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food - science and techniques

Reports of the Scientific Committee for Food

(Sixteenth series)

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REPORT OF THE SCIENTIFIC COMMITTEE FOR FOOD ON SWEETENERS

(Opinion expressed 14 September 1984)

TERMS OF REFERENCE

To review the safety in use of certain sweeteners.

BACKGROUND

The Commission is presently developing proposals for legislation on a number of categories of additives for which, as yet, there are no Community rules. The Committee was asked by the Commission to assist by giving an opinion on the safety of the additives included in the Commission's review. Sweeteners are among the additives included in the review.

Sweeteners fulfil several special roles in the diet. They may be food additives, a replacement for sucrose, or tabletop sweeteners, thus complicating their evaluation in terms of safety. Furthermore, the legislative control of sweeteners and their permitted uses in particular foods vary considerably within the Community. Thus it was decided to prepare a separate report on sweeteners, to be published in advance of the general review on additives not yet assessed by the Committee. Added impetus for an early report on sweeteners by the Committee has derived from the availability of a large body of new information on the safety of substances in this class.

The class of sweeteners included in the review comprises substances ranging from products that could be considered almost as foodstuffs in their own right to substances which due to their "intense" sweetness produce their required effect in minute quantities. It is generally accepted that alternative non-carbohydrate sweeteners fall conveniently into two types based on their relative sweetness compared to sucrose. Those substances with a sweetness "value" similar to sucrose may be called "bulk" sweeteners.

The Committee was advised that there is interest in the following bulk sweeteners:

Isomalt
Lactitol
Maltitol and maltitol-based products (hydrogenated glucose syrups)
Mannitol
Sorbitol
Volemitol
Xylitol.

Similarly, interest has been expressed in the following intense sweeteners:

Acesulfame potassium
Aspartame
Cyclamic acid and its calcium and sodium salts
Glycyrrhizin
Miraculin
Monellin
Neohesperidine dihydrochalcone

Saccharin and its calcium, sodium and potassium salts
Stevioside
Thaumatin.

A summary of the evaluations is given in Annex 1. Individual assessments are given in Annex 2.

Societal demands for innovations and the changing pattern of lifestyle has stimulated the food industry to provide foods different from traditional products. Modified food ingredients, e.g. certain polyol-based sweeteners, play an important role in the development of such products.

In the Committee's opinion these developments require to be kept under review, bearing in mind their potential nutritional implications and the effect of bulking agents, fibre, modified starches, etc. on the gut microflora. These questions have not been addressed in detail in this report but should be researched in the future. The Committee would like to review the state of knowledge in three years.

In considering the safety of sweeteners the Committee has also taken some account of the advantages to the consumer from the availability of sweeteners other than sugar. Some sweeteners have other technological functions. The Committee has evaluated these substances only in the context of their use as sweeteners.

NUTRITIONAL CONSIDERATIONS

Sucrose has been a sweetener for centuries but sugar consumption has increased considerably since the beginning of the 20th century, particularly in the north of Europe and in Anglo-Saxon countries (FAO, 1980). Although the proportion of energy supplied by total ingested carbohydrates decreases generally with rising income, there has been a sharp rise in the portion of energy supplied by sucrose.

Sucrose plays a role not only as a source of energy. It increases insulin demand and is an important factor in the aetiology of dental caries, but whether it is the major one remains controversial. In the opinion of many nutritional experts, some control of sugar consumption is indicated. This is essential for diabetics but applies also to individuals whose body weight is excessive, and is of importance for the dental health of the general population.

If it is desirable to reduce sugar consumption, several approaches are possible. Some nutritionists think that sustained educational efforts might alter eventually the dietary preferences of the population in relation to sweet foods. Foods and beverages simply with reduced sucrose content might therefore become more acceptable to the general consumer.

Non-carbohydrate sweeteners provide an alternative. Among these, polyols have approximately the same heat of combustion but are not absorbed nor metabolised to the same extent as sucrose, and thus their bioavailable energy is less than that of sucrose for most of them.

Intense sweeteners offer technological advantages in ordinary foods and in foods for special nutrition purposes, especially low-energy foods. Some of these sweeteners may be a source of calories, but at the technologically effective dose, none of the intense sweeteners will make a significant contribution to the energy value of the food in which they were to be incorporated as the levels of use are so low.

PATHOPHYSIOLOGICAL CONSIDERATIONS

On the available evidence none of the bulk sweeteners can be regarded as non-cariogenic. If a partially-fermentable sweet substance is substituted for sucrose or other fermentable carbohydrate, significant reductions in the incidence of dental caries might reasonably be expected. Such an effect is also achievable with intense sweeteners. On the basis of the available information, it is clear that the polyols resist fermentation by oral bacteria to various degrees. Studies made with animals and human volunteers provide support for the link between non-fermentability and non-cariogenicity. Four bulk sweeteners, namely hydrogenated glucose syrup, isomalt, sorbitol and xylitol have proved to be less cariogenic than sucrose in both animal and human experiments.

