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RIFM fragrance ingredient safety assessment, phenylacetaldehyde, CAS Registry Number 122-78-1.

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*

A B S T R A C T

The existing information supports the use of this material as described in this safety assessment.

The material (phenylacetaldehyde) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data show that phenylacetaldehyde is not genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose and developmental and reproductive toxicity endpoints. Data from phenylacetaldehyde provided a No Expected Sensitization Induction Level (NESIL) of 590 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was completed using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to phenylacetaldehyde was below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on data and ultraviolet (UV) spectra; phenylacetaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; phenylacetaldehyde was not found to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) environmental standards and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]) are <1.

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

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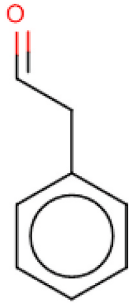
Version: 032,720. This version replaces any previous versions.

Name: Phenylacetaldehyde
CAS Registry Number: 122-78-1



Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD -
Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA -
North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD -
Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant -
Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources

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(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.

The material (phenylacetaldehyde) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data show that phenylacetaldehyde is not genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose and developmental and reproductive toxicity endpoints. Data from phenylacetaldehyde provided a No Expected Sensitization Induction Level (NESIL) of 590 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was completed using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to phenylacetaldehyde was below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on data and ultraviolet (UV) spectra; phenylacetaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; phenylacetaldehyde was not found to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) environmental standards and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]) are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic	(RIFM, 2015a; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 33.33 mg/kg/day	RIFM (2017)
Developmental and Reproductive Toxicity: NOAEL = 100 mg/kg/day	RIFM (2017)
Skin Sensitization: NESIL = 590 μg/cm^2	(RIFM, 2003a; RIFM, 2004)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM Database; RIFM, 1975)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 85% (OECD 301B)	RIFM (1994)
Bioaccumulation: Screening-level: 6.941 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 538.9 mg/L	(RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 538.9 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.5389 μg/L

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

1. Identification

1. **Chemical Name:** Phenylacetaldehyde
2. **CAS Registry Number:** 122-78-1
3. **Synonyms:** Benzeneacetaldehyde; Benzylcarboxaldehyde; Hyacinthin; 1-Oxo-2-phenylethane; Phenylacetic aldehyde; α-Tolualdehyde; α-Toluic aldehyde; Phenyl Acetic Aldehyde (pure); フェニルア□キル (C = 1–4) アルデヒド; Phenyl acetaldehyde pure; Phenylacetaldehyd; Phenylacetaldehyde
4. **Molecular Formula:** C_8H_8O
5. **Molecular Weight:** 120.15
6. **RIFM Number:** 197

2. Physical data

1. **Boiling Point:** 206 °C (Fragrance Materials Association [FMA] Database), 201.51 °C (EPI Suite)
2. **Flash Point:** 160 °F, CC (FMA Database)
3. **Log K_{OW}:** 1.54 (EPI Suite)
4. **Melting Point**: −10.41 °C (EPI Suite)
5. **Water Solubility:** 3026 mg/L (EPI Suite)
6. **Specific Gravity:** 1.07 g/mL (RIFM, 1994), 1.03 (FMA Database)
7. **Vapor Pressure:** 0.217 mm Hg @ 20 °C (EPI Suite v4.0), 0.3 mm Hg 20 °C (FMA Database), 0.354 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorption in the region 290–700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless to slightly yellow, oily liquid with very powerful and penetrating, pungent, green-floral, sweet hyacinth, lilac odor

3. Volume of use (Worldwide Band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0046% (RIFM, 2015b)
2. **Inhalation Exposure*:** 0.000032 mg/kg/day or 0.0022 mg/day (RIFM, 2015b)
3. **Total Systemic Exposure**:** 0.00023 mg/kg/day (RIFM, 2015b)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

