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Short Review

RIFM fragrance ingredient safety assessment, 3-methylbutyraldehyde, CAS Registry Number 590-86-3

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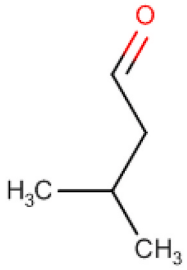

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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

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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.

3-Methylbutyraldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog n-pentanal (CAS # 110-62-3) show that 3-methylbutyraldehyde is not expected to be genotoxic. Data on read-across material isobutyraldehyde (CAS # 78-84-2) provide a calculated margin of exposure (MOE) > 100 for the repeated dose, reproductive, and local respiratory toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3-methylbutyraldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-methylbutyraldehyde was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Isovaleraldehyde; ECHA, 2011b)
Repeated Dose Toxicity: NOAEL = 1310 mg/kg/day.	NTP (1999)
Reproductive Toxicity: Developmental toxicity: 2937 mg/kg/day; Fertility: 2586 mg/kg/day.	(ECHA REACH Dossier: Isobutyraldehyde; ECHA, 2011a; NTP, 1999)
Skin Sensitization: Not a concern for skin sensitization at current, declared use levels; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 147.44 mg/m^3.	(Abdo et al., 1998)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 49.5% (OECD 301 D)	(ECHA REACH Dossier: Isovaleraldehyde; ECHA, 2011b)
Bioaccumulation: Screening-level: 3.028 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 543.3 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: 543.3 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.5433 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level.

1. Identification

1. **Chemical Name:** 3-Methylbutyraldehyde
2. **CAS Registry Number:** 590-86-3
3. **Synonyms:** Butanal, 3-methyl-; Isoamyl aldehyde; Isopentaldehyde; Isovaleraldehyde; Isovaleral; Isovaleric aldehyde; 3-Methylbutanal; 3-Methyl-1-butanal; Isoamylaldehyde; Isopentanal; アルカナール(C = 4 ~ 19); 3-Methylbutyraldehyde
4. **Molecular Formula:** $C_5H_{10}O$
5. **Molecular Weight:** 86.13
6. **RIFM Number:** 1147
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 95 °C at 760 mm Hg (Bedoukian), 94.52 °C (EPI Suite)
2. **Flash Point:** 1 °C (Globally Harmonized System), <40 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 1.23 (Biobyte Corp.), 1.23 (EPI Suite)
4. **Melting Point**: 79.26 °C (EPI Suite)
5. **Water Solubility:** 11230 mg/L (EPI Suite)
6. **Specific Gravity:** 0.8043 (RIFM), 0.80±0.01 (Bedoukian)
7. **Vapor Pressure:** 39.8 mm Hg at 20 °C (EPI Suite v4.0), 29 mm Hg at 20 °C (FMA), 51.6 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless mobile liquid. Very powerful, penetrating, acrid-pungent odor, causing cough-reflexes unless highly diluted. In extreme dilution, the odor becomes fruity, rather pleasant, and the flavor is peach-like, heavy-fruity below 10 ppm (Arctander, 1969)

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000052% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000066 mg/kg/day or 0.0048 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and 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

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

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Valeraldehyde (n-pentanal; CAS # 110-62-3)
   b. **Repeated Dose Toxicity:** Isobutyraldehyde (CAS # 78-84-2)
   c. **Reproductive Toxicity:** Isobutyraldehyde (CAS # 78-84-2)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Isobutyraldehyde (CAS # 78-84-2)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

3-Methylbutyraldehyde is reported to occur in the following foods by the VCF*:

Beer	Maize (*Zea mays* L.)
Peanut (*Arachis hypogaea* L.)	Whiskey
Tea	Tomato (*Lycopersicon esculentum* Mill.)
Truffle	Cocoa Category
Wine	Honey

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH Dossier

Available; accessed 01/02/20 (ECHA, 2011b).

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, 3-methylbutyraldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3-Methylbutyraldehyde has been evaluated in 2 separate Ames study that were not conducted according to OECD guidelines. These studies also used a limited number of strains and were concluded to be negative for mutagenicity (ECHA, 2011b). There are limited studies assessing the mutagenic activity of 3-methylbutyraldehyde; however, read-across can be made to n-pentanal (CAS # 110-62-3; see Section VI). The mutagenic activity of n-pentanal has been evaluated in a bacterial reverse mutation assay conducted in accordance with OECD TG 471 using the standard preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535 were treated with 3-methylbutyraldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 2000 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, 2011b). Under the conditions of the study, n-pentanal was not mutagenic in the Ames test, and this can be extended to 3-methylbutyraldehyde.

