Food Additives and Contaminants Committee report on the review of sweeteners in food.

MINISTRY OF
AGRICULTURE, FISHERIES AND FOOD

Food Additives and Contaminants Committee Report on the Review of Sweeteners in Food

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Food Additives and Contaminants Committee

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'To advise the Minister of Agriculture, Fisheries and Food, the Secretary of State for Social Services, the Secretary of State for Wales, the Secretary of State for Scotland and, as respects Northern Ireland, the Head of the Department of Health and Social Services, on matters referred to it by Ministers in relation to food contaminants, additives and similar substances which are, or may be, present in food or used in its preparation, with particular reference to the exercise of powers conferred on Ministers by sections 4, 5 and 7 of the Food and Drugs Act 1955 and the corresponding provisions in enactments relating to Scotland and Northern Ireland.'

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J Sherlock, Esq, PhD, MI Cor T and D A Whitmore, Esq, BSc, D Phil were responsible for the collection and presentation of a considerable amount of the scientific and technical information required for this Review.

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REPORT ON THE REVIEW OF SWEETENERS IN FOOD

PART I

INTRODUCTION

Background

1. In 1977 we were asked by Ministers to carry out a review of all sweeteners, other than sugars, which were required for use in food, whether or not they were permitted by existing Regulations. We welcomed this opportunity to carry out the first full review of this important class of substances since in the past we have been asked to consider certain artificial sweeteners on an individual basis only. Developments concerning saccharin[a)] and growing interest in other sweeteners had made a comprehensive review particularly desirable. A list of those who made representations is at Appendix I.

2. In 1966 and 1967 we issued reports[b)] on cyclamate[c)]. In 1969 we considered new evidence which threw doubts on the safety-in-use of cyclamate and advised Ministers that it would be prudent to withdraw permission for its use pending the results of other work being carried out in the UK and elsewhere. This was effected by the Artificial Sweeteners in Food Regulations 1969[d)] and the Soft Drinks (Amendment) Regulations 1969[e)].

3. In 1974 aspartame was submitted to us following an application for approval for its use in food, but completion of our consideration of this representation was delayed because of questions, which have now been answered, about the validity of the supporting toxicological data. In 1977 it was reported that tests, which had been carried out on saccharin in Canada and the USA, were said to cast doubts on its safety. We were therefore asked to advise on its continued use. We were also asked, in March 1978, to consider a recommendation by the Commission of the European Communities that Member States should observe certain provisions on the labelling of saccharin and its use in food. At that time the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) advised that further information, which was expected, was necessary before it could make a full evaluation of saccharin. Nevertheless on the basis of the available evidence the COT saw no reason to ban or further restrict the use of saccharin as a sweetener in food. We concluded therefore that there was no immediate

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a) unless otherwise stated the term 'saccharin' when used in this Report includes its sodium and calcium salts.

b) FAC/REP/3: HMSO 1966; FAC/REP/16: HMSO 1967.

c) unless otherwise stated the term 'cyclamate' when used in this Report includes its sodium and calcium salts.

d) SI 1969, No 1817.*

e) SI 1969, No 1818.

*For convenience the references quoted in this Report are to the legislation applying in England and Wales. Separate but similar legislation applies in Scotland and Northern Ireland.

need to recommend additional restrictions on the use of saccharin in the UK (see paragraphs 4 and 6) and that we would await the results of the full review by the COT before advising whether any action was necessary. We now have the benefit of additional advice from the COT in its report on this review, which is at Appendix II, and we make further recommendations on saccharin in this Report.

Current Legislation

4. The Artificial Sweeteners in Food Regulations contain the following definition:-

" 'artificial sweetener' means any chemical compound which is sweet to the taste but does not include any sugar or any polyhydric alcohol".

The only sweetener permitted by these regulations is saccharin (and its sodium and calcium salts). The regulations also lay down specifications and controls on the composition and labelling of saccharin tablets.

5. Certain sweet polyhydric alcohols, although defined out of the Artificial Sweeteners Regulations, are permitted for use in food by other additive regulations. Sorbitol and mannitol are permitted by the Miscellaneous Additives in Food Regulations 1980[a)] and glycerol is permitted by the Solvents in Food Regulations 1967[b)]. It is conventional in UK legislation to have separate regulations for different classes of additives eg. colours, antioxidants, preservatives and to include substances in one permitted list only. However, some substances are capable of performing a number of different functions in food and the regulations are so framed that their inclusion in only one of the permitted lists does not prevent their use for these other purposes. Thus, under existing regulations sorbitol, mannitol and glycerol may be used to sweeten food.

6. The regulations mentioned above place no restriction on the foods in which sweeteners may be used or the levels at which they may be added to food. Nevertheless the general provisions of the Food and Drugs Act 1955 and, where appropriate, compositional regulations also apply. Thus the Ice Cream Regulations 1967[c)] specifically prohibit the use of artificial sweeteners (ie saccharin) and the Soft Drinks Regulations 1964[d)] (as amended) lay down maximum permitted levels of saccharin. The Jam and Similar Products Regulations 1981[e)] restrict the use of replacement sweeteners in 'reduced sugar' jams to permitted artificial sweeteners (saccharin). Saccharin and/or sorbitol

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a) SI 1980, No 1934.

b) SI 1967, No 1582.

c) SI 1967, No 1866.

d) SI 1964, No 760 and subsequent amendments.

e) SI 1981, No 1063.

may be used in jams described as 'specially prepared for diabetics'.

7. The Labelling of Food Regulations 1970[a] require the presence of saccharin, sorbitol and mannitol to be indicated by name in the ingredient list of a food. New regulations[b] implementing an EC Directive on food labelling[c] which come fully into force on 1 January 1983, will in addition require that the generic term 'artificial sweetener' shall precede the specific name or EC reference number where appropriate.

8. The Labelling of Food Regulations 1970 exempt artificial sweetening tablets prepacked and sold as such from the requirement to list ingredients. However, from 1 January 1983 a list of ingredients will have to be included on the label of all artificial sweetener preparations sold as such to the ultimate consumer. Sorbitol and mannitol are subject to the specific labelling requirements contained in the Miscellaneous Additives in Food Regulations and glycerol to those in the Solvents in Food Regulations.

