Food and Chemical Toxicology 130 (2019) 110587

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

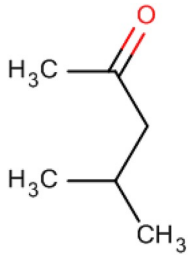
Short Review

RIFM fragrance ingredient safety assessment, 4-methyl-2-pentanone, CAS Registry Number 108-10-1

A.M. Api[a], D. Belsito[b], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], L. Jones[a], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Version: 112018. This version replaces any previous versions.
Name: 4-Methyl-2-pentanone
CAS Registry Number: 108-10-1



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., 2015, 2017) compared to a deterministic aggregate approach

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2019.110587
Received 21 November 2018; Received in revised form 16 May 2019; Accepted 14 June 2019
Available online 17 June 2019

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
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
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.
4-Methyl-2-pentanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4-methyl-2-pentanone is not genotoxic and provided an MOE > 100 for the repeated dose, reproductive, and local respiratory toxicity endpoints. Data show that there are no safety concerns for 4-methyl-2-pentanone for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 4-methyl-2-pentanone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-methyl-2-pentanone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (O'Donoghue et al., 1988)
Repeated Dose Toxicity: NOAEL = 862 mg/kg/day. (National Toxicology Program, 2005)
Reproductive Toxicity: Developmental: NOAEL = 1187 mg/kg/day; Fertility: NOAEL = 2120 mg/kg/day. (Tyl et al., 1987; Nemec et al., 2004)
Skin Sensitization: No safety concerns under the current, declared levels of use. (ECHA Dossier: 4-methylpentan-2-one; ECHA, 2011)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOEC = 205 mg/m^3. (Phillips et al., 1987)

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 83% (OECD 301F) (ECHA Dossier: 4-methylpentan-2-one; ECHA, 2011)
Bioaccumulation: Screening-level: 3.39 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 726.9 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: 726.9 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.7269 µg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 4-Methyl-2-pentanone
2. **CAS Registry Number:** 108-10-1
3. **Synonyms:** Hexone; Isobutyl methyl ketone; Isohexanone; Isopropylacetone; Methyl isobutyl ketone; MIBK; 2-Pentanone, 4-methyl-; 4-Methyl-2-oxopentane; 4-Methylpentan-2-one; 4-Methyl-2-pentanone
4. **Molecular Formula:** $C_6H_{12}O$
5. **Molecular Weight:** 100.16
6. **RIFM Number:** 6105
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 117 °C (FMA Database), 104.57 °C (EPI Suite)
2. **Flash Point:** 18 °C (GHS), 75 °F; CC (FMA Database)
3. **Log K_{ow}:** 1.16 (EPI Suite)
4. **Melting Point**: 66.73 °C (EPI Suite)
5. **Water Solubility:** 8888 mg/L (EPI Suite)
6. **Specific Gravity:** 0.800 (FMA Database)
7. **Vapor Pressure:** 16.6 mm Hg @ 20 °C (EPI Suite v4.0), 15 mm Hg 20 °C (FMA Database), 21.8 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium sharp, solvent, green, herbal, fruity, dairy, spicy odor and a taste described as green, vegetative, herbal, and fruity with dairy nuances*

*http://www.thegoodscentscompany.com/data/rw1032841.html#toorgano, retrieved 1/12/2018.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000018% (RIFM, 2016)
3. **Inhalation Exposure*:** < 0.00010 mg/kg/day or < 0.00010 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0000011 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 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; Safford et al., 2017; and Comiskey et al., 2017).

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)

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.

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

6. Metabolism

Gingell, 2003, #42755 **and Granvil, 1994**, #22872: Toxicokinetic studies have been performed in male Sprague Dawley rats orally dosed with 4-methyl-2-pentanol (synonym: methyl isobutyl carbinol, MIBC) or 4-methyl-2-pentanone (synonym: methyl isobutyl ketone, MIBK) at 5 mmoL/kg in corn oil (equivalent to approximately 500 mg/kg). MIBC was rapidly and extensively metabolized to MIBK and then subsequently to 4-hydroxy-4-methyl-2-pentanone (CAS # 123-42-2; synonym: diacetone alcohol, HMP). The metabolic scheme for MIBK and MIBC is shown below in Fig. 1 (see Table 1).

