Food and Chemical Toxicology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, formaldehyde cyclododecyl ethyl acetal, CAS Registry Number 58567-11-6

A.M. Api [a], D. Belsito [b], 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], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

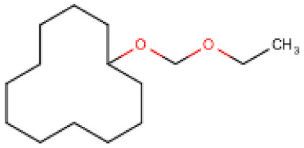
[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department 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), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling editor: Dr. Jose Luis Domingo

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

https://doi.org/10.1016/j.fct.2021.112503
Received 15 April 2021; Received in revised form 29 June 2021; Accepted 7 August 2021
Available online 11 August 2021



Version: 021021. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: Formaldehyde cyclododecyl ethyl acetal

CAS Registry Number: 58567-11-6

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

CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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 Observed 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

(*continued on next column*)

(*continued*)

(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.

Formaldehyde cyclododecyl ethyl acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that formaldehyde cyclododecyl ethyl acetal is not genotoxic. Data on formaldehyde cyclododecyl ethyl acetal provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided formaldehyde cyclododecyl ethyl acetal a No Expected Sensitization Induction Level (NESIL) of 3500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; formaldehyde cyclododecyl ethyl acetal is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to formaldehyde cyclododecyl ethyl acetal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; Formaldehyde cyclododecyl ethyl acetal was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2013d; RIFM, 2013a)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM (2013b)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: (Ethoxymethoxy) cyclododecane; ECHA, 2013; RIFM, 2013b)
Skin Sensitization: NESIL = 3500 μg/cm^2.	RIFM (2016a)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV Spectra; RIFM Database; RIFM, 1991)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 5% (OECD 301B)	RIFM (1999)
Bioaccumulation: Critical Measured Value: BCF: 729 L/kg	(ECHA REACH Dossier: (Ethoxymethoxy) cyclododecane; ECHA, 2013)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 1.6 mg/L	RIFM (2013c)
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: 48-h *Daphnia magna* EC50: 1.6 mg/L	RIFM (2013c)

RIFM PNEC is: 1.6 μg/L

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

1. Identification

1. **Chemical Name:** Formaldehyde cyclododecyl ethyl acetal
2. **CAS Registry Number:** 58567-11-6

3. **Synonyms:** Boisambrene forte; Cyclodecane, (ethoxymethoxy)-; (Ethoxymethoxy)cyclododecane; エトキシメトキシシクロドデカン; Amberwood; Amberwood F; Formaldehyde cyclododecyl ethyl acetal
4. **Molecular Formula:** $C_{15}H_{30}O_2$
5. **Molecular Weight:** 242.4
6. **RIFM Number:** 1060
7. **Stereochemistry:** Isomer not specified. One chiral center and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** 290.1 °C (RIFM, 2012b), 94 °C (RIFM), 308.37 °C (EPI Suite)
2. **Flash Point:** 136 °C (Globally Harmonized System), 136 °C (RIFM, 2012a), 145 °C (RIFM), estimated half-life at 25 °C was 299, 259, and 243 h at pH 4, 7, and 9, respectively (expected products of hydrolysis are cyclododecanol, formaldehyde, and ethanol) (RIFM, 2013i)
3. **Log K_{OW}:** 5.4 at 25.0 ± 0.5 °C (RIFM, 2012d), 5.51 (EPI Suite), >6.0 (RIFM, 1997a)
4. **Melting Point**: 24.71 °C (EPI Suite)
5. **Water Solubility:** 0.5108 mg/L (EPI Suite)
6. **Specific Gravity:** 0.9336 (RIFM)
7. **Vapor Pressure:** 0.00144 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg at 20 °C (Fragrance Materials Association), 0.00234 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Light yellow liquid

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.64% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00091 mg/kg/day or 0.066 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.012 mg/kg/day (RIFM, 2019)

*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

6.1. Cramer Classification

Class I*, Low (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	III

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See the Appendix below for further detail.

6.2. Analogs Selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity**/Photoallergenicity**:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across Justification

None

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

Formaldehyde cyclododecyl ethyl acetal is not reported to occur in foods by the VCF*.

