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Short Review

RIFM fragrance ingredient safety assessment, anisyl alcohol, CAS registry number 105-13-5

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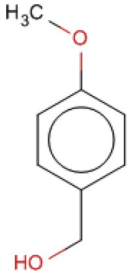
Version: 031519. This version replaces any previous versions.
Name: Anisyl alcohol
CAS Registry Number: 105-13-5
Additional CAS Numbers:
1331-81-3 Anisyl alcohol (*o*-, *m*-, *p*-)



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

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DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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
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
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.

Anisyl alcohol (CAS # 105-13-5) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that anisyl alcohol is not genotoxic. Data on read-across analogs *p*-methoxybenzaldehyde (CAS # 123-11-5) and *p*-methylanisole (CAS # 104-93-8) provide a calculated MOE > 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. Data provide anisyl alcohol a NESIL of 1700 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was evaluated using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material, and the exposure to anisyl alcohol is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. Anisyl alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; anisyl alcohol 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, 2003; RIFM, 2014a)
Repeated Dose Toxicity: NOAEL = 6.7 mg/kg/day. (Japanese Environmental Health BureauMinistry of Health and Welfare, 2010)
Developmental and Reproductive Toxicity: NOAEL = 20 mg/kg/day. (Japanese Environmental Health BureauMinistry of Health and Welfare, 2010)
Skin Sensitization: NESIL = 1700 μg/cm^2. (RIFM, 2005; RIFM, 1971)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 92% (OECD 310) RIFM (2013a)
Bioaccumulation: Screening-level: 1.37 L/kg (EPI Suite v4.11; US EPA, 2012)
Ecotoxicity: Screening-level: Fish LC50: 1002 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: 1002 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 1.002 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

Chemical Name: Anisyl alcohol	**Chemical Name**: Anisyl alcohol (*o*-, *m*-, *p*-)
CAS Registry Number: 105-13-5	**CAS Registry Number:** 1331-81-3
Synonyms: Anisalcohol; Anise alcohol; Anisic alcohol; Benzyl alcohol, *p*-methoxy-; *p*-Methoxybenzyl alcohol; アニスアルコール; (4-Methoxyphenyl)methanol; Anisalkohol; Anisyl alcohol	**Synonyms:** Benzenemethanol, ar-methoxy-; (4-Methoxyphenyl) methanol
Molecular Formula: $C_8H_{10}O_2$	**Molecular Formula:** $C_8H_{10}O_2$
Molecular Weight: 138.17	**Molecular Weight:** 138.17
RIFM Number: 187	**RIFM Number:** 5237

2. Physical data*

1. **Boiling Point:** 259 °C (FMA Database), 243.8 °C (EPI Suite)
2. **Flash Point:** > 212 °F; CC (FMA Database)
3. **Log K_{OW}:** 1.16 (EPI Suite)
4. **Melting Point**: 23–25 °C at 760 mm Hg (Atul), 28.73 °C (EPI Suite)
5. **Water Solubility:** 31710 mg/L (EPI Suite)
6. **Specific Gravity:** 1.110–1.115 (FMA Database), 1.1136 (EOA, 1973 Sample 73-6), 1.112–1.117 (FMA Database)
7. **Vapor Pressure:** 0.00102 mm Hg @ 20 °C (EPI Suite v4.0), 0.0018 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless to slightly yellow liquid having a floral odor.

*Physical data is identical for both materials in this assessment.

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.03% (RIFM, 2016f)
2. **Inhalation Exposure*:** 0.00036 mg/kg/day or 0.026 mg/day (RIFM, 2016f)
3. **Total Systemic Exposure**:** 0.0010 mg/kg/day (RIFM, 2018)

