Commission of the European Communities

food - science and techniques

REPORTS OF THE SCIENTIFIC COMMITTEE FOR FOOD (Eleventh series)

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SUMMARY

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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON EXTRACTION SOLVENTS

(Opinion expressed 15 January 1981)

TERMS OF REFERENCE

To advise primarily on extraction solvents, but where information on the use of a particular extraction solvent as a carrier solvent is provided, to take this into consideration in the safety assessment.

BACKGROUND

The Community's programme for harmonization of laws on food additives includes extraction solvents as a subject on which the Commission is requested to make proposals. Carrier solvents have been included already in a number of food additive Directives, but the provisions in these Directives are not always alike. As some carrier solvents may also be used as extraction solvents, and in order to align more closely the texts of the various Directives, the Commission has decided to review the whole question of solvents used for whatever purpose.

TECHNOLOGICAL CONSIDERATIONS

Solvents are used in food technology for a variety of purposes. For some solvents the pattern of use is clear cut, because they are used solely as extraction solvents or solely as carrier solvents. However, a large number of solvents do not have exclusively either one or other usage but serve dual functions. Solvents used for extraction purposes only are typified by the chlorinated hydrocarbons such as dichloromethane. They find their main application in the extraction of fats and oils, for defattening fish and other meals, and for the decaffeination of coffee and tea. They are chosen principally for their ability to dissolve selectively the desired food constitutents, and their volatility, which promotes easier separation from the extracted material. Their presence in food is considered undesirable and they are removed from food, as far as is practicable, once they have fulfilled their function.

Carrier solvents have the potential to be used as extraction solvents since they are capable of dissolving food or some component of food. Their exclusive use extends to dissolving and dispersing a wide variety of food ingredients, for example nutrients, flavourings, anti-oxidants, emulsifiers, and other additives. Carrier solvents may occur at higher levels in food for two reasons; frequently no attempt is made to remove them, and some of these solvents are relatively non-volatile. Examples of carrier solvents are low-molecular aliphatic alcohols and certain esters.

The majority of solvents serve dual functions. For example, propan-2-ol is used as an extraction folvent in the preparation of fish protein concentrate and as a carrier solvent for food colours. Such dual function solvents may be used also in a consecutive fashion with the same food. A natural flavouring might be extracted into a solvent and the resulting extract, which includes the solvent, is then added to food. An example of such a process is the extraction of vanilla flavouring in propane-1,2-diol and the incorporation of the solution of the extract into food.

A number of solvents occur naturally in a wide variety of foods. Some others are foodstuffs which possess solvent properties, for example, water, fat and edible oils, wines and spirits.

SPECIFICATIONS

Criteria in a specification of purity of a solvent fall into two broad groups; those measuring properties inherent in the solvent and those specifically measuring impurities in the solvent. Solubility, relative density and distillation range are inherent physical characteristics, whereas residue on evaporation, lead, arsenic and acidity are examples of impurities. Where possible, quantitative limits should be specified.

Industrial grades and food grades of solvents often vary widely in the content of impurities. Food use is frequently a minor application, and food grade requirements may be given insufficient attention before use of a solvent in food processing and in selecting material for toxicological testing. Impurities and additives may not have the same volatility as the solvent, and may be retained in the extracted food after removal of the solvent. The possibility of reaction with food components needs consideration and evidence covering this possibility is needed where there is either data or other reasons to suspect such reaction.

For meaningful evaluation of the safety of the use of solvents in food information is required on (a) identity and content of the impurities, including those formed, acquired or concentrated on re-use, (b) the identity and content of stabilisers or other additives, and (c) residues of the solvent or of additives and impurities left in food as a result of its use.

Food grade specifications are available for most solvents considered in this report. Details are referenced in the data sheets which summarize the toxicological studies, oral as well as inhalational, requested by the Committee. Data sheets have not been published but have been made available to Government Departments and the EEC Advisory Committee for Foodstuffs. The references on which the data sheets were prepared for each individual substance are annexed to this report.

STABILISERS IN SOLVENTS

Several of the solvents, particularly the chlorinated hydrocarbons, contain stabilisers. The function of a stabiliser is essentially to ensure that the solvent does not undergo chemical change during storage and shipment, so that it reaches the user while still complying with the manufacturer's specification. Stabilisers are also added to prevent the formation of dangerous substances. For example, stabilisers prevent in chloroform oxidation to phosgene, and in diethylether the production of unstable and explosive peroxides. All stabilisers are believed to exert an antioxidant effect. However those in chlorinated hydrocarbon solvents also function as acid acceptors to prevent corrosion of equipment and storage vessels by any acids formed on storage.

