Food and Chemical Toxicology 130 (2019) 110629

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 2-phenoxyethanol, CAS Registry Number 122-99-6

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ARTICLE INFO

Keywords:
Genotoxicity
Repeated Dose, Developmental, and Reproductive Toxicity
Skin Sensitization
Phototoxicity/Photoallergenicity
Local Respiratory Toxicity
Environmental Safety

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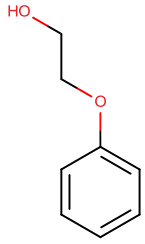
https://doi.org/10.1016/j.fct.2019.110629
Received 8 November 2018; Received in revised form 22 May 2019; Accepted 19 June 2019
Available online 23 June 2019

Version: 110818. This version replaces any previous versions.
Name: 2-Phenoxyethanol
CAS Registry Number: 122-99-6



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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
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.

2-Phenoxyethanol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data from 2-phenoxyethanol show that this material is not genotoxic. Data on the read-across analog 2-(4-methylphenoxy)ethanol (CAS # 15149-10-7) show that 2-phenoxyethanol does not present a concern for skin sensitization. Data on 2-phenoxyethanol provide an MOE of > 100 for the repeated dose toxicity, developmental and reproductive toxicity, and local respiratory toxicity endpoints. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; 2-phenoxyethanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-phenoxyethanol 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.	(ECHA Dossier: 2-Phenoxyethanol; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 249 mg/kg/day.	(SCCS, 2016)
Developmental and Reproductive Toxicity: NOAEL = 486 mg/kg/day and 400 mg/kg/day, respectively.	(SCCS, 2016; Heindel et al., 1990)
Skin Sensitization: No safety concerns under the current, declared levels of use.	(ECHA Dossier: 2-Phenoxyethanol; ECHA, 2011; RIFM, 2002; RIFM, 1978b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database; RIFM, 2015)
Local Respiratory Toxicity: NOAEC = 40 mg/m^3.	(ECHA Dossier: 2-Phenoxyethanol; ECHA, 2011)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 99% (OECD 301F)	(ECHA Dossier: 2-Phenoxyethanol; ECHA, 2011)
Bioaccumulation: Screening-level: 1.-5 L/kg	(EPI Suite v 4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: LC50: 11-30 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: LC50: 11-30 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 1.13 µg/L	
● **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** 2-Phenoxyethanol
2. **CAS Registry Number:** 122-99-6
3. **Synonyms:** Dowanol EP; DowanolEPh; Ethanol, 2-phenoxy-; Ethylene glycol monophenyl ether; 1-Hydroxy-2-phenoxyethane; Phenoxethol; Phenoxetol; Phenyl cellosolve; Protacide P-OH; CoSept PHE; Dowanol EPh; Emeressence 1160; Igepal OD 410; Phenoxen; Phenoxyethyl Alcohol/Arosol; REWOPAL MPG 10; Sepicide LD; Tri-K Phenoxyethanol; Polioxol F-01; 2-Phenoxyethyl alcohol; Phenoxytol; 2-Hydroxyethyl phenyl ether; Phenoxyethanol; エチレングリコールモノフェニルエーテル; フェノキシエタノール; ポリオキシアルキレンモノフェニルエーテル（n = 1 ~ 200）; β-Phenoxyethanol; 2-Phenoxyethanol
4. **Molecular Formula:** $C_8H_{10}O_2$
5. **Molecular Weight:** 138.17
6. **RIFM Number:** 64

2. Physical data

1. **Boiling Point:** 230 °C (FMA Database), 243.84 °C (EPI Suite)
2. **Flash Point:** 185°F; CC (FMA Database)

3. **Log K_{OW}**: 1.1 (EPI Suite)
4. **Melting Point**: 22.47 °C (EPI Suite)
5. **Water Solubility:** 28180 mg/L (EPI Suite)
6. **Specific Gravity:** 1.097 (FMA Database)
7. **Vapor Pressure:** 0.0026 mm Hg @ 20 °C (EPI Suite v4.0), 0.006 mm Hg 20 °C (FMA Database), 0.00449 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 liquid. Sweet, slightly spicy, vegetable, beet-like odor. Bitter, slightly burning taste at concentrations higher than 50 ppm in water.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.25% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0021 mg/kg/day or 0.16 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.016 mg/kg/day (RIFM, 2016)

