Evaluation of certain food additives

Twenty-third Report of the Joint FAO/WHO Expert Committee on Food Additives

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<table>
<thead>
<tr>
<th>CONTENTS</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Introduction .............................................................................</td>
<td>7</td>
</tr>
<tr>
<td>2. General considerations ................................................................</td>
<td>7</td>
</tr>
<tr>
<td>2.1 Modification of the agenda ..................................................</td>
<td>7</td>
</tr>
<tr>
<td>2.2 Principles governing the toxicological evaluation of compounds on the agenda</td>
<td>8</td>
</tr>
<tr>
<td>2.3 Principles governing the establishment and revision of specifications</td>
<td>8</td>
</tr>
<tr>
<td>2.4 Food additives and drugs .......................................................</td>
<td>9</td>
</tr>
<tr>
<td>2.5 Nitrates and nitrates .............................................................</td>
<td>10</td>
</tr>
<tr>
<td>2.6 Solvents used in food ...............................................................</td>
<td>10</td>
</tr>
<tr>
<td>3. Comments on specific food additives .........................................</td>
<td>12</td>
</tr>
<tr>
<td>3.1 Food colours .............................................................................</td>
<td>12</td>
</tr>
<tr>
<td>3.2 Carrier solvents ........................................................................</td>
<td>14</td>
</tr>
<tr>
<td>3.3 Extraction solvents ....................................................................</td>
<td>18</td>
</tr>
<tr>
<td>3.4 Flavouring substances ..................................................................</td>
<td>24</td>
</tr>
<tr>
<td>3.5 Inorganic salts and salts of organic acids ..................................</td>
<td>30</td>
</tr>
<tr>
<td>3.6 Miscellaneous food additives ...................................................</td>
<td>31</td>
</tr>
<tr>
<td>4. Establishment and revision of certain specifications ..................</td>
<td>32</td>
</tr>
<tr>
<td>5. Future status of the Joint FAO/WHO Expert Committee on Food Additives</td>
<td>33</td>
</tr>
<tr>
<td>6. Future work .................................................................................</td>
<td>33</td>
</tr>
<tr>
<td>7. Recommendations to FAO and WHO ...............................................</td>
<td>34</td>
</tr>
<tr>
<td>Annex 1. Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives</td>
<td>36</td>
</tr>
<tr>
<td>Annex 2. Acceptable daily intakes, and information on specifications ....</td>
<td>40</td>
</tr>
<tr>
<td>Annex 3. Further toxicological studies and information required .........</td>
<td>44</td>
</tr>
</tbody>
</table>
JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Geneva, 2-11 April 1979

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EVALUATION OF CERTAIN FOOD ADDITIVES

Twenty-third Report of the Joint FAO/WHO Expert Committee on Food Additives

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 2 to 11 April 1979. The meeting was opened by Dr B. H. Dieterich, Director, Environmental Health Division, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and of the World Health Organization. He observed that the growing concern in industrial countries about establishing safety criteria for chemicals in food was shared by the health and food regulatory authorities in developing countries; thus the work of the Committee had a substantial impact on the economies of countries that depended on the export of food.

1. INTRODUCTION

The tasks before the Expert Committee were: (1) to prepare specifications and carry out the toxicological evaluation of certain food additives; (2) to review the findings of toxicological studies of carrier and extraction solvents; (3) to undertake the toxicological re-evaluation of certain substances previously examined; and (4) to give further general consideration to the principles and procedures of toxicological evaluation and to the establishment of specifications for the identity and purity of food additives.

2. GENERAL CONSIDERATIONS

2.1 Modification of agenda

The Committee agreed to consider a report concerning the validation of the data on aspartame that had been evaluated by the Committee at the nineteenth, twentieth, and twenty-first meetings (see Annex 1, references 37, 40 and 43), but the validation of which had been requested (see Annex 1, reference 43). It further decided to include nitrates and nitrites on the agenda.
The following compounds were dropped from the agenda: dichlorofluoromethane, 1,2-dichlorotetrafluoroethane, hexylene glycol, denatured alcohols (methylated spirits), and naphtha.

2.2 Principles governing the toxicological evaluation of compounds on the agenda

The Committee concluded that if the chemical structure of a compound under consideration did not closely resemble that of any known toxic or carcinogenic compound, and if the toxicological data on it, its metabolites, and its homologues did not give any cause for concern, then less extensive toxicological data might be used for the evaluation of the compound. In such a case, however, the acceptable daily intake (ADI) would have to be more conservatively set than if ample data were available.

In the evaluation of a series of structurally related compounds, complete toxicological data should be available for at least one member of the series. Other compounds in the series could be evaluated on the basis of these data, plus data on their natural occurrence and metabolism, and on the toxicology of their homologous compounds.

2.3 Principles governing the establishment and revision of specifications

In 1966 the Committee had discussed a revised approach to the establishment of specifications (see Annex 1, reference 12). The Third Joint FAO/WHO Conference on Food Additives and Contaminants further considered this matter and stated that the three main objectives of the specifications were:

1) to identify the substance that is to be subjected to biological testing;
2) to ensure that the substance is of the quality required for safe use in food; and
3) to promote good manufacturing practice.

At its twelfth meeting, held in The Hague in October 1978, the Codex Committee on Food Additives expressed the need for the specifications to be more explicit in the use of the term “tentative”. According to the present use, the term “tentative” either implies that
the ADI is temporary or conditional, or implies that the available chemical data on the substance are inadequate. This often creates problems since the missing information is not clearly specified.

The Committee agreed that the term “tentative” should be used only in cases where data on the purity and identity of the substance are required.

The Committee contemplated the following four possibilities with regard to the preparation of specifications for the purity and identity of food additives.

(1) The title of a compound may be without the term “tentative” and without an asterisk. This would imply that both the toxicological data and the data for specifications are adequate in the opinion of the Committee.

(2) The title may be without the term “tentative” but may have an asterisk. This would mean that the data for specifications are adequate but further data on the compound's toxicity are required before the Committee can establish an ADI.

(3) The title may not have an asterisk but be qualified by the term “tentative”. This would imply that data are required either on the substance's identity and purity criteria or on the analytical methodology.

(4) The title may have both the term “tentative” and an asterisk. This would imply that further data are required both on the toxicity of the substance and on the specifications.

2.4 Food additives and drugs

The Committee emphasized the importance of the interactions that may result from the simultaneous absorption of food additives or contaminants and drugs. In this context it stressed the following points.

(1) A number of compounds used as food additives are also used in pharmaceutical preparations.

(2) Some food additives and drugs are known to trigger and inhibit the enzyme systems that bring about metabolic transformations; hence antagonism or synergism may result when such compounds are taken together.
(3) The use of some compounds, such as antibiotics, in animal feed and in human and veterinary medicine should be taken into consideration when exposure risks from such compounds are being assessed.

In view of these factors, active liaison should be promoted between experts in food and drug toxicology.

2.5 Nitrates and nitrites

At the sixth, eighth, and seventeenth meetings, the Committee discussed nitrates with respect to their acute effects such as methaemoglobinemia and the production in the body of potentially carcinogenic nitrosamines (as a result of reaction between nitrates and various amines). At the present meeting the Committee discussed in detail a recent study showing in rats the occurrence of lymphoma due to nitrates. The Committee also noted that this study was being reviewed and its histopathology re-examined. In view of this the Committee decided that it would be premature to change the previously established ADIs of 0-0.2 mg/kg of body weight and 0.6-3.0 mg/kg of body weight for nitrates and nitrites respectively.

