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Short Review

RIFM fragrance ingredient safety assessment, butyl acetate, CAS Registry Number 123-86-4

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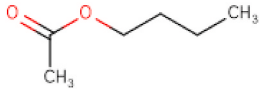

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Name: Butyl acetate CAS Registry Number: 123-86-4

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; Comiskey 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 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.

Butyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog ethyl acetate (CAS # 141-78-6) show that butyl acetate is not expected to be genotoxic. Data on butyl acetate provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data from read-across analog pentyl propionate (CAS # 624-54-4) show that there are no safety concerns for butyl acetate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; butyl acetate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; butyl 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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: N-butyl acetate; ECHA, 2011a; ECHA REACH Dossier: Ethyl acetate; ECHA, 2011b)
Repeated Dose Toxicity: NOAEL = 616 mg/kg/day.	(David et al., 2001)
Reproductive Toxicity: Developmental toxicity: NOAEL = 833 mg/kg/day. Fertility: NOAEL = 2222 mg/kg/day.	(ECHA REACH Dossier: N-butyl acetate; ECHA, 2011a)
Skin Sensitization: No concern for skin sensitization.	(ECHA REACH Dossier: Pentyl propionate; ECHA, 2013)
Photoirritation/ Photoallergenicity: Not expected to be photoirritating/ photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 2375 mg/m^3. (ECHA REACH Dossier: N-butyl acetate; ECHA, 2011a; David et al., 2001)	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 98% (301D)	(ECHA REACH Dossier: N-butyl acetate; ECHA, 2011a)
Bioaccumulation: Screening-level: 6.941 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96hr Algae EC50: 17.59 mg/L	(EPI Suite v4.11; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint 96hr Algae EC50: 17.59 mg/L	EPI Suite v4.11; US EPA, 2012b)
RIFM PNEC is: 1.759 μg/L	
• Revised PEC/PNECs (2019 IFRA VoU): North America and Europe: <1	

1. Identification

1. **Chemical Name:** Butyl acetate
2. **CAS Registry Number:** 123-86-4
3. **Synonyms:** Acetic acid, butyl ester; Butyl ethanoate; TBAC; 1-Acetoxybutane; 酢酸ブチル; n-Butyl acetate; Butyl acetate
4. **Molecular Formula:** $C_6H_{12}O_2$
5. **Molecular Weight:** 116.16 g/mol
6. **RIFM Number:** 827
7. **Stereochemistry:** No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 125 °C (Fragrance Materials Association [FMA]), 125.79 °C (EPI Suite)
2. **Flash Point:** 27 °C (Globally Harmonized System), 72 °F; closed cup (FMA)
3. **Log K_{OW}:** 2.0 (RIFM, 2013), 1.82 (Abraham and Rafols, 1995), 1.85 (EPI Suite), partition coefficient in water/air = 32.7 (SD 2.7) (Kaneko et al., 1994)
4. **Melting Point**: -56.83 °C (EPI Suite)

5. **Water Solubility:** 3128 mg/L (EPI Suite)
6. **Specific Gravity:** 0.879 (FMA)
7. **Vapor Pressure:** 8.85 mm Hg at 20 °C (EPI Suite v4.0), 9.3 mm Hg at 20 °C (FMA), 11.9 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 $mol^{-1} \bullet cm^{-1}$)
9. **Appearance/Organoleptic:** Water-white, clear, nearly colorless, mobile liquid with a non-residual, fruity odor

3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.016% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00023 mg/kg/day or 0.017 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0024 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification: class I, low

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

6.2. Analogs selected

a. **Genotoxicity:** Ethyl acetate (CAS # 141-78-6)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Pentyl propionate (CAS # 624-54-4)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-***across*** justification

See Appendix below.

