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

14. GRAS Substances

Bernard L. Oser, Carrol S. Weil, Lauren A. Woods, and Bruce K. Bernard

□ SOON AFTER the enactment of the Food Additives Amendment of 1958 the Flavor and Extract Manufacturers' Association (FEMA) initiated a program of gathering all available data on the identity, production, and usage of natural and flavoring substances for safety evaluation by a panel of "experts qualified by scientific training and experience" as specified in the statute. This year marks the 25th anniversary of the organization by the senior author of an expert panel commissioned to review and evaluate the vast amount of data assembled by experienced technologists in the food and flavor industries. In 1965, the first comprehensive paper was published listing over 1,100 GRAS substances and their use levels in at least 10 major categories of food.

With the passage of years, there have resulted changes in the composition of the expert panel, as described below, as a result of the "normal processes of attrition." However, the panel's efforts have kept pace both with the increasing demands of safety evaluation and with the increasing number of flavoring substances developed by industrial scientists. These advances have resulted in large part from replication of newly identified flavor compounds in natural foods through the application of more sophisticated analytical technology and instrumentation.

The panel's conclusions must always be unanimous and are based on the judgement that they could reasonably be expected to be shared by other qualified scientists equally informed of the underlying scientific and technical data. The policy of publishing its conclusions was adopted from the beginning, as recommended by the Food and Drug Administration (FDA).

The growth in the number of substances the panel has declared to be GRAS, up to the present, is illustrated in Figure 1, based on the series of 14 GRAS lists published in this journal from 1960 to date under the title "Recent Progress in the Consideration of Flavoring Substances under the Food Additives Amendment" and listed in the References section.

Author Oser is with Bernard L. Oser Associates, Inc., Bayside, N.Y. Author Weil is with Carrol S. Weil, Inc., Pittsburgh, Pa. Author Woods is Professor Emeritus, Medical College of Virginia, Richmond, Va. Author Bernard is Consulting Director of Scientific Affairs, Flavor and Extract Manufacturers' Association, Washington, D.C.

Criteria for GRAS Consideration

As previously described (Oser and Hall, 1977) the criteria for the GRAS decisions of the expert panel included, inter alia, "experience in common use in food" taking into account naturally occurring as well as added substances and, where indicated, "scientific procedures," i.e. chemical structure and analogies, metabolic fate, and toxicological tests when necessary.

Among the latter, acute oral toxicity in rats as measured in terms of oral LD_{50} values were frequently considered. FEMA and the expert panel have never attached much probative value to these crude, but widely used estimates of acute toxicity. However, such tests did serve to (1) support structural analogy among closely related compounds, and, in other cases, (2) provide range-finding data for longer-term screening tests. Because of its limitations, the conventional LD_{50} has gradually been abandoned by many scientists, including those of the FDA, in favor of more informative screening tests for oral toxicity. The expert panel has therefore been studying an abbreviated version of a screening test based on dietary inclusion of the test substance for a short period, but including more observations than simply mortality.

Studies are underway based principally on the published experience of Weil et al. (1963, 1969), in which estimates of toxicity are predicted from dosage periods as short as 7 or 14 days. They will be reported later when sufficient data are accumulated to justify the added time and expense of these routine tests. It is the present opinion of the panel that short-term tests, which include body weight, food efficiency, and limited behavioral and pathological observations, will provide substantially more significant data than the simplistic LD_{50} type of tests.

It should be mentioned in this connection that the classification for priority-setting, based on natural occurrence, chemical structure, and estimated maximum levels of exposure as proposed by Cramer, Ford, and Hall (1978), has played a useful role in predicting

Reprint Requests should be addressed to Director of Scientific Affairs, Flavor and Extract Manufacturers' Association, Suite 650, 900 17th St., N.W., Washington, DC 20006.

potential degrees of risk in the use of the majority of flavoring substances.

