Food and Chemical Toxicology xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

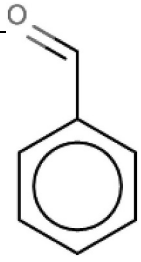
RIFM fragrance ingredient safety assessment, benzaldehyde, CAS Registry Number 100-52-7

A.M. Api[a], D. Belsito[b], S. Biserta[a], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.A. Cancellieri[a], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], F. Siddiqi[a], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2019.110878
Received 13 May 2019; Received in revised form 10 September 2019; Accepted 8 October 2019

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/cm^2 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/cm^2.	RIFM (2009b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 217 mg/m^3.	(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

1. **Chemical Name:** Benzaldehyde
2. **CAS Registry Number:** 100-52-7
3. **Synonyms:** Benzaldehyde; Benzene carboxaldehyde; Benzenecarbonal; Benzenemethylal; Benzoic aldehyde; Bitter almond oil, synthetic; Phenylmethanol aldehyde; Benzenecarboxaldehyde; Phenylformaldehyde; Artificial almond oil; ﾍﾞﾝｽﾞｱﾙﾃﾞﾋﾄﾞ
4. **Molecular Formula:** C_7H_6O
5. **Molecular Weight:** 106.13
6. **RIFM Number:** 155

2. Physical data

1. **Boiling Point:** ~178°C–179 °C (Bowles and Juneja, 1998), 179 °C (FMA Database), 181.22 °C (US ECHA, 2012)
2. **Flash Point:** 62 °C (GHS), 145 °F; CC (FMA Database)
3. **Log K_{OW}:** 1.48 (Patel et al., 2002), 1.50 (Wenzel et al., 1997), 1.71 (US ECHA, 2012)
4. **Melting Point:** −21.97 °C (US ECHA, 2012)
5. **Water Solubility:** 6100 mg/L (US ECHA, 2012)
6. **Specific Gravity:** 1.041–1.046 (FMA Database), 1.043–1.048 (FMA Database)
7. **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)
8. **UV Spectra:** Minor absorbance within the range of 290–700 nm; molar absorption is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **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

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0077% (RIFM, 2013c)
3. **Inhalation Exposure*:** 0.00027 mg/kg/day or 0.021 mg/day (RIFM, 2013c)

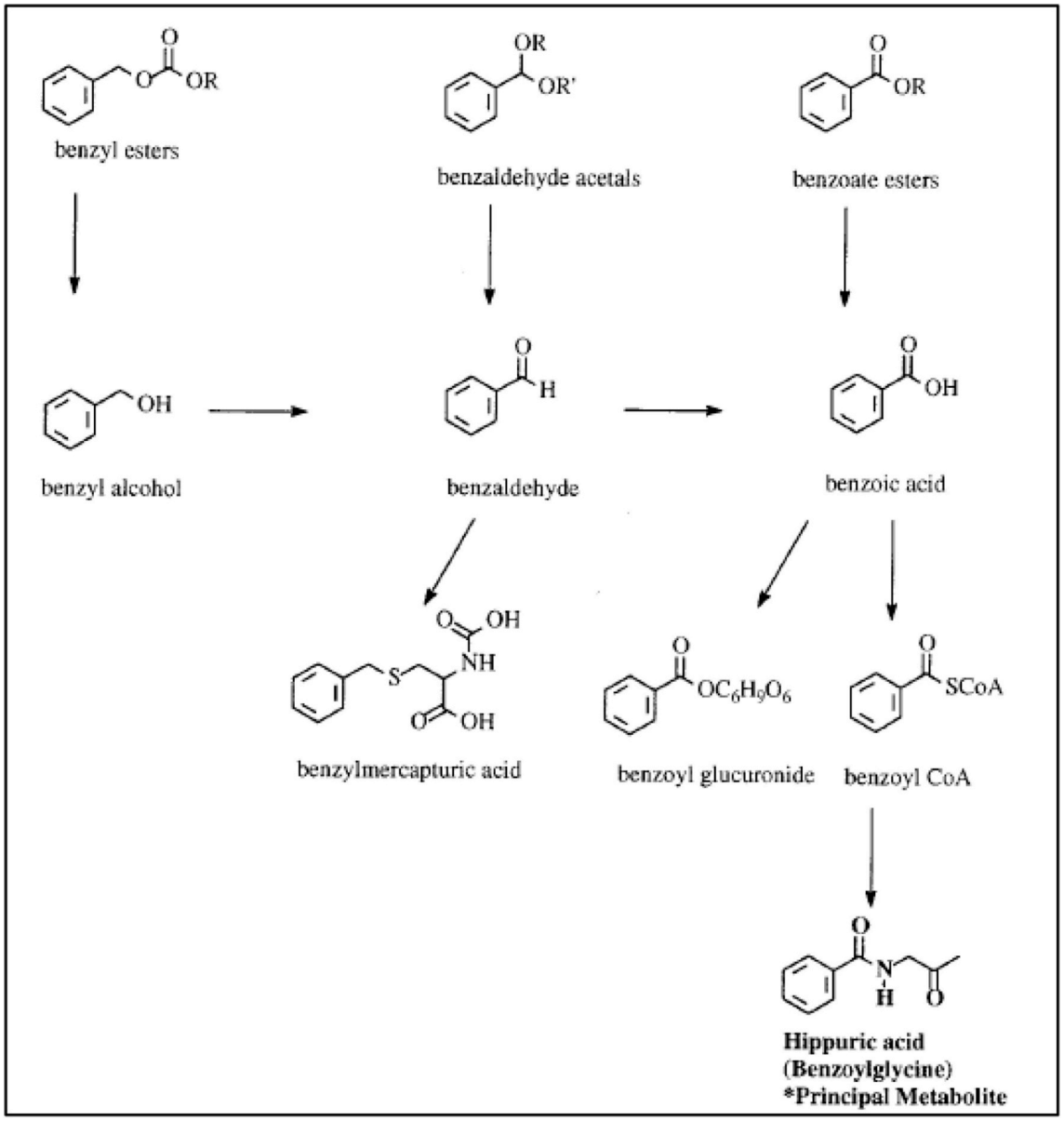


Fig. 1. (Adapted from Adams et al., 2005).