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

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

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

1. **Dermal:** 57%

RIFM, 1993: A study was conducted to assess the excretion and tissue distribution of read-across material *p*-methylanisole (CAS # 104-93-8; see Section V) after topical application in the rat. Groups of 4 male Sprague Dawley CD rats were administered topical doses of [14]C-*p*-methylanisole formulated in diethyl phthalate. Each group was administered separate doses at nominal levels of 100, 320, and (approximately) 1000 mg/kg body weight. The treated area was occluded for 6 h after dose application. The dose dressing and residual dose were removed using cotton wool swabs moistened with diethyl phthalate. Urine, feces, and expired air were collected for 72 h after application. Rats were then euthanized, and whole blood and tissues were taken for measurement of radioactivity. After topical application to groups of 4 rats, the total urinary excretion accounted for about 12% of the dose in rats dosed at 100 and 320 mg/kg and about 20% of the dose in rats dosed at 1000 mg/kg. Total excretion of radioactivity in feces accounted for 0.05%–0.17% of the dose. Radioactivity present in expired air traps accounted for about 11%, 23%, and 37% of the dose at dose levels of 100, 320, and 1000 mg/kg, respectively. After the 6-h exposure period, approximately 74%, 59%, and 36% of the dose was recovered in washings of the treated skin in rats dosed at 100, 320, and 1000 mg/kg, respectively. At 72 h after dosing, 0.02%–0.05% of the dose was in the treated skin taken from these rats after being euthanized. Radioactivity recovered from each group of rats dosed accounted for means of about 94%–97% of the [14]C-*p*-methylanisole administered. At the high dosage of 1000 mg/kg, the conservative total absorbed dose (urine, feces, expired air, carcass, tissues, blood, and treated skin) was determined to be approximately 57%.

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** *p*-Methoxybenzaldehyde (CAS # 123-11-5); *p*-methylanisole (CAS # 104-93-8)
   c. **Developmental and Reproductive Toxicity:** *p*-Methoxybenzaldehyde (CAS # 123-11-5); *p*-methylanisole (CAS # 104-93-8)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across justification: See Appendix below

7. Metabolism

Bray et al., 1955a: The fate of some substituted anisoles in the rabbit has been studied, and over 74% of the dose of each compound has been accounted for. A single dose of *p*-methylanisole (CAS # 104-93-8) was given to rabbits. Urine was collected for 24 h. *p*-Methylanisole was excreted in the urine as anisic acid and *p*-cresol.

RIFM, 2012c: A metabolism study was conducted with *p*-methoxybenzaldehyde (anisaldehyde, CAS # 123-11-5) to compare the *in vitro* metabolism by hepatocytes of the test material between 4 species (mouse, rat, rabbit, and human). The analytical method utilized HPLC coupled with mass spectrometry (LC-MS) to profile and identify the metabolites generated. Interspecies comparison of incubations of the

test material (1, 10, and 100 μM) using cryopreserved hepatocytes from mouse, rat, rabbit, and human were conducted in triplicate at incubation times of 0, 1, and 4 h. For hepatocyte incubations of anisaldehyde, 7 components were observed, and interspecies differences were generally small. A glycine conjugate of anisic acid was the largest component in most incubations. For rat incubations, a glucuronide conjugate of anisic alcohol was generally the second largest component, while for the other species this was typically anisic acid.

RIFM, 2016a: A 14-day repeated dose study comparing gavage and dermal applications was conducted in rats. Five rats/sex/dose were administered 0, 100, 250, 500, and 1000 mg/kg/day *p*-methoxybenzaldehyde (anisaldehyde, CAS # 123-11-5) in a corn oil vehicle percutaneously (using Hill Top Chambers) once daily for 14 consecutive days. A total volume of 0.50 mL was placed in each Hill Top Chamber. Four chambers were attached to the application site of each rat (total of 2 mL). Each exposure period was at least 6 h in duration. An additional 5 rats/sex/dose were administered 0, 20, 100, and 500 mg/kg/day *p*-methoxybenzaldehyde in a corn oil vehicle orally (via gavage) once daily for 14 consecutive days. All rats were euthanized on day 15 following blood sample collection. Each rat was subjected to a complete necropsy examination *in situ*. The following parameters were evaluated: viability, clinical observations, skin observations (percutaneous phase only), body weights, feed consumption, organ weights, toxicokinetics, and gross and microscopic observations. In addition, urine and fecal samples were collected from each rat for possible future evaluation. Percutaneous administration of *p*-methoxybenzaldehyde to rats once daily for 14 consecutive days at doses of 100, 250, 500, or 1000 mg/kg/day did not result in any unscheduled deaths, adverse clinical signs, or organ weight changes. There were gross and microscopic test substance-related changes in the skin administration sites in males and females treated with 500 and/or 1000 mg/kg/day. The gross changes (erythema grades 1 and 2 and epidermal flaking grade 1) correlated with microscopic changes of minimal to mild focal cellular infiltrates and epithelial hyperplasia. Bodyweight gains were reduced for the cumulative dosage period in male rats administered 1000 mg/kg/day of *p*-methoxybenzaldehyde. A transient reduction in feed consumption occurred in each treated group during the first 3 days of the dosage period. Oral (gavage) administration of *p*-methoxybenzaldehyde to rats once daily for 14 consecutive days at doses of 20, 100, or 500 mg/kg/day did not result in any unscheduled deaths, gross pathology findings, organ weight changes, or microscopic findings attributed to the test substance. Transient losses in body weight occurred in both male and female rats at ≥20 mg/kg/day. However, the effects on bodyweight gain persisted in male rats given 500 mg/kg/day, resulting in an overall reduction in bodyweight gain for the cumulative dosage period. Corresponding reductions in feed consumption were apparent only in female rats in the 500 mg/kg/day for the first 3 days of the dosage period. Metabolism identification in blood following oral or dermal application resulted in measurable quantiites of glycine conjugated anisic acid, p-anisic acid, and glucuronide conjugate of anisic alcohol.

