

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

10. GRAS Substances

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□ THIS PAPER is the latest in a series reporting the results of deliberations of the independent panel of experts retained by the Flavor and Extract Manufacturers' Association (FEMA) for evaluation of GRAS (Generally Recognized as Safe) status of new flavoring substances. This panel consists of members chosen as described before (Hall and Oser, 1961) and is made up of experts who are qualified by training and years of experience in pharmacology and toxicology as well as in the safety evaluation of flavors. The panel currently consists of: Dr. Anthony M. Ambrose, Medical College of Virginia; Dr. David W. Fassett; Dr. Maurice H. SeEVERS, University of Michigan; Dr. Howard C. Spencer; Dr. R.T. Williams, St. Mary's Hospital Medical School, University of London; and Dr. Lauren A. Woods, Virginia Commonwealth University. Dr. Frank Strong was a member during much of the deliberations reported herein, and Dr. Williams did not become a member until after the deliberations.

CRITERIA FOR JUDGEMENTS

The criteria employed by the Expert Panel in arriving at judgments of GRAS status have been discussed in previous publications of GRAS lists (Hall, 1960; Hall and Oser, 1961, 1965) and in a review on the safety of flavoring substances (Hall and Oser, 1968). 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 flavoring substances has evolved certain general principles which have established the rationale and facilitated the process of safety evaluation by the Expert Panel.

PRIORITY LOW-USAGE MINIMAL (PLUM)

A survey conducted by FEMA in 1971 of over 1400 flavoring ingredients showed that approximately 75% were used in foods at levels not exceeding 100 ppm. Furthermore the annual usage of 71% of GRAS flavoring substances was less than 1,000 pounds. (On a per capita basis this is equivalent to 0.1 $\mu\text{g}/\text{kg}$ body

weight/day.) Considered together with the fact that the majority of so called synthetic flavoring substances are analogous to naturally occurring substances in foods or body tissues, are relatively simple chemical structures, and are readily metabolized and detoxified in mammals, such low usage of flavoring substances has been regarded as insignificant from the view point of potential toxicity. Criteria for toxicologically insignificant usage (TIU) were adopted by the Expert Panel of FEMA in executing its mission to assess the GRAS status of flavoring agents which began in 1959 (Hall and Oser, 1968).

A report published ten years later by the Food Protection Committee (FPC) of the National Academy of Sciences/National Research Council recognized the need to establish a reasonable system of priorities for the study of the thousands of natural and synthetic substances in foods at low and intermediate levels. The FPC stated that, "It is neither practical nor necessary to undertake experimental toxicological studies of every chemical to which man is exposed; to do so would be to assign equal importance to problems of unequal risk." Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Foods (NRC, 1970) developed by the FPC were based on chemical structure and purity, the low levels of use (ie, 1 ppm or less in the human diet), and the absence of evidence of toxicological hazard after a substantial period of production or use. It was pointed out that "Chemicals that exert significant biological effects," (including known or suspected carcinogens) "that are useful in food or any other part of the environment," or "are intentionally used for their biological activity," (e.g., pesticides or potent drugs) would "continue to be subjected to laboratory investigations to establish safe levels." These guidelines were criticized by certain oncologists who, despite the above caveats, contended that the concept of toxicological insignificance cannot be applied to carcinogens.

At the request of Dr. Philip Handler of the National Academy of Sciences and Dr. DeWitt Stetten, in behalf of the Surgeon General, an ad hoc group was convened in an effort to resolve this apparent disagreement and clarify the purpose of the FPC guidelines. It consisted of representatives of the FPC and of an Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens. The following points were agreed upon:

1. The FPC report was intended to suggest criteria for determining priorities for testing;
2. Suggesting a low priority for testing does not imply (a)

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the conclusion that a material is "safe" at all conditions of exposure or use, and (b) that testing is not needed—or will never be needed;

3. Refinements and other approaches or schemes for setting testing priorities for specific purposes (particularly long term toxicity) must be encouraged.

4. Issues of "zero tolerance", "negligible quantities", and "safe levels" are not at issue here. The phrases such as "toxicological insignificance" are intended to indicate low priority for testing—but not as a final judgment of absence of any hazard involved in the use of any materials so labeled.

