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RIFM fragrance ingredient safety assessment, γ-valerolactone, CAS Registry Number 108-29-2

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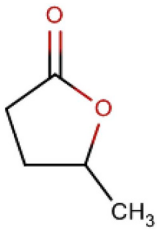


Abbreviation/Definition List:

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., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

γ-Valerolactone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that γ-valerolactone is not genotoxic. Data on read-across analog γ-caprolactone (CAS # 695-06-7) provide a calculated MOE > 100 for the repeated dose and developmental toxicity endpoints. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to γ-valerolactone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from γ-valerolactone and read-across analog 4-hydroxybutanoic acid (CAS # 96-48-0) show that there are no safety concerns for γ-valerolactone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; γ-valerolactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; γ-valerolactone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (RIFM, 2017a; RIFM, 2017b)

Repeated Dose Toxicity: NOAEL = 333.3 mg/kg/day ECHA Dossier: Nonan-4-olide; ECHA (2013)

Developmental and Reproductive Toxicity: Developmental Toxicity: NOAEL = 1000 mg/kg/day. Reproductive Toxicity: No NOAEL available. Exposure is below the TTC ECHA Dossier: Nonan-4-olide; ECHA (2013)

Skin Sensitization: Not a safety concern under current, declared levels of use (ECHA Dossier: γ-Butyrolactone; ECHA, 2011)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening-level: 3.1 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 5954 mg/L (RIFM Framework; Salvito et al., 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 et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 5954 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 5.954 μg/L
Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** γ-Valerolactone
2. **CAS Registry Number:** 108-29-2
3. **Synonyms:** 2(3H)-Furanone, dihydro-5-methyl-; 4-Hydroxypentanoic acid, γ-lactone; γ-Methyl-γ-butyrolactone; 4-Methyl-4-hydroxybutanoic acid lactone; Pentanolide-1,4; 4-Valerolactone; γ-Valeryllactone; γ-アルキルラクトン(C = 0–14); γ-バレロラクトン (γ-メチルブチロラクトン); 5-Methyldihydrofuran-2(3H)-one; γ-Pentalactone; γ-Valerolactone
4. **Molecular Formula:** $C_5H_8O_2$
5. **Molecular Weight:** 100.11
6. **RIFM Number:** 37
7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 191.57 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 0.11 (EPI Suite)
4. **Melting Point**: −34.29 °C (EPI Suite)
5. **Water Solubility:** 93810 mg/L (EPI Suite)
6. **Specific Gravity:** 1.050 (FMA Database)
7. **Vapor Pressure:** 1.46E-10 mm Hg @ 20 °C (EPI Suite v4.0), 0.3 mm Hg 20 °C (FMA Database), 3.76e-010 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless oily liquid. Warm, sweet, hay- and tobacco-like, herbaceous odor of moderate to poor tenacity. Very sweet, warm-herbaceous, mildly spicy taste at concentrations lower than 100 ppm. The material has a considerable range of "pleasant concentration" and the upper limit for pleasant taste impression is very high, but the taste effect and power is not very great (Arctander Volume, 1969).

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.015% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00012 mg/kg/day or 0.0087 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.0013 mg/kg/day (RIFM, 2014)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low* (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	II	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 Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** γ-caprolactone (CAS # 695-06-7)
   c. **Reproductive Toxicity:** γ-caprolactone (CAS # 695-06-7)
   d. **Skin Sensitization:** 4-hydroxybutanoic acid (CAS # 96-48-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

Lactones are formed by intramolecular cyclization of hydroxycarboxylic acids. In body fluids, γ-lactonase catalyzes the hydrolysis of lactone rings to form an open-chain hydroxy carboxylate anion; however, the reaction exists in equilibrium depending on pH. For

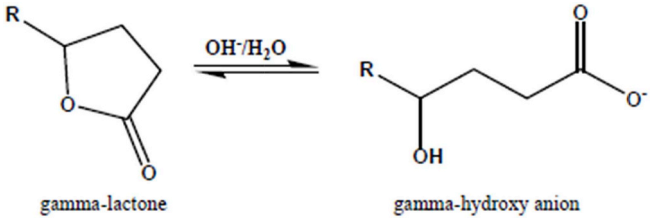


Fig. 1. Equilibrium of γ-lactone and hydroxy carboxylate anion (EFSA, 2011).

