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Short Review

RIFM fragrance ingredient safety assessment, ethyl acetate, CAS Registry Number 141-78-6

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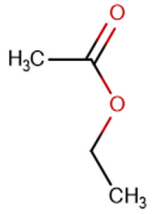


Name: Ethyl acetate
CAS Registry Number: 141-78-6

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).

(*continued on next column*)

(*continued*)

*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.

Ethyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that ethyl acetate is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and local respiratory toxicity endpoints. Data on read-across analog propyl propionate (CAS # 106-36-5) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from read-across analog methyl propionate (CAS # 554-12-1) show that there are no safety concerns for ethyl acetate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; ethyl acetate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; ethyl acetate 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 genotoxic. (ECHA REACH Dossier: Ethyl Acetate; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 327 mg/kg/day. (ECHA REACH Dossier: Ethyl Acetate; ECHA, 2011)
Reproductive Toxicity: NOAEL = 616 mg/kg/day. (ECHA REACH Dossier: Propyl Propionate; ECHA, 2018b)
Skin Sensitization: No concern for skin sensitization. (ECHA REACH Dossier: Methyl Propionate; ECHA, 2018a)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.
(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 126.12 mg/m^3 (ECHA REACH Dossier: Ethyl Acetate; ECHA, 2011)

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 3.14 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 1166 mg/L (RIFM Framework; Salvito, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 1166 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 1.166 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Ethyl acetate
2. **CAS Registry Number:** 141-78-6
3. **Synonyms:** Acetic acid, ethyl ester; Acetic ether; Ethyl ethanoate; Vinegar naphtha; 酢酸エチル; Ethyl acetate
4. **Molecular Formula:** $C_4H_8O_2$
5. **Molecular Weight:** 88.1 g/mol
6. **RIFM Number:** 276
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 77 °C (Fragrance Materials Association [FMA]), 77.91 °C (EPI Suite)
2. **Flash Point:** −4 °C (Globally Harmonized System), <40 °F; CC (FMA)
3. **Log K_{OW}:** 0.73 (Abraham, 1995), 0.86 (EPI Suite), partition coefficient in water/air = 71.5 (SD 2.1) (Kaneko et al., 1994)
4. **Melting Point**: −82.08 °C (EPI Suite)
5. **Water Solubility:** 29930 mg/L (EPI Suite)
6. **Specific Gravity:** 0.896 (FMA)
7. **Vapor Pressure:** 77 mm Hg at 20 °C (EPI Suite v4.0), 74 mm Hg at 20 °C (FMA), 98.3 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:** A colorless, mobile liquid that has a pleasant, ethereal-fruity, Brandy-like odor, somewhat nauseating in high concentration

3. Volume of use (Worldwide band)

1. 100–1000 metric tons per year (IFRA, 2019).

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.026% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00029 mg/kg/day or 0.022 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0044 mg/kg/day (RIFM, 2018)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** Propyl propionate (CAS # 106-36-5)
d. **Skin Sensitization:** Methyl propionate (CAS # 554-12-1)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

US EPA, 2006: Ethyl acetate is rapidly hydrolyzed to ethanol and acetic acid when administered orally, and the ethanol is eliminated through primarily exhaled air, urination, or metabolism. Ethyl acetate undergoes complete metabolism primarily in the liver, and it has been reported that very little unchanged ethyl acetate will be excreted.

Additional References: ECHA, 2011

8. Natural occurrence

Ethyl acetate is reported to occur in the following foods by the VCF*:
Beer
Whisky
Citrus fruits
Wine
Grape brandy
Honey
Rum
Apple Fresh (*Malus* Species).
Mangifera species
Guava And Feyoa

*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. This is a partial list.

9. REACH Dossier

Available; accessed on 01/26/22 (ECHA, 2011).

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, ethyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of ethyl acetate has been evaluated in a bacterial reverse mutation assay conducted following methods equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were treated with ethyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, ethyl acetate was not mutagenic in the Ames test.

