

Short review

RIFM fragrance ingredient safety assessment, benzyl butyrate, CAS Registry Number 103-37-7



A.M. Api^{a,*}, D. Belsito^b, S. Bhatia^a, M. Bruze^c, P. Calow^d, M.L. Dagli^e, W. Dekant^f, A.D. Fryer^g, L. Kromidas^a, S. La Cava^a, J.F. Lalko^a, A. Lapczynski^a, D.C. Liebler^h, V.T. Politano^a, G. Ritacco^a, D. Salvito^a, T.W. Schultzⁱ, J. Shen^a, I.G. Sipes^j, B. Wall^a, D.K. Wilcox^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, Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmö SE-20502, Sweden

^d Member RIFM Expert Panel, Humphrey School of Public Affairs, University of Minnesota, 301 19th Avenue South, Minneapolis, MN 55455, USA

^e 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

^f Member RIFM Expert Panel, University of Würzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany

^g Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA

^h 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

ⁱ Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA

^j 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

ARTICLE INFO

Article history:

Received 28 June 2016

Accepted 5 August 2016

Available online 7 August 2016

Keywords:

Genotoxicity

Repeated dose

Developmental and reproductive Toxicity

Skin sensitization

Phototoxicity/photoallergenicity

Local respiratory toxicity

Environmental safety

ABSTRACT

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog benzyl acetate (CAS # 140-11-4) show that this material is not genotoxic nor does it have skin sensitization potential and also provided a MOE > 100 for the repeated dose, developmental and reproductive, and local respiratory toxicity endpoints. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

© 2016 Elsevier Ltd. All rights reserved.

1. Identification

1. **Chemical NAME:** Benzyl butyrate
2. **CAS Registry Number:** 103-37-7

3. **Synonyms:** Benzyl butyrate, Benzyl butanoate, Butanoic acid, phenylmethyl ester, アルカン酸(C = 1 ~ 6)ベンジル
4. **Molecular Formula:** C₁₁H₁₄O₂
5. **Molecular Weight:** 178.23
6. **RIFM Number:** 376

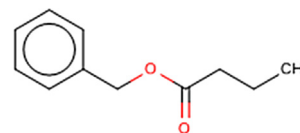
2. Physical data

1. **Boiling Point:** 240 °C [FMA], 252.15 °C [EPI Suite]
2. **Flash Point:** >212 °F; CC [FMA database]

* Corresponding author.

E-mail address: AApi@rifm.org (A.M. Api).

Version: 052416. This version replaces any previous versions.
 Name: Benzyl butyrate
 CAS Registry Number: 103-37-7



Abbreviation list:

2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by [Cadby et al. \(2002\)](#) and [Ford et al. \(2000\)](#).
AF- Assessment Factor
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

- Log K_{ow}**: 3.06 [[EPI Suite](#)]
- Melting Point**: 21.44 °C [[EPI Suite](#)]
- Water Solubility**: 136 mg/L [[EPI Suite](#)]
- Specific Gravity**: 1.006–1.009 [FMA database], 1.008–1.011 [FMA database]
- Vapor Pressure**: 0.0313 mm Hg @ 20 °C [[EPI Suite 4.0](#)], 0.02 mm Hg @ 20 °C [FMA database], 0.0488 mm Hg @ 25 °C [[EPI Suite](#)]
- UV Spectra**: Minor absorption between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ cm⁻¹).
- Appearance/Organoleptic**: A colorless to very pale yellow liquid having a fruity odor, suggesting plum.

3. Exposure

- Volume of Use (worldwide band)**: 1–10 metric tons per year ([IFRA, 2011](#))
- Average Maximum Concentration in Hydroalcohols: 0.06% ([IFRA, 2008](#))
- 97.5th Percentile: 0.096% ([IFRA, 2008](#))
- Dermal Exposure***: 0.0024 mg/kg/day ([IFRA, 2008](#))
- Oral Exposure: Not available
- Inhalation Exposures****: 0.00015 mg/kg/day or 0.0089 mg/day ([IFRA, 2008](#))

- Total Systemic Exposure (Dermal + Inhalation)**: (0.0024 mg/kg/day x 78.7% absorption) + 0.00015 mg/kg/day = 0.0020 mg/kg/day

*Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) ([Cadby et al., 2002](#); [Ford et al., 2000](#)).

**Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcohols for a 60 kg individual.

4. Derivation of systemic absorption

- Dermal**: 78.7%

[Bronaugh, et al., 1990](#): The skin absorption of read across material [7-¹⁴C] benzyl acetate (CAS # 104-11-1; see Section 5) was measured in 4 female rhesus monkeys. The test material in acetone was applied at a concentration of 4 µg/cm² to a 1 cm² area of abdominal skin for 24 h. Urine was collected for an additional 4

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog benzyl acetate (CAS # 140-11-4) show that this material is not genotoxic nor does it have skin sensitization potential and also provided a MOE > 100 for the repeated dose, developmental and reproductive, and local respiratory toxicity endpoints. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (Tennant et al., 1987; Shelby et al., 1993)

Repeated Dose Toxicity: NOAEL = 14.5 mg/kg/day (NTP, 1993)

Developmental and Reproductive Toxicity: NOAEL = 100 mg/kg/day (Ishiguro et al., 1993)

Skin Sensitization: Not sensitizing (RIFM, 1987; RIFM, 1988a; RIFM, 1988b; NTP, 1993, RIFM, 1988c; RIFM, 1988d; RIFM, 1985b; RIFM, 1985c; RIFM, 1986a; RIFM, 1961; RIFM, 1985a; RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e; Klecak, 1985; RIFM, 1973)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)

Local Respiratory Toxicity: NOAEC = 61.4 mg/m³ (RIFM, 2013a)

Environmental Safety Assessment**Hazard Assessment:**

Persistence: Screening Level: 2.96 (BIOWIN 3) (EpiSuite ver 4.1)

Bioaccumulation: Screening Level: 48.76 L/kg (EpiSuite ver 4.1)

Ecotoxicity: Screening Level: 96 h Algae EC50: 3.806 mg/L (EpiSuite ver 4.1)

Conclusion: Not PBT as per IFRA Environmental Standard

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 96 h Algae EC50: 3.806 mg/L (EpiSuite ver 4.1)

RIFM PNEC is: 0.3806 µg/L

•Revised PEC/PNECs (2011 IFRA VoU): North America and Europe < 1

days. The extent of dermal absorption was estimated from the amount of ¹⁴C-equivalents excreted in the urine over the 5 day collection period. When the application site was occluded with either plastic wrap or a glass chamber, the absorption of benzyl acetate was 17.3 ± 2.7% and 78.7 ± 7.5%, respectively. When the site was not occluded, the absorption was 34.6 ± 9.4%.

2. **Oral:** Data not available – not considered.

