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Second report on extraction solvents

(Opinion expressed on 21 June 1991)

1. Terms of reference

To advise on the safety in use of extraction solvents currently in use, or requested for use, in food.

2. Background

The provisions of Directive 88/344/EEC lay down that all solvents to which the Directive is applicable shall be re-examined by the Commission after it has consulted the Scientific Committee for Food. The Committee last reported on extraction solvents in 1981 (Report of the Scientific Committee for Food, 11th Series) at which time it requested further information on a number of the substances concerned. In the light of the possible advent of a further proposal for a Community measure on extraction solvents, the Committee has reviewed its position on all of the solvents with the exception of trichloroethylene. The Commission is required to make a proposal on trichloroethylene in 1995 and the Committee will advise on that solvent at that time.

3. General remarks

For extraction solvents, as with other additives and food contaminants, toxicology has evolved, thanks to advances in the fundamental sciences from which it has adopted methodological approaches, into a multi-disciplinary science which allows refinement of the interpretation of the results of experimental and epidemiological studies. This interpretation must be carried out in an integrated context which takes into consideration, and is in conjunction with, results obtained in different fields with diverse parameters (technological applications, conditions of exposure, toxicokinetics). Its continuing

refinement explains changes in certain of the toxicological evaluations and, in some cases, of the requirements set out in the Committee's previous report.

Nevertheless, the Committee strongly deplores the fact that, despite its previous acceptances for many of the solvents having been given on a temporary basis only, the response to the requests for further information set out in its 11th Report has been poor. As a result, in the absence of adequate information, it has not proved possible to extend the temporary acceptances of a number of the substances. Where temporary acceptances have been extended, unless otherwise stated, the Committee would wish to see the data necessary to enable full acceptance to be made available within two years.

The Committee notes that from a toxicological point of view the content of non-volatile impurities in extraction solvents may be of greater significance with respect to presence in food as consumed than small residues of the solvents themselves. In this regard, and in relation to the principle that food additives should be adequately specified, the Committee expressed concern that Community specifications of purity have not yet been drawn up for all extraction solvents. As and when specifications of purity are drawn up, they should address where relevant the presence of substances which are added to some solvents as stabilisers.

4. Summary of conclusions

	Decision
Alkanes	
propane	acceptable (1)
butane	acceptable (1)
isobutane	acceptable (1)
hexane	temporarily acceptable (1)
cyclohexane	not acceptable
Alcohols	
methanol	acceptable
ethanol	acceptable
propan-1-ol	acceptable (1)
propan-2-ol	acceptable (2)
butan-1-ol	acceptable (1)
butan-2-ol	acceptable (1)
methyl propan-1-ol	temporarily acceptable (3)
methyl propan-2-ol	not acceptable
Ketones	
acetone	acceptable (1)
ethylmethylketone	acceptable (1)
Ethers	
diethyl ether	acceptable
1,4-dioxane	not acceptable
Esters	
methyl acetate	acceptable (1)
ethyl acetate	acceptable
butyl acetate	temporary ADI 0-6 mg/kg bw (4)
Halogenated compounds	
dichloromethane	acceptable (5)
Others	
carbon dioxide	acceptable
nitrous oxide	acceptable
2-nitropropane	not acceptable

(1) Subject to residue limits (see comments on individual solvents)

(2) Acceptable as extraction solvent only; further work required for other applications

(3) Adequate dossier required to enable a full evaluation

(4) Data on residues in food or other reassurance that available daily intake will not be exceeded required

(5) For decaffeination of tea and coffee only and subject to residue limit

5. Comments on individual extraction solvents

Where reference is made to the Committee's previous evaluation this should be taken as a reference to the opinion expressed in the Reports of the Scientific Committee for Food, 11th series, 1981.

Alkanes

5.1 Propane

The Committee previously considered it unnecessary to establish an acceptable daily intake (ADI) for propane but found it temporarily acceptable pending receipt of a suitable specification of purity and information on residues in food. No new information has been received but the Committee considers the use of this gas **acceptable** in conjunction with a limit on its residues in food of not more than 1 mg/kg. If analytical data confirm that residues are normally below this level then the Committee agrees that the imposition of explicit conditions of use would be unnecessary.