The clastogenic activity of 3-methylbutyraldehyde 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 DMSO intraperitoneally to groups of male NMRI mice. Doses of 25, 50, and 100 mg/kg body weight were administered. Mice from each dose level were euthanized after 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011b). Under the conditions of the study, 3-methylbutyraldehyde was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 3-methylbutyraldehyde does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/23/20.

11.1.2. Repeated dose toxicity

The MOE for 3-methylbutyraldehyde is sufficient for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-methylbutyraldehyde. Read-across material isobutyraldehyde (CAS # 78-84-2, see Section VI) has sufficient repeated dose toxicity data.

Isobutyraldehyde was evaluated for repeated dose systemic toxicity in NTP 13-week and 105-week studies on groups of 10–50 F344N strain rats/sex/dose and 10–50 B6C3F1 mice strain mice/sex/dose. In the 13-week study, 10 animals/sex/dose of both species were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm (equivalent to 0, 655, 1310, 2621, 5242, and 10484 mg/kg/day, respectively) through inhalation (6 h and 12 min per day, 5 days per week). Mortality was observed in both sexes of both species at ≥4000 ppm when exposed for 13 weeks. No other systemic adverse effects were observed up to 2000 ppm in either sex of either species. Based on these results, in the carcinogenicity study, 50 animals/sex/dose of both species were exposed to isobutyraldehyde by whole-body inhalation at concentrations of 0, 500, 1000, or 2000 ppm (equivalent to 0, 655, 1310, and 2621 mg/kg/day, respectively) for 105 weeks (6 h and 12 min per day, 5 days per week). No systemic adverse effects were observed up to 2000 ppm in either sex of either species during the 105-week exposure period except decreased body weight in female mice at 2000 ppm. Hence, the mid dose (1000 ppm; 1310 mg/kg/day) from the 2-year carcinogenicity study in mice was considered to be the systemic No Observed Adverse Effect Level (NOAEL) based on decreased average body weight at the high dose (2000 ppm; 2620 mg/kg/day) (NTP, 1999).

The most conservative NOAEL of 1310 mg/kg/day, based on the 105-week study on mice, was considered for risk assessment of the repeated dose toxicity endpoint.

Therefore, the 3-methylbutyraldehyde MOE can be calculated by dividing the isobutyraldehyde NOAEL in mg/kg/day by the total systemic exposure to 3-methylbutyraldehyde, 1310/0.00014, or 9357142.

In addition, the total systemic exposure to 3-methylbutyraldehyde (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Abdo et al., 1998.

Literature Search and Risk Assessment Completed On: 01/24/20.

11.1.3. Reproductive toxicity

The MOE for 3-methylbutyraldehyde is sufficient for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 3-methylbutyraldehyde. Read-across material isobutyraldehyde (CAS # 78-84-2, see Section VI) has sufficient reproductive toxicity data.

There are sufficient developmental toxicity and fertility data on isobutyraldehyde. In an OECD TG 414 and GLP-compliant prenatal developmental toxicity study, a group of 25 Wistar rats/sex/dose were exposed through inhalation (whole-body exposure) with isobutyraldehyde at concentrations of 0, 3, 7.6, and 12 mg/L (equivalent to 0, 734.4, 1860, and 2937 mg/kg/day, respectively) for 6 h/day through gestational day (GDs) 6–15. No treatment-related adverse effects were reported for conception rate, pre-and post-implantation loss, viability, number of corpora lutea, number of implantation sites, external examination, fetal weight, visceral observations, and skeletal observations in fetuses. Therefore, the NOAEL for developmental toxicity was considered to be 2937 mg/kg/day based on the absence of adverse developmental effects up to the highest tested dose (ECHA, 2011a).

In an NTP 13-week repeated dose toxicity study, a group of 10 F344N strain rats/sex/dose were exposed with isobutyraldehyde at concentrations of 0, 500, 1000, 2000, and 4000 ppm through inhalation (equivalent to 433, 866, 1732, and 3464.2 mg/kg/day, respectively) 6 h and 12 min/day, 5 days/week, for 13 weeks. No treatment-related reproductive adverse effects were reported for sperm concentration, sperm motility, sperm density, sperm morphology, weights of right cauda epididymis, and right testis in males and estrous cycle evaluation (di-estrous, pro-estrous, estrous, and met-estrous) in females up to the highest tested dose. Therefore, the NOAEL for fertility was considered to be 3464.2 mg/kg/day (NTP, 1999).