The Committee felt that this study should be repeated, preferably in another strain of rat and in other species. Since a high incidence of chronic murine pneumonia had been observed in the rats, it was suggested that the study be repeated in pathogen-free conditions.

2.6 Solvents used in food

At its fourteenth meeting the Committee described two distinct classes of solvents (see Annex I, reference 22)—those used for extraction of substances from foodstuffs and those used as carriers of food ingredients. Although some solvents are used for both purposes, the questions concerning their safe use have to be dealt with separately.

Extraction solvents are used *inter alia* in the extraction of fats and oils (including flavouring oils and oleoresins), defatting fish and other meals, and in decaffeinating coffee and tea. They are chosen mainly for their ability to dissolve the desired food constituents selectively and for their volatility, which enables them to separate easily from the extracted material with minimum damage. The points raised by their use relate to:
— toxicity of their residues;
— toxicity of any impurities in them;
— toxicity of substances such as solvent stabilizers and impurities that may be left behind after the solvent is removed; and
— toxicity of any substances produced as a result of a reaction between the solvent and food ingredients.

Before any extraction solvent can be evaluated, information is required on:

(1) identity and amount of impurities in the solvent (including those that are formed, acquired, or concentrated owing to continuous reuse of the solvent);
(2) identity and amount of stabilizers and other additives; and
(3) toxicity of residues of solvents, additives, and impurities.

Impurities are particularly important because there are wide differences in the purities of the food grade and industrial grade of solvents. The food use of extraction solvents is frequently much less than the industrial use, and hence their food-grade requirements may receive insufficient consideration both in food use and in toxicological testing. Furthermore, the impurities or stabilizers may not have the same volatility as the solvent itself, and as a result, these may be left behind in the food after the solvent is removed. Finally, the possibility of any solvent, impurity, stabilizer, or additive reacting with food ingredients should be checked.

When biological and toxicological data raise doubts about a substance's safety, two approaches are possible: (1) to set an ADI for the substance or (2) to discourage its use altogether. When data indicate a wide margin of safety for a substance, or when there is a paucity of toxicological data on the substance but no problems concerning the impurities, residues, and any chemical reaction with food ingredients, it would be appropriate to limit the use of the substance to the minimum possible level.

When the data on a substance indicate the presence of certain impurities in the tested material, considerable problems arise in its evaluation. This is especially true if industrial-grade rather than food-grade material has been used in the toxicological study. For example, when evaluating the solvents 1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene, the Committee noted that the toxicological data indicated the presence of certain known toxic and carcinogenic substances. The interpretation of these data became
extremely difficult because the studies had used industrial-grade material. The Committee stressed that only food-grade material should be used in toxicological studies and that the impurities in the material should be fully identified.

Carrier solvents raise somewhat different issues. They are used for dissolving and dispersing nutrients, flavours, antioxidants, emulsifiers, and a wide variety of other food ingredients and additives. With the exception of carrier solvents for flavours, they tend to occur at higher levels in food than extraction solvents, mainly because frequently no attempt is made to remove them, and because some of them are relatively non-volatile. Since carrier solvents are intentional additives and are often not removed from the processed food, it is important to evaluate their own safety along with the safety of any additives or stabilizers in them.

3. COMMENTS ON SPECIFIC FOOD ADDITIVES

The Committee evaluated a number of food additives for the first time and re-evaluated some substances that had been considered at previous meetings. Comments and decisions arising from these evaluations are set out below.

3.1 Food colours

*Allura Red*¹

Allura Red when administered orally undergoes partial azo reduction prior to absorption. Metabolic studies indicate that the colour is poorly absorbed in the body, and the major route of excretion is via the faeces. In a multigeneration reproductive study on rats it was shown that the progeny of the parents who were fed 51.9 g of the colour per kg of food demonstrated a slight growth depression. The "no-effect" level on reproductive physiology of this colour in the

¹ The toxicological evaluation on Allura Red agreed upon at the twenty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives is given in this report. However, following the meeting in April 1979, WHO was advised that further analysis of toxicological data on Allura Red would be forthcoming shortly that might have an influence on the present evaluation. In the light of this information, the compound will be placed on the agenda for re-evaluation at the next meeting of the Expert Committee to be held in Rome in 1980.
rat is 13.9 g/kg of food. Teratogenicity studies in rats and rabbits failed to show any compound-related embryotoxic effects. A variety of mutagenicity studies carried out with Allura Red indicated that there were no mutagenic effects. Another study on acute and short-term oral toxicity of Allura Red in several species revealed that apart from the coloration of the urine and faeces, there were no other compound-related responses. Dermal studies (both short- and long-term) also indicated an absence of colour-induced toxic responses. In long-term feeding studies on mice and rats, the most consistent observation was that the animals that received the greatest amount of colour (51.9 g/kg of food) exhibited lower body weights compared to control animals. One study suggested that mice fed on this colour demonstrated an earlier onset of tumours of the lymphatic system compared to control mice. However, a second, more extensive mouse study has not borne this out. The long-term studies and the mutagenicity studies suggest that Allura Red does not possess carcinogenic potential. The data were sufficient to establish an acceptable daily intake for man (ADI) of 0–7 mg/kg of body weight. No toxicological monograph was prepared. The existing “tentative” specifications were revised and the Committee agreed to delete the “tentative” qualification.

Chocolate Brown HT

In 1977 the Committee had evaluated this substance and had requested a teratology study in rats (see Annex 1, reference 43). This study was now available, and it showed that daily oral doses of up to 500 mg/kg of body weight throughout pregnancy did not adversely influence the development or survival of the offspring.

The Committee was informed that reproduction and metabolic studies had been initiated, and were expected to be completed by 1980. Consequently, the temporary ADI for man of 0–0.25 mg/kg of body weight was extended until 1981.

No toxicological monograph was prepared, but the existing “tentative” specifications were revised and the Committee agreed to delete the “tentative” qualification.

Iron oxides and hydrated iron oxides

These compounds were last evaluated by the Committee in 1978 (see Annex 1, reference 48). Studies on the bioavailability of iron from these compounds suggest that ferric oxide is less available as a source of biologically active iron than are other forms of iron. A few
studies on experimental animals (dogs and cats) indicate that relatively high levels of iron oxide in the diet (up to 10 g/kg) do not result in adverse effects. It was also shown that rats consuming more than 50 mg/kg of body weight of iron oxide for 8 generations showed no effects on reproduction.

In the light of new metabolism data from three animal species, the Committee felt that the need for human absorption studies, as expressed at the twenty-second meeting of the Committee, no longer existed. An ADI of 0–0.5 mg/kg of body weight was established. No toxicological monograph was prepared, but the existing "tentative" specifications were revised and the Committee agreed to delete the "tentative" qualification.

**Red 2G**

In 1977 the Committee had established a temporary ADI for man of 0–0.006 mg/kg of body weight for this compound (see Annex I, reference 43). Further work required included a multigeneration study and studies on bone marrow to elucidate the toxic effects on erythropoiesis. None of these studies had yet been completed. Consequently, the Committee decided to extend the previously established temporary ADI. A toxicological monograph was prepared, and the existing "tentative" specifications were revised and the Committee agreed to delete the "tentative" qualification.