5.2 Butane

In its previous evaluation the Committee had found butane temporarily acceptable pending information on residues in food and an appropriate specification of purity. The Committee now finds butane **acceptable** providing its use is subject to a residue limit in food of 1 mg/kg and an appropriate specification of purity is imposed. If analytical data confirm that residues are normally below 1 mg/kg then the Committee agrees that the imposition of explicit conditions of use would be unnecessary.

5.3 Isobutane

The Committee previously found isobutane temporarily acceptable pending receipt of data on residues in food and a satisfactory food-grade specification. No new information has been submitted but the Committee now agrees that the use of this solvent is **acceptable** providing residues are subject to a limit in food of not more than 1 mg/kg. If analytical data confirm that residues are normally below this level, explicit conditions of use would be unnecessary.

5.4 Hexane (light petroleum)

The Committee previously considered hexane under the name light petroleum at which time it was found to be temporarily acceptable pending receipt of the results of a long-term study, later reduced to a 90-day study, using a material of specified composition. The Committee also noted at that time that there was a need for a specification which limited the presence of unsaturated aliphatic hydrocarbons and polycyclic aromatic hydrocarbons. The results of a 90-day study were available to the Committee during the

course of its present review. The Committee was unable to establish whether the no observed effect level (NOEL) of 40 mg/kg bw claimed by the study authors was truly a NOEL or a minimal effect level. However, in view of the large margin between this level and the level of actual exposure reported to the Committee, the Committee has **no objection on toxicological grounds** to the continued use of this solvent on a temporary basis and subject to the existing residue limits, while a more detailed analysis of the pathology data from the study is performed.

Meanwhile the Committee recommends information is sought on actual residues occurring in food to allow an evaluation of whether the existing limits are still appropriate. In view of the differences in the toxicity of n-hexane, its isomers and other components present in technical hexane, the Committee recommends that the appropriate limits should in future be specified in terms of n-hexane and reduced accordingly.

The Committee further recommends that the specification of purity which was presented to it during the course of its review should form the basis for further discussion.

5.5 Cyclohexane

In its previous evaluation of cyclohexane, the Committee found that the available data did not permit the establishment of a formal acceptable daily intake (ADI). The solvent was considered to be temporarily acceptable pending receipt of the results of an adequate long-term study in a rodent species and information on residue levels by 1985. During its present review the Committee was informed that residues of cyclohexane in food do not exceed 1 mg/kg. However, in the continued absence of the further safety data requested, **the Committee withdrew its temporary acceptance** of cyclohexane as an extraction solvent.

Alcohols

5.6 Methanol

During its previous review the Committee was informed that residues of methanol in food resulting from its use as an extraction solvent were of the order of 5-10 mg/kg. Although there were insufficient toxicological data to establish an acceptable daily intake (ADI) for methanol the Committee considered the residues arising from its use to be minimal, constituting no safety problem, and therefore saw no need to set an ADI. The use of methanol as an extraction solvent was considered acceptable.

The Committee received no new data during its present review which would warrant any change to its previous opinion. The Committee confirmed that the use of methanol as an extraction solvent is **acceptable**.

5.7 Ethanol

The Committee confirmed its previous opinion that, in view of the large amount of toxicological information available, it is not necessary to establish an acceptable daily intake (ADI) or to set residue limits in food and that the use of ethanol as an extraction solvent is **acceptable**.

5.8 Propan-1-ol

During its previous evaluation the Committee found the data available insufficient to establish an acceptable daily intake (ADI). It concluded that propan-1-ol was temporarily acceptable subject to a residue in food of not more than 5 mg/kg and requested the results of an adequately performed 90-day study. The Committee added, however, that if the substance were to be used as a carrier solvent resulting in residues in food greatly exceeding 5 mg/kg, the results of a long-term study in a rodent species would be necessary to permit an evaluation of such a use.

The Committee regrets that no new data have been received. The Committee concludes, however, that the use of propan-1-ol as an extraction solvent **would be acceptable if the limit on its residues in food were reduced** from its present level of 5 mg/kg to a level of 1 mg/kg.

5.9 Propan-2-ol

On the basis of studies then available, the Committee previously established a temporary acceptable daily intake of 0-1.5 mg/kg for propan-2-ol and requested the results of an adequate single generation reproduction study. Pending receipt of these results, the Committee considered propan-2-ol temporarily acceptable as a food extraction solvent.

