

*Recent Progress in the Consideration of Flavoring Ingredients
Under the Food Additives Amendment*

8. GRAS Substances

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□ IN KEEPING with previously outlined policies of the Flavor and Extract Manufacturers' Association, this paper reports the latest results of evaluations of the GRAS (Generally Recognized as Safe) status of a number of substances.

These evaluations were carried out by an independent panel of experts chosen as described before (Hall and Oser, 1961) and consisting of: Dr. Anthony M. Ambrose, Medical College of Virginia; Dr. David W. Fassett; Dr. Maurice H. SeEVERS, University of Michigan; Dr. Howard C. Spencer, Dow Chemical Co.; Dr. Frank Strong, University of Wisconsin; and Dr. Lauren A. Woods, Virginia Commonwealth University. Dr. Horace W. Gerarde, Fairleigh Dickinson University, participated in the deliberations but subsequently suf-

fered an accidental death. Dr. Gerarde had been a member of the Panel since its inception and his contributions to the Panel's activities were meaningful and significant.

The F.E.M.A. has continually maintained the policy of urging member companies to submit to the 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. The F.E.M.A. adopted the policy of publishing the GRAS lists consistent with the view of the U.S. Food and Drug Administration, which is to encourage publication so as to provide the scientific community with 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 provide additions to the lists of GRAS substances published since 1965 (Hall, 1960; Hall and Oser, 1961;

—Text continued on page 80

THE AUTHORS are, respectively, past chairman of Food and Drug Research Laboratories Inc., now at 60 E. 42nd St., New York, N.Y. 10017; and assistant professor, Department of Chemistry, Montgomery College, Takoma Park, Md. 20012

SURVEY OF FLAVORING INGREDIENT USAGE LEVELS

Flavor and Extract Manufacturers' Association average maximum levels (in ppm) on which the Expert Panel based its judgments that the substances are generally recognized as safe for their intended uses.

	Bever- ages (non- alcoholic)	Frozen desserts (Ice Cream, Confec- tionery)	Baked Goods	Puddings, Gelatins, Jams	Chewing Gum	Meat, Meat Sauces, Soups	Milk, Dairy Products	Condi- ments, Pickles	Other Category Use
Acetaldehyde dimethyl acetal (see 3426)									
β -Acetylpyridine (see 3424)									
3424									
3-ACETYLPIRIDINE	2.0	2.0	3.0	3.0	2.0	—	—	—	—
α -Aminoisovaleric acid (see 3444)									
2-Amino-3-methylbutanoic acid (see 3444)									
Civetone (see 3425)									
3425									
CYCLOHEPTADECA-9-EN-1-ONE	0.03	0.03	0.05	0.05	0.02	—	—	—	Beverages, alcoholic—0.02
3426									
1,1-DIMETHOXYETHANE	3.0	3.0	6.0	6.0	3.0	—	—	—	Preserves & spreads—3.0
Dimethylacetal (see 3426)									
3427									
2,4-DIMETHYLBENZALDEHYDE	2.0	2.0	3.0	—	2.0	—	—	1.0	Preserves & spreads—1.0
6,6-Dimethyl-2-oxymethylbicyclo[1,1,3]- hept-2-ene (see 3439)									
Ethyl hexyl ketone (see 3440)									
3428									
ETHYL 3-HYDROXYBUTYRATE	3.0	3.0	5.0	5.0	3.0	50	—	3.0	—
Ethylidene dimethyl ether (see 3426)									
Farnesyl acetone (see 3442)									

