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REPORTS OF THE SCIENTIFIC COMMITTEE FOR FOOD CONCERNING :

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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON

COLOURING MATTERS

(Opinion expressed 10 December 1987)

TERMS OF REFERENCE

To review the safety in use of certain colouring matters, particularly those previously classed by the Committee as temporarily acceptable.

BACKGROUND

The Committee carried out a comprehensive review of colouring matters in 1983[1].

Since that time further data have become available on Caramels and Erythrosine, colours assessed as temporarily acceptable at that time.

In addition to the data now provided on these colouring matters the Committee has been asked to reassess Allura Red, Beta-Carotene and Canthaxanthin on the basis of new information submitted to the Commission.

One new colouring matter, an extract containing crocin, has been submitted for evaluation.

Finally the Committee has been asked to give clarification to its opinion on lycopene produced synthetically, and on marking inks for meats.

CURRENT REVIEW

Most of the substances examined by the Committee during their review were extracts of materials the chemical composition of which was not well defined.

The Committee has insisted on several occasions that colourings isolated from natural materials, even if they are derived from foods, cannot be held to be safer a priori than synthetic materials; nor could synthetic equivalents of substances present in food be

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(1) 14th Series of Reports, p. 47, EUR 8752.

automatically given the same evaluation as the food from which they are derived. What is important is the technical nature of the colouring, the conditions of its isolation and processing, its purity, and the quantities absorbed.

The Committee reaffirms that whilst it could accept a number of colouring matters from foods without a formal ADI (paragraph 7 of the 1983 Report) it draws attention to the fact that the acceptance is limited to situations under which the use of colouring matters extracted from foods would not be expected to result in ingestion differing substantially from the amounts likely to be ingested from the normal consumption of the foods in which they occur.

However, colouring matters derived from natural sources which are not natural foods or their synthetic equivalents, or colouring matters found in foods, prepared synthetically, require suitable testing.

The Committee is also aware that there have been significant technological advances in the isolation, preparation and extraction of colouring matters from natural sources. The Committee expresses considerable concern at the tendency for foods to be increasingly coloured by so-called "natural" colouring matters and be labelled as such. This tendency results in misinterpretation by the consumer that such products are a priori safe. The Committee deplores this commercial exploitation of the lack of consumer awareness of the situation and recalls its opinions expressed in the 12th Series (2) (on intolerance and hypersensitivity) and the 14th Series (general safety) that the use of colouring matters could be reduced.

These problems are specifically illustrated by some of the colouring matters subject to review by the Committee in the report.

The Committee reiterates its request for a review of the considerable significant technological advances in the isolation, preparation and extraction of colouring matters from natural sources to assess the impact of these changes on the evaluation of these materials and to improve the specifications of purity in the light of the increased potential for use.

Annexes 1 and 2 contain respectively a summary of evaluations and an assessment of individual materials considered in this review.

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(2) 12th Series of Reports 1981 EUR 7823.

ANNEX 1

SUMMARY OF EVALUATIONS

Allura Red AC	ADI	0-7 mg/kg bw
Caramels		
- plain	Acceptable	
- caustic sulphite	Temporarily** acceptable in alcoholic beverages	
- ammonia	Temporary** ADI	0-200 mg/kg bw
- ammonia sulphite	ADI	0-200 mg/kg bw
Canthaxanthin	Temporary** ADI	0-0.05 mg/kg bw
Beta-Carotene extracts from algae	Not acceptable	
Crocin extracts	Not acceptable	
Erythrosine	ADI	0-0.1 mg/kg bw
Lycopene	Acceptable	

** Limit 5 years.

ALLURA RED

The Committee has already reviewed comprehensive data relating to the metabolism, including identification of cresidine sulphonic acid as the major metabolite, reproduction and teratogenicity, in vivo and in vitro mutagenicity, acute toxicity including skin sensitisation, short-term studies in rats, dogs and pigs as well as several long-term studies in rats and mice. The question of the increase in the incidence of lymphomas in the first long-term mouse study was not confirmed in the second long-term mouse study.

Orally administered allura red undergoes partial azo reduction prior to absorption. Gastrointestinal absorption is poor, most dye being excreted in the faeces. The "no-adverse effect" level for reproductive function in the rat was 1.39% in the diet. Several teratogenic studies revealed no embryotoxic nor teratogenic potential. The available mutagenicity studies did not show any genotoxic activity. The acute, short-term and dermal toxicity studies on several species indicated no colour-induced toxic responses.

The long-term studies in mice and rats did not reveal any carcinogenic potential.

On the basis of these data the Committee set an ADI of 0-7 mg/kg bw in 1983.

Questions have been raised recently on the metabolic data assessed by the Committee, particularly in relation to the fact that a number of metabolites had not been identified, and the number of test animals was too small.

The Committee accepted that the metabolic data were less than totally adequate but considered that in the context of an overall assessment of all the data there was no need to repeat the studies.

Furthermore comments had been received that the in vivo formation of the carcinogen p-cresidine had not been ruled out.

The Committee considers that p-cresidine sulphonate was unlikely to break down into p-cresidine. Further information was summarized tending to confirm the Committee's understanding that in vivo formation of p-cresidine was unlikely. If p-cresidine were a metabolite in vivo the fact that the long-term studies showed no carcinogenic effect was reassuring. If this possibility was found to be a reality, the question of the safety of all colouring matters based on sulphonated azo compounds should be re-examined.

A behavioural study was taken into account by the Committee. In fact the behavioural effects reported were obtained at much higher doses than those on which the ADI had been based.

The Committee decided to maintain the ADI of 0-7 mg/kg bw.

CARAMELS

In its 1983 Report the Committee was unable to make a final evaluation of caustic sulphite caramels, ammonia caramels or ammonia sulphite caramels and requested further information on specification of the materials which were encompassed by the toxicological data being generated by studies in progress at the time, and which have now been evaluated by the Committee.

During the intervening period since the publication of the 1983 Report the Committee has been appraised at regular intervals of the progress being made (as requested in the Report).

The Committee has investigated with manufacturers the possibility of reducing the range of starting materials for caramels and setting well defined reaction conditions.

The Committee also requested from industry information to demonstrate the ways in which the chemical and toxicological properties of caustic sulphite caramels differ from sulphite ammonia caramels, clarification and causes of the toxicological effects for ammonia caramels and new data on ammonia sulphite caramels.

The Committee was also concerned that while the products currently being produced commercially may be reasonably homogeneous, there was no guarantee that other caramels might not be produced in accordance with the specifications in the submissions, but which might in an extreme case have a different toxicological profile.

Caramel colours for food use are produced by heating solutions of edible carbohydrates (usually simple sugars or glucose syrups) in the presence of acids or alkalis to promote caramelization. Four main types of caramel are distinguished :

(a) those which do not include either ammonium compounds or sulphites as reactants (plain caramels);

(b) those which contain sulphites but not ammonium compounds (caustic sulphite caramels);

(c) those which contain ammonium compounds but not sulphites (ammonia caramels);

(d) those which include ammonium compounds and sulphite compounds as additional reactants (ammonia sulphite caramels).