The clastogenic activity of ethyl acetate has been assessed extensively *in vitro* in rodent cell lines and human peripheral blood lymphocytes leading to varying results. However, these studies deviated significantly from regulatory guidelines. The clastogenic activity of ethyl acetate was evaluated in an *in vivo* micronucleus test conducted

following methods equivalent to OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female Chinese Hamsters at a single dose of 2500 mg/kg body weight. Hamsters were euthanized at different time points of 12, 24, 48, and 72 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, 2011). Under the conditions of the study, ethyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, ethyl acetate does not present a concern for genotoxic potential.

Additional References: Loveday et al., 1990; Hayashi et al., 1988; Ishidate et al., 1984; Perocco et al., 1983; Basler (1986); Shirasu et al., 1976; Chen et al., 1984; Nonaka (1989); Zimmermann et al., 1985a; Zimmermann et al., 1985b.

Literature Search and Risk Assessment Completed On: 01/21/22

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient data on ethyl acetate to support the repeated dose toxicity endpoint. The systemic toxicity of ethyl acetate has been studied in several inhalation and oral studies. Table 1 summarizes other available studies with equal or higher NOAEL than that described in this risk assessment. In a 13-week subchronic inhalation study (GLP and EPA OTS 798.2450 guideline compliant), ethyl acetate was administered to 10 Sprague Dawley rats through inhalation (whole-body exposure) at concentrations of 0, 350, 750, and 1500 ppm. These concentrations were converted to doses using standard minute volume and body weights of Sprague Dawley rats and were equivalent to 327, 701, and 1402 mg/kg/day. No treatment-related mortalities were reported at any dose level. In addition, no treatment-related effects for ophthalmology, urinalysis, organ weight, sperm analysis, and necropsy were reported during the study. However, decreases in bodyweight gain were significant in both sexes at the highest dose and in females receiving the mid dose. These decreases were accompanied by significantly reduced food consumption and feed efficiency in these animals. Several minor hematological and biochemical changes were reported, but these were not considered to be of toxicological significance, either due to the small magnitude of change or due to lack of a dose response. In the mid- and high-dose groups, animals were reported to have a diminished startle response following the treatment. This effect was attributed to the rapid hydrolysis of ethyl acetate to produce ethanol and acetic acid. Based on decreased bodyweight gain and the average body weight and food consumption at the mid and high doses, the NOAEC for the repeated dose toxicity endpoint was considered to be 350 ppm. Using standard minute volume and body weights of Sprague Dawley rats, the NOAEL was considered to be 327 mg/kg/day (ECHA, 2011).

Therefore, the MOE for repeated dose toxicity endpoint can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure to ethyl acetate, 327/0.0044, or 74318.

In addition, the total systemic exposure to ethyl acetate (4.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Smyth, 1928; Blina (1933).

Literature Search and Risk Assessment Completed On: 01/15/22

11.1.3. Reproductive toxicity

The MOE for ethyl acetate 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 and insufficient fertility data on ethyl acetate. An inhalation 13-week subchronic toxicity study was conducted in Crl:CD BR (Sprague Dawley) rats. Groups of 10 rats/sex/dose were exposed to 0, 350, 750, or 1500 ppm ethyl acetate via whole-body inhalation 6 h/day, 5 days/week, for 94 days (68 total exposures). In addition to systemic toxicity parameters, histopathological evaluation of male and female reproductive organs and analysis of sperm parameters in male rats during necropsy were also conducted. There were no treatment-related changes in the number or concentration of spermatids in the testes, the number or concentration of sperm in the epididymides, sperm motility, or sperm morphology. No treatment-related pathological findings in the reproductive tissues were observed. The NOAEC for male fertility was considered to be 1500 ppm, the highest dose tested. Using standard minute volume and bodyweight values for male and female Sprague Dawley rats, the NOAEL was calculated to be 1402 mg/kg/day (ECHA, 2011). Since limited female fertility data (no evaluation on estrous cycle) were available on ethyl acetate, a NOAEL could not be derived for female fertility.