*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 11/13/20 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for formaldehyde cyclododecyl ethyl acetal are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.27
2	Products applied to the axillae	0.080
3	Products applied to the face/body using fingertips	1.6
4	Products related to fine fragrances	1.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.38
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.38
5C		0.38

(continued on next page)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	
5D	Baby cream, oil, talc	0.13
6	Products with oral and lip exposure	0.49
7	Products applied to the hair with some hand contact	3.1
8	Products with significant ano-genital exposure (tampon)	0.13
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	11
10B	Aerosol air freshener	11
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.13
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 formaldehyde cyclododecyl ethyl acetal, the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 3500 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). [c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, formaldehyde cyclododecyl ethyl acetal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Formaldehyde cyclododecyl ethyl acetal was assessed in the BlueScreen assay and found positive for genotoxicity in the presence of S9, which occurred in the presence of cytotoxicity. Results were negative for genotoxicity in the absence of S9 (RIFM, 2013e). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of formaldehyde cyclododecyl ethyl acetal 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with formaldehyde cyclododecyl ethyl acetal 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, 2013d). Under the conditions of the study, formaldehyde cyclododecyl ethyl acetal was not mutagenic in the Ames test.

The clastogenic activity of formaldehyde cyclododecyl ethyl acetal 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 formaldehyde cyclododecyl ethyl acetal in ethanol at concentrations of up to 2500 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 20 h. Formaldehyde cyclododecyl ethyl acetal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2013a). Under the conditions of the study, formaldehyde cyclododecyl ethyl acetal was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, formaldehyde cyclododecyl ethyl acetal does not present a concern for genotoxic potential.

Additional References: RIFM, 2013f; RIFM, 2014b.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

The MOE for formaldehyde cyclododecyl ethyl acetal 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 formaldehyde cyclododecyl ethyl acetal to support the repeated dose toxicity endpoint. An OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Wistar rats. Groups of 11 rats/sex/dose were administered via oral gavage with test material, formaldehyde cyclododecyl ethyl acetal at doses of 0, 50, 300, or 1000 mg/kg/day in corn oil. Male rats were treated for 28 days, whereas female rats were treated 14 days prior to pairing, through the pairing and gestation, until post-partum day 3. There was a statistically significant increase in blood creatinine concentration among all treatment group males and a statistically significant decrease in blood phosphorus concentration in males of the mid and high groups. Histopathological examination revealed lesions in the kidneys in males of the mid- and high-dose groups. Therefore, the alterations in creatinine and phosphorus concentrations were considered to most probably be secondary to these lesions. Furthermore, hyaline droplets associated with tubular basophilia and the presence of granular casts were observed in males treated at 300 and 1000 mg/kg/day. These kidney alterations in males were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). A statistically significant increase in liver weights with associated statistically significant lower concentrations of total bilirubin and bile acids was observed in high-dose males. Macroscopic examination revealed an enlarged liver found in a single high-dose female. Microscopic examinations revealed treatment-related findings in the liver of males and females treated at 1000 mg/kg/day. These changes consisted of centrilobular hypertrophy of the hepatocytes and were considered to be an adaptive change due to lack of histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage and clinical chemistry alterations (Hall, 2012). High-dose males also exhibited hypertrophy of the follicular epithelium of the thyroid gland, which was considered to be secondary to the increased metabolism in the liver. Thus, the NOAEL systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2013b).

A default safety factor of 3 was used when deriving a NOAEL from an 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 1000/3 or 333 mg/kg/day.

Therefore, the formaldehyde cyclododecyl ethyl acetal MOE for the repeated dose toxicity endpoint can be calculated by dividing the formaldehyde cyclododecyl ethyl acetal in mg/kg/day by the total systemic exposure to formaldehyde cyclododecyl ethyl acetal, 333/0.012, or 27750.

In addition, the total systemic exposure to formaldehyde cyclododecyl ethyl acetal (12 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I

material at the current level of use.