illustrative purposes, shown in Fig. 1 is gamma-lactone hydrolysis to form a gamma-hydroxy anion. In blood, the open-chain hydroxy carboxylate anion is favored, whereas in acidic pH (urine and gastric fluids), the lactone ring predominates. Both the lactone ring and the open ring hydroxycarboxylic acid are readily absorbed from the gastrointestinal tract. Moreover, γ-valerolactone is a simple aliphatic lactone capable of crossing the cell membrane more easily than the open-chain acidic analog. In humans, γ-valerolactone is readily hydrolyzed by paraoxonase (PON1), a serum enzyme belonging to the class of α-carboxyesterases, prior to absorption or upon entering systemic circulation. The hydrolysis of γ-valerolactone is greater by liver homogenate than simulated intestinal fluids. This was evidenced by an *in vitro* incubation of rat liver homogenates with γ-valerolactone for 1 h at a concentration of 2 mM, resulting in 93% hydrolysis; 1 mM γ-valerolactone incubated with simulated intestinal fluid for 4 h resulted in 32% hydrolysis. γ-Valerolactone is metabolized to 4-methyl γ-hydroxy butyrate, which can cross the blood-brain barrier with a potential to cause locomotor dysfunction.

Upon hydrolysis, the linear saturated 4-hydroxy carboxylic acid participates in the metabolism of fatty acid. In this pathway, the acid is condensed with coenzyme A (CoA) followed by a catalytic dehydrogenation mediated by acyl-CoA dehydrogenase, which results in a trans-2,3-unsaturated ester (*trans*-delta2-enoyl-CoA) that is further converted into 3-ketothioester. 3-Ketothioester undergoes β-cleavage to yield an acetyl-CoA fragment, which enters the citric acid cycle to yield a new α-hydroxy thioester reduced by 2 carbons. This α-hydroxy thioester undergoes α-oxidation and oxidative decarboxylation to yield a linear carboxylic acid and subsequently forms carbon dioxide. γ-Valerolactone is also naturally excreted in the urine of normal human adults (EFSA, 2011; WHO, 1999; EFSA, 2008; RIFM, 1963; RIFM, 1962).

RIFM, 1963; NTRL, 1985: The metabolism of γ-valerolactone was studied *in vitro* by incubating 2 g of rat liver homogenate for 1 h with γ-valerolactone (purity 98.6%) at concentrations of 0, 0.5, 1, and 2 mM in 50 mL of phosphate buffer (pH 7.5) at 37 °C. The degrees of opening of the lactone ring at 0.50, 1, and 2 mM were reported as 93%, 92%, and 93%, respectively.

RIFM, 1962; NTRL, 1985: The effect of pH on lactone ring hydrolysis of γ-valerolactone was studied *in vitro* by incubating the material with simulated intestinal fluid. One mM of γ-valerolactone (purity 98.7%) was incubated with 50 mL of simulated intestinal fluid for 15, 30, 45, 60, and 240 min; an additional 1 mM was incubated with 100 mL of intestinal fluid for 60 and 240 min. All samples were maintained at 37 °C and pH 7.5. The degrees of opening of the lactone ring at 15, 30, 45, 60, and 240 min following incubation with 50 mL of intestinal fluid resulted in 32%, 34%, 31%, 35%, and 32%, respectively; whereas incubation with 100 mL for 60 and 240 min resulted in 48% and 50%, respectively. The results indicated that there was only a partial breakdown of the lactone ring at intestinal pH levels.

Marinetti et al., 2012: In a neurotoxicity study (no details on GLP or guidelines used) conducted on male rats, γ-valerolactone was administered intraperitoneally at dose levels of 0 (vehicle) and 400 mg/kg/day. At the end of the study, 4-methyl hydroxybutyrate and γ-valerolactone were detected in the blood and brain. 4-Methyl γ-hydroxy butyrate was found in the blood and brains of all rats examined, which indicated that γ-valerolactone is metabolized to 4-methyl γ-hydroxy butyrate and that it can cross the blood-brain barrier with a potential to cause locomotor dysfunction.