Following oral dosing of MIBC or MIBK, absorption was rapid with the C_{max} for both compounds occurring at approximately 0.25–0.5 h post dosing. The half-life for both compounds in blood was short (approximately 2.3 and 2.5 h, respectively). MIBC was not detectable by 9 h following MIBC dosing. Total exposure (based on AUC_{0-12hr}) to MIBK following dosing with either MIBC or MIBK was similar (2.3 and 3.6 mmol h/L, respectively) as was exposure to HMP (10.4 and 13.8 mmol h/L, respectively). Compared to MIBK and HMP, internal exposure to MIBC was minimal, and following dosing with MIBC (0.8 mmol h/L), it represented approximately 6% of the exposure to the 3 compounds over 12 h. Therefore, the internal exposure to MIBC is minimal following MIBC dosing, and oral dosing of MIBC or MIBK results in similar internal exposure to MIBK and HMP. The extent of metabolism of MIBC to MIBK was determined by comparing the combined AUC for MIBK plus HMP, after administration of MIBC, to the combined AUC for these same materials after administration of MIBK. This analysis indicates the proportion of MIBC metabolized through MIBK to HMP is 12.76/17.3, or 73% of the administered dose of 5 mol/kg. As a result of this extensive conversion of MIBC to MIBK, toxicological data obtained on MIBC can be extended to MIBK.

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

4-Methyl-2-pentanone is reported to occur in the following foods by the VCF*:

Apple Brandy (Calvados)
Beef

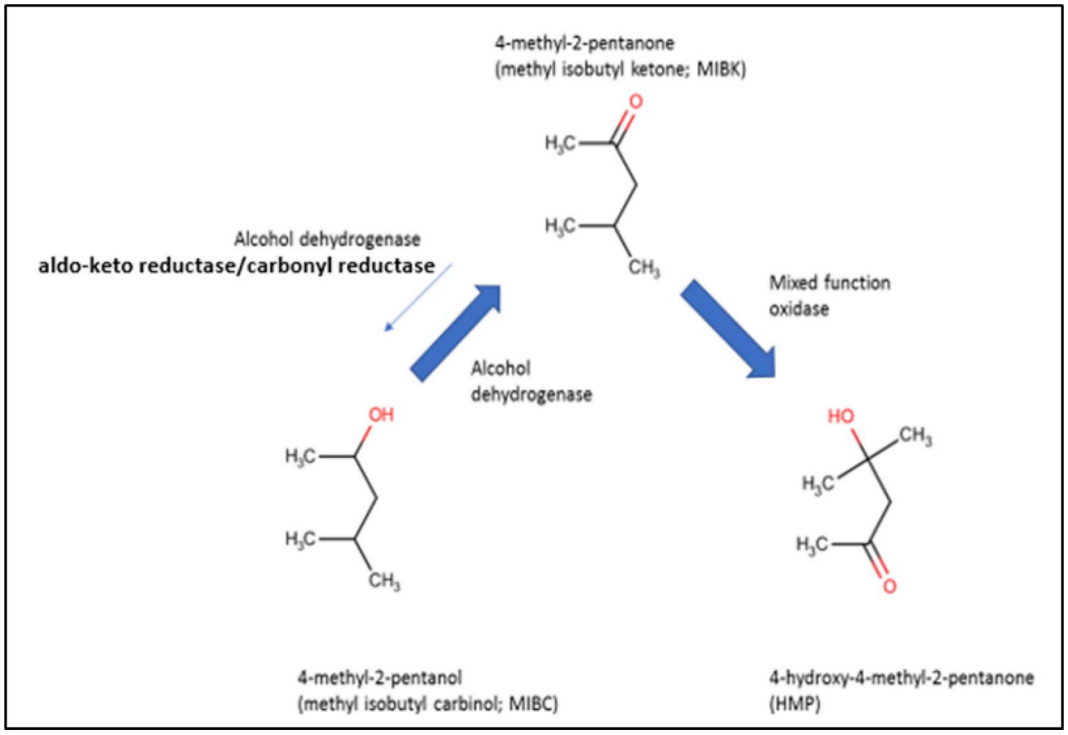


Fig. 1. Plasma levels of MIBC, MIBK, and HMP were determined up to 12 h after oral gavage of MIBK or MIBC (n ≥ 3 blood samples/sampling time). Selected pharmacokinetic parameters are shown below in Table 1.

Table 1
Selected pharmacokinetic parameters after oral administration of MIBK or MIBC.