**Yellow 2G**

This compound was last evaluated in 1977 (see Annex I, reference 43). The studies requested by the Committee were not available at the meeting, and the Committee had not been informed whether any of those studies were in progress. Hence the Committee withdrew the previously established ADI.

3.2 Carrier solvents

**Amyl acetate**

The Committee noted that amyl acetate was a mixture of the acetic acid esters of normal amyl alcohol and isooamyl alcohol. Data from two studies on isooamyl alcohol in rats showed that it was completely metabolized when administered interperitoneally. Data on isooamyl butyrate indicated that prior to absorption it underwent hydrolysis to give butyric acid and isooamyl alcohol. Since studies on isooamyl acetate also indicated a similar in vivo hydrolysis, the Committee decided to include this compound in the group ADI for
isoamyl butyrate—0–3.7 mg/kg of body weight expressed as isoamyl alcohol. New specifications were prepared, but no toxicological monograph.

**Benzyl alcohol and benzyl benzoate**

There was ample evidence for the *in vivo* oxidation of both benzyl alcohol and benzaldehyde to benzoic acid in man and rabbit. There was also evidence for the hydrolysis of benzyl benzoate to benzyl alcohol and benzoic acid. The Committee decided to establish a group ADI of 0–5.0 mg/kg of body weight for the benzyl/benzoic moiety. This was in agreement with the ADI for benzoic acid (representing total benzoate from all food-additive sources) established by the Committee in 1973 (see Annex 1, reference 32). New specifications were prepared, but no toxicological monograph.

**1,3-Butane diol**

Several metabolic tests and feeding studies designed to study the acute and long-term toxicity of this compound in mice, rats, dogs, and cattle have demonstrated that at high dietary levels (around 200 g/kg) this compound may produce ketosis. These studies have further established that 1,3-butane diol may be used as a source of energy in food; short-term metabolic studies in man show that up to 10% of total dietary energy may be obtained from it without any adverse effects.

Although the administration of 1,3-butane diol produced hypoglycaemic effects in man and rat, there appeared no obvious adverse effects in humans ingesting up to 10% of their energy intake as 1,3-butane diol for 5 days, or in rats fed the material at a level of 100 g/kg of food for two years. In a two-year feeding study in the dog, 1,3-butane diol was added to their food at levels of up to 30 g/kg and no toxic effects were observed. Although there were considerable human data available, there were no long-term or reproduction studies available. The Committee therefore relied on the animal feeding studies and established an ADI for man of 0–4 mg/kg of body weight. A toxicological monograph and new specifications were prepared.

**Castor oil**

The Committee noted that at low doses castor oil is readily absorbed in man, but as the oral dose increases absorption decreases
and laxation occurs. However, apart from its laxative effect castor oil has been used without harm. At laxation levels castor oil is reported to inhibit the absorption of fat-soluble nutrients, notably vitamin A and D. In view of this the Committee recommended that the amount of castor oil used in food should be kept well below the level at which absorption of nutrients is inhibited. At doses of 4 g in adults absorption appears to be complete, and the Committee considered this to be the no-effect level. An ADI for man of 0–0.7 mg/kg of body weight was established. Owing to the lack of adequate long-term studies the Committee decided to leave a wide margin of safety in the establishment of this ADI. A toxicological monograph and new specifications were prepared.

**Diethylene glycol**

Diethylene glycol produces renal damage, calcium oxalate stones, and liver damage in a number of species, including man. In the rat, bladder tumours were associated with stone formation at dietary levels above 20 g/kg of food. The Committee felt that diethylene glycol was not suitable as a food additive. However, in view of the secondary nature of the bladder tumours produced and the relatively high levels of the substance required to produce kidney stones or liver damage, its presence as a contaminant in food additives at low levels may be tolerated. Nevertheless, each case should be examined on its own merits and stringent specifications consistent with good manufacturing practices should be laid out. No toxicological monograph and no specifications were prepared.

**Diethylene glycol monoethyl ether**

This compound was last evaluated in 1976 (see Annex 1, reference 40). The Committee at that time had recommended further work on this substance. In the absence of any further data, the Committee could not evaluate this compound. No toxicological monograph was prepared, but the existing “tentative” specifications were revised and the Committee agreed to delete the “tentative” qualification.

**Diethylene glycol monopropyl ether**

The evaluation of this compound was not possible with the data available. No toxicological monograph and no specifications were prepared.
Diethyl tartrate

The evaluation of this compound was not possible with the data available. No toxicological monograph and no specifications were prepared.

Dipropylene glycol

The evaluation of this compound was not possible with the data available. No toxicological monograph and no specifications were prepared.

Glyceryl monoacetate

No specific data on the toxicity of this compound were available. However, the Committee believed that glyceryl monoacetate was likely to be rapidly hydrolysed by the hydrolytic enzymes in the gastrointestinal tract as well as by the esterases in other tissues to yield acetate and glycerol which could be metabolized by the body. The Committee decided to include the ADI for this compound in the "ADI not specified" previously established for glycerol and glyceryl diacetate (see Annex 1, reference 40). No toxicological monograph and no specifications were prepared.

Isopropyl myristate

No oral toxicity studies in either animals or man were available for this compound; hence no evaluation was possible. New specifications were prepared, but no toxicological monograph.

Polyethylene glycols

The reported studies on the acute and short-term toxicity of these compounds cover a wide range of animal species. Several studies have also been carried out on their long-term toxicity, absorption in the body, and excretion.

All pure polyethylene glycols have essentially similar toxicological properties. In all cases toxicity is inversely proportional to the relative molecular mass—i.e., the lower the relative molecular mass of the compound, the higher the toxicity, and vice versa; absorption from the gastrointestinal tract decreases with increasing relative molecular mass.
An ADI of 0–10 mg/kg of body weight was established for man. A toxicological monograph and new specifications were prepared.

1.2-Propylene glycol acetates

The evaluation of these compounds was not possible since no data on their toxicity were available. No toxicological monograph and no specifications were prepared.

Triethyl citrate

The Committee believed that this compound was likely to be hydrolysed in vivo to yield citrate and ethyl alcohol. Data from two-year feeding studies indicate that rats can tolerate triethyl citrate up to 2.0 g/kg of body weight. Dogs tolerated up to 0.25 ml/kg of body weight for six months without any adverse effects. Several microbiological assay studies indicate that triethyl citrate is not mutagenic. A temporary ADI for man of 0–10 mg/kg of body weight was established by the Committee. A toxicological monograph and new specifications were prepared.

Triglycerides (synthetic)

Triglycerides are often synthesized by simple glycerolysis and transesterification using alkalis and heat. However, in some cases specific catalysts are employed for this purpose. Since no data were available on the kinds of catalysts used, the Committee decided to postpone their evaluation. No toxicological monograph and no specifications were prepared.

3.3 Extraction solvents

Benzene

In view of the many known toxic effects of benzene in man the Committee agreed that it was not suitable for use as an additive in food. No toxicological monograph or specifications were prepared.

Butane

The evaluation of this compound was not possible on the data available. No toxicological monograph or specifications were available.
1-Butanol

There was a lack of data on the effects of long-term oral exposure to 1-butanol. There were some results of studies on workers exposed for periods of up to 11 years to known vapour concentrations, but these were inadequate for setting an ADI for man. The evaluation of this compound was not possible on the basis of the data available. New specifications were prepared, but no toxicological monograph.

