Food and Chemical Toxicology 138 (2020) 111191

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

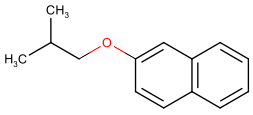
RIFM fragrance ingredient safety assessment, β-naphthyl isobutyl ether, CAS Registry Number 2173-57-1

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

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE 20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM 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 RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM 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 RIFM 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 RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM 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 RIFM 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*

Version: 061019. This version replaces any previous versions.
Name: β-Naphthyl isobutyl ether

CAS Registry Number: 2173-57-1



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary in silico tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 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

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

https://doi.org/10.1016/j.fct.2020.111191
Received 8 November 2019; Received in revised form 14 January 2020; Accepted 12 February 2020
Available online 17 February 2020
0278-6915/

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

β-Naphthyl isobutyl ether was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog β-naphthyl methyl ether (CAS # 93-04-9) show that β-naphthyl isobutyl ether is not expected to be genotoxic. The skin sensitization endpoint was completed using DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. Data provided a calculated MOE > 100 for the repeated dose toxicity endpoint. Data from read-across analogs β-naphthyl methyl ether (CAS # 93-04-9) and β-naphthoxyacetic acid (CAS # 120-23-0) provided a calculated MOE > 100 for the developmental and reproductive toxicity endpoint. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material; exposure is below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was evaluated based on UV spectra; β-naphthyl isobutyl ether is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; β-naphthyl isobutyl ether 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 expected to be genotoxic. JECDB (2011)
Repeated Dose Toxicity: 7 mg/kg/day. OECD (2011)
Developmental Toxicity: NOAEL = 60 mg/kg/day.**Reproductive Toxicity:** NOAEL = 153.8 mg/kg/day. (ECHA REACH Dossier: Methyl 2-naphthyl ether; ECHA, 2012a)
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.
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: 2.69 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 543.1 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-hr *Daphnia magna* LC50: 0.498 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-hr *Daphnia magna* LC50: 0.498 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0498 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name:** β-Naphthyl isobutyl ether
2. **CAS Registry Number:** 2173-57-1
3. **Synonyms:** Fragarol; 2-Isobutoxynaphthalene; Isobutyl β-naphthyl ether; Isobutyl 2-naphthyl ether; Naphthalene, 2-(2-methylpropoxy)-; Nerolin fragarol; 2-ﾅﾌﾁﾙｱﾙｷﾙ(C = 1～4)ｴｰﾃﾙ; β-Naphthyl isobutyl ether
4. **Molecular Formula:** $C_{14}H_{16}O$
5. **Molecular Weight:** 200.28
6. **RIFM Number:** 1034
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** > 200 °C (FMA Database Database), 304.45 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200°F; CC (FMA Database)
3. **Log K_{ow}:** 4.65 (EPI Suite)
4. **Melting Point**: 32 °C (FMA Database), 58.68 °C (EPI Suite)
5. **Water Solubility:** 4.664 mg/L (EPI Suite)
6. **Specific Gravity:** 1.01000 @ 25.00 °C*
7. **Vapor Pressure:** 0.000738 mm Hg @ 20 °C (EPI Suite), 0.00136 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** White crystals with a sweet and fruity, very tenacious, delicate Neroli-Orange blossom-floral odor

*http://www.thegoodscentscompany.com/data/rw1020171.html#tophyp, retrieved 10/20/2015.

3. Exposure

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.000% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00015 mg/kg/day or 0.011 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00047 mg/kg/day (RIFM, 2014)

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

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

2. Analogs Selected:
   a. **Genotoxicity:** β-naphthyl methyl ether (CAS # 93-04-9)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** 2-naphthyloxyacetic acid (CAS # 120-23-0) and β-naphthyl methyl ether (CAS # 93-04-9)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

β-Naphthyl isobutyl ether is not reported to occur in food 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.

