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Short Review

RIFM fragrance ingredient safety assessment, 2-hydroxyethyl phenoxyacetate, CAS Registry Number 1984-60-7

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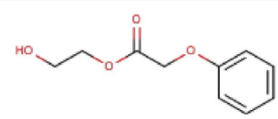
Version: 050219. This version replaces any previous versions.

Name: 2-Hydroxyethyl phenoxyacetate
CAS Registry Number: 1984-60-7



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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.
Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (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-Hydroxyethyl phenoxyacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-hydroxyethyl phenoxyacetate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class III material, and the exposure to 2-hydroxyethyl phenoxyacetate is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The existing data and data from read-across analog 2-phenoxyethyl isobutyrate (CAS # 103-60-6) show that there are no safety concerns for skin sensitization for 2-hydroxyethyl phenoxyacetate under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-hydroxyethyl phenoxyacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-hydroxyethyl phenoxyacetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 1978; RIFM, 2015a)
Repeated Dose Toxicity: No NOAEL is available. Exposure is below TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	RIFM (2002)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening-level: 3.03 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.16 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 4035 mg/L	(RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 4035 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 4.035 μg/L	
•**Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; Cleared at screening-level	

1. Identification

1. **Chemical Name:** 2-Hydroxyethyl phenoxyacetate
2. **CAS Registry Number:** 1984-60-7
3. **Synonyms:** Acetic acid, phenoxy-, 2-hydroxyethyl ester; 2-hydroxyethyl phenoxyacetate
4. **Molecular Formula:** $C_{10}H_{12}O_4$
5. **Molecular Weight:** 196.2
6. **RIFM Number:** 5268
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 311.45 °C (EPI Suite)
2. **Flash Point:** 164 +/- 2 °C (RIFM, 2003), > 93 °C (GHS)
3. **Log K_{OW}:** 0.64 (EPI Suite)
4. **Melting Point**: 74.65 °C (EPI Suite)
5. **Water Solubility:** 41990 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.0000103 mm Hg @ 20 °C (EPI Suite v4.0), 2.19e-005 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:** Not Available

3. Volume of use (Worldwide band)

1. **Volume of Use (Worldwide Band):** 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95th Percentile Concentration in Shampoo:** 0.065% (RIFM, 2016)

(No reported use in hydroalcoholics).

2. **Inhalation Exposure*:** 0.000030 mg/kg/day or 0.0023 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0013 mg/kg/day (RIFM, 2016)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High (Expert Judgment)

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-phenoxyethyl isobutyrate (CAS # 103-60-6)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

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

2-Hydroxyethyl phenoxyacetate is not reported to occur in foods by the VCF*.

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

9. REACH Dossier

2-Hydroxyethyl phenoxyacetate is pre-registered for 2010; no dossier available as of 05/02/19.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. 2-Hydroxyethyl phenoxyacetate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2015b). BlueScreen HC is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2-hydroxyethyl phenoxyacetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the standard plate test (overlay) method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, and *Saccharomyces cerevisiae* strain D4 were treated with 2-hydroxyethyl phenoxyacetate in either deionized water or dimethyl sulfoxide (DMSO) at concentrations up to 500 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1978). Under the conditions of the study, 2-hydroxyethyl phenoxyacetate was not mutagenic in the Ames test.

The clastogenic activity of 2-hydroxyethyl phenoxyacetate 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 2-hydroxyethyl phenoxyacetate in DMSO at concentrations up to 1960 μg/mL in a DRF study; micronuclei analysis was conducted at 600 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h 2-Hydroxyethyl phenoxyacetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system

(RIFM, 2015a). Under the conditions of the study, 2-hydroxyethyl phenoxyacetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2-hydroxyethyl phenoxyacetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/18/19.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 2-hydroxyethyl phenoxyacetate or any read-across materials. The total systemic exposure to 2-Hydroxyethyl phenoxyacetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-hydroxyethyl phenoxyacetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-hydroxyethyl phenoxyacetate (1.3 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/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: 04/04/19.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 2-hydroxyethyl phenoxyacetate or on any read-across materials. The total systemic exposure to 2-hydroxyethyl phenoxyacetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-hydroxyethyl phenoxyacetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-hydroxyethyl phenoxyacetate (1.3 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the 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: 04/05/19.

