Short review

RIFM fragrance ingredient safety assessment, 2-methyl-3-buten-2-ol, CAS Registry Number 115-18-4

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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 toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential as well as environmental safety. Repeated dose, developmental, and reproductive toxicities were determined to have the most conservative systemic exposure derived NOAEL of 50 mg/kg/day, based on OECD gavage toxicity studies in rats, that resulted in a MOE of 4545455 after considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

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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).

This safety assessment is based on RIFM’s Criteria Document (Api et al., 2015) and should be referred to for clarification.

*RIFM’s Expert Panel* concludes that this material is safe under the limits described in this safety assessment. This safety assessment is based on RIFM’s Criteria Document (Api et al., 2015) and 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.

### Abbreviation list

- **Box Model** – a RIFM, Inc. proprietary in silico tool used to calculate fragrance air exposure concentration
- **BCE** – 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

*RIFM’s Expert Panel* concludes that this material is safe under the limits described in this safety assessment. This safety assessment is based on RIFM’s Criteria Document (Api et al., 2015) and 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).

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### Human Health Safety Assessment

**Genotoxicity:** Not Genotoxic

**Repeated Dose Toxicity:** NOAEL = 50 mg/kg/day

**Developmental and Reproductive Toxicity:** NOAEL = 50 mg/kg/day

**Skin Sensitization:** Not sensitizing

**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergic

**Local Respiratory Toxicity:** No NOAEC available. Exposure is below TTC.

### Environmental Safety Assessment

**Persistence:** Critical Measured Value: 67%
1. **Identification**

1. **Chemical Name:** 2-Methyl-3-buten-2-ol
2. **CAS Registry Number:** 115-18-4
3. **Synonyms:** 3-Buten-2-ol, 2-methyl-, 1,1,-Dimethyl-2-propenol, 2-Methyl-3-buten-2-ol, \( \gamma \)-H \( \gamma \)-z \( \gamma \)-3-\( \gamma \)-C \( \gamma \)-5-8), 2-Methylbut-3-en-2-ol
4. **Molecular Formula:** \( \text{C}_6 \text{H}_{10} \text{O} \)
5. **Molecular Weight:** 86.13
6. **RIFM Number:** 6122

2. **Physical data**

1. **Boiling Point:** 93.27 °C [EPI Suite]
2. **Flash Point:** 56.0 °F TCC (13.33 °C)\(^1\)
3. **Log Kow:** 1.08 [EPI Suite]
4. **Melting Point:** –62.39 °C [EPI Suite]
5. **Water Solubility:** 48,740 mg/L [EPI Suite]
6. **Specific Gravity:** 0.81800 to 0.82700 @ 25.00 °C
7. **Vapor Pressure:** 17 mm Hg @ 20 °C [EPI Suite 4.0], 23.4 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Does not significantly absorb in the region of 290–700 nm; molar absorption coefficient is below the benchmark.

3. **Exposure**

1. **Volume of Use (worldwide band):** [IFRA, 2011]
   - <1 metric tons per year
2. **Average Maximum Concentration in Hydroalcohols:** 0.002% [IFRA, 2007]
3. **97.5th Percentile:** 0.0005% [IFRA, 2007]
4. **Dermal Exposure:** \( a \): 0.00001 mg/kg/day [IFRA, 2007]
5. **Oral Exposure:** Not available
6. **Inhalation Exposure:** \( b \): 0.0000008 mg/kg/day [IFRA, 2007]
7. **Total Systemic Exposure (Dermal + Inhalation):** 0.000011 mg/kg/day

\(^a\) 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).

\(^b\) 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.

1. **Bioaccumulation:** Screening Level: 2.4 L/Kg
2. **Ecotoxicity:** Screening Level: 734 mg/L
3. **Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**

- **Screening Level:** PEC/PNEC (North America and Europe) < 1
- **Critical Ecotoxicity Endpoint:** 734 mg/L
- **RIFM PNEC:** 0.734 μg/L
- **Revised PEC/PNECs** (2011 IFRA VoU): North America and Europe Not Applicable, cleared at Screening Level

4. **Derivation of systemic absorption**

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.000011 mg/kg/day

5. **Computational toxicology evaluation**

1. **Cramer Classification:** Class III, High

**Expert judgment**

- **Toxtree** (v 2.6.0)
- **OECD QSAR toolbox** (v 3.2)

| III | III | III |

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

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)**

   2-Methyl-3-buten-2-ol is reported to occur in the following foods:\(^2\):

\(^2\) 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.
The above data demonstrate that 2-Methyl-3-buten-2-ol does not have the potential to be genotoxic.

