SPECIFICATIONS FOR THE IDENTITY AND PURITY OF FOOD ADDITIVES AND THEIR TOXICOLOGICAL EVALUATION: SOME FLAVOURING SUBSTANCES AND NON-NUTRITIVE SWEETENING AGENTS

Eleventh Report of the Joint FAO/WHO Expert Committee on Food Additives

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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Geneva, 21-28 August 1967

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Specifications for the substances considered in this report will be available on request from the Food Standards, Additives and Regulations Section, Nutrition Division, FAO, Rome.

Monographs containing biological data and toxicological evaluations will be issued by FAO and WHO in a separate document entitled:

Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents.

FAO Nutrition Meetings Report Series, 1968, No. 44 A; WHO/Food Add./68. 33.
SPECIFICATIONS
FOR THE IDENTITY AND PURITY OF FOOD ADDITIVES
AND THEIR TOXICOLOGICAL EVALUATION:
SOME FLAVOURING SUBSTANCES
AND NON-NUTRITIVE SWEETENING AGENTS

Eleventh Report
of the Joint FAO/WHO Expert Committee
on Food Additives

INTRODUCTION

A Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 21 to 28 August 1967. The meeting was opened by Dr P. Dorolle, Deputy Director-General of WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. Professor G. Brownlee was unanimously elected Chairman and Mr R.-A. Dehove, Vice-Chairman. Dr. G. J. van Esch agreed to serve as Rapporteur.

As a result of the recommendations of the Joint FAO/WHO Conference on Food Additives held in September 1955, 1 ten Joint FAO/WHO Expert Committees on Food Additives have met (see Annex 1).

The present meeting was convened on the recommendations made in the tenth report of the Joint FAO/WHO Expert Committee on Food Additives. Its terms of reference were: to draw up specifications for and to make a toxicological evaluation of a number of flavouring substances and non-nutritive sweeteners. Most of the substances considered had been suggested by the Codex Committee on Food Additives, to which the Expert Committee acts as an advisory body on questions of specifications and toxicity.

In order to facilitate the discussions, the Committee constituted itself into two groups, one of which gave major attention to chemical specifications and the other to toxicological evaluation.

1. GENERAL CONSIDERATIONS

1.1 General observations

There are three main reasons why flavouring substances have not been considered at any of the earlier meetings of the Joint FAO/WHO Expert Committee on Food Additives: (a) the number of these substances is very large; (b) the great majority of them occur in natural products used as food; and (c) their level of use is generally low.

It has, however, become increasingly obvious that toxicological hazards might arise from certain diets if high levels of some of these flavouring substances were used. Some flavouring substances of natural origin that were previously considered innocuous are now known, as a result of animal experiments and more modern investigations, to be toxic; examples are safrole and coumarin. Certain other flavouring substances, such as capsacin and zingiberin, when ingested in minute amounts, have been shown to induce hypersensitivity reactions. In addition, some flavouring substances are consumed in large amounts by children.

All these considerations appear to lend an urgency to the consideration of the possible toxicological hazards of flavouring substances. Some of the many factors to be considered in such evaluation are set out later in this report.

Similar arguments have been advanced for the non-nutritive sweetening agents. In particular, some of them are suspected of toxicity and there is also a likelihood of excessive intake by some sections of the population.

Flavouring substances and non-nutritive sweetening agents might exert less obvious effects than those seen with other food additives. It must not be assumed that these effects are always to be thought of as deleterious. Indeed, the beneficial effects in improving the palatability and physiological acceptability of foodstuffs need equal emphasis. On the other hand, it may be important to obtain information on the interaction among the various components of flavouring mixtures and also on their interaction with the foodstuffs to which they are added. Many of these substances might exert additional effects by the induction of physiological reflexes in the gastrointestinal tract or in other organ systems of the human body. Other aspects about which the Committee was concerned included possible allergic hypersensitivity; in the case of menthol, evidence was advanced to justify this concern. There is a need for research into suitable methodology for demonstrating such potential effects in experimental animals and man.
1.2 Principles

