

## **RECENT PROGRESS in the Consideration of Flavoring Ingredients Under the Food Additives Amendment**

# **5. GRAS Substances**

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□ RESEARCH in the field of food flavors has been greatly stimulated by the application of modern analytical techniques, particularly gas chromatography and mass spectroscopy, which have permitted the identification of the chemical components of many natural flavors (1-5). As a consequence, improved artificial flavoring agents have been and are being developed which faithfully reproduce the nuances of natural flavors and intensify their characteristic properties.

### **THE EXPERT PANEL**

It has been the policy of the Flavor and Extract Manufacturers Association (FEMA) to urge member companies to submit to an independent panel of qualified scientists, flavoring substances intended for commercial application, whether or not they are analogs of natural substances, for appraisal of safety under conditions of proposed use. Results of this expert panel's GRAS (generally recognized as safe) evaluations have been published in *Food Technology* (6-9).

The basis for selection of the original panel of toxicologists, pharmacologists, and biochemists, has been previously described (7). It should be emphasized that the members of the panel were affiliated with academic institutions and organizations having no connection with the flavoring industry, either directly or indirectly. The panel that evaluated the items reported herein consisted of: Dr. Anthony M. Ambrose, Medical College of Virginia; Dr. Frank R. Blood, Vanderbilt University; Dr. David W. Fassett, Eastman Kodak Company; Dr. Horace W. Gerarde, Fairleigh Dickinson University; Dr. Maurice H. SeEVERS, University of Michigan; Dr. Howard C. Spencer, Dow Chemical Co.; Dr. Frank M. Strong, University of Wisconsin; Dr. Lauren A. Woods, Medical College of Virginia.

### **WHY PUBLISH GRAS LISTS?**

Data concerning the usage levels of flavoring substances, and all available scientific information relevant to safety evaluation have been the basis for the development over a period of several years of lists of GRAS flavoring substances. The policy of FEMA to publish the GRAS lists has resulted in their receiving wide recognition. The Federal Food And Drug Administration has adopted (with very few deletions) the first such list of substances in the form of two Food Additive Regulations (10).

It has been the view of the U.S. Food and Drug Administration, with which there can be no disagreement, that only by publication can the scientific community have the opportunity to comment on, or take issue with, the opinion of other specialists in the field of food safety evaluation. The purpose of the present report is to present the additions to the list of GRAS substances made in 1970-71.

### **CRITERIA FOR JUDGEMENTS**

The criteria employed by the Expert Panel in arriving at judgements of GRAS status have been discussed in previous publications of GRAS lists (6-9) and in a review on the safety of flavoring substances by Hall and Oser (11). In essence, these requirements include evidence for the identity and purity of the substance, its chemical and pharmacological relation to structurally analogous substances, its presence and

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level as a naturally occurring constituent of foods, intended use levels, and any pertinent metabolic or toxicologic data. From the accumulated experience in the evaluation of large numbers of chemically related substances has evolved certain general principles which have established the rationale and facilitated the process of safety evaluation by the Expert Panel.

### TOXICOLOGICAL INSIGNIFICANCE

A nationwide survey of the flavor and food industries conducted in 1960 revealed that of the 1121 substances on the FEMA GRAS list, 859 were estimated to be used in total amounts not exceeding 1000 lb annually. Moreover, the average maximum use levels in food were below 10 ppm in 399 of these substances. These criteria of total annual usage and minimal levels in foods, together with a safe history of common use in food, have been regarded by the FEMA panel as a basis for "toxicological insignificance," in the absence of any specific evidence or reasonable suspicion (based, for example, on chemical structure) to the contrary.

In this connection, reference may be made to the recent guidelines for evaluating toxicological insignificance published by the Food Protection Committee of the National Academy of Sciences-National Research

Council (12), from which the following quotation is relevant.

For many substances that are functionally effective in food at dietary concentrations above 0.1 ppm, but still much below any reasonable judgment as to their maximum safe level, as previously defined, there is need to arrive at estimates of toxicologically insignificant levels. For these substances, it is justifiable to employ accumulated scientific experience and to recognize their structural analogy to other chemicals whose metabolism or toxicity is known. Reasoning by analogy may be used to arrive at conclusions of toxicological insignificance. If a substance meets all the following criteria, it may be presumed to be toxicologically insignificant at a level of 1.0 ppm or less in the human diet:

1. The substance in question is of known structure and purity;
2. It is structurally simple;
3. The structure suggests that the substance will be readily handled through known metabolic pathways; and
4. It is a member of a closely related group of substances, that, without known exception, are or can be presumed to be low in toxicity.