The physical and chemical properties of these four classes differ substantially one from another, e.g. the colour intensity of ammonia sulphite caramels is generally much higher than that of plain caramels; the colloidal material in ammonia caramels is much more electropositive than that of the other caramels, so that it is stable in some media in which they are not and vice versa; and so on. Even within one class of caramels, the nitrogen content, the sulphur content, the molecular weight distribution etc, can vary widely. These properties will be influenced by, among other things, the relative proportions of the various reactants present and the time and temperature of the caramelization reaction.

Although the caramelization reaction is a complex one, and many different compounds are formed, especially in the presence of ammonia, within a given class there is a broad similarity in qualitative chemical composition. Each of the main classes of caramel (ammonia and ammonia sulphite) can be delineated in terms of an "envelope of acceptability" which defines those materials of technological value in terms of colour, nitrogen content and nitrogen/colour ratio, and includes those materials toxicologically tested. The only significant toxic effect, namely the lymphopenia produced by ammonia caramel at low pyridoxine status, has been specifically traced to 2-acetyl-4(5)-tetrahydroxybutylimidazole (THI) and a limit for this material included in the specification.

Plain caramel seems to be generally acceptable for food use; it contains no added ammonia or sulphite and is likely to be produced in normal cooking processes, although this is no absolute guarantee of safety in itself. For caustic sulphite caramel however, the data on the chemistry of the material are insufficient to allow widespread use of the material.

With these reservations, the Committee agreed that the specifications included in the Commission proposal for a Directive (8th modification of the Directive on colouring matters) were a reasonable description of the products toxicologically tested and currently marketed, but the Committee felt that changes for caustic sulphite caramels requested by industry were also acceptable.

The secretariat confirmed that Commission Services would study the possibility of aligning the Community text with the purity criteria being developed by the FAO/WHO JECFA in due course.

The Committee sees no reason to change its opinion on caramel colours produced by the controlled heat treatment of carbohydrates with or without the presence of alkali or acid (so called plain caramel colour).

For caustic sulphite caramels (prepared by the controlled heat treatment of carbohydrates together with sulphite containing compounds, with or without the presence of alkali or acid), the Committee was provided with figures that this variety of caramel represents less than 1% of the total usage worldwide of caramel (compared with 90% for ammonia and ammonia sulphite caramels). It is therefore not surprising that the amount of chemical information is not as extensive as for other classes.

The Committee noted the new information on caustic sulphite caramel. The original data on six samples showed a somewhat higher sulphur content than that of the second series of eight samples (used mainly in the production of alcoholic beverages). The suggested widening of the sulphur specification to 0.3-3.5% on a colour intensity basis was accepted, recognizing that this change introduced less homegenicity in the class.

The Committee concluded that on theoretical grounds there was no reason to suppose that the caramels of this class would be toxicologically more suspect than those of ammonium sulphite caramels; however, no detailed information was available to support this. In addition, there was less homogenicity between the new range of caustic sulphite caramel.

Nevertheless an adequate 90-day study was available on one representative sample of caustic sulphite caramel and on this basis the Committee accepted the temporary use of this class of caramels for alcoholic beverages. The Committee wishes to see further information confirming its assumptions, on composition and homogenicity, particularly if this caramel was to be considered for other food uses. This decision should be reviewed at the latest in 5 years.

In 1983 the Committee recorded that it was awaiting further data on ammonia caramels (prepared by the controlled heat treatment of carbohydrates with ammonium compounds) on characterizing the compound actually in use and on the significance to man of low levels of THI unavoidably present in the end product.

The industries involved in the production and use of caramel colours have put a great deal of effort into decreasing the levels of THI in their products, and, at the moment, batches of ammonia caramel containing less than 25 mg/THI/kg/product can be manufactured (to be compared with the 125 mg of some years ago). In the evaluation of the toxicological data on this caramel, it was clear that the reduction in circulating lymphocytes in the rat is mainly, if not only, determined by the presence of THI in the product. Besides the presence of this substance in ammonia caramel colour, another factor, i.e. the content of pyridoxine (Vitamin B_6) in the diet, modulates the effect. With high doses of Vitamin B_6 in the rat, no effect is found; with low levels, a reduction of the number of lymphocytes occurs. The question arose whether it would be possible to establish a no-effect level for THI; in other words, to establish and calculate a quantitative relationship between the degree of reduction of the absolute numbers of circulating lymphocytes by feeding THI (as ammonia caramel having known contents of THI) and the pyridoxine content of the diet.

In extrapolating these figures to man, there is a question whether the decrease in lymphocytes should be considered as a toxic effect since recovery takes place. If the decrease is considered a toxic effect, then account must be taken that certain groups of the population are deficient in Vitamin B_6, or have a low vitamin B_6 in the diet. In fact, it is not known whether or not man would be affected at all.

On the basis of this information and having in mind that heavy beer drinkers would be expected to be the group consuming the most ammonia caramel, the Committee concluded that THI should not be present at more than 10 mg/kg caramel (on a colour intensity basis) in caramel.

However, the Committee can temporarily accept a level of 25 mg of THI/kg of caramel to allow for industry to adapt, and would be willing to review the situation.

A no-effect level for the lymphocytophenic effect of ammonia caramels of known THI content can be established. This level depends on the vitamin B_6 content of the animal diet. An intake of 5 mg vitamin B_6/kg animal diet, which is considered by the Committee to be equivalent to a marginal vitamin B_6 intake in humans, was chosen for the calculation. A safety factor of 10 was then applied in view of the transient nature of the lymphocytopenia, and this approach yields an acceptable intake for ammonia caramel with a THI content of 25 mg/kg of up to 400 mg/kg bw.

With regard to other toxicological effects, the Committee's re-examination of the 90-day study and the mutagenicity test reassured it as to their adequacy. A conventional safety factor of 100 was applied to these data to give an ADI of 0-200 mg/kg bw, but the Committee considered this to be temporary pending the review mentioned above. This review should be undertaken at the latest in five years.

New long-term studies using ammonia sulphite caramel on rats and mice showed no significant effects.

The Committee considers that this caramel (prepared by the controlled heat treatment of carbohydrates with ammonium and sulphite containing compounds) is toxicologically acceptable and the Committee set an ADI of 0-200 mg/kg bw.

BETA-CAROTENE

The Committee was informed that beta-carotene may be produced by a new process from a species of algae Dunaliella S. which is not used as human food, from which the colouring is extracted. Because this is a new source material and a new process, safety problems might arise. The product can be marketed in several forms. As regards crystalline beta-carotene, the Committee foresees no health hazards in using this material, provided the beta-carotene complies with the specification for synthetic beta-carotene. The Committee would like to be informed of the presence of possible impurities arising from the source and the manufacturing process.

The colouring may also be sold as a vegetable oil extract with lower content of beta-carotene.

For the products containing low concentrations of beta-carotene, additional detailed information on their composition should be provided to confirm that the possibility of the presence of toxins and other biologically-active substances is excluded. Furthermore, information is needed on methods used in harvesting and on the constancy of the source organism, its microbiological purity and the methods used to determine these parameters. Some toxicological data were provided which were inadequate to complete the assessment of

safety. The further information referred to above should be provided to enable the Committee to decide on the need and extent of further testing of the safety of these products.