8. REACH Dossier

Available; accessed 02/09/18.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, β-naphthyl isobutyl ether does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. β-Naphthyl isobutyl ether was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, T1537, TA98, TA100, and *Escherichia Coli* WP2uvrA were treated with β-naphthyl isobutyl ether in dimethyl sulfoxide (DMSO) at concentrations up to 5 mg/plate in the presence and absence of exogenous metabolically active microsomal mix (S9 mix). No increase in the number of revertant colonies was observed in the tester strains at any concentration (JECDB, 2011). Under the conditions of the study, β-naphthyl isobutyl ether was considered not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of β-naphthyl isobutyl ether; however, read-across can be made to β-naphthyl methyl ether (CAS # 93-04-9; see Section V). The clastogenic activity of β-naphthyl methyl ether 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 β-naphthyl methyl ether in DMSO at concentrations up to 1582 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. β-Naphthyl methyl ether did not induce binucleated cells with micronuclei when tested up to cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, β-naphthyl methyl ether was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, β-naphthyl methyl ether does not present a concern for genotoxic potential, and this can be extended to β-naphthyl isobutyl ether.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/03/17.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for β-naphthyl isobutyl ether is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on β-naphthyl isobutyl ether for the repeated dose toxicity endpoint. In an OECD 407 28-day repeated dose oral toxicity study in rats, animals were administered β-naphthyl isobutyl ether at doses of 0 (corn oil), 20, 100, or 500 mg/kg bw/day with an additional recovery group of control and high-dose animals retained treatment-free for a period of 14 days. Loose stools, mucous feces, watery diarrhea, and salivation were observed, and 2 females were found dead at 500 mg/kg bw/day. In the 500 mg/kg bw/day group, body weight was lowered in both sexes. Browning of urine was found in both sexes at 100 mg/kg bw/day or more, and a positive bilirubin reaction was increased in both sexes at 500 mg/kg bw/day. Hematological and blood biochemical examination revealed a decrease in glucose and an increase in ALT in males as well as decreases in red blood cell count, hemoglobin, hematocrit, and total protein and increases in triglyceride and ALP in females at 500 mg/kg bw/day. The relative liver weight increased at 500 mg/kg bw/day in males and at 100 mg/kg bw/day or more in females. Increases were seen in the relative kidney weight in males at 100 mg/kg bw/day or more, the relative spleen weight in both sexes at 500 mg/kg bw/day, and the relative adrenal weight in males at 500 mg/kg bw/day. Histopathological changes were found in the forestomach, cecum, colon, liver, spleen, adrenal gland, and prostate and/or seminal vesicle in both sexes at 500 mg/kg bw/day. Colonic changes (i.e., increase in mitosis) was also found in males at 100 mg/kg bw/day. Based on these results, the NOAEL of this study was 20 mg/kg bw/day (OECD, 2011).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day, OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 20/3 or 7 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.

Therefore, the β-naphthyl isobutyl ether MOE for the repeated dose toxicity endpoint can be calculated by dividing the β-naphthyl isobutyl ether NOAEL in mg/kg/day by the total systemic exposure to β-naphthyl isobutyl ether, 7/0.00047 or 14894.

In addition, the total systemic exposure to β-naphthyl isobutyl ether (0.47 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/08/

18.

10.1.3. Developmental and reproductive toxicity

The MOE for β-naphthyl isobutyl ether is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on β-naphthyl isobutyl ether. Read-across materials 2-naphthyloxyacetic acid (CAS # 120-23-0; see Section V) and β-naphthyl methyl ether (CAS # 93-04-9; see Section V) have sufficient developmental and reproductive toxicity data.