7. Metabolism

Metabolism data available on butyl acetate have been reviewed by several organizations, including CIR (2008), ECHA (2011a), OECD (2001), NICNAS (2014), and WHO (2005), among others. Studies conducted among rats show that butyl acetate is readily absorbed by the respiratory tract, skin, and gastrointestinal tract. Butyl acetate is rapidly distributed to all the major tissues in the body, including the brain (WHO, 2005). Distribution of butyl acetate to tissues is preferred over blood, based on tissue/blood partition coefficients, with a greater partition coefficient for fat followed by liver, kidney, brain, and muscle. Butyl acetate is metabolized extensively by rapid hydrolysis to n-butanol and acetic acid, which is catalyzed by esterases present in several tissues and blood; n-butanol was found at higher concentrations in both blood (Cmax = 52 μg equivalents/g at Tmax 2.6 min) and brain (Cmax = 79 μg equivalents/g at Tmax 2.5 min), which was also eliminated from both tissues (biphasic elimination; t1/2, of 1–1.2 min) and was undetectable beyond 20 min post-dosing. Moreover, 99% of butyl acetate was hydrolyzed within 2.7 min in rats when administered intravenously (ECHA, 2011a). Acetic acid is oxidized via the citric acid cycle to carbon dioxide (CO_2) and water, and butanol is metabolized by alcohol dehydrogenase to the respective aldehyde and by aldehyde dehydrogenase to the corresponding butyric acid, which is further oxidized to carbon dioxide (WHO, 2005). Unchanged butyl acetate and its metabolites are expected to excrete primarily through exhaled air and urine. Humans excreted about 50% of inhaled butyl acetate through exhalation when exposed to a concentration of 200 mg/m^3 (WHO, 2005). In rats, intravenous administration of butyl acetate at a dose of 30 mg/kg led to rapid biphasic elimination from both blood and brain with an elimination half-life ($t_{1/2}$) of 0.4 min for butyl acetate and 1 min for butanol; both butanol and butyl acetate were undetectable after 20 min post-dosing. In addition, other metabolites identified were butyric acid, glucuronide, and sulfate conjugates of butanol, which were found in the blood and brain (only butyric acid) of rats when administered intravenously (ECHA, 2011a).

Additional References: None.

8. Natural occurrence

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

Acerola (*Malpighia*)	Melon
Apple (*Malus* species)	Passion fruit (*Passiflora* species)
Apricot (*Prunus armeniaca* L.)	Plum (*Prunus* species)
Grape (*Vitis* species)	Strawberry (*Fragaria* species)
Mangifera species	Wine

*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 01/27/22 (ECHA, 2011a).

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, butyl acetate does not present a

concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of butyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with butyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011a). Under the conditions of the study, butyl acetate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of butyl acetate; however, read-across can be made to ethyl acetate (CAS # 141-78-6; see Section VI).

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. 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, 2011b). Under the conditions of the study, ethyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to butyl acetate.

Based on the data available, ethyl acetate does not present a concern for genotoxic potential, and this can be extended to butyl acetate.

Additional References: Zeiger et al., 1992.

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

11.1.2. Repeated dose toxicity

The MOE 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 butyl acetate.