Test substance	Analyte	C_{max} [mmole/L]	Time of C_{max} [hr]	Half-Life [hr]	AUC_{0-12hr} [mmole*hr/L]	% Total AUC
MIBK	MIBC	0.014	NA	4.657	0.089	0.05
	MIBK	0.644	0.25	2.529	3.558	20
	HMP	2.030	9	4.831	13.756	79
Total AUC					17.436	
MIBC	MIBC	0.588	0.5	2.256	0.819	6
	MIBK	0.450	1.5	1.571	2.268	17
	HMP	1.64	9	3.377	10.408	77
Total AUC					13.495	

Beer
Buckwheat
Cheddar cheese
Cheese, various types
Chestnut (*Castanea* species)
Chicken
Chinese quince (*Pseudocydonia sinensis* Schneid)
Citrus fruits
Clam
Coffee
Crab
Egg
Elderberry (*Sambucus nigra* L.)
Ginger (*Zingiber* species)
Grape (*Vitis* species)
Grape brandy
Guinea hen
Hop (*Humulus lupulus*)
Lamb and Mutton
Malt
Milk and Milk Products
Mushroom
Olive (*Olea europaea*)
Papaya (*Carica papaya* L.)
Plum (*Prunus* species)
Plum brandy
Pork
Potato (*Solanum tuberosum* L.)
Rambutan (*Nephelium lappaceum* L.)
Salvia species
Sesame seed (roasted)
Shrimps (prawn)
Swiss Cheeses
Tea
Trassi (cooked)
Vanilla
Vinegar
Walnut (*Juglans* species)
Wheaten Bread

*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.

8. IFRA standard

None.

9. REACH dossier

Available, accessed 1/12/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 4-methyl-2-pentanone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 4-methyl-2-pentanone has been evaluated in a non-GLP bacterial reverse mutation assay using guidelines similar to OECD TG 471 with the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 4-methyl-2-pentanone in dimethyl sulfoxide (DMSO) at concentrations up to 4 μL/plate (3200 μg/plate). No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (O'Donoghue et al., 1988). Under the conditions of the study, 4-methyl-2-pentanone was not mutagenic in the Ames test. Additionally, 4-methyl-2-pentanone was assessed in a non-GLP mammalian gene mutation assay similar to OECD 476. Mouse lymphoma L5178Y cells were treated with 4-methyl-2-pentanone in DMSO at concentrations up to 4.2 μL/mL for 4 h in the presence and absence of S9 metabolic activation. No toxicologically significant increases in the frequency of mutant colonies were observed in the presence of metabolic activation. Ambiguous results were obtained in the absence of metabolic activation; however, there was no clear dose-dependent response, and increases were only observed at cytotoxic concentrations (O'Donoghue et al., 1988). Based on the results from both mutagenicity assays, 4-methyl-2-pentanone was not considered mutagenic.

The clastogenic activity of 4-methyl-2-pentanone was evaluated in an *in vivo* micronucleus test conducted in a non-GLP study using guidelines similar to OECD TG 474. The test material was administered in corn oil via intraperitoneal injection to groups of male and female CD-1 mice at a dose of 0.73 mL/kg body weight. Mice from each dose level were euthanized at 12, 24, and 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 (O'Donoghue et al., 1988). Under the conditions of the study, 4-methyl-2-pentanone was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 4-methyl-2-pentanone does not present a concern for genotoxic potential.

Additional References: Zeiger et al., 1992; National Toxicology Program, 2005; Brooks et al., 1988; PPG, 1991.

Literature Search and Risk Assessment Completed On: 1/2/2018.

10.1.2. Repeated dose toxicity

The margin of exposure for 4-methyl-2-pentanone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 4-methyl-2-pentanone. 4-Methyl-2-pentanone was administered to groups of 50 F344/N rats or B6C3F1 mice/sex/group at 0, 450, 900, or 1800 ppm by inhalation for 6 h (plus T90: 12 min) per day, 5 days per week, for 104 weeks. The equivalent doses were 0, 431, 862, or 1725 mg/kg/day based on standard minute volume and body weight for F344 rats. For mice, the equivalent doses were 0, 793, 1585, or 3171 mg/kg/day based on standard minute volume and body weight for B6C3F1 mice. Survival among high-dose rats was significantly decreased as compared to controls. The mean body weights of the mid- and high-dose group rats were less than those of the chamber controls after weeks 97 and 89, respectively. The kidney was the primary site of 4-methyl-2-pentanone-related toxicity. Chronic progressive nephropathy (CPN), similar to that which occurs in aged rats, was also reported among all rats (including controls). Although chronic nephropathy is one of the most commonly recognized spontaneous lesions in the rat (Seely et al., 2002), this condition can be exacerbated by chemical exposure (Lock and Hard, 2004). There were treatment-related significant increases in both the incidence and severity of renal tubule hyperplasia and renal tubule adenomas among males, with the incidence in the 1800 ppm group significantly increased compared to the chamber control group. The kidney changes in males were consistent with documented changes of alpha-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992 and Lehman-McKeeman et al., 1990). A NOAEC was not identified by the authors. However, the REACH dossier on 4-methyl-pentan-2-ol (ECHA, 2011) has derived a NOAEC of 450 ppm (equivalent to 862 mg/kg/day) for 4-methylpentanone, which is based on the extensive metabolism of 4-methyl-pentan-2-ol to 4-methylpentanone (as described in the metabolism section) (National Toxicology Program, 2005). For treated mice, there was no effect of treatment on survival. The liver was the site of 4-methyl-pentan-2-ol-related toxicity. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were increased in all exposed groups of males and in 900 and 1800 ppm females. The incidences in the 1800 ppm groups were significantly greater than those in the chamber controls. The incidences of eosinophilic foci were increased in all exposed groups of female mice, and the differences from the chamber controls were significant in the 450 and 1800 ppm groups. The histologic appearance of the hepatocellular proliferative lesions was consistent with commonly observed spontaneous lesions in mice. A NOAEC was not determined in the original study report. The REACH dossier on 4-methylpentan-2-ol (ECHA, 2011) identified a NOAEC of 450 ppm (equivalent to 1585 mg/kg/day) in mice for 4-methylpentanone (as described in the metabolism section), based on liver lesions among treated animals at higher doses (National Toxicology Program, 2005). The NOAEL for 4-methyl-2-pentanol was considered to be 450 ppm or 862 mg/kg/day from the 2-year rat carcinogenicity study on 4-methyl-2-pentanone.