*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 4. 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:** 81%

SCCS Opinion on Phenoxyethanol (accessed on 06/15/2017): The percutaneous absorption of 2-phenoxyethanol (PE) was evaluated in a cleaning gel (a rinse-off formulation) and body lotion (a leave-on formulation) containing either 0.2% or 1% of 2-phenoxyethanol. Human skin samples (obtained from surgery) were mounted in Franz static diffusion cells and maintained at 32 °C. The different formulations were applied, and each cell was covered with a semi-occlusive filter. For the rinse-off experiments, the cleaning gel formulation was washed from the skin surface at 30 min. For the leave-on experiments, the body lotion formulation remained on the skin until the last sampling point at 24 h. The lower compartment was filled with phosphate buffered saline as receptor fluid, and the receptor fluid was completely collected at 3, 6, 9, and 12 h and replaced by fresh fluid at the last sampling point of 24 h. At the end of the 24-h period, the cells were dismantled, and the skin was analyzed to determine the amount of radiolabel present in the tissue. The epidermis with stratum corneum was separated from the dermis using forceps. The amount of radiolabel present in skin compartments, receptor fluid, and rinsing solution was measured by liquid scintillation counting. A mass balance was calculated. Therefore, the amount measured in the epidermis, stratum corneum, dermis, and receptor fluid (E + SC + D + RF) was summed to calculate the extent of dermal absorption. The mass balance for recovery of radioactivity in the experiments with the rinse-off formulation was 88.59 ± 6.38% and 86.47 ± 3.67% of the applied dose for the 1% and 0.2% concentrations, respectively. For the leave-on formulations, the mass balance was 88.65 ± 5.95% and 99.00 ± 6.49% of the applied dose for the 1% and 0.2% concentrations, respectively. The amount absorbed through the skin, expressed as a percentage of the applied dose for the rinse-off formulation, was similar for the 2 concentrations studied (37 ± 10% and 34 ± 8% for the 1% and 0.2% concentrations, respectively). Likewise, for the leave-on formulation, the percentage absorbed was independent of the concentration (78 ± 7% and 81 ± 10% for the 1% and 0.2% concentrations, respectively). The most conservative skin absorption value considered for the safety assessment was with the leave-on product that resulted in 81 ± 10% of the absorbed dose.

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-(4-Methylphenoxy)ethanol (CAS # 15149-10-7)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

SCCS Opinion on Phenoxyethanol (accessed on 06/15/2017): Several metabolism studies are available on 2-phenoxyethanol. The results indicate that 2-phenoxyethanol is rapidly absorbed, distributed, and eliminated from the body, and the dose excreted in the urine was primarily 2-phenoxyacetic acid (more than 90%), independent of the exposure route. The enzymes responsible in rats were considered to be a cytosolic alcohol dehydrogenase and an aldehyde dehydrogenase, mainly found in the liver, but also in the skin. The general metabolism scheme is provided below (Fig. 1). The metabolism rate was found to be different among different species as investigated in an *in vitro* study using liver S9 fractions. The results showed that the rate of metabolism to 2-phenoxyacetic acid from 2-phenoxyethanol from highest to lowest is as follows: human > rat > mouse > rabbit. Low dose dermal plasma kinetics experiments conducted in rats after dermal and intravenous administration of 2-phenoxyethanol demonstrated that much higher proportions of 2-phenoxyethanol were found in blood after dermal exposure than after oral exposure. This suggests that first pass metabolism after oral exposure plays a major role in elimination of 2-phenoxyethanol, thereby reducing its adverse effects. This is unlike dermal exposure, where plasma levels of 2-phenoxyethanol are comparatively higher. Tissue distribution studies in rats showed that the 2-phenoxyethanol tissue-to-plasma partition coefficients ranking is: kidney > spleen > heart > brain > testis > liver > lung. For 2-phenoxyacetic acid, the partitioning in the kidney was highest followed by the liver, which suggests that the kidney may be the target organ more susceptible to effects of 2-phenoxyethanol administration (see repeated dose toxicity section).

