Morrissey et al., 1988; EPA Hazard Characterization Document: Benzyl derivatives; Bronaugh et al., 1990; RIFM, 2012b; RIFM, 2012c; RIFM, 2013b; NTP, 1986; RIFM, 1957; Abdo and Wenk, 1995; Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young (1989); Abdo et al., 1985; Caldwell et al., 1987; Snapper et al., 1925; Hotchkiss et al., 1992a; Nasser-Sina et al., 1992; Chidgey and Caldwell, 1986b; Grundschober (1977); Miyashita and Robinson, 1980; Chidgey et al., 1987; McMahon et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahon et al., 1989b; Schunk et al., 1986; Hotchkiss et al., 1989a; Hotchkiss et al., 1992b; Caldwell et al., 1987; Hotchkiss (1998); Hotchkiss et al., 1992c; Meyer (1965); Garnett et al., 1994; Jimbo (1983a); Hotchkiss et al., 1988; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; Garnett et al., 1989; Hotchkiss et al., 1989b; Hotchkiss et al., 1992d; NTP, 1989; NTP, 1980a; RIFM, 2012d; Belsito et al., 2012a; CIR, 2001; RIFM, 2001; NTP, 1980b; RIFM, 2009b; Merriman et al., 2003; Miller et al., 1983; Duncan and Jarvis, 1943; Foulon et al., 2005; deJouffrey et al., 2004; Jost (1953); MacMillan (1973); Duraiswami (1954); Blair et al., 2000; Bray et al., 1958; McCloskey et al., 1986a; McCloskey (1987), McCloskey et al., 1986b; LeBel et al., 1988; Hotchkiss et al., 1992a; Nasser-Sina et al., 1992; Sloane (1965); Diack and Lewis, 1928; Snapper et al., 1925; Fisher (1985); McCormack et al., 1982; Jimbo (1983a); Jimbo et al., 1983b; Kasting et al., 1987; Procter Gamble, 1996; Saiyasombati and Kasting, 2003; Miller et al., 2006; Boehnlein et al., 1994; Van Hulst et al., 1997; Mikulak et al., 1998; RIFM, 2009c; Menczel, 1970; Menczel, 1972; Barry et al., 1985; Meyer (1965); Anderson and Raykar, 1989; ECHA, 2011b; SCCNFP, 2002; Kreis et al., 1971; Bedford, 1972; Graham and Kuizenga, 1945; Shtenberg and Ignat'ev, 1970; RIFM, 2009b; Sodemoto and Enomoto, 1980; Lemini et al., 1995; Kimmel et al., 1971; Ashby et al., 1997; Benton et al., 1955; Dawson et al., 1996; Picard et al., 2001; Kolle et al., 2010; Minor and Becker, 1971; Verrett et al., 1980; Daston et al., 1995; Peterka et al., 1986; Okubo and Kano, 2003.

Literature Search and Risk Assessment Completed On: 02/02/15.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for benzaldehyde is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on benzaldehyde. Precursor, benzyl alcohol (CAS # 100-51-6; see Section V) is oxidized to benzaldehyde, which is then further oxidized to benzoic acid (CAS # 65-85-0; see Section V) (numerous references, metabolic scheme detailed in Chidgey et al., 1986a; Yuan et al., 1995; see Section VI). A gavage postnatal screening study conducted in mice with benzyl alcohol determined the developmental NOAEL to be 550 mg/kg/day, the only dosage tested (Hardin, 1986). In a separate

gavage postnatal screening study conducted in mice with benzyl alcohol at 750 mg/kg/day, statistically significant reduced pup body weights were noted (Hardin et al., 1987). This effect occurred in the presence of maternal toxicity. Therefore, the benzaldehyde MOE for developmental toxicity is equal to the benzyl alcohol NOAEL in mg/kg/day divided by the total systemic exposure to benzaldehyde, 550/0.0024 or 208333.

There are no reproductive toxicity data on benzaldehyde. Benzaldehyde is oxidized to benzoic acid (CAS # 65-85-0; see Section V) (numerous references, metabolic scheme detailed in Chidgey et al., 1986a; Yuan et al., 1995). Benzoic acid has a dietary chronic toxicity and 4-generation reproductive toxicity study conducted in rats, which determined the NOAEL for reproductive toxicity to be 1% or 500 mg/kg/day, the highest dose tested (Kieckbusch and Lang, 1960). Therefore, the benzaldehyde MOE for reproductive toxicity is equal to the benzoic acid NOAEL in mg/kg/day divided by the total systemic exposure to benzaldehyde, 500/0.0024 or 208333.