Therefore, the 4-methyl-2-pentanone MOE for repeated dose toxicity can be calculated by dividing the 4-methyl-2-pentanone NOAEL in mg/kg/day by the total systemic exposure to 4-methyl-2-pentanone, 862/0.0000011 or 783636364.

In addition, the total systemic exposure for 4-methyl-2-pentanone (0.0011 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/05/2018.

10.1.3. Reproductive toxicity

The margin of exposure for 4-methyl-2-pentanone is adequate for the developmental and fertility toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 4-methyl-2-pentanone. 4-Methyl-2-pentanone (methyl isobutyl ketone, MIBK) has a GLP developmental toxicity study conducted equivalent to the OECD 414 guidelines with 2 species, Fischer-344 rats and B6C3F1 mice (Tyl et al., 1987). Female rats and mice (35 animals/group) were exposed via whole-body exposure to MIBK vapor concentrations of 0, 300, 1000, or 3000 ppm (0, 1.23, 4.09, or 12.3 mg/L) on gestation days 6 through 15 for 6 h/day. The animals were euthanized on gestation day 21. No notable effects were observed with 300 and 1000 ppm. The high concentration resulted in maternal toxicity including neuromuscular effects (both species) and statistically significant changes in body weight, relative kidney weights, decreased food consumption (rats only), and increased liver weight (mice only). Reduced fetal body weight per litter and reduced skeletal ossification were observed in rats at the high concentration. An increased incidence of dead fetuses, reduced fetal body weight per litter, and reductions in skeletal ossification were observed in mice from the high concentration group. No treatment-related increase in embryotoxicity or teratogenicity was observed in either species. The NOAEC for maternal and developmental toxicity was 1000 ppm (4.09 mg/L) in both rats and mice. Using standard minute volume and body weights for female Fischer 344 rats and B6C3F1 mice, the equivalent developmental NOAELs are 1187 mg/kg bw/day for the rat and 1472 mg/kg bw/day for the mouse. The NOAEL of 1187 mg/kg/day from the rat study was considered for the developmental toxicity endpoint. **Therefore, the 4-methyl-2-pentanone MOE for developmental toxicity can be calculated by dividing the 4-methyl-2-pentanone NOAEL in mg/kg/day by the total systemic exposure to 4-methyl-2-pentanone, 1187/0.0000011 or 1079090909.**

A GLP-compliant, 2-generation inhalation reproduction study was conducted on Crl:CD(SD)IGS BR Sprague Dawley rats (Nemec et al., 2004). Groups of 60 F0 animals (30/sex) were randomly bred to produce the F1 generation. Exposures were 0, 500, 1000, and 2000 ppm (0, 2.04, 4.09, and 8.18 mg/L) of MIBK for 6 h/day, 7 days/week. Treatment began 70 days prior to mating for the F0 and F1 generations and continued to the end of the mating period for males and to day 20 of gestation for females; treatment of females resumed at day 5 of lactation. Group sizes were 30/sex/dose. CNS depression was observed in pups upon initiation of exposures on day 22 (1 F1 pup died on day 22). Therefore, exposures were terminated and restarted on day 28. Increased male kidney weights associated with hyaline droplet inclusions were observed at all concentrations of MIBK. There were no effects on reproductive parameters, developmental landmarks, or andrology measurements. The NOAEC for systemic toxicity was 1000 ppm (4.09 mg/L) based on slight body weight and feed consumption reductions at 2000 ppm (excluding the increased male kidney weights). The NOAEC for reproductive toxicity was 2000 ppm (8.18 mg/L), the highest dose tested. Using standard minute volume and body weight for Sprague Dawley rats, the equivalent NOAEL for systemic toxicity is 1060 mg/kg/day and for reproductive toxicity 2120 mg/kg/day. **Therefore, the 4-methyl-2-pentanone MOE for fertility toxicity can be calculated by dividing the 4-methyl-2-pentanone NOAEL in mg/kg/day by the total systemic exposure to 4-methyl-2-pentanone, 2120/0.0000011 or 1927272727.**