At that time the Committee will be better able to decide on the safety of such products, and indeed whether they are adequately designated "beta-carotene" or an alternative designation which reflects the low content of beta-carotene in the extract.

CANTHAXANTHIN

Since the Committee's evaluation of canthaxanthin as a food additive, a number of requests had been received by the Commission to review the safety of the substance because of reports of the production of crystalline deposits in the human retina through its use as an orally-administered skin pigmenting agent. The dose used for this effect was found to be well below that for calculating the existing ADI. A precise no-effect level for crystal deposition has not been established, but 30 mg per person per day appears to be a minimal effect level. There is some evidence that the presence of retinal deposits can cause a reduction in normal dark adaptation and produce electroretinographic changes.

The ADI for canthaxanthin has been re-evaluated to take account of these data.

Not all the animal data used in the past were now available to the Committee. Indeed the unexpected effect now recognized in man had not been thoroughly investigated in animal models used when the studies were conducted on rats in the early 1960s.

The Committee felt that the observation in humans required thorough elucidation.

The Committee, in common with the FAO/WHO Joint Expert Committee on Food Additives which has carried out a concurrent evaluation of the substance, believes that it is appropriate to apply a 10-fold safety factor to the minimal effect level in these human studies, giving a limit of 3 mg canthaxanthin per person per day, or an ADI of 0.05 mg/kg bw. Because of uncertainties in the human studies, this is adopted as a temporary ADI pending receipt of further data.

The further data required include animal studies on the absorption, distribution and excretion of canthaxanthin, with special reference to the extent of tissue deposition and whether this has any effects on organ functions. Human studies are also required to :

1. devise a more accurate dose/response relationship for retinal deposition;

2. define what functional effects are caused by the retinal deposits;

3. establish the reversibility of crystal formation and any functional changes.

Data on the pharmacokinetics of canthaxanthin in humans, especially with respect to distribution and tissue deposition, would also be desirable.

The data should be submitted by 1989.

The ADI is intended to cover its use as a food additive and the amount ingested through its use as an additive in animal feeds.

The manufacturers of the substance have informed the Committee that the "oral skin tanning" products have now largely disappeared from the market.

Canthaxanthin is also used for therapeutic reasons under medical supervision. In the opinion of the Committee this use is a matter for clinical judgement and falls outside its remit.

CROCIN

A submission was made to the Committee for the use of a material denominated as "crocin" which was in fact an extract of a mixture of carotenoid pigments from the fruit of Gardenia jasminoides Ellis (fam. Rubiaceae). Crocin ($C_{44}H_{64}O_{24}$) and Crocetin ($C_{20}H_{24}O_4$) are said to be the two main components. A product may also be prepared from dried saffron by extraction and purification.

The sponsor of the data reported various extraction processes (aqueous, alcoholic) in different parts of the submission and the supporting toxicological data.

The Committee was unable to give an evaluation of the extracts on the basis of the toxicological data submitted. It appears that the pigment has some effect on the liver but the data were difficult to interpret.
The identity of the materials to which they referred was not clear.

Before these extracts of saffron or gardenia fruits could be assessed for their acceptability as food colours, the Committee would require the submission of studies carried out using the Committee's guidelines (10th Series of Reports) as follows :

1. suitable testing on a well specified material;

2. as a priority a proper 90-day study including, especially, monitoring of hepatic function.

Estimates of usage envisaged by the food industry should be provided, including intake of similar material (saffron) as a source of flavourings.

ERYTHROSINE

Since erythrosine was last considered by the Committee a considerable amount of new data have become available including new long-term studies, animal and human studies on hormonal effects, and new mutagenicity studies. These were reviewed by the Committee.

Erythrosine has been shown to cause an increase in the incidence of thyroid follicular adenomas in male rats when fed at high doses in a 2-generation long-term study. There is also some equivocal evidence for an increased incidence of thyroid carcinoma. Studies in animals have been performed to investigate the effects of erythrosine on thyroid and pituitary function, and these show a generally consistent picture. Levels of serum hyroxine (T4) and of thyroid stimulating hormone (TSH) are increased while levels of serum tri-iodothyronine (T3) are reduced. In vitro studies have shown that erythrosine inhibits the conversion of T4 to T3 in the liver. These findings suggest a mechanism of action for the effects of erythrosine in producing thyroid hyperplasia. Inhibition of conversion of T4 to T3 will produce reduced tissue and plasma levels of T3, which will in turn reduce the inhibitory effect of T3 on secretion of TSH. The resultant increased secretion of TSH will stimulate the thyroid, leading to hypertrophy, adenoma formation and possibly malignant changes.

Earlier mutagenicity data based mainly on bacterial assays were largely negative, although there was an indication that the compound could produce gene mutation in yeasts, albeit only in the dark, and chromosome damage in vitro; negative results however were obtained in 2/3 in vivo assays for clastogenicity. Recently negative results have been obtained in assays for point mutations in bacteria, and for gene mutation in cultured mammalian cells. Negative results were also obtained in tests for clastogenic effects in vivo. In addition negative results were obtained in 2 tests indicative of DNA damage, namely a recombination assay in yeasts and an UDS assay in rat hepatocytes in vitro.

In the light of the new data it is now possible to conclude that erythrosine is not mutagenic in mammals.

In view of the above findings the Committee concluded that the oncogenic effects seen in the long-term studies were likely to be secondary to the effects of erythrosine on thyroid and pituitary function, and that an acceptable daily intake could be established based on the no-effect level for these hormonal effects. Although it is not possible to define a no-effect level from the animal studies, which employed relatively high doses, it is possible to define a no-effect level for endocrine effects in humans. Available clinical studies have shown that erythrosine has a minimal effect in humans at a dose of 200 mg daily over 14 days, while a dose of 60 mg daily was without effect. The latter dose was

taken to be equivalent to 1 mg/kg bw/day, and the Committee has set an ADI using a safety factor of 10 to allow for the small number of subjects used in the study and its relatively short duration.

The Committee has therefore concluded that the use of erythrosine was acceptable subject to an ADI of 0-0.1 mg/kg bw.

LYCOPENE

The Committee has already in 1975[1] accepted the use of lycopene obtained from foods by physical means although it had been unable to set an ADI. The Committee has no objection to the continued use of such a material but points out that it has already commented about the use of natural products and the possible extension of their use in the present report.

If a synthetic substance would become available, the Committee would expect to evaluate it in terms of a modern toxicological data base appropriate to the substance and its intended use.

MARKING INKS FOR MEAT

The Committee was requested to comment on the safety aspects of a change from Methyl Violet to either Brown HT or Erythrosine for the marking of meat in intra-Community-trade.

The Committee has already expressed an opinion on the marking of fresh meat by Methyl Violet in which it suggested that such use be reconsidered because of the potential adverse effects on health due to this colouring matter[2].

The Committee therefore supports the change from this colouring matter.

Brown HT is considered acceptable as a food additive[3]. The use of Erythrosine should be restricted, because of the considerable reduction in the ADI.

In view of the foregoing the Committee believes that of the two alternatives, a change to Brown HT would be the more desirable. However, as it could be expected that there would be only a limited ingestion of colouring matter from the meat mark, the Committee concludes that neither Brown HT nor Erythrosine would be expected to have a harmful effect on the consumer of the meat from its use as a meat mark, providing the total ingestion from food does not exceed the ADI.