The results of a pilot one-generation study, a single generation reproduction and embryotoxicity study and a teratology study, all in the rat and carried out since the previous review, were made available to the Committee during its present review. These studies satisfied the Committee's previous concerns about possible adverse effects at low doses reported in an earlier reproduction study. The Committee noted, however, that the existing long-term studies are inadequate for a full evaluation of the carcinogenic potential of propan-2-ol and there are no data available from mutagenicity studies which would enable an assessment of its genotoxic potential. In the absence of such data the Committee is unable to establish a full acceptable daily intake (ADI). In view of the low residues which result from its use an extraction solvent, the Committee agrees that propan-2-ol may be considered **acceptable for this use** without the need to establish a full ADI. For other applications, for example as a carrier solvent, which result in significantly higher residues in food it would be necessary to establish a full ADI before these too could be considered acceptable.

5.10 Butan-1-ol and butan-2-ol

The Committee previously found butan-1-ol and butan-2-ol temporarily acceptable pending the receipt of an adequate 90-day feeding study on each in the rat and analytical data on residues in food, provided residues in food were limited to 30 mg/kg. No new data have been received but, considering that the present residue limits in the Directive are at a maximum of 1 mg/kg food for each of these substances, the Committee has **no toxicological objections to their continued use** under these conditions.

5.11 Methyl propan-1-ol

This solvent has not been evaluated by the Committee previously but is nevertheless included in the list of solvents in Directive 88/344/EEC subject to a residue limit in food of not more than 1 mg/kg. There is insufficient information on this substance to enable a complete assessment but in view of the low residue limit the Committee has **no objection to its continued use on a temporary basis** pending provision of a dossier which will enable a full evaluation.

5.12 Methyl propan-2-ol

Methyl propan-2-ol was previously evaluated by the Committee under its synonym tertiary-butanol. At that time it was considered temporarily acceptable, subject to a maximum residue in food of 10 mg/kg, and an adequate feeding study in a rodent species was requested. The toxicological data requested have not been provided and there is no information available to the Committee on the technological need for this solvent. The Committee therefore **withdrew its temporary acceptance** of the substance.

Ketones

5.13 Acetone

The Committee received no new data warranting a change in its previous evaluation. Acetone remains **acceptable** for food use providing residues are not more than 5 mg/kg in food as consumed and its content of mesityloxide is limited to a maximum of 10 mg/kg by an appropriate specification of purity.

5.14 Ethyl methyl ketone

In its previous evaluation of ethyl methyl ketone (evaluated as methyl ethyl ketone) the Committee considered the substance to be temporarily acceptable and requested the results of adequate long-term studies, reproduction studies (including embryotoxicity) and mutagenicity studies. In view of evidence that the substance appeared to enhance the neurotoxicity of other solvents such as methyl butyl ketone and n-hexane, the Committee requested that special emphasis be given to possible neurotoxicity aspects in

any further work carried out and recommended that the combined use of ethyl methyl ketone with methyl butyl ketone or n-hexane should be avoided. It further recommended that the specification of purity should limit the presence of n-hexane in ethyl methyl ketone to not more than 50 mg/kg.

The Committee was informed that Directive 88/344/EEC presently limits the use of ethyl methyl ketone as an extraction solvent to fats and oils with a residue limit of 20 mg/kg, to tea and coffee with a residue limit of 5 mg/kg, and to flavourings with a residue limit of 1 mg/kg. In the light of new data available during its present review, the Committee agrees that ethyl methyl ketone is **acceptable for these uses** subject to a continuation of the residue limits.

The Committee was also asked to consider the use of ethyl methyl ketone as an extraction solvent in the manufacture of sucrose esters of fatty acids where residues in the esters would be not more than 10 mg/kg. These esters are approved in the Community as emulsifiers and they are subject to specific purity criteria which limit the solvents that may be used in their manufacture and their residues. The Committee considers the carry-over of ethyl methyl ketone to foods from this use would be of no significance for health and agrees that this use of ethyl methyl ketone is **also acceptable** subject to a residue limit of 10 mg/kg in the esters.

Ethers

5.15 Diethyl ether

No new data warranting any change in the Committee's previous opinion were received. The Committee therefore confirmed its earlier opinion that, in view of the low residues likely to remain in food, it is unnecessary to establish an acceptable daily intake (ADI) for diethyl ether and its use as an extraction solvent is **acceptable**. It should be subject to a specification of purity which includes limits for named stabilisers.