In an NTP 13-week repeated dose toxicity study, a group of 10 B6C3F1 strain mice/sex/group. were exposed with isobutyraldehyde at concentrations of 0, 500, 1000, 2000, and 4000 ppm through inhalation (equivalent to 646.5, 1293, 2586, and 5172 mg/kg/day, respectively) 6 h and 12 min/day, 5 days/week, for 13 weeks. No treatment-related reproductive adverse effects were reported for sperm concentration, sperm motility, sperm density, sperm morphology, weights of right cauda epididymis, and right testis in males and estrous cycle evaluation (di-estrous, pro-estrous, estrous, and met-estrous) in females up to the highest tested dose. Mortality was reported in 9 males and all females at 4000 ppm. Therefore, the NOAEL for fertility was considered to be 2586 mg/kg/day (NTP, 1999).

The NOAEL of 2937 mg/kg/day was considered for risk assessment of developmental toxicity endpoint. The NOAEL of 2586 mg/kg/day in rats was considered for risk assessment of fertility endpoint.

The 3-methylbutyraldehyde MOE for developmental toxicity endpoint can be calculated by dividing the isobutyraldehyde NOAEL in mg/kg/day by the total systemic exposure to 3-methylbutyraldehyde, 2937/0.00014, or 20978571.

The 3-methylbutyraldehyde MOE for fertility endpoint can be calculated by dividing the isobutyraldehyde NOAEL in mg/kg/day by the total systemic exposure to 3-methylbutyraldehyde, 2586/0.00014, or 18471428.

In addition, the total systemic exposure to 3-methylbutyraldehyde (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Abdo et al., 1998.

Literature Search and Risk Assessment Completed On: 01/27/20.

11.1.4. Skin sensitization

Based on the existing data, 3-methylbutyraldehyde is a sensitizer. However, based on the application of DST, 3-methylbutyraldehyde does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 3-methylbutyraldehyde. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a human

maximization test, no skin sensitization reactions were observed at 1% (690 μg/cm^2) in petrolatum (RIFM, 1980). The positive reaction observed in the human maximization test suggests that 3-methylbutyraldehyde is a sensitizer. However, limited data exist to derive a NESIL. Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 3-methylbutyraldehyde that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/26/19.

Table 1
Maximum acceptable concentrations for 3-methylbutyraldehyde that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	0.0010%
2	Products applied to the axillae	0.0015%	5.0×10^{-4}%
3	Products applied to the face using fingertips	0.029%	1.3×10^{-4}%
4	Fine fragrance products	0.027%	5.2×10^{-5}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	0.0041%
6	Products with oral and lip exposure	0.016%	0.0010%
7	Products applied to the hair with some hand contact	0.056%	0.0011%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	8.6×10^{-4}%
10	Household care products with mostly hand contact	0.19%	0.011%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	0.33%

Note.
[b]No reported use.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-methylbutyraldehyde in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 3-methylbutyraldehyde does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/13/20.

11.1.6. Local respiratory toxicity

There are insufficient inhalation data available on 3-methylbutyraldehyde; however, in a 2-year inhalation study for the read-across analog isobutyraldehyde (CAS # 78-84-2; see Section VI), a LOAEC of 1474.44 mg/m^3 was reported (Abdo et al., 1998).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. A 2-year carcinogenicity study was carried out in F344/N rats 50/sex/group (Abdo et al., 1998; also available in NTP, 1999). The animals were exposed to isobutyraldehyde via inhalation at 0, 1474.44, 2948.88, and 5897.75 mg/m^3 for 6 h/day, 5 days/week. Treatment-related non-neoplastic lesions were limited to the nose and consisted of respiratory epithelium squamous metaplasia, olfactory epithelium degeneration, and suppurative inflammation. Females were more susceptible to the treatment-related effects pertaining to minimal to mild squamous metaplasia, which was observed to be significantly greater in males and females from the 2948.88 and 5897.75 mg/m^3 groups and in females from the 1474.44 mg/m^3 group as compared to chamber controls. All other local effects were observed in the animals from mid- and high-exposure groups. Considering the local respiratory effects observed, a LOAEC was identified at 1474.44 mg/m^3. Therefore, by using a safety factor of 10, the NOAEC is estimated to be 147.44 mg/m^3.

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

- (147.44 mg/m^3) × (1m^3/1000 L) = 0.14744 mg/L
- Minute ventilation (MV) of 0.17 L/min for a F344/N rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.14744 mg/L) × (61.2 L/d) = 9.023 mg/day
- (9.023 mg/day)/(0.0016 kg lung weight of rat*) = 5639.4 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0048 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015a). 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 0.0074 mg/kg lung weight/day resulting in an MOE of 762081 (i.e., [5639.4 mg/kg lung weight of rat/day]/[0.0074 mg/kg lung weight of human/day]) (Abdo et al.,

1998; NTP, 1999).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0048 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: Steinhagen and Barrow, 1984; Salem and Cullumbine, 1960; Carpenter et al., 1974; Safronkina (1983).