11.1.4. Skin sensitization

Based on the existing data and read-across material 2-phenoxyethyl isobutyrate (CAS # 103-60-6), 2-hydroxyethyl phenoxyacetate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2-hydroxyethyl phenoxyacetate. Based on the existing data and read-across material 2-phenoxyethyl isobutyrate (CAS # 103-60-6; see Section VI), 2-hydroxyethyl phenoxyacetate is not considered a skin sensitizer. The chemical structure of these materials indicate that 2-hydroxyethyl phenoxyacetate would be expected to react with skin proteins (Roberts, 2007; OECD Toolbox v4.2), while read-across material 2-phenoxyethyl isobutyrate would not be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material 2-phenoxyethyl isobutyrate was found to be a non-sensitizer up to 100% (RIFM, 2002). In a human maximization test, no skin sensitization reactions were observed up to 4% (2760 μg/cm^2) of read-across material 2-phenoxyethyl isobutyrate (RIFM, 1973). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with an unknown concentration of the target material, 2-hydroxyethyl phenoxyacetate, no reactions indicative of skin sensitization were observed in any of the 53 volunteers (RIFM, 1978). In an HRIPT with the read-across material, 2-phenoxyethyl isobutyrate in alcohol SDA 39C, no reactions indicative of sensitization was observed in any of the 38 volunteers when 0.5% or 388 μg/cm^2 was used (RIFM, 1965).

Based on the WoE from structural analysis, animal and human studies, and read-across material 2-phenoxyethyl isobutyrate, 2-hydroxyethyl phenoxyacetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1967; RIFM, 1968.

Literature Search and Risk Assessment Completed On: 03/13/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-hydroxyethyl phenoxyacetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-hydroxyethyl phenoxyacetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 2-hydroxyethyl phenoxyacetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/03/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-hydroxyethyl phenoxyacetate is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-hydroxyethyl phenoxyacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0023 mg/day. This exposure is 204.35 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: 04/04/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-hydroxyethyl phenoxyacetate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates.

Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-hydroxyethyl phenoxyacetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

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

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-hydroxyethyl phenoxyacetate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. 2-Hydroxyethyl phenoxyacetate has been pre-registered for REACH with no additional data at this time.

11.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	4035			1000000	4.035	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.64	0.64
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

The RIFM PNEC is 4.035 μg/L. The revised PEC/PNECs for EU and NA (No VoU): 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: 03/07/19.

12. Literature Search*

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

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 09/23/19.

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.2020.111192.

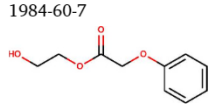
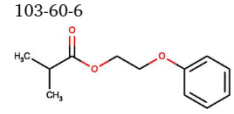
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European 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 material 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	2-Hydroxyethyl phenoxyacetate	2-Phenoxyethyl isobutyrate
CAS No.	1984-60-7	103-60-6
Structure		
Similarity (Tanimoto Score)		0.69
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{10}H_{12}O_4$	$C_{12}H_{16}O_3$
Molecular Weight	196.20	208.25
Melting Point (°C, EPI Suite)	74.65	37.71
Boiling Point (°C, EPI Suite)	311.45	276.18
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.00292	0.701
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	0.64	3.01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	4.199e + 004	105.7
J_{max} (μg/cm^2/h, SAM)	40.914	22.235
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.64E-005	1.80E-001
Skin Sensitization		
Protein Binding (OASIS v1.1)	• SN2|SN2 ≫ Nucleophilic substitution at sp3 carbon atom|SN2 ≫ Nucleophilic substitution at sp3 carbon atom ≫ alpha-Activated acetates	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• SN2|SN2 ≫ Nucleophilic substitution at sp3 carbon atom|SN2 ≫ Nucleophilic substitution at sp3 carbon atom ≫ alpha-Activated acetates	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-hydroxyethyl phenoxyacetate (CAS # 1984-60-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2-phenoxyethyl isobutyrate (CAS # 103-60-6) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2-Phenoxyethyl isobutyrate (CAS # 103-60-6) was used as a read-across analog for the target material 2-hydroxyethyl phenoxyacetate (CAS # 1984-60-7) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The target material and the read-across analog share an alkyl ester functionality and a phenoxy moiety.
  - o The key difference between the target material and the read-across analog is that the target material is the ethylene glycol monoester of 2-phenoxy acetic acid, whereas the read-across analog is the 2-phenoxyethyl ester of isobutyric acid. These structural differences are toxicologically insignificant.

- o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The target material is predicted to have protein binding alerts by OASIS for skin sensitization specific for α-activated acetates. A chemical with this structural alert could interact with proteins via nucleophilic substitution at sp3 carbon atom. A detailed explanation can be found within the QSAR Toolbox. All the other skin sensitization alerts are negative. Therefore, the alert can be ignored. Data for read-across superseded predictions in this case.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

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

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? Yes
Q27. Rings with substituents? Yes
Q28. More than one aromatic ring? No
Q30. Aromatic ring with complex substituents? Yes
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No
Q32. Contains only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms or c) a polyoxyethylene ($n > = 4$) on the aromatic or aliphatic side chain? No
Q22. Common component of food? No
Q33. Has sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No, High (Class III)

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