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Review

The FEMA GRAS assessment of α,β-unsaturated aldehydes and related substances used as flavor ingredients

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ABSTRACT

This publication is the 12th 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. Since then, the number of flavoring substances has grown to more than 2200 chemically-defined substances. Elements that are fundamental to the safety evaluation of flavor ingredients include exposure, structural analogy, metabolism, toxicodynamics and toxicology. Scientific data relevant to the safety evaluation for the use of aliphatic, linear α,β-unsaturated aldehydes and structurally related substances as flavoring ingredients are evaluated. The group of substances was reaffirmed as GRAS (GRASr) based, in part, on their self-limiting properties as flavoring substances in food; their low level of flavor use; the rapid absorption and metabolism of low in vivo concentrations by well-recognized biochemical pathways; adequate metabolic detoxication at much higher levels of exposure in humans and animals; the wide margins of safety between the conservative estimates of intake and the no-observed-adverse effect levels determined from subchronic and chronic studies. While some of the compounds described here have exhibited positive *in vitro* genotoxicity results, evidence of in vivo genotoxicity and carcinogenicity occurs only under conditions in which animals are repeatedly and directly exposed to high irritating concentrations of the aldehyde. These conditions are not relevant to humans who consume α,β-unsaturated aldehydes as flavor ingredients at low concentrations distributed in a food or beverage matrix.
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Abbreviations: ABS, chromosomal aberrations; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; BSA, bovine serum albumin; dG, deoxyguanosine; FEMA, Flavor and Extract Manufacturers Association; FPG, formamidopyrimidine DNA glycosylase; GRAS, generally recognized as safe; GSH, glutathione; GSSG, glutathione disulfide; GST, glutathione *S*-transferase; K_M, Michaelis constant; LDL, low density lipoprotein; LPO, lipid peroxidation; MN, micronuclei; NOEL, no-observed-effect level; PCE, polychromatic erythrocyte; PCNA, proliferating cell nuclear antigen; PUFA, polyunsaturated fatty acids; SCE, sister chromatid exchange; UDS, unscheduled DNA synthesis; V_{max}, maximum reaction rate.

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1. Introduction

This review presents the key scientific data relevant to the safety evaluation for the flavor use of 91 aliphatic linear α,β-unsaturated aldehydes, and related alcohols, acetals, carboxylic acids, and esters. All aldehydes in this group contain α,β-unsaturation or extended conjugation (2,4-dienals and trienals). This group contains alcohols and esters that hydrolyze to alcohols which are then readily and sequentially oxidized to yield the corresponding α,β-unsaturated aldehydes and carboxylic acids. This group also contains acetals which readily hydrolyze into α,β-unsaturated aldehydes and alcohols that are converted to α,β-unsaturated aldehydes and esters that further hydrolyze to linear α,β-unsaturated carboxylic acids. Summarily, the group contains flavoring substances that may hydrolyze and/or oxidize to yield linear α,β-unsaturated aldehydes, α,β-unsaturated aldehydes with extended conjugation, and corresponding α,β-unsaturated carboxylic acids (see Table 1).

2. Flavor use, natural occurrence in food, and endogenous formation

Approximately 66% of the reported total annual volume (14,278 kg) reported in the most recent survey (Gavin et al., 2008) of 91 flavor ingredients in this group, is accounted for by *trans*-2-hexenal, its corresponding alcohol, acetate ester, and ethyl acetal. *trans*-2-Hexenal (No. 21) has a reported annual volume of use as a flavor ingredient in the USA of 6183 kg. It also is ubiquitous in the food supply as a naturally occurring substance (Nijssen et al., 2006). Formed mainly by the action of lipoxygenases on unsaturated fatty acids in plants (Almosnino and Belin, 1991; Andrianarison et al., 1991), it is a constituent of most fruits and vegetables, occurring at concentrations in the range from 0.01 to 20 ppm (Nijssen et al., 2006). These levels approximate mean added usual use levels as a flavor ingredient. An estimated daily intake from consumption of fruits and vegetables has been reported to be between 31 and 165 μg/kg bw (Schuler and Eder, 1999). It also occurs widely in non-alcoholic (e.g., tea) and alcoholic beverages (e.g., wine) and in cooked meats as a result of lipid thermal breakdown.

The combined daily *per capita* intake of *trans*-2-hexenal from foods that contain *trans*-2-hexenal is calculated to be approximately 2390 μg/person per day (see Table 2). The highest intake of *trans*-2-hexenal occurs from consumption of bananas. The estimated daily *per capita* intake of *trans*-2-hexenal from intentional addition as a flavor ingredient is 57 μg/person per day. Intake of *trans*-2-hexenal from consumption of traditional foods exceeds intake as an added flavoring substance by a factor ≈40 (Stofberg and Kirschman, 1985; Stofberg and Grundschober, 1987; Gavin et al., 2008; Nijssen et al., 2006; United States Department of Agriculture Economic Research Service) (see Tables 1 and 2).

Other members in this group of α,β-unsaturated aldehydes and alcohols that show significant reported annual volumes as flavor ingredients include ethyl *trans*-2-*cis*-4-decadienoate (No. 79,746 kg/yr), a key component of pear aroma, and *trans*-2-*cis*-6-nonadienal (No. 62,971 kg/yr), a substance commonly recognized as violet leaf aldehyde that is characteristic of cucumber. Substances in this group that have intakes from traditional food that far exceed that from flavor use (i.e., consumption ratio >1) include 2-decenal (No. 70), 2-dodecenal (No. 86), 2-hexen-1-ol (No. 9), 2-hexenal (No. 21), 2-hexen-1-yl acetate (No. 12), *trans*-2-heptenal (No. 40), 2-nonenal (No. 57), 2-octenal (No. 47), 2-pentenal (No. 6), *trans*-2-nonen-1-ol (No. 55), 2-undecenal (No. 83), 2,4-pentadienal (No. 7), *trans,trans*-2,4-hexadienal (No. 30), 2,4-heptadienal (No. 42), *trans,trans*-2,4-octadienal (No. 49), 2,6-nonadien-1-ol (No. 60), 2,4-nonadienal (No. 59), nona-2-*trans*-6-*cis*-dienal (No. 62); 2-*trans*,4-*trans*-decadienal (No. 73), ethyl *trans*-2-*cis*-4-decadienoate (No. 79), and 2,4-undecadienal (No. 84).

Dienals have been detected in many of the same foods as their α,β-unsaturated aldehyde homologues (apples, grapes, broccoli, chicken, tea and beer) (Nijssen et al., 2006). Compared to *trans*-2-hexenal, *trans,trans*-2,4-hexadienal (No. 30) has been detected at lower levels in a more limited number of foods. Higher homologous dienals and trienals (>C_9) have been detected in heated

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