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**SPECIFICATIONS FOR THE IDENTITY AND
PURITY OF FOOD ADDITIVES AND THEIR
TOXICOLOGICAL EVALUATION :
FOOD COLOURS AND SOME
ANTIMICROBIALS AND ANTIOXIDANTS**

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

Geneva, 8-17 December 1964

WORLD HEALTH ORGANIZATION

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JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Geneva, 8-17 December 1964

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Monographs on food colours, containing specifications for identity and purity, biological data, and toxicological evaluation, will be issued later by FAO and WHO in a document entitled :

Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Food Colours.

Monographs on some antimicrobials and antioxidants, containing specifications for identity and purity, biological data, and toxicological evaluation, will be issued later by FAO and WHO in a document entitled :

Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Antimicrobials and Antioxidants.

**SPECIFICATIONS FOR THE IDENTITY AND PURITY
OF FOOD ADDITIVES
AND THEIR TOXICOLOGICAL EVALUATION :
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**Eighth 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 8-17 December 1964. The meeting was opened by Dr F. Grundy, Assistant Director General, WHO, on behalf of the Directors-General of the World Health Organization and of the Food and Agriculture Organization of the United Nations. Professor S. Dalgaard-Mikkelsen and Mr F. Morecombe were unanimously elected Chairman and Vice-Chairman respectively. Dr L. Golberg 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 seven Joint FAO/WHO Expert Committees on Food Additives have met and issued the following reports: "General Principles Governing the Use of Food Additives: First Report",² "Procedures for the Testing of Intentional Food Additives to Establish their Safety for Use: Second Report",³ "Specifications for Identity and Purity of Food Additives (Antimicrobial Preservatives and Antioxidants): Third Report",⁴ "Specifications for Identity and Purity of Food Additives (Food Colours): Fourth Report",⁵ "Evaluation of the

¹ *FAO Nutrition Meetings Report Series*, 1956, No. 11; *Wld Hlth Org. techn. Rep. Ser.*, 1956, 107.

² *FAO Nutrition Meetings Report Series*, 1957, No. 15; *Wld Hlth Org. techn. Rep. Ser.*, 1957, 129.

³ *FAO Nutrition Meetings Report Series*, 1958, No. 17; *Wld Hlth Org. techn. Rep. Ser.*, 1958, 144.

⁴ These specifications were subsequently revised and published as *Specifications for identity and purity of food additives. Vol. I Antimicrobial preservatives and antioxidants*, Rome, Food and Agriculture Organization of the United Nations, 1962.

⁵ These specifications were subsequently revised and published as *Specifications for identity and purity of food additives. Vol. II. Food Colors*, Rome, Food and Agriculture Organization of the United Nations, 1963.

Carcinogenic Hazards of Food Additives : Fifth Report ”,¹ “ Evaluation of the Toxicity of a Number of Antimicrobials and Antioxidants : Sixth Report ”,² “ Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Emulsifiers, Stabilizers, Bleaching and Maturing Agents.” Seventh Report ”.³

This meeting was convened on recommendations made in the previous reports of the Committee. Its terms of reference were :

1. To evaluate the toxicological hazards involved in the use of food colours and a number of antimicrobials and antioxidants.

2. To prepare specifications for the identity and purity of those additives considered by the present Committee as well as for those additives that were considered in the sixth report of the Joint FAO/WHO Expert Committee on Food Additives but for which no specifications had been prepared.

1. THE NEED FOR AND VALUE OF SPECIFICATIONS FOR PURITY ⁴

The Committee again emphasized the need for establishing at an international level specifications for the identity and purity of food additives. It noted that for many years national pharmacopoeias and similar compendiums have contained specifications for the more important drugs and drug components, while the *International Pharmacopoeia*, published by WHO, has provided similar data at the international level. In recent years, certain governments have begun to prepare specifications for the chemicals that enter the national food supply. There is a great need to prepare such data at an international level.

1.1 Value in protecting the consumer

Whereas a natural food may vary in composition, sometimes to a considerable degree or in undefined ways, considerations of public health dictate that, as a matter of principle, additives to food should be of known composition and purity. In fact, modern methods make it possible to

¹ *FAO Nutrition Meetings Report Series*, 1961, No. 29 ; *Wld Hlth Org. techn. Rep. Ser.*, 1961, 220.

² *FAO Nutrition Meetings Report Series*, 1962, No. 31 ; *Wld Hlth Org. techn. Rep. Ser.*, 1962, 228.

³ *FAO Nutrition Meetings Report Series*, 1964, No. 35 ; *Wld Hlth Org. techn. Rep. Ser.*, 1964, 281.

⁴ This section is reproduced, with slight modifications, from *Specifications for identity and purity of food additives. Vol. II. Food colors*, Rome, Food and Agriculture Organization of the United Nations, 1963, pp. 3-6.

produce chemicals of greater purity and uniformity by synthesis than is usually achieved by derivation from substances of natural origin. The adoption of official specifications for food additives would give assurance to the consuming public that substances meeting established standards of purity are available for use in food.

1.2 Value for regulatory purposes

At the present time most food legislation merely indicates by name the substances which may be used in a particular food. It is a well-known fact that chemicals are produced in a variety of technical and refined grades. Toxicological evaluation, which is a costly and time-consuming procedure, must be related to the particular grade or quality of chemical intended for use in food. The adoption of specifications for purity for food additives would provide a means of accurate identification of the additive for regulatory purposes and would limit the known undesirable ingredients or contaminants to acceptable tolerance levels.