(1) 1st Report of the Scientific Committee for Food.
(2) 4th Series of Reports of the SCF, 1977.
(3) 14th Series of Reports of the SCF, 1983.

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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON

SWEETENERS

(opinion expressed 11 December 1987 and 10 November 1988)

TERMS OF REFERENCE

To update the Committee's review on the safety in use of certain sweeteners.

BACKGROUND

The Committee reviewed sweeteners in 1984 and its opinion was published as the Sixteenth Series of Reports of the Committee [1].

Since that time the Commission has received a number of requests for a reevaluation of certain sweeteners for which the Committee was unable to advise definitively and has also been asked to review a new sweetener (a chlorosucrose) being commercialised under the trade name sucralose not included in the initial review. Further comments have criticised the Committee's evaluation of polyols (in particular the references to laxative effects) and aspartame.

For these reasons, and because the Commission believes that the forthcoming Directive on sweeteners should be as up to date as possible, the Committee was asked to give a new opinion on sweeteners.

Economic interests, particularly through European Trade Associations and Governments, were informed of the review (in September 1986) and were asked to submit comments.

The Committee received scientific information on the following sweeteners, already evaluated in 1984 :

- polyols (in general);
- isomalt;
- lactitol;
- aspartame;
- cyclamates;
- neohesperidine dihydrochalcone;
- saccharin (opinion expressed 10 November 1988);
- stevioside;
- thaumatin.

1) EUR 10210

No information was submitted on other sweeteners mentioned in the 1984 report.

The Committee was also supplied with comprehensive data on a new chlorosucrose sweetener (sucralose).

Final opinion was expressed 10 November 1988.

SUMMARY OF COMMENTS RECEIVED AND CONCLUSIONS

Polyols (general)

It was submitted to the Committee that the use in the 1984 Report of the term "diarrhoea" to describe the laxative effects of polyols was incorrect because the laxation was caused by osmotic pressure and is not a gastro-enteritic sickness.

The Committee accepted that the term "osmotic diarrhoea" describes the effect more accurately.

Furthermore the Committee was informed that the figure of 20 g/person/day at which polyols might cause osmotic diarrhoea was being interpreted as requiring legislative restrictions.

The Committee had not made this recommendation as close reading of its report made clear. The figure was a general safety net, not specific to individual polyols.

Isomalt

In 1984 the Committee reported that no laxative effects were noted at 10-20 g/day.

It was put to the Committee that this figure did not refer to daily doses, and that depending on the form of application no osmotic diarrhoea was observed at single doses of up to 31.6 g, and that after a few days adaptation 50 g isomalt per day could be tolerated.

The Committee did not agree with the proposals in the new submission and maintained the original evaluation. Even though repeated dosing might be less of a problem than single ingestion, the Committee felt that the suppliers could not guarantee a consumption pattern of this nature - nor had any information been supplied on the dosing interval.

Lactitol

Recent studies on metabolism and metabolic energy of lactitol were reported to the Committee.

The Committee evaluated in vitro studies in which lactose and lactitol were incubated with homogenates of human and guinea pig small intestines. The Committee was also provided with information on studies with volunteers.

From these studies it appears that lactitol is not hydrolized to galactose and sorbitol by human small intestinal disaccharidases. Lactitol is, however, totally fermented by microbes in the large intestines. The endpoints are not known, but lactic acid is thought to be the most probable, rather than the volatile fatty acids acetic, propionic, and butyric acid.

However, some of the volunteers on the lactitol diet were affected by an accumulation of intestinal gases and a higher water content of the faeces.

Taking all the data into account, the Committee did not believe it to be justified to change the opinion expressed in its earlier report.

Aspartame

Since the Committee expressed its initial opinion on aspartame, further data have been produced concerning the effect of aspartame on blood and tissue levels of phenylalanine, and the possibility of behavioural and other neurotoxic effects due to consumption of aspartame. The Committee therefore carried out a critical review of this new information.

When aspartame is consumed at levels within the ADI-limit there is no significant risk for an aspartate-induced neurotoxic effect in the brain. The experimental evidence indicates that this conclusion holds for adults, infants, sucklings as well as fetuses.

The phenylalanine-moiety of aspartame potentially exerts adverse effects on brain function in humans. Plasma phenylalanine concentrations of 1200 µmol/l are toxic in this respect. For the lower concentration range no firm conclusion can be drawn. Controversy exists on the question whether the deleterious effects on brain function caused by hyperphenylalaninemia follows a linear or a threshold pattern. Controlled studies in this field are virtually lacking. Clearly, as yet there are no observational data supporting the view that adverse effects occur at moderately elevated plasma phenylalanine concentrations (200-400 µmol/l).

In humans there is considerable intra-species variation in plasma concentration reached after ingestion of a given aspartame-dose. Nevertheless the evidence shows that after aspartame ingestion at the ADI-level, even when the ADI is consumed as a bolus dose, the plasma phenylalanine concentrations mostly are practically within the normal postprandial range; elevation to plasma concentrations commonly associated with adverse effects has not been observed. This statement holds for normal subjects (adults, infants), for PKU-heterozygous adults and probably also for PKU-heterozygous infants and pregnant subjects (normal, PKU-heterozygous). For the consumption of aspartame within the ADI-limit under practical conditions, the more gradual intake pattern and the competitive effect of simultaneously consumed other amino acids mostly will provide a moderating effect on plasma phenylalanine concentrations reached.

Ingestion of aspartame at the ADI-level would significantly increase the phenylalanine intake of PKU-homozygotes, thus deranging the phenylalanine restriction maintained by these persons. The PKU-homozytes on the phenylalanine-restricted diet should therefore avoid aspartame consumption. PKU-homozytes on the phenylalanine-liberalised diet should be made aware of the phenylalanine content of aspartame and its use by these people be discouraged.

Consumer complaints have raised the point of a possible effect of aspartame on behaviour. The available behavioural studies in animals showed effects after long-term administration at dose levels of 1000 mg/kg bw or higher. In the available acute dosing studies in humans no effects were observed. Long-term studies on behaviour and cognitive function in (sensitive) humans are lacking.

Analyses of adverse reaction reports made by consumers in the USA have not yielded a specific constellation of symptoms clearly related to aspartame that would suggest a widespread public health hazard associated with aspartame use. The possibility of an as yet undefined sensitivity to aspartame in at least some of the complainants could, however, not be ruled out. Focussed clinical studies are now being carried out in the USA; the results should provide additional evidence concerning the interpretation of the adverse reaction reports of aspartame.

In the regulation of admitted uses for aspartame the possibility of intake levels exceeding the ADI-limit in some groups of consumers should be a point of attention.

Cyclamate

The Committee was informed about new studies which confirmed that cyclohexylamine, the metabolite of cyclamate, was handled similarly by rat and man. The toxicological data obtained in the rat were therefore valid for extrapolation to man. Further studies on the comparative pharmacokinetics of cyclamate in rat and man are ongoing. The Committee did not consider it necessary to change the present assessment of cyclamate.