Basic Research

FEMA continues to sponsor research on the safety of individual and structurally related classes of flavoring substances. Recently such work has resulted in publications on cinnamyl anthranilate (Anthony et al., 1983) as well as trans-anethole (Caldwell et al., 1983; Sangster et al., 1984b; Sangster et al., 1984a) p-propylanisole (Sangster et al., 1983), eugenol (Caldwell et al., 1985; Sutton et al., 1985) and benzyl acetate (Caldwell and Chidgey, 1985). Work continues on the metabolism of substituted propyl benzene substances, cinnamyl compounds, and benzyl acetate. The interaction of α,β-unsaturated ketones with DNA model systems is currently being investigated.

Panel Membership

Previous issues of the FEMA series of GRAS lists have indicated the membership of the expert panels that participated in the decisions reported therein. The panel regretfully reports the retirement, since the publication of GRAS 13 in 1984, of Dr. David W. Fassett, who was a member of the original panel established in 1960. The panelists who participated in the present GRAS 14 determinations and their affiliations are: Lauren A. Woods, Ph.D., M.D., Professor Emeritus, Medical College of Virginia, Virginia Commonwealth University; John Doull, M.D., Ph.D., Professor, University of Kansas Medical School; Paul M. Newberne, D.V.M., Ph.D., Professor Emeritus, Massachusetts Institute of Technology. Carrol S. Weil, M.A., Carrol S. Weil, Inc.; Robert L. Smith, Ph.D., D.Sc., Professor, St. Mary's Hospital, University of London; Bernard M. Wagner, M.D., Professor, Columbia University and Director of Laboratories, Overlook Hospital; Philip S. Portoghese, Ph.D., Professor, University of Minnesota.

Drs. Oser and Woods served as co-chairmen, Dr. Richard A. Ford as liaison with The Research Institute for Fragrance Materials, and Dr. Bruce K. Bernard as executive secretary during the proceedings that led to the current additions to the lists of GRAS substances.

Notes to the Reader

Readers should be aware of a typographical error occurring in GRAS 13 (Oser et al., 1984, p. 72 and 89). The correct chemical name for the substance identified by FEMA number 3735 is 2,2,6-trimethyl-6-vinyltetrahydropyran, not 2,6,6-trimethyl-6-vinyltetrahydropyran as reported therein. Scientific Literature Reviews (SLRs) containing the revisions associated with the additions found in GRAS 13 are available through the

