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RIFM fragrance ingredient safety assessment, coumarin, CAS Registry Number 91-64-5

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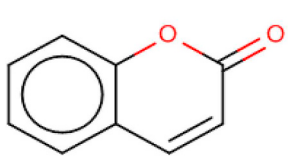
Version: 031219. This version replaces any previous versions.
Name: Coumarin
CAS Registry Number: 91-64-5



Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency

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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.
Coumarin was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that coumarin is not genotoxic and provide a calculated MOE > 100 for the repeated dose toxicity and the developmental and reproductive toxicity endpoints. Data provide a NESIL of 3500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; coumarin is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to coumarin is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; coumarin 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. (https://echa.europa.eu/registration-dossier/-/registered-dossier/11472; NTP, 1993; Sasaki et al., 1987a; RIFM, 1999; https://echa.europa.eu/registration-dossier/-/registered-dossier/11472 ECHA, 2013)

Repeated Dose Toxicity: RIFM (1984)
NOAEL = 16 mg/kg/day.

Developmental and Reproductive Toxicity:
Developmental Toxicity NOAEL = 150 mg/kg/day. Reproductive Toxicity NOAEL = 96 mg/kg/day.
(Roll and Bar, 1967; Preuss-Ueberschar et al., 1984)

Skin Sensitization: NESIL = 3500 μg/cm^2. (RIFM, 2004; RIFM, 2005)

Phototoxicity/Photoallergenicity: Not Phototoxic/Photoallergenic.
(Kaidbey and Kligman, 1981; RIFM, 1979a; Kaidbey and Kligman, 1980; RIFM, 2002; RIFM, 1979b; RIFM, 1979c)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 92.7% (OECD 301B) RIFM (1993)

Bioaccumulation: Screening-level: 3.838 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 37-.62 mg/L (EPI Suite v4.1; US EPA, 2012a)

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: Fish LC50: 3-7.62 mg/L (EPI Suite v4.1; US EPA, 2012a)