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
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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 (*Capparis spinoza*)	Maize (*Zea mays* L.)
Cinnamomum species	*Ocimum* species
Curry (*Bergera koenigii* L.)	Plum (*Prunus* species)
Indian cress absolute (*Tropaelum majus* L.)	Salvia species
Lemon balm (*Melissa officinalis* 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: [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 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/cm^2.

[b]For 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; Nasseri-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; Nasseri-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.

The 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 (Kieckebusch 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; Nasseri-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; Nasseri-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) μg/cm[b]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (Induction) μg/cm[b]	NOEL-HMT (Induction) μg/cm[b]	LOEL[b] (Induction) μg/cm[b]	WoE NESIL[c] μg/cm[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 μg/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 μg/cm^2) (Basketter et al., 2002). In a human maximization test, a Lowest Observed Effect Level (LOEL) of 2760 μg/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 μg/cm^2, benzaldehyde induced sensitization reactions in 12/104 subjects (RIFM, 2008b). However, in another confirmatory HRIPT with 590 μg/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 μg/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 L mol^{-1} · 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) (1m^3/1000L) = 0.217 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.217 mg/L) (61.2 L/d) = 13.3 mg/day
- (13.3 mg/day)/(0.0016 kg lung weight of rat*) = 8312.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.021 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, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: “Comparative Physiology and Anatomy,” subsection, “Comparative Airway Anatomy.”

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

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 µg/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>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 μg/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/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/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 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.

Appendix A. Supplementary data

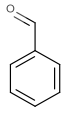
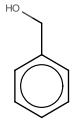
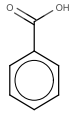
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110878.

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		• Developmental and Reproductive toxicity	• Developmental and Reproductive toxicity
Molecular Formula	C_7H_6O	C_7H_8O	$C_7H_6O_2$

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} (μg/cm^2/h, SAM)	201.376	643.343	120.948
Henry's Law (Pa·m^3/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) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2	No 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.

References

Abdo, K.M., Wenk, M.L., 1995. Requirement for adequate glycine for the detoxification of benzyl acetate and maintenance of its detoxification pathways. Toxicologist 15 (1), 19.

Abdo, K.M., Huff, J.E., Haseman, J.K., Boorman, G.A., Eustis, S.L., Matthews, H.B., Burka, L.T., Prejean, J.D., Thompson, R.B., 1985. Benzyl acetate carcinogenicity, metabolism, and disposition in fischer 344 rats and B6C3F1 mice. Toxicology 37 (1–2), 159–170.

Abdo, K.M., Wenk, M.L., Harry, G.J., Mahler, J., Goehl, T.J., Irwin, R.D., 1998. Glycine modulates the toxicity of benzyl acetate in F344 rats. Toxicol. Pathol. 26 (3), 395–402.

Abramovici, A., Rachmuth-Roizman, P., 1983. Molecular structure-teratogenicity relationships of some fragrance additives. Toxicology 29, 143–156.

Adams, T.B., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., Wagner, B.M., 2005. The FEMA GRAS assessment of benzyl derivatives used as flavor ingredients. Food Chem. Toxicol. 43 (8), 1207–1240.

Anderson, B.D., Raykar, P.V., 1989. Solute structure-permeability relationship in human stratum corneum. J. Investig. Dermatol. 93, 280–286.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Ashby, J., Lefevre, P.A., Odum, J., Tinwell, H., Kennedy, S.J., Beresford, N., Sumpter, J.P., 1997. Failure to confirm estrogenic activity for benzoic acid and clofibrate: implications for lists of endocrine-disrupting agents. Regul. Toxicol. Pharmacol. 26 (1),