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, 2020) and a reference dose of 3.33 mg/kg/day.

Derivation of reference dose (RfD)

The RfD for formaldehyde cyclododecyl ethyl acetal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 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: 11/13/20.

11.1.3. Reproductive toxicity

The MOE for formaldehyde cyclododecyl ethyl acetal 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 toxicity data on formaldehyde cyclododecyl ethyl acetal to support the developmental toxicity endpoint. An OECD/GLP 414 prenatal developmental toxicity study was conducted in female Sprague Dawley rats. Groups of 24 rats were administered daily via oral gavage with test material at doses of 0, 100, 300, or 1000 mg/kg/day from gestation days 5–20. There were no treatment-related effects on the gravid uterus weights, the number of corpora lutea, implantation sites, live fetuses, sex ratio, dead fetuses, resorptions, or pre- and post-implantation losses. No treatment-related effects on fetal weights or any external, internal, or skeletal anomalies were observed. Thus, the NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). **Therefore, the formaldehyde cyclododecyl ethyl acetal MOE for the developmental toxicity endpoint can be calculated by dividing the formaldehyde cyclododecyl ethyl acetal in mg/kg/day by the total systemic exposure to formaldehyde cyclododecyl ethyl acetal, 1000/0.012, or 83333.**

There are sufficient reproductive toxicity data on formaldehyde cyclododecyl ethyl acetal to support the reproductive toxicity endpoint. An OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Wistar rats. Groups of 11 rats/sex/dose were administered via oral gavage with test material, formaldehyde cyclododecyl ethyl acetal at doses of 0, 50, 300, or 1000 mg/kg/day in corn oil. Male rats were treated for 28 days, whereas female rats were treated 14 days prior to pairing, through the pairing and gestation, until post-partum day 3. In addition to the systemic toxicity parameters, reproductive organs were also assessed. Normal stages of spermatogenesis and histopathology of interstitial cell structure were also noted. There were no treatment-related effects on mating performance, fertility, corpora lutea count, duration of gestation, implantation rate and post-implantation loss, litter size, or postnatal loss. The examination of the ovaries and the female genital tract did not reveal any difference in estrous cycling, and the qualitative assessment of the male genital organs did not reveal any treatment-related effects. Thus, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2013b). **Therefore, the formaldehyde cyclododecyl ethyl acetal MOE for the reproductive toxicity endpoint can be calculated by dividing the formaldehyde cyclododecyl ethyl acetal in mg/kg/day by the total systemic exposure to formaldehyde cyclododecyl ethyl acetal, 1000/0.012, or 83333.**

In addition, the total systemic exposure to formaldehyde cyclododecyl ethyl acetal (12 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: 10/30/20.

11.1.4. Skin sensitization

Based on the existing data, formaldehyde cyclododecyl ethyl acetal is considered a skin sensitizer with a defined NESIL of 3500 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, formaldehyde cyclododecyl ethyl acetal is considered a skin sensitizer. The chemical structure of formaldehyde cyclododecyl ethyl acetal indicates that it would not be expected to be reactive to skin proteins directly (Roberts, 2007; OECD Toolbox v4.2; Toxtree v3.1.0). Formaldehyde cyclododecyl ethyl acetal was negative in the Direct Peptide Reactivity Assay (DPRA) and KeratinoSens Assay (RIFM, 2016b; RIFM, 2017), but positive in the human cell line activation test (h-CLAT) (RIFM, 2018). However, in a murine local lymph node assay (LLNA), formaldehyde cyclododecyl ethyl acetal was found to be a weak sensitizer with an EC3 value of 25.1% (6275 μg/cm^2) (RIFM, 2012c). In a human maximization test, no reactions indicative of sensitization were observed with 2% (1380 μg/cm^2) formaldehyde cyclododecyl ethyl acetal (RIFM, 1980). In a Confirmation of No Induction in Humans test (CNIH), 3% (3543 μg/cm^2) formaldehyde cyclododecyl ethyl acetal in 1:3 ethanol:diethyl phthalate did not induce sensitization reactions in 112 subjects (RIFM, 2016a).