RIFM PNEC is: 3.762 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

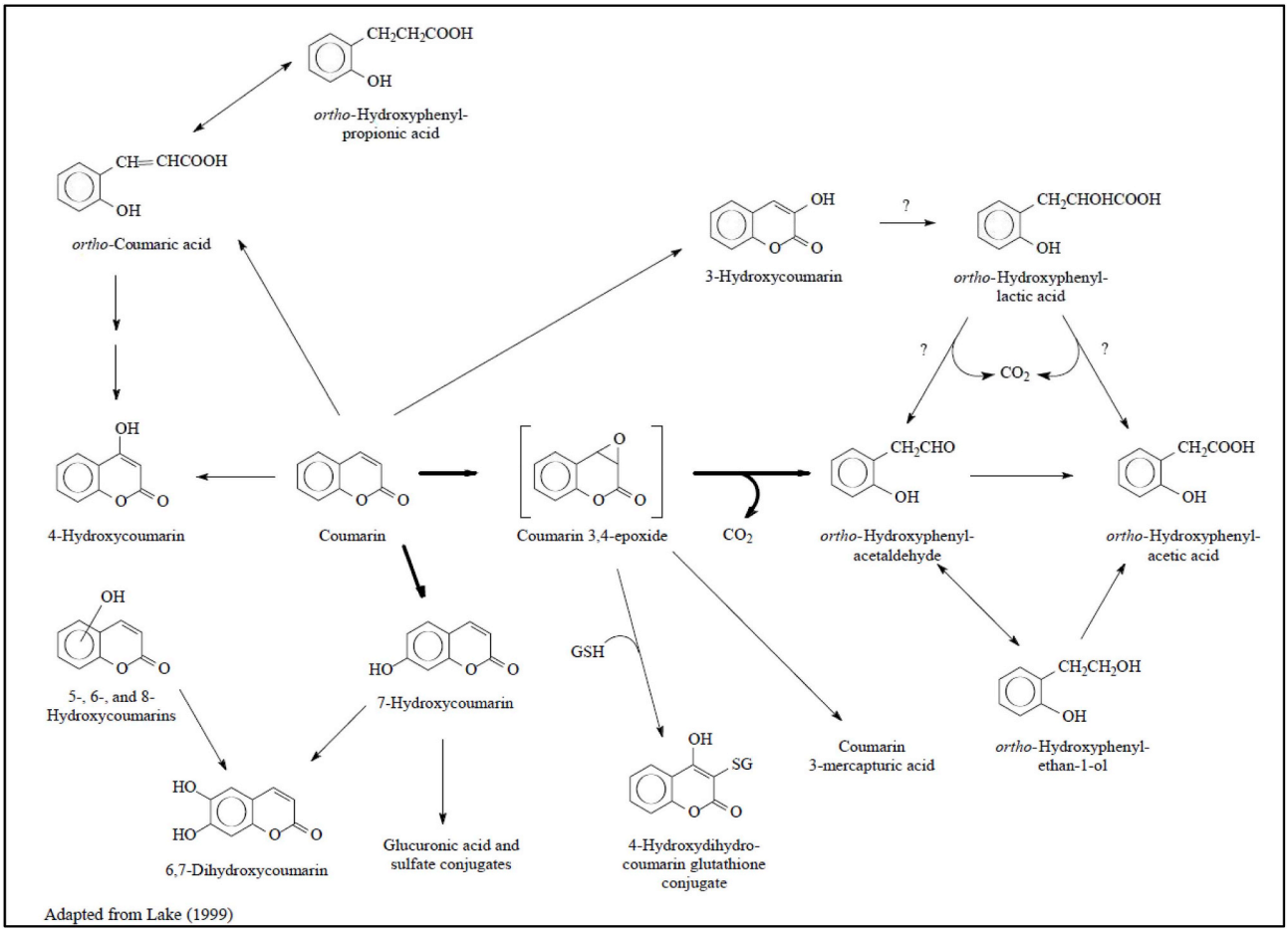

Fig. 1. Metabolism pathway for coumarin (https://monographs.iarc.fr/wp-content/uploads/2018/06/mono77-9.pdf IARC, 2018).

1. Identification

1. **Chemical Name:** Coumarin
2. **CAS Registry Number:** 91-64-5
3. **Synonyms:** 2H-1-Benzopyran-2-one; 1,2-Benzopyrone; cis-o-Coumaric acid lactone; Coumarinic anhydride; 2-Oxo-1,2-benzopyran; Tonka bean camphor; クマリン; 2H-Chromen-2-one; Coumarin
4. **Molecular Formula:** $C_9H_6O_2$
5. **Molecular Weight:** 146.15
6. **RIFM Number:** 120

2. Physical data

1. **Boiling Point:** 301 °C (FMA Database), (calculated) 290.74 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 1.4 (Procter and Gamble Company, 1996), 1.32 (Abraham and Rafols, 1995), 1.3 at 35 °C (RIFM, 1998b)
4. **Melting Point**: 68 °C (FMA Database), (calculated) 33.34 °C (EPI Suite)
5. **Water Solubility:** 5126 mg/L (EPI Suite)
6. **Specific Gravity:** 0.935 (https://pubchem.ncbi.nlm.nih.gov/compound/coumarin, retrieved 3/12/19)
7. **Vapor Pressure:** < 0.001 mm Hg 20 °C (FMA Database), 0.000348 mm Hg @ 20 °C (calculated) (EPI Suite v4.0), 0.000657 mm Hg @ 25 °C (calculated) (EPI Suite)
8. **UV Spectra:** Absorbs in the region of 290–700 nm with a peak at 270 nm gradually returning to baseline by 350 nm; the molar absorption coefficient is above the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless crystals or white, orthorhombic, rectangular plates with a pleasant, fragrant odor resembling that of vanilla beans, with a burning taste

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** > 1000 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:** 0.37% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0011 mg/kg/day or 0.082 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0057 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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that

include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** 59.7%

Ford et al., 2001; RIFM, 1996: A skin absorption study was conducted with human subjects. ^{14}C-coumarin was applied to a 100-cm^2 skin area on each of 3 male subjects at an application rate of 0.02 mg coumarin/cm^2. The application vehicle was 70% aqueous ethanol. The absorption and excretion of the radiolabeled material were studied for 120 h after application. Mean applied radioactivity (AR) in the urine accounted for 58.6%, whereas in the feces, mean AR accounted for 1.1%. The total urinary and fecal radioactivity represented the most accurate measure of absorption. The plasma/whole-blood kinetics were consistent with ^{14}C-coumarin being rapidly absorbed and excreted after topical application. Similar proportions of metabolites occurred in the urine of all 3 subjects. The major urinary metabolites in each subject after topical application of ^{14}C-coumarin were the β-glucuronide and sulfate conjugates of 7-hydroxycoumarin and free 7-hydroxycoumarin. 7-Hydroxycoumarin and its conjugates in urine accounted for a mean of 50% AR after 12 h. A minor component was identified as 2-hydroxyphenylacetic acid. A mean of 66.3% AR was recovered from the 3 subjects. Similar amounts of radioactivity were absorbed and excreted in the urine and feces from all 3 subjects, with a mean of 59.7% ± 4.5% AR.

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

6. Computational toxicology evaluation

1. Cramer Classification: Class III, High

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2 (OECD, 2018)
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

IARC Monographs Volume 77: Coumarin **(IARC, 2018; accessed 03/07/19):** Coumarin is rapidly and extensively absorbed after topical or oral administration to human subjects. It undergoes metabolism along 2 major pathways, 7-hydroxylation, and ring-opening to *ortho*-hydroxyphenylacetaldehyde (Fig. 1). There are numerous minor metabolites, many of which are secondary products from the primary metabolites. The relative extent of these 2 major pathways is highly variable between species. Ring-opening predominates in rodents, while 7-hydroxylation is particularly evident in humans. In humans exposed to coumarin for treatment of various clinical conditions, a few cases of hepatotoxicity have been reported. However, a clear relationship between the dose of coumarin and the hepatotoxic responses observed has not been established. The target organs for coumarin toxicity are primarily the liver in rats and the liver and lung in mice. There are marked species differences in these responses, with the mouse being particularly susceptible to coumarin-induced Clara cell injury. *In vitro*, coumarin is toxic in either hepatocytes or liver slices from rats, mice, rabbits, and guinea pigs, whereas monkey and human cells and/or slices appear to be resistant. Hamsters and gerbils are resistant to acute coumarin-induced hepatotoxicity. The IARC concluded that since epidemiological data relevant to the carcinogenicity of coumarin were unavailable and animal carcinogenicity data on coumarin are inconclusive, coumarin is not classifiable as to its carcinogenicity to humans (Category 3).