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

γ-Valerolactone is reported to occur in the following foods by the VCF*:

Acerola (*Malpighia*)	Beef
Barley	Beer
Beli, bael (*Aegle marmelos* Correa)	Plum (*Prunus* species)
Cheese, various types	Pork
Chicken	Quince, marmelo (*Cydonia oblonga*
Coco	Mill.)
Coffee	Rooibos tea (*Aspalathus linearis*)
Date (*Phoenix dactylifera* L.)	Shoyu (fermented soya hydrolysate)
Filbert, hazelnut (*Corylus avellano*)	Soybean (*Glycine max.* L. Merr.)
Honey	Strawberry (*Fragaria* species)
Katsuobushi (dried bonito)	Swiss cheeses
Manifera species	Tea
Milk and milk products	Tomato (*Lycopersicon esculentum* Mill.)
Mushroom	Vanilla
Olive (*Olea europaea*)	Wheaten bread
Peach (*Prunus persica* L.)	Wild rice (*Zizania aquatica*)
Peanut (*Arachis hypogaea* L.)	Wine

*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.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 10/31/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, γ-valerolactone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. γ-Valerolactone was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through alterations in gene expressions in a human cell line. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of γ-valerolactone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with γ-valerolactone in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017a). Under the conditions of the study, γ-valerolactone was not mutagenic in the Ames test.

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

Table 1
Summary of results from the subchronic studies (non-GLP and non-Guidelines) conducted with γ-valerolactone (Note: These studies were not considered to be adequate to determine a NOAEL because they are single dose studies or lacking in study details).

Duration in Detail	GLP/Guideline	Species (Strain, Sex) No. of Animals/ Dose	Route (by) (Vehicle)	Doses in Detail mg/kg/day (Purity)	Parameters Evaluated	Conclusion (NOAEL/LOAEL)	Reference
90 Days	Non-guideline and non-GLP compliant	Rats, FDRL strain rats, 15/sex/dose	Diet (test item dissolved in cotton seed oil and mixed with diet)	0, 49.0 mg/kg/day (males), 51.1 mg/kg/day (females)	Body weights, feed consumption, hematology (hematocrit, hemoglobin, RBC, WBC, neutrophils, lymphocytes), clinical chemistry (at both 6 weeks (8 rats of each sex) and 12 weeks (all animals); blood urea nitrogen (BUN), blood glucose), organ weights (liver and kidney), histopathology (liver, kidney, stomach, small and large intestine, spleen, pancreas, heart, lungs, bone marrow, muscle, brain, spinal cord, bladder, adrenals, thyroid, pituitary, gonads, salivary glands, and lymph nodes)	NOAEL: 49 mg/kg/day based on absence of treatment-related effects	Oser et al., 1965; NTRL, 1985
12 Weeks	Non-guideline and non-GLP compliant	Rats (no details mentioned about strain or number)	Oral (gavage), vehicle details were not mentioned	45.9 mg/kg/day	Not mentioned	NOAEL: 45.9 mg/kg/day based on no treatment-related effects	Bar and Griepentrog, 1967
13 weeks	Non-guideline and non-GLP compliant	Rats (no details mentioned about strain or number)	Oral (gavage), vehicle details were not mentioned	10000 ppm (equivalent to 500 mg/kg/day based on SOP)	Not mentioned	NOAEL: 500 mg/kg/day based on no treatment-related effects	Bar and Griepentrog, 1967
No details were found	Non-guideline and non-GLP compliant	Rats	No details were found	0, 200–1600 mg/kg/day	Acoustic Startle Reflex (ASR), and the classically-conditioned enhancement of startle, the Startle Anticipated Potentiation of Startle (SAPS) response	Dose-dependent reduction in ASR was reported and little or no effect on SAPS response reported except at doses that produced mild effect on noise alone acoustic startle reflex	https://www.ncbi.nlm.nih.gov/pubmed/22349589, Marinetti et al. (2012)
No details were found	Non-guideline and non-GLP compliant	Rats	No details were found	0, 400 mg/kg	Noise alone ASR, estimation of 4-methyl γ-hydroxy butyrate (4-methyl GHB) in blood and brain	4-methyl GHB was reported in both blood and brain and change in startle response is inversely correlated to brain concentrations	https://www.ncbi.nlm.nih.gov/pubmed/22349589, Marinetti et al. (2012)
No details were found	Non-guideline and non-GLP compliant	Rats	Drinking water	0.25%–1% (250–1000 mg/kg, as per the conversion factors for Rat (old) mentioned in SOP)	Body weight, water consumption, clinical and morphological signs of neuropathy	No neurotoxic effects were reported	Krasavage et al., 1978
No details were found	Non-guideline and non-GLP compliant	Rats	Oral gavage	200–1200 mg/kg	Body weight, clinical and morphological signs of neuropathy	No neurotoxic effects were reported	Krasavage et al., 1978

