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Short Review

RIFM fragrance ingredient safety assessment, allyl phenoxyacetate, CAS Registry Number 7493-74-5

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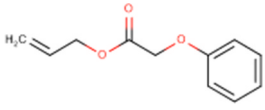
Version: 092,722. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: Allyl phenoxyacetate CAS Registry Number: 7493-74-5

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

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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

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

This safety assessment is based on the RIFM Criteria Document (Api 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.

Allyl phenoxyacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that allyl phenoxyacetate is not genotoxic. Data on allyl phenoxyacetate provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided allyl phenoxyacetate a No Expected Sensitization Induction Level (NESIL) of 700 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; allyl phenoxyacetate is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to allyl phenoxyacetate is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; allyl phenoxyacetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2015f; RIFM, 2015e)
Repeated Dose Toxicity: NOAEL = 16.7 mg/kg/day. (RIFM, 2018)
Reproductive Toxicity: NOAEL = 50 mg/kg/day. (RIFM, 2018)
Skin Sensitization: NESIL = 700 μg/cm^2 (RIFM, 2008)

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(*continued*)

Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 85% (OECD 301B) — RIFM (1994)
Bioaccumulation:
Screening-level: 19.51 L/kg (EPI Suite v4.11; — US EPA (2012a)
Ecotoxicity:
Screening-level: 96-h Fish LC50: 1.181 mg/L (ECOSAR v2.0; — 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 et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 1.181 mg/L (ECOSAR v2.0; — US EPA (2012b)
RIFM PNEC is: 0.1181 μg/L
•F020 **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: <1

1. Identification

1. **Chemical Name:** Allyl phenoxyacetate
2. **CAS Registry Number:** 7493-74-5
3. **Synonyms:** Acetate PA; Acetic acid, phenoxy-, 2-propenyl ester; 2-Propenyl phenoxyacetate; ﾌｪﾉｷｼ酢酸ｱﾘﾙ; Allylphenoxyacetat/corps 519; Allyl phenoxyacetate
4. **Molecular Formula:** $C_{11}H_{12}O_3$
5. **Molecular Weight:** 192.21 g/mol
6. **RIFM Number:** 489
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 268.49 °C (EPI Suite), 270–273 °C at 1013 hPa (Symrise, 2016a)
2. **Flash Point:** >200 °F; closed cup (Fragrance Materials Association [FMA]), >93 °C (Globally Harmonized System), 140 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015d)
3. **Log K_{OW}:** 2.5 at 25 °C (RIFM, 1995b), 2.46 (EPI Suite), 2.33 at 24.7 °C (RIFM, 2016c)
4. **Melting Point**: 36.45 °C (EPI Suite), 1.1 °C at 1005 hPa (Symrise, 2016a)
5. **Water Solubility:** 379.6 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00454 mm Hg at 20 °C (EPI Suite v4.0), 0.008 mm Hg at 20 °C (FMA), 0.00807 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with a honey- and pineapple-like odor of great tenacity with the same type of flavor

3. Volume of use (Worldwide band)

1 10–100 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.32% (RIFM, 2019)

2. **Inhalation Exposure*:** 0.00058 mg/kg/day or 0.042 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0045 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