Rietjens et al., 2008; EFSA Scientific Opinion on Coumarin **(EFSA, 2008; accessed 04/06/15)**: The major route of coumarin bioactivation is the 3,4-epoxidation to coumarin epoxide, followed by rearrangement of epoxide to *o*-hydroxyphenylacetaldehyde (*o*-HPA), the hepatotoxic intermediate. *o*-HPA can be detoxified by reduction to *o*-hydroxyphenylethanol (*o*-HPE) especially by oxidation to *o*-hydroxyphenylacetic acid. Coumarin metabolites are subjected to enzymatic and chemical conjugation to glutathione, where enzymatic conjugation is favored in rats and mice. Rats and mice predominantly favor the 3,4-epoxidation pathway, and humans detoxify coumarin through 7-hydroxylation. Among humans, the prevalence of genetic polymorphism in CYP2A6, the CYP450 enzyme isoform, catalyzing the detoxifying 7-hydroxylation of coumarin can be of concern due to its potential hepatotoxic effects. A study was conducted with 231 patients treated with coumarin or placebo, and the results showed that in 9 patients serum liver enzymes were elevated, which is a biomarker for liver damage. Of the 231 patients, 16 were lacking in the CYP2A6 genotype and heterozygous CYP2A6*2 allele; liver enzymes were not elevated in these patients. Of the 9 patients showing elevated liver enzymes, only 1 had a CYP2A6*2 variant allele; all other affected patients had wild-type homozygotes. It was thus concluded that CYP2A6 genetic polymorphisms are not coupled to liver toxicity upon coumarin exposure (Burian et al., 2003). Rietjens et al. (2008) defines physiologically based biokinetic (PBBK) models to predict liver levels of the toxic *o*-HPA metabolite of coumarin in rats and in human subjects with normal or deficient CYP2A6 catalyzed coumarin 7-hydroxylation. The results reveal that the predicted maximum tissue concentration (C_{max}) of *o*-HPA in the liver of wild-type human subjects and of subjects deficient in CYP2A6 catalyzed 7-hydroxylation are, respectively, 3 and 1 order of magnitude lower than the values predicted for rat liver. Another difference between CYP2A6-deficient and wild-type human subjects is a 500-fold difference in the area under the curve, 0- to 24-h ($AUC_{0–24h}$) for the time-dependent *o*-HPA liver concentration, pointing at a relatively higher percentage of the original dose converted in time through this pathway when CYP2A6 is deficient. For wild-type human subjects and the subjects with completely deficient coumarin 7-hydroxylation, the $AUC_{0–24h}$ values for *o*-HPA in the liver are, respectively, 3 and 1 order of magnitude lower than that for rat liver. Even when 7-hydroxylation is deficient, the chances of the formation of the hepatotoxic *o*-HPA metabolite will be significantly lower in the liver of humans than those expected in the liver of rats when exposed to a similar dose on a bodyweight basis. This conclusion should be considered when extrapolating data from experimental studies in sensitive animals (e.g., rats) to the general human population. The EFSA Scientific Opinion (http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/793.pdf EFSA, 2008) concluded there are no *in vivo* studies currently available on the metabolic pathway of coumarin in humans that have homozygous alleles for polymorphism in the CYP2A6* enzyme that could lead to impaired metabolism of coumarin to 7-hydroxycoumarin.

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

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

Cinnamomum species

Cloudberry (*Rubus chamaemourus* L.)
Guava and feyoa
Honey
Matsutake (*Tricholoma matsutake*)
Mentha oils
Salvia species
Soybean (*Glycine max.* L. merr.)
Sweetgrass oil (*Hierochloe odorata*)
Tea
Vaccinium 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 05/08/13 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for coumarin are detailed below

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.024
2	Products applied to the axillae	0.080
3	Products applied to the face/body using fingertips	0.023
4	Products related to fine fragrances	1.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.30
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.034
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.045
5D	Baby cream, oil, talc	0.011
6	Products with oral and lip exposure	0.00068
7	Products applied to the hair with some hand contact	0.050
8	Products with significant ano-genital exposure (tampon)	0.011
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.14
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.14
10B	Aerosol air freshener	0.44
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.011
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	9.0

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 coumarin, the basis was the reference dose of 0.16 mg/kg/day, a skin absorption value of 59.7%, and a skin sensitization NESIL of 3500 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, coumarin does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The genotoxic potential of coumarin has been extensively evaluated. While some *in vitro* studies demonstrate genotoxic effects, these results are not consistent and more importantly not congruent with the results from *in vivo* studies. For example, both positive and negative effects have been demonstrated in Ames tests, sister chromatid exchange (SCE) assays, and chromosomal aberration tests. In Ames assays, no evidence of mutagenicity was demonstrated when coumarin was evaluated in *Salmonella typhimurium* strains TA98, TA1535, TA1537, and TA1538, both with or without metabolic activation (Florin et al., 1980; Haworth et al., 1983; RIFM, 1978; RIFM, 1980). However, at high concentrations of coumarin, a weak positive effect in strain TA100 was demonstrated, only in the presence of metabolic activation (Haworth et al., 1983). The relevance of this result is questionable considering that TA100 was found negative in numerous other such tests, and no dose response was observed (Florin et al., 1980; RIFM, 1978; RIFM, 1980).