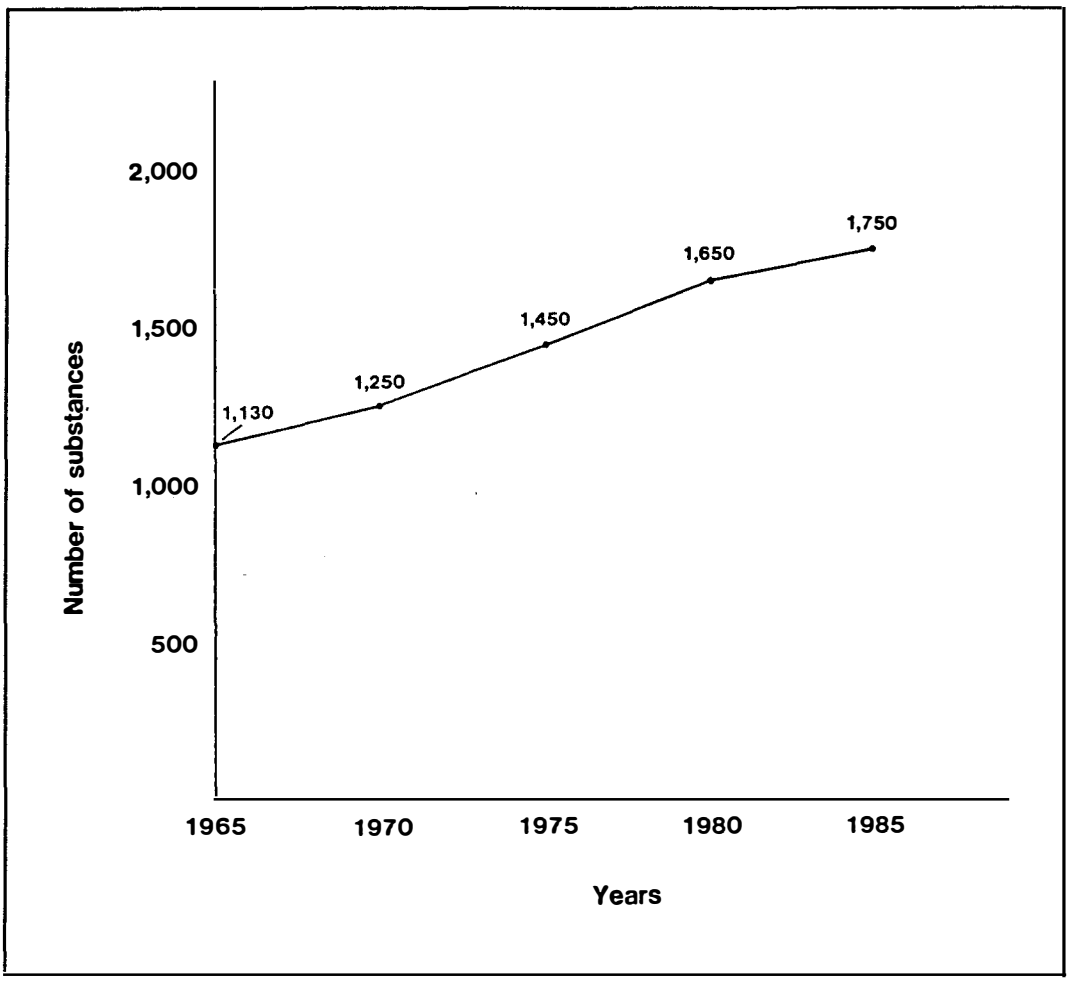

Fig. 1—Cumulative Totals of FEMA GRAS Flavoring Substances

National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161. The location of the individual GRAS substances, including those found in GRAS 13, in the 69 SLRs can be found in "Flavor and Fragrance Materials 1985" (Bernard, 1985).

Table I of this report is an alphabetical cross reference list. Substances with cis-trans stereochemical designations have also been named according to the more recent and less ambiguous IUPAC (E)–(Z) nomenclature system.

References

Anthony, A., Caldwell, J., Cotgreave, I.A., Sangster, S.A., and Sutton, J.D. 1983. The dose dependency of the disposition and enzyme-inducing properties of cinnamyl anthranilate in the C3B6F1 mouse. Brit. J. Pharmacol. 80: 447P.

Bernard, B.K. (Ed.). 1985. "Flavor and Fragrance Materials 1985," Allured Publishing Corp., Wheaton, Ill.

Caldwell, J. 1984. Significance of dose-dependent metabolism of flavor chemicals for their safety evaluation. Proceedings of the 4th European Toxicology Forum, Geneva. Toxicology Forum, Washington, D.C.

Caldwell, J. and Chidgey, M.A.J. 1985. Dose- and vehicle-related variation in the disposition of benzyl acetate. Brit. J. Pharmacol. 85: 207P.

Caldwell, J., Anthony, A., Cotgreave, I.A., Sangster, S.A., and Sutton, J.D. 1985. Influence of dose size and sex on the disposition and hepatic effects of cinnamyl anthranilate in the B6C3F1 mouse. Fd. Chem. Toxicol. 23(6): 559.

Caldwell, J., Farmer, P.B., Sangster, S.A., and Smith, R.L. 1983. Dose-dependent disposition of trans-anethole in the rat. Brit. J. Pharmacol. 79: 212P.

Caldwell, J., Sangster, S.A., and Sutton, J.D. 1985. The fate of eugenol in the rat and its variation with dose. Brit. J. Pharmacol. 84: 24P.

Cramer, G.M., Ford, R.A., and Hall, R.L. 1978. Estimation of toxic hazard—decision tree approach. Fd. Cosmet. Toxicol. 16: 255.

Hall, R.L. 1960. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. Food Technol. 14(10): 488.

Hall, R.L. and Oser, B.L. 1961. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 2. GRAS substances. Food Technol. 15(12): 20.

Hall, R.L. and Oser, B.L. 1965. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 3. GRAS substances. Food Technol. 19(2): 151.

Hall, R.L. and Oser, B.L. 1970. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment 4. GRAS substances. Food Technol. 24(5): 25.

Oser, B.L. and Ford, R.A. 1973a. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 6. GRAS substances. Food Technol. 27(1): 64.