Some bulk sweeteners cause laxation and flatulence. The general nature of the laxative effect, sometimes known clinically as "osmotic diarrhoea", indicates that the condition results from osmosis across the intestinal wall owing to the presence in the lumen of unabsorbed bulk sweetener and its metabolites. The amounts of the various sweeteners required to cause laxation depends upon the sweetener, whether the dose is spread over a number of meals or consumed all at once, whether the person or animal receiving the dose is fasting or not, and on individual differences in susceptibility to the laxative effect of these sweeteners. For example, young children, 2-3 years of age, tend to be more susceptible than children of 5-6 years of age to the same dose calculated on a g/kg bw basis. Moreover, the susceptibility of individuals to the laxative effect varies considerably as shown by human studies, in which sensitive individuals experience an effect at intakes of 10 g, while others can tolerate 90 g or more without adverse effects. The phenomenon of adaptation to the laxative effect of bulk substances has also been observed in animals and man. On the available evidence a consumption of the order of 20 g of polyols per day is unlikely to cause any undesirable laxative symptoms.

The Committee recommends that control be exercised to limit the consumption of polyol-containing sweeteners from all sources to levels below those at which they induce diarrhoea. The Committee is also of the opinion that these substances should not be used in foods specially prepared for infants and young children (up to 3 years of age).

The problems associated with the way in which consumers are to be informed require further study by the appropriate authorities. The medical profession should be aware that excessive ingestion of polyol-based sweeteners may cause such undesirable effects. Diabetics represent a population group which may be particularly exposed to polyol sweeteners.

TECHNOLOGICAL CONSIDERATIONS

(a) General considerations

Sweeteners also have technological functions such as water retention or provision of bulk. Sucrose fulfils all these three functions when added to food. The alternative sweeteners all provide sweetness but some may have other properties which can be harnessed to perform additional functions in food. Other alternative sweeteners, weight for weight, are hundreds or even thousands of times as sweet as sucrose. Consequently, at the dilutions these substances must be used in food to avoid excessive sweetness, any other functions which they may perform are lost.

Relative sweetness is subjective; it is dependent upon a number of factors. The relative sweetness of an intense sweetener decreases as its concentration in food is increased. It is also affected by temperature and by other substances consumed at the same time. Consequently, when determined by comparisons between aqueous solutions of sucrose and aqueous solutions of the substance, it can only be used as a rough guide to the likely sweetness of the substance in food. It provides, however, a useful comparative guide under well-defined conditions.

Alternative sweetener	Approximate sweetness (sucrose = 1)
Acesulfame K	200
Aspartame	200
Cyclamate	30
Dihydrochalcones	300-2 000
Glycyrrhizin	50-100
Mannitol	0.7
Monellin	1 500-2 000
Saccharin	300
Sorbitol	0.54-0.7
Stevioside	300
Thaumatin	2 000-3 000
Xylitol	1

(O'Brien and Gelardi, 1981).

(b) Bulk sweeteners

Some bulk sweeteners have a negative heat of solution. This property means that they require heat for dissolution which is obtained from their surroundings, resulting in a cooling effect. When dissolved in the mouth a "mouth-cooling effect" is generated. Xylitol, sorbitol and mannitol exhibit this property to different degrees. Bulk sweeteners are also used because of their action as humectants, to reduce caramelization, and to provide body and mouth feel in soft drinks. In certain ice-creams, bulk sweeteners may replace sucrose because of their technological advantage in preventing the development of a gritty texture from crystallization at low storage temperatures.

(c) Intense sweeteners

Only low levels of the intense sweeteners are necessary to provide the desired sweetness in food. They make no significant contribution to the bulk of the food.

In a way similar to the bulk sweeteners, intense sweeteners can be used in frozen food as a partial or total replacement for sucrose to overcome certain problems associated with high carbohydrate concentrations. Such food is difficult to freeze because of the freezing point depression of water and intense sweeteners are a useful alternative to high carbohydrate levels for these foods.

By allowing the carbohydrate content to be reduced, intense sweeteners can improve the texture of certain foods. For example, the mouth feel of soft drink requiring a high degree of sweetness can be made more acceptable by using intense sweeteners to replace some sucrose. In addition, water-ices containing high levels of sucrose tend to be sticky and suffer from surface crystallization. This may be overcome by intense sweeteners partially replacing sucrose. Certain concentrated soft drinks require intense sweeteners to supplement their sweetness and maintain the cloudy nature of the product. Lowering the density of the solution by partial replacement of the sucrose overcomes the tendency for separation of some components of the drink during storage.

TOXICOLOGICAL CONSIDERATIONS

Special considerations relating to polyols

Polyol sweeteners are prepared by hydrogenation of carbohydrates. Their comparatively high level of incorporation in prepared foods prevents their incorporation at 100-fold or higher levels in the diet of test animals. The dietary imbalance produced by feeding large doses of polyols to experimental animals is associated with physiological and metabolic disturbances including effects on calcium uptake and excretion. The renal pelvic nephrocalcinosis, adrenal medullary hyperplasia and phaeochromocytomata observed in these studies may be secondary to such disturbances and the Committee considered these findings to be of doubtful relevance to the evaluation of the safety to man of these compounds.

The Committee recognizes the difficulties which may arise from testing modified food ingredients in the same manner as food additives in animal feeding studies. Inclusion of inherently non-toxic substances at high dietary levels in an attempt to demonstrate any potential toxic effect and establish a dose-response relationship, may result in non-specific effects due to dietary imbalance, while failing to achieve the 100-fold higher experimental dietary level compared with likely human intake, necessary for establishing an ADI with a safety factor of 100, because of the relatively high levels (1% or more) of incorporation of these substances into human food. In the Committee's opinion it would be inappropriate to establish an ADI for polyols.