Studies that investigated the ability of coumarin to induce SCE and chromosomal aberrations (CA) also give mixed results, but the weight of evidence indicates that coumarin is not clastogenic. In Chinese hamster ovary cells (CHO), coumarin has been shown to induce SCE in the absence but not in the presence of metabolic activation in a non-dose-dependent manner. Coumarin was also shown to have a weak positive effect on CA in CHO cells in the presence of metabolic activation (Galloway et al., 1987; https://echa.europa.eu/registration-dossier/-/registered-dossier/11472 ECHA, 2013). However, in other studies, coumarin has not demonstrated either SCE or CA in CHO cells (Sasaki et al., 1987b) or in human peripheral lymphocytes (Kevekordes et al., 2001). Additionally, an *in vitro* micronucleus test also demonstrated negative effects (Muller-Tegethoff et al., 1995). Based on the mixed results from multiple *in vitro* genotoxicity studies and carcinogenic effect, the EFSA Scientific Panel on food additives suggested conducting an *in vivo* DNA adduct formation study in rats in the relevant target organs (liver and kidney) to rule out an epoxide formation pathway contributing to a genotoxic mechanism leading to a carcinogenic effect. Based on the results of the study, coumarin did not bind covalently to DNA in the target organs. This result was further supported by another study in which coumarin did not cause unscheduled DNA synthesis in the hepatocytes of male Sprague Dawley (SD) rats *in vivo* after administration of coumarin at dose levels up to the maximum tolerated dose (http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/793.pdf EFSA, 2008). Furthermore, *in vivo* mouse micronucleus assays were also negative in CD-1 Swiss, IRC, and B6C3F$_1$ mouse strains following exposure to coumarin (RIFM, 1999; Morris and Ward, 1992; NTP, 1993).

Comprehensive independent reviews of the data by the EFSA (http://www.efsa.europa.eu/en/efsajournal/doc/793.pdf EFSA, 2008) and the NSCFS (NSCFS, 2010) have concluded that coumarin is not a genotoxic chemical.

Based on the available data, it can be concluded that coumarin does not present a concern for genotoxic potential.

Additional References: Florin et al., 1980; Stoltz and Scott, 1980; Stoltz et al., 1982; Morris and Ward, 1992; Witt et al., 2000; RIFM, 2001; RIFM, 1980.

Literature Search and Risk Assessment Completed On: 08/22/17.

11.1.2. Repeated dose toxicity

The margin of exposure for coumarin is adequate for the repeated

dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on coumarin. Groups of 10 Osborne-Mendel rats/sex were administered diets containing 10000 ppm (500 mg/kg/day) of coumarin for 1–8 weeks. No animals survived beyond the 8-week treatment. Marked growth retardation and slight to moderate microscopic liver damage were observed (Hagan et al., 1967). In another adjacent study, groups of 12 Osborne-Mendel rats were administered coumarin via diet for 2 years at doses of 1000 (6 rats/sex), 2500 (6 rats/sex), and 5000 (6 rats/sex) ppm. An additional group of 5 males and 7 females were administered coumarin at 2500 ppm with corn oil added to the diet. No effects were observed with 1000 ppm, but with 2500 ppm, minimal liver damage was reported. Animals in the high-dose group exhibited hematological alterations, liver enlargement, and microscopic alteration in the liver and bile ducts. The NOAEL was considered to be 2500 ppm or 125 mg/kg/day (Hagan et al., 1967).

In another study, mongrel and beagle dogs were orally administered varying doses of coumarin for 35–350 days. The dose groups were 10 (2 m/2f), 25 (2 m/1f), 50 (2 m/1f), and 100 (1 m/1f) mg/kg/day. One high-dose male was euthanized on day 9, and 1 female was found dead on day 16; these animals were reported to have jaundice and marked emaciation. The liver of the animals receiving 100, 50, and 25 mg/kg/day doses showed discoloration. The 100 mg/kg/day group showed slightly pale spleens, thin and fatty bone marrow, and moderately distended gall bladders. Furthermore, microscopic alterations in the liver and bile duct were reported in the high-dose group animals. In the 50 mg/kg/day dose group, mortality was reported. The bone marrow was pale in color in the 50 mg/kg/day animals. Microscopic alteration in the liver and spleen was reported in the animals of the 50 and 25 mg/kg/day dose group. Of the 25 mg/kg/day dose group animals, 1 was reported to have jaundice and moderate emaciation. The gall bladder was slightly distended among these animals. The NOAEL was considered to be 10 mg/kg/day (Hagan et al., 1967).