The Committee reviewed the general principles for the establishment of acceptable daily intakes (ADIs) set out in previous relevant reports of the Joint FAO/WHO Expert Committee on Food Additives, and paid particular attention to the emphasis put on the more recent advances in toxicological and biochemical methodology and interpretation set forth in the report of the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives.¹

It was considered desirable that, once an ADI had been established on the basis of the available scientific evidence, this should be followed up by controlled observations in man, as suggested in the above-mentioned WHO Scientific Group report.

2. SPECIFICATIONS

Previous reports have drawn attention to the necessity for compiling precise and detailed specifications and this is again emphasized.

Specifications were drafted for all the substances listed in Annex 2 (see page 4). These will be further reviewed within the scope of the Joint FAO/WHO Food Standards Program and subsequently redrafted and published in the Codex Alimentarius.

2.1 Flavouring substances

The Committee was faced with the need to prepare alternative specifications for products that could be either derived from nature or prepared synthetically. In the present report, the toxicological evaluations relate in some instances to products derived from nature, in others to those from synthetic sources, and in some cases to both. The evaluations made by the Committee relate only to the chemically defined products, regardless of source.

2.1.1 Toxic trace elements

As a measure of good manufacturing practice, specific limits are sometimes set for arsenic, lead or other elements precipitable by hydrogen sulfide under acid conditions. It was agreed that this is not necessary in the case of flavouring substances that are distilled. Flavouring materials are added to food in concentrations of a few parts per million and the concentrations of toxic trace elements in these materials—if present at all—are likely to be of a similar order. Consequently, the concentrations

of such toxic elements in food resulting from the addition of flavouring substances will be only a few parts per $10^{10}-10^{12}$ parts of food. This would not represent a significant increase over the variable background load of these toxic trace elements naturally present in foods.

2.1.2 Other components

In general, the other components of the food additive, making up the difference between the assay figure and 100%, will not be mentioned in the specification if they are considered, on the basis of the manufacturing processes, to be of the same general class as the material specified. For example, for esters, the other components are likely to be the starting acid and alcohol and the higher and lower homologous esters, acids and alcohols; in the case of aldehydes, the corresponding acids may be produced by oxidation. Limits on impurities will be specified only where this is deemed necessary for toxicological reasons in the light of knowledge of present day technological practice.

It was agreed that the unequivocal identification of the flavouring substances could not be based only on the criteria of identity and purity detailed in the specifications. The identity can be determined unequivocally using methods such as gas-liquid chromatography, infrared spectrometry, nuclear magnetic resonance or other physicochemical methods of analysis. When using such techniques to compare the substance with standard samples, account has to be taken of the fact that many flavouring substances may not be stable in the medium in which they are present. In addition, the presence of the characteristic odour and the absence of foreign odours or tastes, essential to the use of these products, constitute an additional means of identification and indication of purity.

2.2 Non-nutritive sweetening agents

The specifications for these substances were drawn up in accordance with the principles set forth in the previous reports. Specifications for cyclohexylsulfamic acid were also prepared.

3. BIOLOGICAL DATA

3.1 Possible substitution of biochemical and metabolic studies for formal toxicity studies

The importance of metabolic and biochemical studies has been emphasized in the report of the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives.\textsuperscript{1} For certain

substances for which formal toxicity studies were incomplete, the Committee accepted evidence that the flavouring material was broken down into normal body constituents or that it followed a well established metabolic pathway. The esters constitute a good example of this kind.

3.2 Acute toxicity

The Committee noted that for a number of flavouring substances the data for acute oral toxicity were such as to suggest that little absorption occurred by this route. In such cases, information on acute toxicity following intraperitoneal administration could give a guide to the toxic potential of the substance. It was noted, too, that a short description of the toxic signs and an indication of the time and cause of death would be useful when reporting such studies.