5.16 1,4-Dioxane

1,4-Dioxane has not previously been evaluated by the Scientific Committee for Food. In the course of its present review the Committee received no substantiated information on its use as an extraction solvent in the context of food nor any detailed toxicological data. Taking the toxic potential of the substance into account, the Committee declined to evaluate its acceptability in the absence of compelling evidence of need and sufficient toxicological data to make an evaluation of safety in use a possibility. Meanwhile 1,4-dioxane is **not acceptable** for use as an extraction solvent in food.

Esters

5.17 Methyl acetate

The Committee previously found methyl acetate to be temporarily acceptable pending receipt of the results of an *in vivo* hydrolysis study and on condition that residues in food would be no higher in molar terms than those of methanol. Although no new data have been received, the Committee now agrees that the use of methyl acetate is **acceptable** under the present circumstances of its use where residues do not exceed 20 mg/kg as the ester.

5.18 Ethyl acetate

The Committee received no new data warranting any change in its previous opinion on ethyl acetate. Ethyl acetate remains **acceptable** for use as an extraction solvent in food.

5.19 Butyl acetate

The previous **temporary acceptable daily intake of 0-6 mg/kg bw was extended** and the Committee re-iterated its request for analytical data on residues in food or for other reassurance that the ADI will not be exceeded.

Halogenated compounds

5.20 Dichloromethane

In its previous evaluation the Committee found the data then available insufficient to establish an acceptable daily intake (ADI) and concluded that dichloromethane was temporarily acceptable pending receipt of the results of long-term studies in rats and mice by gavage, in drinking water and by inhalation known to be planned or underway. At that time the Committee also recommended that residues in food as consumed should not exceed 10 mg/kg, that the material should comply with a suitable food-grade specification and that the stabilisers used in the solvent should be made known.

Since then, the Committee has received extensive documentation on the additional data it requested. There is evidence of weak carcinogenic activity and of possible clastogenic activity *in vivo*. However, information made available to the Committee on residues resulting from the use of dichloromethane for decaffeination purposes indicated that residues in beverages as consumed are below the current limit of detection of 50 µg/kg. The Committee agrees that on the basis of the toxicity data currently available the use of dichloromethane as an extraction solvent is **acceptable for the limited use of the decaffeination of tea and coffee** providing that levels in the beverage as consumed are subject to a limit of not more than 50 µg/litre.

Others

5.21 Carbon dioxide

The Committee confirmed its previous opinion that carbon dioxide is **acceptable** for use as an extraction solvent and that the establishment of an acceptable daily intake (ADI) and residue limits in food are unnecessary.

5.22 Nitrous oxide

On the basis of the knowledge of the pharmacological and pharmacokinetic properties of nitrous oxide gained through its use as a human anaesthetic and the low residues likely to result in food from its use as an extraction solvent, the Committee previously considered this gas to be acceptable. The Committee recommended, however, that the specification of purity should exclude the presence of other oxides of nitrogen.

During the course of its present review the Committee received no information that warranted any change in its previous opinion and confirmed that, subject to a specification which excludes other oxides of nitrogen, nitrous oxide is **acceptable** for use as a food extraction solvent.

5.23 2-Nitropropane

During its previous review the Committee noted the results of inhalation studies in which 2-nitropropane was associated with hepatocellular carcinoma in rats, haematological damage in rabbits and cats, and liver damage in rats, cats and humans. The Committee concluded that the compound was unacceptable as an extraction solvent for food.

In the course of its present review the Committee received a request to consider the acceptability of 2-nitropropane for the extraction of certain fats and oils. The Committee was concerned about the carcinogenic potential of the substance and considered that interim results from an on-going gavage study which were made available to it did not add anything to existing knowledge. Although acknowledging that residues from the use requested were very low (less than 10 μg/kg of fat), the Committee took the view that as a general principle genotoxic carcinogens should not be used in food or in food processes, except possibly in cases where there were clear technological benefits and where worst case estimates of exposure were exceptionally low. As the existing data did not allow an estimate of the potential risk from the proposed use, albeit that the exposure would be very low, the Committee saw no reason to change its previous opinion and confirmed that 2-nitropropane is **not acceptable** as a food extraction solvent.

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Recommendation on ammonium chloride in liquorice products

(Opinion expressed on 11 October 1991)

The Committee was asked to consider whether a ban imposed by one Member State on traditional liquorice products containing more than 2% ammonium chloride could be justified on the ground of adverse effects on health.