1.3 Value to industry

The existence of specifications, agreed upon by qualified specialists, serves to ensure a degree of reproducibility and of conformity to criteria of quality which are acceptable to both chemical manufacturers and food processors. Furthermore, established specifications might well act as a guide in the development of new chemicals of a quality suitable for food use.

It is important that specifications for identity and quality of a food additive should be no more stringent than necessary to accomplish their purpose and that they should be reasonably attainable by the producing industries. Otherwise, the consuming public would ultimately bear an unnecessary additional cost of production and control.

1.4 Value in determining safety for use

One of the most important areas in which specifications for purity would be of particular value is in the determination of the safety for use of food additives. It is essential to know the identity and concentration of the major component or components of a food additive before carrying out an effective toxicological investigation of its properties. Even small differences in composition of a compound may materially alter the results of toxicity tests. The investigator must also know the nature and quantity of the important impurities. Toxicologists have frequently emphasized that impurities or minor constituents may have a significance far greater

than their amounts might indicate. Information relating to physical properties, such as solubility, is also essential.

In many animal tests, particularly with some of the relatively inert food additives, large amounts of the chemical are required and therefore the investigator must be certain that he has sufficient material of a uniform nature or a reliable source of the material of the same composition. In certain instances, years of animal studies have been discarded because the composition of the food additive changed during the test period. Furthermore, even if tests demonstrate beyond any reasonable doubt that a particular substance is safe for use, their value is impaired when the food additive used commercially differs significantly from the material tested.

The results of a single investigation are not likely to answer for all time the question of the safety for use of a particular material. The Joint FAO/WHO Expert Committee on Food Additives stated at its first session that permitted additives should be subjected to continuing observation for possible deleterious effects under changing conditions of use and should be reappraised whenever indicated by advances in knowledge. Specifications based on the material used in previous tests would therefore be of great value in making certain that a comparable product was employed in such reappraisals. The divergent results which are occasionally encountered in the toxicological investigation of the same product may conceivably be due to variations in the composition of batches of the material under test.

1.5 Source and nature of impurities

The purity of a food additive, as the term is here employed, refers to its freedom from substances other than those named in specifications. "Foreign substances" or "impurities" not included in the specifications may be, for example, simple inorganic salts or other substances not necessarily deleterious from the functional or safety standpoint.

Impurities may arise from the raw materials used in the manufacture of chemicals (especially when they are complex natural substances), from substances used in processing steps, from solvents used in extraction or crystallization, and from equipment. They may also be unreacted intermediates or by-products formed in the course of processing, such as incompletely esterified acids or isomeric derivatives. Products of decomposition during storage, such as may result from oxidation, hydrolysis, or polymerization, are likewise regarded as impurities. However, the constituents of polymeric or other mixtures of reproducible composition are not regarded as impurities if they contribute to the functional properties of the substance as a whole and are not deleterious.

Obviously contaminants like dirt, soot, rust, lubricants and insect fragments must be avoided in manufacture, packaging, and storage of food additives. Whereas their presence is generally revealed in the applica-

tion of the tests given in the specifications, no specific tests for the detection and identification of these contaminants are included.

From the foregoing discussion it is obvious that, depending on the original materials and manufacturing procedure, impurities may be volatile or nonvolatile, organic or inorganic, deleterious or nondeleterious. The important factors to be considered are :

(a) Is the impurity one which might jeopardize the safe use of the food additive ?

(b) Is the amount of impurity sufficient to affect the activity or usefulness of the food additive ?

(c) Can the impurity be reduced in amount or avoided by good manufacturing practice ?

(d) Is the impurity of sufficient consequence to justify a limitation ?

Whereas food additives are usually employed in relatively small quantities and traces of impurities may pose no serious health hazards, prudence dictates that reasonable limits be established for impurities, consistent with good manufacturing practice as judged by modern standards.

2. GENERAL CONSIDERATIONS ON FOOD COLOURS

2.1 General principles governing the establishment of specifications for identity and purity

2.1.1 *Natural colours*

Natural colours have been used in food over a long period of time and have been accepted for such use without supporting toxicological evidence in much the same manner as vegetables and cereal products. In considering such food colours, the Committee was faced with serious problems owing to the lack of published information relating to adequate identification and chemical composition. It was noted that natural colours may be available in different forms ; in the case of botanical products both the powdered plant and the extract of the powdered plant have been used as colouring agents for many years. Also, because of differences in soil, climatic conditions, age of plant, and time of harvest, the nature and proportions of the coloured and other components of the same species of the same plant may vary widely. Such products may contain a large percentage of substances which have not been defined. Morphological and histological examination of such botanicals has been used for a long time for the identification and quality evaluation of these materials, but in the opinion of the Committee the information obtained in this way is inadequate.

For certain products of other than plant origin—for example, natural and synthetic ultramarines, cochineal and caramel—similar problems of chemical identification have been encountered. For this reason, the Committee concluded that it was impossible to prepare adequate specifications for these products.

The Committee considers it essential that methods of analysis, including adequate identification and quality data, should be provided whenever any toxicological evaluation is undertaken on colouring matters of natural origin. It is hoped that future studies will provide such information.