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

7. Metabolism

Panoutsopoulos (2005): The metabolism of phenylacetaldehyde to phenylacetic acid was studied in freshly prepared and cryopreserved guinea pig liver slices. The study compared the relative contribution of aldehyde oxidase, xanthine oxidase, and aldehyde dehydrogenase in the oxidation of phenylacetaldehyde using specific inhibitors for each oxidizing enzyme (isovanillin for aldehyde oxidase, allopurinol for xanthine oxidase, and disulfiram for aldehyde dehydrogenase). In freshly prepared liver slices, phenylacetaldehyde was converted mainly to phenylacetic acid, with traces of 2-phenylethanol being present. Disulfiram inhibited phenylacetic acid formation by 80%–85%, whereas isovanillin inhibited acid formation to a lesser extent (50%–55%), and allopurinol had little or no effect. In cryopreserved liver slices, phenylacetic acid was also the main metabolite, whereas the 2-phenylethanol production was more pronounced than that in freshly prepared liver slices. Isovanillin inhibited phenylacetic acid formation by 85%, whereas disulfiram inhibited acid formation to a lesser extent (55%–60%), and allopurinol had no effect. The results in this study show that, in freshly prepared and cryopreserved liver slices, phenylacetaldehyde is converted to phenylacetic acid by both aldehyde dehydrogenase and aldehyde oxidase, with no contribution from xanthine oxidase. Therefore, aldehyde dehydrogenase and aldehyde oxidase both play an essential role in the metabolism of phenylacetaldehyde to less chemically reactive metabolites. The metabolism scheme is as shown below (Fig. 1).

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

Phenylacetaldehyde is reported to occur in the following foods by the

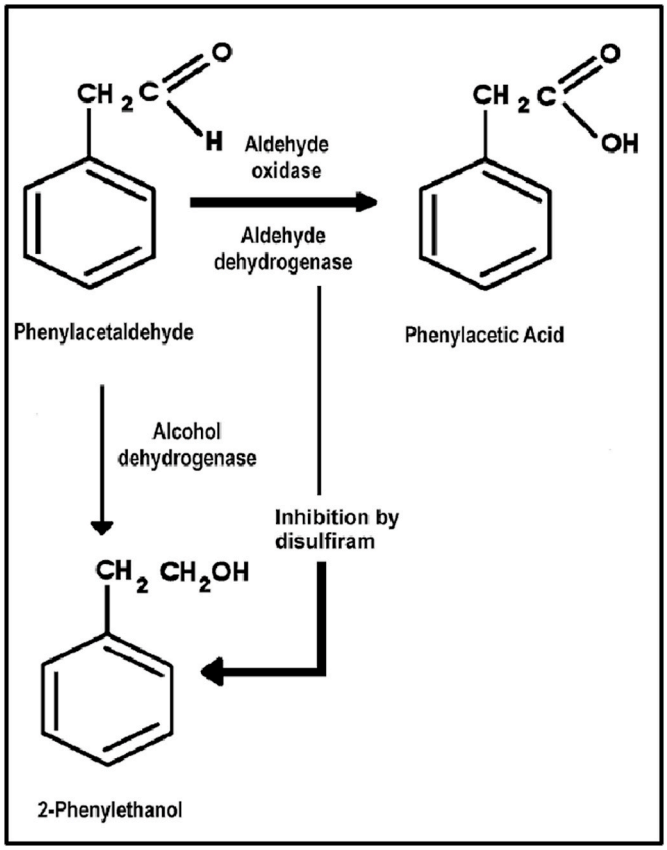

Fig. 1. Adapted from (Panoutsopoulos, 2005).

VCF*:

Acerola (*Malpighia*)	Licorice (*Glycyrrhiza* species)
Apple brandy (calvados)	Loquat (*Eriobotrya japonica* Lindl.)
Apple processed (*Malus* species)	Lovage (*Levisticum officinale Koch*)
Apricot (*Prunus armeniaca* L.)	Macadamia nut (*Macadamia integrifolia*)
Artichoke	Maize (*Zea mays* L.)
Artocarpus species	Malt
Asparagus (*Asparagus officinalis* L.)	*Mangifera* species
Aubergine, eggplant (*Solanum melongena* L.)	Mangosteen (*Garcinia mangostana* L.)
Banana (*Musa sapientum* L.)	Mate (*Ilex paraguayensis*)
Beans	Matsutake (*Tricholoma matsutake*)
Beef	Melon
Beer	Mentha oils
Beetroot (*Beta vulgaris* L.)	Milk and milk products
Black chokeberry juice (*Aronia melanocarpa* Ell.)	Plum (*Prunus* species)
Blue cheeses	Popcorn
Buckwheat	Pork
Cabbage (*Brassica oleracea*)	Potato (*Solanum tuberosum* L.)
Capers (*Capparis spinoza*)	Potato chips (American)
Capsicum species	Prickly pear (*Opuntia ficus indica*)
Cashew apple (*Anacardium occidentale*)	Pumpkin (*Cucurbita pepo* L.)
Cassava (*Manihot esculenta crantz*)	Pumpkin seed oil
Cauliflower and broccoli	Quince, marmelo (*Cydonia oblonga* Mill.)
Celery (*Apium graveolens* L.)	Raspberry, blackberry, and boysenberry
Chayote (*Sechium edule* L.)	Rice (*Oryza sativa* L.)
Cheddar cheese	Rice cake
Cheese, various types	Rooibos tea (*Aspalathus linearis*)
Cherimoya (*Annona cherimolia Mill.*)	Rum
Cherry (*Prunus avium*-sweet, *P. cerasus*-sour)	Rye bread
Chestnut (*Castanea* species)	Sake
Chicken	Salami
Cider (apple wine)	*Salvia* species
Citrus fruits	Sea buckthorn (*Hippophaë rhamnoides* L.)
Clam	Sherry
Cocoa category	Shoyu (fermented soya hydrolysate)
Coconut (*Cocos nucifera* L.)	Southernpea (*Vinga unguiculata* L.)
Coffee	Soybean (*Glycine max. L. merr.*)
Crispbread	Starfruit (*Averrhoa carambola* L.)
Dill (*Anethum* species)	Sukiyaki
Egg	Sweet grass oil (*Hierochloe odorata*)
Elderberry (*Sambucus nigra* L.)	Sweet potato (*Ipomoea batatas*) (heated)
Endive (*Cichorium endivia* L.)	Swiss cheeses
Filbert, hazelnut (*Corylus avellano*)	Tamarind (*Tamarindus indica* L.)
Fish	Tea
Grape (*Vitis* species)	Tequila (*Agave tequilana*)
Grape brandy	Tomato (*Lycopersicon esculentum* Mill.)
Guava and feyoa	Trassi (cooked)
Guinea hen	Turkey
Honey	*Vaccinium* species
Hop (*Humulus lupulus*)	Vanilla
Katsuobushi (dried bonito)	Vinegar
Kiwifruit (*Actinidia chinensis, syn. A. deliciosa*)	Water yam (*Dioscorea alata*)
Krill	Wheaten bread
Kumazasa (*Sasa albo-marginata*)	Whey protein hydrolysate
Lamb and mutton	Wine
Lemon balm (*Melissa officinalis* L.)	Wormwood oil (*Artemisia absinthium* L.)

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C. A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 03/27/20.

10. Conclusion

The maximum acceptable concentrations[a] in the finished products for phenylacetaldehyde 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	Not Restricted

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For phenylacetaldehyde, the basis was a reference dose of 0.3 mg/kg/day, a 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 (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the existing data, phenylacetaldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Phenylacetaldehyde was tested in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity (RIFM, 2013). The mutagenic activity of phenylacetaldehyde has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with phenylacetaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, phenylacetaldehyde was not mutagenic in the Ames test.

The clastogenic activity of phenylacetaldehyde was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations

and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with phenylacetaldehyde in DMSO at concentrations up to 1202 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 20 h. Phenylacetaldehyde did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2016a). Under the conditions of the study, phenylacetaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: Kato (1989); Mendelson (1965). bib_Mendelson_and_Fraser_1965

Literature Search and Risk Assessment Completed On: 05/15/14.