96–101.
Augustinsson, K.-B., Ekedahl, G., 1962. On the specificity of arylesterases. Acta Chem. Scand. 16 (part 1), 240–241.
Babiuk, C., Steinhagen, W.H., Barrow, C.S., 1985. Sensory irritation response to inhaled aldehydes after formaldehyde pretreatment. Toxicol. Appl. Pharmacol. 79 (1), 143–149.
Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel Fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Medizin Ernahr 8, 244–251.
Barry, B.W., Harrison, S.M., Dugard, P.H., 1985. Correlation of thermodynamic activity and vapour diffusion through human skin for the model compound, benzyl alcohol. J. Pharm. Pharmacol. 37 (2), 84–90.
Basketter, D.A., Wright, Z., Gilmour, N.J., Ryan, C.A., Gerberick, G.F., Robinson, M.K., Dearman, R.J., Kimber, I., 2002. Prediction of human sensitization potency using Local Lymph Node Assay EC3 values. Toxicologist 66 (1-S), 240.
Becker, T.W., Kreiger, G., Witte, I., 1996. DNA single and double strand breaks induced by aliphatic and aromatic aldehydes in combination with copper (II). Free Radic. Res. 24 (5), 325–332.
Bedford, P.G.C., Clarke, E.G.C., 1972. Experimental benzoic acid poisoning in the cat. Vet. Rec. 90 (3), 53–58.
Belsito, D., Bickers, D., Bruze, M., Calow, P., Dagli, M.L., Fryer, A.D., Greim, H., Miyachi, Y., Saurat, J.H., Sipes, I.G., 2012. A toxicological and dermatological assessment of aryl alkyl alcohols when used as fragrance ingredients. Food Chem. Toxicol. 50 (Suppl. 2), S52–S99.
Benton, D.A., Harper, A.E., Winje, M.E., Elvehjem, C.A., 1955. Compounds other than threonine that affect fat deposition in the livers of rats fed low protein diets. J. Biol. Chem. 214 (2), 677–684.
Blair, R.M., Fang, H., Branham, W.S., Hass, B.S., Dial, S.L., Moland, C.L., Tong, W., Shi, L., Perkins, R., Sheehan, D.M., 2000. The estrogen receptor relative binding affinities of 188 natural and xenochemicals: structural diversity of ligands. Toxicol. Sci. 54 (1), 138–153.
Boehnlein, J., Sakr, A., Lichtin, J.L., Bronaugh, R.L., 1994. Characterization of esterase and alcohol dehydrogenase activity in skin. Metabolism of retinyl palmitate to retinol (vitamin A) during percutaneous absorption. Pharmacol. Rev. 11 (8), 1155–1159.
Bowles, B.L., Juneja, V.K., 1998. Inhibition of foodborne bacterial pathogens by naturally occurring food additives. J. Food Saf. 18 (2), 101–112.
Bray, H.G., Thorpe, W.V., White, K., 1951. Kinetic studies of the metabolism of foreign organic compounds. The formation of benzoic acid from benzamide, toluene, benzyl alcohol and benzaldehyde and its conjugation with glycine and glucuronic acid in the rabbit. Biochem. J. 48, 88–96.
Bray, H.G., James, S.P., Thorpe, W.V., 1958. Metabolism of some omega-halogenoalkylbenzenes and related alcohols in the rabbit. Biochem. J. 70, 570–579.
Bronaugh, R.L., Wester, R.C., Bucks, D., Maibach, H.I., Sarason, R., 1990. In vivo percutaneous absorption of fragrance ingredients in rhesus monkeys and humans. Food Chem. Toxicol. 28 (5), 369–373.
Buchbauer, G., Jirovetz, J., Jaeger, W., 1992. Passiflora and lime-blossoms: motility effects after inhalation of the essential oils and of some of the main constituents in animal experiment. Archiv Pharmazie (Weinheim. Germany) 325 (4), 247–248.
Buchbauer, G., Jirovetz, L., Jager, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. J. Pharm. Sci. 82 (6), 660–664.
Caldwell, J., Kennedy, J.F., Chidgey, M.A.J., 1987. Absorption and Disposition of Topically-Applied Methylene-Carbon-14 Benzyl Acetate in the Rat. In Pharmacology and the Skin, vol. 1. Skin Pharmacokinetics, pp. 209–213.
Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.
Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.
Chidgey, M.A.J., Caldwell, J., 1986. Studies on benzyl acetate I. Effect of dose size and vehicle on the plasma pharmacokinetics and metabolism of [methylene-(14)C]benzyl acetate in the rat. Food Chem. Toxicol. 24 (12), 1257–1265.
Chidgey, M.A.J., Kennedy, J.F., Caldwell, J., 1986. Studies on benzyl acetate II. Use of specific metabolic inhibitors to define the pathway leading to the formation of benzylmercapturic acid in the rat. Food Chem. Toxicol. 24 (12), 1267–1272.
Chidgey, M.A.J., Kennedy, J.F., Caldwell, J., 1987. Studies on benzyl acetate. III. The percutaneous absorption and disposition of [Methylene{14}C]benzyl acetate in the rat. Food Chem. Toxicol. 25 (7), 521–525.
Cosmetic Ingredient Review, 2001. Final report on the safety assessment of benzyl alcohol, benzoic acid and sodium benzoate. Int. J. Toxicol. 20 (Suppl. 3), 23–50.
Cosmetic Ingredient Review Expert Panel, 2006. Final report on the safety assessment of benzaldehyde. Int. J. Toxicol. 25 (Suppl. 1), 11–27.
Clapp, J.J., Young, L., 1970. Formation of mercapturic acids in rats after the administration of aralkyl esters. Biochem. J. 118 (5), 765–771.
Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.
Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.
Daston, G.P., Baines, D., Elmore, E., Fitzgerald, M.P., Sharma, S., 1995. Evaluation of chick embryo neural retina cell culture as a screen for developmental toxicants. Fundam. Appl. Toxicol. 26 (2), 203–210.