2.1.2 *Synthetic organic food colours*

Identification of dyes is a difficult task, particularly in the case of the water-soluble sulfonated dyes. Most of the colours for which specifications were drawn up are of this type. Dyes in commerce may be diluted for convenience of use or other reasons. The Committee made no attempt to specify limits of purity for the large number of such mixtures marketed.

It should be noted that specifications were not recommended for certain synthetic organic food colours because there were not sufficient analytical data at hand to define good manufacturing practice. However, the Committee recommends that any synthetic organic colour used in food should meet specification requirements similar to those set forth for such colours as Amaranth, Sunset Yellow and Tartrazine. Furthermore, specifications for colours synthesized from non-sulfonated aromatic amines should limit such impurities to not more than 0.02%. It should be emphasized that in no circumstances may known carcinogenic amines be used as starting materials in the production of food colours.

The Committee agreed that the availability of substances as reference materials for the synthetic organic food colours is essential for their identification and assay.

2.1.3 *Substances studied*

The Committee had before it a provisional list of food colours for which as much information as possible had been collected. The Committee examined this list from the standpoint of chemical specifications and classified the colours into one of the following four categories :

- I. Food colours for which the Committee prepared specifications.
- II. Food colours for which the Committee was not ready to prepare specifications at this time, since toxicological studies are known to be in progress on substances of defined composition.
- III. Food colours for which the chemical information available to the Committee was not adequate to permit the preparation of a completely satisfactory specification.

IV. Food colours for which the Committee did not attempt to prepare specifications either because the toxicological data were totally lacking or because the colours were found to be harmful and their use in foods was not considered desirable.

In Annex 1 are shown the common names of the colours, the 1956 Colour Index numbers, and the categories into which the colours were placed.

2.2 General principles governing the toxicological evaluation

The second and fifth reports of the Joint FAO/WHO Expert Committee on Food Additives have laid down the fundamental principles on which the evaluation of the acceptability of food additives should be based.

Advances in scientific knowledge and experience in the application of these principles have served to emphasize their importance. Certain aspects of the toxicological data required for adequate evaluation have been further elaborated in the sixth and seventh reports of the Joint FAO/WHO Expert Committee on Food Additives.

In applying these recommendations to the evaluation of food-colouring agents, the Committee had to take into consideration the fact that the use of this class of additives in food is considered by many to be unnecessary. At a meeting of the Joint FAO/WHO Expert Committee on Food Additives in 1956 it was agreed "that there are cases in which the use of food colours is justified and that the best method for regulation is the establishment of a list of permitted colours which have been tested adequately by animal experimentation."¹ On general grounds it is now felt that there should be insistence on the fulfilment of the complete requirements deemed necessary for reliable evaluation.

The decisions of the Committee have been reached solely on the basis of toxicological and related information. Questions concerning the need for food colours or their technical suitability are the province of other bodies—on the international level, the Codex Alimentarius Committee on Food Additives.

It is useful to list here the main headings under which information was sought:²

Chemical and physical specifications (second report, page 7 ; fifth report, pp. 7-8)

Acute toxicity (second report, p. 9)

Short-term toxicity (second report, p. 10)

¹ *FAO Nutrition Meetings Report Series*, 1961, No. 29, p. 25 ; *Wld Hlth Org. techn. Rep. Ser.*, 1961, 220, 25.

² The full references to the reports mentioned in brackets will be found in the foot-notes on pp. 5 & 6.

Long-term toxicity (second report, pp. 11-12)

Carcinogenicity studies (fifth report, pp. 8-14 and 22-23)

Metabolic studies (second report, pp. 13-14 ; sixth report, p. 8).

In evaluating food colours the main emphasis must be placed on studies of metabolism and long-term toxicity. In the past, many investigations of a long-term nature were tests for carcinogenicity. Often, the number of animals employed was small and comparisons with control groups were not made. Many of the reports contained no mention of the majority of the observations considered to be an essential part of long-term toxicity studies.

The criteria for long-term studies that are especially relevant in the case of food colours are :

(a) Growth curves and associated data (second report, pp. 11-12)

(b) Studies of haemopoietic function

(c) Studies of hepatic and renal function, and, where indicated, the function of other organs

(d) Organ weights at autopsy

(e) Histopathological investigations (fifth report, pp. 15-16). The effects on reproduction and the foetus need to be studied (second report, p. 12).

It should be added that, even when such studies are carried out in adequate detail, the final reports are often not presented in a form that permits independent assessment of the validity of the conclusions reached. Statistical treatment of the results is also often lacking. It must be stressed that a reliable evaluation can be reached only if detailed information is available concerning the experimental results (fifth report, Annex 2, p. 33).

It is regrettable that a substantial proportion of the available information is to be found only in unpublished reports. In the past, this has been attributed in part to the lack of suitable media for the publication of results in this field. This situation has now been remedied by the foundation of specialist periodicals, such as "Toxicology and Applied Pharmacology" and "Food and Cosmetics Toxicology". One of these even undertakes to summarize unpublished data, to submit the summary to the authors for approval and to arrange for prompt publication. In view of these changed circumstances, it may in future be undesirable to assess acceptable daily intakes solely on the basis of unpublished work.

