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RIFM fragrance ingredient safety assessment, *p*-propylanisole, CAS Registry Number 104-45-0

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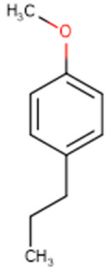
Name: *p*-Propylanisole



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CAS Registry Number: 104-45-0

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
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; 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
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, 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.

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p-Propylanisole was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog *p*-methylanisole (CAS # 104-93-8) show that *p*-propylanisole is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog *p*-methylanisole (CAS # 104-93-8) show that there are no safety concerns for *p*-propylanisole for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; *p*-propylanisole is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog anisole (CAS # 100-66-3). The environmental endpoints were evaluated; *p*-propylanisole 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 1984; RIFM, 1989; ECHA REACH Dossier: 4-Methylanisole; ECHA, 2015)
Repeated Dose Toxicity: NOAEL = 33 mg/kg/day.	RIFM, (2013)
Reproductive Toxicity: Developmental NOAEL = 100 mg/kg/day. Fertility NOAEL = 580 mg/kg/day.	(RIFM, 2010a; RIFM, 2010b)
Skin Sensitization: Not a concern for skin sensitization under the current, declared use levels.	(ECHA REACH Dossier: 4-Methylanisole; ECHA, 2015)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 3000 mg/m^3.	(ECHA REACH Dossier: Anisole; ECHA, 2011)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening-level: 2.7 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 110.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 2.95 mg/L	(ECOSAR ; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 2.95 mg/L	(ECOSAR ; US EPA, 2012b)
RIFM PNEC is: 0.295 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1	

1. Identification

1. **Chemical Name:** p-Propylanisole
2. **CAS Registry Number:** 104-45-0
3. **Synonyms:** Benzene, 1-methoxy-4-propyl-; Dihydroanethole; 1-Methoxy-4-propylbenzene; Methyl *p*-propylphenyl ether; 4-Propyl-methoxybenzene; *p*-Propylanisole
4. **Molecular Formula:** $C_{10}H_{14}O$
5. **Molecular Weight:** 150.22 g/mol
6. **RIFM Number:** 539
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 211.38 °C (EPI Suite)
2. **Flash Point:** 85 °C (Globally Harmonized System), 185 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 3.6 (EPI Suite)

4. **Melting Point**: 0.12 °C (EPI Suite)
5. **Water Solubility:** 63.36 mg/L (EPI Suite)
6. **Specific Gravity:** 0.942 (FMA)
7. **Vapor Pressure:** 0.1 mm Hg at 20 °C (FMA), 0.135 mm Hg at 20 °C (EPI Suite v4.0), 0.202 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 to pale yellow liquid with a sweet herbaceous, quite powerful odor

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.044% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000087 mg/kg/day or 0.0065 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

1. **Dermal:** 58% from read-across *p*-methylanisole (CAS # 104-93-8)

RIFM, 1993: An *in vivo* excretion and tissue distribution study was conducted with radioactive *p*-methylanisole after topical application in rats. 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 ca. 1000 mg/kg body weight. The dose was applied over an area of 16 cm^2. The treated area was occluded for 6 h after dose application. At this time, 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 dose application. At this time, rats were euthanized, and whole blood and tissues (liver, kidney, GIT, fat, and treated skin) were taken for radioactivity measurement. 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. The 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 6 h of exposure, 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 accounted for a mean of approximately 94%–97% of the [^{14}C] *p*-methylanisole administered. There was a dose-dependent increase in % skin absorption (from approximately 23%, 35%, and 58%, respectively). At the highest dose, a conservative total absorbed dose (urine, feces, expired air, carcass, tissues, blood, and treated skin) was determined to be approximately 58%.