Dawson, D.A., Schultz, T.W., Hunter, R.S., 1996. Developmental toxicity of carboxylic acids to Xenopus embryos: a quantitative structure-activity relationship and computer-automated structure evaluation. Teratog. Carcinog. Mutagen. 16 (2), 109–124.
deJouffrey, S., Mungapen, L., Gaoua, W., Foulon, O., Forster, R., 2004. Safety assessment of benzyl alcohol in juvenile rats. Toxicol. Appl. Pharmacol. 197 (3), 210.
Demir, E., Kocaoglu, S., Kaya, B., 2010. Assessment of genotoxic effects of benzyl derivatives by the comet assay. Food Chem. Toxicol. 48 (5), 1239–1242.
Diack, S.L., Lewis, H.B., 1928. Studies in the synthesis of hippuric acid in the animal organism. VII. A comparison of the rats of elimination of hippuric acid after the ingestion of sodium benzoate, benzyl alcohol and benzyl esters of succinic acid. J. Biol. Chem. 77, 89–95.
Dillon, D.M., McGregor, D.B., Combes, R.D., Zeiger, E., 1992a. Detection of mutagenicity in Salmonella of some aldehydes and peroxides. Environ. Mol. Mutagen. 19 (Suppl. 20), 15.
Dillon, D.M., McGregor, D.B., Combes, R.D., Zeiger, E., 1992b. Optimal conditions for detecting bacterial mutagenicity of some aldehydes and peroxides. Mutation Research. Environmental Mutagenesis and Related Subjects 271 (2), 184.
Dillon, D., Combes, R., Zeiger, E., 1998. The effectiveness of Salmonella strains TA100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. Mutagenesis 13 (1), 19–26.
Duchamp, A., 1982. Electrophysiological responses of olfactory bulb neurons to odour stimuli in the frog. A comparison with receptor cells. Chem. Senses 7 (2), 191–210.
Duncan, D., Jarvis, W.H., 1943. A comparison of the actions on nerve fibers of certain anesthetic mixtures and substances in oil. Anesthesiology 4 (5), 465–474.
Duraiswami, P.K., 1954. Experimental teratogenesis with benzyl alcohol; preliminary report. Bull. Johns Hopkins Hosp. 95 (2), 57–67.
ECHA, 2011a. Benzaldehyde registration dossier. Retrieved from. https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/15940.
ECHA, 2011b. Benzoic acid registration dossier. Retrieved from. https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/13124.
ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.
ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.
Emter, R., Ellis, G., Natsch, A., 2010. Performance of a novel keratinocyte-based reporter cell line to screen skin sensitizers in vitro. Toxicol. Appl. Pharmacol. 245 (3), 281–290.
Ferrari, C.P., Kaluzny, P., Roche, A., Jacob, V., Foster, P., 1998. Aromatic hydrocarbons and aldehydes in the atmosphere of Grenoble, France. Chemosphere 37 (8), 1587–1601.
Fisher, L.B., 1985. In vitro studies on the permeability of infant skin. In: Percutaneous Absorption, pp. 213–222 (Chapter 15).
Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames Test. Toxicology 18 (3), 219–232.
Foulon, O., Mungapen, L., Gaoua, W., Forster, R., 2005. Benzyl alcohol: safety assessment in juvenile rats. Toxicologist 84 (S-1), 55.
Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., Zeiger, E., 1987. Chromosome aberration and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ. Mol. Mutagen. 10 (10), 1–175.
Garnett, A., Hotchkiss, S.A., Caldwell, J., 1989. In Vitro Dermal Absorption and Metabolism of Benzyl Acetate. (Unpublished).
Garnett, A., Hotchkiss, S.A.M., Caldwell, J., 1994. Percutaneous absorption of benzyl acetate through rat skin in vitro. 3. A comparison with human skin. Food Chem. Toxicol. 32 (11), 1061–1065.
Gauggel, D.L., Sarlo, K., Asquith, T.N., 1993. A proposed screen for evaluating low-molecular-weight chemicals as potential respiratory allergens. J. Appl. Toxicol. 13 (5), 307–313.
Gee, P., Sommers, C.H., Melick, A.S., Gidrol, X.M., Todd, M.D., Burris, R.B., Nelson, M.E., Klemm, C., Zeiger, E., 1998. Comparison of responses of base-specific Salmonella tester strains with the traditional strains for identifying mutagens: the results of a validation study. Mutation Research. Genetic Toxicology and Environmental Mutagenesis 412 (2), 115–130.
Graham, B.E., Kuizenga, M.H., 1945. Toxicity studies on benzyl benzoate and related benzyl compounds. J. Pharmacol. Exp. Ther. 84 (4), 358–362.
Grundschober, F., 1977. Toxicological assessment of flavouring esters. Toxicology 8, 387–390.
Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet. Toxicol. 5 (2), 141–157.
Hardin, B.D., 1986. Screening of Priority Chemicals for Reproductive Hazards. (Unpublished).
Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V.J., Smith, K.N., 1987. Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratog. Carcinog. Mutagen. 7 (1), 29–48.
Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Zeiger, E., 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5 (Suppl. 1), 3–142.
Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9 (1), 257.
Helmig, D., Klinger, L.F., Guenther, A., Vierling, L., Geron, C., Zimmerman, P., 1999a. Biogenic volatile organic compound emissions (BVOCs). I. Identifications from three continental sites in the U.S. Chemosphere 38 (9), 2163–2187.
Helmig, D., Klinger, L.F., Guenther, A., Vierling, L., Geron, C., Zimmerman, P., 1999b. Biogenic volatile organic compound emissions (BVOCs). II. Landscape flux potentials

