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Short review

RIFM fragrance ingredient safety assessment, 3-methylbutyl valerate, CAS Registry Number 2050-09-1

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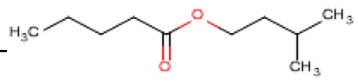

Name: 3-Methylbutyl valerate
CAS Registry Number: 2050-09-1

Abbreviation list:
2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor

(*continued*)

BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015) compared to a deterministic aggregate approach.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA- European Chemicals Agency
EU- Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD- Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA- North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development

(*continued on next page*)

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OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/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 under the limits 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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analogues isoamyl butyrate (CAS # 106-27-4), isoamyl alcohol (CAS # 123-51-3) and valeric (pentanoic) acid (CAS # 109-52-4) show that this material is not genotoxic. Data from the suitable read across analogue isoamyl acetate (CAS # 123-92-2) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose, developmental and reproductive toxicity endpoint was completed using isoamyl alcohol (CAS # 123-51-3) and valeric (pentanoic) acid (CAS # 109-52-4) as suitable read across analogues, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (RIFM, 2015; Ishidate et al., 1984; RIFM, 2007)
Repeated Dose Toxicity: NOAEL = 1250 mg/kg/day (Schilling et al., 1997)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day (ECHA REACH Dossier: 3-methylbutan-1-ol)
Skin Sensitization: Not a sensitization concern (RIFM, 1987)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening Level: 3.25 (Biowin 3) (EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 135 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 7.118 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 7.118 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.007118 μg/L
• **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America (not reported) and Europe: Not applicable; Cleared at screening level

1. Identification

1. **Chemical Name:** 3-Methylbutyl valerate
2. **CAS Registry Number:** 2050-09-1
3. **Synonyms:** Isoamyl valerate; Isoamyl valerianate; Isopentyl valerate; 3-Methylbutyl valerate; 3-Methylbutyl pentanoate; Pentanoic acid, 3-methylbutyl ester; ペンタン酸アルキル (C=1~5)
4. **Molecular Formula:** $C_{10}H_{20}O_2$
5. **Molecular Weight:** 172.27
6. **RIFM Number:** 6186

2. Physical data

1. **Boiling Point:** 198.83 °C [EPI Suite]
2. **Flash Point:** 149.00 °F. TCC (65.00 °C)*
3. **Log K_{OW}:** 3.74 [EPI Suite]
4. **Melting Point**: −20.47 °C [EPI Suite]
5. **Water Solubility:** 38.59 mg/L [EPI Suite]
6. **Specific Gravity:** 0.85800 to 0.86700 @ 25.00 °C*
7. Vapor Pressure: 0.259 mmHg @ 20 °C [EPI Suite 4.0], 0.382 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium, fruity, ripe apple odor.*

* http://www.thegoodscentscompany.com/data/rw1045091.html#toorgano, retrieved 4/7/2016.

3. Exposure

1. **Volume of Use (worldwide band):** <0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Bar soap (No reported use in Hydroalcoholics):** 0.014% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00074 mg/kg/day or 0.049 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00080 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogues Selected:
   a. **Genotoxicity:** Isoamyl butyrate (CAS # 106-27-4); isoamyl alcohol (CAS # 123-51-3); valeric (pentanoic) acid (CAS # 109-52-4)
   b. **Repeated Dose Toxicity:** isoamyl alcohol (CAS # 123-51-3) and valeric (pentanoic) acid (CAS # 109-52-4)
   c. **Developmental and Reproductive Toxicity:** isoamyl alcohol (CAS # 123-51-3) and valeric (pentanoic) acid (CAS # 109-52-4)
   d. **Skin Sensitization:** Isoamyl acetate (CAS # 123-92-2)
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

3-Methylbutyl valerate is reported to occur in the following foods*:

Apple fresh (*Malus species*)	Rum
Banana (*Musa sapientum L.*)	Sea buckthorn (*Hippophaë rhamnoides L.*)
Black choke berry (*Aronia melanocarpa Ell.*)	Tea
Capsicum species	Tomato (*Lycopersicon esculentum Mill.*)
Cider (apple wine)	Trassi (cooked)
Grape brandy	Whisky
Guava and feyoa	Wine
Mastic (*Pistacia lentiscus*)	

*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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 3/15/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3-methylbutyl valerate does not present a concern for genotoxicity.