With regard to the number of animal species required, the Committee endorsed the recommendations for short-term toxicity studies given in the second report, namely that at least two species, one of them a non-rodent, should be used.

In the case of long-term toxicity studies, the requirements of the second report (p. 12) provide for the use of at least two species, in tests extending

over the major part of their life-span. For the evaluation of carcinogenic hazard the fifth report (p. 22) recommends "the acceptance of a life-span feeding study in two species of animal (e.g., rats and mice) carried out along the lines recommended in the second report of the Joint FAO/WHO Expert Committee on Food Additives as a minimum safeguard." Thus, if these recommendations are followed, both toxicity and carcinogenicity can be assessed in the same study.

The second and sixth reports (p. 13 and p. 8 respectively) have stated very clearly why metabolic studies are necessary for purposes of evaluation. In the past, some food additives have been considered acceptable in the absence of adequate information under this heading. For food colours, however, there must be insistence on a knowledge of metabolism, since many of these compounds, by their chemical nature, are liable to give rise to potentially toxic degradation products, either by the action of intestinal micro-organisms or by metabolic transformations within the body.

For the evaluation of the acceptability of food colours derived from natural sources, the same criteria must be applied as for synthetic colours. Here the position is rendered difficult, not only by the paucity of biological studies but also by the lack of knowledge of composition and by the variation in composition according to the source and the method of preparation employed.

This situation is particularly unhappy in the case of colours that may be extracted from edible vegetable products consumed in relatively large amounts, e.g., tomatoes, carrots, beetroot, green leafy vegetables, and fruits. Nevertheless the Committee felt that, in the absence of specifications (see section 2.1.1) and experimental data, the principles set forth in previous reports preclude the possibility of making an evaluation.

In view of the fact that no satisfactory specifications could be established for carbon black, ultramarine, iron oxides, metallic aluminium, silver and gold and that no toxicological data relevant to the use of these substances in food were available, no attempt was made at their toxicological evaluation.

In reviewing the controversial problem of the production of subcutaneous sarcomas at the sites of repeated injection of food colours, the Committee could find no adequate grounds on which to depart from the views expressed in the fifth report (pp. 16-17 and 25). Although the fifth report (p. 17) drew attention to the need for more research in this area, the question of the significance of the experimental findings remains unresolved. In Annex 1, those colours producing more than 10-15% of local sarcomas in the animals injected have been indicated by a footnote, but this has not been allowed to influence the classification arrived at on the basis of the other experimental data.

The significance of conditional zones of acceptability has been explained in the sixth report (p. 10) and in the seventh report (p. 10) of the Joint

FAO/WHO Expert Committee on Food Additives. Having regard to all the circumstances, it was felt that in the case of food colours such latitude is neither desirable nor required.

2.2.1 *Classification of colours in accordance with their toxicological evaluation*

The following categories have been laid down :

Category A. Colours found acceptable for use in food. For these colours a maximum acceptable daily intake has been stated.

Classification of colours in this category should not be interpreted as signifying that further research on them is unnecessary. More work is called for, especially in view of the possibility that new advances in science may provide more delicate and accurate means of toxicological assessment. Additional investigations are particularly needed into the effects on reproduction and the foetus.

The following colours have been placed in Category A :

	<i>C. I. No.</i>	<i>Acceptable daily intakes for man in mg per kg body-weight</i>
Amaranth	16 185	0-1.5
Sunset Yellow FCF	15 985	0-5.0
Tartrazine	19 140	0-7.5

Category B. Colours for which the available data are not entirely sufficient to meet the requirements for Category A.

Category C. I. Colours for which the available data are inadequate for evaluation but for which a substantial amount of detailed information is available concerning results of long-term tests (see the criteria on page 12).

Category C. II. Colours for which the available data are inadequate for evaluation, and for which virtually no information on long-term toxicity is available. Long-term tests for tumour formation unaccompanied by other long-term studies are considered as falling within this category.

Category C. III. Colours for which the available data are inadequate for evaluation but indicate the possibility of harmful effects.

Category D. Colours for which virtually no toxicological data are available.

Category E. Colours found to be harmful and which should not be used in food.

In Annex 1 are shown the common names of the colours, the 1956 Colour Index numbers, and the categories into which the colours were placed.

2.2.2 Conclusion

The Committee wishes to reiterate here the point made in the fifth report (pp. 19-20) that evaluation of acceptability is the function of toxicologists, oncologists and food scientists. The application of their findings is the proper function of the authorities responsible for food legislation and public health. It is the duty of these authorities to ensure that the product used conforms to the appropriate specification and that analytical methods are available for effective control.

The first report of the Joint FAO/WHO Expert Committee on Food Additives (p. 14) states that "the amount of an authorized additive used in food should be the minimum necessary to produce the desired effect." The present Committee emphasized the need to implement this limitation on levels of use, in accordance with good manufacturing practice. On page 15 of the same report attention is drawn to the need "to avoid a gradual and unrecognized increase in the amounts present in the total diet to a point at which an adequate margin of safety is no longer ensured."