The Sweeteners

9. We are aware that there are a number of sweeteners currently being developed but we have confined our review to the following substances which were requested in representations:-

acesulfame potassium
aspartame
cyclamic acid and its sodium and calcium salts
dulcin
dulcitol
glycerol[d]
glycyrrhizin
hydrogenated glucose syrup
isomalt
lactitol
maltitol
mannitol[d]
miraculin
monellin
β-neohesperidin dihydrochalcone
saccharin and its sodium and calcium salts[d]
sorbitol [d]
stevioside
thaumatin
volemitol
xylitol

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a) SI 1970, No 400 and subsequent amendments.

b) SI 1980, No 1849.

c) OJ No L33/1, 18.12.78.

d) permitted by current regulations

Two of those listed, dulcin and dulcitol, were subsequently withdrawn. We have also been asked by the manufacturer concerned to defer consideration of thaumatin until the results of further tests, at present being carried out, are available for evaluation by the COT. Two of the remaining substances, glycerol and glycyrrhizin, have a sweet taste but we understand that their primary function in food is not to provide sweetness. We have previously considered the use of both these substances in other contexts, glycerol as a solvent[a)] and glycyrrhizin as a flavouring[b)] and have recommended that they are suitable for use in food (subject to certain quantitative restrictions in the case of glycyrrhizin). We do not propose, therefore, to consider them further in this Report.

10. Sucrose is used in food for its sweet taste, its physical properties or bulk, and its energy value. Its physical properties also enable it to perform an important preservative function in some foods when used in high concentrations. Alternative non-carbohydrate sweeteners must by definition impart a sufficient degree of sweetness to food but they may or may not also provide bulk and energy. Some substances, weight for weight, are hundreds or even thousands of times as sweet as sucrose. At the dilutions at which these substances must be used in food to avoid excessive sweetness, they cannot at the same time provide bulk or significant energy. The substances submitted to us were of two types; those with a sweetness similar to sucrose, which we have called *bulk sweeteners*, and those with a sweetness many times that of sucrose which we refer to as *intense sweeteners*. The perception of sweetness is subjective and therefore the figures quoted for relative sweetness are, of necessity, approximations. In addition, the relative sweetness perceived depends upon the concentration of the sucrose solution with which any comparison is made. For this reason we quote sweetness relative to a 4% aqueous solution of sucrose wherever possible. Weight for weight the sweetness of the bulk sweeteners ranges from about a half to the same as that of sucrose while the intense sweeteners are thirty to three thousand times sweeter than sucrose.

11. *Bulk sweeteners* may be used to replace some or all of the sucrose in food for technological or physiological reasons. Some bulk sweeteners for example have a negative heat of solution which produces a 'mouth-cooling' effect and this can be exploited in confectionery products and chewing gum. Others are used as humectants or dusting agents on cakes and chewing gum. Bulk sweeteners may also be used in foods specially prepared for diabetics and in foods designed to be less cariogenic. *Intense sweeteners*, on the other hand, are used in food solely for sweetening purposes. Their lack of bulk would produce an alteration in the nature of a particular food if sucrose was replaced wholly or partly by an intense sweetener. In such cases bulk may be restored without increasing the energy value of the food by the addition of a bulking aid[c)].

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a) FACC Report on the Review of Solvents in Food: FAC/REP/25: HMSO 1978.

b) FACC Report on the Review of Flavourings in Food: FAC/REP/22: HMSO 1976.

c) FACC Report on the Review of Bulking Aids: FAC/REP/32: HMSO 1980.

12. It follows that it has been necessary for us to take into account properties other than sweetness when considering the substances submitted to us. We therefore discuss the two groups of sweeteners separately.

PART II

THE BULK SWEETENERS

Some Examples of the 'Need' for Bulk Sweeteners

13. *Foods specially prepared for diabetics.* Diabetes mellitus may be controlled by careful management of the diet or by management of the diet in conjunction with the use of drugs. In consequence, amongst other things, diabetics should control their consumption of confectionery and other foods sweetened with rapidly absorbable carbohydrates such as sucrose. There is evidence that certain bulk sweeteners produce a lower insulin demand than an equivalent amount of sucrose and their use as a replacement allows diabetics to eat foods, such as jams and confectionery, which they would otherwise be unable to enjoy freely.

14. *'Sugar-free' foods.* For many years experts in the field of dental health have contended that caries is initiated by acid produced from the fermentation of carbohydrates by bacteria in the mouth. If this is so, the substitution of a non-fermentable sweet substance for sucrose or other fermentable carbohydrates might be expected to reduce the incidence of dental caries.

15. *Food with high carbohydrate concentrations stored at low temperatures.* If sucrose alone is used to depress the freezing point of food such as soft-scoop ice cream the product tends to develop a grainy or gritty texture and becomes excessively sweet. Use of a bulk sweetener such as sorbitol overcomes these problems because such substances crystallize less readily than sucrose and may also be less sweet, weight for weight.

Individual Bulk Sweeteners

16. Eight of the substances we were asked to evaluate may be considered to be bulk sweeteners. Their individual properties are discussed below:-

a) **Hydrogenated Glucose Syrup** which is about 0.75 times as sweet as sucrose is a glucose syrup in which all free aldehyde groups have been reduced by hydrogenation. There are a number of hydrogenated glucose syrups but the one we were asked to consider consists of maltitol (about 50%), hydrogenated higher polysaccharides (about 20%), hydrogenated tri-to hepta-saccharides (about 20%), and free sorbitol (about 7%). It is marketed as a syrup containing about 75% solids. Hydrogenated glucose syrup does not crystallize at high concentrations. As it does not contain free aldehyde groups it is resistant to browning reactions such as the Maillard reaction in which the free aldehyde groups and the amino groups of amino acids, peptides or proteins react to form brown pigments. We have been told that it has useful

technological advantages over glucose and fructose for some applications. We have also been told that it can be used with conventional sugar boiling and sweet forming machinery without resorting to unorthodox methods of manufacture. The food industry made strong representations for the use of hydrogenated glucose syrup as a substitute for glucose and sucrose because of its claimed reduced cariogenicity and as a substitute for sorbitol because of the claimed reduction in laxative effect. The submissions referred in particular to the use of hydrogenated glucose syrup in confectionery, soft drinks and in 'diabetic' foods as a substitute for sorbitol.

b) **Isomalt** (an equimolar mixture of 6–*O*–α–D–glucopyranosyl–D–glucitol and 1–*O*–α–D–glucopyranosyl–D–mannitol) is about 0.5 times as sweet as sucrose and unlike xylitol and sorbitol does not produce a 'mouth-cooling' effect. It is stable in acid and alkaline media under conditions normally occurring in the manufacture of food, reduces browning in cooked foods and is not decomposed by the majority of yeasts found in food products. Furthermore it is claimed to be less cariogenic than sucrose, to be only 50% metabolized in man and to be less laxative than sorbitol or xylitol. We understand that isomalt can be used as a sugar substitute in a number of foods and industry made strong representations for its use in products such as confectionery, chewing gum, soft drinks and desserts.

