



RIFMTM

RESEARCH INSTITUTE FOR
FRAGRANCE MATERIALS

Anne Marie Api, PhD Vice President

State-of-the-art science can help consumers enjoy fragranced products with confidence in safety.

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For more than 50 years, the Research Institute for Fragrance Materials has worked to fulfill our core purpose:

To build universal acceptance and trust in the safe use of fragrance materials through applied science and research.



The Expert Panel for Fragrance Safety provides the scientific authority and objectivity to RIFM's work.

<http://fragrancesafetypanel.org>



EXPERT PANEL
for FRAGRANCE SAFETY

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Our Mission

To conduct an independent, unbiased assessment of fragrance material safety in accordance with generally accepted scientific criteria, standards and methodologies



The Expert Panel for Fragrance Safety is an international group of academic and clinical experts.



RIFM has a long history of publishing data on fragrance materials.

1973 First Monograph

FRAGRANCE RAW MATERIALS MONOGRAPHS 97

ACETATE C-9

Synonyms: 1-Nonyl acetate; petargonyl acetate.
Structure: $\text{CH}_3(\text{CH}_2)_8\text{COOCH}_3$
Description and physical properties: *Food Chemicals Codex* (1966).
Occurrence: Apparently it has not been reported to occur in nature.
Preparation: By acetylation of alcohol C-9.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	Detergents	Cosmetics	Perfume
Usual	0.01	0.001	0.005	-
Maximum	0.09	0.015	0.02	0.20

Analytical data: Gas chromatogram, RIFM no. 71-5; infra-red curve, RIFM no. 71-5.

Status

Acetate C-9 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 1.11144). The Council of Europe (1970) listed acetate C-9 (nonyl acetate), giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1966) has a monograph on acetate C-9.

Biological data

Acute toxicity. The acute oral LD₅₀ value (RIFM sample no. 71-5) was reported as > 50 g/kg in the rat (Levenstein, 1972). The acute dermal LD₅₀ for sample no. 71-5 was reported to be > 50 g/kg (Levenstein, 1972).

Flame testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 2% concentration in petrolatum and no case of sensitization was reported (Kligman, 1972).

References

Council of Europe (1970). Natural and Artificial Flavoring Substances. Partial Agreement in the Social and Public Health Field. Lie A. O. Series 1, no. 198, p. 39. Strasbourg.
 Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 788. *Flavoring*, Chicago 17 (2), part 4, 125.
Food Chemical Codex (1966). 1st ed. Prepared by the Committee on Specifications of the Food Chemicals Codex of the Food Protection Committee, p. viii. National Academy of Sciences-National Research Council Publ. 1460, Washington, D.C.
 Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. Amer. Derm. Ass.* 12, 221.
 Kligman, A. M. (1972). Report to RIFM, 27 March.
 Levenstein, I. (1970). Report to RIFM, 7 April.

2003 First Group Summary



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Food and Chemical Toxicology

Food and Chemical Toxicology

2014 First Safety Assessment Individual Ingredients

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT
3-(m-tert-BUTYLPHENYL)-2-METHYLPROPIONALDEHYDE (m-BMHCA)
 CAS Registry Number 62518-65-4

Version: Draft as of 04/01/14. This version replaces any previous versions.

Name: 3-(m-tert-butylphenyl)-2-methylpropionaldehyde (m-BMHCA)
 CAS Registry Number: 62518-65-4



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

This material was evaluated for genetic, repeated dose, developmental, reproductive, respiratory and photo-toxicity as well as skin sensitization potential. The critical studies were an OECD 407 genetic subchronic toxicity study conducted on groups of male and female Wistar rats with a NOEL of 50mg/kg and an enhanced OECD 415 genetic 1 generation reproduction study conducted in rats (BASF, 2011; #62368). This resulted in an MOE of 1250.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (Wagner, 1999; #55188; BASF, 2010; #60847; Guel, 2000; #35691; Guel, 2000; #55680; Repeated Dose Toxicity: NOAEL = 50 mg/kg/day (BASF, 2009; #64472).
Developmental and Reproductive Toxicity: NOAEL = 50 mg/kg/day (BASF, 2011; #62368).
Skin Sensitization: NESL = 4120 µg/cm² (IFF, 1980; #52292).
Phototoxicity/Photoallergy: Not Phototoxic (Givaudan, 1982; #34324; Givaudan, 1986; #56764). (Givaudan, 1980; #56767).
Respiratory (Scent) Toxicity: No NOAEC available. Exposure is below the TTC.