3. **Inhalation:** Assumed 100%

4. **Total:** Dermal (78.7%) + Inhalation (assume 100%) absorbed = (0.0024 mg/kg/day x 78.7%) + 0.00015 mg/kg/day = 0.0020 mg/kg/day

5. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert judgement	Toxtree v 2.6	OECD QSAR toolbox v 3.2
I	I	I

2. Analogs selected:

- Genotoxicity:** Benzyl acetate (CAS # 140-11-4)
- Repeated Dose Toxicity:** Benzyl acetate (CAS # 140-11-4)
- Developmental and Reproductive Toxicity:** Benzyl acetate (CAS # 140-11-4)
- Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)

e. **Phototoxicity/Photoallergenicity:** None

f. **Local Respiratory Toxicity:** Benzyl acetate (CAS # 140-11-4)
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

6. Metabolism

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

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

Benzyl butyrate is reported to occur in the following foods* and in some natural complex substances (NCS):

- Acerola (Malpighia)
- Babaco fruit (Carica pentagona Heilborn)
- Cherimoya (Annona cherimolia Mill.)
- Hog plum (Spondias mombins L.)
- Macadamia nut (Macadamia integrifolia)
- Melon.
- Mountain papaya (C. candamarcensis, C. pubescens)
- Papaya (Carica papaya L.)
- Passion fruit (Passiflora species)
- Tea.
- Vanilla.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile

compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 05/24/2016.

10. Summary

10.1. Human health endpoint summaries

Genotoxicity:

Based on the current existing data and use levels, benzyl butyrate does not present a concern for genetic toxicity.

Risk Assessment:

Benzyl butyrate was tested using the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity indicating a lack of genotoxic potential (RIFM, 2013b). There are no studies assessing the mutagenic potential of benzyl butyrate, however, read across can be made to benzyl acetate (CAS # 140-11-4; see Section 5) which has been assessed for mutagenicity in an Ames study. The mutagenic potential of benzyl acetate was assessed by an Ames test similar to OECD TG 471 using the plate incorporation method. *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed to concentrations of benzyl acetate up to 10 mg per plate in the presence and absence of liver S-9 fractions. No substantial increases in revertant colonies were seen with benzyl acetate with or without metabolic activation (S9). The study concluded that benzyl acetate is not mutagenic under the conditions of this test (Tennant et al., 1987).

The clastogenic potential of read across analog, benzyl acetate was assessed in several *in vitro* mouse lymphoma cell assays with and without metabolic activation with varying results. However, several *in vivo* studies assessing the effect of the material on inducing chromosomal aberrations, unscheduled DNA synthesis, demonstrate that benzyl acetate lacks genotoxic potential (NTP, 1993; Steinmetz and Mirsalis, 1984). In an *in vivo* mammalian erythrocyte micronucleus assay performed in equivalent to or similar to OECD TG 474, groups of 5–7 male B6C3F1 mice were administered benzyl acetate in corn oil via intraperitoneal injection for 3 consecutive days at doses up to 600 mg/kg. No genotoxic activity was observed, and the material was considered not clastogenic (Shelby et al., 1993).

Taken together, benzyl acetate does not present a concern for genotoxic potential and this can be extended to benzyl butyrate.

Additional References: NTP, 1993; Florin et al., 1980; Mortelmans et al., 1986; Schunk et al., 1986; Rogan et al., 1986; Mirsalis et al., 1989; Steinmetz and Mirsalis, 1984; Mirsalis et al., 1983; Foureman et al., 1994; Matsuoka et al., 1996; Yoshikawa, 1996; Miyagawa et al., 1995; Mitchell and Caspary, 1987; Zimmermann et al., 1989; Honma et al., 1999; Kevekordes et al., 1999, 2001, 1999; Rossman et al., 1991; Kevekordes et al., 2001; Sekihashi et al., 2002; Yoo, 1986; Demir et al., 2010; Scott et al., 2007; Yasunaga et al., 2004; Witt et al., 2000; Sasaki et al., 2000; Oda et al., 1978; Elmore and Fitzgerald, 1990; Longnecker et al., 1990; Galloway et al., 1987; Caspary et al., 1988; Rudd et al., 1983; Yoo, 1986; McGregor et al., 1988.

Literature Search and Risk Assessment Completed on: 05/07/14
Repeated Dose Toxicity:

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

Risk Assessment:

There are insufficient repeated dose toxicity data on benzyl butyrate. Read across material benzyl acetate (CAS # 140-11-4; see Section 5) has numerous oral repeated dose toxicity studies conducted in rats and mice. A dietary 2-year chronic toxicity study conducted in rats determined a LOAEL for repeated dose toxicity of 3000 ppm, or 145 mg/kg/day for female rats, based on decreased body weights (NTP, 1993). The NOAEL was derived by dividing the LOAEL by a safety factor of 10, which is equal to 14.5 mg/kg/day. Therefore, the MOE is equal to the benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 14.5/0.0020 or 7250.

Additional References: McGinty et al., 2012a; Belsito et al., 2012; RIFM, 1957; Meyer, 1965; McGinty et al., 2012b; Jimbo, 1983; RIFM, 2013a; RIFM, 1986b; RIFM, 1957; Abdo and Wenk, 1995; Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young, 1989; Abdo et al., 1985; Caldwell et al., 1987; Snapper et al., 1925; Hotchkiss et al., 1992a; Nasser-Sina et al., 1992; Chidgey et al., 1986a; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey and Caldwell, 1986b; Chidgey et al., 1987; McMahan et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahan et al., 1989b; Schunk et al., 1986; Hotchkiss et al., 1989; Hotchkiss et al., 1992b, 1992c, 1998; Caldwell et al., 1987; Hotchkiss et al., 1992c; Garnett et al., 1994; Hotchkiss et al., 1988, 1990a, 1990b, 1992d; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; RIFM, 1989a; RIFM 1989b; Hotchkiss et al., 1992d.

Literature Search and Risk Assessment Completed on: 05/02/14.

Developmental and Reproductive Toxicity:

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

Risk Assessment:

There are no developmental toxicity data on benzyl butyrate. Read across material benzyl acetate (CAS # 140-11-4; see Section 5) has a gavage developmental toxicity study that was conducted in rats. The NOAEL for developmental toxicity was determined to be 100 mg/kg/day, based on minor fetal internal anomalies and fetal weights (Ishiguro et al., 1993). Therefore, the MOE for developmental toxicity is equal to the benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.0020 or 50,000.