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

6. Computational toxicology evaluation

6.1. Cramer classification

Class III, High

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

6.2. Analogs selected

a. **Genotoxicity:** *p*-Methylanisole (CAS # 104-93-8)
b. **Repeated Dose Toxicity:** *p*-Methylanisole (CAS # 104-93-8)
c. **Reproductive Toxicity:** *p*-Methylanisole (CAS # 104-93-8)
d. **Skin Sensitization:** *p*-Methylanisole (CAS # 104-93-8)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Anisole (CAS # 100-66-3)
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below

7. Metabolism

Sangster et al., 1987: [Methoxy-^{14}C] labeled test material *p*-propylanisole was taken by 2 male subjects (93 and 95 kg) after an overnight fast and a light breakfast. The test material (100 μg) was dissolved in trioctanoin and contained in a gelatin capsule. Urine and feces were collected for 2 days, and expired air was trapped every 30 min for 8 h. Urinary metabolites were identified by TLC and HPLC. The average percent dose excreted in the urine was 23.75% after 8 h, 24.4% after 24 h, and 24.75% after 48 h; the percent dose for expired air was 42.65% after 8 h. The main ^{14}C urinary metabolites were products of side-chain oxidation, namely, 4-methoxy-hippuric acid (12%), 1-(4′-methoxyphenyl)propan-2-ol (8%), 1-(4′-methoxyphenyl)propan-1-ol (2%), and 1-(4′-methoxyphenyl)propane-1,2-diol (0.7%).

Sangster et al., 1983a: The metabolism of [Methoxy-^{14}C] labeled test material *p*-propylanisole (PPA) was compared between male CD-1 mice, female Wistar rats, and humans. The mice (i.p) and rats (p.o) were administered test material at doses of 0.05–1500 mg/kg and to humans at doses of 0.1–1 mg. Among mice and rats, the ^{14}C was excreted in the urine, feces, and expired air. PPA was metabolized by α- and ω-hydroxylation and by side-chain cleavage to 4-methoxybenzoic acid among rats and mice. The fate of PPA in humans resembled the fate of PPA in mice and rats. The excretion routes and metabolic pattern among humans resembled those seen in low- and medium-dose rodent experiments, with 60% of the dose being O-demethylated. The results concluded that animal toxicity tests using very high doses are not representative of the situations in which man may be exposed to the toxic compound. The alteration in the disposition of each compound at very high doses in rodents compared with the low-dose animal or human situation leads to the tissues being exposed to different metabolites for longer periods of time. Thus, it would be expected that the effects seen at the high doses would be qualitatively different from those seen at low doses.

Sangster et al., 1983b: Female Wistar rats and male CD-1 mice were administered test material, [Methoxy-^{14}C] labeled *p*-propyl anisole

(PPA). The rats were administered test material at doses of 0.05, 0.5, 5, 50, 500, and 1500 mg/kg, and the mice were administered doses of 0.05, 0.5, 50, 500, and 1500 mg/kg. The doses were administered via gavage. The urine, feces, and expired air were collected for 72 h following administration of the test material. The metabolites from urine were characterized by HPLC and TLC analysis. The metabolic pattern of PPA varied with dose size. At lower doses, elimination of test material via CO_2 (arising from oxidative O-demethylation) preceded small amounts present in the urine. At these doses, *p*-methoxyhippuric acid and 2′-hydroxy-p-propylanisole were the major urinary metabolites. With increasing dose, the proportion of administered dose excreted as CO_2 decreased, and this was reflected in an increase in the percent dose eliminated in the urine. At higher doses, larger amounts of 2′-hydroxy-*p*-propylanisole and *p*-methoxyhippuric acid were present in the urine in addition to 1′-hydroxy-*p*-propylanisole (major metabolite). In mice, 1′-hydroxylation exceeded the 2′-hydroxylation, and in rats, the proportion was equal. At higher doses, 1′,2′-diol intermediate was also reported. The pattern of urinary metabolites was not markedly different with dose in either species. As suggested earlier (Sangster et al., 1983a), the pattern of metabolism of PPA in humans resembles that of rodents at low doses. The proposed metabolic pathway for PPA is presented below in Fig. 1.

Additional References: None.

8. Natural occurrence

p-Propylanisole is reported to occur in the following foods by the VCF*:

Capers (*Capparis spinoza*)

Katsuobushi (dried bonito)

Mangifera species.

*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 on 02/25/22.

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, *p*-propylanisole does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of *p*-propylanisole; however, read-across can be made to *p*-methylanisole (CAS # 104-93-8; see Section VI).