As a result of this conference, the FEMA panel felt that it could more clearly state its objective by adopting criteria for toxicologically insignificant usage that (a) substitute the more specific phrase "Priority Low—Usage Minimal" (PLUM) and (b) define this in relation to average daily dietary intake of a particular substance instead of its average maximum use level in food categories.

Recent U.S. food consumption surveys, conducted under contract for FDA, and usage data compiled by the food and flavor industries in connection with current GRAS reviews, provide much better estimates of potential intake of flavoring substances than were hitherto available.

For PLUM classification every one of the following criteria must be satisfied:

1. The substance must not be used at levels that would result in an average daily intake of more than 2.0 mg;
2. The substance must be a simple structure and of known composition and purity;
3. The structure of the substance must suggest that it would be readily handled through known metabolic pathways, and will be excreted without toxic effect;
4. The substance must be a member of a structurally related group that, without known exception, is or can be presumed to be of low toxicity.

RELATIONSHIP TO LABELING REQUIREMENTS

There is an interrelationship between the publication of GRAS lists by FEMA, the preparation and evaluation of the Scientific Literature Reviews on flavor ingredients, and the labeling requirements of FDA. The FDA provides in 21 CFR Section 1.12 (g) (2) that mixtures of flavor ingredients shipped to food manufacturers or processors should be declared on the label. In lieu of the declaration, the label may state, "all flavor ingredients contained in this product are approved for use in a regulation of the Food and Drug Administration," with the nonflavor and unapproved flavor ingredients listed separately by name.

The FDA has gradually expanded its application of Section 1.12, exempting from disclosure on the label any flavor ingredients that have appeared on the GRAS list of a reliable, published, industry association list. This exemption is subject to several limitations related to the status of the various Scientific Literature Reviews on flavor ingredients and the publication dates of the GRAS lists. Flavor ingredients on GRAS lists 3-9 need not be disclosed on the label until FDA has completed an evaluation of the Scientific Literature Reviews covering those ingredients and specifically determines that any or all of the substances are no longer to be considered as approved.

On February 3, 1976, the FDA interpreted the

regulation as it applied to GRAS list 10 and any subsequent GRAS lists, stating that (1) flavor ingredients in categories covered by Scientific Literature Reviews submitted to and evaluated by the FDA at the time of publication of the GRAS list will not be considered approved by FDA until an appropriate petition has been filed by industry and the flavor therefore must be declared on the label until FDA approval is given, and (2) flavor ingredients in categories covered by Scientific Literature Reviews in preparation at the time of publication of the GRAS list, or that will be covered subsequently, will be incorporated into the appropriate Scientific Literature Reviews for evaluation and need not be disclosed on the label until FDA specifically determines that any of those substances are no longer to be considered as approved.

All of the flavoring ingredients listed in GRAS List 10 are contained either in Scientific Literature Reviews in preparation or scheduled for preparation. Therefore, none of the flavor ingredients are required to be disclosed on the label of a mixture being delivered to a food manufacturer or processor.

CORRECTIONS

In GRAS 9 (Oser and Ford, 1975) the number 3476 was assigned to a synonym, vitamin U, for substance number 3445, DL-(3-amino-3-carboxypropyl) dimethylsulfonium chloride. This number should not be assigned to vitamin U but it is assigned to the first substance in GRAS 10, bis-(2,5-dimethyl-3-furyl) disulfide. Also *cis*-3-hexenyl formate, number 3431 in GRAS 8, is a duplication of hexenyl formate, number 3353 in GRAS 6. The GRAS 8 listing should be deleted and the GRAS 6 usage amended to include the use at 0.2 ppm in milk and dairy products.