The US NTP conducted a 13-week range finding study on groups of 20 F344/N rats (10/sex) gavaged with 0, 19, 38, 75, 150, and 300 mg/kg of coumarin in corn oil. Mortality was reported in the high-dose group. Bodyweight gain and terminal body weights of male rats in the 150 and 300 mg/kg/day groups were significantly lower than controls. Hematological alterations were reported among treated animals. Treatment-related alterations in blood chemistry parameters were reported in the animals of the high-dose group only. A statistically significant liver weight increase along with microscopic alteration was reported in animals of the 150 and 300 mg/kg/day dose groups. The NOAEL was considered to be 75 mg/kg/day (NTP, 1993). Following the dose range finding study, a 2-year chronic carcinogenicity study on rats was conducted with coumarin. Groups of 60 F344/N rats/sex/group were administered coumarin in corn oil via gavage at doses of 0, 25, 50, or 100 mg/kg/day for 103 weeks. Mortality was reported in the 50 and 100 mg/kg/day dose groups. The mortality among male rats included treatment-related spontaneously occurring renal disease. Body weights among high-dose females were lower than the control, but no clinical signs of toxicity were reported. However, hematological alterations were reported among animals of the 50 and 100 mg/kg/day dose groups. The major target organs affected by coumarin administration were the liver, kidney, and forestomach. Microscopic hepatic lesions were reported among all treated males and females of the 50 and 100 mg/kg/day dose groups. A treatment-related increase in incidences in nephropathy were reported in all treated rats. Hepatic lesions were observed in all treated males and among females dosed with 50 and 100 mg/kg/day coumarin. The lesions included hepatocellular necrosis, fibrosis, cytologic alteration, and increased severity of bile duct hyperplasia. The incidences of hepatocellular neoplasms were not increased in treated rats. Treated males showed an increase in parathyroid gland hyperplasia as a result of the compromised renal function. Low incidences of renal adenomas were seen in all groups of males and in 100 mg/kg/day females. Renal tubule focal hyperplasia was reported in all treated animals. Forestomach ulcers in all male rats and in 100 mg/kg/day female rats were significantly higher than controls. The NOAEL was considered to be 25 mg/kg/day (NTP, 1993).

In another experiment, a 13-week gavage dose range finding study for a 2-year carcinogenesis study was conducted on groups of 20 B6C3F1 mice (10/sex) with 0, 19, 38, 75, 150, and 300 mg/kg/day of coumarin in corn oil. Mortality was reported in the animals of the high-dose group. Bodyweight gain and a terminal bodyweight decrease of the surviving male mice was lower than the controls. Hematological alterations were reported in all treated animals. Liver weight increase was reported in animals of the 150 and 300 mg/kg/day dose groups. Microscopic alteration only in the high-dose groups was reported. Centrilobular hepatocyte hypertrophy was observed in male and female mice receiving the 300 mg/kg/day. The NOAEL was determined to be 75 mg/kg/day (NTP, 1993). Following the 13-week study in mice, a 2-year chronic carcinogenicity study was conducted on mice. Groups of 70 B6C3F1 mice/sex were administered coumarin in corn oil via gavage at doses of 0, 50, 100, or 200 mg/kg/day for 103 weeks. Body weights of the high-dose animals remained significantly lower as compared to the control. Hematological alterations were reported in the high-dose animals. Pathologically, the liver was the major organ affected by coumarin administration. Hepatic hypertrophy was observed in males treated with 100 and 200 mg/kg/day and females of the high-dose group. The overall incidence of hepatocellular neoplasms both benign and malignant in the 50 and 100 mg/kg/day females was higher than the historical control range. The overall pulmonary neoplasms in the high-dose animals were higher than the historical control range. Squamous cell papilloma of the forestomach among the 50 mg/kg/day males was higher than the controls, but the incidences in males only exceeded the incidences of recently conducted studies. The LOAEL was considered to be 50 mg/kg/day (NTP, 1993).

In another study, groups of 25 albino rats (12 females and 13 males) were fed a diet containing 50, 250, and 2500 ppm of coumarin (5, 25, and 250 mg/kg, respectively). Reduction in food efficiency was observed in females treated with 2500 ppm. Liver damage (macroscopic and microscopic) was reported in animals of the 2500 ppm group, and liver weight increase was seen in animals of the high-dose group. A NOAEL of 25 mg/kg/day was determined (Hazleton et al., 1956). In another study, groups of CD-1 mice (52/sex/dose group) were fed a diet containing coumarin at 300, 1000, and 3000 ppm (equivalent to 45, 150, and 450 mg/kg/day). The male mice were treated for 100 weeks, and female mice were treated for 108 weeks. Lower bodyweight gain was reported during the first half of the treatment period for the mid- and high-dose animals. No treatment-related effect on tumor incidence or type or any other histopathological changes were reported. The NOAEL was determined to be 150 mg/kg/day (RIFM, 1983a). Following this study, another study was conducted with Charles River CD SD-derived rats. They were fed diets containing coumarin at doses of 333, 1000, 2000, 3000, and 5000 ppm for 104–110 weeks (equivalent to 13, 42, 87, 130, and 234 mg/kg/day for males and 16, 50, 107, 156, and 283 mg/kg/day for females). Macroscopically, there was an increase in the incidence of liver masses noted among rats exposed to 5000 ppm. Increased liver weights were recorded in males and females of the 3000 and 5000 ppm groups and females of the 1000 and 2000 ppm groups. Microscopically, cholangiocarcinoma was reported among the rats of the high-dose group along with an increase in the incidence of cholangiofibrosis of the parenchymal liver cell tumors. A single incidence of cholangiocarcinoma in a male rat treated with 3000 ppm of coumarin was reported. The NOAEL was determined to be 1000 ppm (equivalent to 50 mg/kg/day) (RIFM, 1984).

