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EVALUATION OF CERTAIN FOOD ADDITIVES

Sixty-ninth report of the
Joint FAO/WHO Expert Committee on
Food Additives

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2.3 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives, the Committee took into consideration the principles established and contained in WHO Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), as well as the principles elaborated at subsequent meetings of the Committee (Annex 1, references *77*, *83*, *88*, *94*, *101*, *107*, *116*, *122*, *131*, *137*, *143*, *149*, *152*, *154*, *160*, *166*, *173*, *176*, *178*, *184* and *187*), including the present one. WHO Environmental Health Criteria, No. 70, contains the most important observations, comments and recommendations made, up to the time of its publication, by the Committee and associated bodies in their reports on the safety assessment of food additives and contaminants.

2.4 The safety evaluation of flavouring agents

2.4.1 *Dietary exposure assessment of flavouring agents: Incorporation of the single portion exposure technique (SPET) into the Procedure for the Safety Evaluation of Flavouring Agents*

Introduction

JECFA employs the maximized survey-derived intake (MSDI) method as a measure of the dietary exposure to flavouring agents for use in the Procedure for the Safety Evaluation of Flavouring Agents (the Procedure). The MSDI provides a per capita estimate of the dietary exposure to a flavouring agent that is compared with the relevant threshold of toxicological concern (TTC) for each structural class in a decision tree approach according to the Procedure. The MSDI is based on the reported amount of the flavouring agent introduced into the food supply per year in specific regions, currently Europe, the United States of America (USA) and Japan, corrected for under-reporting, and assuming that 10% of the relevant population would consume foods containing the flavouring agent.

The Committee considered issues related to dietary exposure to flavouring agents at its forty-fourth, forty-sixth, forty-ninth, fifty-fifth, sixty-third, sixty-fifth, sixty-seventh and sixty-eighth meetings (Annex 1, references *116*, *122*, *131*, *149*, *173*, *178*, *184* and *187*). The main concern expressed by the Committee was that the MSDI method may significantly underestimate dietary exposure to some flavouring agents. This could be the case for flavouring agents consumed by less than 10% of the population, especially where they might be used in a few food categories, and for flavouring agents with an uneven distribution of dietary exposure among consumers. The uneven distribution might be due to a combination of factors, including different use

levels across and within food categories, restriction to use in a few foods or food categories and different levels of consumption for different foods.

The single portion exposure technique (SPET) was developed by the Committee at its sixty-seventh meeting (Annex 1, reference *184*) to account for presumed patterns of consumer behaviour with respect to food consumption and the possible uneven distribution of dietary exposure for consumers of foods containing flavouring agents. The SPET provides an estimate of dietary exposure for an individual who consumes a specific food product containing the flavouring agent every day. The SPET combines an average (or usual) added use level with a standard portion size for a food category. Among all the food categories with a reported use level, the dietary exposure from the single food category leading to the highest dietary exposure from one portion is taken as the SPET estimate. The standard portion does not reflect high levels of food consumption reported in national dietary surveys. It was intended that the higher value of the two dietary exposure estimates (MSDI or SPET) would be used within the Procedure.

At its sixty-eighth meeting and its present meeting, the Committee performed a number of SPET and MSDI calculations with the aim of:

- determining whether a set of criteria could be identified for future selection of flavouring agents for which the MSDI could underestimate dietary exposure. In these cases, extra information on added use levels recommended by the industry would be required to calculate a SPET estimate;
- evaluating the possible impact of using both the MSDI and SPET estimates of dietary exposure in the Procedure for different flavour groups.

Investigation to develop criteria for the identification of flavouring agents requiring additional consideration

At its sixty-eighth meeting, the Committee calculated SPET estimates for 57 flavouring agents based on use levels provided by the International Organization of the Flavor Industry (IOFI),[1] 44 with low production volumes (<10 kg/year) and 13 with intermediate to high production volumes (production volumes corresponding to an amount that was greater than one third of the relevant TTC). These flavouring agents were selected from all structural classes and eight different groups. For 4 of the 57 flavouring agents selected, the MSDI was greater than the corresponding SPET estimate. Although for the remaining 53 flavouring agents the SPET estimate was greater than the corresponding MSDI, different steps through the Procedure would have been

[1] IOFI collated data on added use levels from the European Flavour and Fragrance Association (EFFA), the Flavor and Extract Manufacturers Association of the USA (FEMA) and the Japan Flavor & Fragrance Materials Association (JFFMA) and submitted these data on behalf of the three organizations.

required in only two cases where the SPET estimate exceeded the relevant TTC. The Committee concluded that, using this small group of flavours for the analysis, it was not possible to develop any selection criteria (based on production volume, structural class or flavour group) to identify cases where the MSDI would have underestimated dietary exposure and different steps through the Procedure would have been required if the SPET estimate were to be used in the Procedure. Consequently, for the present meeting of the Committee, additional data on use levels for another set of flavouring agents with intermediate to high volumes of production were requested from and provided by IOFI to extend the analysis.