The mutagenic activity of *p*-methylanisole 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with *p*-

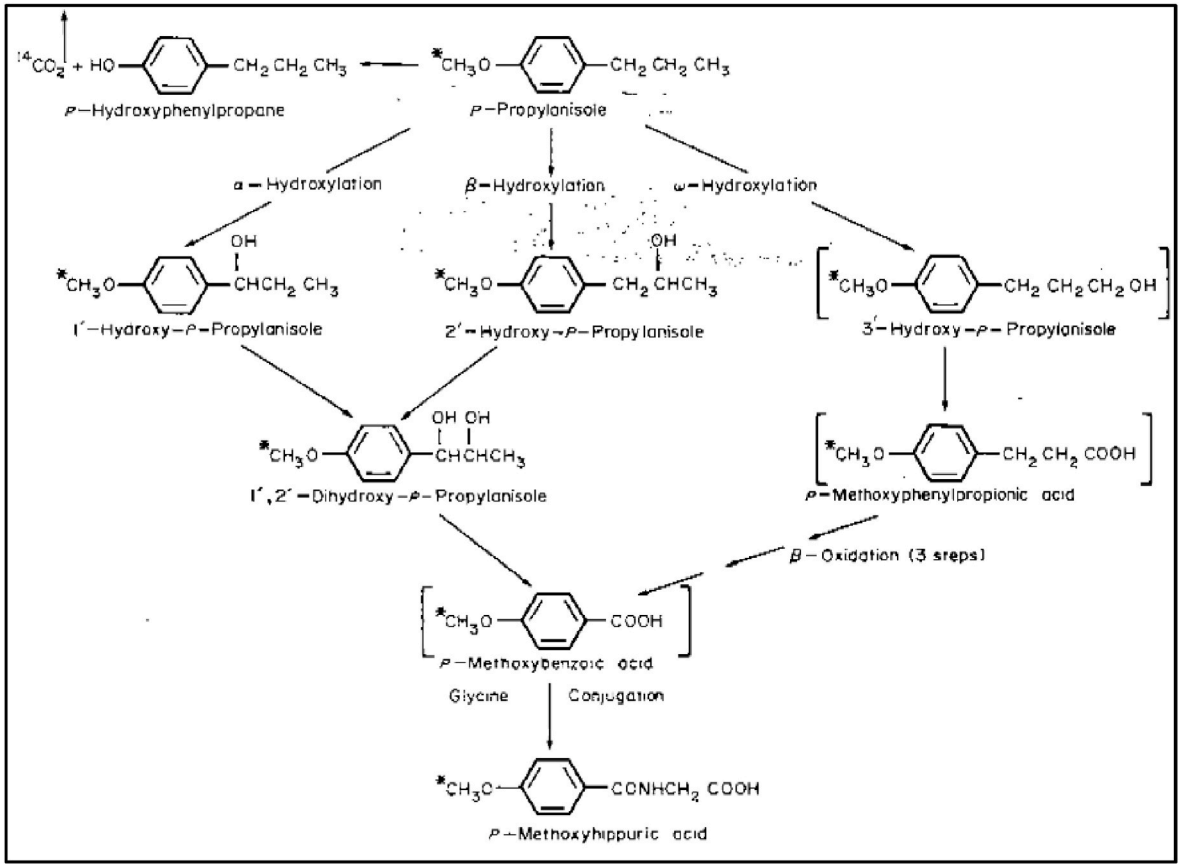


Fig. 1. (Adapted from Sangster et al., 1983b).

methylanisole in dimethyl sulfoxide (DMSO) at concentrations up to 150.0 μL/plate (14535 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, 1984). Under the conditions of the study, *p*-methylanisole was not mutagenic in the Ames test, and this can be extended to *p*-propylanisole.

The clastogenicity of *p*-methylanisole was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovaries were treated with *p*-methylanisole in DMSO at concentrations up to 1510 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed at 252 and 378 μg/mL with S9 metabolic activation in the 20-h assay (RIFM, 1989). Under the conditions of the study, *p*-methylanisole was considered to be clastogenic to in the *in vitro* chromosome aberration assay, and this can be extended to *p*-propylanisole.

To further investigate the positive result observed in the *in vitro* chromosome aberration study, the clastogenic activity of *p*-methylanisole was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female NMRI mice. Doses of 500, 1000, and 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2015). Under the conditions of the study, *p*-methylanisole was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to *p*-propylanisole.