The teratogenic effects of 2-naphthyloxyacetic acid were investigated in developmental toxicity studies conducted in rats and rabbits. In the study conducted in rats, 2-naphthyloxyacetic acid was administered to rats (details on duration, number, species, and sex not provided) via oral gavage at doses of 0, 10, 60, and 300 mg/kg/day. Maternal examinations included body weights and food consumption along with an examination of ovaries and uterine content following termination. The fetuses were examined for incidences of small fetuses and ossification anomalies. Indication of maternal toxicity included a significant reduction in body weight change and food consumption among high-dose females. There was a higher incidence of small fetuses in the high-dose group that indicated slight fetotoxicity. No additional details were provided. The NOAEL for developmental toxicity was considered to be 60 mg/kg/day based on incidences of small fetuses among high-dose group females (ECHA, 2012a). In the rabbit study, 2-naphthyloxyacetic acid was administered to rabbits (details on number, species, and sex not provided) via oral gavage at doses of 0, 3, 10, and 50 mg/kg/day. Maternal examinations included body weights and food consumption along with examination of ovaries and uterine content following termination. The fetuses were examined for incidences of small fetuses and ossification anomalies. There was a significant decrease in maternal bodyweight gain during the treatment period from day 6–30. No test material effects were observed in fetuses at any dose tested. Thus, the NOAEL for teratogenicity study was considered to be 50 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was considered to be 60 mg/kg/day from the rat study based on incidences of small fetuses in the higher dose group. Limited information was available on study details. However, European Food Safety Authority concluded that the NOAEL for developmental toxicity was considered to be 60 mg/kg/day (EFSA, 2011).

Therefore, the β-naphthyl isobutyl ether MOE for the developmental toxicity endpoint can be calculated by dividing the 2-naphthyloxyacetic acid NOAEL in mg/kg/day by the total systemic exposure to β-naphthyl isobutyl ether, 60/0.00047 or 127660.

There are limited reproductive toxicity data available on β-naphthyl methyl ether. The OECD 407 study conducted on β-naphthyl methyl ether also evaluated the levels of testosterone and estrogen from all treated animals. Examinations also included weights of brain, testes, and ovaries (paired ovaries and uterus, including cervix). The results showed that there was a significant increase in the levels of testosterone among high-dose males. The relative testes epididymitis weights were increased among high-dose males. There was a significant increase in the levels of estrogen among mid-dose females. The relative and absolute weight of the ovaries were decreased among treated females. The relative and absolute weight of the uterus was decreased in the mid- and high-dose females. Histopathological examination did not show any treatment-related alterations among high-dose animals. Thus, the NOAEL for male reproductive toxicity was considered to be 250 mg/kg/day, based on an increase in testosterone levels, and the LOAEL for female reproductive toxicity was considered to be 125 mg/kg/day, based on a decrease in ovary weights among treated females (ECHA, 2012a).

Read-across material 2-napthyloxyacetic acid was administered via the diet to male and female rats (number and sex of rats not specified) at doses of 0, 100, 500, or 2500 ppm during a 1-generation reproductive toxicity study. The body weights and food consumption were monitored during the study duration. The estrous cyclicity of parental females and sperm parameters for parental males were recorded. At the end of the treatment duration, gross necropsy and histopathology examinations were conducted (no additional details provided). There was a significant decrease in mean body weights reported at 2500 ppm from weeks 2–6 and in week 8. The food intake on weeks 2 and 8 in males was also decreased. In females, the body weights were significantly lower on a few occasions during the gestation and lactation periods. There were no treatment-related changes in estrous cyclicity, pre-coital time, gestation length, pups survivability, mating, fertility, fecundity, or sperm parameters. There were no treatment-related changes in organ weights or the gross or microscopic findings of parents. No treatment-related changes were observed in pups. Hence, the NOAEL for reproductive toxicity study was considered to be 153.8 mg/kg/day for male rats and 393.6 mg/kg/day for female rats; it is regarded that there are no reprotoxic effects at concentration 153.8 mg/kg/day and 393.6 mg/kg/day or lower. Dose conversions were not provided, and the NOAEL concluded in the EFSA report (EFSA, 2011) was 153.8 mg/kg/day (ECHA, 2012a). Since the decrease in ovary weights during the OECD 407 study were not accompanied by histopathological alterations, and the increase in estrogen was only reported among mid-dose females with no dose-response, this was not considered to be of toxicological relevance. This is supported by the lack of such effects reported among treated females on the read-across material, 2-napthyloxyacetic acid, during the 1-generation reproductive toxicity study. Thus, the NOAEL of 153.8 mg/kg/day was considered for the reproductive toxicity endpoint.