Neohesperidine dihydrochalcone

The Committee could not determine a no-effect level for NDHC using the studies carried out by the USDA up to 1978 because the results found during the various tests were variable and sometimes contradictory. It appeared clear that the diet used in certain of these studies was nutritionally unbalanced and that some effects reported during the administration of large doses of NDHC disappeared if the diet was supplemented by various nutrients, and in particular iodine.

In any case on a toxicological basis even at high dose no significant adverse effect was reported.

The Committee thought it would be useful to examine whether the new studies carried out over ninety days with better-balanced and different diets would produce the same effects of NDHC observed in USDA studies.

In general the reply was in the negative. In the two recent studies (TNO and LSRI), the no-effect level in the rat can be estimated as :

- 1000 mg/kg body weight/day for the LSRI study;
- from 547 to 1214 with an average of about 900 mg/kg body weight/day for the TNO study.

The no-effect level for NDHC in the dog in the USDA two year study can also be estimated at 1000 mg/kg body weight/day. This study, which was considered by the authors to be preliminary, used only a reduced number of animals.

To take into account this observation and to ensure maximum protection, the Committee decided to use the lowest no-effect level of NDHC obtained in all the studies which were carried out : 500 mg/kg/day in the rat.

The Committee established an ADI of 5 mg/kg/day for the substance.

Saccharin

The Committee was informed about additional studies carried out with saccharin but did not consider that these studies were such as to require a change in the Committee's assessment of a temporary ADI on 0-2,5 mg/kg bw.

In its report on saccharin of 24 June 1977, however, the Committee had also advised that saccharin should not be used in food specially prepared for young children and that the intake of saccharin by children and pregnant women should be limited. Following its December 1987 opinion, the Committee was asked to clarify its attitude to this restriction.

The Committee confirms that later studies show that in utero exposure does not contribute to the incidence of bladder tumours and therefore a special warning for pregnant women is no longer warranted.

The contribution of exposure during the lactation period and during exposure in early age remains unknown. However, the ADI is based on a clear no-effect level in well performed tests including exposure at this stage. Furthermore, it is a general policy to be very restrictive in the use of additives in food prepared for young children. Therefore, the Committee finds that there is no longer need specifically to warn against saccharin in this case.

Stevioside

The Committee had requested in 1984 the results of an ongoing long-term study, reproduction studies, metabolic data and an adequate specification which would properly define the material on which the safety assessment should be made.

A number of studies have now been submitted but they contain many deficiencies, particularly if the guidelines of the Committee specified in its 10th Series of Reports are applied.

It is not clear whether the submitted studies have been performed with the compound for which approval is asked. The exact identification of the stevioside preparation in each test should be provided. This identification must include either the description of the preparation procedure and the degree of purity or the sample composition including the identification and quantification of all impurities. Moreover, the compound for which approval is asked must be explicitly indicated and characterized according to the above cited criteria.

Metabolism studies revealed biotransformation of stevioside and rebaudioside A to steviol, a compound showing mutagenic activity in bacterial assays in the presence of a metabolic activation system. If, like the rat, biotransformation to steviol occurs also in the intestine of man, steviol might be absorbed from the lower bowel, reach the liver and exert mutagenic activity after metabolic activation. Results on experimental animals are also suggestive of enterohepatic circulation of stevioside or its metabolites. Therefore toxicokinetic studies should be performed in man with particular reference to the kinetics and routes of excretion and determination of the metabolic pattern after oral administration. Studies with the human intestine microflora may also be helpful.

Mutagenicity studies with stevioside crude crystals are sufficient, and indicate that the sample is not mutagenic. However, if biotransformation to steviol in man is demonstrated, additional mutagenicity studies with steviol in mammalian systems in vitro and in vivo, in the absence and the presence of different metabolic activation systems, should be provided.

The combined chronic toxicity and carcinogenicity study is questionable because of the reported illness in all groups and the high incidence of spontaneous tumours in the testes of male rats. Therefore it is proposed that a second chronic oral toxicity and carcinogenicity study be performed in a strain of rats other than F344 with the compound for which approval is asked.

The fertility and teratogenicity studies do not conform to recognized Principles of Good Laboratory Practice. In the fertility inhibition test, the administered dose is not comparable to that used in other medium- and long-term studies and the data provided do not give clear information on the possible effects on reproduction. Therefore it is proposed that a 2-generation study to assess reproduction toxicity and teratogenicity in rats with the preparation for which approval is asked be carried out.

As for the studies concerning the decreasing effect of blood glucose level by stevia extracts, they are not adequate, and the results are even contradictory. It is proposed that more detailed information on these studies be provided, or that additional studies on these effects be performed in order to make a distinct conclusion.

In the case in which the tested stevioside crude crystal preparations differ substantially from each other or from the preparation for which approval is asked, further testing may be required.

Taking all these factors into account, the Committee continues to believe the substance should be considered as not toxicologically acceptable.

4,1',6'-Trichlorogalactosucrose
(TGS, 1,6-dichloro-1,6-dideoxy-beta-D-fructofuranosyl-4-chloro-4-deoxy-alpha-D-galactopyranoside, Sucralose, Chlorosucrose.)

The Committee reviewed a large number of studies on 4,1',6'-trichlorogalactosucrose (in the following called TGS), its hydrolysis products and certain individual chlorohexoses. These studies included acute, subacute, chronic, metabolic and pharmacokinetic, multigeneration-reproduction, teratogenicity and mutagenicity studies, as well as special studies on neurotoxicity and antifertility. Studies were carried out in mice, rats, dogs, marmoset monkeys and in human volunteers. The Committee was also provided with information on the proposed technological applications, stability of the compound and estimated intakes.

The Committee noted a number of effects in the animal studies on TGS and its hydrolysis products whose significance for humans was not absolutely clear. These were, in particular, effects on lymphoid organs, especially spleen and thymus weights, sporadic but not entirely random statistically significant reductions in peripheral white blood cell and lymphocyte counts and weak mutagenic activity of a hydrolysis product.

There was also evidence of increased relative kidney weights and liver weights in some of the animal studies.

Many of these effects could, at least in part, be secondary to decreased food intake as a result of dietary impalatability in treated rats. However, the Committee could not exclude the possibility that these effects were due to a direct toxic action of TGS itself.

Additional information provided to the Committee included comments on growth rate, food consumption and food conversion efficiency ratios, and on the specific biological changes listed, independent reviews of some of the toxicological aspects and additional mutagenicity and impalatability studies.

The Committee accepts that the questionable findings in the 12-month dog study were due to normal predictable age-related changes characteristic of beagle dogs. The Committee was, however, unable to interpret to its satisfaction the results of an additional high dose gavage study in rats designed to exclude the confounding nutritional effects of impalatability of TGS. Therefore the Committee could not establish a no-adverse-effect level. The Committee did not receive convincing evidence that at the lowest dietary level of TGS used in the rat studies, impalatability would entirely explain the observed significant reductions in body weight in the presence of insignificant alterations in food intake and food conversion efficiency ratios. Nevertheless, the Committee accepted that TGS had not shown any serious target-directed organ toxicity and that the sweetener as such possesses no carcinogenic or genotoxic potential.