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

2-Phenoxyethanol is reported to occur in the following foods*:

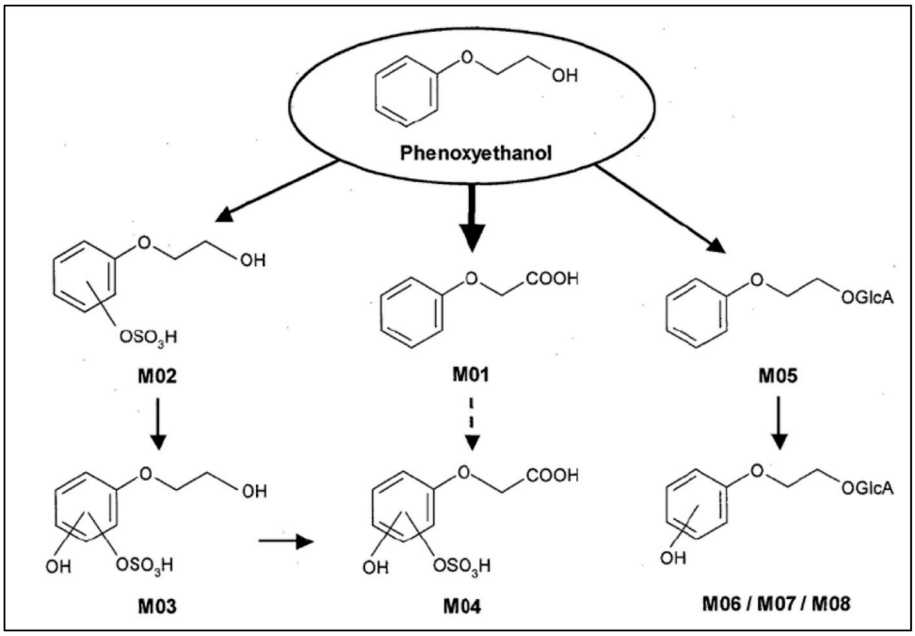


Fig. 1. Adapted from SCCS Opinion on Phenoxyethanol (accessed on 06/15/2017).

Avocado (*Persea americiana* Mill.)
Cocoa.
Endive (*Cichorium endive* L.)
Apple fresh (*Malus* species)
Lamb and mutton.
Rice (*Oryza sativa* L.)
Mangifera species.
Tea.

*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

Available; accessed on 06/23/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, 2-phenoxyethanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 2-Phenoxyethanol was assessed in the BlueScreen assay and found negative for genotoxicity in the presence of metabolic activation and positive for genotoxicity in the absence of metabolic activation. However, these positive results were observed at cytotoxic concentrations (reduced the relative cell density to less than 80%) (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material. The mutagenic activity of 2-phenoxyethanol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP and OECD TG 471 using both the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-phenoxyethanol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, 2-phenoxyethanol was not mutagenic in the Ames test.

The clastogenic activity of 2-phenoxyethanol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in carboxymethyl cellulose via a single intraperitoneal injection to groups of male and female NMRI mice. Doses of 125, 250, and 500 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted then examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, 2-phenoxyethanol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 2-phenoxyethanol does not present a concern for genotoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/07/17.

10.1.2. Repeated dose toxicity

The margin of exposure for 2-phenoxyethanol 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 2-phenoxyethanol. An OECD 408/GLP study was conducted on groups of 10 F344/DuCrj/rats/sex/dose with phenoxyethanol via drinking water at 0, 1250, 2500, 5000, 10000, and 20000 ppm. The mean intakes were calculated to be 0, 96, 185, 369, 687, and 1514 mg/kg/day in males and 0, 163, 313, 652, 1000, and 1702 mg/kg/day in females. The animals were treated for 13 weeks. There was a decrease in food consumption and a related decrease in body weights among