Another study was conducted wherein groups of 4–8 male baboons/dose group received a diet containing coumarin for 16–24 months. The animals received 0, 2.5, 7.5, 22.5, or 67.5 mg/kg/day of coumarin. Mean liver weights of the groups fed 22.5 and 67.5 mg/kg/day of coumarin were heavier than those of the control. No significant

treatment-related alterations were reported for the liver biochemistry parameters. The report concluded that there was no evidence of biliary hypertrophy or fibrosis among the treated animals. Early cell damage as evidenced by the structural changes in the ER was reported in the animals treated with high-dose coumarin. Little or no alteration in the liver enzyme activity was seen in treated animals. The NOEL was determined to be 22.5 mg/kg/day (Evans et al., 1979). Another study was conducted on baboons; coumarin was administered 1 baboon per sex at 50 ppm orally in the diet. The study concluded that differences in the metabolic pattern of coumarin among species are not relevant to the hepatotoxic effects since hepatotoxic effects were only reported among treated animals (Gangolli et al., 1974).

The studies conducted on coumarin indicate that coumarin is hepatotoxic to rats and dogs. Results from studies conducted in mice show evidence of lung tumors in both sexes and some evidence of liver tumors among females only. Tumors reported among mice were regarded as common spontaneous occurrences in the strain of mouse used. Coumarin metabolism among humans has been demonstrated to be different as compared to rats, dogs, and mice (see section VII). Bioactivation of coumarin to the epoxide intermediate was proposed as the mechanism related to coumarin-related toxicity (see section VII). Metabolism rate differences in clearing coumarin have also been demonstrated (Born et al., 2000). *In vitro* kinetic studies in mouse and rat liver microsomes show that the balance between bioactivation (epoxide formation and rearrangement to *o*-HPA) and detoxification (glutathione conjugation of the epoxide and oxidation of *o*-HPA to *o*-HPAA) likely dictates the *in vivo* susceptibility of a species to coumarin-mediated liver toxicity (Born et al., 2000). The intrinsic clearance (Cl*int* = Vmax/Km) of coumarin via epoxidation to *o*-HPA is 4-fold greater in mice than rats. This conclusion is supported by studies demonstrating that a known amount of coumarin epoxide (CE) is extensively detoxified by mouse (64% of the total) and rat (48%) liver cytosolic glutathione transferases (GSTs); however, CE conjugate with GSH (CE-SG) was not as readily formed in human cytosol (5%). In humans almost exclusively *o*-HPAA (95%–100%) is produced as the major CE detoxification product (Vassallo et al., 2003). It was also shown that the intrinsic clearance of *o*-HPA through oxidation to *o*-HPAA in mouse or human liver was 20–50 times higher than that in rat liver. In contrast, reduction of *o*-HPA to *o*-HPE appeared to be only of importance in rat liver but not in those of mice and humans. As mouse liver microsomes produced CE at a higher rate than rat liver microsomes, while the mouse is less sensitive than the rat for coumarin hepatotoxicity, the authors concluded that differences in detoxication of *o*-HPA are the determining factor for species differences in sensitivity to coumarin hepatotoxicity (Vassallo et al., 2003). Therefore, it was concluded that the liver was the major organ affected by coumarin-mediated toxicity.

The lowest NOAEL among all species and studies conducted on coumarin was 10 mg/kg/day from the dog study (Hagan et al., 1967). However, the rat dietary study (RIFM, 1984) showed no liver effects at a dose of 16 mg/kg/day for males and females. The NOAEL for coumarin was considered to be 16 mg/kg/day (Felter et al., 2006).

Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 16/0.0057 or 2807.

Coumarin has been shown to induce liver toxicity in multiple species, liver tumors in rats and mice, and lung tumors in mice; however, these high-dose effects are species-specific, non-genotoxic, and directly associated with species-specific metabolism and detoxification capacities leading to target organ cytotoxicity and regenerative hyperplasia. Threshold doses are clearly evident for rodent tumors in both the liver and lung, and tumorigenic effects only occur at exposures that exceed the threshold for toxicity. There have been no carcinogenic effects reported in humans following dietary intake, and no toxicity has been observed following dermal application even at clinical doses for prolonged periods. In addition, despite widespread chronic use as a pharmacologic agent for the treatment of a variety of disorders, while there are isolated reports of idiosyncratic effects on the liver, there are no reports of cancer as a consequence of such uses. Even if one assumes that the results of the cited rodent cancer studies are relevant to humans, a risk assessment that protects against target organ toxicity would also protect against the secondary tumorigenic response.

IARC Monograph on Coumarin (IARC, 2018):

The IARC concluded that due to the lack of epidemiological data relevant to the carcinogenicity of coumarin as well as animal carcinogenicity data on coumarin being inconclusive, coumarin is not classifiable as to its carcinogenicity to humans (Category 3).