In a subchronic inhalational toxicity study (compliant with GLP and EPA OPPTS 798.2450, 798.6050, 798.6200, 798.6500 guidelines), 15–20 Sprague Dawley rats/sex/group were exposed through inhalation (whole-body) to butyl acetate (purity: ≥99.9%) at doses of 0 (control: sham-exposed), 500, 1500, and 3000 ppm (equivalent to 616, 1848, and 3696.1 mg/kg/day, respectively; converted values using standard minute volume and body weight for Sprague Dawley rats), 6 h/day, 5 days/week, for 13–14 weeks. On day 30, 5 rats/sex/dose were euthanized for necropsy. Clinical signs examination revealed transient sedation with reduced activity of minimal severity in both mid- and high-dose group rats throughout the study. A significant decrease in bodyweight gain was reported in both mid-dose (23% and 30% for males and females, respectively) and high-dose groups (38% and 22% for males and females, respectively) throughout the study. The decrease in bodyweight gain was associated with a significant reduction in feed consumption among mid- and high-dose group animals. Histopathology examination revealed treatment-related changes in nasal passages, including necrosis of olfactory epithelium among high-dose group animals and degeneration of olfactory epithelium among mid-dose (minimal to mild) and high-dose group (mild to moderate) animals. The degenerative lesions were considered to be due to the result of hydrolysis of butyl acetate that led to the formation of butanol and acetic acid rather than the intact ester. Furthermore, degeneration was reported in areas that exhibited carboxylesterase activity. Degenerative lesions with acute inflammation of stomach mucosa (glandular vs. forestomach) were reported in the high-dose females (3/10). However, the degeneration of the stomach was attributed to the swallowing of mucus containing test material and stress. Therefore, based on the degenerative lesions in the glandular stomach at 3000 ppm and reduced activity, decreased body weight, and feed consumption in both the 1500- and 3000-ppm dose groups, the NOAEC was considered to be 500 ppm (equivalent to 616 mg/kg/day). Using standard minute volume and body weights of male and female Sprague Dawley rats, NOAEL was considered to be 616 mg/kg/day (David et al., 1998).

Neurotoxicity of butyl acetate was also evaluated at the same dose levels as the 13-week study and with the same number of animals in each dose level (David et al., 1998). The results from the study show that no treatment-related effects were observed for any of the parameters tested up to the highest dose level; thus, the NOAEC for neurotoxicity was considered to be 3000 ppm (equivalent to 3696.1 mg/kg/day), the highest dose tested.

In several 30- to 80-day repeated dose toxicity studies conducted on 5 rabbits (Ambrosio, 1962a; Ambrosio et al., 1962b), butyl acetate caused toxicity to the hematopoietic system (leukopenia, neutropenia, and anemia) and several ostensible effects on liver, lung, kidneys, heart, CNS, spleen, and testis. However, due to the nature of the effects on the limited number of rabbits in single-dose studies, the above effects were not considered to be true toxicological effects for butyl acetate. Butyl acetate through subchronic inhalational exposure caused only systemic toxic effects like reduced body weight and feed consumption with no cumulative neurotoxicity (David et al., 2001; David et al., 1998) owing to less bioaccumulation potential and rapid elimination. The degenerations to the olfactory and glandular stomach could not be considered to be systemic effects of butyl acetate; rather, they are local effects due to the acidic nature of the test material when metabolized through the routes of administration of inhalation and oral (swallowing of mucus containing test material).

The NOAEL of 616 mg/kg/day was considered for the risk assessment of repeated dose toxicity.

Therefore, the butyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the butyl acetate NOAEL of 616 mg/kg/day by the total systemic exposure to butyl acetate, 616/0.0024, or 256667.

In addition, the total systemic exposure to butyl acetate (2.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for butyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on butyl acetate that can be used to support the reproductive toxicity endpoint. An OECD 416/GLP 2-generation reproduction toxicity study was conducted in Sprague Dawley rats. Groups of 30 rats/sex/dose were exposed via whole-body inhalation to butyl acetate at concentrations of 0, 750, 1500, or 2000 ppm (equivalent to 0, 833, 1667, or 2222 mg/kg/day, respectively, using standard minute volume and body weight of Sprague Dawley rats for chronic exposure) for 6 h/day, 7 days/week. All F0 and F1 animals were exposed for at least 70 days prior to mating. Exposure of F0 and F1 males continued throughout mating and up to the day prior to euthanasia. F0 and F1 females were exposed throughout gestation until day 20 and from lactation day (LD) 5 to the day prior to euthanasia. From gestation day (GD) 21 through LD 4, F0