females of the 10000 ppm dose group and animals of the high dose group. Hematological alterations reported included statistically significant reductions in red blood cells (at ≥10000 ppm in males and females), hemoglobin (at ≥1,000 ppm in females and at 20000 ppm in males), and increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) (at ≥10000 ppm in males and at 20,000 ppm in females). Reticulocyte count was increased only in females of the high-dose group. These changes were consistent with slight anemia at doses of ≥10000 ppm. There were no historical control data comparisons provided in the summary report. Organ weight analysis revealed an increase in the relative liver weights among animals treated with ≥10000 ppm; however, this was not accompanied by alterations in related clinical chemistry parameters, histopathology, or absolute liver weight alterations. Hence, this finding was not considered to be toxicologically relevant. An increase in the relative kidney weight was observed among females at ≥ 10000 ppm and in both sexes at 20000 ppm. Absolute kidney weights were not statistically significantly increased in either males or females. Histopathological examination revealed slight to moderate urothelial hyperplasia of the renal pelvis among animals of the 10000 ppm treatment group. Slight to moderate urinary bladder transitional epithelial hyperplasia was observed among females of the 10000 ppm and 20000 ppm treatment groups. Slight urinary bladder transitional epithelial hyperplasia was observed in 1 male at 20000 ppm. Alterations in kidney weights and histopathology were considered to be treatment-related alterations. The NOAEL was considered to be 5000 pm (equivalent to 369 and 313 mg/kg/day for males and females, respectively), based on changes in the kidney weight and histopathological alteration in the kidney and bladder (females only) among animals of the higher dose groups (SCCS, 2016).

A follow-up OECD 451/GLP 2-year carcinogenicity study was conducted on groups of 50 F344/DuCrlCrlj rats/sex/dose with 2-phenoxyethanol via drinking water at 0, 2500, 5000, and 10000 ppm. Using the chemical intake data, the mean intakes of 2-phenoxyethanol across the duration of the study were estimated to be 0, 124, 249, and 510 mg/kg/day in males and 0, 191, 380, and 795 mg/kg/day in females. There were no incidences of treatment-related carcinogenic activity among treated animals. Hematological alterations were reported but were not considered to be toxicologically relevant due to the lack of dose response. The kidney was a target organ in males in this study with an increased incidence of slight to moderate urothelial hyperplasia and slight papillary mineralization and necrosis in males at 10000 ppm. No histopathological findings in the kidney were observed in females. While liver enzymes (AST, ALT) were statistically significantly increased in males at 10000 ppm and bilirubin was increased (not statistically significant) and triglycerides were statistically significantly decreased in females at 10000 ppm, histopathology of the liver was unremarkable in both sexes. Hence, clinical chemistry alterations in AST and ALT were not considered to be toxicologically relevant. Based on the histopathological findings in the kidney in males, the NOAEL was considered to be 5000 ppm corresponding to 249 mg/kg/day (SCCS, 2016). Since no treatment-related hematological alterations were reported during the 2-year carcinogenicity study and there were no incidences of mortality, the hematological alterations observed during the 13-weeks study were not considered to be toxicologically relevant.

In an OECD 408 90-day study, groups of 10 Cru:BDF1/mice/sex/dose were administered 2-phenoxyethanol via drinking water at 0, 1250, 2500, 5000, 10000, and 20000 ppm. The mean intakes were calculated to be 0, 182, 390, 765, 1178, and 2135 mg/kg/day in males and 0, 236, 478, 948, 1514, and 2483 mg/kg/day in females. Statistically significant decreases in body weights were observed among high-dose males throughout the entire dosing period and in females only during week 7. Hematological alterations revealed statistically significant reductions in hemoglobin and MCHC and a significant increase in MCV among high dose females. Hematological changes among high dose males included statistically significant increases in reticulocytes. There were no comparisons to historical control data provided. Organ weight analysis revealed an increase in the absolute kidney weight among females at ≥ 10000 ppm. No treatment-related histopathological findings were observed among treated animals. The NOAEL was considered to be 5000 ppm (765 and 948 mg/kg/day for males and females, respectively), based on alterations in the kidney weight among higher dose group animals.

