

Available online at www.sciencedirect.com





Food and Chemical Toxicology 43 (2005) 1179-1206

www.elsevier.com/locate/foodchemtox

Review

The FEMA GRAS assessment of phenethyl alcohol, aldehyde, acid, and related acetals and esters used as flavor ingredients

T.B. Adams ^{a,*}, S.M. Cohen ^b, J. Doull ^c, V.J. Feron ^d, J.I. Goodman ^e, L.J. Marnett ^f, I.C. Munro ^g, P.S. Portoghese ^h, R.L. Smith ⁱ, W.J. Waddell ^j, B.M. Wagner ^{k,l}

^a Scientific Secretary to the FEMA Expert Panel, Flavor and Extract Manufacturers Association, 1620 I Street, NW, Suite 925, Washington, DC 20006, USA

^b Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE 68198, USA
^c Department of Pharmacology and Toxicology, University of Kansas Medical Center, Kansas City, KS 66103, USA

d TNO Nutrition and Food Research Toxicology, Zeist, The Netherlands

Department of Pharmacology and Toxicology, Michigan State University, B440 Life Science Building, East Lansing, MI 48824, USA

f Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

g CanTox, Inc., Mississauga, Ontario, Canada

^h Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

ⁱ Division of Biomedical Sciences Section of Molecular Toxicology, Imperial College School of Medicine, South Kensington, London SW7 2AZ, UK

^j Department of Pharmacology and Toxicology, University of Louisville School of Medicine, Louisville, KY 40292, USA

k New York University, School of Medicine, New York, NY 10016, USA

Bernard M. Wagner, Associates Millburn, New Jersey 07078, USA

Received 8 September 2004; accepted 26 November 2004

Abstract

This publication is the ninth in a series of safety evaluations performed by the Expert Panel of the Flavor and Extract Manufacturers Association (FEMA). In 1993, the Panel initiated a comprehensive program to re-evaluate the safety of more than 1700 GRAS flavoring substances under conditions of intended use. Elements that are fundamental to the safety evaluation of flavor ingredients include exposure, structural analogy, metabolism, pharmacokinetics and toxicology. Flavor ingredients are evaluated individually and in the context of the available scientific information on the group of structurally related substances. Scientific data relevant to the safety evaluation of the use of phenethyl alcohol, aldehyde, acid, and related acetals and esters as flavoring ingredients is evaluated. The group of phenethylalcohol, aldehyde, acid, and related acetals and esters was reaffirmed as GRAS (GRASr) based, in part, on their self-limiting properties as flavoring substances in food, their rapid absorption, metabolic detoxication, and excretion in humans and other animals, their low level of flavor use, the wide margins of safety between the conservative estimates of intake and the no-observed-adverse effect levels determined from subchronic and chronic studies and the lack of significant genotoxic and mutagenic potential. This evidence of safety is supported by the fact that the intake of phenethyl alcohol, aldehyde, acid,

* Corresponding author. Tel.: +1 202 293 5800; fax: +1 202 463 8998.

E-mail address: tadams@therobertsgroup.net (T.B. Adams).

Abbreviations: ABS, chromosomal aberration; ALDH, alcohol dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; *B. subtilis, Bacillus subtilis*; bw, body weight; CHO, Chinese hamster ovary; D. melanogaster + Drosophila melanogaster; DNA, deoxyribonucleic acid; *E. coli, Escherichia coli*; F, Female; FDA, United States Food and Drug Administration; FEMA, The Flavor and Extract Manufacturers Association of the United States; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; GRAS, Generally Recognized as Safe; GRASa, GRAS affirmed; GRASr, GRAS reaffirmed; ip, intraperitoneal; LD₅₀, medianlethal dose; M, male; NAS, National Academy of Science; NOAEL, no-observed-adverse effect level; NR, not reported; NTP, National Toxicology Program; PCE, polychromatic erythrocytes; PFC, plaque-forming cell; ppm, parts per million; SRBC, sheep red blood cell; *S. typhimurium*, *Salmonella typhimurium*; SCE, sister chromatid exchanges; SLR, scientific literature review; UDS, unscheduled DNA synthesis.

and related acetals and esters as natural components of traditional foods is greater than their intake as intentionally added flavoring substances.