The Committee therefore points out that for future toxicological work in this field it is essential to have available an adequate specification for each substance. In order to obtain a satisfactory specification it may be necessary to define the starting material from a botanical standpoint, as well as to describe the colouring matter in terms of chemical composition. This will probably involve the extraction and purification of the active principle or principles. A general toxicological evaluation can be based only on a knowledge of the biological properties of the chemically defined compound or compounds. The Committee recommends that, when the chemical data become available, a group of experts, which should include a pharmacognosist as well as chemists, should reconsider the possibility of drawing up specifications for food colours obtained from natural sources.

3. GENERAL CONSIDERATIONS ON SOME ANTIMICROBIALS AND ANTIOXIDANTS

3.1 General principles governing the establishment of specifications for identity and purity

The principles governing the establishment of specifications for food additives have been extensively dealt with in previous reports of the Joint FAO/WHO Expert Committee on Food Additives. It may, however, be useful to restate here the objectives :

(a) to identify the substance that has been subjected to biological and toxicological testing ;

(b) to ensure that the substance is of the quality required for safe use in food ;

(c) to reflect and encourage good manufacturing practice.

3.1.1 *Substances studied*

The Committee had before it a list of antimicrobials and antioxidants that had been considered by the Joint FAO/WHO Expert Committee on Food Additives that met in June 1961 but for which no specifications for identity and purity were available at that time. It was agreed that it would be advisable to delete from this list any substance that was not known to be in use as a food additive, or on which the information available to the Committee was insufficient for compilation of specifications or for toxicological evaluation. On this basis the following three substances were deleted from the list :

(a) Distearyl thiodipropionate. According to information available to the Committee, this antioxidant is not on any of the permitted lists.

(b) Gum guaiac. This additive being a natural substance does not lend itself to precise definition.

(c) Isopropyl citrate mixture. This additive is produced only by one company, which has a use patent, and the specifications have not been made available to the Committee.

The substances for which the Committee has prepared specifications are :

Diphenyl
Formic acid
Potassium nitrate
Sodium nitrate
Potassium nitrite
Sodium nitrite
Ortho-phenylphenol
Sodium-ortho-phenylphenol
Thiodipropionic acid
Dilauryl thiodipropionate.

3.1.2 *Impurities*

The nature of the impurities that might be present in a food additive has already been discussed. In the case of arsenic and lead, limits of 3 and 10 mg/kg, respectively, may be considered acceptable unless otherwise stated in the specifications. It is stressed that these limits are established to ensure good manufacturing practice and not, in most cases, because of any great toxicological concern, since food additives are commonly used in relatively

low concentrations. However, the Committee agreed that it is always desirable to keep the levels of arsenic and lead in the food as low as possible.

The question of tolerance limits for mercury, cadmium, selenium, and fluorine was considered by the Committee. As traces of these elements in food additives are likely to arise only in rare cases, the Committee agreed to fix limits only when these elements may be introduced through raw materials or conditions of manufacture.

3.2 General principles governing toxicological re-evaluation

The Joint FAO/WHO Expert Committee on Food Additives was requested by a Committee reporting to the Codex Alimentarius Commission to re-consider, in the light of new biological data, some antimicrobials and antioxidants which had previously been evaluated in the sixth report of the Joint FAO/WHO Expert Committee. These compounds are :

- Butylated hydroxytoluene (BHT)
- Propyl, octyl and dodecyl gallates
- Hexamethylenetetramine
- Nordihydroguaiaretic acid (NDGA)
- Phosphoric acid
- Sulfur dioxide, sodium sulfite, sodium metabisulfite and sodium hydrogen sulfite
- Tartaric acid

The general principles governing the re-evaluation of these additives were essentially those laid down in previous reports of the Joint FAO/WHO Expert Committee on Food Additives.¹

The meaning of the two zones of acceptability is made clear in the sixth and seventh reports. The following extract from the seventh report² is included for clarification :

“The concept of using zones of acceptability was put forward in the Committee's sixth report³ for several reasons. First, the primary intention of the Committee is to give guidance to national bodies to assist them in their choice of food additives which are suitable for their particular needs,

¹ *FAO Nutrition Meetings Report Series*, 1956, No. 11 ; *Wld Hlth Org. techn. Rep. Ser.*, 1956, 107. *FAO Nutrition Meetings Report Series*, 1957, No. 15 ; *Wld Hlth Org. techn. Rep. Ser.*, 1957, 129. *FAO Nutrition Meetings Report Series*, 1961, No. 29 ; *Wld Hlth Org. techn. Rep. Ser.*, 1961, 220. *FAO Nutrition Meetings Report Series*, 1962, No. 31 ; *Wld Hlth Org. techn. Rep. Ser.*, 1962, 228. *FAO Nutrition Meetings Report Series*, 1964, No. 35 ; *Wld Hlth Org. techn. Rep. Ser.*, 1964, 281.

² *FAO Nutrition Meetings Report Series*, 1964, No. 35, p. 10 ; *Wld Hlth Org. techn. Rep. Ser.*, 1964, 281, 10.

³ *FAO Nutrition Meetings Report Series*, 1962, No. 31 ; *Wld Hlth Org. techn. Rep. Ser.*, 1962, 228.

safe in use, and can be regarded as acceptable for purposes of international trade. Secondly, it is one of the principles underlying food additive control that the quantity of a food additive used should not be greater than is necessary to ensure the technological effect required. Thirdly, the dietary pattern differs greatly from one country to another and consequently the possible benefits and risks may also differ; the final decision on the use of any particular food additive can only be usefully taken on a national or regional rather than an international basis.