3.3 Short-term and long-term studies

In some studies, the only adverse effect noted was a slight but statistically insignificant retardation of growth, compared with the control group. There are two possible explanations for this observation when the food efficiency is unaffected: toxic anorexia or unpalatability of the diet. Additional information, such as the results of food preference tests, paired feeding experiments or related observations would be useful. When discussing the choice of animal species for short-term studies, the Committee agreed with the statement made by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives \(^1\) that the most appropriate species, where known, rather than the most sensitive one should be used.

3.4 Additional information

In certain instances, additional collateral information was of value. Included in this category were a knowledge of the consumption of the flavouring substances and of their distribution in natural food products. It was also valuable to have information on the toxicology of substances of related structure.

3.5 Concept of acceptable daily intakes

The concept of acceptable daily intakes for man is fully described in section 6.2 of Annex 4 of the tenth report of the Joint FAO/WHO Expert Committee on Food Additives, as follows:

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FOOD ADDITIVES

The acceptable daily intake is the daily dose of a chemical that appears to be without appreciable risk on the basis of all the facts known at the time. "Without appreciable risk" is taken to mean the practical certainty that injury will not result even after a lifetime of exposure.

Many factors have to be considered in deriving from the dose level that causes no toxicological effect in an experimental animal an estimate of the acceptable intake in man. It is necessary to take into account species differences, individual variations, incompleteness of available data, and a number of other matters. It must be remembered that food additives may be consumed by people of all ages throughout the whole lifespan, that they are eaten by the sick as well as the healthy, and that there are wide variations in individual dietary patterns. Each case must be judged on its merits.

It will be observed from the above that the acceptable daily intake is only an estimate and depends upon a great number of factors, all of which should be taken into consideration. Therefore an exact maximum acceptable daily intake cannot be calculated. This is one of the reasons why, in some cases, the zone of acceptability is divided into two parts—"conditional" and "unconditional". Although the whole zone of acceptability may be safely used, obviously the smaller the amount of a given chemical consumed, the smaller the risk. However, there are circumstances where one has to weigh one risk against another. For a food colour, for instance, one would be inclined to make the acceptable risk smaller than for an antimicrobial used to preserve food that is scarce in many parts of the world. The conditional zone is one that can be safely used under certain conditions, which are specified where appropriate. Thus, in some cases, the use of the chemical might also be permitted for a limited length of time in order to obtain information from further work. In cases where the conditions are not specified, a final decision on whether intakes that fall within the range of conditional acceptance may be considered acceptable in particular circumstances should be taken by a group of scientists, including a toxicologist, experienced in this field.

In the report of the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives\(^1\) the following recommendations are made concerning the establishment of temporary acceptable daily intakes:

The Group approves in principle the establishment of temporary ADIs for those food additives that would be useful and those that are already in use but for which data may not be fully adequate by current standards. It is recommended that such temporary ADIs be used as a basis for the establishment of temporary tolerances only if the following specific conditions are rigidly adhered to:

1. Each chemical additive must be considered on its merits.
2. The temporary ADI must be established only for a specific and definite period, namely, 3-5 years.
3. In setting a temporary ADI, the additional biochemical and toxicological data required for the eventual establishment of an ADI must be clearly stated. The additional requirements must be justified as being essential for the protection of the consumer.
4. A review of the original and new data must be carried out before the expiration of the provisional period.

The present Committee decided to use the terms unconditional ADI, conditional ADI, and temporary ADI, where appropriate, in the evaluation of flavouring substances and non-nutritive sweetening agents.

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An unconditional ADI was allocated only to those substances for which the biological data available included either the results of adequate short-term and long-term toxicological investigations or information on the biochemistry and metabolic fate of the compound or both.

A conditional ADI was allocated in either of the following two circumstances:

(a) When the Committee considered that the data fell short of the requirements for an unconditional ADI and specified further work that was required.¹

(b) For specific purposes arising from special dietary requirements.