	Beverages (non- alcoholic)	Frozen desserts (Ice Cream, Confectionery Ices, etc.)	Baked Goods	Puddings, Gelatin, Jams	Chewing Gum	Meat, Meat Sauces, Soups	Milk, Dairy Products	Condi- ments, Pickles	Other Category Use
1-Formyl-2,4-dimethylbenzene (see 3427)									
3429 <i>trans,trans</i> -2,4-HEXADIENAL	4.0	4.0	6.0	—	4.0	—	—	4.0	Beverages, alcoholic—1.0; Preserves & spreads—2.0
3430 4-HEXEN-1-OL	2.0	2.0	4.0	4.0	2.0	—	—	—	Vegetables—2.0
3431 <i>cis</i> -3-HEXENYL FORMATE	0.15	0.2	0.5	0.5	0.2	—	0.2	—	—
3432 ISOBUTYL 2-BUTENOATE Isobutyl crotonate (see 3432)	3.0	3.0	5.0	5.0	3.0	25	3.0	—	Preserves & spreads—3.0
2-Methoxy-3- <i>sec</i> -butylpyrazine (see 3433)									
3433 2-METHOXY-3-(1-METHYLPROPYL) PYRAZINE	0.05	0.05	0.05	0.05	0.05	—	—	—	Vegetables— 0.05; Beverages, alcoholic—2.0
3-Methoxy- <i>para</i> - <i>cymene</i> (see 3436)									
3434 3-METHYL-1-CYCLOPENTADECANONE	0.03	0.03	0.05	0.05	0.02	—	—	—	Beverages, alcoholic—0.02
3435 1-METHYL-1-CYCLOPENTEN-3-ONE	2.0	—	—	3.0	—	—	2.0	2.0	Cereals—2.0; Soups—2.0
3-Methyl-2-cyclopenten-1-one (see 3435)									
Methylexaltone (see 3434)									
3-Methylmercapto-1-hexanol (see 3438)									
3436 1-METHYL-3-METHOXY-4- ISOPROPYLBENZENE	2.0	—	3.0	3.0	—	—	2.0	—	2.0
3437 3-METHYLPENTANOIC ACID	2.0	2.0	5.0	5.0	2.0	—	—	—	—
Methyl 3-pyridyl ketone (see 3424)									
3438 3-METHYLTHIO-1-HEXANOL	3.0	5.0	5.0	6.0	4.0	—	4.0	—	4.0
3-Methylvaleric acid (see 3437)									
<i>d,l</i> -Muscone (see 3434)									
3439 MYRTENOL	10	10	10	—	10	—	—	10	—
3440 3-NONANONE	20	—	20	20	20	20	—	20	—
1,2,3,5,6,7,8,8a-Octahydro-1,8a-dimethyl-7- (1-methylethenyl) naphthalene (see 3443)									
Propylene glycol-acetone ketal (see 3441)									
Thymol methylether (see 3436)									
2,2,4-Trimethyl-1,3-dioxolane (see 3441)									
3441 2,2,4-TRIMETHYL- 1,3-OXACYCLOPENTANE	4.0	4.0	6.0	—	4.0	—	—	4.0	Preserves & spreads—2.0; Beverages, alcoholic—1.0
3442 2,6,10-TRIMETHYL-2,6,10- PENTADECATRIEN-14-ONE	2.0	2.0	3.0	—	2.0	—	—	1.0	Preserves & spreads—1.0
6,10,14-Trimethyl-5,9,13-pentadecatrien-2-one (see 3442)									
Sorbic aldehyde (see 3429)									
3443 VALENCENE	0.9	0.9	0.9	0.9	0.9	0.9	—	0.9	—
3444 <i>d,l</i> -VALINE	15	40	80	60	80	200	—	40	—
2,4-Xylylaldehyde (see 3427)									

8. GRAS Substances . . .

1965; 1970; Oser and Hall, 1972; Oser and Ford, 1973a, 1973b).

The Expert Panel periodically reviews the criteria employed to arrive at judgments of GRAS status. 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 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 have evolved certain general principles which have established the rationale and facilitated the process of safety evaluation by the Expert Panel.

TOXICOLOGICAL INSIGNIFICANCE AND THE SECOND F.E.M.A. SURVEY

The F.E.M.A. undertook a second nationwide survey of the food and flavor industry 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. This survey revealed that of the 1249 substances on the F.E.M.A. GRAS list at the time of the survey, 831 were estimated to be used in total amounts not exceeding 1000 lbs annually. Moreover, the average maximum use levels in food were below 10 ppm in 228 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 F.E.M.A. 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 (NAS, 1970), 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.

The report also excludes from the category of toxicologically insignificant substances, those which are found to induce cancer or "any such serious condition," or which "exert significant biological effects." Thus the criteria employed by the Food Protection Committee, like those used by the F.E.M.A. Expert Panel, apply only to substances about which all information and all reasonable assumptions are entirely favorable—and then only at extremely low levels of use.

Based on the results of the survey and a survey of all relevant literature, F.E.M.A. is preparing scientific literature reviews, under contract with FDA, for the purpose of reviewing the GRAS status of flavoring compounds (Fed. Reg. 1973). The first review of 276 aliphatic aldehydes, primary alcohols, acids, and related esters was recently submitted to the FDA.

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