After considering a comprehensive review of the available toxicological and clinical data from animal and human studies, the Committee concluded that:

(i) the available data indicate that potentially adverse effects may occur in humans at levels of ingestion of around 100-150 mg ammonium chloride per kg bodyweight per day;

(ii) it is not possible on the basis of the data available on the physiological /patho-physiological role of ammonium chloride to establish a no adverse effect level for the ingestion of ammonium chloride;

(iii) in absence of a no adverse effect level, it is not possible to allocate an acceptable daily intake (ADI) to ammonium chloride;

(iv) given that a level of ingestion of 100-150 mg ammonium chloride per kg bodyweight per day may give rise to potentially adverse effects in humans, the consumption of liquorice products containing added ammonium chloride at current levels which may be as high as 8% or greater must, under some circumstances, be considered to constitute a hazard to health. However at the lower levels of addition to foodstuffs in general, the presence of ammonium chloride in foods other than liquorice products is not considered to be a hazard to health.

Appropriate measures should therefore be taken to prevent consumers ingesting excessive amounts of ammonium chloride which could be harmful to health.

Recommendation on glycyrrhizin in liquorice products

(Opinion expressed on 11 October 1991)

The Committee was asked whether measures are necessary to protect consumers from adverse effects on health from the ingestion of glycyrrhizin in liquorice products.

The Committee has previously considered the use of glycyrrhizin as a sweetener in 1985. It concluded that the toxicological data were inadequate for the evaluation of the substance as a sweetener but that the findings from clinical studies indicated a possible need to restrict the consumption of liquorice. The Committee was unable to endorse the use of the substance as a sweetener.

The Committee reviewed the toxicological and clinical data now available and considered that they remain inadequate for a full evaluation. It confirmed, however, that the data now indicate a cause for concern for some sectors of the population, particularly those suffering from hypertension. Although the data available are still not sufficient to enable the establishment of a no-effect level allowing the allocation of an acceptable daily intake (ADI), the Committee considered it prudent that regular ingestion should not exceed 100 mg glycyrrhizin per day from all sources, this figure to be regarded as provisional until more extensive data become available. In this latter regard, the Committee encourages the completion of the studies planned in human subjects in the Netherlands at the time of the Committee's previous evaluation but subsequently discontinued.

In recommending that the ingestion of glycyrrhizin be restricted, the Committee suggested that the Flavourings Directive might provide a suitable vehicle for the establishment of limits in food. It recognized that sources of glycyrrhizin other than the liquorice products exist in the diet and should be taken into account. The Committee was informed that it is technologically feasible to reduce the glycyrrhizin content of some liquorice products without detracting from their organoleptic characteristics and recommended that this be explored as another means of achieving a reduction in the levels of glycyrrhizin in commercially manufactured products.

The Committee also recognized that exposure to glycyrrhizin occurs through the use of liquorice and its extracts in pharmaceutical products. It noted that in this area the need to avoid excessive intakes had been dealt with by the appropriate product labelling and instructions for use.

Guidelines for the evaluation of flavourings for use in foodstuffs:

1. Chemically defined flavouring substances

(Opinion expressed on 10 December 1991)

Foreword

The EEC "framework" Directive on Flavourings [1] applies to "flavourings used or intended for use in or on foodstuffs to impart odour and/or taste and to source materials used for the production of flavourings".

The Directive categorizes flavourings into four classes:

- flavouring substances;
- flavouring preparations;
- process flavourings;
- smoke flavourings.

The Directive establishes a list of undesirable substances which may occur in food as a result of the use of flavourings and places limits on them, and stipulates that further appropriate provisions should be adopted concerning flavourings. Although it does not give any time limit for such provisions, as a first step, the Council of Ministers of the European Community has requested [2] that inventories of flavourings and source materials be drawn up.

Inventories of flavouring substances (artificial and nature-identical substances) and of animal and plant sources (divided into food and non-food sources) were presented to the Commission in the first half of 1990 and subsequently to the Scientific Committee for Food which had a first discussion in its Working Group on flavourings on 26 April 1990 and gave the following preliminary opinion at its 73rd meeting on 18 May 1990:

> "The Committee noted that the drawing up of an inventory did not constitute a safety evaluation, it was rather a necessary preliminary step before conducting a systematic safety review. Any inventory should be as complete as possible, and should only include

chemicals or source materials that are actually used in food within the Community. The Committee was not able to offer an opinion on the inventories produced by industry, and it was clear that many of the entries listed were not at present being used as flavours or source materials. The Committee also noted the absence of inventories on flavours obtained by enzymatic processes and smoke flavours. The Committee concluded that a safety evaluation of flavours should be performed and that an inventory of flavours in use, together with information on usage, would be needed for this purpose".