Analysis of data for 40 flavouring agents considered at the present meeting

IOFI data were made available to calculate SPET estimates for 40 flavouring agents from 15 different flavour groups with intermediate to high production volumes. Of these, 28 were in structural class I, 6 in class II and 6 in class III. For class I flavouring agents, none of the SPET estimates exceeded the TTC, whereas the MSDI exceeded the TTC in one case. For class II flavouring agents, one SPET estimate exceeded the TTC, whereas no MSDI estimates exceeded the TTC. For class III flavouring agents, all six SPET estimates exceeded the TTC, whereas two of the MSDI estimates exceeded the TTC. Cases where the SPET estimate exceeded the MSDI and exceeded the TTC occurred in this group of flavouring agents across different production volumes, structural classes and flavour groups, a similar finding to that for the 57 flavouring agents considered at the sixty-eighth meeting.

Analysis of a larger data set of flavouring agents

Because the analyses of flavouring agents considered at the sixty-eighth meeting and the present meeting were inconclusive, the Committee collected use level data from other sources to determine whether suitable criteria for predicting when the MSDI might underestimate dietary exposure could be developed based on a larger group of flavouring agents. Additionally, the likelihood that the SPET estimate would exceed the relevant TTC when the MSDI did not was examined. Overall, SPET estimates for 549 flavouring agents were calculated, based on use levels derived from three main data sets:

- for 225 flavouring agents: recent and refined[1] use level data provided by IOFI to the Committee or to the European Commission (Directorate

[1] In this context, "refined" means that the information is derived from use levels in specific foods or food types, rather than broad food categories (e.g. "fruit-flavoured yogurt" as opposed to "dairy products").

General for Health and Consumer Affairs [DG SANCO]) in 2007 and 2008;

- for 198 flavouring agents: refined[2] use level data collected in an industry survey (National Academy of Sciences/National Research Council [NAS/NRC]) conducted in the USA in 1977;
- for 268 flavouring agents: use levels proposed by industry for flavouring agents registered as FEMA Generally Recognized as Safe (GRAS),[2] published between 1965 and 2007.

Some flavouring agents were assessed using more than one source of use levels, resulting in a total of 691 SPET estimates.

Some of the portion sizes used in the SPET calculations were updated at the present meeting based on reported food consumption levels, including the addition of new portion sizes (Table 1).

Table 1
Updated portion sizes to be used for the calculation of SPET estimates

Food categorization system for the Codex General Standard for Food Additives (GSFA) (see http://www.codexalimentarius.net/gsfaonline/CXS_192e.pdf)	Standard portion (g) (sixty-seventh meeting of Committee)	Revised standard portion (g) (present meeting of Committee)	Notes
01.0 Dairy products and analogues, excluding products of category 02.0			
01.1 Milk and dairy-based drinks	200	200 (30*)	
01.2 Fermented and renneted milk products (plain), excluding food category 01.1.2 (dairy-based drinks)	200	200 (30*)	
01.3 Condensed milk and analogues	NA	70	Differs from United States standard portion, which refers only to milk added to coffee, tea, etc.
01.4 Cream (plain) and the like	NA	15	

[2] GRAS is a regulatory concept specific to the United States Federal Food, Drug, and Cosmetic Act. Any substance added to food requires a food additive regulation for its use, unless its intended use is GRAS. Food ingredients whose use is GRAS are not required by law to receive Food and Drug Administration (FDA) approval before marketing. FEMA has been publishing lists of flavouring substances, and associated use levels at or below which it has deemed their use to be GRAS, for more than 30 years.