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

Anisyl alcohol is reported to occur in the following foods by the VCF*:

Anise (*Pimpinella anisum* L.)
Anise, star (*Illicium verum* Hook, F.)
Bourbon vanilla (*Vanilla planifolia* Andrews).
Bursaria honey (*Bursaria spinosa*).
Haze honey (*Rhus succedanea*).
Honey.
Star anise.
Tahiti vanilla (*Vanilla tahitensis* Moore).
Vanilla.

Anisyl alcohol (*o*-, *m*-, *p*-) is not reported to occur in food by the VCF*.

9. Reach dossier

Anisyl alcohol has a dossier available (accessed 05/10/19); anisyl alcohol (*o*-, *m*-, *p*-) has been pre-registered for 2010 (no dossier available as of 05/10/19).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for anisyl alcohol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.0028
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.025
4	Products related to fine fragrances	0.21
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.041
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0055
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.033
5D	Baby cream, oil, talc	0.0018
6	Products with oral and lip exposure	0.091
7	Products applied to the hair with some hand contact	0.033
8	Products with significant ano-genital exposure (tampon)	0.0018
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.099
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.099
10B	Aerosol air freshener	0.17
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0018
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	14

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 anisyl alcohol, the basis was the reference dose of 0.067 mg/kg/day, a skin absorption value of 57%, and a skin sensitization NESIL of 1700 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, anisyl alcohol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of anisyl alcohol was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD GT 471 using both the standard plate incorporation and modified preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were treated with anisyl alcohol in DSMO at the concentrations 100, 333, 1000, 2500, and 5000 μg/plate in the presence and absence

of metabolic activation (S9 mix). No increase in the number of revertant colonies was observed in the strains at the concentrations tested (RIFM, 2003). Under the conditions of the study, anisyl alcohol was considered not mutagenic in bacteria.

The clastogenic and aneugenic activity of anisyl alcohol 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 anisyl alcohol in dimethyl sulfoxide (DMSO) at concentrations 13.4–1382 μg/mL in the presence and absence of metabolic activation (S9 mix) at the 3-h and 24-h timepoints. Anisyl alcohol did not induce binucleated cells with micronuclei when at any tested concentration in either non-activated or S9-activated test systems (RIFM, 2014a). Under the conditions of the study, anisyl alcohol was considered to be non-clastogenic and non-aneugenic in the *in vitro* micronucleus test.

Based on the available data, anisyl alcohol does not present a concern for genotoxic potential.

Additional References: Ball et al., 1984; RIFM, 2016b; RIFM, 2016c.

Literature Search and Risk Assessment Completed On: 06/03/14.