Therefore, the β-naphthyl isobutyl ether MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-naphthyloxyacetic acid NOAEL in mg/kg/day by the total systemic exposure to β-naphthyl isobutyl ether, 153.8/0.00047 or 32723.

In addition, the total systemic exposure to β-naphthyl isobutyl ether (0.47 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the developmental and reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/05/17.

10.1.4. Skin sensitization

Based on the existing data and the application of DST, β-naphthyl isobutyl ether does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine Local Lymph Node Assay (LLNA), β-naphthyl isobutyl ether was found to be negative up to the maximum tested concentration of 10%, which resulted in a Stimulation Index (SI) of 1.6 (ECHA, 2017). Additionally, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1977).

Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for β-naphthyl isobutyl ether that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Table 1
Maximum acceptable concentrations for β-naphthyl isobutyl ether that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	Reported 95th Percentile Concentration in Finished Products
1	Products applied to the lips	0.07%	0.00%[b]
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.01%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%[b]
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse off	0.75%	0.02%
10	Household care products with mostly hand contact	2.70%	0.01%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.16%

Note:
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

Literature Search and Risk Assessment Completed On: 11/21/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, β-naphthyl isobutyl ether 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 β-naphthyl isobutyl ether in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of significant absorbance in the critical range, β-naphthyl isobutyl ether does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for β-naphthyl isobutyl ether were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/21/17.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for β-naphthyl isobutyl ether is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on β-naphthyl isobutyl ether. Based on the Creme RIFM Model, the inhalation exposure is 0.011 mg/day. This exposure is 42.7 times lower than the Cramer Class III TTC value of 0.47 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: 12/15/16.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of β-naphthyl isobutyl ether was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiers 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, 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, β-naphthyl isobutyl ether 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) did not identify β-naphthyl isobutyl ether as possibly being either 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, 2012b). 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. Based on these model outputs (Step 1), if 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.

10.2.1.1. Risk assessment. Based on current Volume of Use (2015), β-naphthyl isobutyl ether presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2. Key studies

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. β-Naphthyl isobutyl ether has been pre-registered for REACH with no additional data at this time.

10.2.2.4. 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.

		(mg/L)	(mg/L)			
RIFM Framework Screening-level **(Tier 1)**	1.336			1,000,000	0.001336	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.686	0.498	1.020	10,000	0.0498	Neutral Organic

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.65	4.65
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.0498 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/30/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **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/

11.1. 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 01/22/19.

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. 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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111191.

Appendix

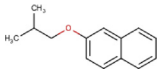
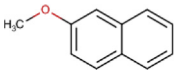
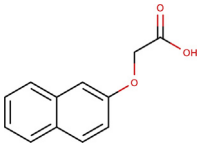
Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European 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, 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.
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