from three continental sites in the U.S. Chemosphere 38 (9), 2189–2204.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
Hoshino, I., 1940. Behavior of Liver in the Long Continued Administration of Aromatic Compounds. Parts 4 to 6, vol. 15. pp. 117–151 Zikken Syokaki-byogaku.
Hotchkiss, S.A.M., 1998. Absorption of fragrance ingredients using in vitro models with human skin. In: Fragrances: Beneficial and Adverse Effects, pp. 125–135.
Hotchkiss, S.A., Fraser, S., Caldwell, J., Miller, J.M., 1988. The percutaneous absorption of benzyl acetate through rat skin in vitro. In: Presented at ISSX-88 Mtg. Kobe,Japan.
Hotchkiss, S.A., Fraser, S., Miller, J.M., Caldwell, J., 1989a. Percutaneous absorption of topically applied benzyl acetate in-vitro effect of vehicle on skin penetration. Hum. Toxicol. 8 (1), 71–72.
Hotchkiss, S.A., Rose, S., Caldwell, J., 1989b. Evidence for the Existence of a Cutaneous Reservoir for Benzyl Acetate. (Unpublished).
Hotchkiss, S.A., Chidgey, M.A.J., Rose, S., Caldwell, J., 1990a. Percutaneous absorption of benzyl acetate through rat skin in vitro. 1. Validation of an in vitro model against in vivo data. Food Chem. Toxicol. 28 (6), 443–447.
Hotchkiss, S.A., Fraser, S., Chidgey, M.A.J., Caldwell, J., 1990b. An in vitro skin diffusion technique for the prediction of in vivo absorption; a case study with benzyl acetate. In: Prediction of Percutan. Penetration-Methods. Measurements Modelling, pp. 123–128.
Hotchkiss, S.A.M., Miller, J.M., Caldwell, J., 1992a. Percutaneous absorption of benzyl acetate through rat skin in vitro. 2. Effect of vehicle and occlusion. Food Chem. Toxicol. 30 (2), 145–153.
Hotchkiss, S.A.M., Nasseri-Sina, P., Garnett, A., Caldwell, J., 1992b. In vitro metabolism of benzyl acetate and benzoic acid in cultured human keratinocytes and full thickness human skin. ISSX International Meeting 2, 158.
Hotchkiss, S.A.M., Garnett, A., Hewitt, P., Mint, A., Caldwell, J., 1992c. Percutaneous absorption of topically applied chemicals through human skin in vitro. In: Proceedings of the British Pharmacological Society. Clinical Pharmacology Section, vols. 8–10. pp. 148 April 1992.
Hotchkiss, S.A.M., Hewitt, P., Mint, A., Garnett, A., Caldwell, J., 1992d. Percutaneous absorption of fragrance chemicals through human skin in vitro. Toxicol. Lett. 1 (Suppl. l), 173.
Hruban, Z., Swift, H., Slesers, A., 1966. Ultrastructural alterations of hepatic microbodies. Lab. Investig. 15 (12), 1884–1901.
Hummel, T., Futschik, T., Frasnelli, J., Huttenbrink, K.-B., 2003. Effects of olfactory function, age, and gender on trigeminally mediated sensations: a study based on the lateralization of chemosensory stimuli. Toxicol. Lett 140-141 273-280.
IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.
Ishiguro, S., Miyamoto, A., Obi, T., Nishio, A., 1993. Teratological studies on benzyl acetate in pregnant rats. Bull. Fac. Agric. Kagoshima Univ. 43, 25–31.
Jansson, T., Curvall, M., Hedin, A., Enzell, C.R., 1988. In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke - a study of structure-activity relationships. Mutat. Res. Genet. Toxicol. 206 (1), 17–24.
Jimbo, Y., 1983. Penetration of fragrance compounds through human epidermis. J. Dermatol. (Tokyo) 10 (3), 229–239.
Jimbo, Y., Ishihara, M., Osamura, H., Takano, M., Ohara, M., 1983. Influence of vehicles on penetration through human epidermis of benzyl alcohol, isoeugenol and methyl isoeugenol. J. Dermatol. (Tokyo) 10, 241–250.
Johnson, B.A., Farahbod, H., Leon, M., 2005. Interactions between odorant functional group and hydrocarbon structure influence activity in glomerular response modules in the rat olfactory bulb. J. Comp. Neurol. 483 (2), 205–216.
Jost, A., 1953. Problems of fetal endocrinology: gonadal and hypophyseal hormones. Recent Prog. Horm. Res. 8, 379–418.
Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T., Urasawa, S., 1982. Genotoxicity of flavoring agents. Mutation Research. Reviews in Mutation Research 105, 387–392.
Kasting, G.B., Smith, R.L., Cooper, E.R., 1987. Effect of lipid solubility and molecular size on percutaneous absorption. In: Pharmacology and the Skin, vol. 1. pp. 138–153.
Kieckebusch, W., Lang, K., 1960. The tolerability of benzoic acid in chronic feeding experiments. Arzneimittel-Forschung [Drug Research] 10, 1001–1003.
Kimmel, C.A., Wilson, J.G., Schumacher, H.J., 1971. Studies on metabolism and identification of the causative agent in aspirin teratogenesis in rats. Teratology 4 (1), 15–24.
Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol. 14. pp. 152–171.
Klecak, G., Geleick, H., Frey, J.R., 1977. Screening of fragrance materials for allergenicity in the Guinea pig. I. Comparison of four testing methods. Journal of the Society of Cosmetic Chemists Japan 28, 53–64.
Kluwe, W.M., Montgomery, C.A., Giles, H.D., Prejean, J.D., 1983. Encephalopathy in rats and nephropathy in rats and mice after subchronic oral exposure to benzaldehyde. Food Chem. Toxicol. 21 (3), 245–250.
Kolle, S.N., Kamp, G.H., Huener, H.-A., Knickel, J., Verlohner, A., Landsiedel, R., Woitkowiak, C., van Ravenzwaay, B., 2010. In house validation of recombinant yeast estrogen and androgen receptor agonist and antagonist screening assays. Toxicol. In Vitro 24 (7), 2030–2040.
Kreis, H., Frese, K., Wilmes, G., 1971. Physiological and morphological changes in rats after oral administration of benzoic acid. Grundfragen Ern 244–254.
Kubo, T., Urano, K., Utsumi, H., 2002. Mutagenicity characteristics of 255 environmental chemicals. J. Health Sci. 48 (6), 545–554.
Kutzman, R.S., Meyer, G.-J., Wolf, A.P., 1978. The distribution and excretion of inhaled (11)C-benzaldehyde by the rat after acute exposure. Pharmacologist 20 (3), 145.
Kutzman, R.S., Meyer, G.-J., Wolf, A.P., 1980. Biodistribution and excretion of [11C] benzaldehyde by the rat after two-minute inhalation exposures. Xenobiotica 10 (4), 281–288.