01.5 Milk powder and cream powder and powder analogues (plain)	NA	30*	Differs from United States standard portion, which refers only to milk added to coffee, tea, etc.
01.8 Whey and whey products, excluding whey cheeses	NA	200 (30*)	
04.0 Fruits and vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes and aloe vera), seaweeds, and nuts and seeds			
04.1 Fruit			
04.1.1 Fresh fruit	NA	140	
04.1.2.5 Jams, jellies, marmalades	NA	30	
04.2 Vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweeds, and nuts and seeds			
04.2.2.5 Vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed purees and spreads (e.g. peanut butter)	NA	30	For nut and similar spreads
06.0 Cereals and cereal products derived from cereal grains, roots and tubers, and pulses and legumes, excluding bakery wares of food category 07.0			
06.1 Whole, broken or flaked grain, including rice	NA	200 (70 raw)	
06.2 Flours and starches (including soya bean powder)	NA	30	
06.5 Cereal and starch-based desserts (e.g. rice pudding, tapioca pudding)	200	200 (30*)	For pudding powder
08.0 Meat and meat products, including poultry and game			
08.1 Fresh meat, poultry and game	NA	200	
08.4 Edible casings (e.g. sausage casings)	NA	1	
09.0 Fish and fish products, including molluscs, crustaceans and echinoderms			
09.1 Fresh fish and fish products, including molluscs, crustaceans and echinoderms			
09.1.1 Fresh fish	NA	200	

09.1.2 Fresh molluscs, crustaceans and echinoderms	NA	200
09.2 Processed fish and fish products, including molluscs, crustaceans and echinoderms	100	100
09.3 Semi-preserved fish and fish products, including molluscs, crustaceans and echinoderms	100	100
09.4 Fully preserved, including canned or fermented, fish and fish products, including molluscs, crustaceans and echinoderms	100	100
10.0 Eggs and egg products		
10.1 Fresh eggs	NA	100
11.0 Sweeteners, including honey		
11.6 Table-top sweeteners, including those containing high-intensity sweeteners	15	1
12.0 Salts, spices, soups, sauces, salads, protein products (including soya bean protein products) and fermented soya bean products		
12.1 Salt and salt substitutes	NA	1
12.5 Soups and broths	200	200 (30*)
12.8 Yeast and like products	NA	1
12.9 Protein products	15	15
13.0 Foodstuffs intended for particular nutritional uses		
13.1 Infant formulae, follow-on formulae and formulae for special medical purposes for infants	NA	1000
13.2 Complementary foods for infants and young children	NA	50
13.3 Dietetic foods intended for special medical purposes (excluding food products of category 13.1)	NA	200 (30*)
13.4 Dietetic formulae for slimming purposes and weight reduction	NA	200 (30*)
13.5 Dietetic foods (e.g. supplementary foods for dietary use) excluding products of food categories 13.1–13.4 and 13.6	NA	200 (30*)
14.0 Beverages, excluding dairy products		
14.1 Non-alcoholic ("soft") beverages	300	300 (12 for coffee or 30 for drink mix powders*)
14.2 Alcoholic beverages, including alcohol-free and low-alcoholic counterparts		

14.2.5 Mead	NA	150	The portion size is derived from that of Grape wines (14.2.3)
16.0 Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01–15	NA	300	Reported uses

NA, not available
* In parentheses, the amount is applicable for powder.

In nearly all cases (92%), the SPET estimate was greater than the MSDI, and it was more likely that the SPET estimate was greater than the TTC of the relevant structural class than the corresponding MSDI. The SPET estimate was most frequently greater than the TTC in class III, but this also occurred in classes I and II (see Table 2).

Table 2
Comparison of SPET and MSDI with TTC for flavouring agents in structural classes I, II and III

	Source of use level data		
	IOFI 2007–2008 (n = 225)	NAS/NRC 1977 (n = 198)	FEMA GRAS 1965–2007 (n = 268)
Class I, SPET > TTC	1/70 (1%)	38/121 (31%)	25/111 (23%)
Class II, SPET > TTC	1/12 (8%)	13/58 (22%)	32/62 (52%)
Class III, SPET > TTC	86/143 (60%)	12/19 (63%)	77/95 (81%)
Total, SPET > TTC	**88/225 (39%)**	**63/198 (32%)**	**134/268 (50%)**
Class I, MSDI > TTC	2/70 (3%)	5/121 (4%)	1/111 (1%)
Class II , MSDI > TTC	0/12 (0%)	4/58 (7%)	1/62 (2%)
Class III, MSDI > TTC	12/143 (8%)	1/19 (5%)	12/95 (13%)
Total, MSDI > TTC	**14/225 (6%)**	**10/198 (5%)**	**14/268 (5%)**

Note: Some flavouring agents were assessed using more than one source of use levels.