The Committee considered it similarly inappropriate to establish an ADI for maltitol and maltitol-based sweeteners (sometimes known as hydrogenated glucose syrups) composed essentially of maltitol, sorbitol and glucose. The commercial products for which specifications are available vary from liquid syrups to crystalline solids containing 55% to 95% maltitol, 5% to 20% maltotriitol, up to 8% sorbitol and hydrogenated tri- to

heptasaccharides and higher polysaccharides. The Committee would wish to evaluate any maltitol-based products containing individual polyols or other by-products not found in the products assessed in this report.

In accepting the continued use of polyol-based sweeteners the Committee emphasized that this should not be interpreted as meaning the acceptance of unlimited use in all foods at any technological level but that the laxative effects should be borne in mind.

ANNEX 1

SUMMARY OF EVALUATIONS OF SWEETENERS

Acesulfame K	ADI	0-9 mg/kg bw
Aspartame** (DKP ADI 0-7.5 mg/kg bw)	ADI	0-40 mg/kg bw
Cyclamate (acid, calcium and sodium salts)	Temporary ADI	0-11 mg/kg bw (expressed as cyclamic acid)
Glycyrrhizin	Not toxicologically acceptable	
Isomalt	Acceptable*	
Lactitol	Acceptable*	
Maltitol (and maltitol-based products)	Acceptable*	
Mannitol	Acceptable*	
Miraculin	Not toxicologically acceptable	
Monellin	Not toxicologically acceptable	
Neohesperidine dihydrochalcone	Not toxicologically acceptable	
Saccharin (sodium, potassium and calcium salts)	Temporary ADI	0-2.5 mg/kg
Sorbitol	Acceptable*	
Stevioside	Not toxicologically acceptable	
Thaumatin	Temporarily acceptable	
Volemitol	Not toxicologically acceptable	
Xylitol	Acceptable*	

*Laxation may be observed at high intakes. Consumption of the order of 20 g/person/day of polyols is unlikely to cause undesirable laxative symptoms.

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

ASSESSMENT OF INDIVIDUAL SWEETENERS

These assessments are arranged in alphabetical order for ease of reference.

Acesulfame potassium (Acesulfame K)

This artificial sweetener is the potassium salt of 3,4-dihydro-6-methyl-2,2,4-trioxo-1,2,lambda,3-oxathiazin-3-ide.

The Committee was provided with extensive toxicological data including metabolic, long-term, reproduction and teratology studies. The long-term studies in the rat and mouse did not show any dose-related increase in specific tumours nor any treatment-related pathological changes of significance. The compound was not genotoxic in several *in vitro* and *in vivo* mutagenicity studies and does not bind covalently to DNA. Acesulfame K does not interact with model food constituents.

In aqueous solutions, hydrolytic decomposition occurs only after prolonged storage under extreme conditions of temperature and pH which are not likely to occur under normal conditions of use. Acetoacetamide and its N-sulphonic acid are then found as decomposition products in the acid range. Acetoacetamide has been examined for acute toxicity and for mutagenicity in *in vitro* tests only. No data are available on the toxicology of the N-sulphonic acid of acetoacetamide.

The highest level tested in rats and dogs was 3% in the diet and may be considered as the no-adverse-effect level, equivalent to 1 500 mg/kg bw in the rat or 900 mg/kg in the dog. The Committee therefore established an ADI of 0-9 mg/kg bw based on the data from the dog, the most sensitive species.

Aspartame

The chemical name of this artifical sweetener is (3s)-3-amino-N/(alpha s)-alpha-methoxycarbonyl-phenethyl/ succinamic acid. Structurally it is N-L-alpha-aspartyl-L-phenylalanine methyl ester.

A very large amount of toxicological data covering acute, subchronic, long-term, reproduction, metabolic and mutagenicity studies were evaluated, including the investigation of neurobehavioural effects. The Committee also reviewed the extensive stability data provided as well as metabolic, acute, long-term and mutagenicity studies on the conversion product of aspartame 5-benzyl-3,6-dioxo-2-piperazine-acetic acid (diketopiperazine DKP). This substance is found in aspartame-containing beverages stored at elevated temperatures. The Committee's critical review of the long-term studies established that the scattered findings of significant deviations from control values showed no consistent relationship to treatment, sex of animals or histopathology, so that 4 000 mg/kg bw could be considered as a no-adverse-effect level for these studies.

The multigeneration reproduction and teratogenicity studies showed consistent adverse effects on the weight of progeny, both at weaning and at terminal examination, at the highest dose levels tested.

The Committee reviewed additional information on the multigeneration reproduction and teratogenicity studies, including recalculations of the actual intake by the offsprings, which suggested the consumption by the pups of levels higher than which would follow from the composition of the test diets. The Committee noted the observed growth depression in the progeny was marginal and related to a decrease in food consumption caused by a high intake of phenylalanine. In the light of these findings the Committee concluded that 4 000 mg/kg bw could be considered as the no-adverse-effect level also in these studies.

The Committee also reviewed the recent evidence on the effects of aspartame in combination with refined carbohydrates on behaviour and mood. It concluded that the data provided no evidence that the occasional transient changes in blood amino acid levels, following simultaneous ingestion of aspartame and glucose, could produce changes in neutrotransmitter levels which might affect mood or behaviour.

The Committee saw no reason for concern over the amounts of methanol likely to be produced by the metabolism of aspartame when compared with those present naturally in food.

