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Review

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

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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,

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; LD_{50}, 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.

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

Keywords: PEA; Flavoring ingredients; FEMA GRAS

Contents

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 phenoxyethyl alcohol (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