### TOTAL PER CAPITA INTAKE OF FLAVORING SUBSTANCES

It is interesting to note in this connection that if a flavoring agent were used at a level of 10 ppm in every major category of flavored foods, the total per capita intake of that substance (based on USDA Food Consumption data for all urbanizations) would be 2.336 mg per day. This would be equivalent to 1.3 ppm of the total diet or 0.0334 mg per kg body weight for a 70 kg adult. On the highly exaggerated assumption of the daily ingestion of average portions of all classes of flavored foods and the presence of 10 ppm of flavoring substance in each of them, the total daily intake would reach 11.5 mg or only 0.164 mg per kg body weight (Table 1).

Nearly a decade has passed since the original survey

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Table 1—TOTAL DAILY PER CAPITA INTAKE OF FLAVORING SUBSTANCES based on the exaggerated assumption of the daily ingestion of average portions of all classes of flavored foods and the presence of 10 ppm in each of them

Class of Flavored Food	Flavored Food Consumption <sup>c</sup>			"Average Portion" (g/day)	Flavor Component at 10 ppm (mg/day)
	per Household <sup>b</sup> (lb/wk)	per Capita <sup>d</sup> (g/day)	Flavor Component at 10 ppm (mg/day)		
Soft drinks	5.09	100.3	1.00	540	5.40
Frozen milk desserts:					
ice cream, ice milk, sherbet	1.36	26.8	0.268	90	0.90
Candy, toppings	0.52	10.2	0.102	40	0.40
Baked goods <sup>a</sup>				340	3.40
prepared mixes	0.48	9.5	0.095		
"other" bakery products	3.28	64.6	0.646		
Jelly, jam, fruit, gelatin				120	1.20
puddings, ices	0.45	8.9	0.089		
popsicles, icings	0.31	6.1	0.061		
Condiments	0.38	7.5	0.075	20	0.20
Total intake, mg per day			2.336		11.50
Total intake, ppm diet <sup>e</sup>			1.30		6.40
Total intake, mg per kg body weight (70 kg)			0.0334		0.164

<sup>a</sup> Includes cakes, pies, crackers, muffins, biscuits, cookies, coffee cake, doughnuts

<sup>b</sup> 3.29 persons

<sup>c</sup> Household food consumption levels based on 1965-66 survey, U.S. Dept. of Agriculture (all urbanizations)

<sup>d</sup> lb per household per week  $\times$  454 g = g per capita per day

$\frac{3.29 \text{ persons} \times 7 \text{ days}}{70 \text{ kg}} = 0.336 \text{ mg per kg body weight}$

<sup>e</sup> 1800 g food per day (estimate based on USDA Food Consumption statistics)

SURVEY OF FLAVORING INGREDIENT USAGE LEVELS

Flavor and Extract Manufacturers Association average maximum use levels (in ppm) on which the expert panel based its judgments that the substances are generally recognized as safe.