“The zone of acceptability represents the limits of intake that can be regarded as presenting no significant hazard to health on the basis of the evidence available. However, the problems that may arise from the introduction of a food additive into the diet may be complex and may sometimes require further study by experts in nutrition or other related fields. This is more likely to occur when high levels of dosage are used or if the food additive is to be used in foods mainly consumed by some special group in the community, such as children. It is for this reason that many countries tie proposed levels of a permitted substance to a specified use or uses. The Committee felt, however, that any attempt to tie zones of acceptability to specified uses would be too restrictive at an international level, and some other solution of this problem was therefore sought. To ensure that expert opinion would be consulted whenever higher dosage levels of certain food additives were used or when special circumstances might arise, the Committee decided to split the zone of acceptability into two parts in selected cases. The first part has been termed the unconditional zone of acceptability and this represents levels of use that are effective technologically, at least for some purposes, and can be safely employed without further expert advice. The second part consists of a conditional zone of acceptability and represents levels of use that can be employed safely, but at which it is thought desirable that some degree of expert supervision and advice should be readily available. The unconditional zones of acceptability are therefore intended mainly to help developing countries that may not be able to call upon appropriate experts to guide them in the handling of particular problems in the field. The conditional zones of acceptability, on the other hand, are more likely to be of interest to those countries that have a more elaborate organization for dealing with food policy and the health hazards to the consumer. It must be emphasized that the whole zone of acceptability may be safely employed, that it provides for an adequate margin of safety, and that it is based on a careful consideration of the evidence available. The added caution imposed by restricting levels of use to the unconditional zone of acceptability is only necessary in the special circumstances already described.”

From the foregoing statement it should be quite clear that the inclusion of a food additive in the conditional zone only does NOT mean that this additive is considered unsuitable for use in food.

As with the evaluation of all food additives, it has been difficult to assess the significance of certain experimental findings. As was stated in the fifth report, there is still no general agreement on the proper assessment of subcutaneous sarcomas. The relationship between the mutagenic effects of food additives on micro-organisms or on insects and possible genetic hazards from their use in human food is still under discussion and no agreed solution has been reached. A similar situation exists in the field of teratogenesis in spite of the intensive studies in progress in many countries. These considerations have raised difficulties, especially in the evaluation of hexamethylenetetramine.

The observation of a relative increase in liver weight in the absence of detectable histological change is also difficult to interpret and requires further studies on the mechanism of this effect. This problem gives special difficulties in the evaluation of the toxicity of butylated hydroxytoluene and butylated hydroxyanisole.

Work on the augmentation of toxicity under the influence of stress, such as partial starvation, has shown that toxic effects can be detected by these methods at dietary levels considerably lower than those that reveal toxicity in the unstressed animal in conventional tests. The assessment of these new methods is difficult at present because of lack of comparative data with different food additives.

Toxicological evaluations of gum guaiac and of isopropyl citrate mixture were presented in the sixth report.¹ The Committee has now re-considered these two additives but is unable to prepare specifications (see section 3.1.1, page 16). The previous evaluations, therefore, are only valid for the materials actually used by the investigators concerned.

After careful consideration of the new evidence put before it and re-consideration of the data available at the time of the sixth report, the Committee decided to change the evaluation of only one of the additives, namely tartaric acid, although several of the comments have been modified. The other evaluations of acceptable daily intakes remain the same as in the sixth report and are listed Annex 2.

4. RECOMMENDATIONS TO FAO AND WHO

In conclusion, the Committee recommends the following further action by FAO and WHO :

FAO should extend the scope of the food balance sheets to give a detailed breakdown of those food items that are prepared using food additives or are likely to contain residues of pesticides, since the acceptable daily intakes

¹ *FAO Nutrition Meetings Report Series*, 1962, No. 31, pp. 51-53 and 65-67 ; *Wld Hlth Org. techn. Rep. Ser.*, 1962, 228, 51-53 and 65-67.

established by this Committee on the basis of toxicological data can be effectively utilized only in conjunction with data on the levels of consumption of the various foods that may contain these additives.

A meeting of the Joint FAO/WHO Expert Committee on Food Additives should be convened as soon as practicable to draw up specifications and to make a toxicological evaluation of some food additives not considered in this or earlier reports, namely those belonging to the classes of antimicrobials, antioxidants, emulsifiers and related substances, and bleaching agents. At that meeting, the Committee should also re-evaluate food additives already considered and review their specifications in the light of new biological and chemical data.

WHO should consider convening a meeting to discuss the present state of scientific knowledge as a guide to future Joint FAO/WHO Expert Committees on Food Additives in establishing acceptable daily intakes. A meeting of this sort is necessary in order to ensure continuity of policy and agreement on the scientific basis on which these decisions should be taken.

It is strongly recommended that FAO and WHO explore the possibility of establishing at an international level, as soon as practicable, machinery for the preparation and distribution of substances to serve as reference materials for synthetic organic food colours.

Natural substances used as food additives should be considered at an appropriate time by a future meeting of the Joint FAO/WHO Expert Committee on Food Additives.