In addition to the absence of inventories of flavours obtained by enzymatic processes and smoke flavours, the Committee notes the absence of inventories of process flavours and flavours produced by biotechnology.

The Committee wishes to reiterate the statements from its first [3] and second [4] Reports on flavourings, and from several subsequent meetings, that before an additive is accepted for use in food it should have been subjected to an adequate toxicological evaluation and sees no reason, on the information available to it concerning flavourings, to depart from this principle. The Committee intends to establish guidelines setting out the data it requires for the evaluation of flavourings on a category by category basis.

The present document addresses the requirements for chemically defined flavouring substances. Later documents will elaborate the Committee's requirements for other categories of flavourings.

Chemically defined flavouring substances

General considerations

In the framework Directive on flavourings (88/388/EEC) a 'flavouring substance' means a defined chemical substance with flavouring properties which is obtained:

(i) by appropriate physical processes (including distillation and solvent extraction) or enzymatic or microbiological processes from material of vegetable or animal origin either in the raw state or after processing for human consumption by traditional food-preparation processes (including drying, torrefaction and fermentation);

(ii) by chemical synthesis or isolated by chemical processes and which is chemically identical to a substance naturally present in material of vegetable or animal origin as described in (i);

(iii) by chemical synthesis but which is not chemically identical to a substance naturally present in material of vegetable or animal origin as described in (i).

In the view of the Scientific Committee for Food there is no reason to expect that occurrence in nature is any guarantee of safety and therefore there is no toxicological reason why these categories should be treated differently.

The number of chemically defined flavouring substances to be considered is so large that the systematic application of a procedure such as that used for food additives proper, as described in the 10th Report of the Scientific Committee [5], would not lead to a useful outcome within a reasonable time scale. Nevertheless, the Committee considers it necessary from the point of view of consumer protection to establish measures of acceptability of those flavouring substances presently in use in food without further delay.

In contrast to food additives only few flavouring substances will have been subjected to full toxicological testing. However, although there are very many flavourings added to foods, many have a long history of use and they are usually added in small amounts. Therefore, the Committee intends to use a more pragmatic and flexible approach in its evaluations as will be explained in the following sections.

In order to avoid unnecessary duplication of work, the Scientific Committee for Food intends to make use of evaluations already carried out by the Council of Europe (CE), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Flavour and Extract Manufacturers' Association Expert Panel (FEMA) and the United States Food and Drug Administration (FDA).

For setting priorities in the evaluation of flavouring substances, the Committee acknowledges the value of the priority ranking system as agreed between the Commission and the Council of Europe based on the decision-tree system of FEMA and the FDA Redbook method [6].

Establishment of a system of lists

In considering the substances evaluated by the CE, FDA and FEMA, the Committee has subdivided them into those which it considers acceptable and those which it considers temporarily acceptable. "Acceptable" and "temporarily acceptable" in this context refer to the use of the substances in food for the general population. Where substances are to be used in foods prepared specially for infants or young children, the Committee would need to consider them on a case by case basis taking into account their toxicological properties, their levels of use and the characteristics of the population sub-group concerned.

List of acceptable substances (List 1):

As a first step this list will contain those substances which are included in part 1, list A of the fourth edition of the CE [7] and concomitantly considered safe by the FDA [8] and/or FEMA expert panel [9]. This list will also include those substances previously considered acceptable as food additives or flavourings by the Scientific Committee for Food.

List of temporarily acceptable substances (List 2):

All other substances evaluated and found acceptable or temporarily acceptable by one or more of the abovementioned bodies [7,8,9] are considered temporarily acceptable by the Committee. In order to enable an evaluation by the Scientific Committee for Food, the Committee should within two years from the publication of these guidelines receive the summary of the data, including main references used as the basis for the evaluations by the CE, the FDA and the FEMA expert panel.

Toxicological considerations

Factors having a bearing on the safety in use of flavourings may be considered in the following categories:

1. Toxicological and other biological properties of the flavouring principle(s).
2. Toxicological and other biological properties of components other than the flavouring principles in the flavouring. These may be different if a given flavouring is derived from natural sources or prepared synthetically. Special care shall be taken to avoid toxic substances which are known to derive from a specific source or method of synthesis.
3. Quantity of flavouring consumed. This, in turn, depends on the amount occurring in food, the number of different foods in which it may be used and the frequency with which these foods are consumed.