The Committee also considered the effects of the phenylalanine contribution, following consumption of aspartame, on individuals heterozygous for phenylketonuria (PKU) and on individuals with variants of PKU causing benign hyperphenylalaninaemia. The blood levels of phenylalanine in these individuals were raised only slightly and none of them showed any neurological or other clinical abnormal findings, thus supporting the view that large intakes of aspartame in the diet would not cause any untoward effects in these genotypes. Foetal effects from excessive maternal aspartame consumption by pregnant women heterozygous for PKU were not likely in view of the available data on phenylalanine levels in maternal blood. It is however essential that sufferers from clinical PKU should be informed that this sweetener may be a source of phenylalanine when ingested.

The Committee therefore established an ADI of 0-40 mg/kg bw for aspartame and an ADI of 0-7.5 mg/kg bw for DKP.

Cyclamic acid and its sodium salts

The systematic chemical name of cyclamic acid is cyclohexylsulphamic acid.

Its microbial metabolite is cyclohexylamine, chemically cyclohexanamine.

The Committee reviewed an extensive collection of toxicological studies on cyclamates, cyclohexylamine and dicyclohexylamine. These covered all aspects ranging from metabolism to long-term carcinogenicity and reproductive function studies. They also included recent studies on cyclohexylamine, a metabolite of cyclamate produced by the gastro-intestinal microbial flora in some individuals, concerned with its toxic effects on the testis and on

reproduction in the rat as well as with its embryotoxic effects in mice. The recent long-term studies have resolved the question of carcinogenicity raised by the earlier long-term study.

The precise mechanism of the testicular damage in rats is still unknown but recent metabolic studies suggest that the rat metabolises cyclohexylamine differently from man and mouse and that the testicular changes observed in the rat may be related to the particular metabolites in this species. Further work on these aspects is in progress. The degree of absorption of cyclamate from the gut appears to be up to 37%. Of the unabsorbed cyclamate, some 30% may be converted to cyclohexylamine but the proportion of human converters is small. A few individuals may convert up to higher percentages, but the safety factor allows for particularly sensitive subgroups of the population. A very carefully executed 90-day feeding study of cyclohexylamine in rats produced a no-adverse-effect level of 100 mg/kg bw with respect to testicular damage as parameter. Although there was a decrease in bodyweight at 50 mg/kg bw, the mean percentage decrease was only significant at the next highest dose (200 mg/kg bw). The only available long-term feeding study with cyclohexylamine in the rat suggested 30 mg/kg bw as NEL for testicular damage, but the scoring system for this effect was less comprehensive.

In view of the existing areas of uncertainty relating to the relevance for man of the testicular damage found in rats fed cyclohexylamine, the Committee decided to base its assessment on the NEL of 100 mg/kg bw in the recent extensive 90-day study. The Committee felt that there was an adequate additional safety margin in the estimation of the conversion rate of cyclamate to cyclohexylamine in man to allow for the use of the usual 100-fold safety factor and to establish a temporary ADI of 0-11 mg/kg bw, expressed as cyclamic acid, for cyclamic acid and its salts. The Committee wishes to review the situation when the results of the further investigations in progress have become available.

Glycyrrhizin

Most commercially available liquorice is an extract prepared from the roots and rhizomes of glycyrhiza glabra L. Glycyrrhizin is an important biologically active constituent of liquorice. It is a saponine in which the aglycone, glycyrrhetic acid, is linked to B, B'-glucuronidoglucuronic acid. Glycyrrhetic acid is 3-B-hydroxy-11-oxoolean-12-en-30-oic acid.

The Committee was informed on the use of this material as a flavouring agent and sweetener. The Committee reviewed studies on the pharmacological and steroidal effects, on the effects of acute, subacute and subchronic administration in laboratory animals as well as on teratology, metabolism and mutagenicity. It also considered a large number of clinical reports following therapeutic use. The animal data were largely concerned with resolving the medical problems arising from excessive ingestion of liquorice preparations. The available data were inadequate for a toxicological evaluation of the substance as a sweetener but the findings from clinical toxicology revealed the possible need to restrict the consumption of liquorice. The Committee was informed of new studies now in progress and wished to be provided with the results. Meanwhile the Committee is unable to endorse its use as a sweetener and suggests a further assessment of the total usage.

Isomalt

This bulk sweetener is an equimolecular mixture of 6-O-alpha-D-glucopyranosyl-D-glucitol and 1-O-alpha-D-glucopyranosyl-D-mannitol.

The Committee reviewed the available information which included acute and subchronic studies, studies on metabolism in various species including man, studies on the effect on the gut flora and absorption of various nutrients. A lifespan study in rats with in utero exposure, a carcinogenicity study in mice, a multigeneration reproduction study and teratogenicity studies were also available for evaluation. Mutagenicity was studied only in a Salmonella reverse mutation test. No carcinogenicity was demonstrated in several studies.

No laxative effects were noted in man at 10-20 g/day. The material is incompletely hydrolysed in the small intestine to glucose, sorbitol and mannitol. Further metabolism by the microbial flora of the large gut results in complete disappearance of the sweetener from the faeces. High doses fed over lifespan result in caecal enlargement and renal pelvic nephrocalcinosis, effects also observed with other polyols (see "Pathophysiological Considerations"). The Committee did not consider it appropriate to establish an ADI for this bulk sweetener but considered its use acceptable provided the limitations due to the laxative action were kept in mind.

Lactitol

This substance is 4-O-beta-D-galactopyranosyl-D-glucitol. It is produced by the catalytic hydrogenation of lactose.