10.1.2. Risk assessment

3-Methylbutyl valerate was assessed in the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). There are no studies assessing the mutagenic activity of 3-methylbutyl valerate however, read across can be made to isoamyl butyrate (CAS # 106-27-4; see Section 5). The mutagenic activity of isoamyl butyrate (CAS # 106-27-4) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strains WP2uvrA were treated with isoamyl butyrate in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015). Under the conditions of the study, isoamyl butyrate was not mutagenic in the Ames test.

The clastogenicity of read across analogue isoamyl butyrate was assessed in an *in vitro* chromosome aberration study. Chinese hamster lung cells were treated with isoamyl butyrate in DMSO at concentrations up to 2 mg/mL in the absence of exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, without S9 metabolic activation (Ishidate et al., 1984). Under the conditions of the study, isoamyl butyrate was considered to be non-clastogenic to in the *in vitro* chromosome aberration assay.

Due to lack of additional clastogenicity data in the presence of metabolic activation, read across can be made while considering 3-methylbutyl valerate will readily hydrolyze into isoamyl alcohol (CAS # 123-51-3; see section 5) and valeric acid (CAS # 109-52-4; see section 5). Metabolite, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient genotoxicity data. The clastogenic activity of isoamyl alcohol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral route, to groups of male and female NMRI mice (5/sex/dose). Doses of 500, 1000, and 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 or 48 h, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007). The clastogenic activity of valeric acid was also evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via intraperitoneal injection, to groups of male and female Swiss Webster mice (5/sex/dose). Doses of 83, 166, or 266 mg/kg were administered. Mice from each dose level were euthanized at 24, 48 and 72 h, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA REACH dossier: Valeric acid,; accessed 09/30/2016). Under the conditions of the study, valeric acid was considered to be not clastogenic in the *in vivo* micronucleus test. Under the conditions of the study, isoamyl alcohol and valeric acid were considered to be non clastogenic in the *in vivo* micronucleus test, which can be extended to 3-methylbutyl valerate based on metabolism.

Based on the data available, isoamyl butyrate and isoamyl

alcohol do not present a concern for genotoxic potential and this can be extended to 3-methylbutyl valerate.

Additional References: Kuroda et al., 1984.

Literature Search and Risk Assessment Completed on: 06/24/2016.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on 3-methylbutyl valerate. 3-Methylbutyl valerate will hydrolyze readily into isoamyl alcohol (CAS # 123-51-3; see section 5) and valeric (pentanoic) acid (CAS # 109-52-4; see section 5). Metabolite, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient repeated dose toxicity data. A gavage OECD 422 combined repeated dose toxicity study was conducted on a group of 12 male and female Sprague-Dawley rats/group that were administered test material isoamyl alcohol via gavage at doses of 0, 30, 100 and 300 mg/kg/day, an additional satellite recovery group of 5 animals/sex/group were administered the test material at doses of 0 and 300 mg/kg/day. The NOAEL was determined to be 100 mg/kg/day, based on reduced body weight gain in the males (ECHA REACH Dossier: 3-methylbutan-1-ol, accessed 07/09/14). In another study, an OECD/GLP 408 study was conducted on a group of 10 SPF-Wistar, Chbb:THOM rats/sex/group administered test material, isoamyl alcohol via drinking water at concentrations of 0, 1000 ppm (about 80 mg/kg/day), 4000 ppm (about 340 mg/kg/day) & 16,000 ppm (about 1250 mg/kg/day). Although there were slight alterations in the hematological parameters, the NOAEL was determined to be 16,000 ppm or 1250 mg/kg/day, the highest dose tested, since the effects were not considered to be treatment related (Schilling et al.,1997, data also available in RIFM, 1991). In another study, a group of 15 rats/sex/group were gavaged with the test material isoamyl alcohol at doses of 0, 150, 500 and 1000 mg/kg/day for 17 weeks. There were no adverse effects reported due to the test material administration up to the highest dose tested. Thus, the NOAEL was determined to be 1000 mg/kg/day (Carpanini et al., 1973). There are no repeated dose toxicity data on the metabolite, n-pentanoic acid, that can be used to support the repeated dose toxicity endpoint. Since no adverse effects were reported among the animals during the 13 and 17 week studies, the NOAEL was determined to be 1250 mg/kg/day. **Therefore, the MOE can be calculated by dividing the isoamyl alcohol NOAEL by the total systemic exposure, 1250/0.0008 or 1562500.**