EFSA Scientific Opinion on Coumarin (EFSA, 2008):

The EFSA Scientific Panel concluded that the TDI for coumarin is 0.1 mg coumarin/kg bw considering the toxicity studies and studies on the metabolism of coumarin in humans with CYP2A6 polymorphism. Considering the toxicity data on coumarin, including the timing of the onset of liver effects, recovery of these effects after cessation of exposure to coumarin, and the elimination half-life, the Panel concluded that exposure to coumarin resulting in an intake 3 times higher than the TDI for 1–2 weeks is not a safety concern.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (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 of 0.16 mg/kg/day.

The RfD for coumarin was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 16 mg/kg/day by the uncertainty factor, 100 = 0.16 mg/kg/day.

Additional References: NTP, 1993; Hagan et al., 1967; Ueno and Hirono, 1981; Evans et al., 1979; Griepentrog (1973); Nashed and Brendel, 1983a; Bar and Griepentrog, 1967; Hazleton et al., 1956; Evans et al., 1989; Gangolli et al., 1974; Nashed et al., 1983b; Preuss-Ueberschar and Ueberschar, 1988; Omarbasha et al., 1988; Omarbasha et al., 1989; Dickens and Jones, 1965; RIFM, 1984; Seidel and Kreuser, 1979; Evans et al., 1990; Lake et al., 1994; Lake and Grasso, 1996; Adler and Eitner, 1994; Eustis et al., 1994; Born et al., 1999; Lake et al., 2002; Thomas et al., 2007.

Literature Search and Risk Assessment Completed On: 04/06/16.

11.1.3. Developmental and Reproductive Toxicity

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

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on coumarin for the developmental toxicity endpoint. A dietary developmental toxicity study was conducted in pregnant NMRI mice in 2 phases (breeding and Caesarean section). In the breeding phase, groups of pregnant NMRI mice (31–39) were fed diets containing 0%, 0.05%, 0.1%, or 0.25% coumarin from post coitum (p.c.) days 6–17. At concentrations of 0.1% and 0.5%, only the descendants of the dams were examined. At the concentration of 0.25%, the testing was performed in a breeding test of the descendants of 3 treated generations up to the F2 generation (N = 39, 10, and 20 dams for the P, F1, and F2 generations, respectively). The 6.1% stillbirth rate in the 3 generations at 0.25% was significantly higher than that of the controls, while no significant variations were observed in the number of stillbirths between the controls and 0.1% and 0.05%. In the Caesarean section phase, groups of pregnant NMRI mice (26–30) were fed diets containing 0%, 0.05%, or 0.25% coumarin from p.c. days 6–17. The fetuses were delivered on day 18 or 19 p.c. by Caesarean section and examined microscopically for skeletal anomalies. Coumarin at 0.05% had no direct effect on embryonic and fetal development. At 0.25%, increased late resorptions (8.4%

compared to 4.3% for controls) and the weights of the removed fetuses on day 18 or 19 p.c. were reduced. On day 18 p.c. at 0.25%, significantly more bony nuclei of the calcaneus were lacking. Similarly, there were significant differences in the ossification of the talus. Although the lack of ossification should not be viewed as skeletal anomalies (the cartilaginous features were already present), the different development levels of the controls and 0.25% suggests a development inhibiting effect of coumarin, which was confirmed by the reduced fetal weights. Therefore, the NOAEL for developmental toxicity was considered to be 0.1% or 150 mg/kg/day, based on delays in the development of fetuses and increased stillbirths at 0.25% (Roll and Bar, 1967).

Additionally, no developmental toxicity was observed in studies with a mixture of coumarin and rutin conducted in rats, rabbits, or minipigs (Grote et al., 1977; Grote et al., 1977; Grote et al., 1977) and in a reproduction study with a mixture of coumarin and troxerutin conducted in rats (Preuss-Ueberschar et al., 1984). **Therefore, the coumarin MOE for the developmental toxicity endpoint can be calculated by dividing the coumarin NOAEL in mg/kg/day by the total systemic exposure to coumarin, 150/0.0057 or 26316.**

There are sufficient reproductive toxicity data on coumarin. An oral gavage multi-generation reproductive toxicity study was conducted in rats with Venalot (a mixture of 15 mg coumarin and 90 mg troxerutin). The 0 (control), 1-, 8-, 64-, and 128-fold of the daily therapeutic doses for humans were suspended in tap water and administered orally by gavage to groups of 23 male and 46 female Wistar rats. Males were subjected to a pretreatment of 10 weeks, whereas the females were subjected to 3 weeks. The treatment continued during the mating phase (maximum 3 weeks). Half of the females were scheduled for Caesarean section and received the test material until the day of laparotomy (gestation day 20). The remaining females, those selected for littering, received treatment through lactation day 24 postpartum. From the littered offspring of the 0, 64-, and 128-fold groups, 34, 33, and 38 mating pairs were randomly chosen for continued breeding. No adverse reproductive effects (parental fertility, deformity rates in the fetuses, or postnatal developments of pups) were observed on either the treated P generation or the untreated F1 and F2 generations up to the highest dose of 128-fold of the daily therapeutic dose for humans or approximately 96–192 mg/kg/day of coumarin. The most conservative reproductive toxicity NOAEL was considered to be 96 mg/kg/day (Preuss-Ueberschar et al., 1984). **Therefore, the coumarin MOE for the reproductive toxicity endpoint can be calculated by dividing the coumarin NOAEL in mg/kg/day by the total systemic exposure to coumarin, 96/0.0057 or 16842.**

Additional References: Grote et al., 1977; Grote et al., 1977; Grote et al., 1977; Carlton et al., 1996; https://echa.europa.eu/registration-dossier/-/registered-dossier/11472 ECHA, 2013 (accessed 03/08/19).