1. **Dermal:** 59.7%

RIFM, 2015a: *In vitro* skin penetration was determined using 4 control cells (1/donor, unoccluded conditions) and 12 active dosed diffusion cells for both unoccluded and occluded conditions. Epidermal membranes from 4 female (abdominal skin) donors were used; their integrity was assessed by measuring electrical resistance following the application of allyl phenoxyacetate (APA) in 70% ethanol. Permeation of APA from a 5 μL/cm^2 dose of 1.05% (w/v) donor solution was measured at 12 time points over 24 h using a pH 5 phosphate-buffered saline (PBS) receptor phase. For the occluded group, donor chambers were occluded using greased glass coverslips. At the end of 24 h, epidermal membranes were wiped and tape stripped following APA content determination in the wipes, strips, and remaining epidermis. To allow for mass balance, filter paper skin supports and diffusion cell donor chambers (and the glass coverslip for occluded cells) were washed. Under both experimental conditions, rapid permeation of APA was observed following the application of 52.5 μg/cm^2 APA. The data suggest that under both application conditions, APA permeates the membrane rapidly, followed by a gradual reduction in permeation rate. The amount absorbed was determined as a total of APA and PAA at the end of 24 h (represented as % of the applied dose in mean ± SE). From the applied dose, 59.7% ± 1.7% and 31.8% ± 1.7% were absorbed in occluded and unoccluded conditions, respectively. In comparison to the unoccluded conditions (18.3 ± 0.9 μg/cm^2, or 34.8% ± 1.8%), the amount of material recovered was higher in occluded conditions (41.5 ± 0.7 μg/cm^2, or 79.1% ± 1.3%). In addition, loss of treatment material due to evaporation was accounted for by measuring the loss from PTFE sheets under unoccluded conditions.

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class III, High (Expert Judgment)

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

*See the Appendix below for further details.

6.2. Analogs selected

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

6.3. Read-across justification

None.

7. Metabolism

Silver and Murphy, 1977, 1978: Inhibitors of carboxylesterases were used to determine the importance of enzymatic hydrolysis in the production of liver injury by esters of allyl alcohol. Groups of 4 rats were administered intraperitoneal (IP) injections of 1 mg/kg corn oil or 125 mg/kg triorthotolyl phosphate (TOTP) and euthanized 18 h later; the livers were homogenized for a manometric carboxylesterase assay. Allyl phenoxyacetate (0.016 M) was added to a flask containing 5 mg of liver homogenate in a bicarbonate buffer. The flasks were equilibrated for 5 min at 37 °C, with shaking. The amount of CO_2 evolved during a 20-min period was used to assess hydrolytic activity. The hydrolysis rate of 0.016 M allyl phenoxyacetate by the homogenated liver was 496 ± 101 μL CO_2/5 mg liver/20 min. In the animals pretreated with TOTP (an inhibitor of non-specific esterases), hydrolysis of allylphenoxyacetate was inhibited by 95.4%. In another experiment, TOTP (125 mg/kg) or corn oil was administered to male Holtzman rats (number not reported) by IP injection. The rats fasted for 18 h and were then gavaged with allyl phenoxyacetate in corn oil at doses of 0, 100, 150, 200, 250, or 400 mg/kg. The animals were euthanized 24 h later. Allyl phenoxyacetate at doses of 200 mg/kg and greater produced severe liver injury in the corn oil pretreated rats. Hepatotoxic effects were also seen in a few rats at lower dosages of allyl phenoxyacetate. TOTP pre-treatment protected against the hepatotoxicity of 200 mg/kg allyl phenoxyacetate and prevented an increase in plasma alanine-α-ketoglutarate transaminase (AKT) activity. TOTP pre-treatment of rats treated with 250 mg/kg allyl phenoxyacetate rats had significantly lower plasma AKT activity compared to rats pretreated with corn oil followed by 250 mg/kg allyl phenoxyacetate; however, both liver appearance and plasma AKT activity indicated the considerable liver injury was present in these rats. In a third experiment, fasted rats were injected with saline or 375 mg/kg pyrazole, an inhibitor of alcohol dehydrogenase. Two hours later, the rats were gavaged with corn oil or 250 mg/kg allyl phenoxyacetate, and the rats were euthanized 24 h later. Plasma AKT was greatly elevated in saline-pretreated allyl phenoxyacetate–treated rats, and liver appearance indicated severe injury. Pyrazole pre-treatment completely protected against the hepatotoxic effects of allyl phenoxyacetate (AKT activity or liver appearance). As a result of pyrazole completely protecting against allyl phenoxyacetate-induced liver injury, the authors determined that it is unlikely that allyl phenoxyacetate, free phenoxyacetic acid, or a metabolite produced by a pathway other than that catalyzed by alcohol dehydrogenase contributed to the hepatotoxicity of allyl phenoxyacetate.

Additional References: None.