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GRAS FLAVORING INGREDIENTS AND USAGE LEVELS

Flavor and Extract Manufacturer's 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-al- coholic)	Frozen desserts (Ice Cream, Ices, etc.)	Confec- tionery	Baked Goods	Puddings, Gelatins, Jams	Chewing Gum	Meat, Meat Sauces, Soups	Milk, Dairy Products	Condi- ments, Pickles	Other Category Use
<i>iso</i> -Amyl isobutyrate see 3507										
<i>iso</i> -Amyl 2-methylbutanoate see 3505										
<i>iso</i> -Amyl 2-methylpropanoate see 3507										
Amyl vinyl ketone see 3515										
Benzyl methyl disulfide see 3504										
3476 BIS-(2,5-DIMETHYL-3-FURYL) DISULFIDE	-	-	-	0.1	-	-	0.1	-	-	
3477 2,3-BUTANEDITHIOL*	-	-	-	0.2	-	-	0.2	-	-	
3478 1-BUTANETHIOL	-	-	-	-	-	-	0.02	-	0.02	Seasonings-0.02
n-Butyl mercaptan see 3478										
3479 CANDELILLA WAX (wax from stems & branches of Euphorbia Cerifera)	30	10	15	-	-	-	-	-	-	Beverages, alcoholic-30
3480 o-CRESOL	-	-	-	-	-	-	0.5	-	0.5	Cereals-0.5, Seasoning-0.5
2,3-Dimercaptobutane see 3477										
1,2-Dimercaptoethane see 3484										
1,6-Dimercaptohexane see 3495										
1,9-Dimercaptononane see 3513										
1,8-Dimercaptooctane see 3514										
1,2-Dimercaptopropane see 3520										
S-(2,5-Dimethyl-3-furyl) thio-2-furoate see 3481										
S-(2,5-Dimethyl-3-furyl) thioisovalerate see 3482										
3,7-Dimethyl-1,6-octadien-3-yl phenyl- acetate see 3501										
3481 2,5-DIMETHYL-3-THIOFUROYL- FURAN	-	-	-	0.2	-	-	0.2	-	-	
3482 2,5-DIMETHYL-3-THIOISOVALE- RYLFURAN	-	-	-	0.2	-	-	0.2	-	-	
3483 2,8-DITHIANON-4-EN-4-CARBOX- ALDEHYDE	-	-	-	-	-	-	0.2	-	0.2	Seasoning-0.2
Dithioglycol see 3484										
3484 1,2-ETHANEDITHIOL*	-	-	-	0.2	-	-	0.2	-	-	
3485 o-(ETHOXYMETHYL) PHENOL	-	-	-	-	-	-	4.0	-	4.0	Cereals-4.0; Seasoning-4.0

*Total dithiol added to any food not to exceed 1.0 ppm

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	Bever- ages (non-al- coholic)	Frozen desserts (Ice Cream, Ices, etc.)	Confec- tionery	Baked Goods	Puddings, Gelatin, Jams	Chewing Gum	Meat, Meat Sauces, Soups	Milk, Dairy Products	Condi- ments, Pickles	Other Category Use
<i>3486</i> ETHYL <i>trans</i> -2-BUTENOATE	3.0	8.4	16.1	20.7	5.71	—	—	—	—	Beverage, alcoholic-4.0
Ethyl crotonate see 3486										
Ethyl α -crotonate see 3486										
Ethylene dithioglycol see 3484										
2-Ethylfenchol see 3491										
Ethyl hendecanoate see 3492										
2-Ethyl-3-hydroxy-4H-pyran-4-one see 3487										
<i>3487</i> ETHYL MALTOL	12.4	144	139	152	119	83	19.6	—	—	Misc.-140; Hard candy-27.9; Beverages, alcoholic-18.6
<i>3488</i> ETHYL 2-METHYLPENTANOATE	5	100	500	400	—	1500	—	—	30	
<i>3489</i> ETHYL 2-METHYL-4-PENTENOATE	—	1.0	3.0	—	1.0	5.0	—	1.0	—	Beverages, alcoholic-0.5
Ethyl 2-methylvalerate see 3468										
<i>3490</i> ETHYL OCTADECANOATE	2.0	8.0	16.0	—	—	—	—	—	—	Beverages, alcoholic-4.0
2-Ethylpyromeconic acid see 3487										
Ethyl stearate see 3490										
<i>3491</i> 2-ETHYL-1,3,3-TRIMETHYL-2-NOR- BORNANOL	0.1	0.02	—	0.05	—	0.5	—	0.1	0.07	
<i>3492</i> ETHYL UNDECANOATE	2.0	8.0	16.0	—	—	—	—	—	—	Beverage, alcoholic-8.0
Ethyl undecylate see 3492										
<i>3493</i> <i>trans</i> -3-HEPTENYL ACETATE	2.0	2.0	3.0	—	2.0	5.0	—	—	—	
<i>trans</i> -3-Heptenyl isobutyrate see 3494										
<i>3494</i> <i>trans</i> -3-HEPTENYL 2-METHYLPRO- PANOATE	2.0	2.0	—	2.0	2.0	5.0	—	—	—	
<i>3495</i> 1,6-HEXANEDITHIOL*	—	—	—	0.2	—	—	0.2	—	—	
<i>3496</i> <i>cis</i> -4-HEXENAL	—	—	—	—	—	—	0.2	—	0.2	Seasoning-0.2
3-Hexenyl isopentanoate see 3498										
3-Hexenyl isovalerate see 3498										
Hexenyl isovalerianate see 3498										
<i>3497</i> 3-HEXENYL 2-METHYLBUTAN- OATE	14.0	16.0	28.7	37.0	14.7	0.57	—	—	—	Beverage, alcoholic-7.0
<i>3498</i> 3-HEXENYL 3-METHYLBUTAN- OATE	14.0	16.0	28.7	37.0	14.7	2.6	—	—	—	Beverage, alcoholic-7.0
3-Hexenyl 2-methylbutyrate see 3497										