In addition, the total systemic exposure for 3-methylbutyl valerate (0.80 μg/kg/day) is below the TTC (30 μg/kg/day) for the repeated dose toxicity endpoint at the current level of use.

Additional References: ECHA REACH Dossier: 3-Methylbutan-1-ol; RIFM, 1992; ECHA REACH Dossier valeric acid.

Literature Search and Risk Assessment Completed on: 6/23/2016.

10.1.5. Developmental and reproductive toxicity

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

10.1.6. Risk assessment

There are no developmental toxicity data on 3-methylbutyl valerate. 3-Methylbutyl valerate will hydrolyze readily into isoamyl alcohol (CAS # 123-51-3; see section 5) and valeric (pentanoic) acid (CAS # 109-52-4; see section 5). Metabolite, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient developmental toxicity data. There is an OECD 414 developmental toxicity study conducted on 15 female pregnant Himalayan rabbits/dose group administered the test material isoamyl alcohol via inhalation at doses of 0, 0.5, 2.5 and 10 mg/L equivalent to 0, 68, 341 and 1365 mg/kg/day, respectively, according to standard minute volume and body weight parameters of New Zealand rabbits. The NOAEL for developmental toxicity was determined to be 10 mg/l or 1365 mg/kg/day the highest dose tested (RIFM, 1990b). In another study, an OECD 414 developmental toxicity study was conducted on a group of 25 female pregnant Wistar rats/group which were administered the test material isoamyl alcohol at doses of 0, 0.5, 2.5 and 10 mg/L, equivalent to 0, 135, 674 and 2695 mg/kg/day according to standard minute volume and body weight parameters of Wistar rats. The NOAEL for developmental toxicity was determined to be 10 mg/L or 2695 mg/kg/day the highest dose tested (RIFM, 1990a). Subsequently, an OECD 422 gavage combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test was conducted on a group of 12 Sprague-Dawley rats/sex/group which were administered the test material isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity on the development of the fetus up to the highest dose tested (ECHA REACH Dossier: 3-Methylbutan-1-ol). Thus, the NOAEL was determined to be 300 mg/kg/day, the highest dose tested. In addition, a developmental toxicity study was conducted in rats administering metabolite valeric (pentanoic) acid (CAS # 109-52-4; see section 5) at doses of 50, 100 or 200 mg/kg/day. There were developmental effects and significant maternal toxicity at all doses. A NOAEL for developmental toxicity was determined to be 50 mg/kg/day (Narotsky et al., 1994)*. However in another study, a group of 22 pregnant rats were administered test material n-pentanoic acid from GD 6–15 at doses of 0 and 750 mg/kg/day. There were no signs of adverse developmental toxicity reported among the treated animals even in the presence of maternal toxicity reported as gross pathological alterations in the stomach and renal pelvis. There was also a decrease in maternal body weight and clinical signs reported among the treated females (ECHA REACH Dossier Valeric acid, accessed on 7/5/2016). The most conservative NOAEL of 300 mg/kg/day was selected for the developmental toxicity endpoint.