Based on the available data, summarized in Table 1, formaldehyde cyclododecyl ethyl acetal is considered to be a weak skin sensitizer with a defined NESIL of 3500 μg/cm^2. 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, 2020) and a reference dose of 3.33 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/02/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis spectra and available data, formaldehyde cyclododecyl ethyl acetal would not be expected to 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 guinea pig phototoxicity test, the application of up to 50% test material did not

Table 1
Data summary for formaldehyde cyclododecyl ethyl acetal.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
6275 [1]	Weak	3543	1380	N/A	3500

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans 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 CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

result in phototoxic reactions (RIFM, 1991). Based on the *in vivo* study data and the lack of absorbance in the critical range, formaldehyde cyclododecyl ethyl acetal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The 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: 10/23/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for formaldehyde cyclododecyl ethyl acetal 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 formaldehyde cyclododecyl ethyl acetal. Based on the Creme RIFM Model, the inhalation exposure is 0.066 mg/day. This exposure is 21.2 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: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of formaldehyde cyclododecyl ethyl acetal was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, formaldehyde cyclododecyl ethyl acetal 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 v4.11 (US EPA, 2012a) identified formaldehyde cyclododecyl ethyl acetal as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), formaldehyde cyclododecyl ethyl acetal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

RIFM, 1999: Biodegradation of formaldehyde cyclododecyl ethyl acetal was evaluated using the CO_2 evolution test according to the ISO Method 14593 and OECD 301B. After 28 days, biodegradation of <5% was observed.

RIFM, 1998: The ready biodegradability of the test material was evaluated using a manometric respirometry test according to the OECD 302C method. Under the conditions of this study, no biodegradation was observed after 41 days.

RIFM, 1997b: The ready biodegradability of the test material was evaluated using a manometric respirometry test following the OECD 301F method. No biodegradation was observed after 33 days.

RIFM, 2013h: The ready biodegradability of the test material was determined using the respirometric method (modified MITI Test II) according to the OECD 301C method. Under the conditions of this study, biodegradation of 4% was observed after 28 days via GC analysis.

Ecotoxicity

RIFM, 2013c: A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value based on mean measured concentration was reported to be 1.6 mg/L (95% CI: 0.68–3.7 mg/L).

RIFM, 2013g: A 96-h fish (*Danio rerio*) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. Under the conditions of this study, the LC50 value based on the mean measured concentration was reported to be 1.9 mg/L (95% CI: 1.3–2.8 mg/L).

RIFM, 2014a: A 72-h algae growth inhibition test was conducted according to the OECD 201 method, under static conditions, closed system without headspace. The EC50 value based on the mean measured concentration for both growth rate and yield was >2.0 mg/L.

Other available data

Formaldehyde cyclododecyl ethyl acetal has been registered under REACH, and the following additional data is available (ECHA, 2013):

Bioconcentration of the test material to fish (Carp) was evaluated according to the OECD 305 method under flow-thru conditions. The stead state BCF was reported to be 729 L/kg (normalized to 5% lipid content).

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.0	6.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3

(*continued on next page*)

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.11			1000000	0.00011	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.14	0.11	0.312	10000	0.011	Neutral Organic
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.9					
Daphnia		1.6		1000	1.6	
Algae		>20				

(*continued*)

Exposure	Europe (EU)	North America (NA)
Regional Volume of Use Tonnage Band	100–1000	10–100
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 1.6 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 VoU.

Literature Search and Risk Assessment Completed On: 11/05/20.

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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **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 04/14/21.

Declaration of competing interest

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

Appendix

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.

Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17. Readily hydrolyzed to a common terpene? No.
Q23. Aromatic? No.
Q24. Monocarbocyclic with simple substituents? No.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation of the list of categories). No. Class I (Class low)

References

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.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

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.

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.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2013. Ethoxymethoxy)cyclododecane Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/5943/1.