*Total dithiol added to any food not to exceed 1.0 ppm

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	Beverages (non-alcoholic)	Frozen desserts (Ice Cream, Ices, etc.)	Confectionery	Baked Goods	Puddings, Gelatins, Jams	Chewing Gum	Meat, Meat Sauces, Soups	Milk, Dairy Products	Condiments, Pickles	Other Category Use
Hexyl isopentanoate see 3500										
Hexyl isovalerate see 3500										
Hexyl isovalerianate see 3500										
3499 HEXYL 2-METHYLBUTANOATE	18.7	21.8	36.7	51.6	31.3	0.34	—	—	—	Beverage, alcoholic-7.0
3500 HEXYL 3-METHYLBUTANOATE	21.5	25.0	36.7	51.7	31.3	0.23	—	—	—	Beverage, alcoholic-7.0
Hexyl 2-methylbutyrate see 3499										
3-Hydroxy-2-butanethiol see 3502										
2-Hydroxy-3-butanethiol see 3502										
2-Hydroxy-1-methylbenzene see 3480										
1-(2-Hydroxyphenyl)propane see 3522										
o-Hydroxytoluene see 3480										
Isoamyl isobutyrate see 3507										
Isoamyl 2-methylbutanoate see 3505										
Isoamyl 2-methylbutyrate see 3505										
Isoamyl 2-methylpropanoate see 3507										
Isopentyl isobutyrate see 3507										
Isopentyl 2-methylbutanoate see 3505										
Isopentyl 2-methylpropanoate see 3507										
3501 LINALYL PHENYLACETATE	4.0	3.0	4.0	6.0	4.0	—	—	—	—	
Linalyl α -toluate see 3501										
3502 2-MERCAPTO-3-BUTANOL	—	—	—	0.2	—	—	0.2	—	—	
3-Mercapto-2-butanol see 3502										
3-[(2-Mercapto-1-methylpropyl)thio]-2-butanol see 3509										
3503 2,3 or 10-MERCAPTOPINANE	0.03	0.02	0.03	0.03	0.01	—	—	—	—	
Methialdol see 3483										
3504 METHYL BENZYL DISULFIDE	—	—	—	0.3	—	—	0.3	—	—	
2-Methylbutyl isopentanoate see 3506										
2-Methylbutyl isovalerate see 3506										
2-Methylbutyl isovalerianate see 3506										
3505 3-METHYLBUTYL 2-METHYLBUTANOATE	29.9	29.9	50.0	50.0	29.9	—	—	—	—	Beverage, alcoholic-20.0
3506 2-METHYLBUTYL 3-METHYLBUTANOATE	11.0	11.0	14.5	18.2	11.0	—	—	—	—	Beverage, alcoholic-50.0
3507 3-METHYLBUTYL 2-METHYLPROPANOATE	48.1	74.0	114	128.7	103	—	—	—	—	Hard candy 0.09; Beverage, alcoholic-21.1; Misc.-760