c) **Lactitol** (4–*O*–β–D–galactopyranosyl–D–glucitol) has been requested for use in ice cream at levels from 3–5%, where it would function both as a sweetener and as a freezing point depressant, and in confectionery.

d) **Maltitol** (4–*O*–α–D–glucopyranosyl–D–glucitol) is about 0.9 times as sweet as sucrose and is claimed to be resistant to heat and acids, stable at food processing temperatures, not fermented by micro-organisms and to have useful moisture retaining properties. The food industry has suggested that it might be used in 'slimming' foods requiring sweetness and for use in ice cream as a freezing point depressant at levels of 3–5%.

e) **Mannitol** (D–mannitol) occurs naturally in a number of foods such as pumpkins, mushrooms, onions, beets, celery and olives. It is about 0.6 times as sweet as sucrose. The submissions state that mannitol is stable at temperatures used in the preparation of confectionery, boiled sweets, fondant and other goods manufactured by sugar boiling processes. It is used not only for its sweetening properties but also to improve the palatability and 'mouthfeel' of products such as cakes. It is also used as a dusting agent to prevent stickiness on the surface of chewing gum and to facilitate the formation of gum into sheets without tearing or breaking and as a diluent for products such as vitamin supplement tablets. It is reported to have a pleasant, slightly sweet, cool taste with a smooth 'mouthfeel'.

f) **Sorbitol** (D–glucitol) like mannitol occurs naturally in food especially fruit such as cherries, plums, pears, apples and berries. It is often marketed as a non-crystallizing solution containing a small amount of hydrogenated oligosaccharides. It is about 0.5 times as sweet as sucrose, is stable in the dry state and, because it is not utilized by yeast, may be used in industrial baking processes. It is also stable at the temperatures used in the preparation of confectionery, boiled sweets, fondant and other goods manufactured by sugar

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19. We asked the DHSS Standing Dental Advisory Committee (SDAC) to consider and advise on the evidence for reduced cariogenicity of the substances submitted. The SDAC confirmed that sucrose is certainly an important factor in the aetiology of dental caries but whether it is **the** major factor remains controversial. On the available evidence, none of the bulk sweeteners submitted was regarded as non-cariogenic. However, the SDAC considered four of them, namely hydrogenated glucose syrup, isomalt, sorbitol and xylitol had proved to be less cariogenic than sucrose in short-term experiments and could therefore be regarded as promising possibilities. We recognise the complexities of the issues involved but we have no wish to discourage any development that might lead to improved dental health. In assessing the overall case of need for individual sweeteners therefore, we allowed the possible reduced cariogenicity of hydrogenated glucose syrup, isomalt, sorbitol and xylitol to weigh in their favour. This should not however be taken as an endorsement of any claims for the effectiveness of these substances in reducing cariogenicity.

20. We have already discussed in paragraphs 13–15 the reasons why bulk sweeteners are used in food. However, of the substances submitted to us for consideration, food manufacturers expressed only limited interest in the use of lactitol and volemitol and information on manufacture and potential use of these sweeteners was inadequate. The requests for the use of maltitol relied on the understanding that it was not metabolised by man but we have since been given evidence to the contrary[a)]. This issue would have to be resolved or other evidence provided before we could give any further consideration to the case of need for this substance. We have already explained (paragraph 18) that hydrogenated glucose syrup, mannitol, sorbitol and xylitol could be used in foods designed for diabetics and that three of these substances together with isomalt might be of value in foods designed to be of reduced cariogenicity (paragraph 19). We accepted that no one bulk sweetener was ideal for all purposes and decided that a case of need had been established for hydrogenated glucose syrup, isomalt, mannitol, sorbitol and xylitol. We referred these to the COT for evaluation of safety-in-use.

21. The COT has classified all five sweeteners in Group B (temporarily acceptable for use in food) and we *recommend* that only these bulk sweeteners

ie hydrogenated glucose syrup
isomalt
mannitol
sorbitol
and xylitol

should be permitted for use in food. We endorse the recommendation made in the COT's Report (Appendix II) that further work should be carried out on these substances within two years of the publication of the Report and that information on intake should be collected within five years of the introduction of the new sweeteners on to the market. We further *recommend* that their continued inclusion in the permitted list should be dependent upon receipt and satisfactory evaluation of this information by the COT.

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a) Metabolism and Caloric Utilization of Orally Administered Maltitol – ^{14}C in Rat, Dog and Man; H H Rennhard, J R Bianchine J Ag Food Chem (1976) Vol 24 (part 2) pages 287–291

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Intense sweeteners which by definition are many times sweeter than sucrose can be used as replacement sweeteners in these foods because they provide an equivalent sweetness without contributing significantly to the energy value.

Individual Intense Sweeteners

26. The individual properties of the intense sweeteners we were asked to consider are discussed below:–

(a) **Acesulfame potassium** (potassium 3,4–dihydro–6–methyl–2,2,4–trioxo–2λ^6–1,2,3–oxathiazin–3–ide) is approximately 130 times sweeter than a 4% solution of sucrose. It is reported to have a clean, sweet taste, leaving no aftertaste or taint at levels at which it would be used in food. It is stable in the pH range 3.5 – 8.0 for four months at temperatures up to 40°C and can withstand heat treatment at 120°C for 1 hour at pH 4.0. The food industry expressed considerable interest in the use of this sweetener. It has been proposed as a replacement for sucrose or as a total or partial replacement for the existing uses of saccharin in foods such as normal and 'reduced energy' soft drinks, 'reduced energy' preserves and baked goods.

(b) **Aspartame** (*N*–L–α–aspartyl–L–phenylalanine methyl ester) is approximately 200 times sweeter than a 4% solution of sucrose. It is reported to have a taste similar to sucrose although the sweetness develops more slowly and persists longer. It is free of the bitter aftertaste associated with saccharin. Aspartame is not stable in aqueous solution and its instability increases with increasing temperature. It is difficult to use, therefore, in foods prepared, stored and sold in liquid form. Nevertheless industry has expressed substantial interest in the use of aspartame in dry or frozen foods such as confectionery, powdered soft drinks, dessert mixes, pre-sweetened breakfast cereals, chewing gum and water ices.