2-Butanol

The evaluation of this compound was not possible on the basis of the data available. New specifications were prepared, but no toxicological monograph.

Carbon dioxide

Since carbon dioxide is a natural metabolite and humans are constantly exposed to it from the atmosphere, the Committee felt that in comparison to the exposure from the atmosphere and food and drink, the exposure from its use as a solvent in the food industry was insignificant, and it was unnecessary to establish an ADI for man. No toxicological monograph or specifications were prepared.

Chloroform

A vast amount of data, relating to several routes of exposure, on the effects of exposure to chloroform in man and animals is available. In rodents chloroform is both hepatotoxic and nephrotoxic at high levels of exposure; however, it is possible to obtain a no-effect level from the data.

In a recent study, chloroform was shown to be carcinogenic in mice and in one strain of rat. However, toxicologists believe that the doses of chloroform given to animals in this study were too high, and that the neuroplastic damage reported in the study may have been due to initial toxic damage. The Committee considered this substance to be unsuitable for use as a food additive. A toxicological monograph, but no specifications were prepared.

Cyclohexane

Although there is a paucity of toxicological data relating to long-term oral exposure of animals and man to cyclohexane, the available biological data indicate that it has a low order of toxicity.
The early findings of haemopoietic injury described in the literature could be attributed to benzene contamination, and hence the Committee felt that any specification for purity should include a limit for benzene content. The Committee did not establish an ADI for man for this compound. New specifications were prepared, but no toxicological monograph.

1,1-Dichloroethane

There was a dearth of detailed metabolic data of the compound, but short-term exposure studies suggest that it has low toxicity. Long-term feeding studies in the mouse and rat have been inconclusive owing to high mortality among treated animals. The Committee felt that further information was required before the compound could be evaluated; hence, no ADI was established. No toxicological monograph and no specifications were prepared.

1,2-Dichloroethane

This compound was last evaluated in 1970 (see Annex 1, reference 22), since when a bioassay study has indicated that it is carcinogenic in rat and mouse. The Committee concluded that it was not suitable for use as a food additive. No toxicological monograph was prepared; the existing specifications were withdrawn.

Dichloromethane (methylene chloride)

There are no adequate short or long-term oral toxicity studies available on this solvent. However, the available data indicate that the metabolism and excretion patterns are the same for all routes of exposure. In both animals and man the administered dose is exhaled unchanged in the expired air; however, a small percentage of this dose is converted into carbon monoxide which is bound to haemoglobin, resulting in a high concentration of carbon monoxide-bound haemoglobin in the blood.

Although high doses cause narcosis, long-term industrial exposure does not cause any major adverse effects. The long-term inhalation data available to the Committee were in summary form, and were considered to be insufficient for the evaluation of methylene chloride. Short-term studies indicated that food extracted with this solvent was non-toxic.

20
The Committee recommended that this solvent be used according to good manufacturing practice. This would result in minimum residues and prevent any significant toxicological effects. Nevertheless, residues from each application should be examined individually.

The Committee established a temporary ADI for man of 0–0.5 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.

**Diethyl ether**

There were few data available on the oral toxicity of diethyl ether in man and animals, and these were not sufficient for its evaluation. No toxicological monograph was prepared. New specifications were drawn up, but these apply only to toxicological products that have no added stabilizing substances.

**Di-isopropyl ether**

The data available on the toxicity of this compound were very limited; hence, no evaluation was possible. No toxicological monograph and no specification were prepared.

**Ethylmethyl ketone**

This compound is a normal constituent of human urine. At high oral doses and after inhalation it stimulates the microsomal oxidative enzyme system of the liver. Its metabolism has been well studied, and the data indicate that its oral toxicity is low. The long-term toxicity of this compound had been less well studied; however, it appears that the compound has no neuropathic properties such as those shown by n-hexane and methyl n-butyrlketone.

There are no oral toxicity studies available. The Committee recommended that this potentially useful solvent be tested thoroughly. The data available were not sufficient for the evaluation of the compound. New specifications were prepared, but no toxicological monograph.

**Furfural**

The limited data available indicate that this compound can produce liver damage. Owing to the paucity of data on this compound and to the fact that many flavouring compounds are
substituted furfurals, the Committee concluded that furfural should be subjected to a full toxicological examination, including: long-term studies in two species, a short-term study in a non-rodent species, a multigeneration reproduction study and teratology and metabolic studies in several species. No ADI was established for this compound. New specifications were prepared, but no toxicological monograph.

Isopropyl acetate

The Committee believed that prior to absorption this compound would quickly hydrolyse to yield acetic acid and propan-2-ol, and the evaluation would then depend on the evaluations already made for acetic acid and isopropyl alcohol. However, since there were no data to support this belief, and since other toxicological data were inadequate, the Committee was unable to set an ADI for this compound. No toxicological monograph and no specifications were prepared.

Light petroleum (petroleum ether)

No relevant data were available; hence, no ADI was established. New specifications were prepared, but no toxicological monograph.

2-Methyl-2-propanol ("isobutanol")

The evaluation of this compound was not possible owing to the paucity of toxicological data. New specifications were prepared, but no toxicological monograph.

2-Nitropropane

There is a lack of toxicological data on the long-term oral exposure of animals and man to small quantities of 2-nitropropane. Following its inhalation, haematological changes have been reported in rabbits and cats, which can be explained by its being metabolized into nitrate. There are also reports of liver damage in rats and cats. Liver damage has also been reported to occur in workers exposed to high levels of this compound by inhalation. The Committee was unable to evaluate this compound on the basis of the data available. New "tentative" specifications were prepared, but no toxicological monograph.
Propane

Owing to the limited use and limited residues in food of this compound the Committee decided it was not necessary to establish an ADI. No toxicological monograph or specifications were prepared.

Propanol

The available studies are limited to those on acute inhalation toxicity. Only one short-term oral toxicity study on rats has been reported in which the liver was the only organ studied. This compound could not be evaluated on the data available. New specifications were prepared, but no toxicological monograph.

Tetrachloroethylene

The available data were not sufficient for the evaluation of this compound; hence, no ADI was established. No toxicological monograph and no specifications were prepared.

Toluene

No relevant data were available for this compound; hence, no evaluation was possible. New specifications were prepared, but no toxicological monograph.

1,1,1-Trichloroethane

No evaluation of this compound was possible on the basis of the data available. No toxicological monograph and no specifications were prepared.

Trichloroethylene

This compound was last evaluated in 1976 (see Annex 1, reference 41). At that time two long-term studies in rats and mice had been evaluated. The Committee now had evidence that the material used in those studies was industrial-grade rather than food-grade and contained a potent mutagenic stabilizer. The Committee reiterated the recommendation made by it at the twentieth meeting (see Annex 1, reference 40) that this compound should be re-evaluated for carcinogenicity, and added that food-grade material should be used in any such study. Since no data were forthcoming, no ADI could be established for the compound.
Industrial-grade trichloroethylene contains stabilizers for the prevention of oxidation and accumulation of hydrochloric acid and the autocatalytic degradation and catalytic effects of metals. The Committee was not aware of the existence of a grade of product containing "inhibitors" which had been approved for food use. More information was therefore required before any specifications could be recommended. No toxicological monograph or specifications were prepared.