8. Natural occurrence

Allyl 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

Available; accessed 09/12/22 (ECHA, 2018)

10. Conclusion

The maximum acceptable concentrations[a] in finished products for allyl phenoxyacetate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.054
2	Products applied to the axillae	0.016
3	Products applied to the face/body using fingertips	0.31
4	Products related to fine fragrances	0.30
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.076
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.076
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.076
5D	Baby cream, oil, talc	0.025
6	Products with oral and lip exposure	0.039
7	Products applied to the hair with some hand contact	0.39
8	Products with significant ano-genital exposure (tampon)	0.025
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.59
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.27
10B	Aerosol air freshener	2.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.025
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	59

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For allyl phenoxyacetate, the basis was the reference dose of 0.167 mg/kg/day, a skin absorption value of 59.7%, and a skin sensitization NESIL of 700 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Allyl 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, 2014a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of allyl phenoxyacetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with allyl phenoxyacetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2015f). Under the conditions of the study, allyl phenoxyacetate was not mutagenic in the Ames test.

The clastogenic activity of allyl 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 allyl phenoxyacetate in DMSO at concentrations up to 1922.0 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1922.0 μg/mL in the presence and absence of metabolic activation. Allyl phenoxyacetate did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2015e). Under the conditions of the study, allyl phenoxyacetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: RIFM, 2015c.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

The MOE for allyl phenoxyacetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data for allyl phenoxyacetate. In an OECD 422/GLP-compliant study, groups of 12 Sprague Dawley rats/sex/dose were administered allyl phenoxyacetate via gavage at dose levels of 0, 15, 50, or 150 mg/kg/day. Males were treated for at least 50 days (2 weeks prior to mating up to the day prior to scheduled necropsy), while females were treated for 2 weeks prior to mating, during mating, and continuing through to lactation day (LD) 13. Additional groups of 6 rats/sex/dose were maintained as recovery groups and were administered allyl phenoxyacetate at 0 and 150 mg/kg/day for at least 50 days without mating, followed by a 14-day treatment-free recovery period. Systemic observations including mortality, clinical signs, body weight, bodyweight gain, food consumption, functional behavior examination, motor activity examination, macroscopic findings, hematology, coagulation, clinical chemistry, organ weights, and microscopic findings were conducted and measured. No treatment-related deaths or moribund animals were reported in any group. In systemic observations, treatment-related salivation was observed in both sexes at all dose levels, but the effect was attributed to the palatability of the test material. Hematological changes in both sexes involved a 2-fold increase in WBC, monocyte, and large unstained cell counts at 150 mg/kg/day dose. In males, an increase in platelet counts was observed at 50 and 150 mg/kg/day doses. Since these changes were reversed during the recovery period and were not dose dependent, they were not considered to be treatment-related adverse events. In both sexes of the highest-dose group, notable organ weight (absolute and relative) changes in the liver, spleen, testis, and epididymides were reported, but these effects recovered during the recovery period. Microscopic findings in the liver were consistent with the discoloration, focus/foci, enlarged, small, abnormal shape, and/or irregular surface in macroscopic findings and significantly increased weights. In the liver, cholangiofibrosis, hydropic degeneration, and necrosis were observed microscopically in both sexes at 150 mg/kg and considered to be an adverse effect of the test material. Although cholangiofirosis was reversed during the recovery period, periportal fibrosis and pigmented macrophage persisted. These effects were accompanied by increases in ALT (approximately 3-fold), AST (approximately 2-fold), GGT (approximately 9-fold), and bilirubin in both sexes in the highest dose groups. These changes were considered adverse. In addition, lymphoid hyperplasia in the spleen and hepatic lymph node and congestion in the hepatic lymph node were observed in males and/or

females at 150 mg/kg, which correlated with increased spleen weights (absolute and relative) and/or enlarged spleen and hepatic lymph node. Since the increase in weight and lymphoid hyperplasia in the spleen recovered following the recovery period, these changes were considered to be a secondary response to the inflammatory changes in the liver. In the stomach, squamous cell hyperplasia in the non-glandular region was observed in both sexes at 150 mg/kg. This change was considered to be an adaptive response following local irritation by the test material due to full recovery after the recovery period. The NOAEL was determined to be 50 mg/kg/day, based on the hepatotoxic effects during the study (RIFM, 2018).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for repeated dose toxicity is 50/3 or 16.7 mg/kg/day.