© 2004 Elsevier Ltd. All rights reserved.

Keywords: PEA; Flavoring ingredients; FEMA GRAS

Contents

1.	Chen	Chemical identity		
2. Exposure				1181
	2.1.	2.1. Flavor use and natural occurrence		
3.	Hydr	Hydrolysis, absorption, distribution, excretion and metabolism		
	3.1.	Hydro	lysis	1181
	3.2.	Absorption, distribution and excretion.		1181
		3.2.1.	Phenethyl alcohol (no. 1) and phenylacetic acid (no. 21)	1181
		3.2.2.	Phenoxyethyl alcohol and phenoxyacetic acid (no. 40) derivatives	1187
	3.3.	Metabolism		1190
		3.3.1.	Phenethyl alcohol derivatives	1190
		3.3.2.	Phenylacetic acid	1190
		3.3.3.	Phenoxyethyl derivatives	1191
		3.3.4.	Biochemical studies	1192
4.	Toxicological studies			1193
	4.1. Acute toxicity		toxicity	1193
	4.2.	Short-1	term studies of toxicity	1193
		4.2.1.	Phenethyl senecioate (no. 12) and isopropylphenylacetaldehyde (no. 38)	1193
		4.2.2.	Phenethyl phenylacetate (no. 13)	1196
		4.2.3.	Ethyl (p-tolyloxy)acetate (no. 41)	1196
		4.2.4.	Sodium 2-(4-methoxyphenoxy)propanoate (no. 43)	1196
	4.3.	Long-term studies of toxicity and carcinogenicity		1197
		4.3.1.	Phenethyl alcohol (no. 1)	1197
	4.4.	Genotoxicity studies		1197
		4.4.1.	In vitro	1197
		4.4.2.	In vivo	1199
		4.4.3.	Conclusion	1199
	4.5.	Other relevant studies		1199
		4.5.1.	Phenethyl alcohol (no. 1) and phenylacetic acid (no. 21)	1199
		4.5.2.	Phenoxyethyl alcohol	1200
		4.5.3.	Phenoxyacetic acid (no. 40)	1201
		4.5.4.	Sodium 2-(4-methoxyphenoxy)propanoate (no. 43)	1201
		4.5.5.	Phenethyl alcohol (no. 1) and phenethyl acetate (no. 3)	1201
		4.5.6.	Phenylacetic acid (no. 21)	1202
		4.5.7.	Sodium 2-(4-methoxyphenoxy)propanoate (no. 43)	1202
5.	Reco	gnition (of GRASr status	1203
	Refer	References		
	Further reading			

1. Chemical identity

This review presents the key data relevant to the safety evaluation of 39 phenethyl alcohol derivatives and 4 phenoxyethyl alcohol derivatives. The group of flavoring ingredients includes the following: phenethyl alcohol (No. 1), 28 esters formed from phenethyl alcohol or phenylacetic acid (Nos. 2–13 and 22–36), six acetals of phenethyl alcohol or phenylacetaldehyde (Nos. 14, 15, 17–20), three related phenylacetaldehydes (Nos. 16,

37–39), and phenylacetic acid (No. 21). The four phenoxyacetic acid derivatives include phenoxyacetic acid (No. 40), an ester of phenoxyacetic acid (No. 41), an ester of phenoxyacetic acid (No. 42) and a homologue of phenoxyacetic acid (No. 43) (see Table 1).

The substances in this group are structurally related because they each have a 2-phenethyl or 2-phenoxyethyl-carbon skeleton containing a primary oxygenated functional group. Data indicates that the phenethyl

Download English Version:

https://daneshyari.com/en/article/9030661

Download Persian Version:

https://daneshyari.com/article/9030661

<u>Daneshyari.com</u>