A temporary ADI was allocated when not quite enough data were available to fully establish the safety of the substance and it was considered necessary that the additional evidence be provided within a stated period of time. If the further data requested do not become available within the stated period, it is possible that the temporary ADI will be withdrawn by a future Committee.

In some instances the Committee was unable to arrive at an acceptable daily intake, either because adequate data were lacking or because the available information was unsuitable.² This circumstance should not be interpreted as casting doubt on the safety of the substance nor should it be considered tantamount to a recommendation for its withdrawal from use.

On the basis of the information before it, the Committee recommended that the use of certain substances be discontinued. Should further evidence be made available to a future Committee, such compounds might be re-evaluated.

In conformity with previous practice, the ADIs established for those substances occurring naturally in foods do not include the contribution from this source. A list of the ADIs allocated will be found in Annex 2.

4. COMMENTS ON MONOGRAPHs

The Committee agreed that the monographs³ dealing with the evaluation of the biological data should be drafted in accordance with the principles adopted in previous reports, including the report of the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives.⁴

¹ If this work has not been carried out by the time the additive is re-evaluated at a future meeting, this may influence the allocation of an ADI.
² A note on compounds falling into this category is found on page 13.
³ See page 4.
4.1 Flavouring substances

In its evaluations of flavouring substances, the Committee took into consideration not only the toxicological and biological data but also such aspects as levels of use and occurrence in natural foodstuffs.

The Committee was able to allocate unconditional acceptances on the basis of adequate toxicological information to the following compounds:

- benzaldehyde
- ethyl acetate
- ethyl vanillin
- \((\rightarrow)\) and \((\pm)\)-menthol
- piperonal
- \(\gamma\)-undecalactone
- benzyl acetate
- ethyl butyrate
- methyl salicylate
- \(\gamma\)-nonalactone
- vanillin

For benzaldehyde and benzyl acetate, the allocated ADI is given in terms of benzoic acid, representing total benzoate from all food additive sources.

Where a flavouring substance is also a therapeutic agent, as for menthol and for methyl salicylate, the Committee followed the usual practice of applying a safety factor to the therapeutic dose in order to calculate the ADI for the use of the substance as a food additive.

For the undermentioned substances, conditional acceptances were allocated:

- trans-anethole
- \((\rightarrow)\) and \((\rightarrow)\)-carvone
- citral
- ethyl heptanoate
- ethyl laurate
- eugenol
- \(\alpha\)-ionone
- linalol
- methyl anthranilate
- octanal
- isoamyl butyrate
- cinnamaldehyde
- citronellol
- ethyl formate
- ethyl lactate
- ethyl nonanoate
- geranyl acetate
- \(\beta\)-ionone
- linalyl acetate
- nonanal

For all these substances the further work required was specified. For eugenol, although a conditional ADI was allocated, the Committee was of the opinion that the additional work required should be made available within a reasonable period.

The conditional ADIs for ethyl formate and ethyl lactate have been established at the same levels as those of formic acid and lactic acid respectively.
When considering the group of flavouring substances citral, citronellol, linalol, linalyl acetate and geranyl acetate, the Committee stressed the urgent need to elucidate the metabolic pathways that may be common to these widely distributed substances. It would seem reasonable to limit the requirement for long-term studies to one or more of these substances. Whether such a limitation can be made and which substance or substances should be chosen can be decided only in the light of the biochemical evidence when this becomes available.

Temporary ADIs were established for two flavouring substances: ethyl methylphenylglycidate and maltol. For ethyl methylphenylglycidate the Committee required that, within four years, the results should be made available of further metabolic studies, adequate long-term studies with special emphasis on neurological effects, and investigations on bone-marrow and testes. The Committee made this requirement not only because of the importance to industry of this material, but also because of the suspected radiomimetic activity and the demonstration of demyelination changes during the available long-term studies.