1,1,2-Trichlorotrifluoroethane

No long-term oral toxicity or carcinogenicity studies were available, and hence it was not possible to evaluate the safety of this compound. No toxicological monograph and no specifications were prepared.

3.4 Flavouring substances

Trans-anethole

Anethole is of special toxicological interest owing to its close structural relationship to substances shown to be carcinogenic such as safrole, β-asarone, dihydrosafrole, iso-safrole, and estragole. The further work requested during the eleventh meeting of the Expert Committee (see Annex 1, reference 14) on the metabolism of trans-anethole was available. It showed that the compound was rapidly metabolized in the body. Long-term studies in mice and rats though not totally satisfactory, indicate that trans-anethole is probably not a carcinogen. The previous conditional ADI was changed into a temporary ADI for man of 0–2.5 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.

(+)-Carvone and (−)-carvone

These substances were evaluated on the basis of a one-year toxicity study in the rat, and on information concerning its metabolism. The previous conditional ADI was changed into a temporary ADI of 0–1.0 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.
Cinnamaldehyde

Cinnamaldehyde was last reviewed at the eleventh meeting of the Committee (see Annex 1, reference 14), when a conditional ADI of 0-1.25 mg/kg of body weight was established. Two new short-term feeding studies were made available to the Committee, but since they did not include histopathology they could not be employed in establishing an ADI. The previous conditional ADI was changed into a temporary ADI of 0-0.7 mg/kg body weight. A toxicological monograph was prepared and the existing specifications were revised.

Terpenoid flavours structurally related to citral

Considering the close chemical, biochemical, and toxicological relationship between citral, geraniol, citronellol, linalool, and their simple esters and acetals, the Committee decided to evaluate these compounds together.

![Chemical structures of Linalool, Citronellol, Citral, Geraniol, 2,6-Dimethyl-2,6-Octadienedioic ("Hildebrandt") Acid, and "Hildebrandt" Acid, Dihydro Form]
Data indicate that all these compounds are rapidly absorbed in the body. Citronellol, geraniol, and citral follow the same metabolic pathway. All are first oxidized to yield closely related carboxylic acids. A portion of these is decarboxylated, and the resultant carbon dioxide is expired. The remaining portion which was not immediately decarboxylated undergoes omega oxidation to yield 2,6-dimethyl-2,6-octadienedioic acid from citral and geraniol, or the dihydro form of the acid from citronellol. In addition, a portion of the acid formed from citral and geraniol further reduced to the dihydro acid. At low doses, the decarboxylation route is relatively more important; at higher doses, some of the parent compound is excreted unchanged. Excretion is rapid with little enterohepatic circulation (except at high doses) and no significant accumulation in other tissues. The metabolites have not all been identified, but most of them are polar, hexane-insoluble unsaturated compounds, like the acid and the dihydro acid just discussed.

Linalool and its esters, though structurally related, follow somewhat different routes. Linalool is a tertiary alcohol readily conjugated to the corresponding glucuronide. Linalyl acetate is readily cleaved \textit{in vitro}. As with all tertiary alcohols, oxidative metabolism is known to proceed somewhat more slowly than with the related primary alcohols. There is, therefore, more enterohepatic circulation and a much larger proportion is excreted as the glucuronide of the unchanged alcohol.

The acute toxicities of these compounds are similar and extremely low. Short-term studies have shown that geraniol, geranyl acetate, citral, linalyl isobutyrate, and linalyl cinnamate have no effects up to levels of 10 g/kg in the diet.

While evaluating citral, citronellol, geranyl acetate, linalool, and linalyl acetate, the Committee at its eleventh meeting (see Annex 1, reference 14) recommended that at least one member of this group of compounds should be studied for effects of long-term exposure. Since that time data on the metabolic fate of the members of this class have become available. Considering the clearly defined metabolism of these compounds, their rapid excretion, and their low toxicity in short-term studies, a group ADI based on a more conservative margin of safety was granted. However, none of the above should be construed as lessening the Committee’s feeling that long-term feeding studies would still be desirable. A group ADI of 0–0.5 mg/kg of body weight was established for citral, geranyl acetate, citronellol, linalool, and linalyl acetate, expressed as citral.


Estragole

Estragole was studied in the CD-1 strain of mouse by the intraperitoneal and oral routes, and an increase in the incidence of hepatocellular carcinoma was observed. No ADI could be established for this compound since a no-effect level could not be obtained from the data. The Committee felt that, in view of the importance of this compound it would be desirable if this study were repeated in another strain of mouse. A long-term feeding study in two rodent species and metabolic studies in several species would be required before an ADI could be established. No specifications, but a toxicological monograph was prepared.

Ethyl dodecanoate

Ethyl dodecanoate has been shown to hydrolyse to dodecanolic acid and ethyl alcohol. Dodecanolic acid is readily metabolized as a naturally occurring fatty acid and the toxicity of ethyl alcohol is known. The previous conditional ADI was changed into ADI of 0–1.0 mg/kg of body weight. No toxicological monograph was prepared but the existing specifications were revised.

Ethyl formate

Short-term studies, metabolic studies, and toxicological data on formic acid and formic acid esters formed the basis of the evaluation of this compound. The Committee concluded that ethyl formate could be included in the group ADI for formic acid—i.e., 0–3.0 mg/kg of body weight. A toxicological monograph was prepared, and the existing specifications were revised.

Ethyl heptanoate (See ethyl nonanoate)

Ethyl lactate

Data to show enzymatic hydrolysis of ethyl lactate to ethyl alcohol and lactic acid are not available. However, this postulated hydrolysis is well supported by data on closely related esters, including ethyl acetate and ethyl butyrate. Ethyl lactate was evaluated on the basis of a short-term study and on the assumption that it follows the same metabolic pathway as the compounds closely related to it. The Committee decided to subsume this compound under the group ADI for lactic acid. Its place under this group would
be confirmed only when data on its hydrolysis became available. A toxicological monograph was prepared and the existing specifications were revised and designated as "tentative".

**Ethyl nonanoate**

The previous conditional ADI was changed to an ADI of 0–2.5 mg/kg of body weight. The evaluation of ethyl nonanoate and ethyl heptanoate was based on a short-term toxicity study and data on their metabolic fate. A toxicological monograph was prepared, and the existing specifications were revised.

**Ethyl 3-phenylglycidate**

The evaluation of this compound was not possible on the data available. No toxicological monograph or specifications were prepared.

**Eugenol**

High doses of eugenol are hepatotoxic to dogs and rats. The data on metabolites are incomplete but suggest that there is no special cause for concern. Various mutagenicity tests have given negative results. Carcinogenicity studies are in progress. Certain short-term studies were available to the Committee and provided some basis for toxicological evaluation. A temporary ADI of 0–2.5 mg/kg of body weight was allocated to this compound. A toxicological monograph was prepared and the existing specifications were revised.

**Eugenyl methyl ether**

The lack of relevant data from short and long-term studies precluded the evaluation of this compound. No toxicological monograph or specifications were prepared.