Hall, A.P., Elcombe, C.R., Foster, J.R., Harada, T., Kaufmann, W., et al., 2012. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes–conclusions from the 3rd International ESTP expert workshop. Toxicol. Pathol. 40 (7), 971–994.

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.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Lehman-McKeeman, L.D., Caudill, D., 1992. a-2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. Toxicol. Appl. Pharmacol. 116 (2), 170–176.

Lehman-McKeeman, L.D., Rivera-Torres, M.I., Caudill, D., 1990. Lysosomal degradation of alpha2u-globulin and alpha2u-globulin-xenobiotic conjugates. Toxicol. Appl. Pharmacol. 103 (3), 539–548.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D. (2020). Fragrance Skin Sensitization Evaluation and Human Testing, Dermatitis: November 16, 2020. Volume Publish Ahead of Print Issue. Retrieved from: doi: 10.1097/DER.0000000000000684.

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1790. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1991. Toxicology Studies of Formaldehyde Cyclododecyl Ethyl Acetal in the guinea Pig. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Takasago International Corporation. RIFM report number 35053.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997a. Partition Coefficient N-Octanol/water of Formaldehyde Cyclododecyl Ethyl Acetal (Boisambrene Forte). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 63486.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997b. Ready Biodegradability of Formaldehyde Cyclododecyl Ethyl Acetal (Biosambrene Forte). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 63488.

RIFM (Research Institute for Fragrance Materials, Inc.), 1998. Inherent Biodegradability of Formaldehyde Cyclododecyl Ethyl Acetal (Boisambrene). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 63487.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Formaldehyde Cyclododecyl Ethyl Acetal (Ethoxymethyl Cyclododecylether): Determination of Ready Biodegradability (CO2 Evolution Test). RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 35095.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012a. Flash Point of Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F). Unpublished Report from Symrise. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 64743.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012b. Boiling Point of Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F). Unpublished Report from Symrise. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 64744.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012c. Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F): Local Lymph Node Assay (LLNA) in Mice to Identify Contact Allergens. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 67901.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012d. Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F): Determination of Partition Coefficient by the Slow-Stir Method. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 67903.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. In Vitro Micronucleus Test in Human Lymphocytes with Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F). Unpublished Report from Symrise. RIFM Report Number 64786. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in the Han Wistar Rat with Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 64787.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013c. Acute Toxicity to Daphnia Magna in a 48-hour Immobilization Test with Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F). Unpublished Report from Symrise. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 64788.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013d. Formaldehyde Cyclododecyl Ethyl Acetal: Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65009.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013e. Report on the Testing of Formaldehyde Cyclododecyl Ethyl Acetal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65026.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013f. Gene Mutation Assay in Chinese Hamster V79 Cells in Vitro in Chinese Hamster V79 Cells in Vitro (V79/HPRT) with Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F). Unpublished Report from Symrise. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65219.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013g. Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F.): Acute Toxicity to Zebra Fish (Danio rerio) in a 96-hour Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 65256.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013h. Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F): Biodegradation Study. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 67904.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013i. Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F): Hydrolysis as a Function of pH. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 75484.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F): Toxicity to Pseudokirchneriella Subcapitata in a 72-hour Algal Growth Inhibition Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 67905.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. Formaldehyde Cyclododecyl Ethyl Acetal (Amberwood F): in Vitro Chromosome Aberration Test in Human Lymphocytes. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 69352.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Repeated Insult Patch Test with Formaldehyde Cyclododecyl Ethyl Acetal. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 71171.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Direct Peptide Reactivity Assay (DPRA) in Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 72230.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Induction of Antioxidant-Response-Element Dependent Gene Activity and Cytotoxicity (Using MTT) in the Keratinocyte ARE-Reporter Cell Line KeratinoSens. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 72237.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Formaldehyde Cyclododecyl Ethyl Acetal: in Vitro Sensitization: Dendritic Cell Line Activation Assay Human Cell Line Activation Test (H-CLAT). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 73329.

RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey, 25. October 2019.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76775.

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.

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.

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.

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, v2.0. United States Environmental Protection Agency, Washington, DC, USA.