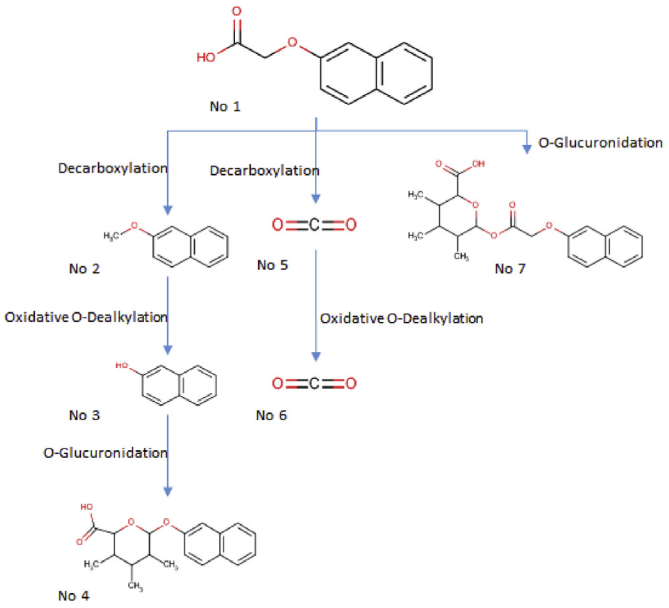
	Target Material	Read-across Material	
Principal Name	β-Naphthyl isobutyl ether	β-Naphthyl methyl ether	2-Naphthoxyacetic acid
CAS No.	2173-57-1	93-04-9	120-23-0
Structure			
Similarity (Tanimoto Score)		0.63	0.8
Read-across Endpoint		• Genotoxicity • Developmental and Reproductive toxicity	• Developmental and Reproductive toxicity
Molecular Formula	$C_{14}H_{16}O$	$C_{11}H_{10}O$	$C_{12}H_{10}O_3$
Molecular Weight	200.28	158.20	202.21
Melting Point (°C, EPI Suite)	58.68	38.43	125.51
Boiling Point (°C, EPI Suite)	304.45	267.31	363.49
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.182	0.365	0.000385
Log Kow (KOWWIN v1.68 in EPI Suite)	4.65	3.47	2.53
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.664	75.88	731.3
J_{max} (μg/cm^2/h, SAM)	0.667	8.70	10.18
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.38E+000	3.15E+000	1.66E-004
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• No alert found	• No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	
Oncologic Classification	• No alert found	• No alert found	
Developmental and reproductive toxicity			
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (low reliability)	• Toxicant (moderate reliability)	• Toxicant (good reliability)
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

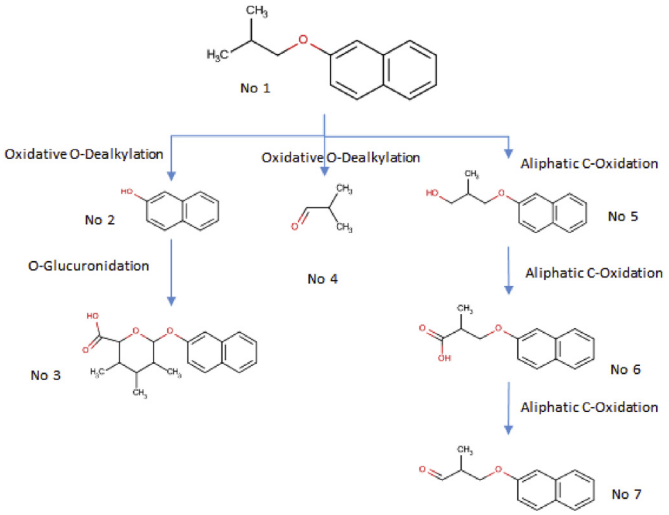
There are insufficient toxicity data on β-naphthyl isobutyl ether (CAS # 2173-57-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, β-naphthyl methyl ether (CAS # 93-04-9) and 2-naphthoxyacetic acid (CAS # 120-23-0) were identified as read-across materials with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the read-across analog (2-naphthyloxy)acetic acid (CAS # 120-23-0) and the target material β-naphthyl isobutyl ether (CAS # 2173-57-1) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The read-across analog undergoes decarboxylation, and the target material undergoes oxidative dealkylation to produce β-naphthyl methyl ether (CAS # 93-04-9) in the first step with 0.95% probability. The chart shown below explains metabolic transformations predicted for the target material as well as for the read-across analog. It shows that once the read-across analog and the target substance are transformed into the same substance, further ADME properties can be expected to be the same for both. Hence, (2-naphthyloxy)acetic acid (CAS # 120-23-0) can be used as read-across for the target material.



Metabolic transformations of the read-across analog (2-naphthyloxy)acetic acid (CAS # 120-23-0) are predicted by the *in vitro* rat liver S9 metabolism model in TIMES. The target material (No. 2) is produced as a step 1 metabolic product thereafter following oxidative dealkylation and O-glucuronidation as the path for clearance.



Metabolic transformations of the target material β-naphthyl isobutyl ether (No. 1, CAS # 2173-57-1) are predicted by the *in vitro* rat liver S9 metabolism model in TIMES. The target material here follows oxidative dealkylation and O-glucuronidation as the path for clearance.