Oser, B.L. and Ford, R.A. 1973b. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 7. GRAS substances. Food Technol. 27(11): 56.

Oser, B.L. and Ford, R.A. 1984. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 8. GRAS substances. Food Technol. 28(9): 76.

Oser, B.L. and Ford, R.A. 1975. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 9. GRAS substances. Food Technol. 29(8): 70.

Oser, B.L. and Ford, R.A. 1977. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 10. GRAS substances. Food Technol. 31(1): 65.

Oser, B.L. and Ford, R.A. Recent progress in the consideration of flavoring ingredients under the Food Additives Admendment. 11. GRAS substances. Food Technol. 32(2): 60.

Oser, B.L. and Ford, R.A. 1979. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 12. GRAS substances. Food Technol. 33(7): 65.

Oser, B.L., Ford, R.A. and Bernard, B.K. 1984. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 13. GRAS substances. Food Technol. 38(10): 66.

Oser, B.L. and Hall, R.L. 1972. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 5. GRAS substances. Food Technol. 26(5): 35.

Oser, B.L. and Hall, R.L. 1977. Criteria employed by the expert panel of FEMA for the GRAS evaluation of flavoring substances. Fd. Cosmet. Toxicol. 15: 457.

Sangster, S.A., Caldwell, J., Hutt, A.J., and Smith, R.L. 1983. The metabolism of *p*-propylanisole in the rat and mouse and its variation with dose. Fd. Chem. Toxicol. 21(3): 263.

Sangster, S.A., Caldwell, J., and Smith, R.L. 1984a. Metabolism of anethole. II. Influence of dose size on the route of metabolism of trans-anethole in the rat and mouse. Fd. Chem. Toxicol. 22(9): 707.

Sangster, S.A., Caldwell, J., Smith, R.L., and Farmer, P.B. 1984b. Metabolism of anethole. I. Pathways of metabolism in the rat and mouse. Fd. Chem. Toxicol. 22(9): 695.

Sutton, J.D., Sangster, S.A., and Caldwell, J. 1985. Dose-dependent variation in the disposition of eugenol in the rat. Biochem. Pharmacol. 34(3): 465.

Weil, C.S. and McCollister, D.D. 1963. Relationship between short- and long-term feeding studies in designing an effective toxicity test. J. Agr. Food Chem. 11: 486.

Weil, C.S., Woodside, M.D., Bernard, J.R., and Carpenter, C.P. 1968. Relationship between single-peroral, one-week, and ninety-day rat feeding studies. Toxicol. and Appl. Pharmacol. 14: 426.