There are no reproductive toxicity data on benzyl butyrate. Read across material benzyl acetate (CAS # 140-11-4) has a gavage developmental toxicity study conducted in rats that determined the NOAEL for maternal toxicity to be 500 mg/kg/day, based on maternal body weight gain (Ishiguro et al., 1993). In 13-week dietary subchronic toxicity studies in rats and mice with benzyl acetate, sperm morphology and vaginal cytology examinations were evaluated (Morrissey et al., 1988; data also available in NTP, 1993). There were no effects on sperm parameters in mice or rats up to the high dosage of 7900 or 3900 mg/kg/day, respectively. There were no effects on estrous cycling in female rats up to the high dosage of 4500 mg/kg/day. Lengthening of the estrous cycle occurred in high-dose female mice (9400 mg/kg/day), which the authors concluded was related to decreases in body weight. These data indicate no specific concern for reproductive toxicity. Therefore, the MOE for reproductive toxicity is equal to the benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.0020 or 250,000.

RIFM's Expert Panel* and the adjunct Reproduction Advisory Group reviewed the Ishiguro et al. (1993) results and concluded that the minor fetal anomalies observed at the highest dose level were most likely a developmental delay. An increased fetal body weight may indicate an adverse effect. For example, chemicals which induce maternal diabetes mellitus may increase fetal weight. Early embryocidal effects leading to a reduced litter size may secondarily increase fetal weight. The Panel members and the

Reproduction Advisory Group concluded that the increased fetal body weight observed in the 100 and 10 mg/kg/day groups was biologically insignificant and that no additional reproductive or developmental toxicity studies are needed. They concluded that the maternal NOAEL was 500 mg/kg/day based on weight gain and the fetal NOAEL is 100 mg/kg/day based on weight and internal organ malformations.

*RIFM's Expert Panel and adjunct Reproduction Advisory Group are composed of scientific and technical experts in their respective fields. These groups provide advice and guidance.

Additional References: McGinty et al., 2012a; Belsito et al., 2012; RIFM, 1957; Meyer, 1965; McGinty et al., 2012b, Jimbo, 1983; RIFM, 2013a; RIFM, 1986b; RIFM, 1957; Abdo and Wenk, 1995; ; Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young, 1989; Abdo et al., 1985; Caldwell et al., 1987; Snapper et al., 1925; Hotchkiss et al., 1992a; Nasseri-Sina et al., 1992; Chidgey et al., 1986a; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey and Caldwell, 1986b; ; Chidgey et al., 1987; McMahan et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahan et al., 1989b; Schunk et al., 1986; Hotchkiss et al., 1989; Hotchkiss et al., 1992b, 1992c, 1992d, 1998; Caldwell et al., 1987; Hotchkiss et al., 1992c; Garnett et al., 1994; Hotchkiss, 1988; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; RIFM, 1989a; RIFM, 1989b; Hotchkiss et al., 1992d.

Literature Search and Risk Assessment Completed on: 05/02/14.
Skin Sensitization:

Based on existing material specific data and read across to benzyl acetate (CAS# 140-11-4); benzyl butyrate does not present a concern for skin sensitization.

Risk Assessment:

Based on existing material specific data and read across to benzyl acetate (CAS# 140-11-4; see Section 5); benzyl butyrate does not present a concern for skin sensitization. While the chemical structure of these materials indicates that they would be expected to react with skin proteins, the reactivity would be expected to be low (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig test methods no reactions indicative of sensitization were observed to benzyl acetate (RIFM, 1985b; RIFM, 1985c; RIFM, 1985a; Klecak, 1985; RIFM, 1986a). Additionally, no reactions indicative of skin sensitization were observed in both the human repeated insult patch test and the human maximization test to benzyl acetate (RIFM, 1987; RIFM, 1988a; RIFM, 1988b; NTP, 1993; RIFM, 1988c; RIFM, 1988d; RIFM, 1961; RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e). Finally, in the human maximization test no reactions indicative of sensitization were observed to benzyl butyrate (RIFM, 1973).

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/05/14.
Phototoxicity/Photoallergenicity:

Based on UV/Vis absorption spectra, benzyl butyrate would not be expected to present a concern for phototoxicity or photoallergenicity.

Risk Assessment:

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/21/15.
Local Respiratory Toxicity:

There are no inhalation data available on benzyl butyrate;

however, in an acute, two week inhalation study for the analog benzyl acetate (CAS # 140-11-4; see Section 5), a NOAEC of 61.4 mg/m³ was reported by RIFM, 2013a.

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 two week, acute inhalation study conducted in rats, a NOAEC of 61.4 mg/m³ was reported for benzyl acetate (RIFM, 2013a). Test substance-related increase in bronchoalveolar lavage fluid lactate dehydrogenase values were noted in the 61.4 mg/m³ group (for both males and females) when compared to the control group; therefore, the no-observed-adverse-effect concentration (NOAEC) was considered to be 61.4 mg/m³ (equivalent to 10 ppm), the middle exposure concentration tested.

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

- $(61.4 \text{ mg/m}^3) (1 \text{ m}^3/1000 \text{ L}) = 0.0614 \text{ mg/L}$
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- $(0.0614 \text{ mg/L}) (61.2 \text{ L/day}) = 3.76 \text{ mg/day}$
- $(3.76 \text{ mg/day}) / (0.0016 \text{ kg lung weight of rat}^*) = 2350 \text{ mg/kg lung weight/day}$

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.096%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) the combined inhalation exposure would be 0.0089 mg/day—as calculated using RIFM's 2-Box/MPPD *in silico* models, and based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics. 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 0.014 mg/kg lung weight/day resulting in a MOE of 167857 (i.e., $[2350 \text{ mg/kg lung weight/day}] / [0.014 \text{ mg/kg lung weight/day}]$).

The MOE is greater than 100. Without the adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.096% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd 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: RIFM, 1977; RIFM, 1997b; Silver, 1992; RIFM, 1997a; Isola et al., 2003a; Rogers et al., 2003; RIFM, 2003b; RIFM, 2003a; Isola et al., 2003b; Isola et al., 2004a, 2004b; Smith et al., 2004; RIFM, 2004; Rogers et al., 2005; Randazzo et al., 2014; Vethanayagam et al., 2013.

Literature Search and Risk Assessment Completed on: 5/2016.

10.2. Environmental endpoint summary

Screening-Level Assessment:

A screening level risk assessment of benzyl butyrate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as

discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, benzyl butyrate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify benzyl butyrate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

Risk Assessment:

Based on the current Volume of Use (2011), benzyl butyrate presents a risk to the aquatic compartment in the screening level assessment.

Key Studies:

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data: Benzyl butyrate has been pre-registered under REACH with no additional data at this time.

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.