Due to the greater biological relevance of the *in vivo* micronucleus test when compared to the *in vitro* chromosome aberration study, it can be concluded that there is no concern for clastogenicity from *p*-methylanisole, and this can be extended to *p*-propylanisole.

Based on the data available, *p*-methylanisole does not present a concern for genotoxic potential, and this can be extended to *p*-propylanisole.

Additional References: Howes et al., 1990; RIFM, 1980.

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

11.1.2. Repeated dose toxicity

The MOE for *p*-propylanisole is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on *p*-propylanisole. Read-across material *p*-methylanisole (CAS # 104-93-8; see Section VI) has sufficient repeated dose toxicity data. In a GLP/OECD 407 study, 5 Wistar rats/sex/dose were administered *p*-methylanisole via gavage (vehicle: olive oil) at doses of 0, 100, 300, or 1000 mg/kg/day for 4 weeks. At 1000 mg/kg/day, treatment-related effects included clinical signs (salivation, ataxia, and tremor, labored respiration), increased cholesterol (females), increased liver weights accompanied by diffuse hypertrophy of the hepatocytes, and single-cell necrosis of hepatocytes. Decreased spleen and thymus weights in males and increased kidney weights in females were not accompanied by histopathological changes. At 300 mg/kg/day, treatment-related effects included salivation and decreased spleen weights in the males that were not accompanied by histopathological changes. Clinical symptoms of salivation, ataxia, and tremor were observed only after the administration of the test material, most probably a result of the irritating potential of the test material not related to systemic toxicity. Hyperkeratosis and focal hyperplasia were observed in the forestomach of one male in the highest-dose group. Thus, the NOAEL for repeated dose toxicity was considered to be 100 mg/kg/day, based on organ weight changes in the higher dose groups (RIFM, 2013).

In a GLP/OECD 421-compliant study, 10 Wistars rats/sex/dose were administered *p*-methylanisole via both the oral and dermal routes at doses of 0, 100, 300, or 1000 mg/kg/day for a pre-mating period of 2 weeks and a mating period of 2 weeks. Observations included clinical exams, mating and reproductive performances, food consumption, body weights, pup viability, gross pathology, organ weights, and histopathology. Following oral exposure, clinical signs among high-dose animals included abdominal position after treatment and unsteady gait after treatment among high-dose females. There was a significant decrease in body weights and bodyweight gains among high-dose males and females. There was a significant decrease in terminal body weights among mid-dose males as well. Gross pathological analyses on parental animals showed a dose-dependent increase in liver size characterized by centrilobular hepatocyte hypertrophy. There were no other treatment-related alterations reported among treated animals. Thus, the NOAEL for systemic toxicity was considered to be 100 mg/kg/day, based on decreased body weights (RIFM, 2010b).

Following dermal exposure, no treatment-related adverse effects were observed in parental generation animals. Thus, the NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2013).

The most conservative NOAEL of 100 mg/kg/day was taken from the GLP/OECD 407-compliant study.

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study (ECHA, 2012). The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33 mg/kg/day.

Therefore, the *p*-propylanisole MOE for the repeated dose toxicity endpoint can be calculated by dividing the *p*-methylanisole NOAEL in mg/kg/day by the total systemic exposure to *p*-propylanisole, 33/0.0016 or 20625.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/17/21.

11.1.3. Reproductive toxicity

The MOE for *p*-propylanisole is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on *p*-propylanisole. Read-across material *p*-methylanisole (CAS # 104-93-8; see Section VI) has sufficient developmental toxicity data. In a GLP/OECD 421-compliant study, 10 Wistars rats/sex/dose were administered *p*-methylanisole via both the oral and dermal routes at doses of 0, 100, 300, or 1000 mg/kg/day for a pre-mating period of 2 weeks and a mating period of 2 weeks. There was a dose-dependent significant increase in the pre- and postnatal developmental effects of the offspring at the mid- and high-dose levels. At the high-dose level, a decrease in the number of delivered/live-born pups and total litter loss of all females was observed; this was characterized as an increase in post-implantation loss. Similar effects were reported among mid-dose group animals but with lower incidences. There was a significant decrease in the pup weight/pup weight gain among the mid-dose group as compared to controls. This comparison could not be made for high-dose animals due to a significant increase in litter loss. The reduction in pup survival was considered to be secondary to a disturbance in maternal care since the stomachs of the pups were empty in 20% and 15% of the mid- and high-dose offspring, respectively. After oral gavage exposure, the NOAEL for developmental toxicity was determined to be 100 mg/kg/day, based on reduced pup weights and pre- and postnatal offspring mortality at the mid- and high-dose levels (RIFM, 2010b). The postnatal effects were at least partially secondary to disturbed maternal care. After dermal exposure, the NOAEL for developmental toxicity was considered to be