The finding of increased liver weight and kidney weight in several of the animal studies, in the absence of histological evidence using light microscopy, was not considered to be without toxicological significance despite the sporadic nature of these observations and the frequent absence of any dose-response relationship. Electron microscopy studies and a broader investigational basis of liver enzymes would be essential to clarify the mechanisms underlying these observations.

The decrease in thymus weight observed occasionally in the rat studies were on the evidence provided not entirely explainable by the effects of under-nutrition or stress as these factors were not consistently present in all instances. However, no apparent adverse effect on the function of the immune system had been observed so that in the opinion of the Committee the biological significance of the thymic findings still remain unclear.

In conclusion, the Committee has not been able to resolve all the questions relating to some of the observed treatment-related effects. Furthermore, the interpretation of the available toxicological data does not enable at present a definite no-effect level greater than 0.3% to be established, but its precise value cannot be defined until the Committee has been provided with additional information to clarify the precise role of impalatability in the production of the observed treatment-related effects on body weight, organ weights and haematological parameters. The Committee was particularly concerned with the relevance of the findings relating to thymus and spleen weight and the white cell counts.

The Committee was therefore unable to establish an ADI.

The Committee considered various names suggested for the sweetener. None of the proposals combined the precise chemical descriptions with some basic linguistic simplicity. The name also ought to be different from common names for other foods and food additives to avoid confusion. The Committee noted that the name "sucralose" has been requested as a British-Approved name and for adoption as a WHO international non-proprietary name. Final adoption is subject to freedom from conflict with registered trademarks. A final decision is not expected before May 1989. Until this situation is clarified the Committee decided to use the full chemical name, 4,1',6'-trichlorogalactosucrose or the abbreviation TGS without prejudice to the future adoption of an official name.

Thaumatin

In 1984 the Committee requested that data be provided within three years on a number of questions raised by the Committee.

The Committee notes that the questions have been addressed and that the new information confirms that a satisfying degree of safety seems now to be available.

The Committee concludes that as the additional data on relative organ weights and histopathology of various endocrine organs in the two rat and the dog studies show no consistent treatment-related effects, it is therefore unlikely that digestion in these species produces any neuroendocrine-active small peptides from thaumatin in the diet. The three serum parameters in men exposed for 12 weeks to large doses of thaumatin showed no treatment-related changes. Structural and conformational considerations make it most unlikely that thaumatin will give rise on digestion to neuroendocrine or hormonally active small peptides. In addition there is likely to be only a small exposure to occur from the technologically restricted use of thaumatin in a few food commodities (e.g. in chewing gum and flavourings).

Therefore the Committee agreed that the substance could be considered as acceptable from the toxicological point of view.

SUMMARY OF CONCLUSIONS

Aspartame[1]	ADI 0-40 mg/kg bw (DKP ADI 0-7.5 mg/kg bw)
Isomalt	Acceptable[2,3]
Lactitol	Acceptable[2,3]
Neohesperidine dihydrochalcone	ADI 0-5 mg/kg bw
Stevioside	Not toxicologically acceptable[3]
4,1',6'-trichloro-galactosucrose (sucralose)	Not toxicologically acceptable[3]
Thaumatin	Acceptable[3]
Cyclamate (acid, calcium and sodium salts)	Temporary ADI 0-11 mg/kg bw (expressed as cyclamic acid)
Saccharin (sodium, potassium and calcium salts)	Temporary ADI 0-2.5 mg/kg bw

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1) It is essential that sufferers from clinical phenylketonuria should be informed that this sweetener may be a source of phenylalanine when ingested.

2) Laxation may be observed at high doses. Consumption of the order of 20 g/person/day of polyols is unlikely to cause undesirable laxative symptoms. The level for individual polyols ingested singly is higher in many cases.

3) The term "not toxicologically acceptable" is used either when the existing data suggest undesirable effects when the substance is used in food or when the data are insufficient to assess the safety in use of the additive in food. The reader is referred to the relevant paragraphs in the text for precise details for the use of the terms "acceptable" and "not toxicologically acceptable".

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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON

QUININE

(Opinion expressed 19 February 1988)

TERMS OF REFERENCE

To investigate the safety-in-use of quinine in food and drinks.

BACKGROUND

During 1980 and 1981 the question of the desirability of using quinine as a food additive had been drawn to the attention of the Commission which decided to ask the Committee for its opinion on the question.

In June 1981 the Committee considered a preliminary report on the safety of the substance. Preliminary calculations using the figures in the report to the Committee suggested that the maximum acceptable dose of quinine could be close to the dose which might be ingested from beverages containing quinine. It should be stressed that lack of detailed information in a number of areas made it impossible to determine whether these calculations were realistic.

The Commission, on the Committee's advice, requested information from governments and industry to enable the Committee to verify its calculations, and to enable the Committee to decide whether any further information would be required for the assessment of quinine.

The Committee requested :

1. An adequate 90-day study in the rat.

2. a) Further histological studies on the optic nerves from rats receiving high dose levels in an earlier 90-day study.

   b) More sophisticated audiometric tests in rats at high dose levels.

3. An adequate embryotoxicity and teratogenicity study in the rat.

4. A battery of mutagenicity tests.

5. Adequate information on intake of quinine, as quinine salts and from the use of cinchona extracts, from all sources (not excluding therapeutic use).

6. Technological justification for adding quinine to drinks.

7. Information on the breakdown products of quinine on storage and the toxicity of these breakdown products.

8. A human volunteer study on whether toxicological effects at levels of intake of the order of 100 mg/day would occur. (Information on the effect of quinine on American air force pilots.)

Replies to these questions were received during 1982-1986 and the present report is based on the assessment of these data and the existing data available in the extensive literature on the subject.

CURRENT REVIEW

Quinine is derived from the bark of the cinchona tree and has been used to produce a bitter flavour in soft drinks for more than half a century in many countries.

The medicinal properties of the cinchona bark have been known for many centuries. The first cure of a European from malaria was reported in the 17th century but natives of South America are thought to have known of these properties from very early times.

It became a regular custom for Europeans to take a tincture of quinine as a preventative against fevers in general and malaria in particular. In due course quinine blended with sugar and other flavourings became known as a pleasant and refreshing drink.

Quinine produces an intense characteristic bitter taste in soft drinks such as tonic waters (maximum levels of about 80 mg/1 were proposed to the Committee by UNESDA (Union des Associations de Boissons Gazeuses des Pays membres de la CEE) and bitter citrus drinks (UNESDA proposed maximum levels of about 45 mg/1). A small number of alcoholic aperitifs also incorporate quinine (about 10 mg/1). The Committee was informed by CIAA (Confedération des Industries agro-alimentaires de la CEE) that this ingredient is not used in other foodstuffs.

It was put to the Committee that quinine is unrivalled as a bittering agent because its flavour appears quickly on the palate as the drink is consumed and does not linger in the mouth afterwards, particularly in tonic drinks where the required dry type of bitterness

free from aromatic notes is provided by quinine. Experiments have shown that none of the other bittering agents currently known (for example, those in the Council of Europe's list of flavouring substances) can be substituted for quinine.

Bitter citrus drinks, which occupy a rather small position on the European market compared to tonic drinks, contain more sugar (10 to 12%) than tonic drinks (8.5 to 9.5% sugar). Some manufacturers market bitter citrus drinks with and without quinine, the "bitter" drinks being formulated with the same level of added sugar as the citrus drink without quinine.