FEMA No. and Substance	Beverages	Ice Cream, Ices, Etc.	Candy	Baked Goods	Gelatins & Puddings	Chewing Gum	Meat, Meat Sauces, Soups	Milk, Dairy Product	Condi- ments, Pickles	Other Category Uses
3,250 2-Acetyl-3-ethyl pyrazine	10.	10.	10.	10.	10.	—	10.	10.	—	Cereals 10.
2-Acetyl-3-ethyl-1,4-diazine (see 3,250)										
3,251 2-Acetylpyridine	—	—	3.0	5.0	—	—	3.0	3.0	—	Cereals 3.0
3,252 β-Alanine	10.	—	—	10.	—	—	10.	10.	10.	Cereals 10.
3,253 Allyl methyl trisulfide	—	—	—	2.0	—	—	2.0	—	2.0	
Allyl trisulfide (see 3,265)										
Aminoacetic acid (see 3,287)										
Aminoethanoic acid (see 3,287)										
Aminoglutaric acid (see 3,285)										
α-Aminoisocaproic acid (see 3,297)										
2-Amino-3-methylpentanoic acid (see 3,295)										
2-Amino-4-methylpentanoic acid (see 3,297)										
2-Amino-3-mercaptopropanoic acid (see 3,263)										
α-Amino-β-mercaptopropionic acid (see 3,263)										
2-Amino-4-(methylthio)-butanoic acid (see 3,301)										
α-Amino-γ-(methylthio)-butyric acid (see 3,301)										
α-Amino-β-methylvaleric acid (see 3,295)										
2-Aminopropanoic acid (see 3,252)										
β-Aminopropionic acid (see 3,252)										
α-Angelica lactone (see 3,293)										
3,254 Arabinogalactan	—	—	85%	—	—	—	—	—	—	Preserves & Spreads 450.
3,255 L-Arabinose	450.	—	450.	450.	—	—	—	—	450.	
3,256 Benzothiazole	0.5	—	0.5	0.5	—	—	0.5	0.5	—	
3,257 Bis(2-furfuryl) disulfide	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	
3,258 Bis(2-furfuryl) sulfide	5.0	5.0	5.0	5.0	5.0	5.0	5.0	—	5.0	
3,259 Bis(2-methyl-3-furyl) disulfide	—	—	—	0.1	—	—	0.1	—	0.1	
3,260 Bis(2-methyl-3-furyl) tetrasulfide	—	—	—	0.1	—	—	0.1	0.1	0.1	Cereals 0.1
3,261 2-sec-Butylcyclohexanone	25.	25.	150.	100.	—	1000.	—	—	—	
γ-Butyrolactone (see 3,291)										
Cinnamic acid, tetrahydrofurfuryl ester (see 3,320)										
Cyclohexapyrazine (see 3,321)										
3,262 Cyclopentanethiol	—	—	—	0.1	—	—	0.1	0.1	0.1	Cereals 0.1
Cyclopentyl mercaptan (see 3,262)										
3,263 L-Cysteine	100.	—	—	100.	—	—	100.	100.	100.	Cereals 100.
3,264 4-Decenal	—	0.5	—	1.0	—	—	0.5	0.5	—	
3,265 Diallyl trisulfide	—	—	—	1.0	—	—	1.0	—	1.0	
Difurfuryl disulfide (see 3,257)										
Difurfuryl sulfide (see 3,258)										
3,266 4,5-Dihydro-3(2H) thiophenone	1.0	1.0	1.0	—	1.0	1.0	1.0	1.0	1.0	Cereals 1.0
3,267 2,4-Dimethyl-5-acetylthiazole	—	10.	10.	6.0	—	—	10.	—	—	
3,268 3,4-Dimethyl-1,2-cyclopentadione	—	0.3	4.0	—	—	1.9	—	—	—	Protein Foods 3.5
3,269 3,5-Dimethyl-1,2-cyclopentadione	2.4	6.0	5.0	—	—	—	—	—	—	
3,270 spiro[2,4-Dithia-1-methyl-8-oxabicyclo[3.3.0]octane-3,3'-(1'-oxa-2'-methyl) cyclopentane] and spiro[2,4-dithia-6-methyl-7-oxabicyclo[3.3.0]octane-3,3'-(1'-oxa-2'-methyl) cyclopentane]	0.045	0.25	0.1	—	—	—	0.07	—	—	Protein Foods 0.4 Mayonnaise 2.4
2,3-Dimethyl-1,4-diazine (see 3,271)										
2,5-Dimethyl-1,4-diazine (see 3,272)										
2,6-Dimethyl-1,4-diazine (see 3,273)										
3,271 2,3-Dimethylpyrazine	10.	10.	10.	10.	10.	—	10.	—	—	





## GRAS Substances . . . .

of usage of flavoring substances by the food industry was conducted by the Flavor and Extract Manufacturers Association. The accumulated data from this survey were considered in relation to certain arbitrary daily consumption levels of the various categories of flavored food in arriving at the FEMA lists of GRAS flavoring substances published in 1960 and 1965.

### GRAS LIST REVIEWS & POSSIBLE REVISIONS

Recognizing that the patterns of use of flavoring substances may change in both kind and degree, the FEMA undertook to repeat and extend the survey. It is currently underway (1972), concomitantly with the survey of GRAS food substances by the National Academy of Sciences-National Research Council under contract with the Food and Drug Administration.

Data from both of these surveys will be computerized and analyzed for the purpose of reviewing and possibly revising the status of substances listed therein. In this connection it should be recognized that the FEMA survey will cover all adjuncts and flavoring ingredients used in foods, including those originally published in the FEMA GRAS list which were subsequently incorporated by the Food and Drug Administration into Food Additive Regulations for natural and synthetic flavoring substances (10).

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