For maltol it was decided to request, within three years, additional biochemical studies in animals and man, since the only available information came from short-term investigations. This was done because of the importance to industry of this flavouring substance and doubts arising from its chemical structure about possible toxicity.

Because of lack of data, the Committee was unable to arrive at ADIs for the following compounds:

- butyl acetate
- diacetyl
- methyl phenyl acetate

For decanal, ethyl isovalerate, phenyl acetaldehyde

For the significance of this decision reference should be made to the remarks set out in paragraph 3.5. No separate monographs on these substances will be published for the time being. However, tentative specifications have been prepared and are available on request. The Committee recommended that these substances be reconsidered the next time that flavouring substances are on the agenda.

4.2 Non-nutritive sweetening agents

The Committee allocated an unconditional ADI to saccharin and its calcium and sodium salts. A conditional ADI was also established to cover the special needs for dietetic foods. In the case of sodium and calcium cyclamate, a temporary ADI was allocated because of the necessity for making the additional studies required, including those on cyclohexylamine, within the next three years. The Committee recommended that $p$-phenetylcarba-
mide (Dulcin) should not be used as a food additive because of its tumorigenic potentialities.

5. CRITERIA
TO BE USED IN GROUPING FURTHER FLAVOURING SUBSTANCES ACCORDING TO PRIORITY

The Committee felt that no distinction should be made between a substance occurring naturally and the same compound made by synthesis. Therefore, consideration should be given to all flavouring substances irrespective of whether they are artificial or natural. It has not proved feasible to undertake consideration of a diverse group of complex flavouring substances including such products as herbs and spices. The substances to be given priority can be grouped conveniently using the following criteria.

(a) Appearance on restrictive positive lists of flavouring substances available from various governmental sources.

(b) An estimated per capita consumption exceeding 3.65 mg per year.

(c) Use in foods at a level higher than 10 mg per kg of food. The Committee noted in this respect that these higher levels frequently occurred in confectionery and baked goods, in which the processing causes a large loss by volatilization. It would therefore be useful, for purpose of comparison, to have information on the levels of flavouring substances added to foods that are subject to heat processing as well as the levels of these substances in foods that are not subject to heat processing.

(d) Valid reasons for doubting the safety of a particular substance.

(e) In the case of esters, the fact that the acidic and alcoholic components have already been examined, either as such or as components of other esters.

6. RECOMMENDATIONS TO FAO AND WHO

1. In future meetings of the joint FAO/WHO Expert Committee on Food Additives, consideration should be given to evaluation of the toxic hazards that may result from the use of antibiotics as additives to food and feedstuffs; the administration of drugs leaving residues in meat and meat products; the presence in food of mycotoxins, toxic trace elements such as lead and mercury, and other toxicants occurring naturally in food; and the use of enzyme preparations, solvents, anti-caking, firming and release agents, processing aids, flavouring substances and packaging materials. Where appropriate, specifications for these materials should also be established.
2. Those flavouring substances allocated a temporary acceptable daily intake and those substances for which the Committee was unable to arrive at an ADI because of absence of appropriate data should be considered at a further meeting of this Committee.

3. A special Subcommittee of the Joint FAO/WHO Expert Committee on Food Additives should be set up, including among its members paediatricians, to study the special problems arising from exposure of infants and young children to food additives, as recommended in the tenth report of the Joint FAO/WHO Expert Committee on Food Additives.

7. RECOMMENDATION TO THE JOINT FAO/WHO CODEX ALIMENTARIUS COMMISSION

A number of groups both national and international are at present investigating flavouring materials from a toxicological aspect and the Committee estimated that it will be several years before these investigations are complete. It is recommended that in providing lists of substances for consideration by future meetings of the Joint FAO/WHO Expert Committee on Food Additives, the Joint FAO/WHO Codex Alimentarius Commission should take account of these national and international investigations.
Annex 1

REPORTS AND OTHER DOCUMENTS RESULTING FROM PREVIOUS MEETINGS OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES


* These documents can be obtained on request from: Food Additives, World Health Organization, Avenue Appia, 1211 Geneva, Switzerland or, Food Science and Technology Branch, Food and Agriculture Organization of the United Nations, Rome, Italy.