and F1 females were treated via oral gavage at doses of 0 (control: deionized water), 1125, 2250, or 3000 mg/kg/day. Inhalation exposure for F1 and F2 rats was initiated on postnatal day (PND) 22. Following 2–3 weeks of exposure for the F1 and F2 generation, pups were selected for the maturation phase for each generation. In summary, F0 males and females were exposed for 113–114 and 121–127 days, respectively; F1 males and females were exposed for 134–135 and 140–153 days, respectively; and F2 males and females were exposed for 47–50 days. No treatment-related mortalities or clinical signs of toxicity were reported in F0, F1, or F2 generations at any dose level. A significant decrease in bodyweight gain was reported in the mid- and high-dose groups in all generations throughout treatment in males except F2 males. A significant decrease in bodyweight gain was reported in females in the mid- and high-dose groups in all generations throughout treatment except F0 females during gestation. The decreased body weights were accompanied by significant decreases in feed consumption in the mid- and high-dose groups for all generations in both sexes throughout treatment, except for F0 females and F1 males, which showed an occasional significant decrease in feed consumption during lactation (F0 females) and throughout treatment (F1 males). No treatment-related changes were reported in the reproductive parameters (estrous cycle evaluation, sperm analysis, gestation length, process of parturition, and necropsy) in both males and females of the F0 and F1 generations at any dose level. No treatment-related changes were reported in litter parameters (number of pups born, live litter size, sex ratio, and postnatal survival) for both F1 and F2 generations at any dose level. No treatment-related mortalities or clinical signs of toxicity were reported in F1 and F2 pups at any dose level. A significant decrease in pup body weight was reported in the mid- and high-dose groups of both F1 and F2 litters, except for F2 male litters, which reflected decreased pup body weight only at 2000 ppm. Regarding sexual maturation, the average age of attainment of balanopreputial separation in F1 and F2 high-dose males was slightly higher than the controls, and the average age of attainment of vaginal patency was slightly higher in the F2 high-dose females. Significant decreases in the absolute and relative thymus weights were reported in all treatment group pups on PND 21 in both F1 and F2 generations with no dose-response. The reduced body weights led to an unclear relationship between the test material and organ weight changes. No treatment-related changes were reported in the necropsy and developmental landmarks (pinna detachment, incisor eruption, and eye opening) in both F1 and F2 generations at any dose level. The NOAEL for fertility effects was considered to be 2000 ppm or 2222 mg/kg/day, the highest dose tested. The NOAEL for maternal toxicity was considered to be 750 ppm or 833 mg/kg/day, based on decreased body weight accompanied by decreased feed consumption in F0 and F1 generation dams at concentrations ≥1500 ppm. The NOAEL for developmental toxicity was considered to be 750 ppm or 833 mg/kg/day, based on decreased pup body weights in both F1 and F2 generations at concentrations ≥1500 ppm and a slight delay in sexual maturation among the F1 and F2 pups at 2000 ppm (ECHA, 2011a).

Butyl acetate did not induce any male or female fertility effects up to the highest tested dose of 2222 mg/kg/day in the 2-generation reproductive toxicity study (ECHA, 2011a) and up to 3696 mg/kg/day in a 13-week toxicity study for males (David et al., 2001; see table for details). The most conservative NOAEL for fertility was considered to be 2222 mg/kg/day. **Therefore, the butyl acetate MOE for the fertility endpoint can be calculated by dividing the butyl acetate NOAEL in mg/kg/day by the total systemic exposure to butyl acetate, 2222/0.0024, or 925833.**