Read-across material propyl propionate (CAS # 106-36-5; see Section VI) has sufficient reproductive toxicity data that can be used to support the developmental toxicity and fertility endpoints. In an OECD 422- and GLP-compliant study, groups of 12 Crl:CD(SD) rats/sex were administered test material *n*-propyl propionate via whole-body exposure at target concentrations of 0, 50, 250, and 500 ppm (equivalent to 0, 62, 308, and 616 mg/kg/day, respectively, as per standard minute volume and bodyweight parameters for Sprague Dawley rats) for 6 h per day, 7 days per week. Females were exposed for 2 weeks prior to breeding, through breeding (approximately 2 weeks), and continued through gestation day 20; the females were then subjected to gross necropsy on postpartum day 5. Males were exposed to the test material 2 weeks prior to breeding and continued through breeding (approximately 2 weeks) before being subjected to gross necropsy (day 38). In addition to systemic toxicity parameters, reproductive toxicity parameters and neurological function were also assessed. There were no treatment-related adverse effects in the reproductive performance or survival and growth of pups. The NOAEL for fertility effects and the development of pups was considered to be 500 ppm or 616 mg/kg/day, the highest dose tested (ECHA, 2018b). **Therefore, the ethyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the propyl propionate NOAEL in mg/kg/day by the total systemic exposure to ethyl acetate, 616/0.0044, or 140000.**

In addition, the total systemic exposure to ethyl acetate (4.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Table 1
Summary of other studies on ethyl acetate with equal or higher NOAEL.

Duration	GLP/Guideline	# Animals/dose	Route	Doses	NOAEL	Justification of NOAEL	Reference
90 days	GLP and similar to EPA OTS 795.2600 guideline	30 SD rats/sex/dose	Oral	0, 300, 900, and 3600 mg/kg/day	900 mg/kg/day	Decreased bodyweight gain in males, increased salivation, irregular breathing, moist rales	ECHA, 2011
90 days	Non-GLP but EPA guideline compliant	10 SD rats/sex/dose	Inhalation	0, 350, 750, 1500 ppm (= 0, 327, 700, and 1401 mg/kg/day)	327 mg/kg/day	Decreased bodyweight gain and feed consumption	Christoph et al., 2003; ECHA, 2011

Table 2
Summary of existing data on methyl propionate as a read-across for ethyl acetate.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	NA	1380	NA	NA	NA	NA	NA
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	Negative	Negative	NA		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

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

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

Additional References: None

Literature Search and Risk Assessment Completed On: 01/15/22

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material methyl propionate (CAS # 554-12-1), ethyl acetate presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for ethyl acetate. Therefore, methyl propionate (CAS # 554-12-1; see Section VI) was used for the risk assessment of methyl propionate. The data on the read-across material are summarized in Table 2 Based on the existing data on the read-across material, ethyl acetate is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material methyl propionate was predicted not to be skin sensitizing in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (ECHA, 2018a). In the guinea pig maximization test, ethyl acetate was not found to be sensitizing (ECHA, 2011). In human maximization tests, no skin sensitization reactions were observed with ethyl acetate and read-across material methyl propionate at 6900 μg/cm^2 and 1380 μg/cm^2, respectively (RIFM, 1972; RIFM, 1977).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, and animal and human studies on the read-across material as well as the target material, ethyl acetate does not present a concern for skin sensitization.

Additional References: Klecak (1985).

Literature Search and Risk Assessment Completed On: 01/13/22

11.1.5. Photoirritation/photoallergenicity

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

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

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

Additional References: None

Literature Search and Risk Assessment Completed On: 01/11/22

11.1.6. Local Respiratory Toxicity

The MOE for ethyl acetate is adequate for the respiratory endpoint at the current level of use.

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 13-week study, 10 Crl:CD BR (Sprague Dawley) rats/sex/group were treated with 0, 1261.15, 2702.45, or 5404.91 mg/m^3 of ethyl acetate via whole-body inhalation exposures for 6 h/day, 5 days/week (ECHA, 2011). Standard observations included mortality, clinical signs, body weight, feed consumption, ophthalmological evaluations, hematology, clinical chemistry, urinalysis, sperm analyses, gross necropsy on all organs (including lung, trachea, larynx, pharynx, and nose), organ weights, and histopathology. Test substance-related local respiratory effects were limited to the degeneration of olfactory mucosa observed at all exposure concentrations and increased in incidence and severity with exposure. These effects were of minimal severity in 8 out 20 animals in the low-exposure group. All animals in the mid- and high-exposure groups showed minimal to moderate and minimal to severe olfactory mucosa degeneration, respectively. Based on the effects observed in the respiratory tract, the LOAEC for local respiratory effects was determined to be 1261.15 mg/m^3. By using a safety factor of 10, the NOAEC is estimated at 126.12 mg/m^3.