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

Exposure	Europe (EU)	North America (NA)
Log K _{ow} used	3.06	3.06
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 0.3806 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 5/06/14.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PUBMED:** <http://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <http://toxnet.nlm.nih.gov/>
- **IARC:** (<http://monographs.iarc.fr>)
- **OECD SIDS:** <http://www.chem.unep.ch/irptc/sids/oecd/sids/sidspub.html>
- **EPA Actor:** <http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7>
- **US EPA HPVIS:** <http://www.epa.gov/hpv/hpvvis/index.html>

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level (Tier 1)	<u>28.75 mg/l</u>			1,000,000	0.02875 µg/l	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	5.705 mg/l	10.58 mg/l	<u>3.806 mg/l</u>	10,000	0.3806 µg/l	Esters
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	16.24 mg/l	10.17 mg/l	11.37 mg/l			Neutral Organics SAR (Baseline Toxicity)

- **US EPA Robust Summary:** <http://cfpub.epa.gov/hpv-s/>
- **Japanese NITE:** <http://www.safe.nite.go.jp/english/db.html>
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** <https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4>

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2016.08.007>.

Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2016.08.007>.

Appendix

	Target material	Read across material
Principal name	Benzyl butyrate	Benzyl acetate
CAS no.	103-37-7	140-11-4
Structure		
3D structure	http://www.thegoodscentscompany.com/opl/103-37-7.html	http://www.thegoodscentscompany.com/opl/140-11-4.html
Read-across endpoint		<ul style="list-style-type: none"> • Genotoxicity • Repeated Dose • Devel/Repro • Skin sensitization • Respiratory
Molecular formula:	C11H14O2	C9H10O2
Molecular weight:	178.23	150.17
Melting point (°C)	21.44	-0.5
Boiling point (°C)	252.15	215.57
Vapor pressure (mmHg @ 25°C)	0.0488	0.187
Log Kow (KOWWIN v1.68 estimate)	3.06	2.08
Water solubility (mg/L, @ 25°C, WSKOW v1.42 estimate)	136	1605
J _{max} (mg/cm ² /h, RIFM SAM)	33.5	64.0
Henry's Law (Pa·m ³ /mol, bond method)	2.53	1.4337
Similarity (tanimoto score) ¹		74%
Genotoxicity		
DNA binding by OASIS v 1.1 QSAR Tool Box (3.1)	<ul style="list-style-type: none"> • No alerts 	<ul style="list-style-type: none"> • Schiff base formers • Schiff base formers >> Direct acting Schiff base formers • Schiff base formers >> Direct acting Schiff base formers >> Specific Acetate Esters • SN1 • SN1 >> Carbenium ion formation • SN1 >> Carbenium ion formation >> Specific Acetate Esters • SN2 • SN2 >> Acylating agents • SN2 >> Acylating agents >> Specific Acetate Esters • SN2 >> SN2 at sp³-carbon atom • SN2 >> SN2 at sp³-carbon atom >> Specific Acetate Esters • Michael addition • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals >> Arenes • No alerts
DNA binding OECD	<ul style="list-style-type: none"> • Michael addition • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals >> Arenes • No alerts 	<ul style="list-style-type: none"> • Michael addition • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals >> Arenes • No alerts
Carcinogenicity (genotox and non-genotox) alerts by ISS	<ul style="list-style-type: none"> • No alerts 	<ul style="list-style-type: none"> • Schiff base fomers • Schiff base fomers >> Direct acting Schiff base formers • Schiff base fomers >> Direct acting Schiff base formers >> Specific Acetate Esters • SN1 • SN1 >> Carbenium ion formation • SN1 >> Carbenium ion formation >> Specific Acetate Esters • SN2 • SN2 >> Acylating agents • SN2 >> Acylating agents >> Specific Acetate Esters • SN2 >> SN2 at sp³-carbon atom • SN2 >> SN2 at sp³-carbon atom >> Specific Acetate Esters
DNA alerts for ames, MN, CA by OASIS v 1.1	<ul style="list-style-type: none"> • No alerts 	<ul style="list-style-type: none"> • Schiff base fomers • Schiff base fomers >> Direct acting Schiff base formers • Schiff base fomers >> Direct acting Schiff base formers >> Specific Acetate Esters • SN1 • SN1 >> Carbenium ion formation • SN1 >> Carbenium ion formation >> Specific Acetate Esters • SN2 • SN2 >> Acylating agents • SN2 >> Acylating agents >> Specific Acetate Esters • SN2 >> SN2 at sp³-carbon atom • SN2 >> SN2 at sp³-carbon atom >> Specific Acetate Esters

(continued)

	Target material	Read across material
In-vitro mutagenicity (ames test) alerts by ISS	• No alerts	• No alerts
In-vivo mutagenicity (micronucleus) alerts by ISS	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor
Oncologic classification	• Not classified	• Not classified
Repeated dose toxicity		
Repeated dose (HESS)	• Not categorized	• Not categorized
Developmental and reproductive toxicity		
Developmental toxicity model by CAESAR v2.1.6	• Non toxicant (low reliability)	• Toxicant (medium reliability)
ER Binding by OECD QSAR Toolbox (3.1)	• Non binder	• Non binder
Skin sensitization		
Protein binding by OASIS v1.1	<ul style="list-style-type: none"> • SN2 • SN2 >> Nucleophilic substitution at sp3 Carbon atom • SN2 >> Nucleophilic substitution at sp3 Carbon atom >> Activated alkyl esters 	<ul style="list-style-type: none"> • SN2 • SN2 >> Nucleophilic substitution at sp3 Carbon atom • SN2 >> Nucleophilic substitution at sp3 Carbon atom >> Activated alkyl esters
Protein binding by OECD	<ul style="list-style-type: none"> • SN2 • SN2 >> SN2 reaction at sp3 carbon atom • SN2 >> SN2 reaction at sp3 carbon atom >> Allyl acetates and related chemicals 	<ul style="list-style-type: none"> • SN2 • SN2 >> SN2 reaction at sp3 carbon atom • SN2 >> SN2 reaction at sp3 carbon atom >> Allyl acetates and related chemicals
Protein binding potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	<ul style="list-style-type: none"> • SN2 • SN2 >> Nucleophilic substitution at sp3 Carbon atom • SN2 >> Nucleophilic substitution at sp3 Carbon atom >> Activated alkyl esters 	<ul style="list-style-type: none"> • SN2 • SN2 >> Nucleophilic substitution at sp3 Carbon atom • SN2 >> Nucleophilic substitution at sp3 Carbon atom >> Activated alkyl esters
Skin sensitization model (CAESAR) (version 2.1.5)	• Sensitizer (medium reliability)	• Sensitizer (low reliability)
Metabolism		
OECD QSAR Toolbox (3.1) rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

¹ Values calculated using Pipeline Pilot with FCFP fingerprint. J. Chem. Inf. Model. 2010, 50: 742 (Rogers and Hahn, 2010).