In principle, all the information specified in the Committee's 10th Report is required and, in any event, the Committee should be provided with all relevant original reports or articles published in the recognized scientific press. Acceptable daily intakes (ADI's) can only be allocated when adequate long-term and other studies specified in the Committee's 10th Report are available. However, the Committee accepts that these requirements are presently unrealistic for most flavourings and that the allocation of an ADI will most often not be possible. Under these circumstances, the Committee may set acceptable conditions of use. With these considerations in mind and without prejudice to requirements specified in the Annexes to this document, the following should be provided:

- detailed information on typical and maximum levels of use as well as indications of the foods in which the flavouring will be used. In cases where an ADI cannot be allocated, this information may provide a basis for setting acceptable technological upper limits of use. Although such limits will be set at levels which are technologically necessary, they will not necessarily reflect the maximum levels which are toxicologically acceptable;

- information on the natural occurrence, if any, in normal food and food ingredients may give useful information in relation to judging the significance of the addition of substances as flavourings. The foods and ingredients in question should be specified and normal levels of occurrence should be given, together with relevant documentary references.

Annex 1 sets out the principles for the re-evaluation of flavouring substances in List 2 for possible inclusion in List 1.

Annex 2 sets out the specific requirements for the evaluation of flavouring substances not adequately evaluated elsewhere for possible inclusion in List 1.

Annex 1

Principles for the re-evaluation of the chemically defined flavouring substances in List 2 for possible inclusion in List 1

In contrast to other food additives, toxicological information available for chemically defined flavouring substances is rather limited. Therefore other criteria such as use levels in food and potential daily intake, structure-activity relations, metabolic fate and natural occurrence in normal food must be used in an integrated approach to safety evaluation in addition to toxicity data. Consequently, the following criteria are taken into consideration in the evaluation procedure for chemically defined flavouring substances in List 2 :

- **Use levels in food and potential daily intake:**

  Unlike many other substances added to food, flavouring substances are generally used in small amounts. Although this fact does not sufficiently guarantee their safety in use, the risk of adverse effects diminishes with decreasing intake. Therefore, a graduated approach to toxicity testing requirements depending on exposure levels appears reasonable. As a general rule, the lower the daily intake the less toxicological information is necessary for approving a flavouring substance. The question of at which threshold of intake changes in toxicological requirements are justified, depends, however, on other factors as well, e.g. chemical structure, metabolic fate, and natural occurrence in normal food.

- **Toxicity data, including data on mutagenicity, carcinogenicity, reproductive toxicity and teratogenicity of both individual and structurally related flavouring substances:**

  The toxicological requirements for flavouring substances depend on their chemical structure, metabolism and potential intake. In general, at least information on subacute (28-day study) or subchronic (90-day study) oral toxicity as well as data on mutagenicity are needed for evaluation.

- **Chemical structure:**

  Many chemically defined flavouring substances have simple organic structures and belong to classes of compounds which are easily handled by known metabolic pathways without adverse effects. This category of flavourings includes homologous series of

aliphatic alcohols, aldehydes, acids, and other compounds whose biotransformation and toxicological profile are well understood. The members of such homologous series often differ from each other to a minor degree in terms of toxicity, so that toxicological data from one substance can be used to predict the potential toxicity and metabolic fate of its homologues.

- **Metabolic fate:**

  Information on metabolic fate plays an important role in the safety evaluation of flavouring substances. In particular, biotransformation to compounds with well understood toxicological properties, to physiological substances or to components of normal food, can contribute considerably to the presumption of safety. Esters and acetals that are easily hydrolyzed by gastric, pancreatic and hepatic esterases or under acid conditions in the stomach are examples of flavourings substances which can be evaluated essentially on the basis of their parent acids, aldehydes and alcohols.

- **Natural occurrence in normal food:**

  The fact that man has ingested flavouring substances of natural origin through the years without any apparent adverse effects does not by itself constitute proof of safety. Nevertheless, human experience with flavour components of normal food has important supportive value for the safety evaluation of flavouring substances and will be taken into account unless a special health concern is indicated.