If the difference between the boiling points of the stabiliser and solvent is large, with the stabiliser having the higher boiling point (e.g. thymol b.p. 280°C in trichlorethylene b.p. 87°C) then the stabiliser will concentrate in the food during evaporation of the solvent. In processes using recycling of solvents concentration of non-volatile impurities from solvent in the extract will only be of concern when a completely fresh batch of solvent is used.

Stabilisers used in solvents can be considered from the toxicological point of view to fall into two broad groups, substances currently permitted for food use as additives and those not previously considered. The first group includes citric acid, ethanol, methanol and butylated hydroxytoluene. There is no need to object to the use of these substances on the grounds of safety.

The second group of stabilisers includes thymol, triethylamine, pyrogallol and 2-methylbut-2-ene (amylene) but others might possibly be used by manufacturers in different countries. The use of these materials is likely to result in small residues in food but the implications of their presence require toxicological evaluation. Hence toxicological testing should be carried out on solvents containing these stabilisers. In general it is recommended that stabilisers from the first group of substances should be used as far as is possible in solvents for food use. The Committee recommends that a list of acceptable stabilisers be established and revised periodically.

TOXICOLOGICAL CONSIDERATIONS

The toxicological issues raised by the use of solvents in food are threefold:

1. the toxicity of the solvent residues themselves;

2. the toxicity of impurities, additives and stabilisers, which may be left behind preferentially after removal of the solvent;

3. the potential for interaction of the solvent with food constituents.

As proposed by the Commission data from occupational or inhalational observations have been taken into consideration, where appropriate, by the Committee in arriving at its assessments. Where biological or toxicological data provide a more than ample margin of safety, or where considerations of the points listed above raise no concern, limitation of residues to the minimum levels attainable with appropriate technology appears to be an adequate safeguard for the health of the consumer. Where the toxicological data dictate limitations for reasons of safety, it is appropriate to establish an acceptable daily intake (ADI) or

discourage the use of the material. In those cases where the available information was adequate to support the conclusion of the continued use in food on a temporary basis, no hazard to health was considered to arise from this use, but during this time additional studies have been requested to permit a more precise re-evaluation to be made in the light of the forthcoming information. The Committee's assessments "acceptable", "temporarily acceptable" or "not acceptable" are to be regarded as toxicological evaluations and do not take into consideration other factors which might affect the ultimate legislative decision.

For the safety evaluation of some of the solvents e.g. propane, butane, isobutane, carbon dioxide and nitrous oxide the Committee did not require the provision of the whole spectrum of studies normally demanded for the safety assessment of food additives, set out in the Committee's guidelines of February 1980*

The Committee was aware of reports on the chemical reaction of solvents with nutrient components, on the possible loss of nutrients due to solvent extraction and on the reactions of solvents with food components giving rise to toxic compounds. Where such information was available, it was taken into consideration in the evaluation of the acceptability of the solvent.

The Committee has been asked to evaluate the safety of a number of fluorinated hydrocarbons. In the assessment of these compounds the Committee has not considered the environmental implications of the use of these solvents in food technology, but recognises that environmental considerations should take precedence over its own evaluations on this occasion.

A large number of solvents considered are esters of acids and alcohols which are common constituents of the body or known non-toxic metabolites. An important point in evaluating their safety was the availability of evidence of rapid and complete hydrolysis under in-vitro and in-vivo conditions simulating human digestion. In these cases the Committee evaluated the safety of these solvents without necessarily requiring the provision of all studies normally demanded for the evaluation of the safety of food additive (see guidelines).

The Committee draws attention to the use of foods possessing solvent properties as extraction solvents e.g. vegetable oils and fats. Since this particular application involves the continuous use of food as part of a recycling procedure, it is necessary to ensure that these foods do not as a result of processing technology accumulate impurities giving rise to adverse toxicological considerations. Any proposals for a Directive should take into account the need for controls to ensure that this usage does not result in consumption of unsafe foods e.g. due to the presence of peroxides and polymers in recycled fats.

For solvents whose use was considered temporarily acceptable by the Committee the stated residue limits are not based entirely on the toxicological data but on actual analytical data. The Committee considers it advisable to retain these residue limits in view of the temporary nature of the acceptance.

The Committee has been requested to evaluate the safety of a number of acids and bases, although these compounds are not used as extraction solvents in the sense of the report. The Committee has no objections to this use of acetic acid, lactic acid and sodium hydroxide.

The Committee has been requested to evaluate the safety of the following compounds on which, however, no data were submitted to enable this to be done: n-methyl pyrrolidone, methyl isobutylketone, di-isopropyl ether.