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

- (126.12 mg/m^3) × (1 m^3/1000 L) = 0.126 mg/L
- Minute volume of 0.17 L/min for a Sprague Dawley rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.126 mg/L) × (61.2 L/d) = 7.7 mg/day
- (7.7 mg/day)/(0.0016 kg lung weight of rat**) = 4812.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.022 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 et al., 2009) to give 0.034 mg/kg lung weight/day resulting in a MOE of 141544 (i.e., [4812.5 mg/kg lung weight of rat/day]/[0.034 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.022 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**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: Smyth et al., 1962; Smyth, 1928; Kawasaki et al., 1975; Kane et al., 1980; Nelson et al., 1943; Schumacher et al., 1962; Freundt et al., 1989; Vangala et al., 1991; Blina (1933); Frantik et al., 1994; EPA, 1995a; EPA, 1995b; Hasegawa et al., 1989; Bowen, 1997; Seeber et al., 1997; Christoph et al., 2003; Lang et al., 2008; Kleinbeck et al., 2008; Jalowayski et al., 2001.

Literature Search and Risk Assessment Completed On: 01/20/22

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl acetate 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, ethyl acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify ethyl acetate as possibly being 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, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), ethyl acetate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. Ethyl acetate has been registered under REACH, and the following additional data is available (ECHA, 2011):

In a 96-h acute toxicity study conducted according to the US EPA E03-05 method under flow-through conditions, fathead minnows (*Pimephales promelas*) were exposed to ethyl acetate at measured concentrations up to 400 mg/L. An LC50 value of 230 mg/L was reported.

A 32-day early life stage toxicity test was conducted with *Pimephales promelas* (fathead minnow) according to the OECD 210 method under flow-through conditions. Under the conditions of the study and based on the results, the authors conclude that the study shows a NOEC value of <9.65 mg/L.

The chronic toxicity of ethyl acetate was evaluated in the 21-day *Daphnia* reproduction test under static renewal conditions following the OECD 211 guidelines. A NOEC of 2.4 mg/L (measured concentration) was reported based on parental mortality and reproduction rate.

A 72-h algae inhibition test was conducted according to the OECD 201 method. A 72-h NOEC of >100 mg ethyl acetate/L was reported.

11.2.1.5. Risk assessment refinement. Since ethyl acetate has passed the screening criteria (Level 1), measured data are included in this document for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	0.86	0.86
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 1.166 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 05/24/22

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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1166			1000000	1.166	

- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 06/21/22.

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.2022.113363.

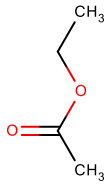
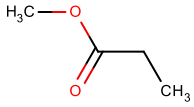
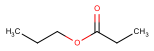
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 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, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), 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 analogs 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	Ethyl acetate	Methyl propionate	Propyl propionate
CAS No.	141-78-6	554-12-1	106-36-5
Structure			
Similarity (Tanimoto Score)		0.62	0.64
Endpoint		Skin sensitization	Reproductive toxicity
Molecular Formula	$C_4H_8O_2$	$C_4H_8O_2$	$C_6H_{12}O_2$
Molecular Weight (g/mol)	88.11	88.11	116.16
Melting Point (°C, EPI Suite)	−83.60	−87.50	−75.90
Boiling Point (°C, EPI Suite)	77.10	79.80	122.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	12425.61	11199.05	1853.18
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	80000.00	62400.00	5300.00
Log K_{OW}	0.73	0.84	1.85
J_{max} (μg/cm^2/h, SAM)	1095.21	1024.60	210.65
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	13.58	17.63	40.63
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)		Toxicant (low 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)	Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Reaction at sp3 carbon atom (SN2)	
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 ethyl acetate (CAS # 141-78-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, methyl propionate (CAS # 554-12-1) and propyl propionate (CAS # 106-36-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Methyl propionate (CAS # 554-12-1) was used as a read-across analog for the target material, ethyl acetate (CAS # 141-78-6), for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a class of aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target is an acetate ester while the read-across analog is a propionate ester. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Propyl propionate (CAS # 106-36-5) was used as a read-across analog for the target material, ethyl acetate (CAS # 141-78-6), for the reproductive toxicity endpoint.
  - o The target material and the read-across analog belong to a class of aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target is an acetate ester while the read-across analog is a propionate ester. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