Annex 2

ACCEPTABLE DAILY INTAKES FOR MAN OF SOME FLAVOURING SUBSTANCES AND NON-NUTRITIVE SWEETENING AGENTS *

Specifications have been prepared for all the substances designated in the following table (see page 4).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Unconditional ADI (mg/kg body-weight)</th>
<th>Conditional ADI (mg/kg body-weight)</th>
<th>Temporary ADI (mg/kg body-weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoamyl Butyrate</td>
<td>0-5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>trans-Anethole</td>
<td>0-1-25</td>
<td>0-1-25</td>
<td></td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>0-5 a</td>
<td>0-1-25</td>
<td></td>
</tr>
<tr>
<td>Benzyl Acetate</td>
<td>0-5 a</td>
<td>0-1-25</td>
<td></td>
</tr>
<tr>
<td>(+)-Carvone and (-)-Carvone</td>
<td>0-1</td>
<td>0-1-25</td>
<td></td>
</tr>
<tr>
<td>Cinnamaldehyde</td>
<td>0-1</td>
<td>0-1-25</td>
<td></td>
</tr>
<tr>
<td>Citral</td>
<td>0-1</td>
<td>0-1-25</td>
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<tr>
<td>Citronellol, 90% and 90% total alcohols</td>
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<td>0-1-25</td>
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<td>Ethyl Butyrate</td>
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<td>Ethyl Formate</td>
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<td>Ethyl Nonanoate</td>
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<tr>
<td>Ethyl Vanillin</td>
<td>0-10</td>
<td>0-1-25</td>
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</tr>
<tr>
<td>Eugenol</td>
<td>0-5</td>
<td>0-1-25</td>
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<tr>
<td>Geranyl Acetate</td>
<td>0-5</td>
<td>0-1-25</td>
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</tr>
<tr>
<td>α-Ionone</td>
<td>0-0.1</td>
<td>0-1-25</td>
<td></td>
</tr>
<tr>
<td>β-Ionone</td>
<td>0-0.1</td>
<td>0-1-25</td>
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</tr>
<tr>
<td>Linalool, 90% and 90%</td>
<td>0-0.25</td>
<td>0-1-25</td>
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<tr>
<td>Linalyl Acetate, 90% and 96%</td>
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<tr>
<td>Maltol</td>
<td>0-0.2</td>
<td>0-1-25</td>
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<tr>
<td>(±)-Menthol and (−)-Menthol</td>
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<td>0-1-25</td>
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<tr>
<td>Methyl Anthranilate</td>
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<tr>
<td>Methyl Salicylate</td>
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<tr>
<td>γ-Nonalactone</td>
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<td>0-1-25</td>
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<tr>
<td>Nonanal</td>
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<tr>
<td>Octanal</td>
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<tr>
<td>Piperonal</td>
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<tr>
<td>γ-Unidecalactone</td>
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<tr>
<td>Vanillin</td>
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<tr>
<td>Calcium Cyclamate</td>
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<td>0-1-25</td>
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<tr>
<td>Sodium Cyclamate</td>
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<tr>
<td>α-Phenyl-β-carbamide (Dulcin)</td>
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<tr>
<td>Saccharin</td>
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<tr>
<td>Calcium Saccharin</td>
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<tr>
<td>Sodium Saccharin</td>
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</tbody>
</table>

* As total benzoic acid from all food additive sources.
\[ As total D(-)-lactic acid from all food additive sources.
\[ The Committee recommended that this substance should not be used as a food additive.
\[ For dietic foods only.

* Monographs containing biological data on, and toxicological evaluation of, these substances will be issued by FAO and WHO in a separate document entitled: Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, 1968, No. 44 A; WHO/Food Add./68, 33.