Therefore, the allyl phenoxyacetate MOE can be calculated by dividing the allyl phenoxyacetate NOAEL in mg/kg/day by the total systemic exposure to allyl phenoxyacetate, 16.7/0.0045, or 3711.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic reference dose (RfD) of 0.167 mg/kg/day.

11.1.2.2. Derivation of subchronic RfD. The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for allyl phenoxyacetate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 16.7 mg/kg/day by the uncertainty factor, 100 = 0.167 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/23/21.

11.1.3. Reproductive toxicity

The MOE for allyl phenoxyacetate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on allyl phenoxyacetate that can be used to support the reproductive toxicity endpoint. In an OECD 422/GLP-compliant study, groups of 12 Sprague Dawley rats/sex/dose were administered allyl phenoxyacetate via gavage at dose levels of 0, 15, 50, or 150 mg/kg/day. Males were treated for at least 50 days (2 weeks prior to mating, during mating, and up to the day prior to scheduled necropsy), while females were treated for 2 weeks prior to mating, during mating, and continuing through to LD 13. Additional groups of 6 rats/sex/dose were also administered allyl phenoxyacetate at 0 and 150 mg/kg/day for at least 50 days but did not mate; these animals were assigned to serve as the 14-day treatment-free recovery groups. In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. At 150 mg/kg/day, statistically significant decreases in the absolute weights of the left and right testis (88% of control, respectively) and the left and right epididymides (91% of control, respectively) were observed in males. These changes recovered after the 14-day treatment-free recovery period. At 150 mg/kg/day, a statistically significant decrease in pup body weight was observed on PND 13 (male and female pups: 90% of control, respectively). No other treatment-related adverse effects were observed in the fertility and/or development of pups. Although reversibility of the testes and epididymides weight was observed, the more conservative NOAEL of 50 mg/kg/day was considered for fertility, based on decreases in the testes and epididymides weight among high-dose group males. The NOAEL for developmental toxicity was considered to be 50 mg/kg/day, based on a decrease in body weight among high-dose group pups (RIFM, 2018).

Therefore, the allyl phenoxyacetate MOE for the reproductive toxicity endpoint can be calculated by dividing the allyl phenoxyacetate NOAEL in mg/kg/day by the total systemic exposure to allyl phenoxyacetate, 50/0.0045, or 11,111.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/23/21.

11.1.4. Skin sensitization

Based on the existing data, allyl phenoxyacetate is considered a skin sensitizer with a defined NESIL of 700 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.4.1. Risk assessment. Based on the existing data, allyl phenoxyacetate is considered a skin sensitizer (Table 1). The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Allyl phenoxyacetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and U-SENS test but positive in KeratinoSens (RIFM, 2014b; RIFM, 2020; RIFM, 2015b). In a murine local lymph node assay (LLNA), allyl phenoxyacetate was found to be sensitizing with an EC3 value of 3.1% (775 μg/cm^2) (ECHA, 2018; RIFM, 2007). In a guinea pig maximization test, allyl phenoxyacetate did not lead to skin sensitization reactions (RIFM, 1981a). In 2 human maximization tests, no skin sensitization reactions were observed with 1% or 690 μg/cm^2 of allyl phenoxyacetate (RIFM, 1974a; RIFM, 1974b). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 0.6% or 709 μg/cm^2 of allyl phenoxyacetate in 1:3 ethyl alcohol: diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 2008). In another CNIH, with 1% allyl phenoxyacetate in DEP, no reactions indicative of sensitization were observed in any of the 10 volunteers (RIFM, 1978).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, allyl phenoxyacetate is a sensitizer with a WoE NESIL of 700 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 0.167 mg/kg/day.