The Committee was provided with the results of acute, subchronic, metabolic, multigeneration reproduction, teratology and long-term carcinogenicity studies in several species including mice, rats and dogs. The results of a Salmonella/microsome reverse mutation test and an *in vitro* test on human lymphocytes, of some cariogenic studies, and of tolerance studies in man were also available. Lactitol is metabolised to galactose and sorbitol, partly in the upper intestinal tract, and also by the microbial flora of the large intestine. The implications of the observed effects on the kidneys and adrenals are discussed under "Toxicological Considerations". Human studies showed that lactitol was hydrolysed at a slow rate and caused diarrhoea at an intake of about 50 g/day. The Committee did not consider it appropriate to establish an ADI for lactitol, but considered its use acceptable provided the limitations due to its laxative action were kept in mind.

Maltitol and maltitol-based products

The Committee was informed that the commercially available products are mixtures of substances obtained from food grade raw materials following enzymatic hydrolysis to high-maltose-containing glucose syrups and subsequent catalytic hydrogenation to reduce all free aldehyde groups. The commercial products vary from liquid syrups to crystalline solids, containing from about 50% maltitol (4-O-alpha-D-glucopyranosyl-D-glucitol) and hydrogenated tri- to heptasaccharides and higher polysaccharides.

The range of minor components in the products evaluated is similar.

The Committee considered a large number of studies, the bulk of the data having been obtained on a product containing about 55% of maltitol. Other data related to products with a maltitol content between 60 and 95%. The studies referring to the product with 55% maltitol were adequate and comprised acute toxicity, subchronic toxicity in two species, a large number of mutagenicity tests, metabolic investigations and several clinical tolerance studies. The studies referring to products with a maltitol content ranging from about 60 to 95% covered acute and subchronic toxicity, carcinogenicity, multigeneration reproduction, teratogenicity, metabolism, mutagenicity, clinical tolerance in man and cariogenicity. However, many of these latter studies were inadequate in terms of modern toxicological requirements. The only studies on pure maltitol available to the Committee were studies on the metabolism of radiolabelled maltitol in the rat and man.

The metabolic studies indicated that the maltitol component was slowly but completely metabolised into glucose and sorbitol in rats and man, particularly by the intestinal flora. The considerable data base on sorbitol was also used by the Committee for the evaluation of these products. A multigeneration reproduction study without a teratological component has been performed only with the low maltitol product but this study did not conform to present-day protocols. An adequate teratology study was carried out on the high maltitol product. The available mutagenicity studies on several high maltitol products showed no genotoxic potential. The existing human tolerance studies showed a laxative effect at intake levels of 30-50 g/day.

The Committee considered it inappropriate to establish an ADI for these products but considers the continued use of maltitol and maltitol-based products acceptable provided the limitations due to their laxative action were kept in mind. The Committee did not require a long-term study on these compounds in view of the metabolic fate and the fact that long-term studies on the metabolite sorbitol are already available but draws attention to its comments on modified food ingredients (under "Background").

Mannitol

This polyol is a 1,2,3,4,5,6-hexanehexol. It is prepared by the reduction of glucose. The Committee reviewed studies on the metabolism in man and rats, on acute toxicity, limited studies on subchronic toxicity, several long-term feeding/carcinogenicity studies in rats and mice, a teratology study and the results of several mutagenicity tests. No multigeneration-reproduction study was available. Data on human tolerance were also considered. This polyol is poorly absorbed and considerable clinical experience exists in

man. Laxative effects have been reported with doses as low as 10-20 g. The implications of the observed effects on adrenals and kidneys are discussed under "Toxicological Considerations". The Committee considered it inappropriate to establish an ADI, but has no objection to the continued use of this sweetener provided the limitations due to its laxative action are kept in mind.

Miraculin

This substance is a glycoprotein of uncertain composition extracted from the West African miracle fruit (Synsepalum dulcificum). It is a taste modifier that makes acid foods taste sweet, if a drop is chewed prior to eating. The sweet taste may last up to two hours after ingestion.

The Committee was not provided with the full data nor was the identity of the substance tested clarified. The Committee was therefore not able to assess the safety of this substance.

Monellin

This protein comprises two non-identical polypeptide chains containing a total of about 90 amino acids. It is present in the West African serendipity berry (Dioscoreophyllum cumminsii) from which it is extracted by a complex process. No toxicological data were available to the Committee on which to base an assessment.

Neohesperidine dihydrochalcone

This compound is a flavanone glucoside prepared from naringin by various chemical processes. It is a member of the dihydrochalcones, which are sweeteners derived from the bioflavonoids of citrus fruits and which all share the same basic chemical structure as the component responsible for sweetness.

The Committee reviewed studies on the metabolism, acute toxicity, subchronic toxicity, multigeneration reproduction, teratogenicity, and chronic toxicity. Several in vitro and in vivo mutagenicity studies were also available. Neither of the chronic toxicity studies in rats and dogs established a clear no-adverse-effect level. The Committee was therefore unable to assess the safety of this sweetener until a no-adverse-effect level was established in an adequately conducted 90-day study in the rat.

Saccharin and its sodium, potassium and calcium salts

This sweetener is 1,2 benzisothiazol-3(2H)-one-1,1-dioxide.