oThe 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 OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The read-across analog is alerted for being a toxicant for developmental toxicity by the CAESAR model. The data described in the developmental toxicity section confirm that the MOE is adequate at the current level of use. Therefore, the predictions are superseded by the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

Abraham, M.H., Rafols, C., 1995. Factors that influence tadpole narcosis. An LFER analysis. J. Chem. Soc., Perkin Trans. 2 (10), 1843–1851.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Basler, A., 1986. Aneuploidy-inducing chemicals in yeast evaluated by the micronucleus test. Mutat. Res. Lett. 174 (1), 11–13.

Blina, L.V., 1933. Experimental researches on the toxic action of the esters of acetic acid. (Note 1). Ethyl acetate. Clin. Med. Ital. 64, 632–652.

Bowen, S.E., Balster, R.L., 1997. A comparison of the acute behavioral effects of inhaled amyl, ethyl, and butyl acetate in mice. Fund. Appl. Toxicol. 35 (2), 189–196.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Chen, T.-H., Kavanagh, T.J., Chang, C.C., Trosko, J.E., 1984. Inhibition of metabolic cooperation on Chinese hamster V79 cells by various organic solvents and simple compounds. Cell Biol. Toxicol. 1 (1), 155–171.

Christoph, G.R., Hansen, J.F., Leung, H.-W., 2003. Subchronic inhalation neurotoxicity studies of ethyl acetate in rats. Neurotoxicology 24 (6), 861–874.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis-based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. Toxicol. Vitro 248–260. Apr;32.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718, 2020.

ECHA, 2011. Ethyl Acetate Registration Dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/15437/1/2.

ECHA, 2017a. Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

ECHA, 2018a. Methyl propionate registration dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/26540/1/2.

ECHA, 2018b. Propyl propionate registration dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/21994/1/2.

Environmental Protection Agency, 1995a. Ethyl acetate: an acute vapor inhalation neurotoxiciy in the rat. Unpublished.

Environmental Protection Agency, 1995b. A ten-day vapor inhalation study with ethyl acetate in the rat. Unpublished.

Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. Toxicol. Vitro 37, 178–188.

Frantik, E., Hornychova, M., Horvath, M., 1994. Relative acute neurotoxicity of solvents: isoeffective air concentrations of 48 compounds evaluated in rats and mice. Environ. Res. 66 (2), 173–185.

Freundt, K.J., Romer, K.G., Federsel, R.J., 1989. Decrease of inhaled toluene, ethyl benzene, m-xylene or mesitylene in rat blood after combined exposure to ethyl acetate. Bull. Environ. Contam. Toxicol. 42 (4), 495–498.

Hasegawa, R., Nakaji, Y., Kurokawa, Y., Tobe, M., 1989. Acute toxicity tests on 113 environmental chemicals. Sci. Rep. Res. Inst. Tohoku Univ. Ser. C Med. 36 (1–4), 10–16.

Hayashi, M., Kishi, M., Sofuni, T., Ishidate Jr., M., 1988. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem. Toxicol. 26 (6), 487–500.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2019. Volume of Use Survey, January-December 2019.

Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22 (8), 623–636.

Jalowayski, A.A., Johnson, B.N., Wise, P.M., Schmid-Schonbein, G.W., Cain, W.S., 2001. Orbital response indicates nasal pungency: analysis of biomechanical strain on the skin. Chem. Senses 26 (8), 1005–1013.

Kane, L.E., Dombroske, R., Alarie, Y., 1980. Evaluation of sensory irritation from some common industrial solvents. Am. Ind. Hyg. Assoc. J. 41 (6), 451–455.