*Reports of the Scientific Committee for Food, Tenth Series, 1980 (EUR 6892)

ASSESSMENT OF INDIVIDUAL SOLVENTS

GASES USED AS EXTRACTION SOLVENTS

Propane

Although the level of propane residues in food as consumed were claimed to be less than 1 mg/kg, no analytical results were presented to the Committee. Toxicological data appropriate for establishing an ADI are absent but an ADI is unnecessary for this gas. A specification for foodgrade quality and residue data are needed. Meanwhile the Committee considers the use of this compound acceptable as extraction solvent.

Butane

Although the level of butane residues in food as consumed were claimed to be less than 1 mg/kg, no analytical results were presented to the Committee. Toxicological data appropriate for establishing an ADI are absent but an ADI is unnecessary for this gas. A specification for food grade quality and residue data are needed. Meanwhile the Committee considers the use of this compound acceptable as extraction solvent.

Isobutane

Although the level of isobutane residues in food as consumed are claimed to be less than 1 mg/kg, no analytical results were presented to the Committee. Toxicological data appropriate for establishing an ADI are absent but an ADI is unnecessary for this gas. A specification for food grade quality and residue data are needed. Meanwhile the Committee considers the use of this compound acceptable as extraction solvent.

Carbon dioxide (liquid and supercritical gas)

This compound is a natural metabolite and man is permanently exposed to carbon dioxide from the atmosphere, food and drink. Compared to this exposure the residues from its use as extraction solvent are insignificant. The establishment of an ADI for this compound is unnecessary. A specification for food grade material already exists. The Committee considers this compound acceptable as extraction solvent. The setting of residue levels is unnecessary.

Nitrous oxide

The pharmacological and pharmacokinetic properties of this gas are known from its large established use as anaesthetic. Although no residue data are available, these are likely to be so low as to present no hazard to the consumer. The Committee considers the establishment of an ADI unnecessary and its use as extraction solvent acceptable. The specification should exclude the presence of other oxides of nitrogen.

ALCOHOLS

Methanol

The available toxicological data are insufficient to establish an ADI but the Committee considers an ADI unnecessary because residues from its use as extraction solvent are minimal. The Committee was informed that residues of methanol from use as extraction solvent are of the order of 5–10 mg/kg food. Knowledge of its biochemical and metabolic behaviour in man permits the conclusion that no safety problems are likely to arise from its use as extraction solvent. The Committee recognizes that the natural occurrence of methanol may create difficulties in the analytical determination of methanol residues. The Committee considers the use of methanol acceptable as extraction solvent.

Ethanol

In evaluating the safety of this compound the Committee considered its use as extraction and as a carrier solvent. On the basis of the large amount of toxicological information available the Committee did not consider it necessary to specify an ADI. A food grade specification for ethanol is available. The Committee considered it unnecessary to set residue levels in food where ethanol is used as extraction or carrier solvent. The use of this compound as extraction solvent is acceptable to the Committee.

Propan-1-ol

The available toxicological information relates to metabolism studies, acute toxicity studies, and one short-term oral toxicity study in rats in which the liver was the only organ studied. The reported adverse effects in the long-term study in rats are not interpretable in the absence of essential details. The data are insufficient to establish a formal ADI. The Committee considers the use of this compound temporarily acceptable as extraction solvent, if residues from this use in food as consumed do not exceed 5 mg/kg. The Committee requires the results of an adequately performed 90-day study by the end of 1983. If this substance is to be used as a carrier solvent with residues in food greatly exceeding 5 mg/kg the Committee would require in accordance with its report on the general principles (see guidelines) the results of a long-term study in a rodent species to assess the safety of this use.

Propan-2-ol (Isopropanol)

The available toxicological information relates to metabolism, acute, short-term and reproduction oral studies in rats and a long-term oral study in rats. Another recent oral reproduction study of unusual design claimed to show adverse effects at low levels but the lack of specification of the compound tested makes this study difficult to interpret. The Committee established a temporary ADI of 1.5 mg/kg b.w. and wishes to see the results of an adequate single generation reproduction study by 1983. Meanwhile it considers the use of this compound temporarily acceptable as an extraction solvent.

Butan-1-ol

The available toxicological data relate to metabolism and short-term oral studies in rats. No long-term oral studies are available. The Committee was therefore unable to establish an ADI. Residues occur in food from use as extraction and carrier solvent as well as from natural occurrence, but adequate residue data are not available. The Committee considers the use of this compound temporarily acceptable as an extraction solvent provided the residues are limited to 30 mg/kg food. The Committee requires the provision of an adequate 90 day oral study in rats as well as information on residue levels by 1983.

Butan-2-ol

There are insufficient data to establish an ADI but the available two-generation reproduction study shows a definite no-adverse-effect level. No residue data are provided. The Committee considers the use of this compound temporarily acceptable as an extraction solvent provided residues from use as an extraction solvent in food as consumed do not exceed 30 mg/kg food. The provision of an adequate 90-day feeding study in rats as well as information on residue levels is required by 1983.