11.1.2. Repeated dose toxicity

The margin of exposure for anisyl alcohol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on anisyl alcohol. Anisyl alcohol is oxidized to *p*-methoxybenzaldehyde (CAS # 123-11-5; see Sections V and VI), which is then oxidized to anisic acid (CAS # 100-09-4; see Section VI). *p*-Methoxybenzaldehyde has an OECD 422 gavage combined repeat dose and reproductive/developmental toxicity screening test in rats. The repeated dose NOAEL was determined to be 20 mg/kg/day, based on stomach and liver effects (Japanese Environmental Health BureauMinistry of Health and Welfare, 2010). For further weight of evidence, read-across material *p*-methylanisole (CAS # 104-93-8; see Sections V and VI) has a shared metabolite in anisic acid. *p*-Methylanisole has an OECD 407 gavage 28-day subchronic toxicity study conducted in rats which determined the NOAEL to be 100 mg/kg/day, based on decreased spleen weights (RIFM, 2013b). The most conservative NOAEL was selected for this safety assessment.

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

The derived NOAEL for the repeated dose toxicity data is 20/3 or 6.7 mg/kg/day.

Therefore, the MOE is equal to the *p*-methoxybenzaldehyde NOAEL in mg/kg/day divided by the total systemic exposure, 6.7/0.001 or 6700.

In addition, the total systemic exposure for anisyl alcohol (1.00 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

The RIFM Criteria Document (Api et al., 2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. These factors can be refined based on availability of data. Due to insufficient intraspecies susceptibility data for anisyl alcohol, the factor of 10 remains unchanged. For interspecies variability, the factor of 10 can be further sub-divided into 4 and 2.5 based on toxicokinetic and toxicodynamic differences respectively (Renwick, 1993).

Section IX 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. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose 0.067 mg/kg/day.

The RfD for anisyl alcohol was calculated by dividing the NOAEL of 6.7 mg/kg/day by the uncertainty factor, 100 = 0.067 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: RIFM, 2014b; RIFM, 2012a; Belsito et al., 2012; Gershbein (1977); Miller et al., 1983; Draize et al., 1948; Howes et al., 2002; Scheline (1972); Bray, 1958; Matsui (1997); RIFM, 2012b; RIFM, 1994; Brunsborg et al., 1994; Thompson et al., 1996; Dahl and Hadley, 1983; Shillinger (1950); Hagan et al., 1967; Bar and Griepentrog, 1967; RIFM, 1954; RIFM, 1958; Taylor et al., 1964; Zondek and Bergmann, 1938; Sammons and Williams, 1946; Martini and Murray, 1996; Cramer and Michael, 1971; Bray et al., 1955b; van Meeuwen et al., 2008.

Literature Search and Risk Assessment Completed On: 06/05/14.

11.1.3. Developmental and reproductive toxicity

The margin of exposure for anisyl alcohol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on anisyl alcohol. Anisyl alcohol is oxidized to *p*-methoxybenzaldehyde (CAS # 123-11-5; see Section V and VI), which is then oxidized to anisic acid (CAS # 100-09-4; see Section VI). *p*-Methoxybenzaldehyde has an OECD 422 gavage combined repeat dose and reproductive/developmental toxicity screening test in rats (Japanese Environmental Health BureauMinistry of Health and Welfare, 2010). The Reproduction Advisory Group*, adjunct to the Expert Panel for Fragrance Safety, reviewed the report and conservatively determined the NOAEL for developmental and reproductive toxicity to be 20 mg/kg/day, based on a non-significant but clear trend toward decreased litter size in the 100 mg/kg/day group. For further weight of evidence, read-across material *p*-methylanisole (CAS # 104-93-8; see Section V and VI) has a shared metabolite in anisic acid. *p*-Methylanisole has an OECD 421 developmental and reproduction toxicity screening tests conducted in rats by both the oral and dermal routes. After oral gavage exposure, the NOAEL for developmental toxicity was determined to be 100 mg/kg/day, based on pup weights and pre- and postnatal offspring mortality, and the NOAEL for reproductive toxicity was determined to be 100 mg/kg/day, based on maternal toxicity, insufficient material care, and litter indices (RIFM, 2010a). The postnatal effects were at least partially secondary to disturbed maternal care, and there were no effects on fertility up to the high dosage of 1000 mg/kg/day. After dermal exposure, the NOAELs for developmental and reproductive toxicity were determined to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2010b). To account for bioavailability following dermal application, data from an excretion and tissue distribution study conducted in rats following topical application (RIFM, 1993; see Section IV) were used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 57% of the applied dose, the revised developmental and reproductive toxicity NOAEL from the dermal study is 570 mg/kg/day. In a developmental toxicity study conducted on *p*-methyl anisole (CAS # 104-93-8; see Section V) using generational and juvenile exposure protocols with and without direct pup exposure during lactation using 4-methylanisole as test compound. The parental (F0) animals were mated at a ratio of 2:1 male:female. The F0 animals were gavaged with test material at doses of 0, 8, 16, 32, 64, 125, or 250 mg/kg/day. The animals were divided into 4 different cohorts. In cohort 1, the females were dosed 2 weeks premating, during mating, during gestation and lactation, and pups received a vehicle