and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with γ-valerolactone in DMSO at concentrations up to 1001 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. γ-Valerolactone did not induce binucleated cells with micronuclei when tested up to the maximum allowed concentration in either non-activated or S9-activated test systems (RIFM, 2017b). Under the conditions of the study, γ-valerolactone was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, γ-valerolactone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/10/18.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on γ-valerolactone (Table 1). Read-across material γ-caprolactone (CAS # 695-06-7; see Section V) has sufficient repeated dose toxicity data. In a subchronic toxicity study (no details on GLP or guidelines used) conducted on weanling Osborne-Mendel rats (10/sex/dose), γ-valerolactone was administered through the diet at dose levels of 0 (control-normal diet), 1000, 2500, 5000, or 10000 ppm (0, 50, 125, 250, or 500 mg/kg/day, as per the conversion factors for old rats available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives [JECFA, 2000]) for a period of 13 weeks. The NOAEL was considered to be 500 mg/kg/day, based on the absence of any treatment-related effects up to the highest dose level tested (Hagan et al., 1967; NTRL, 1985). In a subchronic toxicity study (GLP and OECD 407-compliant) performed on Crl:CD (Sprague Dawley) IGS BR rats, γ-caprolactone was administered through oral gavage at dose levels of 0 (vehicle control: deionized water), 30, 100, 300, or 1000 mg/kg/day for a period of 28 days. No treatment-related adverse effects were reported up to highest tested dose level; therefore, the NOAEL was considered to be 1000 mg/kg/day (ECHA, 2013). Based on the absence of systemic toxic effects for the repeated dose endpoint, in both studies, the highest NOAEL of 1000 mg/kg/day was selected from the more robust OECD 407 study.

A default safety factor of 3 was used when deriving the NOAEL from an OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333.3 mg/kg/day.

Therefore, the γ-valerolactone MOE for the repeated dose toxicity endpoint can be calculated by dividing the γ-caprolactone NOAEL in mg/kg/day by the total systemic exposure to γ-valerolactone, 333.3/0.0013, or 256385.

In addition, the total systemic exposure to γ-valerolactone (1.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: 05/02/18.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for γ-valerolactone is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on γ-valerolactone or on any read-across materials. The total systemic exposure to γ-valerolactone is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are insufficient developmental toxicity data on γ-valerolactone. Read-across material γ-caprolactone (CAS # 695-06-7; see Section V) has sufficient developmental toxicity data. In a developmental toxicity study (GLP and OECD 414 compliant) performed on Crl:CD (Sprague Dawley) IGS BR rats (25/sex/dose), γ-caprolactone was administered through oral gavage at dose levels of 0 (vehicle control: deionized water), 100, 300, or 1000 mg/kg/day for a period of 14 days during gestation from days 6–19. No treatment-related changes were reported for dams in clinical signs, body weights, gravid uterine weight, feed consumption, and necropsy examination. A significant decrease in fetal body weight was reported in the high-dose group; however, the decrease in body weight was within the historical control range. At 300 mg/kg/day, external malformations including meningocele were reported in 1 fetus, visceral malformations including malpositioned descending aorta were reported in another fetus, and a skeletal malformation (a vertebral centra anomaly: the right half of lumbar centrum number 2 was absent and the right half of lumbar centrum number 1 was malpositioned) was reported in 1 fetus. However, these changes were reported in only 3 of 365 fetuses examined at this dose level and were not present at any other dose level. Other soft tissue and skeletal malformations and variants were reported in a single fetus, but they did not occur in a dose-related manner. In addition, the skeletal variants reported in all treated groups were within the historical control data and therefore not considered to be treatment-related. The NOAEL for maternal and developmental toxicity was considered to be 1000 mg/kg/day, as no treatment-related adverse effects were reported up to the highest dose level tested (ECHA, 2013).