(c) **Cyclamate** (cyclohexylsulphamic acid and its sodium and calcium salts) is approximately 25 times sweeter than a 4% solution of sucrose. Because of the previous food use of cyclamate there are considerable data available on the foods in which it would be used and its levels of use. Most of the uses proposed to us relate to dietetic foods but there are exceptions such as soft drinks and water ices. Because of its synergistic effect with saccharin, which is thought to be linked to the suppression of 'off-taste', industry expressed strong interest in the use of cyclamate and many of the proposals mentioned its employment in combination with saccharin.

(d) **Miraculin** is a glycoprotein extracted from the fruit of the West African shrub *Synsepalum dulcificum* (miracle fruit). It does not itself taste sweet but is said to act as a taste bud receptor modifier which 'miraculously' transforms the taste of sour or acid-tasting foods. Because it is thermolabile it is not suitable for use in heat-treated foods such as pasteurised fruit juices and many canned foods. We understand that when it was first produced in the USA commercial interest in this substance was concentrated on the

production of tablets containing miraculin which could be sucked before a meal, thereby making acidic foods such as grapefruit taste sweet. We received no information on possible levels of use of this sweetener if it were to be permitted in the United Kingdom although it was suggested by the food industry that it might be used in water ices, mousses and sauces.

(e) **Monellin** is a protein extracted from the fruit of the West African tropical vine *Dioscoreophyllum cumminsii* (serendipity berry). It is said to be between 1500 and 3000 times as sweet as sucrose with an impure taste tinged with liquorice flavour. We were told that the taste is not perceived for a few seconds, but gradually builds up to a maximum followed by a decline in sweetness over one or two hours. Monellin is stable in aqueous solution but sweetness is lost on heating to about 60°C and at pH levels below 2 or above 10. It was suggested that monellin might be used in confectionery, water ices, mousses and sauces, but no specific proposals for its use were submitted.

(f) **β–Neohesperidin dihydrochalcone** (3,5–dihydroxy–4–[3–(3–hydroxy–4–methoxyphenyl) propionyl] phenyl 2–*O*–α–L–rhamnopyranosyl–β–D–glucopyranoside) is derived from a flavenone glycoside (naringin) obtained from the peel of citrus fruits. It is about 1000–2000 times as sweet as sucrose with a slow flavour impact which builds up in intensity until a menthol-like taste becomes apparent. It has been suggested that if permitted this substance would be used mainly as a replacement for sugar in 'low energy' products but the food industry expressed only limited interest in its use.

(g) **Saccharin** (saccharin; 1,2–benzisothiazol–3 (2*H*)–one 1, 1–dioxide and its sodium and calcium salts) is approximately 300 times sweeter than sucrose (based on the dilution of a solution in distilled water to threshold sweetness); sodium and calcium saccharins are of comparable sweetness. Under conditions normally encountered in food processing saccharin is chemically stable. At the present time saccharin and its sodium and calcium salts are the only artificial sweeteners permitted for use in food in the United Kingdom. The main uses in food are in soft drinks and 'diabetic' foods. Another important use is as a 'table-top' sweetener. Industry would prefer to use saccharin in combination with another intense sweetener to mask its bitter aftertaste. Such a combination may be advantageous in that any synergistic effect could result in a reduction in the total amount of intense sweetener used.

(h) **Stevioside** (β–D–glucopyranosyl(2*S*,4a*R*,4b*S*,8*R*,8a*S*,10a*R*)–2–(2–*O*–β–D–glucopyranosyl–β–D–glucopyranosyloxy)–4b,8–dimethyl–12–methyleneperhydro–2,10a–ethanophenanthrene–8–carboxylate) is a diterpene glycoside extracted from the leaves of the Paraguayan shrub *Stevia rebaudiana* Bertoni. We are told that it does not have the bitter aftertaste associated with saccharin and it is not metabolised when taken orally. It was suggested that stevioside might be used in water ices, mousses and sauces but no specific proposals for its use or information on levels of use were submitted.

Evaluation of the Intense Sweeteners

27. For many years intense sweeteners have been controlled by permitted list (paragraph 4). We *recommend* that this method of control should continue. As with the bulk sweeteners (paragraph 17) we have evaluated the substances submitted on the basis of need and safety-in-use.

28. Information on the manufacture of stevioside was inadequate and no information was provided on proposed levels of use of this substance or of monellin or miraculin. In view of this lack of interest and information we did not refer these substances to the COT for evaluation of safety-in-use. We were however satisfied that there was sufficient demand for the use of acesulfame potassium, aspartame, cyclamate and saccharin for us to refer them to the COT. Saccharin, as we have explained, was already being evaluated (paragraph 3).

29. In its Report the COT classifies two of the intense sweeteners (aspartame and acesulfame potassium) in Group A (substances that the available evidence suggests are acceptable for use in food). Cyclamate and saccharin are classified in Group B (temporarily acceptable for use in food).

30. Saccharin has a long history of use in food. Its organoleptic properties in individual food formulations produced on a full commercial scale are well understood and industry regards it as of high importance. We accept that there is a continuing and established need for saccharin. It is not, however, an ideal intense sweetener as it has a bitter aftertaste which many consumers find unattractive. There remains therefore a need for an intense sweetener with a clean sweet taste.

31. We have explained that there was considerable interest in the use of acesulfame potassium and aspartame although in the case of the latter it was recognised that its lack of stability in aqueous solution might limit its applications. Neither acesulfame potassium nor aspartame has an unpleasant aftertaste and we accept that there is a case of need for both of these new intense sweeteners. Their addition to the permitted list would allow food manufacturers a degree of flexibility which they have been denied for many years because of the lack of suitable alternatives to saccharin.

32. There was a strong demand from industry for the use of cyclamate which has the particular advantage in that, in combination with saccharin, it suppresses its bitter aftertaste. We considered carefully whether there was now a need to restore cyclamate to the permitted list. If our other recommendations are implemented, industry will have two new intense sweeteners, acesulfame potassium and aspartame, available both of which have been given a Group A classification by the COT. Admittedly both are as yet untried in full-scale commercial food production and this makes the retention of saccharin with its well proven technology even more important. Cyclamate has the lowest degree of sweetness of the intense sweeteners submitted and ten times the amount of cyclamate is required to provide the equivalent sweetness of a given amount of saccharin. This factor weighed against cyclamate

particularly in view of the recommendation of the COT that its intake should be limited by restricting its use to certain designated food items. The main demand for cyclamate is for use in soft drinks, a commodity frequently consumed in quantity by children. For these reasons, therefore, and even though the COT has classified cyclamate as temporarily acceptable for use in food, we have concluded that it should not be restored to the permitted list.