Tertiary butanol

The available data are insufficient to establish an ADI. Biochemically this solvent will behave like other tertiary carbinols which are generally not very reactive. The residues in food are minimal and are not a hazard to health. The Committee considers the use of this compound temporarily acceptable as an extraction solvent provided residues from use as an extraction solvent in food as consumed do not exceed 10 mg/kg food. The provision of an adequate 90-day feeding study in a rodent species is required by 1983.

Benzyl alcohol

The metabolism by man is well established. Although no specific toxicological studies are available it is acceptable to include benzyl alcohol in the group ADI of 5 mg/kg b.w. established for benzoic acid (representing total benzoates) by JECFA (1973). The Committee considers the use of this extraction solvent acceptable.

Glycerol

This substance occurs naturally in fats and lipid complexes. The available toxicological evidence includes short- and long-term studies in rats as well as metabolic studies showing that glycerol participates in the normal carbohydrate metabolism. No essential toxicological difference exists between naturally derived and synthetically made glycerol. The specification of synthetic glycerols should contain a limit for the contamination by butanetriols. The Committee agrees with the JECFA evaluation (1976) that an ADI for man need not be specified. The Committee considers this substance acceptable for use as solvent for food.

Propan-1,2-diol

There are sufficient data available from oral toxicity studies, including long-term studies in rats and dogs, to establish an ADI of 0-25 mg/kg b.w. (JECFA 1973). The Committee agrees with the ADI established by JECFA and considers the use of this substance acceptable as solvent for food. Because of the information submitted on the extensive use of this substance in food technology the Committee recommended that the intake from all sources should be reviewed in relation to the established ADI.

HYDROCARBON SOLVENTS

Cyclohexane

Although the available toxicological data relating to prolonged oral exposure of animals or man are scanty, the metabolic and other data point to a low toxic potential. The early literature reports of haematological injury were attributable to benzene as contaminant. No residue data were provided. Any specification for this compound should include a limit for benzene and polycyclic aromatic hydrocarbons. The available data do not permit the establishment of a formal ADI. The Committee considers the use of this substance temporarily acceptable as an extraction solvent but requires the provision of an adequate long-term study in a rodent and information on residue levels by 1985.

Light petroleum

This material is difficult to specify but comprises a mixture of saturated aliphatic hydrocarbons with a specified distillation range, containing up to 50% hexane and variable amounts of heptane. The metabolism of hexane may lead to neurotoxic derivatives. The available short-term oral studies in rats and dogs showed no deleterious effects. Hexane is moderately hepatotoxic on inhalational exposure. No data are available to establish an ADI. The Committee considers the use of this material temporarily acceptable for use as extraction solvent when used under conditions resulting in minimal residues provided the results of a long-term study on a specified light petroleum are available by 1985. A specification is needed with limits for unsaturated aliphatic hydrocarbons and polycyclic aromatic hydrocarbons.

2-nitropropane

Appropriate metabolism, short-term and long-term oral toxicity studies are absent. Rats developed hepatocellular carcinomata when exposed for 6 months by inhalation and observed for another 6 months. Rabbits and cats showed haematological damage following inhalation due to conversion of the compound to nitrate, while liver damage after inhalation of high levels has been reported in rats, cats and men. The Committee considers this compound unacceptable as extraction solvent for food.

Toluene

Almost all available toxicological data refer to exposure by routes other than oral and are therefore of little relevance for a meaningful evaluation of this compound. No residue data were available. The existing data do not allow the establishment of an ADI. The Committee considers this compound unacceptable as extraction solvent for food.

ETHERS

Diethyl ether

Most of the available toxicological data refer to inhalational exposure and there is long experience from use in human anaesthesia. No oral toxicological data exist which would permit establishing an ADI. The specification should contain limits for named stabilisers. In view of the small residues likely to remain in food from the use of this substance as extraction solvent the Committee considers it unnecessary to establish an ADI and considers the use as extraction solvent acceptable.

Di-butyl ether

No relevant oral toxicological data are available on this compound nor any residue figures. The existing toxicological information is insufficient for a meaningful evaluation or establishment of an ADI. The Committee considers that this compound is not acceptable for use as extraction solvent for foods.

ALDEHYDES

Furfural

The limited toxicological data indicate that the compound is potentially hepatotoxic. The available information is insufficient to establish an ADI. The Committee does not consider this compound acceptable for use as extraction solvent for food until the result of a full toxicological examination becomes available (see guidelines).