Lacroix, G., Tissot, S., Rogerieux, F., Robidel, F., Cornu, L., Gillet, C., Beaulieu, R., Lefevre, J.P., Lafon, D., 2000. Pulmonary effects of exposure to acetaldehyde or benzaldehyde in ovalbumin-sensitized Guinea pigs. Toxicol. Lett. 16 (Suppl. 1), 20.
Lacroix, G., Tissot, S., Rogerieux, F., Beaulieu, R., Cornu, L., Gillet, C., Robidel, F., Lefevre, J.P., Bois, F.Y., 2002. Decrease in ovalbumin-induced pulmonary allergic response by benzaldehyde but not acetaldehyde exposure in a Guinea pig model. J. Toxicol. Environ. Health, Part A. 65 (14), 995–1012.
Laham, S., Potvin, M., 1987. Biological conversion of benzaldehyde to benzylmercapturic acid in the Sprague-Dawley rat. Drug Chem. Toxicol. 10 (3/4), 209–225.
Laham, S., Potvin, M., Robinet, M., 1988. Metabolism of benzaldehyde in New Zealand White rabbits. Chemosphere 17 (3), 517–524.
Laham, S., Broxup, B., Robinet, M., Potvin, M., Schrader, K., 1991. Subacute inhalation toxicity of benzaldehyde in the Sprague-Dawley rat. American Industrial Hygiene Association Journal (AIHAJ). 52 (12), 503–510.
LeBel, M., Ferron, L., Masson, M., Pichette, J., Carrier, C., 1988. Benzyl alcohol metabolism and elimination in neonates. Dev. Pharmacol. Therapeut. 11, 347–356.
Lemini, C., Silva, G., Rubio-Poo, C., Perusquia, M., 1995. Uterotrophic activity of benzoic acid as compared with estradiol and estrodiol benzoate in CD1 mice. Med. Sci. Res. 23 (4), 257–258.
Longnecker, D.S., Roebuck, B.D., Curphey, T.J., Lhoste, E., Coon, C.I., Macmillan, D., 1986. Effects of corn oil and benzyl acetate on number and size of azaserine-induced foci in the pancreas of LEW and F344 rats. Environ. Health Perspect. 68, 197–201.
Longnecker, D.S., Roebuck, B.D., Curphey, T.J., MacMillan, D.L., 1990. Evaluation of promotion of pancreatic carcinogenesis in rats by benzyl acetate. Food Chem. Toxicol. 28 (10), 665–668.
MacEwen, E.G., 1986. Anti-tumor evaluation of benzaldehyde in the dog and cat. Am. J. Vet. Res. 47 (2), 451–452.
MacMillan, K.L., 1973. The effect of benzyl alcohol on the oestrous cycle of cattle. Australian vet. Journal. 49, 267–268.
Matsui, S., Yamamoto, R., Yamada, H., 1989. The Bacillus subtilis/microsome rec-assay for the detection of DNA damaging substances which may occur in clorinated and ozonated waters. Water Sci. Technol. 21, 875–887.
Matsuoka, A., Hayashi, M., Sofuni, T., 1998. In vitro clastogenicity of 19 organic chemicals found in contaminated water and 7 structurally related chemicals. Environ. Mutagen Res. 20, 159–165.
McCloskey, S.E., 1987. Doctorial Dissertation: Toxicity of Benzyl Alcohol in Adult and Neonatal Mice. (Unpublished. Thesis submitted for the degree of Doctor of Philosophy).
McCloskey, S.E., Lertora, J.J.L., Gershanik, J.J., White, L.A., Simoneaux, D., George, W.J., 1986a. Toxicity of benzyl alcohol in adult and neonatal mice. Clin. Res. 34 (1), 197a.
McCloskey, S.E., Gershanik, J.J., Lertora, J.J.L., White, L., George, W.J., 1986b. Toxicity of benzyl alcohol in adult and neonatal mice. J. Pharm. Sci. 75 (7), 702–705.
McCormack, J.J., Boisits, E.K., Fisher, L.B., 1982. An in vitro comparison of the permeability of adult versus neonatal skin. In: Neonatal Skin. Structure and Function, pp. 149–164.
McGregor, D.B., Brown, A.G., Howgate, S., McBride, D., Riach, C., Caspary, W.J., 1991. Responses of the L5178Y mouse lymphoma cell forward mutation assay. V. 27 Coded chemicals. Environ. Mol. Mutagen. 17 (3), 196–219.
McMahon, T.F., Diliberto, J.J., Birnbaum, L.S., 1989a. Age-related changes in the disposition of benzyl acetate: a model compound for glycine conjugation. Drug Metab. Dispos. 17 (5), 506–512.
McMahon, T.F., Diliberto, J.J., Birnbaum, L.S., 1989b. Age related changes in disposition of benzyl acetate (BA): a model compound for glycine conjugation. Toxicologist 9 (1), 88.
Menczel, E., Maibach, H.I., 1970. In vitro human percutaneous penetration of benzyl alcohol and testosterone: epidermal-dermal retention. J. Investig. Dermatol. 54 (5), 386–394.
Menczel, E., Maibach, H.I., 1972. Chemical binding to human dermis in vitro testosterone and benzyl alcohol. Acta Derm. Venereol. 52 (1), 38–42.
Merriman, L., Carmines, E.L., Gaworski, C.L., Gerstenberg, B., Meisgen, T., Schramke, H., VanMiert, E., 2003. Effects of the addition of benzyl alcohol to tobacco on the chemical composition and biological activity of cigarette smoke. Toxicologist 72 (S-1), 293–294.
Meyer, F., 1965. Penetrating Agents. Patent. British. 1,001,949, M49750IVa/30h, 7/20/61.
Mikulak, S.A., Vangsness, C.T., Nimni, M.E., 1998. Transdermal delivery and accumulation of indomethacin in subcutaneous tissues in rats. J. Pharm. Pharmacol. 50 (2), 153–158.
Miller, E.C., Swanson, A.B., Phillips, D.H., Fletcher, T.L., Liem, A., Miller, J.A., 1983. Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. Cancer Res. 43 (3), 1124–1134.
Miller, J.E., Vlasakova, K., Glaab, W.E., Skopek, T.R., 2005. A low volume, high-throughput forward mutation assay in Salmonella typhimurium based on fluorouracil resistance. Mutation Research. Fundamental and Molecular Mechanisms of Mutagenesis 578 (1–2), 210–224.
Miller, M.A., Bhatt, V., Kasting, G.B., 2006. Dose and airflow dependence of benzyl alcohol disposition on skin. J. Pharm. Sci. 95 (2), 281–291.
Minor, J.L., Becker, B.A., 1971. A comparison of the teratogenic properties of sodium salicylate, sodium benzoate, and phenol. Toxicol. Appl. Pharmacol. 19 (2), 373.
Miyashita, K., Robinson, A.B., 1980. Identification of compounds in mouse urine vapor by gas chromatography and mass spectrometry. Mech. Ageing Dev. 13, 177–184.
Miyoshi, T., Ito, M., Kitayama, T., Isomori, S., Yamashita, F., 2013. Sedative effects of inhaled benzylacetone and structural features contributing to its activity. Biol.