Therefore, the γ-valerolactone MOE for the developmental toxicity endpoint can be calculated by dividing the γ-caprolactone NOAEL in mg/kg/day by the total systemic exposure to γ-valerolactone, 1000/0.0013 or 769231.

In addition, the total systemic exposure to γ-valerolactone (1.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are insufficient reproductive toxicity data on γ-valerolactone or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to γ-valerolactone (1.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Oser et al., 1965; Hagan et al., 1967.

Literature Search and Risk Assessment Completed On: 05/02/18.

10.1.4. Skin sensitization

Based on the existing data and read-across material 4-hydroxybutanoic acid lactone (CAS # 96-48-0), γ-valerolactone does not present a safety concern under current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for γ-valerolactone. Based on the existing data and read-across material 4-hydroxybutanoic acid lactone (CAS # 96-48-0; see Section V), γ-valerolactone does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD toolbox v4.1). In a murine local lymph node assay (LLNA), read-across material 4-hydroxybutanoic acid lactone was not found to be sensitizing up to 100% (ECHA, 2011). In a human maximization test, no skin sensitization reactions observed with γ-valerolactone when tested at 10% (6900 μg/cm^2) (RIFM, 1978).

Based on weight of evidence (WoE) from structural analysis, human data, and read-across material, 4-hydroxybutanoic acid lactone, γ-valerolactone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/25/18.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for γ-valerolactone in experimental models. 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 et al., 2009). Based on lack of absorbance, γ-valerolactone does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for γ-valerolactone is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are insufficient inhalation data available on γ-valerolactone. Based on the Creme RIFM Model, the inhalation exposure is 0.0087 mg/day. This exposure is 161 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/25/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

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

10.2.2. Risk assessment

Based on the current Volume of Use (2015), γ-valerolactone presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. No data available.

10.2.2.1.2. Ecotoxicity. No data available.

10.2.2.1.3. Other available data. γ-Valerolactone has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>5954</u>			1,000,000	5.954	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.11	0.11
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 further assessment is necessary.

The RIFM PNEC 5.954 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 10/11/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/22/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110950.

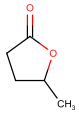
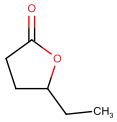
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- Jmax values were calculated using RIFM's Skin Absorption Model (SAM).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	γ-Valerolactone	4-Hydroxybutanoic acid lactone	γ-Caprolactone
CAS No.	108-29-2	96-48-0	695-06-7
Structure			
Similarity (Tanimoto Score)		0.71	0.75
Read-across Endpoint		• Skin Sensitization	• Repeated dose toxicity • Developmental toxicity
Molecular Formula	$C_5H_8O_2$	$C_4H_6O_2$	$C_6H_{10}O_2$
Molecular Weight	100.12	86.09	114.14

Melting Point (°C, EPI Suite)	−34.29	−42.08	−22.87
Boiling Point (°C, EPI Suite)	191.57	176.93	211.41
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.02 E−008	39.4	22
Log Kow (KOWWIN v1.68 in EPI Suite)	0.11	−0.64	0.60
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	9.381E+004	1.00 E+006	3.219E+004
J_{max} (μg/cm^2/h, SAM)	582.013	1381.122	353.995
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.38E+001	1.04E+001	1.83E+001
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized		• Not categorized
Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group		• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)		• Non-toxicant (low reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein Binding (OECD)	• Acylation	• Acylation	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	Supplemental Data 1	Supplemental Data 2	Supplemental Data 3

Summary

There are insufficient toxicity data on γ-valerolactone (CAS # 108-29-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 4-hydroxybutanoic acid lactone (CAS # 96-48-0) and γ-hexalactone (CAS # 695-06-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 4-Hydroxybutanoic acid lactone (CAS # 96-48-0) was used as a read-across analog for the target material γ-valerolactone (CAS # 108-29-2) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - o The key difference between the target substance and the read-across analog is that the target has a methyl substitution on the 5 position while the read-across analog does not have any substitution. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have acylation alerts. Based on limited data on the target and data on the read-across analog, the target does not present a concern for skin sensitization under the current, declared levels of use. Therefore, the predictions are superseded by data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- γ-Caprolactone (CAS # 695-06-7) was used as a read-across analog for the target material γ-valerolactone (CAS # 108-29-2) for the developmental toxicity and repeated dose toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - o The key difference between the target substance and the read-across analog is the target substance has a methyl substitution on the 5 position while the read-across analog has an ethyl substitution on the same position. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between 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.