In the 2-generation reproductive toxicity study, administration of butyl acetate at concentrations ≥1667 mg/kg/day resulted in a decreased growth rate of pups (ECHA, 2011a). Furthermore, butyl acetate also manifested fetal effects, such as misaligned sternebrae and retinal folds in New Zealand white rabbits, facial defects, eye defects, diaphragmatic hernias, generalized brain dysmorphology, dilated ureters, and reduced pelvic ossifications in Sprague Dawley rats at 1500 ppm (equivalent to 1130–2201 mg/kg/day) in developmental toxicity studies conducted by NIOSH (NIOSH, 1982; see Table 1 for details). These effects, including those presented in Saillenfait et al., 2007) and Sporn et al., 1963 (see Table 1 for details), were not considered for the risk assessment since the studies were non-GLP and non-guideline. In addition, some of them were single-dose studies, so a dose-response effect could not be evaluated. Therefore, the NOAEL of 833 mg/kg/day from the more robust 2-generation reproductive toxicity study was considered, which also yielded the most conservative developmental toxicity NOAEL when compared to NOAELs from other studies. **Therefore, the butyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the butyl acetate NOAEL in mg/kg/day by the total systemic exposure to butyl acetate, 833/0.0024 or 347083.**

In addition, the total systemic exposure to butyl acetate (2.4 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.**

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across material pentyl propionate, butyl acetate does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for butyl acetate. Therefore, pentyl propionate (CAS # 624-54-4; see Section VI) was used for the risk assessment of propyl acetate. The data on the read-across material are summarized in Table 2. Based on the existing data on the read-across material, butyl 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). Butyl acetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) (Wass and Belin, 1990). In a murine local lymph node assay (LLNA), read-across material pentyl propionate was found to be non-sensitizing when tested up to 100% (25000 μg/cm^2) (ECHA, 2013). In a human maximization test, no skin sensitization reactions were observed with 2760 μg/cm^2 butyl acetate (RIFM, 1976).

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

Additional References: Gad et al., 1986.

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

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, butyl 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 butyl 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, butyl 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.,

Table 1
Additional studies.

Duration in detail	GLP/ Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/ NOEL	Justification of NOAEL/LOAEL/ NOEL	Reference
13 weeks, (6 h/day)	Non-GLP and non-guideline	Male Sprague Dawley rats (15/group)	Inhalation	0, 500, 1500, or 3000 ppm (equivalent to 616, 1848, and 3696 mg/kg/day, as per standard minute volume and bodyweight parameters for Sprague Dawley rats; USEPA, 1998)	Male fertility NOAEL = 3696 mg/kg/day	No reproductive effects (weight of testis, sperm count, number and concentration of testicular spermatids and epididymal spermatozoa) observed up to the highest tested dose	David et al., 2001
GD 6–20	Non-GLP and non-guideline	Female Sprague Dawley rats (19–21/ group)	Inhalation	0, 500, 1000, 2000, or 3000 ppm (equivalent to 0, 629, 1258, 2515, 3773 mg/kg/day, using standard minute volume and body weight of female Sprague Dawley rats; USEPA, 1998)	Developmental toxicity NOAEL = 2515 mg/kg/day	Decreased fetal body weight at 3000 ppm	Saillenfait et al., 2007
GD 7–19 (7 h/day)	Non-GLP and non-guideline	Female New Zealand White rabbits (30/group)	Inhalation	0 or 1500 ppm (equivalent to 0 and 1130 mg/kg/day, using standard minute volume and body weight of female New Zealand rabbits; US EPA, 1998)	Developmental toxicity LOAEL = 1130 mg/kg/day	Significant increase in incidences of misaligned sternebrae and retinal folds, presence of clear liquid in the gall bladder, rather than bile	NIOSH, 1982; ECHA, 2011a
3 weeks prior to mating and GD 7–16	Non-GLP and non-guideline	Sprague Dawley rats (37–43/ group)	Inhalation	0 ppm (Group 1) or 1500 ppm (equivalent to 2201 mg/kg/day, as per using standard minute volume and body weight of female Sprague Dawley rats; US EPA, 1998) Group 2: 1500 ppm for 7 h/day from GD 7–16 Group 3: 1500 ppm for 7 h/day from GD 1–16 Group 4: 1500 ppm for 7 h/day, 3 weeks prior to mating and GD 1–16.	Reproductive LOAEL = 2201 mg/kg/day	Decreased placental weights; 2 fetuses in Group 2, 1 fetus in Group 3, and 3 fetuses in Group 4 had major malformations, i.e., multiple facial defects, eye defects, diaphragmatic hernias, and generalized brain dysmorphology Incidence of rib dysmorphology increased in treatment groups in comparison to controls Increased incidences of dilated ureters and reduced pelvic ossifications	NIOSH, 1982; ECHA, 2011a
8 months (240 days)	Not reported	Pregnant White rats	Oral gavage (vehicle: oil)	0.1 mL oil solution containing 2 mg/kg test material	Developmental toxicity NOAEL = 2 mg/kg/every other day	No significant effects were observed in the number of pregnant females, number of offspring born, number of offspring born alive, offspring birth weight, offspring body weight at days 7 and 21, and offspring viability	Sporn et al., 1963