Literature Search and Risk Assessment Completed On: 03/08/19.

11.1.4. Skin sensitization

Based on the existing data, coumarin is considered to be a weak skin sensitizer with a defined NESIL of 3500 μg/cm^2.

11.1.4.1. Risk assessment. The available data demonstrate that coumarin is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 3500 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (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 of 0.16 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/13.

11.1.5. Phototoxicity/photoallergenicity

Based on the existing study data, coumarin would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The UV spectra for coumarin indicate absorbance in the region of 290–700 nm, with a peak at 270 nm and a gradual return to baseline by 350 nm; the molar absorption coefficient is above the benchmark of concern for phototoxic effects (Henry et al., 2009). Coumarin was not observed to result in phototoxic responses in the *in vitro* 3T3 Neutral Red Uptake (NRU) Phototoxicity Assay (RIFM, 2002). Guinea pig studies demonstrated no phototoxic and no photoallergic reactions after treatment with 0.5% intradermal coumarin followed by UV exposure (RIFM, 1979b). In multiple human phototoxicity and photoallergenicity studies, solutions of 1% or 5% coumarin did not result in reactions after topical application and UV exposure (Kaidbey and Kligman, 1980; RIFM, 1979a; Kaidbey and Kligman, 1981). In rats, topical application of coumarin at a higher dose (8%) combined with UV exposure resulted in slight erythema and edema at 48 h compared to very slight edema in non-UV exposed control animals (RIFM, 1979c), but these differences were considered minimal.Maximal acceptable concentrations of coumarin in finished products are limited based on skin sensitization and range from 0.00068% to 1.3% for phototoxicity-applicable categories (see Section 10). Based on existing data and maximum acceptable concentrations in finished products, coumarin would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectral analysis. UV/Vis absorption spectra (OECD TG 101; OECD, 2015) were generated for coumarin. The spectra demonstrate that the material absorbs in the range of 290–700 nm. Peak absorbance occurs at 270 nm and gradually returns to baseline by 350 nm. The molar absorption coefficient for λ max within this range is above 1000 L mol^{-1} · cm^{-1}, the benchmark of concern for phototoxic effects (Henry et al., 2009).

Additional References: Pathak and Fitzpatrick, 1959a; Pathak and Fitzpatrick, 1959b

Literature Search and Risk Assessment Completed On: 07/08/16.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on coumarin. Based on the Creme RIFM Model, the inhalation exposure is 0.082 mg/day. This exposure is 5.7 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: UGCM, 1997; Pinching and Doving, 1974; Buchbauer et al., 1993; Gu et al., 1997; Jirovetz et al., 1992; Fukayama et al., 1999.

Literature Search and Risk Assessment Completed On: 03/08/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of coumarin was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In ier 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, coumarin 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 v4.1 identify coumarin as not persistent and not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current VoU (2015) coumarin presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. **RIFM, 1998a:** The Manometric Respiratory Test was conducted according to the OECD Guideline 301F. Flasks containing coumarin and mineral medium inoculated with fresh activated sludge were closed and incubated for 28 days. The biodegradation rate was 85% at day 10 and 90% at day 28.

RIFM, 1993: Biodegradability was evaluated by the sealed vessel test according to OECD Guideline 301B. Vessels containing 7.82 mg/L of coumarin and mineral salts medium inoculated with activated secondary effluent were incubated 28 days. The biodegradation rate at day 10 was 99.1%. The mean biodegradation rate at 28 days was 92.7%.

11.2.3.2. Ecotoxicity. **RIFM, 1983b:** A 24-h acute toxicity test with *Daphnia magna* was conducted. The EC50 was reported to be 55 mg/L.

11.2.3.3. Other available data. Coumarin has been registered under REACH with the following additional data:

A 48-h *Daphnia magna* study according to the ASTM 1980 method has been reported with the EC50 of 30 mg/L.

11.2.4. Risk assessment refinement

Since Coumarin has passed the screening criteria, the measured data are included for completeness only and are not included 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)**	801.0			1,000,000	0.801	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	37.62	82.39	37.87	10,000	3.762	Esters
ECOSAR Acute Endpoints **(Tier 2)**	510.0	271.7	154.9			Neutral Organics

Table 1
Coumarin – data summary.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) < μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c]
> 12500 [2]	Weak	3543	5517	8858	3500

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 uing classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from HRIP or HMT.

[c] WoE NESIL limited to 2significant figures.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.31	1.31
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 3.762 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/08/19.

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 03/12/19.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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