KETONES

Acetone

Oral administration of massive doses to dogs and rabbits suggests nephrotoxic effects and there is some evidence of heptotoxic and nephrotoxic effects in man following massive intoxication. The metabolism in man is well known. No toxicological data on oral administration are available to establish an ADI. The available oral short-term study in rats and mutagenicity studies have shown no adverse effects. The Committee recommends that the specification should include a limit of 10 ppm for mesityloxide. The Committee considers the use of this substance acceptable as extraction solvent for food provided residues are kept to 5 mg/kg food as consumed.

Methyl ethyl ketone

Methyl ethyl ketone (MEK) occurs in traces in normal human urine. Its metabolism has been well studied and it has a low oral toxicity. There are no adequate oral long-term studies available for establishing an ADI. The compound appears to have no neuropathic properties but enhances neurotoxicity of other substances such as methylbutylketone (MBK) or n-hexane, if combined with the latter. The Committee considers the use of this substance temporarily acceptable as extraction solvent, provided the results of adequate long-term studies, reproduction studies, including embryotoxicity and mutagenicity studies are available by 1985. Special emphasis should be placed in animal studies on possible neurotoxicity aspects. The Committee recommends that the specification should limit the amount of hexane in MEK to 50 mg/kg. The combined use of MEK with MBK or n-hexane should be avoided.

Di-isopropyl ketone

No toxicological data are available on this compound nor any information on residues or specification. No meaningful evaluation is therefore possible. The Committee considers this compound not acceptable for use as extraction solvent for food.

HALOGENATED HYDROCARBON SOLVENTS

Chloroform

A large amount of data relating to several routes of exposure is available which shows that the compound is hepatotoxic and nephrotoxic to rodents at high levels of exposure. However a no-effect level for these toxic effects can be determined. There is also sufficient evidence that chloroform is carcinogenic in mice and one strain of rats following oral exposure. However, the neoplastic changes reported only occurred when excessive doses were used causing initial toxic damage. Chloroform is foetotoxic and not mutagenic in the bacterial systems tested. The Committee considers this substance unacceptable for use as extraction solvent in food.

Dichloromethane

The available data on metabolism indicate similarity of pattern whatever the route of administration. Both man and animals excrete most of the administered dose unchanged in the expired air, a small percentage being converted to carbon monoxide which binds to haemoglobin. A few short-term experiments on foods extracted with this solvent showed no toxicity from the minute residues of the solvent or from any potential reaction products with food components. The available short-term test using drinking water as vehicle showed hepatotoxicity in rats and mice at practically all levels tested. Cell transformation studies were negative but in-vitro mutagenicity tests in bacteria were positive. Inhalation studies showed questionable teratogenic effects in rats and mice. The available long-term studies in rats by inhalation were inadequate for meaningful evaluation but raised suspicions because of increased mammary tumour incidence. A long-term study in mice using i.p. administration pointed to a possible increase in lung adenomas. Long-term studies by gavage and in drinking water are either in progress or planned in rats and mice as well as repeat long-term inhalation studies in rats and mice.

The Committee considered that the available toxicological evidence was insufficient to establish an ADI but that meanwhile the use of this solvent was temporarily acceptable. In addition use should be such as to result in minimum residues and in any case not exceeding 10 mg/kg food as consumed, whatever the application, and provided material complying with a food grade specification and stated stabilisers is used. The Committee wishes to review the situation when the results of ongoing studies are available but not later than the end of 1983.

Trichloroethylene

There is a wealth of data on metabolism as well as short-term, long-term and mutagenicity studies. The substance has also been used for many years in human anaesthesia. Only the oral carcinogenicity study in mice in which large doses were used produced hepatocellular carcinoma and lung tumours in both sexes. Both oral carcinogenicity studies in rats are considered not adequate. Other more recent studies have identified carcinogenic/mutagenic stabilisers present in the samples tested which make the carcinogenicity findings questionable. Furthermore, additional inhalation studies in rats and mice and feeding studies using low levels have not shown any evidence of carcinogenicity.

The Committee considers the use of this substance temporarily acceptable as extraction solvent for food. The results of well conducted oral carcinogenicity studies are needed by 1985 as well as data on the levels and nature of residues present in extracted foods.

1,2-Dichloroethane

A considerable amount of data on the metabolism and oral short-term and long-term studies are available. The rat and mouse studies showing a carcinogenic effect were performed on technical grade material, in which any contaminants present were not determined. Another oral long-term study has not shown any carcinogenic effects and long-term inhalation studies in mice and rats were equally negative as regards carcinogenicity. The substance is mutagenic in the bacterial systems tested but a reproduction study showed no effects on offspring. No data on tissue accumulation are available. The evidence on carcinogenicity is conflicting. There is some evidence of interreaction with certain food constituents to form toxic compounds, however under excessively severe conditions. The Committee considers this substance not acceptable for use as extraction solvent for food unless the results of well conducted carcinogenicity studies on food grade material become available for evaluation.