In addition, the total systemic exposure to benzaldehyde (2.4 µg/mg/day) is below the TTC (30 µg/mg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: OECD SIDS, 1994: benzaldehyde; CIR, 2006; WHO, 1996; Laham et al., 1991a; Hruban et al., 1966; Taylor et al., 1964; Kluwe et al., 1983; Hoshino (1940); Sporn et al., 1967; Peresedov (1974); Hagan et al., 1967; Bar and Griepentrog, 1967; Lacroix et al., 2002; Schafer and Bowles, 1985; Schweinsberg et al., 1986; MacEwen (1986); Abramovici and Rachmuth-Roizman, 1983; Nishihara et al., 2000; Kutzman et al., 1980; Kutzman et al., 1978; Bray et al., 1951; Laham et al., 1988; Laham and Potvin, 1987; Teuchy et al., 1971; Smith and Packer, 1972; Walkenstein and Weinhouse, 1953; Sherwin and Crowdle, 1922; NTP, 1993; Ishiguro et al., 1993; Morrissey et al., 1988; EPA Hazard Characterization Document: Benzyl derivatives; Bronaugh et al., 1990; RIFM, 2012b; RIFM, 2012c; RIFM, 2013b; NTP, 1986; RIFM, 1957; Abdo and Wenk, 1995; Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young (1989); Abdo et al., 1985; Caldwell et al., 1987; Snapper et al., 1925; Hotchkiss et al., 1992a; Nasser-Sina et al., 1992; Chidgey and Caldwell, 1986b; Grundschober (1977); Miyashita and Robinson, 1980; Chidgey et al., 1987; McMahon et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahon et al., 1989b; Schunk et al., 1986; Hotchkiss et al., 1989a; Hotchkiss et al., 1992b; Caldwell et al., 1987; Hotchkiss (1998); Hotchkiss et al., 1992c; Meyer (1965); Garnett et al., 1994; Jimbo (1983a); Hotchkiss et al., 1988; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; Garnett et al., 1989; Hotchkiss et al., 1989b; Hotchkiss et al., 1992d; NTP, 1989; NTP, 1980a; RIFM, 2012d; Belsito et al., 2012a; CIR, 2001; OECD SIDS, 2001: Benzoates; RIFM, 2001; NTP, 1980b; RIFM, 2009b; Merriman et al., 2003; Miller et al., 1983; Duncan and Jarvis, 1943; Foulon et al., 2005; deJouffrey et al., 2004; Jost (1953); MacMillan (1973); Duraiswami (1954); Blair et al., 2000; Bray et al., 1958; McCloskey et al., 1986a; McCloskey (1987), McCloskey et al., 1986b; LeBel et al., 1988; Hotchkiss et al., 1992a; Nasser-Sina et al., 1992; Sloane (1965); Diack and Lewis, 1928; Snapper et al., 1925; Fisher (1985); McCormack et al., 1982; Jimbo (1983a); Jimbo et al., 1983b; Kasting et al., 1987; Procter Gamble, 1996; Saiyasombati and Kasting, 2003; Miller et al., 2006; Boehnlein et al., 1994; Van Hulst et al., 1997; Mikulak et al., 1998; RIFM, 2009c; Menczel, 1970; Menczel, 1972; Barry et al., 1985; Meyer (1965); Anderson and Raykar, 1989; ECHA, 2011b; SCCNFP, 2002; WHO, 2000; Kreis et al., 1971; Bedford, 1972; Graham and Kuizenga, 1945; Shtenberg and Ignat'ev, 1970; RIFM, 2009b; Sodemoto and Enomoto, 1980; Lemini et al., 1995; Kimmel et al., 1971; Ashby et al., 1997; Bedford, 1971; Benton et al., 1955; Dawson et al., 1996; Picard et al., 2001; Kolle et al., 2010; Minor and Becker, 1971; Verrett et al., 1980; Daston et al., 1995; Peterka et al., 1986; Okubo and Kano, 2003.

Literature Search and Risk Assessment Completed On: 02/02/15.

Table 1
Data summary for benzaldehyde.

LLNA Weighted Mean EC3 Value (No. Studies) $\mu\text{g}/\text{cm}^{\text{b}}$	Potency Classification Based on Animal Data ^a	Human Data			
		NOEL-HRIPT (Induction) $\mu\text{g}/\text{cm}^{\text{b}}$	NOEL-HMT (Induction) $\mu\text{g}/\text{cm}^{\text{b}}$	LOEL ^b (Induction) $\mu\text{g}/\text{cm}^{\text{b}}$	WoE NESIL ^c $\mu\text{g}/\text{cm}^{\text{b}}$
> 6250 [1] ^d	Weak	590	NA	2760 ^e	590

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.