Summary:

Benzyl butyrate (RIFM# 376, CAS# 103-37-7) lacks toxicity data for skin absorption, genotoxicity, repeated dose, developmental, reproductive, skin sensitization and phototoxicity/photo-allergenicity end points. Hence, *in silico* evaluation was conducted by determining suitable read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physico-chemical properties and expert judgment, benzyl acetate (RIFM# 106, CAS# 140-11-4) was identified as proper read across for their respective toxicity endpoints.

Methods:

- The identified read-across analog was confirmed by using expert judgment
- The physicochemical properties of target and analog were calculated using *EPI Suite*TM v4.11 developed by US EPA (USEPA, 2012)
- J_{\max} was calculated using RIFM skin absorption model (SAM) (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeated dose (HESS) were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR v2.1.6 (Cassano et al., 2010)
- Protein binding was estimated using OECD QSAR Toolbox (v 3.1) (OECD, 2012)

- Skin sensitization was estimated using CAESAR v 2.1.6 (Cassano et al., 2010)
- The major metabolites for the target and read-across analog were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale

- Benzyl acetate (analog) was used as a read-across for Benzyl butyrate (target) based on:
 - The target and analog belong to the generic class of aromatic esters, specifically, esters/aryl alkyl alcohol simple acid/benzylic alcohol.
 - The target and analog have similar carboxylic acid part and the same alcohol part. The only difference is that the target is a butyrate while the analog is an acetate. The difference between structures does not essentially change the physico-chemical properties nor raise any additional structural alerts and therefore, their toxicological profiles are expected to be similar.
 - The analog shows more alerts for DNA binding. This is favorable since it indicates that we are reading from a potentially more reactive to a less reactive species. They show similar alerts for mutagenicity, genotoxicity and oncologic classification.
 - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
 - The target and analog show similar alerts for protein binding.

- The target and analog are expected to be metabolized similarly. As per the OECD Toolbox they are predicted to have similar metabolites.