2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/14/22.

11.1.6. Local respiratory toxicity

The MOE for butyl acetate is adequate for the local respiratory toxicity 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 for local respiratory toxicity. In a 13-week whole-body inhalation study conducted in rats, a NOAEC of 2375 mg/m^3 (500 ppm) was reported (ECHA, 2011a; David et al., 2001). Whole-body inhalation exposure of butyl acetate was administered at target concentrations (0 [sham], 2375, 7126, 14253 mg/m^3) to both male and female Sprague Dawley rats (15/sex/concentration). Clinical observations, body weight, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, gross pathology, and histopathology were all considered. Body weights and food consumption decreased among animals in mid- and high-concentration treatment groups. Organ weight changes were also dependent upon treatment and concentration. Lung weights increased among males exposed to 14253 mg/m^3 butyl acetate compared to the control group. Additionally, histopathology for both the mid- and high-concentration treatment groups demonstrated degenerated olfactory epithelial tissue as well as dorsal medial meatus and ethmotubinates of the nasal passages. The severity of the histopathological findings ranged from mild to moderate for the high-dose group but minimal to mild for the mid-dose group. As there were no observable adverse effects documented for the low-dose treatment group, the NOAEC was determined to be 2375 mg/m^3.

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

- (2375 mg/m^3) × (1 m^3/1000 L) = 2.375 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
- (2.375 mg/L) × (61.2 L/day) = 145.35 mg/day
- (145.35 mg/day)/(0.0016 kg lung weight of rat**) = 90844 mg/kg lung weight/day

The 95th percentile calculated exposure to butyl acetate was reported to be 0.017 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 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 0.026 mg/kg lung weight/day resulting in an MOE of 3494000 (i.e., [90844 mg/kg lung weight/day]/[0.026 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.017 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA[4] Weighted Mean EC3 Value µg/cm²	GPMT[5]	Buehler[5]
No evidence of sensitization[7]	NA	NA	NA	NA	>25000 (negative up to 100%)	NA	NA
	In vitro Data[6]				*In silico* protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	NA	NA	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

[1]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).

[2]Data derived from CNIH or HMT

[3]WoE NESIL limited to 2 significant figures

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

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

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

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

*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., 1954; Smyth and Smyth, 1928; Nelson et al., 1943; McOmie and Anderson, 1949; NIOSH, 1982; Burleigh-Flayer et al., 1991; Querci and Mascia, 1970a; Ambrosio et al., 1962b; Ambrosio, 1962a; Frantik et al., 1994; Querci et al., 1970b; Osina (1959); Sayers et al., 1936; Iregren et al., 1993; Ashley and Prah, 1997; Bowen and Balster, 1997; Norris et al., 1997; Silver (1992); Prah et al., 1998; David et al., 1998; Kodak Company, 1996; Union Carbide Co, 1993; Saillenfait et al., 2007.

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 butyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002),

which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, butyl acetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify butyl 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 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, 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).

11.2.2. Risk assessment

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

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

No data available.

Ecotoxicity:

No data available.

11.2.2.2. Other available data. Butyl acetate has been registered for REACH with the following additional data available (ECHA, 2011a):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D Guideline. Biodegradation of 98% was observed after 28 days.