^d EC3 value from one LLNA, not the mean.

^e LOEL from human maximization test, not a human repeated insult patch test.

10.1.4. Skin sensitization

Based on the existing data, benzaldehyde is considered a weak skin sensitizer with a defined NESIL of 590 $\mu\text{g}/\text{cm}^2$.

10.1.4.1. Risk assessment. Based on the existing data, benzaldehyde is considered a weak skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). Benzaldehyde was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA) but positive in the KeratinoSens human cell line activation test (h-CLAT) or U937-CD86 test (Urbisch et al., 2015; Natsch et al., 2013; Emter et al., 2010; Piroird et al., 2015). In a murine local lymph node assay, benzaldehyde was found to be negative up to the maximum tested concentration of 25% (6500 $\mu\text{g}/\text{cm}^2$) (Basketter et al., 2002). In a human maximization test, a Lowest Observed Effect Level (LOEL) of 2760 $\mu\text{g}/\text{cm}^2$ was observed, but the results were not replicated in another human maximization test (RIFM, 1973). In a human repeat insult patch test (HRIPT), 5900 $\mu\text{g}/\text{cm}^2$, benzaldehyde induced sensitization reactions in 12/104 subjects (RIFM, 2008b). However, in another confirmatory HRIPT with 590 $\mu\text{g}/\text{cm}^2$ of benzaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2009b). Based on the available data, summarized in Table 1, benzaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 590 $\mu\text{g}/\text{cm}^2$. Section IX 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, 2008a; 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>) and a reference dose 2.0 mg/kg/day.

Additional References: Klecak (1985); Klecak et al., 1977; Gauggel et al., 1993; Watanabe et al., 2001.

Literature Search and Risk Assessment Completed On: 06/08/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, benzaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. The available UV/Vis spectra for benzaldehyde indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxic effects. Based on the lack of absorbance in the

critical range, and benchmark evaluation, benzaldehyde does not present a concern for phototoxicity or photoallergenicity.

10.1.6. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) for benzaldehyde 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 $\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/24/17.

10.1.7. Local Respiratory Toxicity

The margin of exposure for benzaldehyde is adequate for the respiratory endpoint at the current level of use.

10.1.7.1. 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, 750, and 1000 ppm (equivalent to 2170, 3255, and 4340 mg/m^3) benzaldehyde (ECHA, 2011a; Laham et al., 1991b). 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) 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, 2011a; accessed 06/15/17). 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) ($1\text{m}^3/1000\text{L}$) = 0.217 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat \times 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 0.021 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015 and 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 0.032 mg/kg lung weight/day resulting in a MOE of 259766 (i.e., [8312.5 mg/kg lung weight/day]/[0.032 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.021 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd 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): Reval 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.

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

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

A screening-level hazard assessment using EPI Suite v4.1 did not identify benzaldehyde as possibly persistent nor 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 v4.1).

10.2.2. Risk assessment

Based on the current VoU (2015), benzaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. *Biodegradation.* No data available.

10.2.3.2. *Ecotoxicity.* No data available.

10.2.4. Other available data

Benzaldehyde has been registered under REACH and the following additional data is available:

A fish (*Lepomis macrochirus*) acute toxicity study was conducted according to the OECD 203 method under flow-through conditions. The 96-h LC50 was reported to be 1.07 mg/L.

A 7-day chronic toxicity test was conducted with Fathead minnows under flow-through conditions. The NOEC (growth rate and survival) was reported to be 0.22 mg/L.

10.2.5. Risk assessment refinement

Since benzaldehyde 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 $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>255.8</u>			1,000,000	0.2558	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	<u>8.601</u>	16.04	22.92	10,000	0.8601	Aldehydes (mono)
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	158.7	87.75	58.52			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.71	1.71
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	100–1000
Risk Characterization: PEC/PNEC	< 1	< 1

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

The RIFM PNEC is 0.86 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/05/19.

11. 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/>

Appendix A. Supplementary data

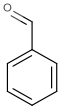
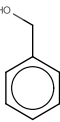
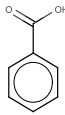
Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2019.110878>.