References

- Abdo, K.M., Huff, J.E., Haseman, J.K., Boorman, G.A., Eustis, S.L., Matthews, H.B., Burka, L.T., Prejean, J.D., Thompson, R.B., 1985. Benzyl acetate carcinogenicity, metabolism, and disposition in Fischer 344 rats and B6C3F1 mice. *Toxicology* 37 (1–2), 159–170.
- Abdo, K.M., Wenk, M.L., 1995. Requirement for adequate glycine for the detoxification of benzyl acetate and maintenance of its detoxification pathways. *Toxicology* 15 (1), 19.
- Abdo, K.M., Wenk, M.L., Harry, G.J., Mahler, J., Goehli, T.J., Irwin, R.D., 1998. Glycine modulates the toxicity of benzyl acetate in F344 rats. *Toxicol. Pathol.* 26 (3), 395–402.
- 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., Renkers, K., Ritacco, G., Salviato, 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.
- Augustinsson, K.-B., Ekedahl, G., 1962. On the specificity of arylesterases. *Acta Chem. Scand.* 16 (part 1), 240–241.
- Belsito, D., Bickers, D., Bruze, M., Calow, P., Dagli, M.L., Fryer, A.D., Greim, H., Miyachi, Y., Saurat, J.H., Sipes, I.G., 2012. A toxicological and dermatological assessment of aryl alkyl alcohol simple ester derivatives when used as fragrance ingredients. *Food Chem. Toxicol.* 50 (Suppl. 2), S269–S313.
- Bronaugh, R.L., Wester, R.C., Bucks, D., Maibach, H.I., Sarason, R., 1990. In vivo percutaneous absorption of fragrance ingredients in rhesus monkeys and humans. *Food Chem. Toxicol.* 28 (5), 369–373.
- Cadby, P.A., Troy, W.R., Vey, M.G.H., 2002. Consumer exposure to fragrance ingredients: Providing estimates for safety evaluation. *Regul. Toxicol. Pharmacol.* 36 (3), 246–252.
- Caldwell, J., Kennedy, J.F., Chidgey, M.A.J., 1987. Absorption and disposition of topically-applied methylene-carbon-14 benzyl acetate in the rat. In: *Pharmacology and the Skin; Vol. 1. Skin Pharmacokinetics*, pp. 209–213.
- 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.
- Caspary, W.J., Langerbach, R., Penman, B.W., Crespi, C., Myhr, B.C., Mitchell, A.D., 1988. The mutagenic activity of selected compounds at the TK locus: rodent vs. human cells. *Mutat. Research-Reviews Genet. Toxicol.* 196 (1), 61–81.
- Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. *Chem. Central J.* 4 (Suppl. 1), S4.
- Chidgey, M.A.J., Kennedy, J.F., Caldwell, J., 1986a. Studies on benzyl acetate II. Use of specific metabolic inhibitors to define the pathway leading to the formation of benzylmercapturic acid in the rat. *Food Chem. Toxicol.* 24 (12), 1267–1272.
- Chidgey, M.A.J., Caldwell, J., 1986b. Studies on benzyl acetate I. Effect of dose size and vehicle on the plasma pharmacokinetics and metabolism of [methylene-(14)C]benzyl acetate in the rat. *Food Chem. Toxicol.* 24 (12), 1257–1265.
- Chidgey, M.A.J., Kennedy, J.F., Caldwell, J., 1987. Studies on benzyl acetate. III. The percutaneous absorption and disposition of [Methylene(14)C]benzyl acetate in the rat. *Food Chem. Toxicol.* 25 (7), 521–525.
- Clapp, J.J., Young, L., 1970. Formation of mercapturic acids in rats after the administration of aralkyl esters. *Biochem. J.* 118 (5), 765–771.
- Demir, E., Kocaoglu, S., Kaya, B., 2010. Assessment of genotoxic effects of benzyl derivatives by the comet assay. *Food Chem. Toxicol.* 48 (5), 1239–1242.
- Elmore, E., Fitzgerald, M.P., 1990. Evaluation of the bioluminescence assays as screens for genotoxic chemicals. *Prog. Clin. Biol. Res.* 340 (Part D (Mutation & Environment)), 379–387.
- Essential Estimation Programs Interface EPI Suite™ (version 4.1) [Software]. (Copyright 2000–2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Retrieved from <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm> Research, 20(6), 482–487.
- Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames Test. *Toxicology* 18 (3), 219–232.
- Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance ingredients. *Regul. Toxicol. Pharmacol.* 31 (2), 166–181.
- Fourreman, P., Mason, J.M., Valencia, R., Zimmering, S., 1994. Chemical mutagenesis testing in *Drosophila*. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environ. Mol. Mutagen.* 23 (3), 208–227.
- Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., Zeiger, E., 1987. Chromosome aberration and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environ. Mol. Mutagen.* 10 (10), 1–175.
- Garnett, A., Hotchkiss, S.A.M., Caldwell, J., 1994. Percutaneous absorption of benzyl acetate through rat skin in vitro. 3. A comparison with human skin. *Food Chem. Toxicol.* 32 (11), 1061–1065.
- Grundschober, F., 1977. Toxicological assessment of flavouring esters. *Toxicology* 8, 387–390.
- 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.
- Honma, M., Hayashi, M., Shimada, H., Tanaka, N., Wakuri, S., Awogi, T., Yamamoto, K.I., Kodani, N.-U., Nishi, Y., Nakadate, M., Sofuni, T., 1999. Evaluation of the mouse lymphoma tk assay (microwell method) as an alternative to the in vitro chromosomal aberration test. *Mutagenesis* 14 (1), 5–22.
- Hotchkiss, S.A., Fraser, S., Caldwell, J., Miller, J.M., 1988. The Percutaneous Absorption of Benzyl Acetate through Rat Skin in Vitro. Presented at ISSX-88 Mtg., Kobe, Japan.
- Hotchkiss, S.A., Fraser, S., Miller, J.M., Caldwell, J., 1989. Percutaneous absorption of topically applied benzyl acetate in-vitro effect of vehicle on skin penetration. *Hum. Toxicol.* 8 (1), 71–72.
- Hotchkiss, S.A., Fraser, S., Chidgey, M.A.J., Caldwell, J., 1990a. An in vitro skin diffusion technique for the Prediction of in vivo absorption; a case study with benzyl acetate. In: *Prediction of Percutan. Penetration-Methods, Measurements Modelling*, pp. 123–128.
- Hotchkiss, S.A., Chidgey, M.A.J., Rose, S., Caldwell, J., 1990b. Percutaneous absorption of benzyl acetate through rat skin in vitro. 1. Validation of an in vitro model against in vivo data. *Food Chem. Toxicol.* 28 (6), 443–447.
- Hotchkiss, S.A.M., Miller, J.M., Caldwell, J., 1992a. Percutaneous absorption of benzyl acetate through rat skin in vitro. 2. Effect of vehicle and occlusion. *Food Chem. Toxicol.* 30 (2), 145–153.
- Hotchkiss, S.A.M., Nasser-Sina, P., Garnett, A., Caldwell, J., 1992b. In vitro metabolism of benzyl acetate and benzoic acid in cultured human keratinocytes and full thickness human skin. *ISSX Int. Meet.* 2, 158.
- Hotchkiss, S.A.M., Hewitt, P., Mint, A., Garnett, A., Caldwell, J., 1992c. Percutaneous absorption of fragrance chemicals through human skin in vitro. *Toxicol. Lett.* 1 (Suppl. 1), 173.
- Hotchkiss, S.A.M., Garnett, A., Hewitt, P., Mint, A., Caldwell, J., 1992d. Percutaneous absorption of topically applied chemicals through human skin in vitro. In: *Proceedings of the British Pharmacological Society, Clinical Pharmacology Section*, 8–10, April 1992., p. 148P.
- Hotchkiss, S.A.M., 1998. Absorption of fragrance ingredients using in vitro models with human skin. In: *Fragrances: Beneficial and Adverse Effects*, pp. 125–135.
- IFRA (International Fragrance Association), 2008. Use Level Survey. September 2008.
- IFRA (International Fragrance Association), 2011. Volume of Use Survey. February 2011.
- Ishiguro, S., Miyamoto, A., Obi, T., Nishio, A., 1993. Teratological Studies on Benzyl Acetate in Pregnant Rats. *Bull. Fac. Agric. Kagoshima Univ.* 43, 25–31.
- Isola, D., Smith, L.W., Ansari, R., Black, M.S., 2003a. Exposure characterization from a fragranced plug-in air freshener. *Toxicology* 72 (S-1), 291.
- Isola, D.A., Smith, L.W., Rogers, R.E., Black, M.S., 2003b. Exposure characterization of fragranced air fresheners. *Allergy and Clinical Immunology International Supplement* 1, 132.
- Isola, D.A., Rogers, R.E., Myshaniuk, A., Jeng, C.-J., Ansari, R., Smith, L.W., 2004a. Exposure characterization from a surrogate fine fragrance. *Toxicology* 78 (S-1), 107.
- Isola, D.A., Rogers, R., Black, M.S., Smith, L.W., 2004b. Exposure characterizations of three fragranced products. *Int. J. Toxicol. Former J. Am. Coll. Toxicol.* 23 (6), 397.
- Jimbo, Y., 1983. Penetration of fragrance compounds through human epidermis. *J. Dermatol.* 10 (3), 229–239.
- Kevekordes, S., Mersch-Sundermann, V., Burghaus, C.M., Spielberger, J., Schmeiser, H.H., Arlt, V.M., Dunkelberg, H., 1999. SOS induction of selected naturally occurring substances in *Escherichia coli* (SOS chromotest). *Mutat. Research-Genetic Toxicol. Environ. Mutagen.* 445 (1), 81–91.
- Kevekordes, S., Spielberger, J., Burghaus, C.M., Birkenkamp, P., Zietz, B., Paufler, P., Diez, M., Bolten, C., Dunkelberg, H., 2001. Micronucleus formation in human lymphocytes and in the metabolically competent human hepatoma cell line Hep G2: results with 15 naturally occurring substances. *Anticancer Res.* 21 (1A), 461–470.
- Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. *Curr. Problems Dermatol.* 14, 152–171.
- Longnecker, D.S., Roebuck, B.D., Curphey, T.J., Lhoste, E., Coon, C.I., Macmillan, D., 1986. Effects of corn oil and benzyl acetate on number and size of azaserine-induced foci in the pancreas of LEW and F344 rats. *Environ. Health Perspect.* 68, 197–201.
- Longnecker, D.S., Roebuck, B.D., Curphey, T.J., MacMillan, D.L., 1990. Evaluation of promotion of pancreatic carcinogenesis in rats by benzyl acetate. *Food Chem. Toxicol.* 28 (10), 665–668.
- Matsuoka, A., Yamakage, K., Kusakabe, H., Wakuri, S., Asakura, M., Noguchi, T., Sugiyama, T., Shimada, H., Nakayama, S., Kasahara, Y., Takahashi, Y., Miura, K.F., Hatanaka, M., Ishidate Jr., M., Morita, T., Watanabe, K., Hara, M., Odawara, K., Tanaka, N., Hayashi, M., Sofuni, T., 1996. Re-evaluation of chromosomal aberration induction on nine mouse lymphoma assay 'unique positive' NTP carcinogens. *Mutat. Research-Reviews Mutat. Res.* 369 (3–4), 243–252.
- McGinty, D., Letizia, C.S., Api, A.M., Vitale, D., 2012a. Fragrance material review on benzyl acetate. *Food Chem. Toxicol.* 50 (Suppl. 2), S363–S384.
- McGinty, D., Letizia, C.S., Api, A.M., 2012b. Fragrance material review on benzyl butyrate. *Food Chem. Toxicol.* 50 (Suppl. 2), S407–S411.
- McGregor, D.B., Brown, A., Cattanchi, P., Edwards, I., McBride, D., Riach, C., Caspary, W.J., 1988. Responses of the L5178Y tk+/tk- mouse lymphoma cell