In addition, the total systemic exposure for 4-methyl-2-pentanone (0.0011 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and fertility toxicity endpoints.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/05/2018.

10.1.4. Skin sensitization

Based on available data, 4-methyl-2-pentanone does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on available data, 4-methyl-2-pentanone does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test, 4-methyl-2-pentanone did not present reactions indicative of sensitization (ECHA, 2011).

Based on weight of evidence from structural analysis and an animal study, 4-methyl-2-pentanone does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/06/2018.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, 4-methyl-2-pentanone would not be expected to present a concern for phototoxicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 4-methyl-2-pentanone 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 lack of absorbance, 4-methyl-2-pentanone does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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 $L\,mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/19/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure for 4-methyl-2-pentanone is adequate for the respiratory endpoint at the current level of use.

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 14-week whole-body inhalation exposure study, Fischer 344 rats (14/sex/group) were exposed to either 0, 205, 1033, or 4106 mg/m^3 MIBK for 6 h/day, 5 days/week (Phillips et al., 1987). Endpoints evaluated included clinical signs, body and organ weights (kidneys, heart, liver, lungs, and testes), urinalysis, hematology, serum chemistry (glucose and hepatic enzyme levels), complete gross pathology, and targeted histopathology (nasal cavity, trachea, liver, kidneys, and lungs) in all animals. Complete histopathology was conducted for the control (sham) and high-exposure (4106 mg/m^3) groups. Across all endpoints, no effects were documented in the low-exposure group (205 mg/m^3) for males or females. All adverse treatment-related effects were systemic (localized primarily to the kidney and liver) and occurred within the mid- and

high-exposure groups (1033 or 4106 mg/m^3 MIBK). Treatment-related effects included increased body weights, increased platelet counts, decreased eosinophil counts, increased serum cholesterol, increased liver weights, increased urine glucose and protein levels, and hyaline droplet formation (severity was concentration-dependent). No lung, nasal cavity, or trachea lesions were reported. Therefore, the NOEC was determined to be 205 mg/m^3.

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

- (205 mg/m^3) (1m^3/1000 L) = 0.205 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.205 mg/L) (61.2 L/day) = 12.55 mg/day
- (12.55 mg/day)/(0.0016 kg lung weight of rat*) = 7844 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be < 0.00010 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015 and 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 0.00015 mg/kg lung weight/day, resulting in a MOE of 52293333 (i.e., [7844 mg/kg lung weight/day]/[0.00015 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at < 0.00010 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: National Toxicology Program, 2005; De Ceaurriz et al., 1984; Abou-Donia et al., 1985; Smyth et al., 1951; De Ceaurriz et al., 1981; Tyl et al., 1987; Silverman et al., 1946; McOmie and Anderson, 1949; Habig et al., 1989; Lam et al., 1990; Hjelm et al., 1990; Abou-Donia et al., 1991; Lapadula et al., 1991: Geller et al., 1979: Exxon, 1982a: Exxon, 1982b: Exxon, 1982c; Hagmar et al., 1988a; Hagmar et al., 1988b; Pero et al., 1988; Dick et al., 1992; Brondeau et al., 1989; Hirota (1991); Duguay and Plaa, 1993; Specht et al., 1940; UnionCarbide, 1992: MacEwen et al., 1971: MacEwen and Vernot, 1970: Duguay and Plaa, 1995: Gagnon et al., 1994; Iregren et al., 1993; Geller et al., 1978; Spencer et al., 1975; Duckett et al., 1979; Duguay and Plaa, 1997a; Bernard et al., 1997; Duguay and Plaa, 1997b; Kumagai et al., 1999; Jang et al., 2001; David et al., 1999; Nemec et al., 2004; Stout et al., 2008; Tsai et al., 2009.