**Geranyl acetate**

The evaluation of geranyl acetate was largely based on short-term toxicity studies and data on the toxicity and metabolism of closely related compounds, mainly linalool and citral. An ADI of 0–0.5 mg/kg of body weight was established for this compound. A toxicological monograph was prepared and the existing specifications were revised.
α-Ionone

The evaluation of α-ionone was based on the evaluation made by the Expert Committee at its eleventh meeting (see Annex I, reference 14). The previous conditional ADI was converted into a temporary ADI of 0–0.05 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.

β-Ionone

The evaluation of β-ionone was based on the evaluation made by the Expert Committee at its eleventh meeting (see Annex I, reference 14) and on some further information on its metabolism. Pending new data from a short-term study, the Committee converted its previous conditional ADI of 0–0.1 into a temporary ADI of 0–0.05 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.

Isoamyl butyrate

The Committee noted that isoamyl butyrate was a mixture of the butyric acid esters of normal amyl alcohol and isoamyl alcohol. The evaluation of this compound was based on short-term studies that established a no-effect level of 10 g/kg of food for this compound, and on data on its metabolic fate. A 90-day feeding study indicated that there were no adverse effects in rats when they were fed (by gavage) isoamyl alcohol at a level of 1 g/kg of body weight per day. The previous conditional ADI was converted into an ADI of 0–3 mg/kg of body weight expressed as isoamyl alcohol; this corresponds to the isoamyl acetate group ADI. No toxicological monograph was prepared, but the existing specifications were revised.

Methyl anthranilate

The evaluation of methyl anthranilate was based on short-term toxicity studies and on data demonstrating the conversion of methyl anthranilate to methyl alcohol and anthranilic acid.

Data from long-term studies in rats and mice with anthranilic acid show that there is no increase in tumour incidence in test animals compared with the controls. The previous conditional ADI was converted into an ADI of 0–1.5 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.
Methyl N-methylantranilate

Methyl N-methylantranilate appears to be of low toxicity in man and rats and is rapidly hydrolysed to yield N-methylantranilic and antranilic acid. In a short-term study in rats a no-effect level of 300 mg/kg of food was found. Relevant data for antranilic acid were discussed in the monograph on methylantranilate. An ADI of 0–0.2 mg/kg of body weight was established for this compound. New specifications and a toxicological monograph were prepared.

Nonanal

In the only available short-term study nonanal showed no adverse effects. The evaluation was based on the assumption that it undergoes in vivo oxidation to yield the corresponding acid. The previous conditional ADI was changed into a temporary ADI of 0–0.06 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.

Octanal

Octanal showed no adverse effects in the only available short-term study. The evaluation was based on the assumption that octanal undergoes in vivo oxidation to yield the corresponding acid.

The previous conditional ADI was changed into a temporary ADI of 0–0.06 mg/kg of body weight. A toxicological monograph was prepared and the existing specifications were revised.

β-Propylanisole

In view of the lack of data on the biochemical aspects and the unavailability of long-term feeding studies, no ADI for man could be established. No toxicological monograph and no specifications were prepared.

3.5 Inorganic salts and salts of organic acids

The Committee considered a number of salts referred to it by the Codex Committee on Food Additives of the FAO/WHO Codex Alimentarius Commission. Since all these were freely ionizable salts, the Committee decided to establish ADIs for them on the basis of their previously evaluated corresponding acids and bases. The decision on the ADIs was taken on the basis of the anions involved. The reader is referred to the references indicated in the following table for ADIs on these salts.
3.6 Miscellaneous food additives

Aspartame

The Committee did not have sufficient time to reassess the data on aspartame which had been evaluated at the nineteenth, twentieth, and twenty-first meetings.

At the last evaluation the Committee had requested a validation of the data (see Annex I, reference 43), and this was presented in a report by the Universities Associated for Research and Education in Experimental Pathology. The Committee accepted the validation.

Dimethylpolysiloxane

This compound was discussed at the eighteenth meeting of the Expert Committee (see Annex I, reference 34) and an ADI for man of 0–1.5 mg/kg of body weight was established. This ADI applies only to compounds with a relative molecular mass in the range of 200 to 300; it was not possible to extend this ADI to cover a broader range of relative molecular mass. The existing specifications were revised and designated as "tentative". No toxicological monograph was prepared.

4-Hydroxymethyl-2,6-dimethylbutylphenol

Since the only studies available were one long-term study on a limited number of animals and one multigeneration study (which the Committee considered inadequate by present-day standards), the evaluation of this compound was not possible. No toxicological monograph was prepared.
The Committee felt that before an ADI could be established the following studies would be necessary:
(1) a lifetime feeding study in two rodent species;
(2) a short-term feeding study in a non-rodent mammalian species;
(3) a multigeneration feeding study including teratogenesis; and
(4) a short-term (90-day) feeding study in which animals are fed fat and oil, containing different concentrations of the substance, heated to exhaustion.

4. ESTABLISHMENT AND REVISION OF CERTAIN SPECIFICATIONS

The Committee revised the specifications for 43 substances including colours, organic and inorganic salts, carrier and extraction solvents, flavouring substances, and miscellaneous additives (see Annex 2).

Tentative specifications were prepared for 13 substances, and the Committee developed new specifications for 22 additional substances.

Certain flavouring agents are contaminated with arsenic and heavy metals. The Committee agreed that if these agents are added to food in small quantities there was no need to set any limits on arsenic and heavy metals in them.

Although the Committee was aware of the practice of adding stabilizers to certain solvents in order to inhibit chemical changes, the specifications were prepared for substances without added stabilizers. However, in cases where a stabilizer might be added to a solvent, attention has been drawn to this possibility in the appropriate specifications.

The microbiological criteria requested by the Committee at the twenty-second meeting (see Annex 1, reference 48) for establishing microbiological specifications for food additives are still required.

Once again the Committee was requested to prepare specifications for a number of substances for which there was little information on their manufacture and use. These substances were: dichlorofluoromethane, 1,2-dichlorotetrafluoroethane, diethyl tartrate, diethylene glycol, di-isopropyl ether, dipropylene glycol, glyceryl monoacetate, hexylene glycol, isopropyl acetate, denatured alcohol (methylated spirits), naphtha, 1,3-propylisole, 1,2-propylene glycol acetate, triglycerides (synthetic), and yellow 2G.
5. FUTURE STATUS OF JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Noting recent World Health Assembly resolutions (WHA30.47 and WHA31.28) on the effects of chemicals on health, the Expert Committee emphasized the specific importance of chemicals in food, a matter on which it had acquired a considerable reputation over the past 25 years. The Committee’s reports had proved of value to the Member States of FAO and WHO and to the FAO/WHO Codex Alimentarius Commission, in presenting unbiased and independent evaluations that had contributed to the solution of many health problems and served as a guide to food and drug agencies.

The Expert Committee was much concerned lest its present functions—namely, the evaluation of the safety of food additives by independent experts at the international level—be discontinued. The complex evaluation programme, which involved nutrition, food science and food technology, was unique of its kind. It would be a retrograde step to dilute that effort by incorporating it into any programme dealing also with the effects of chemicals in air, water, consumer products, and chemicals in the workplace.

In the opinion of the Committee, the programme represented a singularly successful achievement by FAO and WHO and should remain unchanged.

6. FUTURE WORK

1. A number of food additives have been allocated temporary ADIs and should be re-evaluated when the required information becomes available; their specifications should also be revised.