- forward mutation assay: III. 72 Coded chemicals. *Environ. Mol. Mutagen.* 12 (2), 85–153.
- McMahon, T.F., Diliberto, J.J., Birnbaum, L.S., 1989a. Age related changes in disposition of benzyl acetate (BA): a model compound for glycine conjugation. *Toxicology* 9 (1), 88.
- McMahon, T.F., Diliberto, J.J., Birnbaum, L.S., 1989b. Age-related changes in the disposition of benzyl acetate: a model compound for glycine conjugation. *Drug Metabolism Dispos.* 17 (5), 506–512.
- Meyer, F. (1965). Penetrating agents. Patent, British, 1,001,949, M497501Va/30h, 7/20/61.
- Mirsalis, J., Tyson, K., Beck, J., Loh, E., Steinmetz, K., Contreras, C., Austere, L., Martin, S., Spalding, J., 1983. Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. *Environ. Mutagen.* 5 (3), 482.
- Mirsalis, J.C., Tyson, C.K., Steinmetz, K.L., Loh, E.K., Hamilton, C.M., Bakke, J.P., Spalding, J.W., 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: testing of 24 compounds. *Environ. Mol. Mutagen.* 14 (3), 155–164.
- Mitchell, A.D., Caspary, W.J., 1987. Concordance of results between in-vitro mammalian cell mutagenesis and clastogenesis assays. *Envir. Mutagen.* 9 (Suppl. 8), 74.
- Miyagawa, M., Takasawa, H., Sugiyama, A., Inoue, Y., Murata, T., Uno, Y., Yoshikawa, K., 1995. The in vivo-in vitro replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. *Mutat. Res. Gen. Toxicol.* 343 (1), 157–183.
- Miyashita, K., Robinson, A.B., 1980. Identification of compounds in mouse urine vapor by gas chromatography and mass spectrometry. *Mech. Ageing Dev.* 13, 177–184.
- Morrissey, R.E., Schwetz, B.A., Lamb, J.C., Ross, M.D., Teague, J.L., Morris, R.W., 1988. Evaluation of rodent sperm, vaginal cytology and reproductive organ weight data from national toxicology program 13 week studies. *Fundam. Appl. Toxicol.* 11 (2), 343–358.
- Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E., 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mutagen.* 8 (7), 1–119.
- Nasseri-Sina, P., Hotchkiss, S.A., Caldwell, J., 1992. Metabolism of benzyl acetate in rat and human keratinocytes and rat hepatocytes: comparative studies with cells in suspension and in culture. *Toxicol. Lett.* 1 (Suppl.), 168.
- National Toxicology Program, 1993. Toxicology and Carcinogenesis Studies of Benzyl Acetate in F344 Rats and B6C3F1 Mice (Feed Studies). NTP-tr-431. NIH Publication No. 92–3162.
- Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of Food Flavours in Bacteria (1st Report), 9. Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen, pp. 177–181.
- OECD, 2012. The OECD QSAR Toolbox, V. 3.1. <http://www.qsartoolbox.org/>.
- Randazzo, J., Kirkpatrick, D.T., Vitale, D., Singal, M., 2014. Evaluation of nose-only inhalation exposure to aerosolized benzyl acetate in Sprague-Dawley rats. *Toxicology* 138 (1), 416.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1957. Toxicological Screening of Ethyl Benzoate, Isobutyl Benzoate, Benzyl Acetate, Benzyl Butyrate, and Ethyl Methylphenylglycidate in Rats. Class V. Aromatic Esters. Unpublished report from Trubek Laboratories, Inc. RIFM report number 29140 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1961. Sensitization and Irritation Studies. Unpublished Report from Givaudan Corporation. RIFM report number 14581 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1802 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1975a. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. Unpublished Report from International Flavors and Fragrances. RIFM report number 24175 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1975b. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. Unpublished Report from International Flavors and Fragrances. RIFM report number 24176 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1975c. Repeated Insult Patch Test of Benzyl Acetate on Human Subjects. Unpublished Report from International Flavors and Fragrances. RIFM report number 24177 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1975d. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. Unpublished Report from International Flavors and Fragrances. RIFM report number 24178 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1975e. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. Unpublished Report from International Flavors and Fragrances. RIFM report number 24179 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1977. The Comparative Respiratory Irritation Potential of Fourteen Fragrance Raw Materials. Doctoral Dissertation. RIFM report number 9011 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1985a. Open and Closed Epicutaneous and Maximization Tests of Fragrance Materials in Guinea Pigs. Unpublished Report from Givaudan Corporation. RIFM report number 6068 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1985b. Closed Epicutaneous Test of Methyl-2-octynoate, Methyl-2-nonynoate, Benzyl Acetate, Trans,trans-2,4-hexadienal, 2-hexylidene Cyclopentanone, Hexen-2-al, Trans-2-hexenal Diethyl Acetal and Isoeugenol in Guinea Pigs. Report to RIFM. RIFM report number 4474 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1985c. Guinea pig Maximization Test. Report to RIFM. RIFM report number 4899 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1986a. Delayed Contact Hypersensitivity Study of Benzyl Acetate in Guinea Pigs. Report to RIFM. RIFM report number 4513 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1986b. Toxicology and Carcinogenesis Studies of Benzyl Acetate in F344/N Rats and B6C3F1 Mice (Gavage Studies). Unpublished report from the National Toxicity Program. RIFM report number 204 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1987. Report on Human Repeated Insult Patch Test. Report to RIFM. RIFM report number 7973 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1988a. Repeated Insult Patch Test in Human Subjects. Report to RIFM. RIFM report number 27673 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1988b. Repeated Insult Patch Test in Human Subjects. Report to RIFM. RIFM report number 27675 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1988c. Repeated Insult Patch Test in Human Subjects. Report to RIFM. RIFM report number 27674 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1988d. Repeated Insult Patch Test in Human Subjects. Report to RIFM. RIFM report number 8881 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. In Vitro Dermal Absorption and Metabolism of Benzyl Acetate. RIFM report number 10270 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Evidence for the Existence of a Cutaneous Reservoir for Benzyl Acetate. RIFM report number 10271 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1997a. Benzyl Acetate - Acute Inhalation Toxicity in Rats 4-hour Exposure. Unpublished report from Haarmann & Reimer GmbH. RIFM report number 35546 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 1997b. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. Unpublished from the Union of German Candle Manufacturers. RIFM report number 18011 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Indoor Air Quality Evaluation of a Plug-in Air Freshener. RIFM report number 43292 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Airborne Levels of Selected Fragrance Materials in a Simulated Bathroom. RIFM report number 41708 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Airborne Levels of Selected Fragrance Materials Following a Controlled Exposure to a Surrogate Fine Fragrance. RIFM report number 47425 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. A Two-week Inhalation Toxicity Study of Aerosolized Benzyl Acetate in the Sprague Dawley Rat. RIFM report number 65459 (RIFM, Woodcliff Lake, NJ, USA.).
- RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Report on the Testing of Benzyl Butyrate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65310.
- Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chem. Res. Toxicol.* 20 (7), 1019–1030.
- Rogan, E.G., Cavalieri, E.L., Walker, B.A., Balasubramanian, R., Wislocki, P.G., Roth, R.W., Saugier, R.K., 1986. Mutagenicity of benzylic acetates, sulfates and bromides of polycyclic aromatic hydrocarbons. *Chem. Biol. Int. Rep.* 58 (3), 253–275.
- Rogers, R.E., Isola, D.A., Smith, L.W., Jeng, C.J., Dews, P., Myshaniuk, A., 2003. Characterization of potential human exposure to fragrances during residential consumer product use. *J. Allergy Clin. Immunol.* 111 (2), S239.
- Rogers, R.E., Isola, D.A., Jeng, C.-J., Smith, L.W., Lefebvre, A., 2005. Simulated inhalation levels of fragrance materials in a surrogate air freshener formulation. *Environ. Sci. Technol.* 39 (20), 7810–7816.
- Rogers, D., Hahn, M., 2010. "Extended-Connectivity fingerprints." *J. Chem. Inf. Model.* 50 (5), 742–754.
- Rossman, T.G., Molina, M., Meyer, L., Boone, P., Klein, C.B., Wang, Z., Li, F., Lin, W.C., Kinney, P.L., 1991. Performance of 133 compounds in the lambda prophage induction endpoint of the Microscreen assay and a comparison with *S. typhimurium* mutagenicity and rodent carcinogenicity assays. *Mutat. Research-Genetic Toxicol.* 260 (4), 349–367.
- Rudd, C.J., Mitchell, A.D., Spalding, J., 1983. L5178Y Mouse lymphoma cell mutagenesis assay of coded chemicals incorporating analyses of the colony size distributions. *Environ. Mutagen.* 5 (3), 419.