—"Primary Names and Synonyms Alphabetical Cross Reference List" is on page 114

—"GRAS Flavoring Ingredients and Usage Levels" are on pp. 116–117

GRAS 14—Primary Names and Synonyms[a] Alphabetical Cross Reference List

FEMA No.	Substance
	m-Anisaldehyde, 4-hydroxy, isobutyrate (see Vanillin isobutyrate, no. 3754)
	m-Anisaldehyde, 4-hydroxy, 2-methylpropionate (see Vanillin isobutyrate, no. 3754)
3740	ANISYL PHENYLACETATE
	Anisyl α-toluate (see Anisyl phenylacetate, no. 3740)
	Benzaldehyde, 4-hydroxy, 3-methoxy, isobutyrate (see Vanillin isobutyrate, no. 3754)
	Benzaldehyde, 4-hydroxy, 3-methoxy, 2-methylpropionate (see Vanillin isobutyrate, no. 3754)
3741	α-CAMPHOLENIC ALCOHOL
	α-Campholenol (see α-Campholenic alcohol, no. 3741)
	o-Cresyl isobutyrate (see o-Tolyl isobutyrate, no. 3753)
	Cryprocarya massoia (see Massoia bark oil, no. 3747)
3742	5- and 6-DECENOIC ACID
	(-)-2-Decenoic acid, 5-hydroxy, δ-lactone (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
3743	2,5-DIETHYLTETRAHYDROFURAN
	5,6-Dihydro-6-pentyl-2H-pyran-2-one (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
	(R)-5,6-Dihydro-6-pentyl-2H-pyran-2-one (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
	(±)-5,6-Dihydro-6-pentyl-2H-pyran-2-one (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
	1-Ethoxyethyl ether of potassium lactate (see Potassium 2-(1′-ethoxy)ethoxypropanoate, no. 3752)
	4-Formyl-2-methoxyphenyl 2-methylpropanoate (see Vanillin isobutyrate, no. 3754)
	Frescolat (see l-Menthyl lactate, no. 3748)
3744	5-HYDROXY-2-DECENOIC ACID δ-LACTONE
3745	5-HYDROXY-7-DECENOIC ACID δ-LACTONE
	α-Hydroxypropanoic acid, 5-methyl-2-(1-methylethyl)cyclohexyl ester (see l-Menthyl lactate, no. 3748)
	Isobutyric acid, ester with vanillin (see Vanillin isobutyate, no. 3754)
	Jasmin lactone (see 5-Hydroxy-7-decenoic acid δ-lactone, no. 3745)
3746	LINALOOL OXIDE
	Massoia bark (see Massoia bark oil, no. 3747)
3747	MASSOIA BARK OIL
	Massoialactone (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
	Massoia lactone (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
	Massoilactone (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
	(R)(-) Massoilactone (see 5-Hydroxy-2-decenoic acid δ-lactone, no. 3744)
	(-)-p-Menthan-3-yl lactate (see l-Menthyl lactate, no. 3748)
3748	l-MENTHYL LACTATE
	p-Methoxybenzyl phenylacetate (see Anisyl phenylacetate, no. 3740)
	3-Methoxy-4-isobutyrylbenzaldehyde (see Vanillin isobutyrate, no. 3754)
	2-Methylphenyl 2-methylpropanoate (see o-Tolyl isobutyrate, no. 3753)
	cis & *trans*-2-Methyl-2-vinyl-5(2-hydroxy-2-propyl)tetrahydrofuran (see Linalool oxide, no. 3746)
3749	*cis*-5-OCTENAL
	(Z)-5-Octenal (see *cis*-5-Octenal, no. 3749)
3750	OSMANTHUS ABSOLUTE
	Osmanthus fragrans lour. (see Osmanthus absolute, no. 3750)
	Osmanthus fragrans (see Osmanthus absolute, no. 3750)
	cis-5-(2-Pentenyl)pentanolide (see 5-Hydroxy-7-decenoic acid δ-lactone, no. 3745)
	Phenylacetic acid, p-methoxybenzyl ester (see Anisyl phenylacetate, no. 3740)
3751	2-(3-PHENYLPROPYL)PYRIDINE
3752	POTASSIUM 2-(1′-ETHOXY)ETHOXYPROPANOATE
	Potassium o-(1′-ethoxy)ethyllactate (see Potassium 2-(1′-ethoxy)ethoxypropanoate, no. 3752)
	Propanoic acid, 2-hydroxy, 5-methyl-2(1-methylethyl)cyclohexyl ester [1R-{1α(R*), 2β, 5α}] (see l-Menthyl lactate, no. 3748)
	Propanoic acid, 2-methyl, 4-formyl-2-methoxyphenyl ester (see Vanillin isobutyrate, no. 3754)
3753	o-TOLYL ISOBUTYRATE
	o-Tolyl 2-methylpropanoate (see o-Tolyl isobutyrate, no. 3753)
	2,2,3-Trimethyl-3-cyclopentene-1-ethanol (see α-Campholenic alcohol, no. 3741)
	2-(2,2,3-Trimethylcyclopent-3-en-1-yl)ethanol (see α-Campholenic alcohol, no. 3741)
3754	VANILLIN ISOBUTYRATE
	Vanillyl isobutyrate (see Vanillin isobutyrate, no. 3754)
	cis & *trans*-2-Vinyl-2-methyl-5-(1′-hydroxy-1′-methylethyl) tetrahydrofuran (see Linalool oxide, no. 3746)

—"Gras Flavoring Ingredients and Usage Levels" are on pp. 116–117

[a]Primary names, in capital letters, and synonyms, in lower case, are listed alphabetically. Synonyms are followed by reference to the primary name and FEMA number.