from postnatal day (PND) 10–21. The pups were then individually dosed with test material from PND 21 to PND 50. In cohort 2, the females were treated with test material 2 weeks premating to lactation day (LD) 10. The pups were then directly exposed from PND 10 to PND 50. In cohort 3, the F0 females were not dosed with test material. The pups were directly dosed with test material from PND 10 to PND 50. In cohort 4, the F0 females were not dosed with test material. The pups were dosed directly from PND 21 to PND 50. No adverse effects were reported on the F0 females. The fertility and reproductive performance was affected, and the litter size was reduced at the highest dose level only. Relative Liver and kidney weight increased in the F1 animals of the highest dose group. Hormone levels (T4) were affected. Platelet and eosinophil counts were decreased at the highest dose level only. Absolute and relative spleen weights decreased in the highest dose level animals only. Apart from TNF-α and interleukin-13 levels, no other alterations in functional immune parameters were related to treatment with *p*-methyl anisole (Tonk et al., 2015). While the dermal route is more relevant to human exposure to fragrances, the most conservative NOAEL was used for this safety assessment. **Therefore, the MOE for developmental and reproductive toxicity is equal to the *p*-methoxybenzaldehyde NOAEL in mg/kg/day divided by the total systemic exposure, 20/0.001 or 20000.**

In addition, the total systemic exposure for anisyl alcohol (1.00 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints at the current level of use.

*The Expert Panel for Fragrance Safety and adjunct Reproduction Advisory Group are composed of scientific and technical experts in their respective fields. These groups provide advice and guidance.

Additional References: RIFM, 2014b; RIFM, 2012a; Belsito et al., 2012; Gershbein (1977); Miller et al., 1983; Draize et al., 1948; Howes et al., 2002; Scheline (1972); Bray, 1958; Matsui (1997); RIFM, 2012c; RIFM, 1994; Brunsborg et al., 1994; Thompson et al., 1996; Dahl and Hadley, 1983; Shillinger (1950); Hagan et al., 1967; Bar and Griepentrog, 1967; RIFM, 1954; RIFM, 1958; Taylor et al., 1964; Zondek and Bergmann, 1938; Sammons and Williams, 1946; Martini and Murray, 1996; Cramer and Michael, 1971; Bray et al., 1955; van Meeuwen et al., 2008.

Literature Search and Risk Assessment Completed On: 06/05/14.

11.1.4. Skin sensitization

Based on the available data, anisyl alcohol is considered to be a moderate skin sensitizer with a defined NESIL of 1700 μg/cm^2.

11.1.4.1. Risk assessment. Based on the available data, anisyl alcohol is considered to be a moderate skin sensitizer with a defined NESIL of 1700 μg/cm^2 (Table 1). Section IX 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. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose 0.067 mg/kg/day.

Additional References: None.

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

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.2. Key studies. There are no predictive phototoxicity studies available for anisyl alcohol.

11.1.5.3. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for anisyl alcohol were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L mol^{-1} · cm^{-1}, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/31/16.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on anisyl alcohol. Based on the Creme RIFM Model, the inhalation exposure is 0.026 mg/day. This exposure is 53.8 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/05/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of anisyl alcohol was performed following the RIFM Environmental Framework (Salvito et al., 2002),

Table 1
Data Summary for anisyl alcohol.

LLNA weighted mean EC3 value μg/cm[b] [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm[b]	NOEL-HMT (induction) μg/cm[b]	LOEL[b] (induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
1475 [1]	moderate	1771	3448	NA	1700

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. 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, anisyl alcohol 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, 2012) did not identify anisyl alcohol as either being possibly persistent nor bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on current VoU (2015), anisyl alcohol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 2013a: The Ready Biodegradability of anisyl alcohol was evaluated according to the OECD 310 method. Biodegradation of 92% was observed after 28 days.

