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.

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

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