**Additonal References:** RIFM, 1991; RIFM, 2013.

**Literature Search and Risk Assessment Completed on:** 05/17/13.

### 10.1.3. Repeated dose toxicity

The margin of exposure for 2-methyl-3-buten-2-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

### 10.1.4. Risk assessment

The repeated dose toxicity data on 2-methyl-3-buten-2-ol are sufficient for the repeated dose endpoint. An OECD 407 gavage 28-day subchronic toxicity study conducted in rats determined the NOAEL to be 50 mg/kg/day, based on increased liver weights and hypertrophy of hepatocytes (OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.000011 or 454545.

**Additional References:** McGinty et al., 2010a; Belsito et al., 2010; RIFM, 1994; RIFM, 1980; Politano et al., 2008; RIFM, 2006; Letizia et al., 2007; RIFM, 2007a; RIFM, 2007b; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003; Lacznynski et al., 2008a, 2008b, 2008c; Bickers et al., 2003; Belsito et al., 2008; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madystha, 1982; Chadha and Madystha, 1982; RIFM, 1984; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959, 1965; RIFM, 2010; Lacznynski et al., 2008d; McGinty et al., 2010b; Hanley et al., 1997; Blair et al., 2000; Howes et al., 2002; Elliott and Lachance, 1980; Longenecker et al., 1939; OECD SIDS, 2003; Isophytol; McGinty et al., 2010c; Cal, 2003; Cal, 2006a; Cal, 2006b.

**Literature Search and Risk Assessment Completed on:** 05/17/13.

### 10.1.5. Developmental and reproductive toxicity

The margin of exposure for 2-methyl-3-buten-2-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

### 10.1.6. Risk assessment

The developmental and reproductive toxicity data on 2-methyl-3-buten-2-ol are sufficient for the developmental and reproductive toxicity endpoints. An OECD 421 gavage reproduction/developmental toxicity screening test conducted in rats determined the developmental toxicity NOAEL to be 50 mg/kg/day, based on reduced pup viability, and the reproductive toxicity NOAEL to be 50 mg/kg/day, based on clinical signs, decreased male body weight gain, and decreased female feed consumption during lactation (OECD SIDS, 1995: 3-Buten-2-ol, 2-methyl-). Therefore, the MOE for developmental and reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.000011 or 454545.

**Additional References:** McGinty et al., 2010a; Belsito et al., 2010; RIFM, 1994; RIFM, 1980; Politano et al., 2008; RIFM, 2006; Letizia et al., 2007; RIFM, 2007a; RIFM, 2007b; RIFM, 2008a; RIFM, 2008b; RIFM, 2008c; Lalko et al., 2007; Lalko et al., 2008; Letizia et al., 2003; Lacznynski et al., 2008a, 2008b, 2008c; Bickers et al., 2003; Belsito et al., 2008; RIFM, 1958; RIFM, 1979; RIFM, 2012; Stoner et al., 1973; Randazzo et al., 2013; Hood et al., 1978; Howes et al., 2002; Jirovetz et al., 1990, 1991; Parke et al., 1974; Green and Tephly, 1996; Meesters et al., 2007; Chadha and Madystha, 1982; Chadha and Madystha, 1982; RIFM, 1984; Jager et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959, 1965; RIFM, 2010; Lacznynski et al., 2008d; McGinty et al., 2010b; Hanley et al., 1997; Blair et al., 2000; Howes et al., 2002; Elliott and Lachance, 1980; Longenecker et al., 1939; OECD SIDS, 2003; Isophytol; McGinty et al., 2010c; Cal, 2003; Cal, 2006a; Cal, 2006b.
et al., 1992; Schmitt et al., 2010; Meyer and Meyer, 1959, 1965; RIFM, 2010; Łapczynski et al., 2008d; McGinty et al., 2010b; Hanley et al., 1997; Blair et al., 2000; Howes et al., 2002; Elliott and Lachance, 1980; Longenecker et al., 1939; OECD SIDS, 2003: Isophytol; McGinty et al., 2010c; Cal, 2003; Cal, 2006a; Cal, 2006b.

10.1.7. Skin sensitization

Based on the existing data, 2-methyl-3-buten-2-ol does not present a concern for skin sensitization.

10.1.8. Risk assessment

The chemical structure of 2-methyl-3-buten-2-ol indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.0) and in a guinea pig maximization study the material was not observed to result in reactions indicative of sensitization (RIFM, 1991). Based on the existing data, 2-methyl-3-buten-2-ol does not present a concern for skin sensitization.


10.1.9. Phototoxicity/photoallergenicity

Based on the available UV spectra, 2-methyl-3-buten-2-ol does not present a concern for phototoxicity/photoallergenicity.

10.1.10. Risk assessment

Based on the available UV spectra, 2-methyl-3-buten-2-ol does not present a concern for phototoxicity. The available spectra for 2-methyl-3-buten-2-ol demonstrates that this material has limited to no absorption in the region of 290—700 nm. The molar absorption coefficient for λmax between 290 and 700 nm is well below the benchmark (1000 L mol⁻¹ cm⁻¹) considered to be of concern for phototoxic effects (Henry et al., 2009). While there are no phototoxicity studies available on 2-methyl-3-buten-2-ol, the UV spectrum demonstrates that this material does not present a concern for phototoxicity/photoallergenicity.