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D Guideline. Biodegradation of 80% was observed after 5 days and 83% after 28 days.

The acute fish (fathead minnow) toxicity test was conducted according to the OECD 203 Guideline under flow-through conditions. The 96-h LC50 value based on the mean measured concentration was reported to be 18 mg/L (95% CI: 17–19 mg/L).

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 Guideline under static conditions. The 48-h EC50 value was reported to be 44 mg/L.

11.2.3. Risk assessment refinement

Since butyl acetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.85	1.85
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 1.759 μg/L. The revised PEC/PNECs for EU and NA <1. 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/
- **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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	211.6			1000000	0.2116	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	19.093	40.347	17.594	10000	1.7594	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	131.102	73.392	51.557			Neutral Organic SAR

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113439.

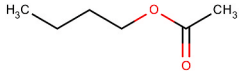
Appendix

Read-across Justification

Methods

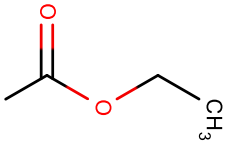
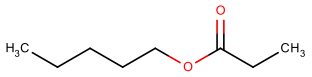
The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) 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	Butyl acetate	Ethyl acetate	Pentyl propionate
CAS No.	123-86-4	141-78-6	624-54-4
Structure			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
			
Similarity (Tanimoto Score)		0.59	0.75
Endpoint		Genotoxicity (Clastogenicity)	Skin sensitization
Molecular Formula	$C_6H_{12}O_2$	$C_4H_8O_2$	$C_8H_{16}O_2$
Molecular Weight (g/mol)	116.16	88.11	144.21
Melting Point (°C, EPI Suite)	−78.00	−83.60	−73.10
Boiling Point (°C, EPI Suite)	126.10	77.10	168.60
Vapor Pressure (Pa @ 25°C, EPI Suite)	1533.20	12425.61	479.96
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	8400.00	80000.00	810.00
Log K_{OW}	1.78	0.73	2.83
J_{max} (μg/cm^2/h, SAM)	301.12	1095.21	63.57
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	28.47	13.58	85.42
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified	
Oncologic Classification	No alert found	No alert found	
Skin Sensitization			
Protein Binding (OASIS v1.1)	DPRA less than 9% (DPRA 13%)|DPRA less than 9% (DPRA 13%) ≫ Non-conjugated carboxylic acids and esters (non-reactive)		DPRA less than 9% (DPRA 13%)|DPRA less than 9% (DPRA 13%) ≫ Non-conjugated carboxylic acids and esters (non-reactive)
Protein Binding (OECD)	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)
Protein Binding Potency	Not categorized		Not categorized
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 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 butyl acetate (CAS # 123-86-4). 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, ethyl acetate (CAS # 141-78-6) and

pentyl propionate (CAS # 624-54-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl acetate (CAS # 141-78-6) was used as a read-across analog for the target material, butyl acetate (CAS # 123-86-4), for the genotoxicity endpoint.
  - The target material and the read-across analog belong to a class of aliphatic esters.
  - The key difference between the target material and the read-across analog is that the target material is an acetate ester of butanol, whereas the read-across analog is an acetate ester of ethanol. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - Both the target material and read-across analog have an alert for Schiff base formation (DNA Binding [OASIS v1.4, QSAR Toolbox v4.2]). This alert is due to the presence of an acetate group in these substances. The data on the read-across analog confirm that the substance does not pose a concern for genotoxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Pentyl propionate (CAS # 624-54-4) was used as a read-across analog for the target material, butyl acetate (CAS # 123-86-4), for the skin sensitization endpoint.
  - The target material and the read-across analog belong to a class of aliphatic esters.
  - The key difference between the target material and the read-across analog is that the target material is an ester of butanol, whereas the read-across analog is an ester of propanol. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - There are no toxicological alerts for the read-across analog or the target material. Data are consistent with *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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