In a follow-up OECD 451 study, a 2-year carcinogenicity study was conducted on groups of 50 B6D2F1 mice/sex/dose administered 2-phenoxyethanol via drinking water at 0, 5000, 10000, and 20000 ppm. Using the chemical intake data, the mean intakes of 2-phenoxyethanol across the duration of the study were estimated to be 0, 468, 898, and 1701 mg/kg/day in males and 0, 586, 1072, and 2058 mg/kg/day in females. Hematological and clinical chemistry alterations reported were not considered to be treatment-related. Organ weight changes were considered to be of no toxicological significance. There was no mortality reported among treated animals. Terminal body weights for the 5000, 10000, and 20000 ppm dose groups were 98%, 84%, and 72% for males and 100%, 94%, and 79% for females, as compared to the respective controls. Food consumption was decreased in both males and females administered ≥10000 ppm. A dose-dependent decrease in water consumption relative to controls was noted in all treatment groups of both sexes. There was no evidence of a treatment-related increase in neoplastic lesions and non-neoplastic histopathological findings in either sex in this study. Therefore, the NOAEL for 2-phenoxyethanol was concluded to be 5000 ppm (corresponding to an intake of 468 mg/kg/day in males and 586 mg/kg/day in females), based on decreased body weights among higher dose group animals (SCCS, 2016). Since no treatment-related hematological alterations were reported during the 2-year carcinogenicity study and there were no incidences of mortality, the hematological alterations observed during the 13-weeks study were not considered to be toxicologically relevant.

In another study, groups of 10 New Zealand White rabbits/sex/dose were administered 2-phenoxyethanol at 0, 50, 150, and 500 mg/kg/day dermally under occlusion for 6 h per day, 5 days/week, for 13 weeks. There were no treatment-related gross pathologic or histopathological changes observed among high dose animals. Thus, the NOAEL was considered to be 500 mg/kg/day, the highest dose tested (SCCS, 2016).

Therefore, the NOAEL for the repeated dose toxicity was considered to be 249 mg/kg/day from the 2-year oral drinking water carcinogenicity study conducted in rats.

In a special investigative study, the potential of 2-phenoxyethanol to cause hemolysis of RBCs *in vitro* was studied for humans, rats, rabbits, dogs, and mice. The results of the hemolysis tests showed the following: relative resistance to lysis from greatest to least: human > dog > rat ≈ rabbit > mouse. Therefore, human RBCs were more resistant to 2-PE than RBCs of rabbit, dog, rat, and mouse. 2-PAA, 2-EE, and 2-EAA did not show significant hemolytic effects at any concentration in any of the species examined. The results showed that human RBCs are more resistant to hemolysis from 2-phenoxyethanol than other species (SCCS, 2016).

Therefore, the 2-phenoxyethanol MOE can be calculated by dividing the 2-phenoxyethanol NOAEL in mg/kg/day by the total systemic exposure to 2-phenoxyethanol, 249/0.016 or 15563.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/17/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2-phenoxyethanol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on 2-phenoxyethanol. A dermal developmental toxicity study was

conducted on groups of 25 pregnant New Zealand White rabbits/dose administered 2-phenoxyethanol at doses of 0, 300, 600, and 1000 mg/kg/day. The application sites were occluded, and the test material was applied for 24 h/day throughout the treatment period. The animals were treated from gestation days 6 through 18. The original study cited in the SCCS dossier was dated 1985. The study was a non-GLP study. Mortality was reported among mid- and high-dose group animals. Hematological and urinalysis revealed signs of hemoglobinuria among high-dose group animals. There was, however, no effect of treatment on the developing fetus up to the highest dose group. The NOAEL for developmental toxicity was considered to be 600 mg/kg/day, since maternal deaths at 1000 mg/kg/day precluded a full evaluation of developmental toxicity in the highest dose group (SCCS, 2016).

In an OECD 414 oral gavage study, groups of 25 female Wistar rats/dose were administered 2-phenoxyethanol at 0, 100, 300, or 1000 mg/kg/day. Mortality and alteration in clinical signs were reported among high-dose group females, but there were no other treatment-related alterations reported among the treated females or the developing fetus up to the highest dose tested. The NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (SCCS, 2016).

The most conservative developmental toxicity NOAEL of 600 mg/kg/day from the dermal rabbit study was selected for this safety assessment. To account for bioavailability following dermal application, data from a human *in vitro* study (see Section 4) was used to revise the NOAEL of 600 mg/kg/day to reflect the systemic dose. At a dermal penetration of 81% of applied dose, the revised 2-phenoxyethanol toxicity NOAEL from the dermal study is 486 mg/kg/day. Therefore, the 2-phenoxyethanol MOE for the developmental toxicity endpoint can be calculated by dividing the 2-phenoxyethanol NOAEL in mg/kg/day by the total systemic exposure to 2-phenoxyethanol, 486/0.016 or 30375.