The Committee reviewed a large number of studies which had become available since its first report on this substance in 1977. A temporary ADI of 0-2.5 mg/kg/day was then established by the Committee but it also recommended that the situation should be kept under review and that this ADI should be reassessed after ongoing studies had been evaluated. Many of these studies, which are now available, were concerned with the promotional effects of saccharin on bladder carcinoma, including human epidemiological data and an extensive long-term feeding study in rats. No further long-term studies were done in the mouse. Saccharin is not genotoxic in mutagenicity studies and is not metabolised by man. The recent long-term study in male rats showed that exposure from birth results in a dose-dependent production of bladder tumours. The difference in the incidence of tumours in the 1% test group compared to controls was not statistically significant, so that the 1% dietary level appears to be a possible no-effect level.

In promotional studies on bladder tumours, no statistically significant difference was observed at the 0.04% level under the conditions of the tests, but their relevance for man is not known. Recent studies in man have shown that the effect of saccharin on the production of indican, a promoter for bladder tumours, by the intestinal bacteria may differ quantitatively for the rat and man, making the findings in rats of questionable significance for man. Epidemiological studies have also not established any evidence that bladder cancer in man is associated with saccharin intake; this is the only association examined.

The Committee therefore decided to maintain the temporary ADI of 0-2.5 mg/kg bw/day, allocated in 1977, but that the situation should be kept under review and that the ADI should be reassessed after the Committee had evaluated the results of ongoing studies on:

(a) the report to be published on the outcome of the two-generation study in hamsters recently completed,

(b) the mechanism of the effect of saccharin on the bladder in the male rat,

(c) the comparability of the rat and human bladder in relation to differences in metabolism and local effects.

Sorbitol

This sweetener is a 1,2,3,4,5,6-hexanehexol.

It is present in a wide variety of fruits, berries and plants. It is produced commercially by hydrogenating dextrose.

The Committee considered the numerous available studies which included metabolic, acute subchronic, two chronic toxicity studies in rats and one in dogs, a three generation reproduction and teratogenicity study. The Committee also reviewed several mutagenicity studies. Extensive human data exist on the use of sorbitol in foods for special nutritional purposes for diabetics, and on human tolerance studies. Laxative effects were noted at intake levels above 50 g/day. The comments on the effects of polyols on calcium metabolism and on laxation apply equally to sorbitol. The Committee did not consider it appropriate to establish an ADI for sorbitol but had no objection to the continued use of this sweetener provided the limitations due to its laxative action were kept in mind.

Stevioside

This sweetener is one of the glycosides isolated from the leaves of Stevia rebaudiana (Bert.) Hemsl. It is an ester of steviol, beta-D-glucosyl and beta-D-sophorosyl groups.

The Committee reviewed the available studies on the pharmacological activity of crude extracts of leaves of Stevia rebaudiana, acute and subchronic toxicity and on mutagenicity. A chronic toxicity combined with carcinogenicity study is in progress. The available reproduction study did not indicate any effect on fertility but only one generation was studied. Little data are available on metabolism. The Committee was not able to assess the safety of stevioside as many of the data referred to inadequately specified materials. The results of long-term and reproduction studies as well as metabolism data are required on a specified material before a safety assessment can be made by the Committee.

Thaumatin

This sweetener is a mixture of closely related sweet proteins extracted from the fruit of the West African plant Thaumatococcus daniellii. It is one of the sweetest substances known, its sweet taste developing slowly but being of long duration. The Committee was informed that the whole seed of the fruit has a history of native use in West Africa. The

main active agents are the proteins thaumatin I and thaumatin II, both of which have a relative mass of about 20 000. They are rich in basic amino acids with an isoelectric point of about pH 11, but they do not contain histidin. Thaumatin is used in food at various levels up to about 30 ppm resulting in an estimated daily intake of 1-2 mg per person/day. This is very different from the intakes experienced with other intense sweeteners. The available studies cover the nature and consumption of the sweetener, the nature and sequence of the constituent amino acids, allergenicity, digestibility, mutagenicity and the absence of other foreign protein. The existing subchronic feeding studies are reassuring regarding the safety of this protein. The question of receptor binding and possible endocrine activity was raised. Some reassuring information was provided, particularly on the relationship between intact natural protein configuration and sweetness; however, some uncertainty remains on the potential for such activity. The Committee did not establish an ADI, but considered the substance to be temporarily acceptable until the situation has been clarified. The Committee wishes to review the situation within three years.

Volemitol

No information on this compound was supplied to the Committee which was therefore unable to evaluate its safety.

Xylitol

This polyalcohol is a xylopentane-1,2,3,4,5-pentol.

It occurs in certain fruits and vegetables, and is formed in the body as intermediate in the metabolism of carbohydrates as part of the pentose phosphate shunt.

The Committee reviewed studies on the metabolism, acute and subchronic toxicity, and on chronic toxicity in rats and dogs, as well as a three generation reproduction study in rats, teratogenicity studies and the results of several *in vitro* and *in vivo* mutagenicity tests. Extensive human data on the tolerance of orally administered xylitol were also reviewed. Xylitol was non-genotoxic. The changes in metabolism and physiology associated with large intakes of polyols were also noticed in the long-term studies with xylitol. The human data do not suggest any hazard from urinary excretion of oxalate but consumption exceeding about 50 g/day leads to diarrhoea. The Committee did not consider it appropriate to establish an ADI for this polyol, but considered its use acceptable provided the limitations due to its laxative effect were kept in mind.

REFERENCES

Food and Agriculture Organization of the United Nations - FAO (1980).

Carbohydrates in human nutrition - a Joint FAO/WHO Report, Food and Nutrition Paper 15, FAO, Rome.

Astier-Dumas, M. (1979) Sucre et Santé, unpublished Report to EEC Commission, ENV 763/79.