11.2.3.2. Ecotoxicity. RIFM, 2016d: In the acute immobilization test with *Daphnia magna*, the effects of the limit concentration 100 mg/L of the test material were evaluated according to the OECD 202 method under semi-static conditions. The 48-h EC50 was greater than 100 mg/L.

RIFM, 2016e**:** An acute fish (Zebra fish) study was conducted according to the OECD 203 guidelines as a limit test with concentration of 64.0 mg/L. The 96-h LC50 was greater than 64.0 mg/L.

Other available data: Anisyl alcohol has been registered under REACH, and the following additional data is available:

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 was reported to be 141 mg/L and 64 mg/L based on growth rate and yield, respectively.

11.2.4. Risk assessment refinement

Since Anisyl alcohol 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1002			1,000,000	1.002	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.16	1.16
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use 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 1.002 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environmental at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/05/19.

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 05/10/19.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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

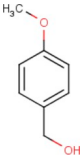
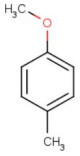
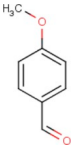
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110702.

Appendix

Read-across Justification

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physical–chemical properties of the target and analogs were calculated using EPI Suite v4.11 developed by the US EPA (US EPA, 2012).
- The J_{max} were calculated using RIFM skin absorption model (SAM); the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2018).

	Target Material	Read-across Materials	
Principal Name	Anisyl alcohol	*p*-Methylanisole	*p*-Methoxybenzaldehyde
CAS No.	105-13-5	104-93-8	123-11-5
Structure			
Read-across endpoint		• Repeated Dose • Developmental and Reproductive	• Repeated Dose • Developmental and Reproductive
Molecular Formula	C8H10O2	C8H10O	C8H8O2
Molecular Weight	138.17	122.17	136.15
Melting Point (°C, EPI Suite)	28.73	−23.00	12.84
Boiling Point (°C, EPI Suite)	243.83	170.80	221.63
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.24	160	4.04
Log Kow (KOWWIN v1.68 in EPI Suite)	1.16	2.62	1.79
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	3.171e+004	527.1	2728
J_{max} (μg/cm^2/h, SAM)	266.5008327	142.3031335	96.72086157
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.001303	35.636002	0.080503
Similarity (Tanimoto score)		NA[1]	NA[2]
Genotoxicity			
DNA binding (OASIS v1.1)	• No alert found	• No alert found	
DNA binding (OECD)	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found	
In vitro mutagenicity (Ames test) alerts (ISS)	• No alert found	• No alert found	
In vivo mutagenicity (Micronucleus) alerts (ISS)	• No alert found	• No alert found	
Oncologic classification (OECD)	• Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized	Not categorized	Not categorized
Developmental and Reproductive Toxicity			
ER binding (OECD)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (good reliability)	Non-toxicant (low reliability)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	105-13-5 PDF	104-93-8 PDF	123-11-5 PDF

[1] The target is the major metabolite of the analog.
[2] The major metabolite of the target.

Summary

There are insufficient toxicity data on anisyl alcohol (CAS # 105-13-5). Hence, *in silico* evaluation was conducted to determine read-across analogs. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, the above shown read-across materials were identified as analogs with sufficient toxicological data for evaluation.

Conclusions

- *p*-Methylanisole was used as a read-across analog for anisyl alcohol (target) based on:
  - o The target is the major metabolite of the analog.
  - o The methyl group in the analog is predicted to be hydrolyzed and become the target. Therefore, the toxicity profiles of the target are expected to be that of the analog.
  - o The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity, and oncologic classification.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a molecular initiating event analogous to protein binding.
  - o As per the OECD Toolbox, the analog is predicted to metabolize to the target (metabolites # 3).
- *p*-Methoxybenzaldehyde was used as a read-across analog for anisyl alcohol (target) based on:
  - o The analog is the major metabolite of the target.
  - o The primary alcohol target is predicted to be oxidized into the analog. Therefore, the toxicity profiles of the target are expected to be that of the analog.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding.
  - o As per the OECD Toolbox, the target is predicted to metabolize to the analog (metabolites # 3).

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