Data are available about the consumption of tonic water and bitter citrus drinks in the EEC countries in 1980. From these data it was estimated that the average intake of quinine from soft drinks, spread over the whole population of the EEC is low, 0.26 (0.11-0,26) mg/person/day. However this figure does not show the intake of subgroups of the population, such as the heavy consumers of drinks containing quinine.

On the basis of a market survey in 1979 in Germany (the country with the largest consumption of soft drinks in Europe), an estimate of the average intake of quinine was obtained from the regular consumers of bitter drinks. The amount was 2.9 mg quinine per person/day.

Furthermore a survey is available on the consumption of bitter drinks by different age groups. These data are taken from surveys in the United Kingdom, a country with the largest consumption of bitter drinks. The results showed that children up the age of 15 years consume only 1% tonic and about 5% bitter lemon drinks of the total consumption. It is unlikely that children form a high consumer group of drinks containing quinine.

A comprehensive survey of actual intakes of bitter drinks was presented to the Committee (in summary form only) on sample populations in the United Kingdom and France. In calculating the mean upper quantile consumption of quinine, the maximum intakes figures were used (over-estimation). From the results it seems unlikely that the mean upper quantile of bitter drinks consumers in any Member State will be much higher than 5 mg of quinine per day.

Specifications for the two common soluble forms of quinine (the hydrochloride and sulphate salts) have been prepared by the FAO/WHO Joint Expert Committee on Food Additives (April 1980) and the materials in commerce comply with these specifications.

A 90-day study was carried out to study specifically the ototoxic potential of quinine. Electrocochleographic investigations of effects on hearing and chochlear pathology (with light and electronmicroscopy) were carried out, with dose levels of 0.85 and 200 mg/kg bodyweight. No indication was found for an ototoxic effect, with the different specific tests.

In the earlier 90-day rat study, the optic nerves from control and the highest dose level, 120 mg quinine hydrochloride/kg body weight, were normal.

In monkeys no abnormalities were found at dose levels up to 200 mg/kg bodyweight administered for 3 days.

A large number of mutagenicity tests was carried out in vitro and in vivo systems essentially confirming the absence of genotoxic activity.

Exposed to daylight, especially sunlight, photo-deterioration of quinine takes place. This photo-deterioration is a complex and interactive process in which different reactions take place. The result is an unresolved mixture of early formed photo-products, desoxyquinine, citric derivative of quinine and of desoxyquinine and a desoxyquinine analogue. The kinetics show that these photo-products reach a maximum concentration in tonic in 2 to 3 hours and thereafter the concentration decreases to zero on further exposure. After long exposure to sunlight (over 10 hours) a complex mixture of products is formed. The structures of the major components are the end products of the photo reactions containing the partly-reduced aromatic ring system of quinine.

The unresolved mixture, desoxyquinine, and the citric derivative of quinine and desoxyquinine were tested for mutagenic potential in a micronucleus test and/or Ames test (TA 98, TA 100, TA 1535, TA 1537, TA 1538). No evidence of mutagenic potential was found.

A teratogenicity study with rats and rabbits was carried out in which desoxyquinine was tested by gavage at dose levels of up to 60 and 135 mg/kg bodyweight respectively. The highest dose levels showed some toxic reactions in the parent animals, e.g. decrease in body weight and increase in mortality (rabbit), anorexia, changed behaviour, convulsions, collapse (rabbit) and growth depression and salivation (rat).

These effects were not seen at 37.8 mg/kg body weight (rat) and 40 mg/kg body weight (rabbit).

No significant embryotoxic or teratogenic effects were found. The various developmental stages of the offspring were comparable to the controls.

A large number of case studies and case reports in man have been reported in the medical literature - involving single and repeated doses and attempted abortion. The toxic effects reported included visual and auditory disturbances, dermatitis, purpura and thrombocytopenia. In general doses over 300 mg cause effects as judged from reports on long-term preventive therapy for malaria. Some individuals are more sensitive to quinine per se. There are also reports of hypersensitivity reactions to quinine.

A study was carried out with 10 volunteers, half serving as controls (aerated drink) and the other half receiving tonic water. The total daily quinine intake in the latter group was 120 mg. An extensive medical examination, including ocular and audimetry tests, was performed. No changes in opthalmological parameters or significant audiometric aberrations were found on day 7 or day 14. Haematological and biochemical findings were comparable with controls and no physical changes or differences in ECG were seen. The mean plasma quinine level was 0.55 mg/litre (range 0.35-0.91) on day 7 and on day 14 0.66 mg/litre (0.31-1.15).

Active-duty military pilots were administered 0, 52.5 or 105 mg of quinine per day in tonic water (4.9 and 4 subjects respectively) and tested for audiovestibular- and electronystagmorgraphic functions and for serum quinine levels.

Only the group with 105 mg showed under extremely strenuous conditions abnormalities on electronystagmorgraphy. The mean values of quinine in serum were 0.07-0.08 mg/litre and 0.17-0.26 mg/litre for the low- and high- dosed group respectively.

CONCLUSIONS

The SCF acknowledges that it has been provided with comprehensive additional information and new studies in response to its requests.

The Committee is now assured that no adverse reproductive or teratological effects will result from the use of quinine in bitter soft drinks.

The Committee has also been provided with information on actual and potential intakes of quinine from bitter soft drinks at a European level. The estimated actual intake in European countries is, on average, of the order of 0.26 mg/person/day, and for regular consumers of bitter drinks it is unlikely that the mean daily intake will exceed 5 mg quinine per person/day. This information is reassuring for the Committee and it has noted that intake appears to be restricted to the adult population.

Military jet-pilots consuming 105 mg quinine daily showed, under extremely strenuous conditions, mild adverse effects, but these effects are not considered relevant in the context of the use of quinine as a food additive. For human volunteers under normal conditions 120 mg/person/day gave no effect. This should be considered in relation to the estimated maximum daily intake of 5 mg/person/day in Member States.

Some individuals are hypersensitive to quinine, as occurs with other food components and food additives. These persons should be informed by the specific mention of the presence of quinine on the label.

The Committee sees no objection from a toxicological point of view to the continued use at present levels (up to max. 100 mg/1) of quinine in bitter drinks.

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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON EMULSIFIERS, STABILIZERS, THICKENERS AND GELLING AGENTS

(Opinion expressed 11 November 1988)

TERMS OF REFERENCE

1. To review the data on the safety of certain emulsifiers, stabilizers, thickeners and gelling agents made available since the report of the Committee adopted 8 July 1983[1].

BACKGROUND

2. When the Council Directive on emulsifiers, stabilizers, thickeners and gelling agents[2] was agreed in 1974, a number of issues were left unresolved. Further investigations have been made on a number of substances since the Committee's first review in 1978[3], which were addressed in its 1983[1] report. Following the 1983 Report, the Council decided to prolong the temporary authorisation of a number of substances and to request a review by the Committee of any new data within five years (i.e. before December 1988)[4]

3. The Committee was also asked to re-examine the status of agar agar following discussions which had taken place between a number of governments and the Commission in the context of a possible litigation before the European Court of Justice.