2. The Committee noted that the Codex Alimentarius Commission, the principal organ of the Joint FAO/WHO Food Standards Programme, has the function of drawing up international food standards to protect the health of the consumer and facilitate

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Editorial Note: Since the twenty-third session of the Joint FAO/WHO Expert Committee on Food Additives the International Programme on Chemical Safety has been discussed at the Thirty-second World Health Assembly (WHO document WHA32/1979/RAC/3, 1979, p. 219) and at the thirteenth session of the Codex Alimentarius Commission (Rome, December 1979—draft report ALNORM 79/38, paragraphs 58-59). Readers should refer to the reports of those discussions.
international trade in food. To provide the necessary scientific basis for the work of the Codex Alimentarius Commission, the Expert Committee should continue to evaluate the food additives and contaminants that are proposed to be included in the Codex Standards.

3. The Committee should consider the food additives that are still outstanding from the priority list of the Codex Committee on Food Additives.

4. The following compounds outstanding from previous meetings of the Committee should be considered: aspartame, potassium nitrate, and polyvinylpyrrolidone.

5. Since gas-liquid chromatography is now used throughout the world as a routine technique of chemical analysis, it should be introduced into the analytical sections of the specifications that do not at present mention it.

7. RECOMMENDATIONS TO FAO AND WHO

The Committee reiterates the recommendations made at the twenty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives:

1. In view of the large number of food additives requiring evaluation or re-evaluation, meetings of the Joint FAO/WHO Expert Committee on Food Additives should continue to be held at least annually, until such time as a quicker procedure for data collection and evaluation has been developed.

2. In order to establish priorities for the toxicological testing and evaluation of intentional and unintentional food additives, the Committee recommended that FAO and WHO should convene an interdisciplinary group of experts to establish an inventory of compounds that have not yet been fully evaluated and to classify them in terms of their potential hazard to health on the basis of toxicological knowledge and extent of use. The Committee could then employ the priority list as a means of selecting the most relevant compounds for future evaluation.

3. The expeditious testing of food additives and contaminants classified as having a low priority for evaluation requires the devel-
opment of in vivo short-term and in vitro tests to verify predictions of
toxicity. The Committee recommended that these tests, the guidelines
for their use, and the evaluation of the data they yield should be
considered by a group of experts assembled by WHO.

4. The need for testing the effects of exposure to food additives
and contaminants in utero and on neonates during suckling was
reaffirmed. However, in view of the complexity of the testing
procedures, the Committee recommended that WHO should convene
a meeting of experts to assess: (a) the degree of any increase in the
sensitivity of toxicological testing afforded by exposure in utero and
through lactation; and (b) the need to include such exposure in
toxicological tests as a means of increasing public health protection.
The experts should also propose guidelines for experimentation,
covering: (a) the dosages used and the relative exposure of mother
and fetus to the agent under study; (b) the possibility of combining
this modified long-term test with reproduction studies; (c) the length
of the studies required; and (d) the most appropriate species to use.

5. The Committee recommended that the toxicological mono-
graphs issued by WHO on each compound considered by the
Committee should include not only the toxicological summaries but
the corresponding comments and evaluations as well.

6. The Committee recommended that active liaison should be
promoted by WHO between specialists in food toxicology and drug
toxicology, both in WHO and outside WHO.

7. Many food additives remain relatively poorly defined. This is
particularly true of certain natural extracts. FAO is requested to
ensure that as much information as possible is available on such
substances so that more comprehensive specifications can be
prepared.
Annex 1

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

Documents marked with an asterisk may be obtained on request from: Food Safety, World Health Organization, 1211 Geneva 27, Switzerland, or from Food Standards and Food Science Service, Food and Agriculture Organization of the United Nations, 00100 Rome, Italy.


4. Specifications for identity and purity of food additives (food colours) (Fourth report of the Expert Committee). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, vol. II. Food colours, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).


20. Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances. FAO Nutrition Meetings Report Series, No. 46 A; WHO/Food Add/70.36.


42. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Series, No. 1 B, 1977.


44. Summary of toxicological data of certain food additives. WHO Food Additives Series No. 12, 1977.


Annex 2

ACCEPTABLE DAILY INTAKES
AND INFORMATION ON SPECIFICATIONS

<table>
<thead>
<tr>
<th>Food colours</th>
<th>Specifications</th>
<th>ADI for man (mg/kg body weight)</th>
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<tbody>
<tr>
<td>Allura Red (see footnote on page 12)</td>
<td>R</td>
<td>0.7</td>
</tr>
<tr>
<td>Chocolate Brown HT</td>
<td>R</td>
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</tr>
<tr>
<td>iron oxides and hydrated iron oxides</td>
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<td>0.5</td>
</tr>
<tr>
<td>Red 2G</td>
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<td>Yellow 2G</td>
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<th>Food salts</th>
<th>Specifications</th>
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<tr>
<td>ammonium chloride</td>
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<tr>
<td>calcium T. malate</td>
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<td>Group ADI</td>
</tr>
<tr>
<td>magnesium chloride</td>
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</tr>
<tr>
<td>magnesium gluconate</td>
<td>RT</td>
<td>Group ADI</td>
</tr>
<tr>
<td>magnesium hydrogen carbonate (hydrated)</td>
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</tr>
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<td>magnesium T. lactate</td>
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<td>Group ADI</td>
</tr>
<tr>
<td>potassium chloride</td>
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<tr>
<td>potassium dihydrogen citrate</td>
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<tr>
<td>sodium T. malate</td>
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<td>Group ADI</td>
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<tr>
<td>triammonium citrate</td>
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<table>
<thead>
<tr>
<th>Carrier solvents</th>
<th>Specifications</th>
<th>ADI for man (mg/kg body weight)</th>
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<tr>
<td>amyl acetate</td>
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<td>benzyl alcohol</td>
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<td>benzyl benzoate</td>
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<td>diethylene glycol monoethyl ether</td>
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### Carrier solvents (continued)

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<tr>
<th>Substance</th>
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<tbody>
<tr>
<td>diethylene glycol monopropyl ether</td>
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<tr>
<td>diethyl tartrate</td>
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</tr>
<tr>
<td>dipropylene glycol</td>
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<td>isopropyl myristate</td>
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<td>polyethylene glycols</td>
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<td>1,2-propylene glycol acetates</td>
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<td>triethyl citrate</td>
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<td>triglycerides (synthetic)</td>
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### Extraction solvents

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<td>benzene</td>
<td>O</td>
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<tr>
<td>butane</td>
<td>O</td>
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<tr>
<td>1-butanol</td>
<td>N</td>
<td>No ADI allocated 14</td>
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<tr>
<td>2-butanol</td>
<td>N</td>
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<tr>
<td>carbon dioxide (liquid)</td>
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<td>chloroform</td>
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<td>cyclohexane</td>
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<td>1,1-dichloroethane</td>
<td>O</td>
<td>No ADI allocated 14</td>
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<td>1,2-dichloroethane</td>
<td>O</td>
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<td>dichloromethane (methylene chloride)</td>
<td>R</td>
<td>0–0.5²</td>
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<tr>
<td>diethyl ether</td>
<td>N</td>
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<tr>
<td>di-isopropyl ether</td>
<td>O</td>
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<tr>
<td>ethylmethyl ketone</td>
<td>N</td>
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<tr>
<td>furfural</td>
<td>N</td>
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<tr>
<td>isopropyl acetate</td>
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<td>light petroleum (petroleum ether)</td>
<td>N</td>
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<td>2-methyl-2-propanol (isobutanol)</td>
<td>N</td>
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<td>2-nitropopane</td>
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<td>propane</td>
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<td>propanol</td>
<td>N</td>
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<td>tetrachloroethylene</td>
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<tr>
<td>toluene</td>
<td>N</td>
<td>No ADI allocated 14</td>
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<tr>
<td>1,1,1-trichloroethane</td>
<td>O</td>
<td>No ADI allocated 14</td>
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<tr>
<td>trichloroethylene</td>
<td>O</td>
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</tr>
<tr>
<td>1,1,2-trichlorotrifluoroethane</td>
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### Flavouring substances