33. We *recommend* therefore that only the following intense sweeteners should be permitted for use in food:-

acesulfame potassium
aspartame
saccharin (and its sodium and calcium salts).

As with bulk sweeteners we endorse the COT's recommendation that information on intake should be collected within 5 years of the introduction on to the market of the new sweeteners.

PART IV

FUTURE CONTROLS ON SWEETENERS

Regulations Controlling Sweeteners

34. New legislation would be necessary to give effect to our recommendations that additional sweeteners should be permitted for use in food. We believe there is merit in taking this opportunity to bring together in one regulation controls for both the bulk and intense sweeteners. We *recommend* therefore that the existing Artificial Sweeteners in Food Regulations be revoked and replaced by new sweeteners regulations.

35. We have considered how the term 'sweetener' should be defined for the purposes of the new regulations and whether all sugars should continue to be exempt from control. By 'sugar' we mean those substances which come within the definition in the current regulations:-

" 'sugar' means any soluble carbohydrate sweetening matter;

'carbohydrate' means a substance containing carbon, hydrogen and oxygen only in which the hydrogen and oxygen occur in the same proportion as in water".

We consider that the substances described by the Specified Sugar Products Regulations 1976[a)] and any other sugars commonly regarded as foods, together with other naturally sweet foods, such as honey, should be excluded from the control of future sweeteners regulations. We therefore *recommend* the following definition of sweetener:-

"any substance, other than a natural food, the primary organoleptic characteristic of which is sweetness".

We would define 'natural food' as follows:-

"any substance suitable for use as food and commonly used as food which is wholly a natural product whether or not that substance has been subjected to any process or treatment and includes any specified sugar product"

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a) SI 1976, No 509.

and "specified sugar product" as:

"any substance complying with Schedule I of the Specified Sugar Products Regulations 1976".

We consider that sorbitol and mannitol should be controlled by future sweeteners regulations. These apart, we *recommend* that any permitted anti-oxidant, permitted bleaching agent, permitted colouring matter, permitted emulsifier, permitted improving agent, permitted miscellaneous additive, permitted preservative, permitted solvent, permitted stabiliser, and modified starch[a)] should be exempted from control by future sweeteners regulations. We also considered whether flavourings should be specifically excluded but concluded that this was unnecessary as their primary characteristic would not be sweetness.

Restrictions on the use of Sweeteners

36. The composition of certain foods is already controlled by existing regulations made under the Food and Drugs Act. In some foods the use of artificial sweeteners is effectively precluded since they do not appear on the list of permitted additives in the appropriate compositional regulations and indeed in the Ice Cream Regulations artificial sweeteners are specifically prohibited. We see no reason to amend these restrictions and we *recommend* accordingly.

37. *The Soft Drinks Regulations 1964 (as amended)* contain quantitative limits on the levels of saccharin which may be used. We *recommend* that these limits continue. We further *recommend* that acesulfame potassium should also be permitted for use in soft drinks. However, as it has been classified in Group A and its use will in any case be self-limiting we see no reason to recommend quantitive limits for this sweetener. Aspartame is not ideal for use in soft drinks retailed in liquid form because of its relative instability in solution, but we are aware of recent indications that these technological problems may have been overcome. In considering any representations that might be made to extend the use of aspartame to soft drinks we would need to seek further advice from the COT. However aspartame can be used in powdered soft drink bases which are outside the scope of the Soft Drinks Regulations. We see no need to prohibit the use of aspartame in these foods.

38. *The Jam and Similar Products Regulations 1981* permit the use of saccharin in 'reduced sugar' jams (products with a total soluble solids content of between 30 and 55%) and in 'diabetic' jams. Sorbitol is also permitted in 'diabetic' jams. We *recommend* that in future all permitted intense sweeteners should be permitted for use in these products. As we have indicated in paragraph 18 certain bulk sweeteners other than sorbitol could be used in 'diabetic' foods generally and we see no reason why they should not be used in 'diabetic' jams. We so *recommend.*

39. *Foods for Babies and Young Children* The COT has recommended in its Report (paragraph 9 of Appendix II) that the use of the substances referred to it should not be permitted in foods manufactured specifically for babies and young children. As far as we are aware none of them is used in the

a) FACC Report on Modified Starches: FAC/REP/31: HMSO 1980

preparation of such foods but we endorse the recommendation that this should be given statutory effect. We have not been informed about any foods prepared for babies or children with special dietary needs in which any of the sweeteners we have considered are used.

EC Recommendations

40. As we explained in paragraph 3 in addition to the studies referred to us in 1977 on saccharin, we were asked in March 1978 to consider recommendations by the Commission of the European Community that Member States should observe certain provisions on the labelling and use of saccharin[a]. These were that:-

(1) national rules on the use of saccharin in foodstuffs should be developed, if necessary, so as to respect the ADI* for saccharin, and to keep to a minimum the intake of saccharin by children;

(2) the use of saccharin in infant foods should be prohibited;

(3) foodstuffs should be labelled in such a way that the presence of saccharin is specifically and clearly mentioned;

(4) appropriate labelling provisions for saccharin sold in tablet form should be implemented to inform the purchaser of the possible dangers of excessive consumption of saccharin especially in the case of pregnant women and children.

However, in the light of the COT's more recent evaluation of saccharin, our view is that the controls we are recommending in this Report will provide sufficient protection for the consumer.

Specifications of Purity

41. The specifications of purity for the currently permitted artificial sweeteners, saccharin and its sodium and calcium salts, are laid down in the Artificial Sweeteners in Food Regulations 1969. In the case of saccharin and sodium saccharin, the regulations refer to the monographs for these substances in the British Pharmacopoeia 1968. The British Pharmacopoeia Commission has since revised these monographs and we *recommend* that new regulations should refer to the updated monographs in the British Pharmacopoeia 1980. Sorbitol and mannitol are currently controlled by the Miscellaneous Additives in Food Regulations 1980 and their statutory specifications reflect those laid down in EC Council Directive 78/663/EEC[b] which we *recommend* should continue to apply. We have drawn up specifications for the remainder of those sweeteners we have recommended for inclusion in the future permitted list and we *recommend* that the general and specific purity criteria set out in Appendix III should be included in future regulations.

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a) OJ No L103, 15.4.1978.

b) OJ No L223, 14.8.78.