4. The present report concerns the information made available to the Committee since 1983 on the substances concerned.

CURRENT REVIEW

5. The Committee was provided with new data on the following substances:

E 406	Agar agar
416	Karaya gum
479	Thermally oxidized soya bean oil interacted with mono- and di-glycerides of fatty acids
E 413	Tragacanth gum

Specifications were made available to the Committee.

6. A summary of decisions taken on the substances evaluated is contained in Annex I. The assessments of individual emulsifiers, stabilizers, thickeners and gelling agents is contained in Annex II, together with key references.

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[1] Reports of the Scientific Committee for Food, 15th Series (1983).

[2] OJ L 189, 12.7.1974, p.1.

[3] Reports of the Scientific Committee for Food, 7th Series (1978).

[4] OJ L 88, 3.4.1987, p.40.

7. The Council also wished to be assured that the Committee, in its 1983 Report, had evaluated the latest data available on polysorbates. The Committee has received no data which would suggest that in its 1983 opinion that an Acceptable Daily Intake of 0-10 mg/kg bw should be attributed to polysorbates requires modification, nor that its 1983 evaluation had overlooked important data.

FURTHER REVIEWS TO BE UNDERTAKEN

8. The Committee wishes to point out that while the evaluation in its reviews of 1978, 1983 and the present review remain valid, a number of developments have taken place in other fora on the use of terms to denote acceptability (or lack of acceptability) of substances used as food additives. The Committee is presently addressing this question in a general way and recommends the Commission that the Committee re-examine the terminology used in the evaluations of food additives when this general review is completed late in 1988.

9. The Committee is also aware that data on tara gum and gellan gum have been submitted by industries concerned to inlcude these gums in the list of emulsifiers, etc. permitted in the Community.

Annex I

Summary of Evaluations

Agar agar	ADI : not specified*
Karaya gum	ADI : 0-12.5 mg/kg bw
Thermally oxidized soya bean oil interacted with mono- and diglycerides of fatty acids (TOSOM)	ADI : 0-25 mg/kg bw
Tragacanth gum	ADI : Not specified*

*It should be noted that when a numerical ADI value has not been specified for a substance, this does not mean that any amount of the substance would necessarily be toxicologically acceptable.

It simply means that, on the basis of the available toxicological, biochemical and clinical data, the total daily intake of the substance arising from its use or uses at the levels necessary to achieve the desired technological effect will not in any circumstances represent a hazard to health. For this reason, the establishment of a numerical limit for the ADI is not considered necessary for these substances.

Any substantial deviations from current use levels as a food additive would require a revision of the evaluation.

In the case of vegetable gums, it should be noted that the evaluation only accounts for uses of the gums as additives to achieve a technological effect in the food and not uses for special dietary or medical purposes, where the use level is likely to be much higher.

Annex II

Assessments of individual substances

Agar agar

The Committee reviewed all the available studies on agar. These included acute, sub-acute, teratology, carcinogenicity and mutagenicity studies. Generally these studies showed no toxic effects at the highest doses utilised. There was no evidence of any teratogenic effect or other adverse effects on reproductive performance. Mutagenicity studies (in vitro and in vivo) showed no evidence of mutagenic activity. Carcinogenicity studies in rats and mice using agar at up to 5% in the diet showed no evidence of any carcinogenic or tumorigenic effect, and no other treatment-related effects were noted in these studies.

One study on the effect of agar on dimethylhydrazine-induced colon carcinoma in the mouse showed that the addition of 8% agar to the diet enhanced the carcinogenic activity of parenternally-administered dimethylhydrazine. The degree of enhancement was relatively modest, and similar to the effect of a high fat diet. The Committee did not consider that these studies were relevant to the food additive use of agar, and they did not provide any evidence that the use of agar would be hazardous, particularly in view of the negative carcinogenicity studies on agar itself.

It has previously been suggested that agar or certain macromolecular constituents of agar might be absorbed from the diet and accumulate in the body. However the long-term carcinogenicity studies showed no histological changes indicative of tissue accumulation, and the Committee did not consider that there was any evidence that significant amounts of absorption and tissue deposition occurred. Preparations of agar have also been used as a laxative, though their efficacy for this purpose is doubtful. However the Committee did not consider that the use of agar as a food additive at low concentrations in the diet could give rise to any adverse laxative effects.

In view of the fact that agar is devoid of toxicity at the highest dose levels used, the Committee does not consider it necessary to specify an ADI.

The Committee notes that the common level of use of agar in food is generally around 1%-2%.

Karaya gum

The Committee reviewed the available studies on acute and subacute toxicity, on metabolism, teratology and on the effects of administration to man. Adequate studies on chronic toxicity and carcinogenicity were not available. The Committee had requested an additional study in a non-rodent species in order to assess whether this gum could be evaluated along similar lines to other natural gums and possibly establishing an ADI not specified. The Committee received the results of a study in monkeys which did not supply the additional information originally requested.

As this gum is practically not digested or degraded in the human gut, the Committee established an ADI of 0-12.5 mg/kg bw/day. The Committee used a higher than usual safety factor to take into account the limited value of the study in monkeys.

The Committee noted that there is a comparatively minor use of this gum in food.

Thermally oxidized soya bean oil interacted with mono- and di-glycerides of fatty acids (TOSOM)

The Committee has examined the results of a combined study of chronic toxicity and carcinogenesis (2.5 years) carried out in rats in accordance with the current standards applying to toxicological practice.

These results are further to those obtained from earlier acute and chronic toxicity and reproduction studies carried out in rats before 1970, to a subchronic study carried out in pigs in 1969 and to a subchronic study carried out in rats in 1981. These data as a whole, together with a metabolism study that it had already examined have caused the Committee to adopt for the TOSOM a no-effect dose of 2.5 g/kg by body weight per day and thus to retain an ADI of 0-25 mg/kg of body weight.

Although the effects observed with high intakes of TOSOM are of debatable toxicological significance, this attitude has been adopted in the light of the complexity of that additive's composition, which is likely to vary within limits depending upon the specifications adopted.

The specifications for TOSOM were discussed by the Committee and considered adequate to ensure that any product meeting them would have a composition close enough to that of the TOSOM used during the toxicological tests to enable the assessment based on their results to be applied to it.

Tragacanth gum

The Committee reviewed all available studies on tragacanth gum. These included acute, subacute, teratology, reproduction, mutagenicity and sensitisation studies. Overall, these studies showed no toxic effects at the doses employed. There was no evidence of any adverse effects on reproductive performance or of any teratogenic effect in several species. In vitro and in vivo studies in bacterial, fungal and mammalian cells showed no evidence of genotoxic activity. No chronic toxicity or carcinogenicity studies were available.

Changes in liver microsomal enzyme activity and in the oxidative phosphorylation function of heart and liver mitochondria reported in an earlier study, could not be confirmed in more recent investigations which also included ultra-structural observations.

Relatively high levels of tragacanth gum are well tolerated by man. Earlier reports of allergic reactions were not substantiated by recent studies which showed no evidence of specific immune responses to this gum.

Evaluation of the toxicological evidence and limited present use of this gum enabled the Committee to establish an ADI "not specified" for this gum.

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