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<td>trans-anethole</td>
<td>R</td>
<td>0-2.5&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>(+)-carvone and (-)-carvone</td>
<td>R</td>
<td>0-1&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>cinnamaldehyde</td>
<td>R</td>
<td>0-0.7&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>citral</td>
<td>R</td>
<td>0-0.5&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>citronellol</td>
<td>RT</td>
<td>0-0.5&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>estragole</td>
<td>O</td>
<td>No ADI allocated&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>ethyl dodecanoate</td>
<td>R</td>
<td>0-1</td>
</tr>
<tr>
<td>ethyl formate</td>
<td>R</td>
<td>Group ADI&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>ethyl heptanoate</td>
<td>R</td>
<td>0-2.5</td>
</tr>
<tr>
<td>ethyl lactate</td>
<td>RT</td>
<td>Group ADI&lt;sup&gt;12,18&lt;/sup&gt;</td>
</tr>
<tr>
<td>ethyl nonanoate</td>
<td>R</td>
<td>0-2.5</td>
</tr>
<tr>
<td>ethyl 3-phenylglycidate</td>
<td>O</td>
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<tr>
<td>eugenol</td>
<td>R</td>
<td>0-2.5&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>eugenyl methyl ether</td>
<td>O</td>
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<td>furfural (see under extraction solvents)</td>
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<td>geranyl acetate</td>
<td>R</td>
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<tr>
<td>α-ionone</td>
<td>R</td>
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<tr>
<td>β-ionone</td>
<td>R</td>
<td>0-0.05&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>isoamyl butyrate</td>
<td>R</td>
<td>0-3&lt;sup&gt;19&lt;/sup&gt;</td>
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<tr>
<td>linalool</td>
<td>R</td>
<td>0-0.5&lt;sup&gt;16&lt;/sup&gt;</td>
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<tr>
<td>linalyl acetate</td>
<td>R</td>
<td>0-0.5&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>methyl anthranilate</td>
<td>R</td>
<td>0-1.5</td>
</tr>
<tr>
<td>methyl N-methylantranilate</td>
<td>N</td>
<td>0-0.2</td>
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<tr>
<td>methyl β-naphthyl ketone</td>
<td>N</td>
<td>No ADI allocated&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>nonanal</td>
<td>R</td>
<td>0-0.06&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>octanal</td>
<td>R</td>
<td>0-0.06&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>β-propylanisole</td>
<td>O</td>
<td>No ADI allocated&lt;sup&gt;14&lt;/sup&gt;</td>
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### Miscellaneous food additives

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<td>S</td>
<td>Decision postponed&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td>dimethylpolysiloxane</td>
<td>RT</td>
<td>0-1.5</td>
</tr>
<tr>
<td>4-hydroxymethyl-2,6-di-tert-butylphenol</td>
<td>NT</td>
<td>No ADI allocated&lt;sup&gt;14&lt;/sup&gt;</td>
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</tbody>
</table>

### Notes to Annex 2

<sup>1</sup> N, new specifications prepared; O, specifications not prepared; R, existing specifications revised; S, specifications exist, revision not considered; T, the existing, new, or revised specifications are tentative and comments are invited.
2 Temporary acceptance.
3 The previous temporary ADI was withdrawn.
4 Included in the ADI for hydrochloric acid and bases.
5 Included in the ADI for DL-malic acid and bases.
6 Included in the ADI for gluconic acid and bases.
7 Included in the ADI for other hydrogen carbonates.
8 Included in the ADI for DL-lactic acid and bases.
9 Included in the ADI for citric acid and bases.
10 Included in the ADI for fumaric acid and bases.
11 Included in the ADI for amyl butyrate, expressed as iso-amyl alcohol.
12 This group ADI for benzy l alcohol and benzy l benzoate should apply to the benzy l/
    benzoic moiety related to benzoic acid representing total benzoate from all food
    additive sources.
13 This substance is not suitable for use as a food additive.
14 Evaluation not possible on data available.
15 Included in the ADI for glycerol, glyc eryl diacetate, and glyc eryl triacetate.
16 A group ADI of 0-0.5 mg/kg of body weight was allocated for citral, geranyl acetate,
    citronellol and linalyl acetate.
17 Included in the ADI for formic acid.
18 Included in the ADI for lactic acid.
19 Group ADI with isoamyl acetate; expressed as isoamyl alcohol.
20 The validation of data was accepted; the Committee did not reassess the data for
    allocating an ADI, postponing the decision.
Annex 3

FURTHER TOXICOLOGICAL STUDIES
AND INFORMATION REQUIRED

Food colours

Chocolate Brown HT^2
(1) Multigeneration reproduction/teratology studies.
(2) Metabolic studies in several species, preferably including man.

Red 2G^2
(1) Multigeneration reproduction/teratology studies.
(2) Studies on the bone marrow to elucidate the toxic effects on erythropoiesis.

Carrier solvents

1,3-butane diol^3
(1) A multigeneration reproduction/teratology study.

triethyl citrate^4
(1) Additional metabolic studies in several animal species, preferably including man.

Extraction solvents

dichloromethane (methylene chloride)^4
(1) Long-term oral studies in two rodent species.

Flavouring substances

trans-anethole^4
(1) Adequate long-term feeding study.

(+) -carvone and (--) -carvone^2
(1) Further biochemical and metabolic studies in several animal species, preferably including man, using current techniques.

cinnamaldehyde^2
(1) Two 90-day studies in rodent and non-rodent species.

ethyl lactate^1
(1) Submission of data confirming enzymatic hydrolysis of ethyl lactate to ethyl alcohol and lactic acid.
eugenol\textsuperscript{3}

(1) Submission of data from the on-going carcinogenicity study.

\textit{\textalpha{}-ionone}\textsuperscript{1}

(1) An additional short-term toxicity study (90 days) on a well-characterized sample of \textit{\textalpha{}-ionone} with one dietary level, comparable to those at which minimum effects were previously observed.
(2) Metabolic studies.

\textit{\textbeta{}-ionone}\textsuperscript{1}

(1) A short-term toxicity study (90 days) on a well-characterized sample of \textit{\textbeta{}-ionone} with one dietary level, comparable to those at which minimum effects were previously observed.

\textit{nonanal}\textsuperscript{2}

(1) Adequate metabolic studies in several animal species, preferably including man.

\textit{octanal}\textsuperscript{2}

(1) Adequate metabolic studies in several animal species, preferably including

\textsuperscript{1} Information required by 1980.
\textsuperscript{2} Information required by 1981.
\textsuperscript{3} Information required by 1982.
\textsuperscript{4} Information required by 1983.
\textsuperscript{5} Information desirable.
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