There are sufficient reproductive toxicity data on 2-phenoxyethanol. A dietary reproductive toxicity study using a continuous breeding protocol was conducted in Swiss CD-1 mice. Dietary levels of 0%, 0.25%, 1.25%, or 2.5% (equivalent to 0, 400, 2000, or 4000 mg/kg/day) 2-phenoxyethanol were fed to pairs of mice (38, 20, 19, or 18 pairs/dose, respectively) for 7 days prior to and during a 98-day cohabitation period. There were both generalized toxic effects (decreased weight gain and increased liver weights) and reproductive effects (reduced number of litters per pair, decreased average litter size, and lower proportion of pups born alive) in the 2.5% group when compared to controls but not at the lower doses. Litters from the F1 generation were randomly selected at day 21 for a crossover mating trial, in which the F1 pups were reared and maintained on the same dietary level of the test material as their F0 parents. Continuous exposure of the F1 mice to 2-phenoxyethanol *in utero* and from birth to 74 days of age resulted in reduced live pup weights, in a dose-dependent manner, and was lethal to 39% mice in the mid-dose group and 87% mice in the high-dose group. Live pup weights were also decreased among offspring in a dose-related manner. The report states that there was clear toxicity of 2-phenoxyethanol to newborn and young growing mice. However, all the reproductive and fetotoxic effects reported may be secondary to generalized toxicity of 2-phenoxyethanol. Therefore, the NOAEL for reproductive toxicity was concluded to be 0.25% in the diet, based on diminished live pup weight in the F2 (offspring of the F1) generation in a dose-dependent manner. A NOAEL of 400 mg/kg/day was calculated for males. The estimated daily intake of 2-phenoxyethanol in females was calculated to be approximately 950 mg/kg/day, from the average body weight and average feed consumption reported during week 18 (Heindel et al., 1990; data also available in National Toxicology Program, 1984; Morrissey et al., 1989). A NOAEL of 400 mg/kg/day was selected for the reproductive toxicity endpoint. Therefore, the 2-phenoxyethanol MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-phenoxyethanol NOAEL in mg/kg/day by the total systemic exposure to 2-phenoxyethanol, 400/0.016 or 25000.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/18/17.

10.1.4. Skin sensitization

Based on the existing data and read-across material 2-(4-methylphenoxy) ethanol (CAS # 15149-10-7), 2-phenoxyethanol does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2-phenoxyethanol. Based on the available data, 2-phenoxyethanol does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure indicates that these materials would not be expected to react directly with skin proteins (Toxtree 2.6.13; OECD Toolbox v3.4). 2-Phenoxyethanol was found to be positive in the *in vitro* U937-CD86 test (Piroird et al., 2015). In the murine local lymph node assay, 2-(4-methylphenoxy) ethanol was reported to be a non-sensitizer (RIFM, 2002). In guinea pig maximization tests, 2-phenoxyethanol was reported to be a non-sensitizer (Bruze et al., 1988; ECHA, 2011). In a human maximization test, 1 (1/18) reaction was observed with 10%, or 6900 μg/cm^2 2-phenoxyethanol in petrolatum; however, upon repeating the test in 26 subjects, no reactions were observed (RIFM, 1982). Similarly, in a separate human maximization test, no reactions were observed in any of the 30 subjects with 10%, or 6900 μg/cm^2 2-phenoxyethanol in petrolatum (RIFM, 1978a). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 1500 μg/cm^2 of 2-phenoxyethanol in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 41 volunteers (RIFM, 1978b). Similarly, in 2 HRIPTs, no reactions were observed when the read-across material at 2.5% (2461 μg/cm^2) in alcohol SDA 39C was used for induction and challenge (RIFM, 1971; RIFM, 1972). Based on weight of evidence from structural analysis, animal and human studies, and read-across material 2-(4-methylphenoxy) ethanol, 2-phenoxyethanol does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: Hausen (1993); Eastman Kodak Company, 1984; Emery Chemicals, 1987

Literature Search and Risk Assessment Completed On: 05/08/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra and the available data, 2-phenoxyethanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In an OECD 432 test with the 3T3 Neutral Red Uptake assay, 2-phenoxyethanol was predicted to have no phototoxic potential (RIFM, 2015). Based on lack of absorbance and experimental data, 2-phenoxyethanol 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} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/20/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure for 2-phenoxyethanol is adequate for the respiratory endpoint at the current level of use.