11.1.2. Repeated dose toxicity

The MOE for phenylacetaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on phenylacetaldehyde. In an OECD 422 (combined repeated dose and reproductive toxicity) and GLP-compliant study, 12 Sprague Dawley (Crl: CD [SD]) SPF rats/sex/dose were orally administered phenylacetaldehyde through gavage at doses of 0, 25, 100, and 400 mg/kg/day. Recovery groups consisting of 6 animals/sex from the control and high doses were maintained for a 2-week post-exposure period. During the main study, 1 female was found to be moribund (day 14), and 2 males (day 40) and 1 female (day 39) were found dead in the 400 mg/kg/day group. Mortality was not reported in other dose groups. Increased salivation was reported in the 400 mg/kg/day treatment group (5 males and 7 females) from day 5 onwards; this was also observed in the 400 mg/kg/day recovery group (5 males, 3 females). Although no change in male body weight was reported during treatment, female body weights were significantly decreased in the 100 and 400 mg/kg/day groups on postpartum day 0 and gestation day 7, respectively. In contrast, in the recovery groups, only male body weights were significantly decreased on treatment days 8 and 14, but the differences were reversed during the recovery period. Since no information on bodyweight gain was reported in the study report, it does not allow for determining if the bodyweight changes were treatment-related adverse events. During the study (including the recovery period), no alterations were reported in male food consumption in any treatment group. However, among females, food consumption was significantly lower in the 100 and 400 mg/kg/day groups. This effect was observed on gestation days 1 and 7 and postpartum day 4 at 100 mg/kg/day dose and on gestation day 7 only in the 400 mg/kg/day group. Moreover, significantly lower food consumption was reported only at the end of the recovery period (study day 63) in the recovery-group females receiving the highest dose. Due to a lack of consistent change, these effects were not considered to be treatment-related adverse effects. No treatment-related effects for hematology, clinical chemistry, auditory reflex, pinna reflex, pupillary reflex, corneal reflex test, and grip strength were reported in animals of both sexes at any dose level. At the highest dose, erythrophagocytosis and diffuse lymphoid hyperplasia of mesenteric lymph nodes and centrilobular hepatocellular hypertrophy were reported in both sexes. Additionally, thymus atrophy was also reported in females of the high-dose group. In the absence of inflammation, degeneration or necrosis, the centrilobular hepatocellular hypertrophy was regarded as a treatment-related adaptive response. Hence, based on the treatment-related erythrophagocytosis and diffuse lymphoid hyperplasia of mesenteric lymph nodes in both sexes as well as thymus atrophy in females at the highest dose, 100 mg/kg/day was considered to be the NOAEL for repeated dose toxicity endpoint (RIFM, 2017).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33.33 mg/kg/day.

Therefore, the phenylacetaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenylacetaldehyde NOAEL in mg/kg/day by the total systemic exposure to phenylacetaldehyde, 33.33/0.00023 or 144,913.

In addition, the total systemic exposure to phenylacetaldehyde (0.23 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose endpoint of a Cramer Class I material at the current level of use.

Derivation of reference dose (RfD):

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.3 mg/kg/day.

The RfD for phenylacetaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 33.33 mg/kg/day by the uncertainty factor, 100 = 0.3 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/07/19.

11.1.3. Developmental and reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on phenylacetaldehyde that can be used to support the developmental and reproductive toxicity endpoints. An OECD 422/GLP study was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered via oral gavage test material phenylacetaldehyde at doses of 0, 25, 100, or 400 mg/kg/day. Males were dosed for a total of 49 days (2 weeks prior to mating, during the 2-week mating period, and up to 21 days post-mating), while females were dosed 2 weeks prior to mating, throughout gestation, and for 13 days after delivery. Additional groups of 6 rats/sex/dose were assigned to the control and high-dose groups to serve as the 14-day treatment-free recovery groups and were not mated. Males and females of the recovery groups were dosed for 49 days. In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. At 400 mg/kg/day, 1 dam was found moribund, and 2 males and 1 dam were found dead. The females showed irregular respiration before their moribund state or death. The dead animals exhibited thickening of the forestomach and centrilobular hepatocellular hypertrophy of the liver. Furthermore, they showed poor condition/stress-related gross observations (i.e., adrenal enlargement, black area/red discoloration of the glandular stomach, and small thymus, or spleen). Thymic atrophy was found in 2 high-dose group dams whose pups were all dead. A statistically significant increase in post-implantation loss and a statistically significant decrease in the live birth index were observed among the 400 mg/kg/day group dams. The viability index on post-natal day (PND) PND 4 for the control, low-, mid-, and high-dose groups were 97.4, 96.1, 98.8, and 68.9%, respectively. Although the viability on PND 4 was not statistically significant at 400 mg/kg/day, this finding was considered to be toxicologically significant since the differences were substantial as compared

to the controls. Thus, the NOAEL for reproductive toxicity was considered to be 400 mg/kg/day for males and 100 mg/kg/day for females, based on increased post-implantation loss and decreased live birth index among high-dose group dams. The NOAEL for developmental toxicity was considered to be 100 mg/kg/day, based on decreased viability on PND 4 among high-dose group pups (RIFM, 2017). **Therefore, the phenylacetaldehyde MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the phenylacetaldehyde NOAEL in mg/kg/day by the total systemic exposure to phenylacetaldehyde, 100/0.00023 or 434,783.**

In addition, the total systemic exposure to phenylacetaldehyde (0.23 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/19.