Literature Search and Risk Assessment Completed On: 09/20/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 4-methyl-2-pentanone 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, 4-methyl-2-pentanone 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 v4.1 (US EPA, 2012a) did not identify 4-methyl-2-pentanone as possibly 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, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on current VoU (2015), 4-methyl-2-pentanone does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2. Key studies

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data

4-Methyl-2-pentanone has been registered under REACH, and the following data is available:

Ready biodegradability of the test material was evaluated according to the OECD 301F method. Biodegradation of 83% was observed after 28 days.

A fish (*Brachydanio rerio*) acute toxicity test was conducted according to the OECD 203 method under static conditions. The 96-h LC50, based on mean measured concentrations, was reported to be greater than 173 mg/L.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be greater than 200 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day NOEC, based on mean measured concentrations, was 30–35 mg/L.

10.2.3. 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) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	726.9			1,000,000	0.7269	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.16	1.16
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	< 1
Risk Characterization: PEC/PNEC	**N/A**	**< 1**

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

The RIFM PNEC is 0.7269 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the 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: 1/2/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **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://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 10/09/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Explanation of cramer classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? Yes
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list (see Cramer et al., 1978 for detailed explanation on list of categories)? No, Class I (Low class)

References

Abou-Donia, M.B., Lapadula, D.M., Campbell, G., Timmons, P.R., 1985. The synergism of n-hexane-induced neurotoxicity by methyl isobutyl ketone following subchronic (90 days) inhalation in hens: induction of hepatic microsomal cytochrome P.450. Toxicol. Appl. Pharmacol. 81 (1), 1–16.

Abou-Donia, M.B., Hu, Z., Lapadula, D.M., Gupta, R.P., 1991. Mechanisms of joint neurotoxicity of n-hexane, methyl isobutyl ketone and o-ethyl o-4-nitrophenyl phenylphosphonothioate in hens. J. Pharmacol. Exp. Ther. 257 (1), 282–289.