Pharm. Bull. 36 (9), 1474–1481.
Morrissey, R.E., Schwetz, B.A., Lamb, J.C., Ross, M.D., Teague, J.L., Morris, R.W., 1988. Evaluation of rodent sperm, vaginal cytology and reproductive organ weight data from national toxicology program 13 week studies. Fundam. Appl. Toxicol. 11 (2), 343–358.
Nambata, T., Terada, N., Mizutani, T., Takeuchi, S., 1980. Effect of benzaldehyde on mouse embryo cells in vitro. Gann 71 (4), 572–573.
Nasseri-Sina, P., Hotchkiss, S.A., Caldwell, J., 1992. Metabolism of benzyl acetate in rat and human keratinocytes and rat hepatocytes: comparative studies with cells in suspension and in culture. Toxicol. Lett. 1, 168 Supple.
Natsch, A., Ryan, C.A., Foertsch, L., Emter, R., Jaworska, J., Gerberick, F., Kern, P., 2013. A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation. J. Appl. Toxicol. 33 (11), 1337–1352.
Nishihara, T., Nishikawa, J., Kanayama, T., Dakeyama, F., Saito, K., Imagawa, M., Takatori, S., Kitagawa, Y., Hori, S., Utsumi, H., 2000. Estrogenic activities of 517 chemicals by yeast two-hybrid assay. Journal of Health Sciences. Journal of Health Science 46 (4), 282–298.
Nohmi, T., Miyata, R., Yoshikawa, K., Ishidate Jr., M., 1985. Mutagenicity tests on organic chemical contaminants in city water and related compounds.I. Bacterial mutagenicity tests. Eisei Shikenjo Hokoku 103 (60), 60–64.
National Toxicology Program, 1980a. Repeated Dose Toxicity Report Benzyl Alcohol (CO6111) in Fischer 344 Rats and B6C3F1 Mice. (in press). Prepublication copy.
National Toxicology Program, 1980b. Subchronic Toxicity Report Benzyl Alcohol (C06111) in Fischer 344 Rats and B6C3F1 Mice. DRAFT (in press). Prepublication copy.
National Toxicology Program, 1986. Toxicology and Carcinogenesis Studies of Benzyl Acetate in F344/N Rats and B6CF1 Mice (Gavage Studies). NTP-TR-250. (Unpublished).
National Toxicology Program, 1989. Toxicology and Carcinogenesis Studies of Benzyl Alcohol in F344/N Rats and B6C3F1 Mice. NTP-TR-343. PB-89-2599.
National Toxicology Program, 1990. Toxicology and Carcinogenesis Studies of Benzaldehyde (CAS No. 100-52-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP-TR-378. Unpublished.
National Toxicology Program, 1993. Toxicology and Carcinogenesis Studies of Benzyl Acetate in F344 Rats and B6C3F1 Mice (Feed Studies). NTP-TR-431. NIH Publication No. 92-3162.
OECD, 1994. SIDS: benzaldehyde. UNEP Publications. Retrieved from: http://www.inchem.org/documents/sids/sids/100527.pdf.
OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
Okubo, T., Kano, I., 2003. Studies on estrogenic activities of food additives with human breast cancer MCF-7 cells and mechanism of estrogenicity by BHA and OPP. Yakugaku Zasshi 123 (6), 443–452.
Ono, Y., Somiya, I., Kawamura, M., 1991. The evaluation of genotoxicity using DNA repairing test for chemicals produced in chlorinated and ozonation processes. Water Sci. Technol. 23 (1–3), 329–338.
Patel, H., ten Berge, W., Cronin, M.T.D., 2002. Quantitative structure-activity relationships (QSARs) for the prediction of skin permeation of exogenous chemicals. Chemosphere 48 (6), 603–613.
Peresedov, V.P., 1974. Substantiation of the maximum permissible concentration of benzaldehyde in the air of a working zone. Gigiena truda i professional'nye zabolevanija. 11, 40–41.
Peterka, M., Havranek, T., Jelinek, R., 1986. Dose-response relationships in chick embryos exposed to embryotoxic agents. Folia morph 34 (1), 69–77.
Pettersen, E.O., Nome, O., Ronning, O.W., Oftebro, R., 1983. Effects of benzaldehyde on survival and cell-cycle kinetics of human cells cultivated in vitro. Eur. J. Cancer Clin. Oncol. 19 (4), 507–514.
Picard, K., Lhuguenot, J.-C., Lavier-Canivenc, M.-C., Chagnon, M.-C., 2001. Estrogenic activity and metabolism of n-butyl benzyl phthalate in vitro: identification of the active molecule(s). Toxicol. Appl. Pharmacol. 172 (2), 108–118.
Piroird, C., Ovigne, J.-M., Rousset, F., Martinozzi-Teissier, S., Gomes, C., Cotovio, J., Alepee, N., 2015. The Myeloid U937 Skin Sensitization Test (U-SENS) addresses the activation of dendritic cell event in the adverse outcome pathway for skin sensitization. Toxicol. In Vitro 29 (5), 901–916.
Price, S., 1977. Specific anosmia to geraniol in mice. Neuroscience Letters. Lond. 4, 49–50.
Procter and Gamble Company, 1996. [Submission to EPA] Dermal Penetration Potential of Perfume Materials, with Letter Dated 5/28/96. (Unpublished).
Rapson, W.H., Nazar, M.A., Butsky, V.V., 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environ. Contam. Toxicol. 24 (4), 590–596.
Renwick, A.G., 1993. Data-derived safety factors for the evaluation of food additives and environmental contaminants. Food Addit. Contam. 10 (3), 275–305.
Revial, M.F., Sicard, G., Duchamp, A., Holley, A., 1982. New studies on odour discrimination in the frog's olfactory receptor cells. I. Experimental results. Chem. Senses 7 (2), 175–190.
RIFM (Research Institute for Fragrance Materials, Inc), 1957. Toxicological Screening of Ethyl Benzoate, Isobutyl Benzoate, Benzyl Acetate, Benzyl Butyrate, and Ethyl Methylphenylglycidate in Rats. Class V. Aromatic Esters. Unpublished report from Trubek Laboratories, Inc.. RIFM report number 29140. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1802. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1982. Mutagenicity Evaluation of Benzaldehyde in the Ames Salmonella/microsome Plate Test. Private Communication to FEMA. Unpublished report from Lorillard Tobacco Company. RIFM report number 36348. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1983. Mutagenicity Evaluation of Benzaldehyde in the Mouse Lymphoma Forward Mutation Assay. Private Communication to FEMA. Unpublished report from Lorillard Tobacco Company. RIFM report number 36349. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2001. Benzyl Alcohol: A 5 Day Inhalation Toxicity Study in the Rat. Unpublished Report from Dotti, A., Huber, H., Kroling, C. & Madorin, B. RIFM Report Number 54635. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Fragrance Material Review on Cis-P-Menthan-7-Ol. RIFM report number 56385. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc)., 2008. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM report number 55663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2009. Micronucleus Assay in Bone Marrow Cells of the Mouse with Benzaldehyde. RIFM report number 56531. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2009. Repeated Insult Patch Test with Benzaldehyde. RIFM report number 57360. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2009. A 4-week Inhalation Toxicity Study of Aerosolized Benzyl Alcohol and Benzoic Acid in Sprague-Dawley Rats. RIFM report number 58285. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Genotoxicity Tests Conducted on a Group of Structurally Related Aldehydes. RIFM report number 58568. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012. Fragrance Material Review on Benzyl Alcohol. RIFM report number 64062. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012. Fragrance Material Review on Benzyl Acetate. RIFM report number 64102. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012. A Toxicological and Dermatological Assessment of Aryl Alkyl Alcohol Simple Acid Ester Derivatives when Used as Fragrance Ingredients. RIFM report number 65259. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012. Report on the Testing of 21 Compounds in BlueScreen HC Assay (-/+ S9 Metabolic Activation). Unpublished report from Firmenich. RIFM report number 65264. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of Benzaldehyde in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65918. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. A Two-Week Inhalation Toxicity Study of Aerosolized Benzyl Acetate in the Sprague Dawley Rat. RIFM report number 65459. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Exposure Survey 01, May 2013.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rockwell, P., Raw, I., 1979. A mutagenic screening of various herbs, spices, and food additives. Nutr. Cancer 1 (4), 10–15.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Roth, R.P., Tansy, M.F., 1972. Effects of gaseous air pollutants on gastric secreto-motor activities in the rat. J. Air Pollut. Control Assoc. 22 (8), 706–709.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Saiyasombati, P., Kasting, G.B., 2003. Disposition of benzyl alcohol after topical application to human skin in vitro. J. Pharm. Sci. 92 (10), 2128–2139.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Sasaki, Y., Endo, R., 1978. Mutagenicity of aldehydes in Salmonella. Mutation Research. Environmental Mutagenesis and Related Subjects 54 (2), 251–252.
Sasaki, Y.F., Imanishi, H., Phta, T., Shirasu, Y., 1989. Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. Mutation Research. Letters 226 (1), 103–110.
SCCNFP, 2002. Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning benzoic acid and sodium benzoate. Retrieved from: http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out166_en.pdf.
Schafer Jr., E.W., Bowles Jr., W.A., 1985. Acute oral toxicity and repellency of 933 chemicals to house and deer mice. Arch. Environ. Contam. Toxicol. 14, 111–129.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Schunk, H.H., Shibamoto, T., Tan, H.K., Wei, C.-I., 1986. Biological and chemical studies on photochemical products obtained from eugenol, benzyl acetate and benzyl benzoate. In: Flavors Frag. A World Persp. Proc. 10th Internat. Cong. Es. Oils, pp. 1045–1068.