* Acceptable Daily Intake

Future Labelling Requirements

42. The Food Labelling Regulations 1980 require that as from 1 January 1983 artificial sweeteners must be identified in a list of ingredients by the generic term 'artificial sweetener' followed by the specific name or serial number (if any) or both (paragraph 7). We have considered carefully whether all of the substances we have recommended for inclusion in a permitted list of sweeteners could justifiably be regarded as 'artificial' sweeteners. We consider that the consumer has come to associate the term 'artificial sweetener' with saccharin, a substance that is intensely sweet compared with sucrose and does not occur naturally in food. We *recommend* therefore that in future sweeteners regulations the term 'artificial sweetener' should be restricted to the permitted intense sweeteners namely acesulfame potassium, aspartame and saccharin.

43. We feel however that if all sweeteners are to be controlled in a single regulation the labelling requirements for bulk and intense sweeteners sold as such should be the same. Sweeteners are often sold direct to the consumer for use in cooking and for sweetening beverages such as tea and coffee ('table-top' sweeteners). In this case we believe that they are regarded by the purchaser as 'food' and as such should be labelled in accordance with the general food labelling legislation (paragraph 8). We so *recommend*. We also *recommend* that sweeteners sold to food manufacturers for use as a food ingredient should be labelled to the extent already required for sorbitol and mannitol (ie Schedule 3 of the Miscellaneous Additives in Food Regulations 1980).

44. The Artificial Sweeteners in Food Regulations contain compositional and labelling requirements for saccharin tablets. These were introduced during the last war to protect the consumer from the sale of low strength tablets. We have already explained that new comprehensive labelling requirements for all food sold to the ultimate consumer (or to caterers) will apply from 1 January 1983 and that unlike previous regulations these will not exempt saccharin tablets from the requirement to bear an ingredient list (paragraph 8). We have also recommended that all sweeteners should be subject to similar provisions (paragraph 43). In view of this we do not think there is any longer a need for specific requirements which only apply to one form of one particular sweetener. We *recommend* therefore that specific standards for saccharin tablets should be omitted from future regulations.

PART V

Summary of Recommendations

45. We *recommend* that:

a) bulk and intense sweeteners should be controlled by permitted list (paragraphs 17 and 27);

b) the list of permitted sweeteners should comprise:–

Bulk Sweeteners	*Intense Sweeteners*
hydrogenated glucose syrup	acesulfame potassium
isomalt	aspartame
mannitol	saccharin (and its sodium and
sorbitol	calcium salts)
xylitol	

and the continued inclusion of the bulk sweeteners in the permitted list should be dependent on the receipt and satisfactory evaluation of the information requested by the COT (paragraphs 21 and 33);

c) the existing Artificial Sweeteners in Food Regulations should be revoked and replaced by new sweeteners regulations (paragraph 34);

d) the new regulations should control all sweeteners other than those which are natural foods. Substances (other than sorbitol or mannitol) already permitted by additives regulations and modified starches should be excluded from the scope of the new regulations (paragraph 35);

e) there should be statutory definitions of 'sweetener' and 'natural food' (paragraph 35);

f) there should be no change to those compositional regulations which prohibit the addition of artificial sweeteners to certain foods (paragraph 36);

g) the current statutory limits for saccharin in liquid soft drinks should be maintained but acesulfame potassium should be permitted for use in liquid soft drinks without restriction (paragraph 37);

h) all permitted intense sweeteners should be permitted for use in 'reduced sugar' and 'diabetic' jams and, in addition, 'diabetic' jams should be permitted to contain hydrogenated glucose syrup, mannitol, sorbitol and xylitol (paragraph 38);

i) sweeteners should not be permitted in foods manufactured specifically for babies and young children (paragraph 39);

j) the specifications for saccharin and its sodium salt in the new sweeteners regulations should refer to the updated monographs in the British Pharmacopoeia 1980, those for sorbitol and mannitol should be as currently laid down in the Miscellaneous Additives in Food Regulations 1980, and those for the remaining permitted sweeteners should be as set out in Appendix III of this Report (paragraph 41);

k) in future sweeteners regulations the term 'artificial sweetener' should be restricted to the permitted intense sweeteners (paragraph 42);

l) sweeteners intended for sale to the ultimate consumer should be labelled in accordance with food labelling legislation and sweeteners sold to food manufacturers for use as a food ingredient should be labelled to the extent already required for sorbitol and mannitol (paragraph 43);

m) specific standards for saccharin tablets should be omitted from future regulations (paragraph 44).

APPENDIX I

List of those who made representations

Abbott Laboratories Ltd
Alwitt Ltd
Approved Prescription Services Ltd
Association of Metropolitan Authorities
Automatic Vending Association of Great Britain

Beecham Products
British Diabetic Association
British Dietetic Association
British Food Manufacturing Industries Research Association
British Soft Drinks Council
The Boots Co Ltd

The Cake & Biscuit Alliance
California Aromatics and Flavours Inc.
The Cocoa, Chocolate and Confectionery Alliance
Colgate-Palmolive Ltd
CPC (UK) Ltd

Fries and Fries

General Foods Europe

T H Grenby – Department of Oral Medicine and Pathology, Guy's Hospital

Halls Hudnut
Hoechst UK Ltd
Honeywill Atlas Ltd

Ice Cream Alliance

Kelloggs

Marks and Spencer Ltd
Mars Ltd
MacAndrews and Forbes Ltd

The National Association of Cider Makers

Parliamentary Committee Co-operative Union Ltd

RHM General Foods Ltd
Roche Products Ltd
Roquette UK Ltd

GD Searle and Co Ltd
Smith Kendon Ltd
Sudzucker

Tate and Lyle Ltd

Unilever Ltd

Van den Bergh and Jurgens Ltd

APPENDIX II

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

REPORT ON REVIEW OF SWEETENERS IN FOOD

TERMS OF REFERENCE

To advise at the request of:

Ministry of Agriculture, Fisheries and Food
Department of the Environment
Department of Health and Social Security
Department of Trade
Health and Safety Executive
Medicines Commission, Section 4 Committees and the Licensing Authority
Committee on Medical Aspects of Food Policy
Home Office
Scottish Home and Health Department
Department of Agriculture and Fisheries for Scotland
Welsh Office
Department of Health and Social Services, Northern Ireland
Other Government Departments

1. To assess and advise on the toxic risk to man of substances which are:–

a. used or proposed to be used as food additives, or used in such a way that they might contaminate food through their use or natural occurrence in agriculture, including horticulture and veterinary practice, or in the distribution, storage, preparation, processing or packaging of food;

b. used or proposed to be used or manufactured or produced in industry, agriculture, food storage or any other workplace;

c. used or proposed to be used as household goods or toilet goods and preparations;

d. used or proposed to be used as drugs, when advice is requested by the Medicines Commission, Section 4 Committees or the Licensing Authority;

e. used or proposed to be used or disposed of in such a way as to result in pollution of the environment.