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

ingredients. Food Chem. Toxicol. 82, S1–S19.
Bernard, L., David, R.M., Tyler, T.R., Banton, M.I., Topping, D.C., O'Donoghue, J.L., 1997. A thirteen-week inhalation schedule-controlled operant behavior study of methyl isobutyl ketone in the rat. Toxicologist 36 (1), 62 part 2.
Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.
Brondeau, M.T., Ban, M., Bonnet, P., Guenier, J.P., DeCeaurriz, J., 1989. Acetone compared to other ketones in modifying the hepatotoxicity of inhaled 1,2-dichlorobenzene in rats and mice. Toxicol. Lett. 49 (1), 69–78.
Brooks, T.M., Meyer, A.L., Hutson, D.H., 1988. The genetic toxicology of some hydrocarbon and oxygenated solvents. Mutagenesis 3 (3), 227–232.
Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.
Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.
Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.
Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.
David, R.M., Bernard, L.G., Banton, M.I., Tyler, T.R., Topping, D.C., Gill, M.W., O'Donoghue, J.L., 1999. The effect of repeated methyl iso-butyl ketone vapor exposure on schedule-controlled operant behavior in rats. NeuroToxicology 20 (4), 583–594.
De Ceaurriz, J.C., Micillino, J.C., Bonnet, P., Guenier, J.P., 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. 9, 137–143.
De Ceaurriz, J., Micillino, J.C., Marignac, B., Bonnet, P., Muller, J., Guenier, J.P., 1984. Quantitative evaluation of sensory irritating and neurobehavioral properties of aliphatic ketones in mice. Food Chem. Toxicol. 22 (7), 545–549.
Dick, R.B., Krieg Jr., E.F., Setzer, J., Taylor, B., 1992. Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. Fundam. Appl. Toxicol. 19 (3), 453–473.
Duckett, S., Streletz, L.J., Chambers, R.A., Auroux, M., Galle, P., 1979. 50 ppm MnBK Subclinical neuropathy in rats. Experientia 35 (10), 1365–1367.
Duguay, A.B., Plaa, G.L., 1993. Plasma concentrations in methyl isobutyl ketone-potentiated experimental cholestasis after inhalation or oral administration. Fundam. Appl. Toxicol. 21 (2), 222–227.
Duguay, A.B., Plaa, G.L., 1995. Tissue concentrations of methyl isobutyl ketone, methyl n-butyl ketone and their metabolites after oral or inhalation exposure. Toxicol. Lett. 75 (1–3), 51–58.
Duguay, A.B., Plaa, G.L., 1997a. Ketone potentiation of intrahepatic cholestasis: effect of two aliphatic isomers. J. Toxicol. Environ. Health 50 (1), 41–52.
Duguay, A., Plaa, G.L., 1997b. Altered cholesterol synthesis as a mechanism involved in methyl isobutyl ketone-potentiated experimental cholestasis. Toxicol. Appl. Pharmacol. 147 (2), 281–288.
ECHA, 2011. Registration dossier 4-Methylpentan-2-one. Retrieved from: https://echa.europa.eu/registration-dossier/-/registered-dossier/14866/1.
ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment. November 2012 v1.1. http://echa.europa.eu/.
Exxon Chemical Americas, 1982a. Submission to. EPA (Unpublished).
Exxon Chemical Americas, 1982b. Submission to. EPA Unpublished.
Exxon Chemical Americas, 1982c. Submission to. EPA (Unpublished).
Gagnon, P., Mergler, D., Lapare, S., 1994. Olfactory adaptation, threshold shift and recovery at low levels of exposure to methyl isobutyl ketone (MIBK). NeuroToxicology 15 (3), 637–642.
Geller, I., Martinez, R.L., Hartmann, R.J., Kaplan, H.L., 1978. Effects of ketones on a match to sample task in the baboon. Proceedings west. pharmac. Soc. 21, 439–442.
Geller, I., Gause, E., Kaplan, H., Hartmann, R.J., 1979. Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. Pharmac. Biochem. Behav. Pharmacology, Biochemistry and Behavior 11, 401–406.
Habig, C., Abou-Donia, M.B., Lapadula, D.M., 1989. Cytochrome P-450 induction in chickens exposed simultaneously to n-hexane and methyl iso-butyl ketone. Toxicologist 9 (1), 194.
Hagmar, L., Bellander, T., Hogstedt, B., Hallberg, T., Attewell, R., Raihle, G., Au, W.W., Legator, M.S., Mitelman, F., Skerfving, S., 1988a. Biological effects in a chemical factory with mutagenic exposure. I. Cytogenetic and haematological parameters. Int. Arch. Occup. Environ. Health 60 (6), 437–444.
Hagmar, L., Bellander, T., Persson, L., Holmen, A., Attewell, R., Hogstedt, B., Skerfving, S., 1988b. Biological effects in a chemical factory with mutagenic exposure. III. Urinary mutagenicity and thioether excretion. Int. Arch. Occup. Environ. Health 60 (6), 453–456.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
Hirota, N., 1991. The metabolism of methyl isobutyl ketone and biological monitoring: Part 2. Qualitative and quantitative study of 4-methyl-2-pentanol excreted in the urine of workers exposed to methyl isobutyl ketone. Okayama Igakkai Zasshi 103 (4), 327–336.
Hjelm, E.W., Hagberg, M., Iregren, A., Lof, A., 1990. Exposure to methyl isobutyl ketone: toxicokinetics and occurrence of irritative and CNS symptoms in man. Int. Arch. Occup. Environ. Health 62 (1), 19–26.
IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.
PPG Industries, Incorporated, 1991. Submission to. EPA (Unpublished).
Iregren, A., Tesarz, M., Wigaeus-Hjelm, E., 1993. Human experimental MIBK exposure: effects on heart rate, performance, and symptoms. Environ. Res. 63 (1), 101–108.