Appendix

Read-across Justification

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in [Schultz et al. \(2015\)](#). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment ([OECD, 2015](#)) and the European Chemicals Agency read-across assessment framework ([ECHA, 2016](#)).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints ([Rogers and Hahn, 2010](#)).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 ([US EPA, 2012a](#)).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model ([Shen et al., 2014](#)).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4.
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4.
- Developmental toxicity was predicted using CAESAR v2.1.7 ([Cassano et al., 2010](#)), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4.

	Target material	Read-across materials	
Principal Name	Benzaldehyde	Benzyl alcohol	Benzoic acid
CAS No.	100-52-7	100-51-6	65-85-0
Structure			
Similarity (Tanimoto score)		0.87	0.89
Read-across endpoint		<ul style="list-style-type: none"> • Developmental and Reproductive toxicity 	<ul style="list-style-type: none"> • Developmental and Reproductive toxicity
Molecular Formula	$\text{C}_7\text{H}_6\text{O}$	$\text{C}_7\text{H}_8\text{O}$	$\text{C}_7\text{H}_6\text{O}_2$

[scifinderExplore.jsf](#)

- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/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 05/10/19.

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.

Molecular Weight	106.13	108.14	122.12
Melting Point (°C, EPI Suite)	-21.97	-5.43	48.85
Boiling Point (°C, EPI Suite)	181.22	205.65	249.51
Vapor Pressure (Pa @ 25 °C, EPI Suite)	135	1.25E+001	0.397
Log Kow (KOWWIN v1.68 in EPI Suite)	1.48	1.10	1.87
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	6100	4.105E+004	2493
J_{max} ($\mu\text{g}/\text{cm}^2/\text{h}$, SAM)	201.376	643.343	120.948
Henry's Law ($\text{Pa}\cdot\text{m}^3/\text{mol}$, Bond Method, EPI Suite)	1.36E+000	2.20E-002	1.10E-002
Developmental and reproductive toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (low reliability)	• Toxicant (low reliability)	• Toxicant (low reliability)
Metabolism			
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2	No metabolites
Rat liver S9 metabolism simulator and structural alerts for metabolites			

Summary

There are insufficient toxicity data on the target material benzaldehyde (CAS # 100-52-7). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties, and expert judgment, benzyl alcohol (CAS # 100-51-6) and benzoic acid (CAS # 65-85-0) were identified as read-across materials with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target substance was considered for the risk assessment as shown in the metabolism section (Section VI) above. Metabolism of the target material benzaldehyde (CAS # 100-52-7) and the read-across material benzyl alcohol (CAS # 100-51-6) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (see table above). The read-across analog benzyl alcohol (CAS # 100-51-6) is oxidized to the target material benzaldehyde (CAS # 100-52-7) in the first step with 0.95 pre-calculated probability. And the target material benzaldehyde (CAS # 100-52-7) is oxidized to the read-across analog benzoic acid (CAS # 65-85-0) in the first step with 0.95 pre-calculated probability. Hence, benzyl alcohol (CAS # 100-51-6) and benzoic acid (CAS # 65-85-0) can be used as read-across analogs for the target material. Both the read-across analogs were out of domain for the *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and justification is provided.

- Benzyl alcohol (CAS # 100-51-6) and benzoic acid (CAS # 65-85-0) are used as read-across analogs for the target material benzaldehyde (CAS # 100-52-7) for the developmental and reproductive toxicity endpoint.
 - o The read-across materials are major metabolites of the target.
 - o The target substance is an aromatic aldehyde. The read-across analog benzyl alcohol (CAS # 100-51-6) is oxidized to the target material benzaldehyde (CAS # 100-52-7). Further, the target material benzaldehyde (CAS # 100-52-7) is then oxidized to the read-across analog benzoic acid (CAS # 65-85-0).
 - o Structural differences between the target substance and the read-across analog are mitigated by the fact that the target could be metabolically oxidized to the read-across analog. Therefore, the toxicity profile of the target is expected to be that of metabolites. Similarity between the target substance and the read-across analogs is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
 - o The differences in the physical-chemical properties of the target substance and the read-across analogs do not affect consideration of the toxicological endpoints.
 - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
 - o The target substance and the read-across analogs are predicted to be toxicants by the CAESAR model for developmental toxicity. This shows that the read-across analogs are predicted to have comparable reactivity with the target substance. The data described in the reproductive and developmental toxicity section show that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert is superseded by the available data.
 - o The structural alerts for the toxicological endpoints are consistent between the metabolites of the read-across analogs and the target substance.
 - o The structural differences between the target material and the read-across analogs do not affect consideration of the toxicological endpoints.

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