Annex 2

Requirements and presentation of data for chemically defined flavouring substances not adequately evaluated elsewhere for possible inclusion in List 1

The dossier shall contain all the information listed below. Where part of the information is considered irrelevant for the substance in question, it may be omitted if an adequate supporting argument is provided. All data, favourable as well as unfavourable, relevant to the toxicological evaluation shall be submitted with copies of all key references. For data not published in the recognized scientific and technical literature, a copy of the full study reports shall be submitted. Two copies of the complete dossier and thirty-five copies of a summary of the dossier, prepared in accordance with the guidelines set out in Presentation and Application for Assessment of a Food Additive Prior to it Authorization [10] shall be provided.

Administrative data

1. *Name, address, etc. of applicant*

2. *Name of manufacturer (if different)*

3. *Name of person responsible for the dossier*

4. *Table of contents of the dossier*

Technical data

5. *Name of the substance*

   Common and systematic name and synonyms.
   CAS, CE, FEMA and other relevant identifying numbers if allocated. Structural formula (if it is considered that the substance could be evaluated in line with other substances with similar structure, the arguments for this should be stated here).

6. Specification of substance

Shall include percentage of main component(s) together with information on impurities.

7. Manufacturing process

Shall be sufficiently described to enable the Committee to define possible undesirable by-products.

8. Methods of analysis

Shall include methods appropriate for assessing compliance with the criteria set out in the specification and for determining presence in food.

9. Technological properties supporting use as a flavouring substance

10. Stability in food

11. Exposure

11.1 Information on normal and maximum use levels intended together with information on foods where the substance may be used.

11.2 Information on total tonnage used in food in Europe.

11.3 Information on exposure from other sources e.g. natural occurrence in foods (the foods and concentration shall be identified together with the relevant references).

11.4 Estimate of likely intake (together with potential intake by high consumers) and consumption ratios. All the data used as the basis for the calculations shall be submitted.

Toxicological data

12. Toxicological data on animals and man, including data on mutagenicity, carcinogenicity and teratogenicity, where available

Normally, a 90-day study performed in a rodent species to existing EC/OECD guidelines together with two *in vitro* mutagenicity studies (one at the chromosome level and one at the gene level) will suffice if there are no indications of adverse effects. A study of 28-day duration in a rodent species may be acceptable in place of a 90-day study if otherwise performed to a 90-day study protocol. These requirements may be modified in the light of other factors (exposure, metabolic fate, structure – activity relationships...).

13. Metabolic fate

If biotransformation to toxicologically acceptable compounds can be shown, the requirement for comprehensive testing may be waived. Where, for example, the chemical structure of a compound suggests that it may be hydrolyzed into components which are toxicologically acceptable, the compound may be evaluated on the basis of its component parts provided adequate studies demonstrate complete hydrolysis.

14. Structure – activity relationships

If the toxicological data presented are less than adequate for full toxicological evaluation, comparison of the chemical structure with that of compounds with known toxicological and biological properties may be of assistance.

15. Allergenicity and hypersensitivity

Where data indicating any allergenic or hypersensitisation potential exist, they shall be submitted to the Committee.

16. Notwithstanding the circumstances listed above where reduced testing procedures may be acceptable, there may be circumstances where additional testing above the basic requirement is necessary to resolve questions that arise in any of the basic studies.

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The Scientific Committee for Food was established by Commission Decision 74/234/EEC of 16 April 1974 (OJ L 136, 20.5.1974, page 1) to advise the Commission on any problem relating to the protection of the health and safety of persons arising from the consumption of food, and in particular the composition of food, processes which are liable to modify food, the use of food additives and other processing aids as well as the presence of contaminants.

The members are independent persons, highly qualified in the fields associated with medicine, nutrition, toxicology, biology, chemistry, or other similar disciplines.

The Secretariat of the Committee is provided by the Directorate-General for Internal Market and Industrial Affairs of the Commission. Recent Council directives require the Commission to consult the Committee on provisions which may have an effect on public health falling within the scope of these directives.

The present report deals with **a second report on extraction solvents** (opinion expressed on 21 June 1991), a **recommendation on ammonium chloride in liquorice products** (opinion expressed on 11 October 1991), a **recommendation on glycyrrhizin in liquorice products** (opinion expressed on 11 October 1991) and **guidelines for the evaluation of flavourings for use in foodstuffs: 1. Chemically defined flavouring substances** (opinion expressed on 10 December 1991).

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