Additional References: None.

10.1.11. Local respiratory toxicity

The margin of exposure for 2-methyl-3-buten-2-ol could not be calculated due to lack of appropriate data. The 2-methyl-3-buten-2-ol exposure level is below the inhalation TTC Cramer Class III* limit for local effects.

10.1.12. Risk assessment

There are no inhalation data available on 2-methyl-3-buten-2-ol to address local respiratory toxicity. Based on the IFRA survey results for hydroalcohols, the 97.5th percentile was reported to be 0.0005%. If 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 inhalation combined exposure would be 0.000046 mg/day, as calculated by RIFM’s 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value. This value is below the Cramer Class III TTC level of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009) and is deemed safe for use at the reported use level.

Key Studies: None.


10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 2-Methyl-3-buten-2-ol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material’s volume of use in a region, its log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, 2-Methyl-3-buten-2-ol 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 2-methyl-3-buten-2-ol as being possibly bioaccumulative or persistent 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., US EPA’s BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current VoU from 2011, 2-Methyl-3-buten-2-ol presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key Studies

10.2.3.1. Biodegradation. None available in the RIFM Database but as discussed below 2-methyl-3-buten-2-ol is expected to be 67% biodegradable.

10.2.3.2. Ecotoxicity. There are 4 studies in the RIFM Database.

There are 2 algae inhibition studies. In one study using Scenedesmus subsipicatus, an EC50 could not be calculated. Protocol details are limited. A 72 h EC20 was reported as 300.7 mg/L (RIFM, 1989b). In another study following OECD Test Guideline 201 and also using S. subsipicatus, the reported 72 h EC50 was >500 mg/L (RIFM, 1992b).

A Daphnia magna immobilization study was performed following Method C2 of Annex V to Directive 79/831 EEC using nominal concentrations of 2-methyl-3-buten-2-ol. The reported EC50 was >500 mg/L (RIFM, 1988a).

An acute fish study following German guideline DIN 38 412, using Leuciscus idus under flow through conditions reported a 96 h LC50 of >2200 and <4600 mg/L (RIFM, 1988b).
10.2.4. Other available data

This material has been registered under REACH. Additional data are reported below. These data were accessed on 14 May 2013. A biodegradation study is reported following OECD Test Guideline 301F. At the end of 28 days 67% biodegradation was observed. The 10-day window was not met. The aquatic toxicity studies are reported above.

10.2.5. Risk assessment refinement

Ecotoxicological data and PNEC derivation. Endpoints used to calculate PNEC are underlined.

Table: RIFM Framework Screening Level (Tier 1)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Europe (EU)</th>
<th>North America (NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Kow used</td>
<td>1.08</td>
<td>1.08</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dilution Factor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Regional Volume of Use Tonnage Band</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Risk Characterization: PEC/PNEC</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

The RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.734 μg/L. The revised PEC/PNECs for EU and NA are <1, cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 05/17/13.

11. Literature Search

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- OECD Toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- IARC: (http://monographs.iarc.fr)
- OECD SIDS: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0E5F5C212B7906229F477472A9A4DD05B7
- US EPA Robust Summary: http://cfpub.epa.gov/hpv-s/

- Japan Existing Chemical Data Base: http://dra4.nih.go.jp/mhw_data/jsp/SearchPageENG.jsp
- Google: https://www.google.com/webhp?tab=wwvei=KMSOUIpIQk-arsQ5324GwBg&ved=0CBQI154

This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.07.009.

References


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


RIFM (Research Institute for Fragrance Materials, Inc.), 1995a. Toxicological Screening of Citronellic and Linalool in Rats. Class VI. Private Communication to FEMA. RIFM report number 54572. RIFM, Woodcliff Lake, NJ, USA.


RIFM (Research Institute for Fragrance Materials, Inc.), 2007a. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from a Dipropylene Glycol (DPG) Vehicle. RIFM report number 54457. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2007b. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from a Dihexyl Phthalate (DHP) Vehicle. RIFM report number 54458. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2008a. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from an Ethanol/diethyl Phthalate Vehicle. RIFM report number 54459. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2008b. In vitro Human Skin Penetration of Fragrance Material Linalool Under Both In-use and Occluded Conditions from a Dipropylene Glycol Vehicle. RIFM report number 54460. RIFM, Woodcliff Lake, NJ, USA.


RIFM (Research Institute for Fragrance Materials, Inc.), 2012. A Two-week Inhalation Toxicity Study of Aerosolized Linalool in the Sprague Dawley Rat. RIFM report number 63821. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. 2-Methyl-3-buten-2-ol: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 66940. RIFM, Woodcliff Lake, NJ, USA.