The Committee considered the use of FEMA GRAS use levels to be less desirable than that of the more specific use levels provided by IOFI, as FEMA GRAS values are projected and probably overestimate actual added use levels. IOFI provided high-quality use level data from recent surveys and informed the Committee that, with very few exceptions, there is a strong agreement between recent and older use level surveys and that comparison of these surveys supports the conclusion that use levels for flavouring agents

with similar flavouring effect are generally similar and have not changed significantly over time.

For the flavouring agents with IOFI use level data only, the differences between the two dietary exposure estimates were examined. The Committee considered that it would be inappropriate to use the SPET estimates based on NAS/NRC data from 1977 or FEMA GRAS levels for this purpose.

Overall, for the group of 225 flavouring agents with IOFI use level data, 50% had a SPET estimate that was less than 2 orders of magnitude higher than the MSDI (median ratio of SPET to MSDI was 85). Twenty-one flavouring agents had an MSDI that was higher than the SPET estimate by up to 2 orders of magnitude. For the remaining 204 flavouring agents, the SPET estimate was higher than the MSDI. Of these, 24 had SPET estimates that were 4–6 orders of magnitude higher than the MSDI.

From the analysis of the MSDI and SPET estimates for the 549 flavouring agents, the Committee concluded that it was not possible to develop criteria, based on production volume, structural class or flavour group, to predict when the MSDI might underestimate dietary exposure and when the SPET estimate, but not the MSDI, was likely to exceed the TTC.

Consideration of the incorporation of the SPET estimate into the Procedure

At its present meeting, the Committee considered the consequences of incorporating the SPET estimate into the Procedure, using two flavour groups as an example. One group was evaluated on the A-side of the Procedure (six hydroxy- and alkoxy-substituted benzyl derivatives; section 4.1.7), and one group on the B-side (14 miscellaneous nitrogen-containing substances; section 4.1.8). In four cases, IOFI use level data were available. For the other 16 flavouring agents, FEMA GRAS levels were used for the SPET estimate for the purposes of this exercise only, as these were the only use levels available.

For these two groups of flavouring agents, the food categories responsible for the highest dietary exposure in one standard portion were beverages, either alcoholic or non-alcoholic (for nine flavouring agents), processed fruit (two cases), processed vegetables (one case), meat products (two cases), cereals and cereal products such as baked goods (four cases), condiments (one case) and milk and dairy-based drinks (one case).

Hydroxy- and alkoxy-substituted benzyl derivatives. In applying the Procedure for the Safety Evaluation of Flavouring Agents using the MSDI for the six flavouring agents in the hydroxy- and alkoxy-substituted benzyl derivatives group of flavouring agents, the Committee assigned five flavouring agents (Nos 1878–1880, 1882 and 1883) to structural class I and the

remaining flavouring agent (No. 1881) to structural class III (*2*). The evaluation of all agents in this group proceeded via the A-side of the Procedure. According to the Procedure using the MSDI, the safety of these six flavouring agents raised no concern, because the dietary exposure was below the relevant TTC.

Incorporation of the SPET estimate into the Procedure would have resulted in different steps through the Procedure for three of the six flavouring agents. SPET estimates based on IOFI use levels were available for only one of the flavouring agents in this group (No. 1882). The estimated dietary exposure to sodium 4-methoxybenzoyloxyacetate (No. 1880) and 4- methoxybenzoyloxyacetic acid (No. 1883) exceeded the TTC for structural class I (1800 μg/day) using the SPET estimate. Similarly, the dietary exposure to divanillin (No. 1881) exceeded the TTC for structural class III (90 μg/day).

Miscellaneous nitrogen-containing substances. In applying the Procedure for the Safety Evaluation of Flavouring Agents using the MSDI for the 14 flavouring agents in the group of miscellaneous nitrogen-containing substances, the Committee assigned 12 (Nos 1884–1890, 1892–1894, 1896 and 1897) to structural class II and the remaining 2 (Nos 1891 and 1895) to structural class III (*2*). None of the flavouring agents in this group could be predicted to be metabolized to innocuous products. The evaluation of these 14 flavouring agents therefore proceeded via the B-side of the Procedure. According to the Procedure using the MSDI, the safety of these 14 flavouring agents raised no concern.

Incorporation of the SPET estimate into the Procedure would have resulted in different steps through the Procedure for 2 of the 14 flavouring agents (Nos 1894 and 1895), as they would not have progressed to step B4. SPET estimates based on IOFI use levels were available for only three flavouring agents in this group (Nos 1889, 1893 and 1894).