2. To advise on important general principles or new scientific discoveries in connection with toxic risks, to co-ordinate with other bodies concerned with the assessment of toxic risks and to present recommendations for toxicity testing.

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Substances Submitted

3. The following alternative sweetening agents were submitted for our opinion under the descriptions below:–

a) Intense sweeteners:

saccharin and its sodium and calcium salts [a)]
cyclamic acid and its sodium and calcium salts
aspartame
thaumatin
acesulfame potassium

b) Bulk sweeteners:

sorbitol (E420)[b)]
mannitol (E421)[b)]
xylitol
hydrogenated glucose syrup
isomalt

Specifications

4. Adequate and appropriate specifications must be laid down and adhered to. A safety assessment can most reliably be made if the specified product as used in food conforms to the specification of the substance which has been subjected to toxicological studies. Therefore in forming our opinions on the substances submitted we have taken into account the availability of satisfactory specifications. For some substances, specifications have been agreed in the European Community, for others it was necessary to refer to the individual manufacturer's product specifications.

General Observations

5. In this Report we do not evaluate thaumatin. After this sweetener had been referred to us by the FACC, we received a request from the manufacturer to defer final evaluation of its safety-in-use, until the results of further studies became available, and this we have agreed to do.

6. There has been much development in the field of alternative sweetening agents in recent years, and many of the compounds submitted to us have not been considered previously. It is difficult to assess the likely effects of the introduction of several new sweetening agents on current food manufacturing practices or to predict the future intake of the new and existing sweeteners.

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a) currently permitted for use in food by the Artificial Sweeteners in Food Regulations 1969.

b) currently permitted for use in food by the Miscellaneous Additives in Food Regulations 1980.

Therefore we *recommend* that, within five years of the implementation of new regulations, data be collected on the use of all sweeteners to provide reliable information on actual human intake levels, both in the general population and in those groups, such as diabetics and children, likely to consume large amounts of food containing sweetening agents. Collection of this information should begin as soon as sufficient time has been allowed for new food manufacturing practices to develop and for the market to stabilise.

7. The animal data available on three of the bulk sweeteners submitted to us, namely sorbitol, mannitol and xylitol, indicate that when administered in the diet at high levels (20% by weight) over long periods of time, all three materials give rise to a similar spectrum of non-specific effects. This consists in rodents of initial gastrointestinal disturbance together with long-term effects which include adrenal medullary hyperplasia and urinary bladder tumour formation associated with the presence of calculi in the bladder. We are aware that initially some of the adrenal medullary lesions were reported to be phaeochromocytomas but accept the later view, based on expert opinion (1) that most of them were hyperplasia. These long-term effects have not been seen with the two other bulk sweeteners submitted, namely hydrogenated glucose syrup and isomalt; however the maximum duration of the studies available on these latter substances is only 90 days.

8. In order to determine more closely the nature of the above effects which are possibly associated with effects on mineral absorption and/or excretion, or to vitamin B_6 status (2,3,4,5,6,7,8,9) we *recommend* that further information be made available on sorbitol, mannitol and xylitol within two years of the publication of this Report to enable determination of the effects on vitamin B_6 and oxalate metabolism and on urinary mineral excretion of feeding a range of levels of the sweeteners (from 1% to 20% of the diet) to rodents over a period of 90 days. The levels of vitamin B_6 and of minerals such as calcium, phosphorus and magnesium in the experimental diets should also be monitored. If significant effects are found in such a study, then further information would be required to determine:–

i. the effects of feeding high levels (up to 20% of the diet) of the bulk sweeteners over very short periods of time (1 or 2 days) interspersed by periods of feeding low levels of sweeteners, to mimic more closely the human consumption patterns;

ii. the effects of feeding more than one of the bulk sweeteners concurrently compared with feeding equivalent levels of a single bulk sweetener.

The need for further long-term studies on individual bulk sweeteners will be considered when the results of the work, requested above, have been evaluated.

9. We understand that, although the law at present does not prevent the use of sorbitol and mannitol in foods for babies and young children, they are not in fact being so used, and, furthermore, that no requests have been received for the use of any alternative sweetening agents in these foods. We will in due course be reviewing the use of all additives in baby foods, but in

the meantime we would not wish to see the use of alternative sweetening agents in normal foods described as being for babies and young children and we *recommend* accordingly. However we would not wish to preclude the use of alternative sweetening agents in foods for babies and young children prepared for special dietary purposes.

Detailed Classification

10. The sweeteners evaluated fell into two of the following five classifications:–

Group A: Substances that the available evidence suggests are acceptable for use in food.

Group B: Substances that on the available evidence may be regarded meanwhile as provisionally acceptable for use in food, but about which further information must be made available within a specified time for review.

Group C: Substances for which the available evidence suggests possible toxicity and which ought not to be permitted for use in food, until adequate evidence of safety has been provided to establish their acceptability.

Group D: Substances for which the available information indicates definite or probable toxicity and which ought not to be permitted for use in food.

Group E: Substances for which inadequate or no toxicological data are available and on which it is not possible to express an opinion as to their acceptability for use in food.

11. Classification in Group A or B may sometimes be accompanied by a recommendation for restriction on use (for example see aspartame – paragraph 13i and cyclamic acid and its salts – paragraph 14ii). It should be noted that these classifications and restrictions may be revised if new evidence becomes available.

12. The remainder of this Report gives a brief summary of our appraisal of the evidence supplied to us with, where appropriate, an indication of any further studies we consider to be necessary.

13. GROUP A

i. **Aspartame**

Extensive data have been submitted to support the safety-in-use of aspartame including data on metabolism, short- and long-term toxicity, carcinogenicity, mutagenicity and reproduction studies. In addition it is known that, on

storage and in certain foods, aspartame breaks down to a diketopiperazine derivative (DKP) by hydrolysis and cyclisation. Some food sweetened with aspartame might contain DKP at levels up to 5% of the amount of aspartame added; the DKP derivative has also been subjected to extensive toxicological testing.