Kaneko, T., Wang, P.-Y., Sato, A., 1994. Partition coefficients of some acetate esters and alcohols in water, blood, olive oil, and rat tissues. Occup. Environ. Med. 51 (1), 68–72.

Kawasaki, Y., Suzuki, S., Kobayashi, K., Tobe, M., Ikeda, Y., 1975. Studies on the inhalation toxicity of A-thinner, its principal constituents and chloroform. Eisei Shikenjo Hokoku 93, 72–77.

Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. Curr. Probl. Dermatol. 14, 152–171.

Kleinbeck, S., Juran, S.A., Kiesswetter, E., Schaeper, M., Blaszkewicz, M., et al., 2008. Evaluation of ethyl acetate on three dimensions: investigation of behavioral, physiological and psychological indicators of adverse chemosensory effects. Toxicol. Lett. 182 (1–3), 102–109.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Lang, I., Bruckner, T., Triebig, G., 2008. Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. Regul. Toxicol. Pharmacol. 50 (1), 23–36.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Loveday, K.S., Anderson, B.E., Resnick, M.A., Zeiger, E., 1990. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V. Results with 46 chemicals. Environ. Mol. Mutagen. 16 (4), 272–303.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

Nelson, K.W., Ege, J.F., Ross, M., Woodman, L.E., Silverman, L., 1943. Sensory response to certain industrial solvent vapors. J. Ind. Hyg. Toxicol. 25 (7), 282–285.

Nonaka, M., 1989. DNA repair tests on food additives. Environ. Mol. Mutagen. 14 (Suppl. 1), 143.

OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

Perocco, P., Bolognesi, S., Alberghini, W., 1983. Toxic activity of seventeen industrial solvents and halogenated compounds on human lymphocytes cultured in vitro. Toxicol. Lett. 16 (1/2), 69–75.

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. The Contact-Sensitization Potential of Fragrance Materials by Maximization Testing in Humans. Report to RIFM. RIFM Report Number 1804. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1702. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Exposure Survey 22. November 2018.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an

aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Schumacher, H., Battig, K., Grandjean, E., 1962. The effects of various solvent vapors on the growth and on the spontaneous mortality of juvenile mice. Zentbl. Arbmed. Arbschutz. 12, 5–8.
Seeber, A., Blaszkewicz, M., Golka, K., Kiesswetter, E., 1997. Solvent exposure and ratings of well-being: dose-effect relationships and consistency of data. Environ. Res. 73 (1–2), 81–91.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Shirasu, Y., Moriya, M., Kato, K., Furuhasihi, A., Kada, T., 1976. Mutagenicity screening of pesticides in the microbial system. Mutat. Res. Genet. Toxicol. 40, 19–30.
Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., 1962. Range-finding toxicity data: list VI. Am. Ind. Hyg. Assoc. J. 23, 95–107.
Smyth, H.F., Smyth Jr., H.F., 1928. Inhalation experiments with certain lacquer solvents. J. Ind. Hyg. 10 (8), 261–271.
US EPA, 2006. Inert Reassessment—Ethyl Acetate (CAS Reg. No 141-78-6) and Amyl Acetate (CAS Reg. No 628-63-7). Retrieved from. https://www.epa.gov/sites/default/files/2015-04/documents/ethyl_amyl_acetate.pdf.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.
Vangala, R.R., Blaszkewicz, M., Bolt, H.M., Golka, K., Kiesswetter, E., Seeber, A., 1991. Acute experimental exposures to acetone and ethyl acetate. Arch. Toxicol Suppl. 14, 259–262.
Zimmermann, F.K., Mayer, V.W., Scheel, I., Resnick, M.A., 1985a. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in saccharomyces-cerevisiae. Mutat. Res., Fundam. Mol. Mech. Mutagen. 149 (3), 339–352.
Zimmermann, F.K., Mayer, V.W., Scheel, I., Resnick, M.A., 1985b. Acetone, methyl ethyl ketone, ethyl acetate, acetonitrile and other polar aprotic solvents are strong inducers of aneuploidy in Saccharomyces cerevisiae. Mutat. Res., Fundam. Mol. Mech. Mutagen. 149 (3), 339–351.