Annex 1

CLASSIFICATION OF COLOURS *

<i>Common name</i>	<i>C.I. No.</i>	<i>Chemical classification^a</i>	<i>Toxicological classification^b</i>
Acid Fast Violet BG	42 561	IV	D
Acid Fuchsine FB	42 685	III	C II
Acilan Brilliant Blue FFR	42 735	IV	D
Acilan Fast Green 10 G	42 170	IV	D
Acridine Orange DH	46 005	IV	D
Alizarin	58 000	IV	D
Alizarin Blue	67 410	IV	D
Alkali Blue	42 750	III	C II
Alkanet and Alkanin	75 520, 75 530	III	... ^c
Aluminium	77 000	III	... ^c
Amaranth	16 185	I	A
Annatto, Bixin and Norbixin	75 120	III	... ^c
Anthocyanins	...	III	... ^c
Auramine	41 000	IV	E
Azo Rubine	14 720	I	C II
Beet Red and Betanin	...	III	... ^c
Benzopurpurine 4 B	23 500	IV	D
Benzyl Bordeaux B	14 910	IV	D
Benzyl Violet 4 B	42 640	I	C III ^d
Bismarck Brown	21 000	IV	D
Black 7984	35 445	III	C II
Blue VRS	42 045	I	C II ^d
Bordeaux B	16 180	IV	D
Brazilwood	75 280	IV	... ^c
Brilliant Black BN Specially Pure	28 440	I	C II
Brilliant Blue FCF (Biological Stain)	42 090	I	B ^d
Brilliant Croceine	27 290	IV	D
Brilliant Green Crystals	42 040	IV	D
Brilliant Milling Green B	42 100	IV	D
Brown FK	included but not numbered	II	C II
Butter Yellow	11 020	IV	E
Canthaxanthine	...	III	C I
Capsanthine	...	IV	... ^c
Capsorubine	...	IV	... ^c
Caramel	included but not numbered	IV	D
Carbo Vegetabilis Medicinalis	...	II	... ^c
Carbon Black	77 266	II	... ^c

* For notes see end of table, page 24.

CLASSIFICATION OF COLOURS (continued)

Common name	C.I. No.	Chemical classification ^a	Toxicological classification ^b
Beta-Apo-8'-Carotenal	...	III	C I
Beta-Apo-8'-Carotenoic Acid Ethyl Ester	...	III	C I
Carotene (natural)	75 130	III	... ^c
Beta-Carotene (synthetic)	...	I	B
Carthamus	75 140	IV	... ^c
Chlorophyll	75 810	III	... ^c
Chlorophyll Copper Complex	75 810	III	... ^c
Chlorozal Sky Blue FF	24 410	IV	D
Chocolate Brown FB	included but not numbered	IV	D
Chocolate Brown HT	20 285	I	C II
Chrysoidine	11 270, 11 270 B	IV	E
Chrysoine	14 270	I	C II
Chrysoin SGX Specially Pure	14 275	III	C II
Citrus Red No. 2	12 156	I	C I
Cochineal and Carminic Acid	75 470	III	... ^c
Congo Red	22 120	III	C II
Coomassie Navy Blue GN	26 400	IV	D
Crystal Ponceau 6R	16 250	IV	D
Direct Blue 2 B	22 610	IV	D
Direct Brown BC	35 060	IV	D
Eosine	45 380	III	C II
Eosine B	45 400	IV	D
Erythrosine	45 430	I	B
Fast Green FCF	42 053	I	B ^d
Fast Red A	15 620	IV	D
Fast Red E	16 045	I	C II
Fast Yellow	13 135	IV	D
Fast Yellow AB	13 015	I	C II
Fluorescein	45 350	III	C III
Fustic	75 240, 75 660	IV	... ^c
Gold	77 480	III	... ^c
Guinea Green B	42 085	IV	E
Hansa Yellow G	11 680	IV	D
Helindon Pink BN	73 375	IV	D
Heliogen Blue G	74 100	IV	D
Helio Red RL	12 120	II	C II
Indanthrene Blue RS	69 800	I	C II
Indigotine	73 015	I	B
Induline Spirit Soluble	50 400	IV	D
Induline Water Soluble	50 405	IV	D
Iron oxides	77 492	III	... ^c
Licorice	...	IV	... ^c
Light Green SF Yellowish	42 095	I	C III ^d
Lithol Rubine BK	15 850	III	C II
Logwood	75 290	IV	... ^c
Lycopene	75 125	III	... ^c

CLASSIFICATION OF COLOURS (*continued*)