Jang, J.-Y., Droz, P.O., Kim, S., 2001. Biological monitoring of workers exposed to ethylbenzene and co-exposed to xylene. Int. Arch. Occup. Environ. Health 74 (1), 31–37.
Kumagai, S., Oda, H., Matsunaga, I., Kosaka, H., Akasaka, S., 1999. Uptake of 10 polar organic solvents during short-term respiration. Toxicol. Sci. 48 (2), 255–263.
Lam, C.-W., Galen, T.J., Boyd, J.F., Pierson, D.L., 1990. Mechanism of transport and distribution of organic solvents in blood. Toxicol. Appl. Pharmacol. 104 (1), 117–129.
Lapadula, D.M., Habig, C., Gupta, R.P., Abou-Donia, M.B., 1991. Induction of cytochrome P450 isozymes by simultaneous inhalation exposure of hens to n-hexane and methyl iso-butyl ketone (MiBK). Biochem. Pharmacol. 41 (6/7), 877–883.
Lehman-McKeeman, L.D., Caudill, D., 1992. a-2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. Toxicol. Appl. Pharmacol. 116 (2), 170–176.
Lehman-McKeeman, L.D., Rivera-Torres, M.I., Caudill, D., 1990. Lysosomal degradation of alpha2u-globulin and alpha2u-globulin-xenobiotic conjugates. Toxicol. Appl. Pharmacol. 103 (3), 539–548.
Lock, E.A., Hard, G.C., 2004. Chemically induce renal tubule tumors in the laboratory rat and mouse: review of the NCI/NTP database and categorization of renal carcinogens based on mechanistic information. Crit. Rev. Toxicol. 34 (3), 211–299.
MacEwen, J.D., Vernot, E.H., 1970. Toxic Hazards Research Unit Annual Technical Report: 1970. (Unpublished).
MacEwen, J.D., Venot, E.H., Haun, C.C., 1971. Effect of 90-day Continuous Exposure to Methylisobutylketone on Dogs, Monkeys, and Rats. Unpublished. NTIS AD Rep, pp. 730291.
McOmie, W.A., Anderson, H.H., 1949. Comparative Toxicologic Effects of Some Isobutyl Carbinols and Ketones, vol. 2. University California Publications Pharmacology, pp. 217–230 (17).
National Toxicology Program, 2005. Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone (CAS No. 108-10-1) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP-TR-538. NIH Publication No. 07-4476.
Nemec, M.D., Pitt, J.A., Topping, D.C., Gingell, R., Pavkov, K.L., Rauckman, E.J., Harris, S.B., 2004. Inhalation two-generation reproductive toxicity study of methyl isobutyl ketone in rats. Int. J. Toxicol. 23 (2), 127–143.
O'Donoghue, J.L., Haworth, S.R., Curren, R.D., Kirby, P.E., Lawlor, T., Moran, E.J., Phillips, R.D., Putnam, D.L., Rogers-Back, A.M., Slesinski, R.S., Thilagar, A., 1988. Mutagenicity studies on ketone solvents: methyl ethyl ketone, methyl isobutyl ketone, and isophorone. Mutat. Res. Genet. Toxicol. 206 (2), 149–161.
Pero, R., Hagmar, L., Seidegard, J., Bellander, T., Attewell, R., Skerfving, S., 1988. Biological effects in a chemical factory with mutagenic exposure. II. Analysis of unscheduled DNA synthesis and adenosine diphosphate ribosyl transferase, epoxide hydrolase, and glutathione transferase in resting mononuclear leukocytes. Int. Arch. Occup. Environ. Health 60 (6), 445–451.
Phalen, R.F., 2009. Inhalation Studies. Foundations and Techniques, second ed. Published by, Informa Healthcare USA, Inc., New York, NY.
Phillips, R.D., Moran, E.J., Dodd, D.E., Fowler, E.H., Kary, C.D., O'Donoghue, J., 1987. A 14-week vapor inhalation toxicity study of methyl isobutyl ketone. Fundam. Appl. Toxicol. 9 (3), 380–388.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 09, January 2016.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Seely, J.C., Haseman, J.K., Nyska, A., Wolf, D.C., Everitt, J.I., Hailey, J.R., 2002. The effect of chronic progressive nephropathy on the incidence of renal tubule cell neoplasms in control male F344 rats. Toxicol. Pathol. 30 (6), 681–686.
Silverman, L., Schultz, H.F., First, M.W., 1946. Further studies on sensory response to certain industrial solvent vapors. The Journal of Industrial Hygiene and Toxicolology. The Journal of Industrial Hygiene and Toxicology 28, 262–266.
Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., 1951. Range finding toxicity data: list IV. Arch. Ind. Hyg. Occup. Med. 4, 119–122.
Specht, H., Miller, J.W., Valaer, P.J., Sayers, R.R., 1940. Acute response of Guinea pigs to the inhalation of ketone vapors. In National Institute Health Bulletin 176, 1–66.
Spencer, P.S., Schaumberg, H.H., Raleigh, R.L., Terhaar, C.J., 1975. Nervous system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch. Neurol. 32 (4), 219–222.
Stout, M.D., Herbert, R.A., Kissling, G.E., Suarez, F., Roycroft, J.H., Chhabra, R.S., Bucher, J.R., 2008. Toxicity and carcinogenicity of methyl isobutyl ketone in F344N rats and

B6C3F1 mice following 2-year inhalation exposure. Toxicology 244 (2–3), 209–219.
Tsai, C.-J., Chen, M.-L., Chang, K.-F., Chang, F.-K., Mao, I.-F., 2009. The pollution characteristics of odor, volatile organochlorinated compounds and polycyclic aromatic hydrocarbons emitted from plastic waste recycling plants. Chemosphere 74 (8), 1104–1110.
Tyl, R.W., France, K.A., Fisher, L.C., Pritts, I.M., Tyler, T.R., Philips, R.D., Moran, E.J., 1987. Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fisher 344 rats and CD-1 mice. Fundam. Appl. Toxicol. 8 (3), 310–327.
Union Carbide Corporation, 1992. Submission to. EPA, Unpublished.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19 (Suppl. 21), 2–141.