Q1. 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
Q8. Lactone or cyclic diester? No
Q9. Lactone, fused to another ring, or 5- or 6-membered α,β-unsaturated lactone? No
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list? No (see Cramer et al., 1978 for detailed explanation on list of categories) Yes, 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.

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II Published by the author, Montclair, NJ (USA).

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel Fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Medizin Ernahr 8, 244–251.

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.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

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 Cosmet. Toxicol. 16 (3), 255–276.

ECHA, 2011. Registration Dossier γ-Butyrolactone. Retrieved from: https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/14990/1.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2013. Registration Dossier Nonan-4-Olide. Retrieved from: https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/5796/1.

ECHA, 2016. European chemical agency read-across assessment framework. ECHA read-across assessment framework. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

EFSA, 2008. Scientific Opinion on Flavouring Group Evaluation 5, Revision 1 (FGE.05Rev1): esters of branched- and straight-chain aliphatic saturated primary alcohols and of one secondary alcohol, and branched- and straight-chain unsaturated carboxylic acids from chemical groups 1, 2, and 5. EFSA J. 643, 1–80 2008.

EFSA, 2011. Scientific Opinion on Flavouring Group Evaluation 10, Revision 2 (FGE.10Rev2): aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group and lactones from chemical groups 9, 13 and 301. EFSA J. 9 (7), 2164 2011.

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet. Toxicol. 5 (2), 141–157.

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.

JECFA, 2000. Guidelines for the Preparation of Toxicological Working Papers for the Joint FAO/WHO Expert Committee on Food Additives. Retrieved from. http://www.who.int/foodsafety/chem/jecfa/en/tox_guidelines.pdf.

Krasavage, W.J., O'Donoghue, J.L., Terhaar, C.J., 1978. The relative neurotoxicity of methyl n-butyl ketone and its metabolites. Toxicol. Appl. Pharmacol. 45 (1), 251.

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.

Marinetti, L.J., Leavell, B.J., Jones, C.M., Hepler, B.R., Isenschmid, D.S., Commissaris, R.L., 2012. Gamma butyrolactone (GBL) and gamma valerolactone (GVL): similarities and differences in their effects on the acoustic startle reflex and the conditioned enhancement of startle in the rat. Pharmacol. Biochem. Behav. 101 (4), 602–608 2012 Jun.

NTRL, 1985. Scientific literature review of aliphatic lactones in flavor usage. Retrieved from scientific literature review of aliphatic lactones in flavor usage. Retrieved from. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB86155850.xhtml.

OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v4.2. http://www.qsartoolbox.org/.

Oser, B.L., Carson, S., Oser, M., 1965. Toxicological tests on flavouring matters. Food Cosmet. Toxicol. 3, 563–569.

RIFM (Research Institute for Fragrance Materials, Inc), 1962. In Vitro Digestion of Four Lactones. Private Communication to FEMA. Unpublished report from Morgareidge, K. RIFM report number 29316. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1963. In Vitro Digestion of Three Lactones. Private Communication to FEMA. Unpublished report from Morgareidge, K. RIFM report number 29317. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1978. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1787. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of Gamma-Valerolactone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65408. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2014. Exposure Survey 03. April 2014.

RIFM (Research Institute for Fragrance Materials, Inc), 2017. Gamma-Valerolactone: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM report number 71494. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017. Gamma-Valerolactone: in Vitro Human Lymphocyte Micronucleus Assay. RIFM report number 71548. RIFM, Woodcliff Lake, NJ, USA.

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.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

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.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.

WHO, 1999. Evaluation of certain food additives and contaminants (Forty-ninth report of the joint FAO/WHO expert committee on food Additives). WHO technical report series, No. 884, 1999. Retrieved from: http://apps.who.int/iris/bitstream/handle/10665/42142/WHO_TRS_884.pdf;jsessionid=D6D8C15ED8C469EB10DF6F91E31AA6D2?sequence=1.