- 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.
- Sasaki, Y.F., Sekihashi, K., Izumiya, F., Nishidate, E., Saga, A., Ishida, K., Tsuda, S., 2000. The comet assay with multiple mouse organs: comparison of comet assay results and carcinogenicity with 208 chemicals selected from the IARC monographs and US NTP Carcinogenicity Database. *Crit. Rev. Toxicol.* 30 (6), 629–799.
- Schunk, H.H., Shibamoto, T., Tan, H.K., Wei, C.-L., 1986. Biological and chemical studies on photochemical products obtained from eugenol, benzyl acetate and benzyl benzoate. *Flavors Frag., A World Persp.* In: Proc. 10th Internat. Cong. Es. Oils, pp. 1045–1068.
- Scott, A., Malcomber, S., Maskell, S.M.C., Windebank, S., Diaz, D., Carmichael, P., 2007. An assessment of the performance of an automated scoring system (Cellomics) for the in vitro micronucleus assay in CHPO-K1 cells. *Toxicology* 231 (2–3), 104–119.
- Sekihashi, K., Yamamoto, A., Matsumura, Y., Ueno, S., Watanabe-Akanuma, M., Kassie, F., Knasmuller, S., Tsuda, S., Sasaki, Y.F., 2002. Comparative investigation of multiple organs of mice and rats in the comet assay. *Mutat. Research-Genetic Toxicol. Environ. Mutagen.* 517 (1–2), 53–75.
- Shelby, M.D., Erexson, G.L., Hook, G.L., Tice, R.R., 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. *Environ. Mol. Mutagen.* 21 (2), 160–179.
- Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. "An in silico skin absorption model for fragrance materials." *Food Chem. Toxicol.* 74 (12), 164–176.
- Silver, W.L., 1992. Neural and pharmacological basis for Nasal irritation. In: *Annals of the New York Academy of Sciences*, 641, pp. 152–163.
- Smith, L.W., Rogers, R.E., Black, M.S., Isola, D.A., 2004. Exposure characterizations of three fragranced products. *Toxicol. Appl. Pharmacol.* 197 (3), 189.
- Snapper, J., Grunbaum, A., Sturkop, S., 1925. About the fission and oxidation of benzyl alcohol and benzyl esters in the human organism. *Biochem. Z.* 155, 163–173.
- Steinmetz, K.L., Mirsalis, J.C., 1984. Measurement of DNA repair in primary cultures of rat pancreatic cells following in vivo treatment. *Environ. Mutagen.* 6 (3), 446.
- Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., Minor, R., 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. *Science* 236, 933–941.
- USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, 4. United States Environmental Protection Agency, Washington, DC, USA, p. 11.
- Vethanayagam, D., Vilagoftis, H., Mah, D., Beach, J., Smith, L., Moqbel, R., 2013. Fragrance materials in asthma: a pilot study using a surrogate aerosol product. *J. Asthma* 50 (9), 975–982.
- Witt, K.L., Knapton, A., Wehr, C.M., Hook, G.J., Mirsalis, J., Shelby, M.D., MacGregor, J.T., 2000. Micronucleated erythrocyte frequency in peripheral blood of B6C3F1 mice from short-term, prechronic, and chronic studies of the NTP carcinogenesis bioassay program. *Environ. Mol. Mutagen.* 36 (3), 163–194.
- Yasunaga, K., Kiyonari, A., Oikawa, T., Abe, N., Yoshikawa, K., 2004. Evaluation of the Salmonella umu test with 83 NTP chemicals. *Environ. Mol. Mutagen.* 44 (4), 329–345.
- Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. *J. Osaka City Med. Cent.* 34 (3–4), 267–288 ([Osaka-shi Igakkai Zasshi]).
- Yoshikawa, K., 1996. Anomalous nonidentity between Salmonella genotoxicants and rodent carcinogens: Nongenotoxic carcinogens and genotoxic non-carcinogens. *Environmental Health Perspectives* 104 (1), 40–46.
- Young, S.S., 1989. What is the proper experimental unit for long-term rodent studies? An examination of the NTP benzyl acetate study. *Toxicology* 54, 233–239.
- Zimmermann, F.K., Scheel, I., Resnick, M.A., 1989. Induction of chromosome loss by mixtures of organic solvents. *Mutation Res. Gen. Toxicol.* 224 (2), 287–303.