Carbon tetrachloride

The available data show that this substance is rapidly absorbed and has considerable hepatotoxicity. The available studies are not adequate for establishing an ADI. The oral long-term studies in rats, mice and hamsters, although not all adequate, show clearly that the substance produces benign liver tumours and hepatocellular carcinomas. The compound is also foetotoxic but non-mutagenic for bacteria. The Committee considers this substance unacceptable for use as extraction solvent for food.

Cis-1,2-dichloroethylene (acetylene dichloride)

No toxicological data are available but oral long-term studies in rats and mice are planned. No food grade specification of this solvent is available. The Committee considers this compound unacceptable for use as extraction solvent for food.

Trans-1,2-dichloroethylene (acetylene dichloride)

The available toxicological studies are scanty and include only one short-term inhalation study in rats. Oral long-term studies in rats and mice are planned. No food grade specification of this solvent is available. The Committee considers this compound unacceptable for use as extraction solvent for food.

Dichlorofluoromethane*

No data are available on the effects of oral administration of this compound. A meaningful evaluation is therefore not possible nor can an ADI be established. The Committee considers this compound not acceptable for use as extraction solvent for foods.

Dichlorodifluoromethane*

Data on the effect of oral administration are available from short-term studies in rats and dogs as well as from a long-term study in rats. Reproduction, teratogenicity and mutagenicity has also been investigated without revealing any adverse effects. Almost all of the ingested compound is excreted unchanged in expired air. The cardiovascular effects noted after inhalation exposure in various species are of no significance in relation to the safety of residues of the compound when used as extraction solvent for foods. An ADI of 0-15 mg/kg bodyweight for man was established by JECFA (1975) and the Committee agrees with this evaluation. The Committee considers this compound acceptable for use as solvent for food.

*see "Toxicological considerations"

Dichlorotetrafluoroethane[*]

The available data on the effects of oral administration of this compound do not permit a meaningful evaluation of the establishment of an ADI. The acute toxicity of this compound appears to be low but the inhalation toxicity is greater than that of other halocarbons. The Committee considers this compound not acceptable for use as extraction solvent of food.

1,1,2-trichlorotrifluorethane[*]

No data are available on the effects of oral administration and therefore no meaningful evaluation of the safety of the compound can be made. The Committee considers this compound not acceptable for use as extraction solvent of food.

ESTERS

Methyl acetate (opinion expressed in March 1981)

This solvent is temporarily acceptable as an extraction solvent. An in vivo hydrolysis study should be provided by the end of 1981. Residues in food should not be higher, in molar terms, than those established for methanol.

Ethyl acetate

A metabolic study using ^{14}C labelled substance has shown that the compound is rapidly hydrolysed in-vivo after oral administration into the constituent acid and alcohol which have well known metabolic fates. In-vitro hydrolysis has been demonstrated satisfactorily. The observed dermal irritancy and possible allergenicity is not relevant to the evaluation as an extraction solvent. No toxicological studies exist to establish an ADI but the metabolic data make it unnecessary for an ADI to be specified. The Committee considers this solvent acceptable for use in food.

Butyl acetate

A metabolic study using ^{14}C labelled substance has shown rapid hydrolysis in-vivo after oral administration and elimination of the acid and alcohol by well known metabolic pathways. In-vitro hydrolysis was shown to be comparatively slow. Several short-term oral studies in rats are available pointing to a no-adverse-effect level of 600 mg/kg b.w. Oral short-term studies in mice point to a no-adverse-effect level of 1,000 mg/kg b.w. No toxic effects were seen in reproduction and teratology tests in rats and mice. The Committee established a temporary ADI of 0-6 mg/kg b.w. The Committee considers this substance temporarily acceptable for use as solvent for food and requires information on the levels of residues present in extracted food by 1983.

Ethyl lactate

Only an in-vitro hydrolysis study is available and there are no other oral studies in existence from which an ADI could be established. It is very likely that this substance will hydrolyse in-vivo similar to other closely related esters and on this assumption the constituent acid and alcohol would follow well established metabolic pathways. The available short-term study in rats was just sufficient to indicate the absence of any acute toxicity at the high dose level tested. The Committee considers the substance as temporarily included in the ADI for lactic acid provided adequate evidence of in-vivo hydrolysis becomes available by the end of 1981. On this basis the Committee considers this substance temporarily acceptable as solvent for food.