There are no reproductive toxicity data on 3-methylbutyl valerate. Metabolite, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient reproductive toxicity data. An OECD 422 gavage combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test was conducted on a group of 12 Sprague-Dawley rats/sex/group which were administered the test material isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity towards the reproductive performance of the parental generation animals up to the highest dose tested (ECHA REACH Dossier: 3-Methylbutan-1-ol). The NOAEL for reproductive toxicity was determined to be 300 mg/kg/day, the highest dose tested. There are no reproductive toxicity data on metabolite n-pentanoic acid that can be used to support the reproductive toxicity endpoint.

Therefore, the MOE for the developmental and reproductive toxicity can be calculated by dividing the isoamyl alcohol NOAEL by the total systemic exposure, 300/0.0008 or 375000.

In addition, the total systemic exposure for 3-methylbutyl valerate (0.80 μg/kg/day) is below the TTC (30 μg/kg/day) at the current level of use for the developmental and reproductive toxicity endpoint.

* The Expert Panel for Fragrance Safety reviewed the available

data from the (Narotsky et al., 1994) manuscript and considered the study to be of limited regulatory value due to the inadequate study description. The Expert Panel agreed the study has no influence towards deriving an adequate NOAEL for the developmental toxicity endpoint.

Additional References: ECHA REACH Dossier Valeric acid.

Literature Search and Risk Assessment Completed on: 6/23/2016.

10.1.7. Skin sensitization

Based on read across to isoamyl acetate (CAS # 123-92-2), 3-methylbutyl valerate does not present a concern for skin sensitization.

10.1.8. Risk assessment

No skin sensitization studies are available for 3-methylbutyl valerate. Based on the existing data on read across material isoamyl acetate (CAS # 123-92-2; see Section 5), 3-methylbutyl valerate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In a guinea pig maximization test, a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne et al., 1986). Similarly, read across material isoamyl acetate was found to be negative in the guinea pig Open Epicutaneous Test (OET) (Klecak, 1979, 1985). In a human maximization test, no skin sensitization reactions were observed with 8% (5520 μg/cm2) isoamyl acetate (RIFM, 1973). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 20% or 23622 μg/cm2 isoamyl acetate in 75:25 Ethanol:DEP, no reactions indicative of sensitization was observed in any of the 197 volunteers (RIFM, 1987). Based on read across to isoamyl acetate, 3-methylbutyl valerate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/11/16.

10.1.9. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 3-methylbutyl valerate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for 3-methylbutyl valerate in experimental models. UV/Vis absorption spectra indicate no significant absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, 3-methylbutyl valerate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/30/16.

10.1.11. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3-methylbutyl valerate, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on 3-methylbutyl valerate. Based on the Creme RIFM model, the inhalation exposure is 0.049 mg/day. This exposure is 28.6 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/12/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3-methylbutyl valerate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 3-methylbutyl valerate 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 EPISUITE ver 4.1 did not identify 3-methylbutyl valerate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver 4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3-methylbutyl valerate does not present a risk to the aquatic compartment in the screening level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.3. Other available data

3-Methylbutyl valerate has been pre-registered for REACH with no additional information at this time.

10.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	7.118 mg/L			1,000,000	0.007118 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.74	3.74
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	Not reported
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 0.007118 µg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 6/20/2016.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.06.007.

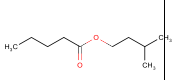
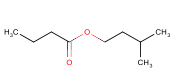
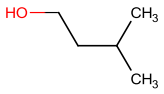
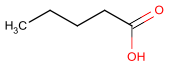
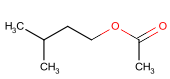
Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.06.007.

Appendix

Methods

- The identified read-across analogues were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of target and analogues were calculated using EPI SuiteTM v4.11 developed by US EPA (USEPA, 2012).
- J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogues were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Strategies on finding and using read across are found in Schultz et al. (2015).