Conclusion. The results for these two flavour groups indicated that the incorporation of the SPET estimate into the Procedure for flavouring agents going through the A-side of the Procedure will more often require appropriate toxicity data on these flavouring agents or on closely related substances to complete the safety evaluation at step A5. For flavouring agents going through the B-side of the Procedure, additional toxicological data will more often be required for those flavouring agents that do not progress to step B4. In all these cases, additional data would need to be included in the submission for the flavouring agents. IOFI use level data would need to be submitted in the data package for all flavouring agents going through either side of the Procedure to enable SPET estimates to be made.

Combined dietary exposure

The SPET estimate for a flavouring agent represents the dietary exposure for a daily consumer of a standard portion of food containing the substance. The combination of SPET estimates for related flavouring agents could greatly overestimate dietary exposure. The Committee therefore considered that the estimate of combined dietary exposure in the Procedure should continue to be based on the MSDI estimates, as outlined in the report of the sixty-eighth meeting.

Conclusion

The Committee noted that MSDI and SPET estimates of dietary exposure provide different and complementary information. Use of the SPET estimate addresses previous concerns expressed by the Committee about the dietary exposure methodology used in the Procedure, because the SPET estimates take account of the possible uneven distribution of dietary exposures to a flavouring agent for consumers of foods containing that substance. The higher value of the two dietary exposure estimates (MSDI or SPET) should be used within the Procedure.

As it was not possible to elaborate criteria to identify the flavouring agents for which the MSDI underestimated dietary exposure and SPET estimates should be used, the Committee concluded that it was necessary to incorporate SPET estimates into the Procedure for all flavouring agents considered at future meetings of the Committee. The Committee agreed that it would not be necessary to re-evaluate flavouring agents that have already been assessed using the Procedure.

To enable a safety evaluation using the Procedure to be undertaken, the Committee requested that added use level data be provided for each flavouring agent in a timely fashion before the meeting, in addition to up-to-date data on production volumes, as part of the data package for the safety evaluation. The Committee will not perform a safety evaluation in the absence of such data.

2.4.2 *Considerations on the thresholds of toxicological concern used in the Procedure*

The Committee received prepublication copies of a paper (*3*) on the use of TTCs in the safety evaluation of flavouring agents and in other risk assessment applications. The TTC values used in the Procedure for the Safety Evaluation of Flavouring Agents for structural classes I, II and III (1800, 540 and 90 μg/person per day, respectively) were derived from analyses of toxicity data for a wide range of chemicals and not just flavouring agents. The

TTC values were calculated by dividing the 5th percentiles of the distributions of no-observed-adverse-effect levels (NOAELs) for each structural class by a 100-fold uncertainty factor and multiplying by an average body weight (bw) of 60 kg. NOAELs of 3.0, 0.91 and 0.15 mg/kg bw per day had been derived from toxicity data on 137, 28 and 448 compounds in structural classes I, II and III, respectively.

The distribution of NOAELs for class III compounds was influenced markedly by the presence of neurotoxic organophosphate and organohalogen pesticides in the database used. The recent publication (*3*) showed that exclusion of compounds with these chemical characteristics, which are not representative of the structures of flavouring agents, would result in a 5th percentile of the distribution of NOAELs for structural class III of about 1.0 mg/kg bw per day, giving a revised TTC value of about 600 µg/person per day, which is similar to that for structural class II.

The Committee is aware that there are various activities currently under way to update and revise the Cramer decision tree (*2*), which is used to determine the structural class, and also to update the toxicology database used to establish the TTC values. There is widespread interest in developing TTC values appropriate to specific applications, such as flavouring agents, certain food additives and residues of pesticides and veterinary drugs in food. The Committee considered that this subject should be discussed in depth at a future meeting.

2.5 Food additive specifications

2.5.1 *Withdrawal of specifications*

2.5.1.1 *Carbohydrase from* Aspergillus niger *varieties*

The Committee reviewed the tentative specifications for carbohydrase from *Aspergillus niger* varieties that had been prepared at its fifteenth meeting (Annex 1, reference *26*) and for which an ADI "not specified" was established at its thirty-fifth meeting (Annex 1, reference *88*). The call for data for the sixty-ninth meeting requested information to revise the existing tentative specifications, stating that the specifications would be withdrawn if no information was forthcoming.

The tentative specifications for carbohydrase include α-amylase, pectinase, cellulase, glucoamylase and β-galactosidase (lactase). The functional uses listed in the specifications are diverse and imply that these enzymes are used in food processing as separate enzyme preparations rather than as a mixture of enzymes. Moreover, carbohydrase is not listed as a commercial enzyme