[*] see "Toxicological considerations"

Benzyl benzoate

No oral toxicological data are available on this compound and in-vivo hydrolysis into its constituents has been proposed. The metabolic fate of both benzyl alcohol and benzoic acid is well established in man. The Committee has temporarily included this substance in the ADI of 0-5 mg/kg b.w. established in 1973 (JECFA) for all benzoate derived from food additive use, subject to provision of adequate confirmation of the in-vivo hydrolysis by the end of 1981. The Committee meanwhile considers this substance temporarily acceptable for use as solvent for food.

Triethyl citrate

This compound is hydrolysed in-vitro into its acid and alcohol moieties of well known metabolic fate in man. The available short-term studies in rat, cat and dog and one long-term study in rat, although not fully adequate by present day standards, allowed the establishment of a temporary ADI of 10 mg/kg b.w. by JECFA with which the Committee agrees. The compound was non-mutagenic in the microbial systems tested. The Committee considers this substance temporarily acceptable for use as solvent for food provided adequate evidence of in-vivo hydrolysis is furnished by the end of 1981.

Diethyl tartrate

No toxicological data are available. However, in the light of existing knowledge on the biological properties of tartrate esters, the Committee considers this compound temporarily acceptable for use as an extraction solvent for food but requires adequate data to be submitted by the end of 1983 on in-vivo hydrolysis as well as the results of a 90-day oral feeding study in rats. Because of the existence of an ADI for tartaric acid total residues of this compound from all uses should not exceed 100 mg/kg food.

Isopropyl myristate

There are no oral toxicity data available to make a meaningful evaluation or establish an ADI. The Committee considers this compound not acceptable for use as extraction solvent for foods.

Glycerol mono-, di- and tri-acetate

These glycerol esters, except for the tri-acetate, occur always as a mixture with glycerol. No biochemical or formal feeding studies are available on the glycerol mono- and di-acetates but the tri-acetate is rapidly hydrolysed in-vitro. The tri-acetate is metabolised efficiently by known metabolic pathways. No formal short- or long-term studies exist for the tri-acetate. Nevertheless the metabolic data permit the reasonable conclusion that all three acetates are likely to be readily hydrolysed into constituents of well known metabolic fate. The Committee agrees with the evaluation by JECFA (1979) that an ADI need not be specified and considers these compounds acceptable for use as solvents for food.

Glycerol tripropionate

There are no oral toxicity data available to make a meaningful evaluation to establish an ADI. The Committee considers this compound temporarily acceptable for use as solvent for the extraction of food provided adequate information on in-vivo hydrolysis is submitted by the end of 1981.

Glycerol tributyrate

There are no oral toxicity data available to make a meaningful evaluation to establish an ADI. However this compound occurs naturally as a constituent of milk fat. The Committee considers the use of this compound acceptable as a solvent for the extraction of food provided the levels of residues comply with good manufacturing practice.

Diethylene glycol monoethyl ether (DGME)

A considerable amount of toxicological data is available on this compound. However, only the short-term studies are adequate and were carried out in several species. The long-term studies are not suitable for establishing an ADI and the available reproduction study is inadequate for meaningful evaluation. Since the evaluation by JECFA (1976) the additional data requested to permit meaningful evaluation have not been presented. The uncertainties regarding a no-effect level for nephrotoxicity and hepatotoxicity as well as effects on reproduction including teratogenicity and carcinogenicity remain unanswered. The Committee considers this compound not acceptable for use as extraction solvent for food, particularly as its non-volatility makes comparatively high levels of residues likely.

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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON SULPHITING AGENTS

(Opinion expressed 15 January 1981)

TERMS OF REFERENCE

To give an opinion on the effects on health due to the ingestion of sulphur dioxide and other sulphiting agents from foodstuffs.

BACKGROUND

The Commission is currently reviewing the technology associated with the use of sulphites in the production of wine and an appreciation of the safety of this practice forms an essential part of the review. The ingestion of sulphites from wine cannot be taken in isolation from its ingestion from other foods and so the Scientific Committee for Food was asked to advise on the safety in use of sulphur dioxide and other sulphites in foodstuffs in view of the extensive use of these substances.

CURRENT REVIEW

The Committee was provided with a number of extensive reports on the problem of the use of sulphiting agents in food and beverages. These included a report by Prof. Jaulmes[1] on the safety of these substances, a publication of the Federation of American Societies for Experimental Biology (FASEB)[2], reports by F.W. Beech, C. Cantarelli, D. Jakob and P. Sudraud[3] on the technological possibilities for reducing sulphur dioxide in wine, and a report by F. Custot[4] setting out the legally permitted and actually detected levels of SO_2 in food within the EEC.