<i>Common name</i>	<i>C.I. No.</i>	<i>Chemical classification^a</i>	<i>Toxicological classification^b</i>
Madder	75 330, 75 340, 75 350, 75 370, 75 410, 75 420	IV	... ^c
Magenta	42 510	IV	E
Malachite Green	42 000	III	C III
Metanil Yellow	13 065	III	C II
Methyl Eosine	45 385	IV	D
Methyl Violet	42 535	III	C II
Methyl Violet 5 B	42 536	IV	D
Naphthol Black 3 B	27 260	IV	D
Naphthol Blue Black	20 470	III	C II
Naphthol Green B	10 020	IV	D
Naphthol Yellow S	10 316	I	C III
Nigrosine	50 420	III	C III
Oil Orange SS	12 100	IV	E
Oil Orange XO	12 140	IV	E
Oil Red O	26 125	IV	D
Oil Red 2R	12 170	IV	D
Oil Yellow AB	11 380	IV	E
Oil Yellow 3G	21 230	IV	D
Oil Yellow OB	11 390	IV	E
Oil Yellow XP	12 740	IV	D
Opal Blue	42 775	IV	D
Orange I	14 600	I	C I ^a
Orange II	15 510	I	C II
Orange G	16 230	I	C II
Orange GGN	15 980	I	C II
Orange RN	15 970	IV	D
Orchil and Orcin	included but not numbered	III	... ^c
Patent Blue A	42 052	IV	D
Patent Blue V	42 051	I	C I
Persian Berries	75 640, 75 430, 75 650, 75 670, 75 690, 75 700, 75 695	IV	... ^c
Phloxine	45 405	IV	D
Phthalocyanine Green	74 260	IV	D
Ponceau 2 R	16 150	I	C III
Ponceau 3 R	16 155	IV	E
Ponceau 4 R	16 255	I	C I
Ponceau 6 R	16 290	I	C II
Ponceau SX	14 700	IV	E
Quercetin and Quercitron	75 670	III	C I
Quinoline Yellow	47 005	I	C II
Red 6 B	18 055	IV	D
Red 10 B	17 200	I	C II
Red FB	14 780	IV	D

CLASSIFICATION OF COLOURS (*end*)

<i>Common name</i>	<i>C.I. No.</i>	<i>Chemical classification^a</i>	<i>Toxicological classification^b</i>
Red 2 G	18 050	I	C II
Resorcine Brown	20 170	III	C II
Rhodamine B	45 170	I	C III ^d
Rhodamine G	45 150	IV	D
Rhodamine 6 G	45 160	III	C II ^d
Riboflavin	...	I	... ^c
Rose Bengale	45 435	IV	D
Saffron, Crocin and Crocetin	75 100	III	... ^c
Sandal Wood	75 510, 75 540, 75 550, 75 560	IV	D
Scarlet GN Specially Pure	14 815	I	C II
Scarlet R	16 020	IV	D
Silver	77 820	III	... ^c
Spirit Eosine	45 386	IV	D
Sudan I	12 055	IV	E
Sudan Blue II	included but not numbered	IV	D
Sudan III	26 100	III	C II
Sudan IV	26 105	III	C III
Sudan G	11 920	III	C II
Sudan Red G	12 150	III	C II
Sunset Yellow FCF	15 985	I	A
Tartrazine	19 140	I	A
Thiazine Brown R	20 220	III	C II ^d
Titanium Dioxide	77 891	I	C I
Turmeric (Curcumin)	75 300	III	... ^c
Turquoise Blue BB	42 035	IV	D
Ultramarine	77 007	III	... ^c
Victoria Blue B	44 045	IV	D
Violamine R (Biological Stain)	45 190	III	C II
Violet 5 BN	42 650	III	C II
Water Blue I	42 755	III	C II
Wool Green BS	44 090	I	C I
Wool Scarlet 5 R	26 905	IV	D
Xanthophylls	...	III	... ^c
Xylene Red B	45 100	IV	D
Yellow 2 G	18 965	IV	D
Yellow 27 175 N Specially Pure	13 445	III	C II
Yellow RFS	13 011	IV	D
Yellow RY	14 330	IV	D

^a See section 2.1.3, page 10.

^b See section 2.2.1, page 14.

^c No attempt was made at a toxicological evaluation for the reasons given in section 2.2, page 13.

^d Colours producing more than 10-15% of local sarcomas at the site of repeated subcutaneous injection.

Annex 2

ACCEPTABLE DAILY INTAKE ZONES FOR MAN
OF SOME ANTIMICROBIALS AND ANTIOXIDANTS

<i>Compounds considered</i>	<i>Unconditional (mg/kg body weight)</i>	<i>Conditional</i>
Butylated hydroxytoluene	—	0-0.5
Formic acid ^a	—	0-5
Gum guaiac	See section 3.1.1, page 16	
Hexamethylenetetramine ^b	—	—
Isopropyl citrate mixture	See section 3.1.1, page 16	
Nitrates of sodium and potassium ^a	0-5	5-10
Nitrites of sodium and potassium ^a	0-0.4	0.4-0.8
Nordihydroguaiaretic acid ^c	—	—
Phosphoric acid ^a	0-5	5-15
Ortho-phenylphenol	0-0.2	0.2-1
Sodium ortho-phenylphenol	0-0.2	0.2-1
Sorbic acid ^a	0-12.5	12.5-25
Sulfur dioxide	0-0.35	0.35-1.5
Sodium sulfites (calculated as SO ₂)	0-0.35	0.35-1.5
Sodium metabisulfite (calculated as SO ₂)	0-0.35	0.35-1.5
Sodium hydrogen sulfite (calculated as SO ₂)	0-0.35	0.35-1.5
Tartaric acid ^a	0-6	6-20
Thiodipropionic acid	0-3	3-15
Dilauryl thiopropionate	0-3	3-15
Diphenyl	0-0.05	0.05-0.25
Distearyl thiodipropionate	See section 3.1.1, page 16	

^a Naturally occurring substances; the estimated acceptable intakes listed above do not include the amounts occurring naturally.

^b Not considered suitable for use in food pending the result of work now in progress.

^c Available scientific evidence inadequate for evaluation.

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