	Target material	Read across material			
Principal Name	3-Methylbutyl valerate	Isoamyl butyrate	Isoamyl alcohol	Valeric acid	Isoamyl acetate
CAS No.	2050-09-1	106-27-4	123-51-3	109-52-4	123-92-2
Structure					
Similarity (Tanimoto score)		0.80	0.47	N/A[a]	0.72
Read across endpoint		• Genotoxicity	• Genotoxicity, • Repeated dose, • Developmental and reproductive	• Genotoxicity, • Repeated dose, • Developmental and reproductive	• Skin sensitization
Molecular Formula	$C_{10}H_{20}O_2$	$C_9H_{18}O_2$	$C_5H_{12}O$	$C_5H_{10}O_2$	$C_7H_{14}O_2$

	Target material	Read across material			
Molecular Weight	172.27	158.24	88.15	102.13	130.19
Melting Point (°C, EPISUITE)	-20.47	-32.06	-61.49	14.76	-56.05
Boiling Point (°C, EPISUITE)	198.83	178.41	123.17	187.75	134.87
Vapor Pressure (Pa @ 25°C, EPISUITE)	51	135	512	95.6	756
Log Kow (KOWWIN v1.68 in EPISUITE)	3.74	3.25	1.16	1.39	2.25
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in	38.59	117.8	4.158e+004	1.86e+004	1100

	Target material	Read across material			
EPISUITE)					
J_{max} (mg/cm^2/h, SAM)	4.488616	11.16992	1142.301	517.2594	55.89014
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.29E+002	9.73E+001	1.34E+000	1.30E-001	5.52E+001
	Genotoxicity				
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	• No alert found	• No alert found	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	• No alert found	• No alert found	

	Target material	Read across material			
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found	• No alert found	
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	• No alert found	• No alert found	
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	• Not classified	• Not classified	
	Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	• Carboxylic acids (Hepatotoxicity) No	

(***continued***).

	Target material	Read across material			
				rank	
	Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder, non cyclic structure		• Non binder, non cyclic structure	• Non binder, non cyclic structure	
Developmental Toxicity Model by CAESAR v2.1.6	• NON-Toxicant (low reliability)		• Toxicant (good reliability)	• Toxicant (good reliability)	
	Sensitization				
Protein binding by OASIS v1.1	• No alert found				• No alert found
Protein binding by OECD	• No alert found				• No alert found

	Target material	Read across material			
Protein binding potency	• Not possible to classify according to these rules (GSH)				• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found				• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)				• Sensitizer (good reliability)
	Metabolism				
OECD QSAR Toolbox (3.4)	See Supplemental Data 1 • 8 metabolites from	See Supplemental Data 2 • 8 metabolites from	See Supplemental Data 3 • 8 metabolites from	See Supplemental Data 4 • 4 metabolites from	See Supplemental Data 5 • 5 metabolites from

	Target material	Read across material			
Rat liver S9 metabolism simulator	Rat S9 simulator. • Aldehydes, anionic surfactants, esters, Schiff base formation.	Rat S9 simulator. • Aldehydes, anionic surfactants, esters, Schiff base formation.	Rat S9 simulator. • Aldehydes, Schiff base formation.	Rat S9 simulator. Aldehydes, anionic surfactants, Schiff base formation.	Rat S9 simulator. Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.

(***continued***).

Summary

There are insufficient toxicity data on 3-methylbutyl valerate (CAS # 2050-09-1). Hence *in-silico* evaluation was conducted by determining suitable read across analogues for this material. Based on structural similarity, reactivity, metabolism data, physico-chemical properties and expert judgment, suitable analogues isoamyl butyrate (CAS # 106-27-4), isoamyl alcohol (CAS # 123-51-3), valeric acid (CAS # 109-52-4), and isoamyl acetate (CAS # 123-92-2) were identified as read across materials with data for their respective toxicity endpoints.