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	Bever- ages (non-al- coholic)	Frozen desserts (Ice Cream, Ices, etc.)	Confec- tionery	Baked Goods	Puddings, Gelatin, Jams	Chewing Gum	Meat, Meat Sauces, Soups	Milk, Dairy Products	Condi- ments, Pickles	Other Category Use
Methyl β -Hydroxycaproate see 3508 3508										
METHYL 3-HYDROXY- HEXANOATE	1.0	1.0	1.0	5.0	1.0	1.0	—	1.0	—	Beverage, alcoholic-1.0; Cereals-5.0
Methyl β -hydroxyhexanoate see 3508 3509										
α -METHYL- β -HYDROXYPROPYL a-methyl- β -mercaptopropyl sulfide 3510	—	—	—	0.75	—	—	0.75	—	—	
4-METHYL-2-PENTENAL	1.0	1.5	—	2.0	1.2	8.0	—	1.0	—	Cereals-1.5; Beverages, alcoholic-1.0
3511										
2-METHYL-4-PENTENOIC ACID	—	2.0	5.0	—	2.0	5.0	—	2.0	—	Beverages, alcoholic-1.0
o-Methylphenol see 3480										
Methyl phenylmethyl disulfide see 3504 3512										
2-METHYLTETRAHYDROTHIO- PHEN-3-ONE	0.5	0.5	0.5	1.0	0.5	—	—	0.5	—	
5-(Methylthio)-2-(methylthio)-methyl- pent-2-en-1-al see 3483 3513										
1,9-NONANEDITHIOL*	—	—	—	0.2	—	—	0.2	—	—	
3514										
1,8-OCTANEDITHIOL*	—	—	—	0.2	—	—	0.2	—	—	
3515										
1-OCTEN-3-ONE	—	—	—	2.0	—	—	1.0	—	—	
3516										
trans-2-OCTEN-1-YL ACETATE	0.01	0.05	0.1	0.15	0.1	—	—	—	—	Beverages, alcoholic-0.05
3517										
trans-2-OCTEN-1-YL BUTANOATE	0.005	0.02	0.04	0.06	0.05	—	—	—	—	Beverages, alcoholic-0.025
trans-2-Octen-1-yl butyrate see 3517										
Octyl 2-furancarboxylate see 3518 3518										
OCTYL 2-FUROATE	5.0	10.0	20.0	—	10.0	20.0	—	—	—	
3519										
2-PHENYL-4-PENTENAL	—	—	—	—	—	—	2.0	—	2.0	
Pinanethiol see 3503										
Pinanyl mercaptan see 3503 3520										
1,2-PROPANEDITHIOL*	—	—	—	0.2	—	—	0.2	—	—	
3521										
PROPANETHIOL	1.0	1.0	1.25	0.929	1.0	—	2.2	—	—	Soups-3.0; Beverages, alcoholic-1.0
1-Propanethiol see 3521										
n-Propyl mercaptan see 3521 3522										
o-PROPYLPHENOL	—	—	—	—	—	—	3.0	—	2.0	Seasonings-2.0
2-Propylphenol see 3522										
Propylthiol see 3521 3523										
PYRROLIDINE	0.5	1.0	3.0	2.0	—	6	—	0.5	—	Cereals-1.5
Tetrahydropyrrole see 3523										
n-Thiopropyl alcohol see 3521										
2,4,5-Trimethyl-2,5-dihydrooxazole see 3525 3524										
3,5,5-TRIMETHYLHEXANAL	3.0	2.0	12	20	7.0	40	—	—	—	
3525										
2,4,5-TRIMETHYL- Δ -3-OXAZOLINE	—	—	—	10	—	—	10	—	—	

*Total dithiol added to any food not to exceed 1.0 ppm