The Committee noted that sulphites were preservative agents for food with antiseptic and antifungal properties, known since antiquity, which have, however, a disagreeable taste and odour limiting their use and which irritate the mucosal surfaces of the body. Even small concentrations in the atmosphere are toxic on inhalation but this aspect, and the contribution to the total body burden of SO_2 from atmospheric intake has not been considered to be relevant in the context of the present evaluation.

Ingestion of sulphiting agents is generally at low levels but derives from their legally controlled uses in specified foods, non-alcoholic beverages, wines, beers and ciders. Sulphites also occur naturally as a by-product of fermentation. Recent estimates made available to the Committee quote daily intakes, as averages for the whole of Europe of 15 mg SO_2 = 0.25 mmol/person from food and non-alcoholic beverages, 40 mg SO_2 = 0.63 mmol/person if an additional 300 ml of wine is consumed, and 90 mg SO_2 = 1.41 mmol/person if 700 ml of wine is drunk daily. Sulphites are present in food and beverages usually in chemical combination with certain constituents. In some beverages they may also be present in the uncombined state. It is of interest that the estimates of intake from food and non-alcoholic beverages are closely similar to estimates made for the U.S. and Belgium.

Sulphites are chemically reactive and their biological importance relates particularly to their destructive effect on the vitamins, especially thiamin. Sulphites in food are partly oxidised during ingestion and digestion to sulphates. Sulphites also react during ingestion and after absorption with cellular and tissue fluid macromolecules in a reversible manner. Extremely rapid conversion to sulphates occurs in the tissues predominantly through the action of the enzyme sulphite oxidase. The latter is present predominantly in the liver, heart, kidneys, spleen, brain and lungs. The sulphates are finally eliminated rapidly in the urine. Sulphites are also formed endogenously from the metabolism of S-containing aminoacids. The average endogenous formation of sulphite in man is estimated to be about 1680 mg SO_2 = 26.25 mmol/day, all of which is eliminated as urinary sulphate.

The toxicity profile of sulphites has been examined in numerous investigations in laboratory animals and also in man[1,2,5,6,7,8]. Large doses are acutely toxic but low doses, administered over prolonged periods or for the lifespan of experimental animals, have shown no specific adverse effects. No deleterious effects have been noted on reproduction nor is there any evidence for a teratogenic or carcinogenic potential. Shapiro[8] has shown that large doses

produce weak mutagenic effects in some in vitro test systems but not under in vivo conditions. These findings are therefore unlikely to be relevant as a mutagenic risk for man from the ingestion of sulphites in food and beverages.

Sulphites perform several useful functions in food technologically including the suppression of unwanted fermentation, as antibacterial agents against microbiological contamination of food, as bleaching agents and antioxidants. These aspects, particularly the antimicrobial activities, need to be considered when a risk assessment for man is being made.

The more recent information presented to the Committee on the low level of intake of sulphites from all food and beverage sources, on the pathway and kinetics of the metabolism of sulphites in animals and man, on the high efficiency of the enzymatic detoxification systems, and on the considerable endogenous production of sulphites being some 20 to 40 fold the dietary intake, is of fundamental importance for the evaluation of the health hazard from ingested sulphites.

OPINION

The Committee noted that a numerical value for the ADI of ingested sulphite had been established by JECFA (1974)[5]. The Committee also considered the results of the study in pigs by Til[6], in which the no-adverse-effect level was reported to be 0.23% SO_2 in the diet equivalent to 92 mg/kg b.w. (92 mg SO_2 = 1.44 mmol). The pig study is of particular relevance because this species is closer to man than the traditional rodent laboratory animals by virtue of the pysiology of its gastro-intestinal tract. Taking the above information together with the knowledge of the efficient metabolism of the sulphite oxidase system in the mamalian tissues and the smallness of the dietary intake of sulphite compared to the daily endogenous production in man, would permit a more flexible approach in the consideration of the safety-in-use of sulphite as preserving agent in food and beverages.

The Committee concluded that for the great majority of the population no hazard to health would arise from the ingestion of sulphites at levels currently found in food and beverages. Nevertheless, the Committee wishes to reemphasize its previously stated opinion, applicable to all food additives, that their use should be restricted to the minimum level necessary technologically, particularly in foods which are an important source of thiamin.

The Committee is aware that congenital deficiency of hepatic sulphite oxidase has been described as a rare metabolic disorder in man. There are only few data on the normal development of this enzyme with age in various species, and on the factors controlling sulphite oxidase activity. Information on these aspects would be helpful in assessing any special risk factors which may apply to select subpopulations or to vulnerable sections of the population, in whom malnutrition has lead to marginal body reserves of thiamin.

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

The present series relates to opinions on the effects on health due to the ingestion of sulphur dioxide and other sulphiting agents from foodstuffs, and extraction solvents.

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