12. Conclusion/rationale

- Isoamyl butyrate (CAS # 106-27-4) could be used as a structurally similar read across analogue for the target material 3-methylbutyl valerate (CAS # 2050-09-1) for the genotoxocity endpoint.
  - The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - The key difference between the target substance and the read across analogue is that the target has a longer straight chain alkane on the acid portion (valerate) while the read across has a shorter straight chain alkane on the acid portion (butyrate). The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analogue have a Tanimoto score as mentioned in the table above. The Tanimoto score is mainly driven by the alkane chain fragment on the acid portion. The differences in the structure which are responsible for the Tanimoto score <1 are not relevant from a toxicity endpoint perspective.
  - The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the genotoxicity endpoint.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for the genotoxicity endpoint are consistent between the target substance and the read across analogue as seen in the table above.
  - The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
  - The structural alerts for the genotoxicity endpoint are consistent between the metabolites of the read across analogue and the target substance.
  - The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.
- Metabolism

The target substance 3-methylbutyl valerate (CAS # 2050-09-1) metabolically hydrolyzes to isoamyl alcohol (CAS # 123-51-3) and valeric acid (CAS # 109-52-4) as described under the human health endpoint repeated dose toxicity. In addition, metabolism of the read across material isoamyl alcohol (CAS # 123-51-3) and valeric acid (CAS # 109-52-4) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (See Appendix). 3-Methylbutyl valerate (CAS # 2050-09-1) is predicted to metabolize to isoamyl alcohol and valeric acid in the first step with 0.95 pre-calculated probability. Hence isoamyl alcohol and valeric acid can be use as read across for 3-methylbutyl valerate. Isoamyl alcohol and valeric acid were out of domain for the *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.

- Isoamyl alcohol (CAS # 123-51-3) and valeric acid (CAS # 109-52-4) are used as a structurally similar read across analogue for 3-methylbutyl valerate (CAS # 2050-09-1) for the genotoxicity, repeated dose, developmental, and reproductive toxicological endpoints.
  - The read across materials are major metabolites of the target substance.
  - The target substance is an ester formed by the read across analogue alcohol and read across analogue acid.
  - The structural difference in the target substance and the read across analogues can be mitigated by the fact that the target could be metabolically hydrolyzed to the read across analogues used here. Therefore, the toxicity profile of the target is expected to be that of metabolites.
  - The target substance and the read across analogues have different physical chemical properties. The physical chemical properties mainly affect the absorption of the target substance through skin or cell membrane. The read across analogues used here are metabolites of the target substance and will only be produced post-absorption of the target substance. Any differences in the physical chemical properties of the target substance and the read across analogue are deemed to be toxicologically insignificant for the genotoxicity, repeated dose, developmental, and reproductive toxicological endpoints.
  - OECD Toolbox (V3.4) shows a Repeated dose (HESS) categorization alert for valeric acid and CAESAR model (V2.1.6) shows a Developmental toxicity toxicant alert for isoamyl alcohol as well as valeric acid, both alerts were not seen for the target. These alerts show that the read across may have increased *in vivo* reactivity and supports the use as read across for the target.
- Isoamyl acetate (CAS # 123-92-2) could be used as a structurally similar read across analogue for the target material 3-methylbutyl valerate (CAS # 2050-09-1) for the skin sensitization endpoint.
  - The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - The key difference between the target substance and the read across analogue is that the target has a longer straight chain alkane on the acid portion (valerate) while the read across has a shorter straight chain alkane on the acid portion (acetate). The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analogue have a Tanimoto score as mentioned in the table abive. The Tanimoto score is mainly driven by the alkane chain fragment on the acid portion. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicity endpoint perspective.
  - The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the skin sensitization endpoint.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for skin sensitization endpoints are consistent between the

target substance and the read across analogue as seen in the table above.
- The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
- The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read across analogue and the target substance.
- The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

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