Human Health Margin of Exposure

Critical Endpoint: Developmental and Reproductive Toxicity NOAEL: 50 mg/kg/day (BASF, 2011; #62368).
Total Systemic Exposure: 0.040 mg/kg/day
Margin of Exposure: 1250

Environmental Safety Assessment

Hazard Assessment:
 Screening-Level Hazard Assessment: Not persistent (P) nor bioaccumulative (B) (EPI Suite ver 4.1)
 Bioaccumulation: Bioadverses to phenylpropionals/dehydro (43% 104%)
 NOT PERSISTENT

Risk Assessment:

Screening-Level PEC/PNEC (North America and Europe) > 1 (RIFM Framework/Safety, 2002; #60331)
 Critical Toxicity Endpoint: Fish LC50 (1.1 mg/l) for β-ketethyl-3-(1-methylthio) benzene propenal (CAS#

Research Institute for Fragrance Materials, Inc.

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RIFM values transparency of its scientific work.

Food and Chemical Toxicology **Fragrance Material Safety Assessment Center**



Safety Assessment Sheet Database

Search Safety Assessment Sheets

CAS Number

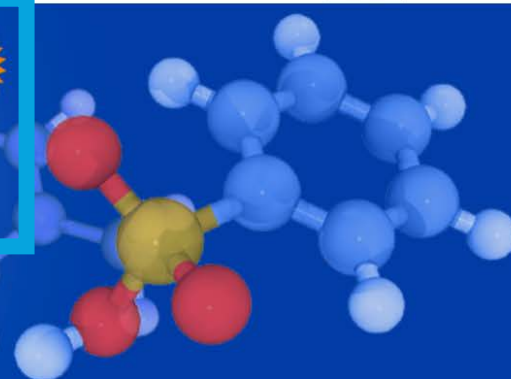
Chemical Name/Synonym

Apply

To access the Safety Assessment Sheet, use the pull down menu above to search by either CAS number or chemical name or synonym.



The purpose of the RIFM safety assessment is to ensure the safe use of fragrance materials in consumer products. Assessments of the data supporting the safe use of fragrance materials follow the updated Criteria Document. The Criteria Document provides guidance on conducting safety assessments and is designed to incorporate the best science to appropriately evaluate fragrance ingredients using the latest testing strategies and methods. The assessments may be found by using the search feature above. Previously published assessments may be found at the links below.



RIFM is the international scientific authority for the safe use of fragrance materials. RIFM's Mission is to engage in research and evaluation of fragrance materials through the guidance of an independent panel of scientific experts and has a long history of disseminating results in peer-reviewed scientific journals. For more information on RIFM and its mission go to www.rifm.org.

Criteria Document

Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) Safety Evaluation Process for Fragrance Ingredients