1000 mg/kg/day, the highest dosage tested (RIFM, 2010a). The most conservative NOAEL of 100 mg/kg/day from the OECD 421 gavage study on *p*-methylanisole was considered for the developmental toxicity endpoint.

Therefore, the *p*-propylanisole MOE for the developmental toxicity endpoint can be calculated by dividing the *p*-methylanisole NOAEL in mg/kg/day by the total systemic exposure to *p*-propylanisole, 100/0.0016, or 62500.

There are no fertility data on *p*-propylanisole. Read-across material *p*-methylanisole (CAS # 104-93-8; see Section VI) has sufficient reproductive toxicity data. In a GLP/OECD 421-compliant study, 10 Wistars rats/sex/dose were administered *p*-methylanisole via both the oral and dermal routes at doses of 0, 100, 300, or 1000 mg/kg/day for a premating period of 2 weeks and a mating period of 2 weeks. There were no treatment-related changes in the genital organs of males and females, thus suggesting no effects of treatment on the reproductive function of the treated animals. After oral gavage exposure, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010b). After dermal exposure, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2010a). Since the dermal route is more relevant to human exposure to fragrances, the NOAEL from the OECD 421 study via dermal exposure was selected for this safety assessment. To account for bioavailability following dermal application, data from an excretion and tissue distribution study conducted in rats following topical administration (RIFM, 1993; see Section V) were used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 58% of the applied dose, the revised reproductive toxicity NOAEL from the dermal study was 580 mg/kg/day.

Therefore, the *p*-propylanisole MOE for the fertility endpoint can be calculated by dividing the *p*-methylanisole NOAEL in mg/kg/day by the total systemic exposure to *p*-propylanisole, 580/0.0016 or 362500.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/17/21.

11.1.4. Skin sensitization

Based on existing limited data and read-across analog *p*-methylanisole (CAS # 104-93-8), *p*-propylanisole does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on existing data and read-across to *p*-methylanisole (CAS # 104-93-8; see Section VI), *p*-propylanisole does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material *p*-methylanisole was found to be non-sensitizing up to 50% (ECHA, 2015). In a guinea pig open epicutaneous test, *p*-propylanisole and *p*-methylanisole did not present reactions indicative of sensitization (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed when 10% (6900 μg/cm^2) *p*-propylanisole (RIFM, 1974) and 2% (1380 μg/cm^2) read-across material *p*-methylanisole in petrolatum were used for induction and challenge (RIFM, 1971).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across to *p*-methylanisole, *p*-propylanisole does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/08/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, *p*-propylanisole 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 *p*-propylanisole 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 phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, *p*-propylanisole 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 absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/21.

11.1.6. Local respiratory toxicity

There are no inhalation data available on *p*-propylanisole; however, in a 28-day inhalation exposure study for the read-across analog anisole (CAS # 100-66-3; see Section VI), a NOAEC of 3000 mg/m^3 was reported (ECHA, 2011).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 28-day inhalation exposure study, male and female Wistar rats (5/sex/dose) were treated with anisole via nose-only exposure to 0, 120, 600, and 3000 mg/m^3 concentrations for 6 h a day and 5 days per week (ECHA, 2011). Standard observations included clinical observations, mortality, body weight changes, food and water consumption, ophthalmologic, hematologic, clinical biochemistry, urinalysis, gross pathology, and histopathology. No treatment-related local respiratory effects were reported up to the highest exposure concentration. The local effects NOAEC was identified as 3000 mg/m^3.