Schweinsberg, F., Danecki, S., Grotzke, J., vonKarsa, L., Burkle, V., 1986. Modifying effects of disulfiram on DNA adduct formation and persistence of benzaldehyde in N-nitroso-N-methyl-benzylamine-induced carcinogenesis in rats. J. Cancer Res. Clin. Oncol. 112 (2), 75–80.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Sherwin, C.P., Crowdle, J.H., 1922. Detoxication in the organism of the fowl. PSEBM (Proc. Soc. Exp. Biol. Med.) 19, 318–320.
Shtenberg, A.J., Ignat'ev, A.D., 1970. Toxicological evaluation of some combinations of food presevatives. Food Cosmet. Toxicol. 8 (4), 369–380.
Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. In: Annals of the New York Academy of Sciences, vol. 641. pp. 152–163.
Sloane, N.H., 1965. Hydroxymethylation of the benzene ring. 1. Microsomal formation of phenol via prior hydroxymethylation of benzene. Biochim. Biophys. Acta 107, 599–602.
Smith, L., Packer, L., 1972. Aldehyde oxidation in rat liver mitochondria. Arch. Biochem. Biophys. 148, 270–276.
Snapper, J., Grunbaum, A., Sturkop, S., 1925. About the fission and oxidation of benzyl alcohol and benzyl esters in the human organism. Biochem. Z. 155, 163–173.
Sodemoto, Y., Enomoto, M., 1980. Report of carcinogenesis bioassay of sodium benzoate in rats: absence of carcinogenicity of sodium benzoate in rats. J. Environ. Pathol. Toxicol. 4 (1), 87–95.
Sofuni, T., Hayashi, M., Matsuoka, A., Sawada, M., Hatanaka, M., Ishidate, M., 1985. Mutagenicity tests on organic chemical contaminants in city water and related compounds. II. Chromosome aberration tests in cultured mammalian cells. Eisei Shikenjo Hokoku 103, 64–75.
Sporn, A., Dinu, I., Stanciu, V., 1967. Investigations on the toxicity of benzaldehyde. Igiena 16 (1), 23–24.
Steinhagen, W.H., Barrow, C.S., 1984. Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. Toxicol. Appl. Pharmacol. 72 (3), 495–503.
Taylor, J.M., Jenner, P.M., Jones, W.I., 1964. A comparison of the toxicity of some allyl, propenyl, and propyl compounds in the rat. Toxicol. Appl. Pharmacol. 6 (4), 378–387.
Teuchy, H., Quatacker, J., Wolf, G., VanSumere, C.F., 1971. Quantitative investigation of the hippuric acid formation in the rat after administration of some possible aromatic and hydroaromatic precursors. Archives int. Physiol. Biochim. 79, 573–587.
The Union of German Candle Manufacturers, 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. (Unpublished).
Urbisch, D., Mehling, A., Guth, K., Ramirez, T., Honarvar, N., et al., 2015. Assessing skin sensitization hazard in mice and men using non-animal test methods. Regul. Toxicol. Pharmacol. 71 (2), 337–351.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Vamvakas, S., Dekant, W., Anders, M.W., 1989. Mutagenicity of benzyl S-haloalkyl and S-haloalkenyl sulfides in the Ames-test. Biochem. Pharmacol. 38 (6), 935–939.
Van Hulst, M., Van Gompel, A.H.P., Cornwell, P.A., 1997. Percutaneous Absorption and Skin Metabolism: the Effects of Formulation Excipients on Metabolism. Perspectives in Percutaneous Penetration. pp. 45–49 5B.
Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., Thomas, C.A., 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol. Appl. Pharmacol. 56 (2), 265–273.
Walkenstein, S.S., Weinhouse, S., 1953. Oxidation of aldehydes by mitochondria of rat tissues. J. Biol. Chem. 200, 515–523.
Watanabe, K., Matsuda, M., Furuhashi, S., Kimura, T., Matsunaga, T., Yamamoto, I., 2001. Skin reaction induced by aldehydes for food flavoring agents. Journal of Health Sciences. Journal of Health Science 47 (3), 327–329.
Wenzel, A., Nendza, M., Hartman, P., Kanne, R., 1997. Test battery for the assessment of aquatic toxicity. Chemosphere 35 (1/2), 307–322.
World Health Organization, 1996. Benzyl acetate, benzyl alcohol, benzaldehyde and benzoic acid and its salts. WHO Food Addit. Ser. 37, 31–79.
Woodruff, R.C., Mason, J.M., Valencia, R., Zimmering, S., 1985. Chemical mutagenesis testing in Drosophilia. V. Results of 53 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7 (5), 677–702.
Yang, Y.-C., Lee, H.-S., Lee, S.H., Clark, J.M., Ahn, Y.-J., 2005. Ovicidal and adulticidal activities of Cinnamomum zeylanicum bark essential oil compounds and related compounds against Pediculus humanus capitis (Anoplura: pediculicidae). Int. J. Parasitol. 35 (14), 1595–1600.
Young, S.S., 1989. What is the proper experimental unit for long-term rodent studies? An examination of the NTP benzyl acetate study. Toxicology 54, 233–239.
Yuan, J.H., Goehl, T.J., Abdo, K., Clark, J., Espinosa, O., Bugge, C., Garcia, D., 1995. Effects of gavage versus dosed feed administration on the toxicokinetics of benzyl acetate in rats and mice. Food Chem. Toxicol. 33 (2), 151–158.
Zeiger, E., Margolin, B.H., 2000. The proportions of mutagens among chemicals in commerce. Regul. Toxicol. Pharmacol. 32 (2), 219–225.