Api AM, Belsito D, Bruze M, et al

Feature Articles

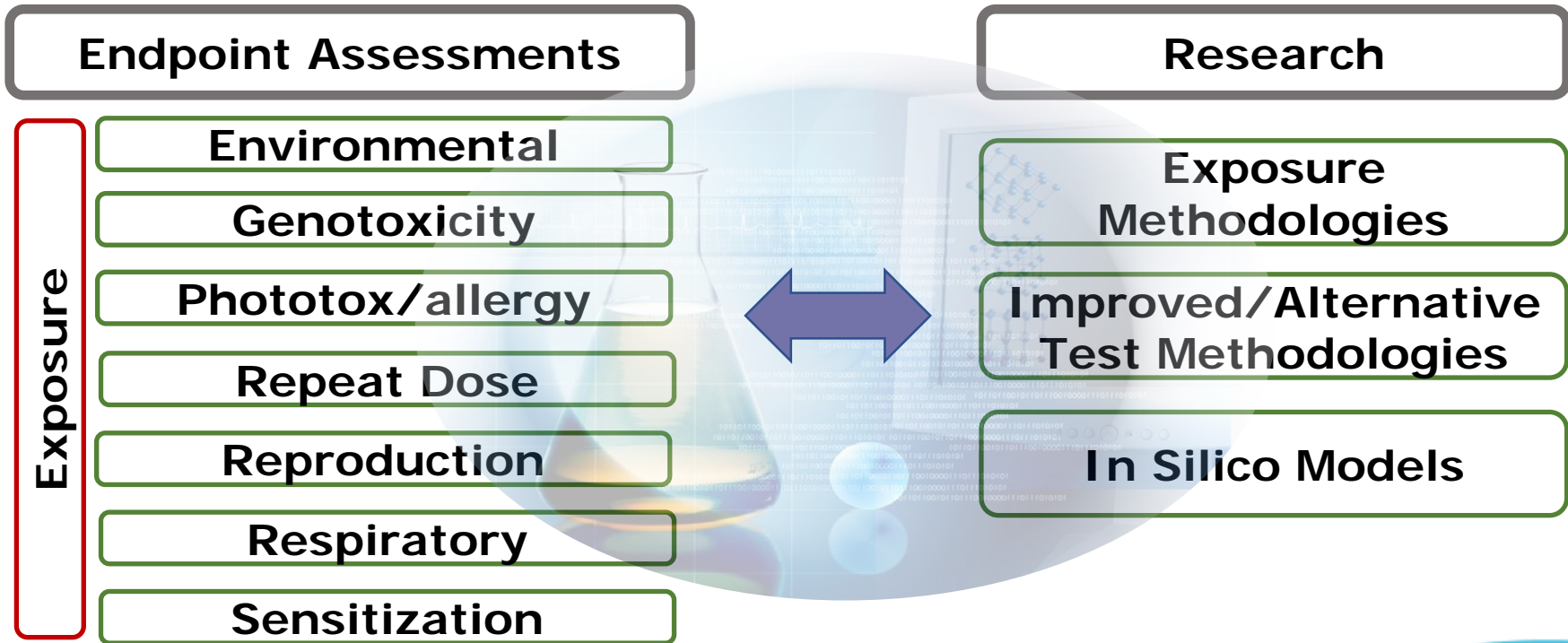
Integrating Habits and Practices Data for Soaps, Cosmetics and Air Care Products into an Existing Aggregate Exposure Model
Comiskey D, Api AM, Barrett C, et al
In order to accurately assess aggregate



About Safety Assessments

- Introduction to Fragrance Material Safety Assessments
- Information for Reviewers

RIFM staff works on two complimentary scientific endeavors to bring the best science to fragrance material safety.



What is the Creme RIFM Model?

A tool to estimate aggregate exposure from consumer product ingredients.

- Cosmetics, personal care products, air care products and household cleaning products.
- United States and Europe populations.
- Systemic, Dermal, Inhalation, Ingestion.
- Probabilistic model based on real world data.
- Flexible and customizable.



Data on consumer use supports the probabilistic model for aggregate dermal and systemic exposure.



Threshold of Toxicological Concern (TTC) continues to be a strategic component of the RIFM safety assessment program

Endpoint	Total (2013-2019)	
	TTC*	Animals Saved
Repeated dose	537	53,700
Developmental	688	68,800
Reproduction	732	73,200
Inhalation	1110	44,400
Sensitization	555	24,975
Total		265,075

*Used in safety assessments (not materials) As of Oct 28, 2019

RIFM continues to support the use of TTC (oral and inhalation) through research programs



Regul Toxicol Pharmacol. 2020 Jun 27;116:104718.
doi: 10.1016/j.yrtph.2020.104718. Online ahead of print.