O'Brien, L. and Gelardi, R.C. (1981). Alternative Sweeteners. Chemtech, 11, 274-278.

ACESULFAME K

Arpe, H.-J. (1978) Acesulfame-K, a new noncaloric sweetener. Proc.Ergob Conf. Geneva, 1978, 178-183.

Hoechst (1980) Acesulfame K - A new non-nutritive Sweetener. Unpubl. doc. submitted to the EEC Scientific Committee for Food.

WHO (1981) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 16, 11-27.

ASPARTAME

Center for Disease Control (1984) Evaluation of Consumer Complaints Related to Aspartame Use. Morbidity and Mortality Weekly Report of Centres for Disease Control, 33(43), 605-607.

FDA (1984) Aspartame. Final Rule. Fed.Reg.,49(36), 6672-6682.

Finkelstein, M.W., Daabees, T.T., Stegink, L.D. and Applebaum, A.E. (1983). Correlation of Aspartate Dose, Plasma Dicarboxylic Amino Acid Concentrati and Neuronal Necrosis in Infant Mice. Toxicology, 29, 109-119.

International Sweeteners Association (1983). Data submitted to the EEC Scientific Committee for Food.

RIV (1982) Monograph on Aspartame. Doc/Tox 300/222.

Sadler, M.J. (1984) Recent Aspartame Studies. Fd.Chem.Toxic.,22(9), 771-785.

WHO (1980) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 15, 18-86.

WHO (1981) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 16, 28-32.

Yokogoshi, H., Roberts, C.H., Caballero, B. and Wurtman, R.J. (1984) Effects of aspartame and glucose administration on brain and plasma levels of large neutral amino acids and brain 5-hydroxyindoles. Amer.J.Clin.Nutr.,40,1-7.

CYCLAMATES AND CYCLOHEXYLAMINE

Calorie Control Council (1983) Cyclamic Acid, Sodium Cyclamate, Calcium Cyclamate. Monograph submitted to the EEC Scientific Committee for Food.

IARC (1980) Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 22, 55-109.

Rostron, C.C. (1984) Bladder Tumour Promotion by Cyclamate. Bibra Bull.,23(9), 403-407.

Schmähl, D. and Habs, M. (1984) Investigation on the carcinogenicity of the artificial sweeteners sodium cyclamate and sodium saccharin in rats in a two-generation experiment. Arzneim.Forsch., 34(5), 604-606.

WHO (1977) Summary of Toxicological Data of Certain Food Additives. WHO Food Add.Ser. No 12, 116-123.
WHO (1982) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 17, 66-77.

GLYCYRRHIZIN

FASEB (1974) Evaluation of the Health Aspects of Licorice, Glycyrrhizin and Ammoniated Glycyrrhizin as Food Ingredients. PB-254529, NTIS, U.S. Dept. of Commerce, Springfield, U.S.A.
Hichara, N. (1979) Problems in food uses of glycyrrhizin. Shokuhin Kogyo, 22(16), 34-39.
Higurashi, A. (1975) Safety problems of glycyrrhizin and its utilisation. Shokuhin Kogyo, 18, 50-55.
International Sweeteners Association (1983) Monograph on Glycyrrhizin.
Kumagai, A. (1981) Biochemistry of glycyrrhizae radix. The mode of action of glycyrrhizin and glycyrrhetinic acid. Gendai Toyo Igaku, 2, 38-45.
RIV (1982) Glycyrrhizin. A review by F.L. von Velsen and B. Sangster.
Sobotka, T. et al., (1981) Neurobehavioural Toxicity of Ammoniated Glycyrrhizin, a licorice component, in Rats. Neurobehav.Toxic.Teratol., 3, 37-44.
Stanford Research Institute (1977) Study of the Mutagenic Effects of ammoniated glycyrrhizin by the Dominant Lethal Test in Rats. PB-279650, NTIS, U.S. Dept. of Commerce, Springfield, U.S.A.

ISOMALT (PALATINIT)

Bayer A.G. & Süddeutsche Zucker A.G. (1983) Isomalt (Palatinit) - A new Sugar Substitute by Dr M. Spengler.
Kirchgessner, M. and Müller, H.L. (1983) Digestibility of Palatinit, Metabolism and Utilization of Energy in Model Trials on Sows. Ztsch.Ernährwiss., 22(4), 234-240.
WHO (1981) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 16, 101-111.
Ziesenitz, S.C. (1983) Bioavailability of Glucose from Palatinit. Ztsch.Ernährwiss., 22, 185-194.

LACTITOL

C.V. Chemie Combinatie Amsterdam (1982/1983) Lactitol - A documentation for a food additive Petition submitted to the Scientific Committee for Food.
RIV (1983) Report on Lactitol by M. van Apeldoorn, Doc/Tox 300/382.
Velthuysen, J.A. (1979) Food Additives Derived from Lactose. Lactitol and Lactitol Palmitate. J.Agric.Fd.Chem.,27(4), 680-686.

MALTITOL AND HGS

EniChem Sintesi (1984) Malbit - a new Sweetener, submission to the EEC Scientific Committee for Food.
Kearsley, M.W., Birch, G.G. and Lian-Loh, R.H.P. (1982) The Metabolic Fate of Hydrogenated Glucose Syrups. Stärke,34(8), 279-283.
Rennhard, H.H. and Bianchine, J.R. (1976) Metabolism and Caloric Utilization of Orally Administered Maltitol-^{14}C in Rat, Dog and Man. J.Agric.Fd.Chem.,24(2), 287-291.
Roquette Frères (1983) Hydrogenated Glucose Syrup Lycasin 80/55. Submission to the EEC Scientific Committee for Food.