Literature Search and Risk Assessment Completed On: 01/24/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-methylbutyraldehyde 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 Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-methylbutyraldehyde was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US ECHA, 2012a) identified 3-methylbutyraldehyde as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 3-methylbutyraldehyde presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 3-Methylbutyraldehyde has been registered for REACH with the following additional information available (ECHA, 2011b):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 49.5% was observed after 28 days.

The acute fish (Fathead minnow) toxicity test was conducted according to the OECD 203 guidelines under flow-through conditions. The 96-h LC50 value based on the mean measured concentration was reported to be 3.25 mg/L (95% CI: 2.98–3.54 mg/L).

The acute toxicity test to algae was conducted according to the German Industrial DIN 38412, part 9, under static conditions. The 72-h EC50 value based on the nominal test concentration for growth rate was reported to be 112.78 mg/L (95% CI: 51.2–248.8 mg/L).

11.2.3. Risk assessment refinement

Since 3-methylbutyraldehyde 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	1.23	1.23
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
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 0.5433 μg/L. The revised PEC/PNECs for EU (No VoU) and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/14/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	543.3			1000000	0.5433	

- **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 05/31/20.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112293.

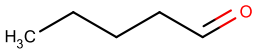
Appendix

Read-across Justification

Methods

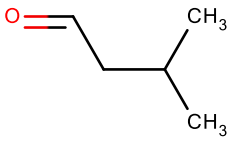
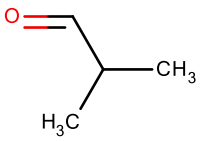
The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity, as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM) (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).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	3-Methylbutyraldehyde	Valeraldehyde	Isobutyraldehyde
CAS No.	590-86-3	110-62-3	78-84-2
Structure			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
			
Similarity (Tanimoto Score)		0.29	0.61
Endpoint		• Genotoxicity	• Local respiratory toxicity • Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_5H_{10}O$	$C_5H_{10}O$	C_4H_8O
Molecular Weight	86.13	86.13	72.11
Melting Point (°C, EPI Suite)	−51.00	−91.50	−65.90
Boiling Point (°C, EPI Suite)	92.50	103.00	64.50
Vapor Pressure (Pa @ 25 °C, EPI Suite)	6666.10	4386.29	23064.71
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	14000.00	11700.00	89000.00
Log K_{OW}	1.23	1.31	0.74
Jmax (μg/cm^2/h, SAM)	451.08	426.19	1875.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	41.04	14.89	18.24
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
In Vitro Mutagenicity (Ames, ISS)	Simple aldehyde	Simple aldehyde	
In Vivo Mutagenicity (Micronucleus, ISS)	Simple aldehyde	Simple aldehyde	
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized		Not categorized
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)		Toxicant (low reliability)
Local Respiratory Toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	No alert found		No alert found
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 3-methylbutyraldehyde (CAS # 590-86-3). 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, isobutyraldehyde (CAS # 78-84-2) was identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Valeraldehyde (CAS # 110-62-3) was used as a read-across analog for the target material 3-methylbutyraldehyde (CAS # 590-86-3) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of saturated aldehydes.
  - o The key difference between the target material and the read-across analog is that the target material has a 1-carbon shorter chain compared to the read-across analog. Moreover, the target material has a methyl substituent at 3rd position, whereas there is no branching in the read-across analog. These structural differences are toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog each have an alert for Schiff base formation by DNA Binding (OECD QSAR Toolbox v4.2). This alert is due to the ability of aliphatic aldehydes to undergo a Schiff base-forming reaction with primary amines. However, the read-across analog (valeraldehyde) was not mutagenic in the Ames test. Thus, based on the current existing data, 3-methylbutyraldehyde does not present a concern for genotoxicity. Therefore, the alert will be superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

- Isobutyraldehyde (CAS # 78-84-2) was used as a read-across analog for the target material 3-methylbutyraldehyde (CAS # 590-86-3) for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of branched saturated aldehydes.
  - The target material and the read-across analog share an aldehyde functional group within a branched saturated aliphatic chain.
  - The key difference between the target material and the read-across analog is that the target material has a 1-carbon longer chain compared to the read-across analog. 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.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog do not have a toxicological alert for local respiratory toxicity.
  - The target material and the read-across analog each have an alert for being a toxicant with low reliability by the CAESAR model for developmental toxicity. The data for the read-across analog confirms that the MOE is adequate at the current level of use. Therefore, the alert will be 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.

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