11.1.4. Skin sensitization

Based on the available data, phenylacetaldehyde is considered to be a moderate skin sensitizer with a defined NESIL of 590 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, phenylacetaldehyde is considered to be a moderate skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree 2.6.13; OECD Toolbox v3.4). Phenylacetaldehyde was found to be positive in the *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, human cell line activation Test (h-CLAT), and U937-CD86 test (Natsch, 2013; Urbisch, 2015). Moreover, in a murine local lymph node assay (LLNA), phenylacetaldehyde was found to be sensitizing with a weighted mean EC3 value of 3.8% (962 μg/cm^2) (Basketter, 2001, 2002, 2003; Gerberick, 2004). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 1% or 1181 μg/cm^2 phenylacetaldehyde and 0.5% tocopherol in 3:1 ethanol:diethyl phthalate (EtOH:DEP), reactions indicative of sensitization were observed in 7/27 volunteers (RIFM, 2003a). However, in another HRIPT, 1% or 1181 μg/cm^2 phenylacetaldehyde with 0.5% tocopherol in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 26 volunteers (RIFM, 2003b). Similarly, in a separate HRIPT with 0.5% or 591 μg/cm^2 of phenylacetaldehyde and 0.5% tocopherol in 1:3 EtOH:DEP conducted according to the method of Politano et al. (Politano, 2008), no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2004). Based on weight of evidence (WoE) from structural analysis and animal and human studies, phenylacetaldehyde is a moderate sensitizer with a WoE NESIL of 590 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.3 mg/kg/day.

Additional References: Klecak (1977); Klecak, 1979; RIFM, 1972; RIFM, 1974a; RIFM, 1976; RIFM, 1974b.

Literature Search and Risk Assessment Completed On: 02/25/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available data and UV/Vis absorbance spectra, phenylacetaldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In a human phototoxicity study, no reactions indicative of phototoxic responses were observed following topical application of 1% and 20% phenylacetaldehyde (RIFM, 1975). Based on the human data and the lack of absorbance, phenylacetaldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available UV/Vis spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/22/19.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for phenylacetaldehyde is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on phenylacetaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.0022 mg/day. This exposure is 636.4 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/26/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenylacetaldehyde was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight

Table 1
Data summary for phenylacetaldehyde.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
962 [2]	moderate	591	NA	1181	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.

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, phenylacetaldehyde was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify phenylacetaldehyde as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

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

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 1994: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test following the OECD 301B method. After 28 days, biodegradation of 85% was observed.

RIFM, 2001: Biodegradability of the test material was evaluated according to the OECD 301D method. The biodegradation came to a maximum of 74% after 21 days.

RIFM, 1999: The purpose of this study was to determine the biological degradation of the test material using the closed bottle method. The test material was dissolved in mineral medium and inoculated with an aquatic mixed population of microorganisms. Biodegradation of 51% was observed after 28 days.

11.2.1.2.2. Ecotoxicity. RIFM, 1999: A 48-h *Daphnia magna* acute toxicity test was conducted according to the Directive 92/69/EEC, C.2 method. The EC0, EC50, and EC100 after 48 h (analytical concentration) were 7.2, 20, and 53 mg/L, respectively, under the conditions employed in this study.

RIFM, 2016b: An algae growth inhibition study was conducted according to the OECD 201 method. The EC50 (0–72 h) was reported to be 1.6 mg/L and 0.85 mg/L, based on growth rate and yield, respectively.

RIFM, 2016c: A fish (zebrafish) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96 h LC50 was reported to be greater than 6.2 mg/L.

11.2.1.3. Other available data. Phenylacetaldehyde has been registered for REACH with no additional data at this time.

11.2.2. Risk assessment refinement

Since phenylacetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>538.9</u>			1000000	0.5389	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.4	1.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.5389 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 02/20/19.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 03/27/20.

Declaration of competing interest

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

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