Additional References: Klecak (1985); RIFM, 1981b; RIFM, 1981c; RIFM, 2017b; SCCS, 2012.

Literature Search and Risk Assessment Completed On: 09/27/22.

11.1.5. Photoirritation/Photoallergenicity

Based on the available UV/Vis absorption spectra, allyl phenoxyacetate would not be expected to present a concern for photoirritation or photoallergenicity.

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

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of

Table 1
Summary of existing data on allyl phenoxyacetate.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[4]	Buehler[4]
Moderate	709	690	NA	700	775 [1]	Negative	NA
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Positive	Negative		SN2	SN2	SN2

290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/24/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on allyl phenoxyacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.042 mg/day. This exposure is 11.2 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of allyl phenoxyacetate 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, allyl phenoxyacetate 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 allyl 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 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, 2017). 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current VoU (2019), allyl phenoxyacetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation:***

RIFM, 1994: Biodegradation of allyl phenoxyacetate was evaluated by a sealed vessel test conducted according to the OECD 301B guidelines. After 28 days, biodegradation of 85.7% was observed.

RIFM, 1995a: The ready biodegradability of allyl phenoxyacetate was evaluated using the manometric respirometry test conducted according to the OECD 301F guideline. Under the conditions of the study, biodegradation of 21% was observed.

RIFM, 2000a: The ready biodegradability of allyl phenoxyacetate was evaluated using the manometric respirometry test conducted according to OECD 301F guidelines. Allyl phenoxyacetate underwent 17% biodegradation after 28 days.

RIFM, 1999: The inherent biodegradability of allyl phenoxyacetate was evaluated using a manometric respirometry test per OECD Guideline 302C. Allyl phenoxyacetate underwent 75% biodegradation after 33 days (66% after 28 days).

RIFM, 2000b: Biodegradation of the test material was evaluated by the closed bottle test according to OECD 301D guidelines. After 28 days, the biodegradation rate was 68%.

Ecotoxicity:

RIFM, 2000c: A 48-h *Daphnia magna* acute toxicity test was conducted according to the OECD 202 I method. Under the conditions of the study, the 48-h EC50 was 4.0 mg/L.

RIFM, 2016a: An Algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 0–72 h EC50 values based on time-weighted average mean measured test concentration was reported to be 24.9 mg/L and 12.6 mg/L for growth rate and yield, respectively.

RIFM, 2016b: A Zebrafish acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 based on the geometric mean of LC0 and LC100 was reported to be 0.133 mg/L.

RIFM, 2017a: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 value based on geometric mean measured test concentration was reported to be 2.07 mg/L (95% CI: 1.56 - >6.91 mg/L).

11.2.3. Other available data

Allyl phenoxyacetate has been registered for REACH, with no additional data available at this time.

11.2.4. Risk assessment refinement

Since allyl phenoxyacetate passed the Tier 2 screening criteria, measured data is included in the document for completeness only and is not included in the PNEC calculations.

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

Endpoints used to calculate PNEC are highlighted.

Exposure	Europe	North America
Log K_{ow} Used	2.33	2.33
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	10–100	1–10
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 0.1181 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: 09/09/22.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	133.9			1000000	0.1339	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	13.83	27.38	10.83			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.181	8.682	2.247	10000	0.1181	Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	60.95	36.11	32.06			Neutral organics

- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **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 09/27/22.

Declaration of competing interest

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

Appendix

Explanation of Cramer Classification

Due to potential discrepancies 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 (Cramer et al., 1978).

Q1. A normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C,H,O,N, 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? **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** 'Residue 1′
Q32. Contains only the functional groups listed in Q30 or Q31 and those listed below? **Yes** Class Intermediate
(Class II) 'Residue 1′
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? **No** 'Residue 2′
Q32. Contains only the functional groups listed in Q30 or Q31 and those listed below? **No** 'Residue 2′
Q22. A common component of food? **No** 'Residue 2′
Q33. Has a sufficient number of sulfonate or sulfamate groups? **No,** Class High (Class III) 'Residue 2′

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