Conclusions

- β-Naphthyl methyl ether (CAS # 93-04-9) was used as a read-across analog for the target material β-naphthyl isobutyl ether (CAS # 2173-57-1) for the genotoxicity endpoint and the developmental and reproductive toxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of ethers.
  - The target substance and the read-across analog share a common naphthyl fragment.
  - The key structural difference between the target substance and the read-across analog is that the target substance has an additional isobutyl fragment while the read-across analog has a methyl fragment. This structural difference is toxicologically insignificant.
  - Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a common naphthyl fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target material and read-across analog are shown to be toxicants by CAESAR v2.1.6. In addition, both also have a 3 methylcholantrene

(hepatotoxicity alert) for repeated dose toxicity. The data described for the read-across analog in the reproductive and developmental toxicity section show the read-across analog does not pose a concern under the current exposure level. Therefore, the alert will be superseded by the data. The ER binding alert, which is another fertility toxicity indicator, is negative for both of the substances.
  - The alerts for genotoxicity are consistent with the data described in the genotoxicity section.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- (2-Naphthyloxy)acetic acid (CAS # 120-23-0) was used as a read-across analog for the target material β-naphthyl isobutyl ether (CAS # 2173-57-1) for the developmental and reproductive toxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of naphthyl ethers.
  - The key difference between the target substance and the read-across analog is that the read-across analog has a carboxylic acid attached to an ether link, while the target substance has an isobutyl ether. This structural difference is not predicted to exert an impact on toxicological properties of the 2 materials.
  - 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.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - Both the read-across analog and the target substance are predicted to be toxicants with moderate reliability by the CAESAR model of developmental toxicity. The ER binding alert is negative for both of the substances. The data described in the developmental and reproductive toxicity section show that the margin of exposure is adequate at the current level of use. Therefore, based on the metabolism prediction of the read-across analog, the structural similarity between the read-across analog and the target substance, and the data for the read-across analog, the predictions are superseded by data.
  - According to the predictions and alert, the read-across analog and the target substance are predicted to be similarly reactive.
  - As shown by TIMES metabolism predictions, the target substance and the read-across analog are expected to be metabolized similarly. In addition to those predictions, other metabolites might be possible. CYP450 and GSH could give rise to sulfate conjugates or additional hydroxylation could occur to produce the catechol. But based on TIMES prediction, it is expected that additional metabolism products will be similar in the read-across analog and the target.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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.

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.

ECHA, 2012a. Methyl 2-naphthyl Ether Registration Dossier. Retrieved from. https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/5694.

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

ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

ECHA, 2017. Isobutyl 2-naphthyl Ether Registration Dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/19834/1.

EFSA, 2011. Conclusion on the peer review of the pesticide risk assessment of the active substance 2-naphthyloxyacetic acid. EFSA J. 9 (5), 2152. 2011 Retrieved from. https://www.efsa.europa.eu/en/efsajournal/pub/2152.

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.

JECDB, 2011. SIAM 32, 19-21 April 2011 JP. Initial Targeted Assessment Profile: 2-(2-Methylpropoxy)naphthalene. Retrieved from. https://hpvchemicals.oecd.org/ui/handler.axd?id=e7981f26-4973-40cc-ae4e-f0da6035bd68.

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.

OECD, 2011. SIDS Dossier Approved at SIAM 32. Substance: 2-(2-Methylpropoxy)naphthalene. Retrieved from. https://hpvchemicals.oecd.org/ui/SIDS_Details.aspx?id=c660a3e5-4586-4c20-9f34-104f18cf4c79.

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

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1691. RIFM, Woodcliff Lake, NJ, USA.

> RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Exposure Survey. 3 April 2014.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Beta-Naphthyl Methyl Ether: Micronucleus Test in Human Lymphocytes in Vitro. RIFM report number 71556. RIFM, Woodcliff Lake, NJ, USA.

Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.

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., 2015a. 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.

Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.

Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015b. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.

Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.

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.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

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.