The research on respiratory sensitizers has changed focus to concentrate on earlier events in the adverse outcome pathway



**1 Reliable
Evidence**

**2 Possible
Evidence**

**3 Unsubstantiated
Report**

Odor thresholds can be used to show that they are much lower than the Observed No Effect Level



Odor threshold

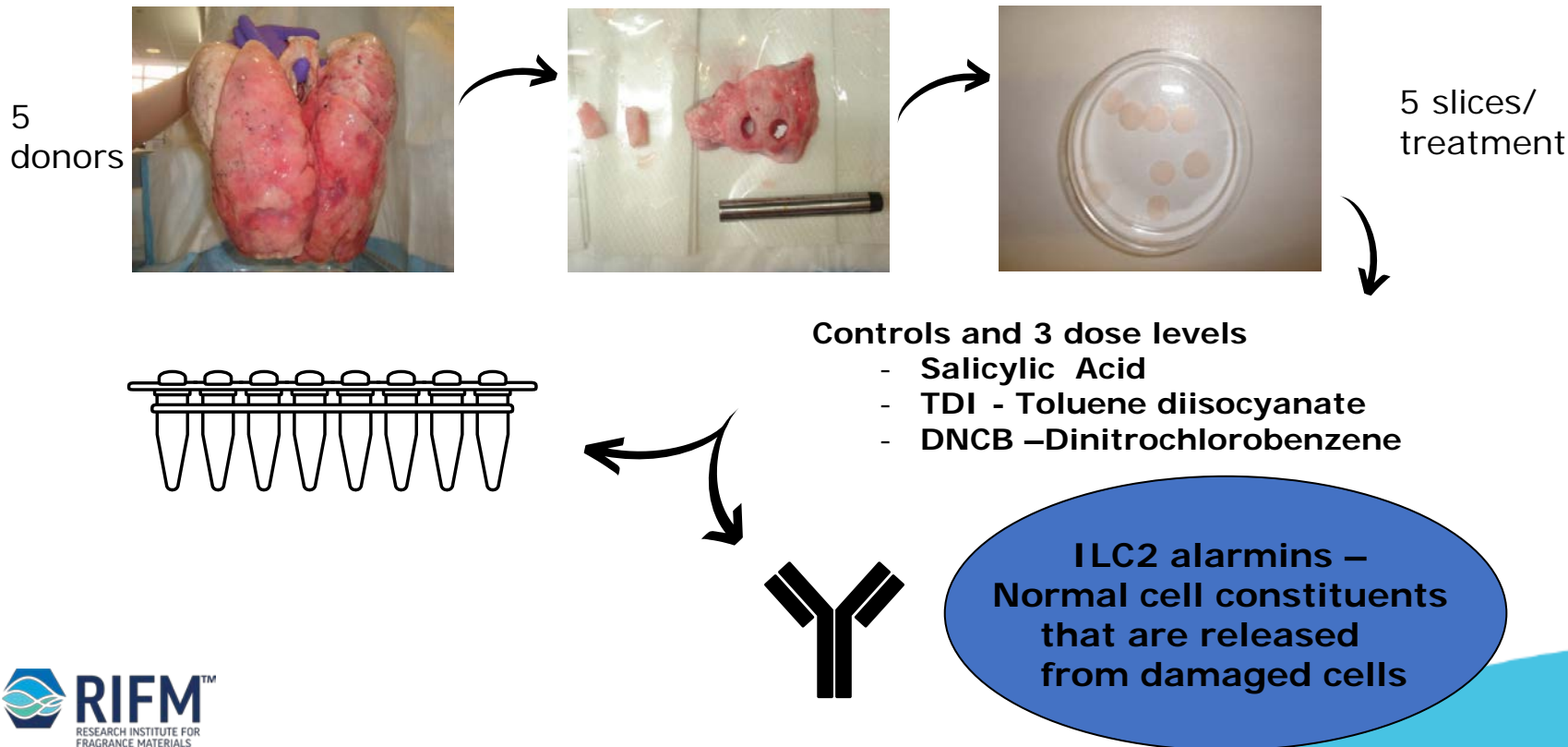


Inhalation exposure



Observed No Effect Level

RIFM is investigating the effects of respiratory irritants and sensitizers in a human precision cut lung slice (hPCLS) assay





QUESTIONS – More Information

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