10.1.7. Risk assessment

The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week repeat dose, nose-only rat inhalation study (GLP), a NOAEC of 40 mg/m^3 was reported (ECHA, 2011; accessed 05/09/17). Test article concentrations of 0, 40, 200, and 1000 mg/m^3 were administered to male and female Wistar rats for 6 h/day, 5 days/week. Detailed clinical observations, body weight, food consumption and efficiency, hematology, clinical chemistry, gross pathology, and histopathology were all considered. Histopathology included the following tissues: nasal cavities, larynx, trachea, lungs, mediastinal lymph nodes, thymus, liver, kidneys, spleen, adrenal glands, heart, stomach, and esophagus. None of the test groups demonstrated clinical signs of toxicity. However, there were statistically significant changes in body and organ weights within the 200 and 1000 mg/m^3 treatment groups (specific to male rats) as well as adverse histopathological results. Both male and female rats displayed increased thickness and increased number of mucous cells in the bronchi, and there was evidence of degeneration, metaplasia, and inflammatory cell infiltrates in the upper respiratory tract. Therefore, the NOAEC was determined to be 40 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (40 mg/m^3) (1 m^3/1000L) = 0.040 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.040 mg/L) (61.2 L/d) = 2.45 mg/day
- (2.45 mg/day)/(0.0016 kg lung weight of rat*) = 1531.25 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.16 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015 and Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.25 mg/kg lung weight/day resulting in a MOE of 6125 (i.e., [1531.25 mg/kg lung weight/day]/[0.25 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.16 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: “Comparative Physiology and Anatomy,” subsection, “Comparative Airway Anatomy.”

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/09/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-phenoxyethanol 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, 2-phenoxyethanol 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 v4.1 (US EPA, 2012a) did not identify 2-phenoxyethanol 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 v4.1). 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 current VoU (IFRA, 2015), 2-phenoxyethanol does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.4. Other available data

2-Phenoxyethanol has been registered under REACH and the following additional data is available:

The ready biodegradability of the test material was evaluated according to the OECD 301F method. After 28 days, biodegradation of 99% was observed.

2-Phenoxyethanol was evaluated in an OECD 301A test. Biodegradation greater than 90% was observed after 15 days.

A fish (Fathead minnow) acute toxicity study was conducted according to the ASTM method under flow-through conditions. The 96-h LC50 was reported to be 334 mg/L.

A fish (*Pimephales promelas*) Early Life Stage toxicity study was conducted according to the OECD 210 method under flow-through conditions. The 34-day NOEC was reported to be 51.3 mg/L.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions, and the 48-h EC50 was reported to be greater than 500 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. The 21-day NOEC was

reported to be 48.2 mg/L and 9.43 mg/L based on growth and reproduction, respectively.

An Algae growth inhibition study was conducted according to the DIN 38412 part 9 method. The 72-h EC50 was reported to be greater than 500 mg/L.

10.2.5. Risk assessment refinement

Since 2-phenoxyethanol has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1130 mg/L			1,000,000	1.130 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.1	1.1
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 1.13 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: 05/03/17.

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 10/09/2018.

12. Conflicts of interest

The authors declare that they have no conflicts of interest.

13. Declaration of interests

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.2019.110629.

Appendix

Read-across justification

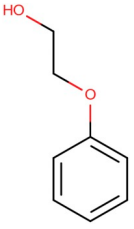
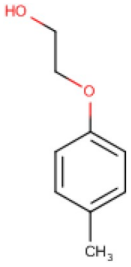
Methods

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 Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were

examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.

- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (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	2-Phenoxyethanol	2-(4-Methylphenoxy)ethanol
CAS No.	122-99-6	15149-10-7
Structure		
Similarity (Tanimoto score)		0.769
Read-across endpoint		• Skin Sensitization
Molecular Formula	$C_8H_{10}O_2$	$C_9H_{12}O_2$
Molecular Weight	138.17	152.19
Melting Point (°C, EPI Suite)	22.47	39.43
Boiling Point (°C, EPI Suite)	243.84	261.19
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.598	0.156
Log Kow (KOWWIN v1.68 in EPI Suite)	1.16	1.65
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	26700	9407
J_{max} (μg/cm^2/h, SAM)	202.036	144.010
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.57E-003	1.73E-003
Skin Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization reactivity domains (ToxTree v2.6.13)	• No alert found	• No alert found
Metabolism		
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2
Rat liver S9 metabolism simulator and structural alerts for metabolites		

Summary

There are insufficient toxicity data on the target material 2-phenoxyethanol (CAS # 122-99-6). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analog 2-(4-methylphenoxy)ethanol (CAS # 15149-10-7) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 2-(4-Methylphenoxy)ethanol (CAS # 15149-10-7) was used as a read-across analog for the target material 2-phenoxyethanol (CAS # 122-99-6) for the skin senzitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of glycol ethers.
  - o The target substance and the read-across analog share a phenoxyethanol fragment.
  - o The key difference between the target substance and the read-across analog is that the read-across analog has an additional methyl substitution at the para position of the phenoxy ring while the target does not. This structure difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - 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 QSAR OECD Toolbox (v3.4), structural alerts for toxicity 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 differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.

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.

Bruze, M., Gruvberger, B., Agrup, G., 1988. Sensitization studies in the Guinea pig with the active ingredients of Euxyl K 400. Contact Dermatitis 18, 37–39.

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.

Eastman Kodak Company, 1984. Submission to EPA. (Unpublished).

ECHA, 2011. 2-phenoxyethanol registration dossier. Retrieved from: https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15160/1.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

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

Emery Chemicals, 1987. Submission to EPA. (Unpublished).

Hausen, B.M., 1993. The sensitizing potency of Euxyl K 400 and its components 1,2-dibromo-2,4-dicyanobutane and 2-phenoxyethanol. Contact Dermatitis 28 (3), 149–153.

Heindel, J.J., Gulati, D.K., Russell, V.S., Reel, J.R., Lawton, A.D., Lamb IV, J.C., 1990. Assessment of ethylene glycol monobutyl and monophenyl ether reproductive toxicity using a continuous breeding protocol in Swiss CD-1 mice. Fundam. Appl. Toxicol. 15 (4), 683–696.

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.

Morrissey, R.E., Lamb IV, J.C., Morris, R.W., Chapin, R.E., Gulati, D.K., Heindel, J.J., 1989. Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. Fundam. Appl. Toxicol. 13 (4), 747–777.

National Toxicology Program, 1984. Ethylene Glycol Monophenyl Ether: Reproduction and Fertility Assessment in CD-1 Mice when Administered in the Feed. NTP-84-410. NTP-83-FACB022.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

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

Phalen, R.F., 2009. Inhalation Studies. Foundations and Techniques, second ed. Published by Informa Healthcare USA, Inc., New York, NY.

Piroird, C., Ovigne, J.-M., Rousset, F., Martinozzi-Teissier, S., Gomes, C., Cotovio, J., Alepee, N., 2015. The Myeloid U937 Skin Sensitization Test (U-SENS) addresses the activation of dendritic cell event in the adverse outcome pathway for skin sensitization. Toxicol. Vitro 29 (5), 901–916.

RIFM (Research Institute for Fragrance Materials, Inc), 1971. Repeated Insult Patch Test with 2-(4-methylphenoxy)ethanol in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 55017. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1972. Repeated Insult Patch Test with 2-(4-methylphenoxy)ethanol in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 55018. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1978a. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1698. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1978b. Repeated Insult Patch Test of 2-phenoxyethanol in Human Subjects. Unpublished Report from International Flavors and Fragrances. RIFM Report Number 7690. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1982. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1643. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2002. Murine local lymph node assay with 2-(4-methylphenoxy)ethanol. Unpublished report from Givaudan International SA. RIFM report number 41989. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 2-phenoxyethanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65049. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2015. 2-Phenoxyethanol: Neutral Red Uptake Phototoxicity Assay in Balb/c 3T3 Mouse Fibroblasts. RIFM Report Number 68303. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Expo. Surv. 11 May 2016.

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.

SCCS, 2016. Opinion on Phenoxyethanol, SCCS/1575/16. Retrieved from: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_195.pdf.

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.