GRAS FLAVORING INGREDIENTS AND 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

Substance	Baked Goods	Frozen Dairy	Meat Products	Soft Candy	Gelatins & Puddings	Soups	Snack Foods	Nonalcoholic Beverages	Alcoholic Beverages	Gravies	Other Uses
3740											
Anisyl phenylacetate	14.7	6.16	—	10.8	6.16	—	—	5.66	10.0	—	
3741											
α-Campholenic alcohol	2.0	1.5	—	3.0	2.0	—	—	2.0	1.5	—	Fruit ices—1.5; Confectionary and frosting—2.0; Jams and jellies—2.0; Hard Candy—2.5; Chewing gum—35.0
3742											
5- and 6-Decenoic acid	25.0	10.0	—	10.0	10.0	—	—	5.0	—	—	Milk products—5.0; Cheese—10.0; Condiments and relishes—5.0; Jams and jellies—10.0; Imitation dairy products—25.0; Hard candy—25.0
3743											
2,5-Diethyltetrahydrofuran	10.0	5.0	—	10.0	5.0	—	—	5.0	5.0	—	—
3744											
5-Hydroxy-2-decenoic acid δ-lactone	1.0	—	—	0.5	—	—	—	0.5	—	0.2	Confectionary and frosting—1.0; Reconstituted vegetables—0.2; Imitation dairy products—2.0; Hard Candy—4.0; Chewing gum—4.0;
3745											
5-Hydroxy-7-decenoic acid δ-lactone	3.0	1.0	—	1.5	3.0	—	—	3.0	5.0	—	Milk products—2.0; Fruit ices—0.1; Confectionary and frosting—3.0; Jams and jellies—3.0; Sweet sauce—3.0; Imitation dairy products—1.0 Hard candy—10.0; Chewing gum—15.0
3746											
Linalool oxide	11.25	7.0	—	10.178	4.61	—	—	3.86	6.75	—	
3747											
Massoia bark oil	50.0	—	—	30.0	—	—	—	20.0	20.0	—	Milk products—20.0
3748											
l-Menthyl lactate	—	—	—	—	—	—	—	—	—	—	Chewing gum—800
3749											
cis-5-Octenal	5.0	5.0	—	10.0	10.0	0.5	15.0	2.5	2.5	0.5	Breakfast cereals—10.0; Fats and oils—3.0; Fruit ices—5.0; Fish products—3.0;

Substance	Baked Goods	Frozen Dairy	Meat Products	Soft Candy	Gelatins & Puddings	Soups	Snack Foods	Nonalcoholic Beverages	Alcoholic Beverages	Gravies	Other Uses
3479 *cis*-5-Octenal (*continued*)											Confectionary and frosting—5.0; Jams and jellies—5.0; Sweet sauce—5.0; Nut products—0.5; Reconstituted vegetables—1.0; Hard candy—10.0; Chewing gum—25.0
3750 Osmanthus absolute	—	0.4	—	0.5	—	—	—	0.03	—	—	Milk products—0.2; Fruit ices—0.15; Jams and jellies—0.3; Hard candy—0.4; Chewing gum—2.0
3751 2-(3-Phenylpropyl) pyridine	2.0	0.3	1.0	—	—	1.0	1.0	2.0	1.0	—	2.0	Breakfast cereals—2.0; Processed vegetables—1.0; Condiments and relishes—2.0; Reconstituted vegetables—1.0; Household seasonings and flavors—2.0
3752 Potassium 2-(1'-ethoxy) ethoxypropanoate	450	100	—	150	400	—	—	100	150	—	Milk products—100; Processed fruit—100; Fruit ices—100; Condiments and relishes—400; Confectionary and frosting—150; Jams and jellies—400; Sweet sauce—400; Nut products—100; Imitation dairy products—150; Hard Candy—150; Chewing gum—1,500; Household seasonings and flavors—400
3753 *o*-Tolyl isobutyrate	9.0	8.0	—	8.0	8.0	—	—	8.0	—	—	
3754 Vanillin isobutyrate	15.0	10.0	—	—	10.0	10.0	—	—	—	—	—	Breakfast cereals—10.0; Confectionary and frosting—15.0; Imitation dairy products—15.0; Chewing gum—20.0