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

- (3000 mg/m^3) × (1 m^3/1000 L) = 3 mg/L
- Minute ventilation of 0.14 L/min for a Wistar rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 50.4 L/day
- (3 mg/L) × (50.4 L/day) = 151.2 mg/day
- (151.2 mg/day)/(0.0016 kg lung weight of rat*) = 94500 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0065 mg/day; this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.01 mg/kg lung weight/day resulting in a MOE of 9450000 (i.e., [94500 mg/kg lung weight of rat/day]/[0.01 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0065 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/12/

21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-propylanisole 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, *p*-propylanisole 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 *p*-propylanisole 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), *p*-propylanisole presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. *p*-Propylanisole has been pre-registered for REACH with no additional data at this time.

11.2.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.6	3.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	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 0.295 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 VoU.

Literature Search and Risk Assessment Completed On: 10/01/21.

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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **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 HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	8.216			1000000	0.008216	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.480	2.950	4.053	10000	0.2950	Neutral organics

&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 02/25/22.

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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113238.

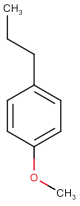
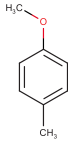
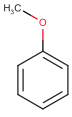
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, the appropriate read-across analog from the cluster was 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 (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 repeated 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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analog were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	p-Propylanisole	p-Methylanisole	Anisole
CAS No.	104-45-0	104-93-8	100-66-3
Structure			
Similarity (Tanimoto Score)		0.72	0.45
SMILES	CCCc1ccc(OC)cc1	COc1ccc(C)cc1	COc1ccccc1
Endpoint		Genotoxicity Repeated dose toxicity Reproductive toxicity Skin sensitization	Local respiratory toxicity
Molecular Formula	$C_{10}H_{14}O$	$C_8H_{10}O$	C_7H_8O

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Molecular Weight (g/mol)	150.221	122.167	108.14
Melting Point (°C, EPI Suite)	0.12	−32.00	−37.50
Boiling Point (°C, EPI Suite)	211.50	175.50	153.70
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.69E+01	1.60E+02	4.72E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6.34E+01	5.27E+02	1.04E+03
Log KOW	3.6	2.66	2.11
J_{max} (μg/cm^2/h, SAM)	8.80	51.39	70.61
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.28E+01	3.57E+01	4.90E+01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Phenacetin (Hepatotoxicity) Alert|Phenacetin (Renal toxicity) Alert	Acetaminophen (Hepatotoxicity) Alert|Acetaminophen (Renal toxicity) Alert|Phenacetin (Hepatotoxicity) Alert|Phenacetin (Renal toxicity) Alert|Toluene (Renal toxicity) Alert	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (good reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	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)	No alert found	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified.	No skin sensitization reactivity domain alerts were identified.	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on the target material, *p*-propylanisole (CAS # 104-45-0). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, *p*-methylanisole (CAS # 104-93-8) and anisole (CAS # 100-66-3) were identified as a read-across material with data for its respective toxicological endpoints.

Conclusions

- *p*-Methylanisole (CAS # 104-93-8) was used as a read-across analog for target material *p*-propylanisole (CAS # 104-45-0) for the skin sensitization, genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aryl alkyl-substituted anisoles.
  - o The target material and the read-across analog share an anisole substructure.
  - o The key difference between the target material and the read-across analog is that the target material has an n-propyl substitution on the *p* position, while the read-across has a methyl substitution on the *p* position of the aromatic ring. This structural difference between the target material and the read-across analog does not affect the consideration of toxicological endpoints.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect the consideration of toxicological endpoints.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are predicted to be toxicants for hepatotoxicity and renal toxicity by HESS categorization. The data described in the repeated dose toxicity section show that the read-across analog has adequate MOE at the current level of use. Therefore, the prediction will be superseded by the available data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- Anisole (CAS # 100-66-3) was used as a read-across analog for target material *p*-propylanisole (CAS # 104-45-0) for the local respiratory toxicity endpoint.

- The target material and the read-across analog are structurally similar and belong to the structural class of aryl alkyl-substituted anisoles.
- The target material and the read-across analog share an anisole substructure.
- The key difference between the target material and the read-across analog is that the target material has an n-propyl substitution on the *p* position, while the read-across has a methyl substitution on the *p* position of the aromatic ring. This structural difference between the target material and the read-across analog does not affect the consideration of toxicological endpoints.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect the consideration of toxicological endpoints.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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