Takizawa, Y. and Hachiya, N. (1984) Bacterial reversion assay and micronucleus test carried out on hydrogenated glucose syrups, 'Malt-Towa' (powder) and maltitol crystal. Mutation Res., 137, 133-137.
Wursch, P. and Koellreutter, B. (1982) Maltitol and Maltotriitol as Inhibitors of Acid production in Human Dental Plaque. Caries Res., 16, 90-95.

MANNITOL

Abdo, K.M., Haseman, J.K., Boorman, G., Farnell, D.R., Prejean, J.D. and Kovatch, R. (1983) Absence of carcinogenic response in F344 rats and B6C3F$_1$ mice given D-mannitol in the diet for 2 years. Fd.Chem.Toxic., 21(3), 259-262.
ASPEC (1983) Toxicological data on Sorbitol and Mannitol submitted to the EEC Scientific Committee for Food.
FASEB (1972) Evaluation of the Health Aspects of Mannitol as a Food Ingredient. PB-221953. NTIS, U.S. Dept. of Commerce, Springfield, U.S.A.
FASEB (1979) Dietary Sugars in Health and Disease. IV Mannitol.
NCI/NTP (1981) Carcinogenesis Bioassay of D-Mannitol. NTP-81-38.

MIRACULIN

Brouwer, J.N. et al. (1968) Miraculin, the sweetness-inducing protein from miracle fruit. Nature, 220, 373-374.
Crosby, G.A. (1976) New Sweeteners. CRC Criticial Reviews in Food Science and Nutrition, 7(4), 297-323.
International Sweeteners Association (1984) Monograph on Miraculin.

MONELLIN

International Sweeteners Association (1984) Monograph on Monellin.

NEOHESPERIDINE DIHYDROCHALCONE

Roelfsma, R.P. (1983) Project No 300/190 submitted to the EEC Scientific Committee for Food.

SACCHARIN AND SALTS

Arnold, D.L., Krewski, D. and Munro, I.C. (1983) Saccharin: A Toxicological and Historical Perspective - Toxicology 27, 179.
Calorie Control Council (1983) Saccharin. Information submitted to the EEC Scientific Committee for Food.
Cranmer, M.F. (1980) Saccharin: A Report, G.H. Scherr (Ed.).
IARC (1980) Monographs. 22, 111-186.
IARC (1982) Monographs Supplement 4. 224-226.
Istituto Superiore di Sanita (1984) A Review of Toxicity Data Published since 1979, submitted to the EEC Scientific Committee for Food.
NRC/NAS (1978) Saccharin: Technical Assessment of Risks and Benefits. Report No 1, Washington, U.S.A.
Taylor, J.M., Weinberger, M.R. and Friedman, L. (1980) Chronic Toxicity and Carcinogenicity to the urinary bladder of Sodium Saccharin in the Utero-Exposed Rat. Toxicol. Appl. Pharmacol., 54, 57.
WHO (1982) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 17, 185-213.

SORBITOL

ASPEC (1984) Summary of Toxicological Data on Sorbitol and Mannitol submitted to the EEC Scientific Committee for Food.
FASEB (1979) Dietary Sugars in Health and Disease. III. Sorbitol. FDA 223-75-2090, Bethesda, U.S.A.
RIV (1983) Monograph Doc/Tox 300/421.
WHO (1978) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 13, 20-25.
WHO (1982) Toxicological Evaluation of Certain Food Additives. ICS/FA/82.

STEVIOSIDE

International Sweeteners Association (1983) Monograph on Stevioside.
Istituto Superiore di Sanita (1984) Stevioside: Occurrence, Uses, Chemical and Biological Properties, submitted to the EEC Scientific Committee for Food.
Nikken Chemicals Co. Ltd, Tokyo (1982) Stevioside. Nikken Stevioside Document G-1 and G-2 from Ministry of Health and Welfare, Government of Japan.
Tama Biochemical Co. Ltd, (1981) Stevix and Steviosin - newly developed natural Sweetening Agents. Safety of Stevia. 7-1, Nishishinjuku 2-Chome, Shinjuku, Tokyo 160 Japan.

THAUMATIN

Higginbotham, J.D., Snodin, D.J., Eaton, K.K. and Daniel, J.W. (1983) Safety Evaluation of Thaumatin (Talin Protein). Fd.Chem.Toxic.,21, 815-823.
International Sweeteners Association (1983) Monograph on Thaumatin.
Tate & Lyle Group R&D (1983/1984) Submission to the EEC Scientific Committee for Food.

VOLEMITOL

No information submitted.

XYLITOL

FASEB (1975) Dietary Sugars in Health and Disease. II. Xylitol. FDA 223-75-2090, Bethesda, U.S.A.
Hoffmann La Roche & Co. (1978) Xylitol Documentation.
Raunhardt, O. and Ritzel, G. (1982) Xylitol - Clinical Investigations in Humans. Hans Haber, Bern.
WHO (1977) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 12, 124-147.
WHO (1978) Toxicological Evaluation of Certain Food Additives. WHO Food Add.Ser. No 13, 28-34.
WHO (1983) Toxicological Evaluation of Certain Food Additives ICS/FA/83.31.
Xyrofin Ltd (1983) Xylitol documentation submitted to the EEC Scientific Committee for Food.

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