In general the data were satisfactory although the results of some long-term studies in the rat with aspartame and its DKP derivative did initially give some cause for concern. In a study with the DKP derivative there appeared to be a treatment-related increase in the incidence of uterine endometrial polyps. However following re-evaluation of the histological material by a group of independent pathologists it was concluded that the polyps were non-neoplastic in nature being formed during the natural ageing process in the rat and that the observed incidence was consistent with the spontaneous incidence for the strain of rats used.

A recent long-term rat study with aspartame alone and together with its DKP derivative (3:1), at levels of up to 10% of the diet has shown dose-related increases in urinary calcium levels and mineralisation of the renal pelvis, with females being more affected than males. Although information on the mineral levels in the basic diet fed to the animals is not available, we consider it probable that the levels of calcium and phosphorus exceeded those recommended[a)]. It is clear from other studies that the inclusion in diets of high concentrations of substances (eg lactose, or chemically modified starches[b)]) that are not readily broken down to easily absorbable derivatives tends to enhance calcium absorption and urinary excretion. We regard the occurrence of pelvic nephrocalcinosis in rats in such circumstances as being mainly a laboratory artefact, attributable to excessive intakes of calcium, phosphorus and the test material and we do not regard it as predictive of toxic risk for man.

The results of one long-term rat study with aspartame were consistent with an increased incidence of intracranial neoplasms in the treated animals; however, the increase was not dose- or sex-related and the overall incidence was within the range previously encountered in untreated animals of the same strain. Furthermore no such increase was seen in two subsequent long-term studies with aspartame, one incorporating *in utero* exposure. Following detailed consideration of these data we are of the opinion that the lesions were not associated with the dietary administration of aspartame. We have also considered the possibility that ingestion of aspartame, alone or together with glutamate, may contribute to mental retardation, brain damage or undesirable effects on neuroendocrine regulatory systems. It is pertinent to note that studies have indicated that the metabolism of aspartame in man is similar to that of phenylalanine and aspartic acid, and that studies in man, involving adults and children, both normal subjects and those heterozygous for phenylketonuria have indicated no untoward effects at levels up to one order of

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a) NAS 1978, Nutrient Requirements of Laboratory Animals. Number 10.

b) FACC Report on Modified Starches FAC/REP/31:HMSO 1980.

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rate in human males by Howe *et al* (1977) have stimulated further studies on this sweetener.

There is a wealth of data available from long-term studies (dating from the early 1960's) in which saccharin alone was administered mainly to rats and less frequently to mice, hamsters and monkeys. In the earlier studies involving administration to one generation of animals only, no increased incidence of urinary bladder cancer was noted. However in later studies in which saccharin was administered to two generations of rats, urinary bladder tumour incidence was increased in the second generation males. These findings were noted first by Taylor *et al* (1973) and WARF (1972) and later confirmed by Arnold *et al* (1980). However there remain difficulties in the interpretation of *in utero* studies.

Saccharin has also been administered orally for long periods of time to rats previously treated with known bladder carcinogens such as *N*–methyl–*N*–nitrosourea, *N*–butyl–*N*–(4–hydroxybutyl)nitrosamine and *N*–[4–(5–nitro–2–furyl)–2–thiazolyl] formamide (Hicks *et al* 1975, Nakanishi *et al* 1980 a and b, and Cohen *et al* 1979). There is some evidence of an increase in bladder tumour incidence following such pretreatment but the findings have not always been confirmed. A more consistent finding has been that of increased hyperplasia of the bladder following pretreatment and saccharin administration.

Saccharin has been subjected to a wide range of *in vitro* mutagenicity tests. There is no convincing evidence for any mutagenic potential of this sweetener (Kramers 1975, Rao *et al* 1979 and Eckhardt *et al* 1980).

Saccharin can be manufactured by two processes, Remsen-Fahlberg or Maumée. The Remsen-Fahlberg process is known to give rise to *o*–toluene sulphonamide (OTS) as an impurity. In the past levels of OTS may have been as high as 5000 ppm but are now commonly of the order of 200 ppm or less. At one time it was postulated that the increased incidence of bladder tumours observed in the second-generation male rats may have been caused by the presence of the OTS impurity in commercial saccharin. However OTS is no longer regarded as a problem (Arnold *et al* 1980, Hoosen *et al* 1980).

Saccharin has been the subject of many epidemiological studies which have investigated possible associations between bladder cancer and artificial sweetener consumption. It is not possible to consider saccharin consumption alone in studies investigating sweetener use before 1969 since until then saccharin was nearly always used in conjunction with cyclamate. In studies reported prior to 1977 no positive association between artificial sweetener consumption and bladder cancer incidence was observed, even in diabetics who consumed greater quantities of artificial sweeteners, and smokers who are thought to have an increased risk of bladder cancer. However Howe *et al* (1977) reported a 60% increased risk of bladder cancer in males consuming table-top sweeteners, but a decreased risk in females. As in all previous epidemiological studies, Howe's conclusions were based on very small group

sizes and the significance of these findings is questionable. A recently completed study by the National Cancer Institute (NCI) (Hoover *et al* 1980) of approximately 3000 cases of bladder cancer has shown that consumption of artificial sweeteners from any dietary source (food, soft drinks, table top sweeteners) had no effect overall on bladder cancer incidence; in particular males were at no increased risk. Thus the findings of the study by Howe *et al* were not confirmed. However in the NCI study positive, albeit minimal, associations between artificial sweetener use and bladder cancer were noted in women at an otherwise low risk for bladder cancer (ie. non-smokers, non-coffee drinkers without occupational exposure to known bladder carcinogens) and heavy smokers, but these sub-groups consisted of few subjects and the associations may have been merely chance variations within the study. More recent epidemiological studies, but with small group sizes, support the overall negative findings of the NCI study (Kessler and Clark, 1978, Wynder and Stellman, 1980, Morrison and Buring, 1980).

Following consideration of all the data available it may be concluded that saccharin is associated with an increased incidence of urinary bladder tumours in second generation **rats** following continuous oral administration at very high doses relative to the amounts consumed by man. However, epidemiological studies have failed to show an association between saccharin use and urinary bladder cancer in man; this is consistent with saccharin being neither a complete carcinogen nor a bladder tumour promotor in humans. Nevertheless, as a measure of prudence we *recommend* only temporary acceptance of saccharin for use in food. Further studies are not recommended at present but the following unresolved problems should be noted:–

a. the mechanism by which saccharin, at very high doses, causes bladder tumours in second generation rats is not known, neither is the reason clear as to why males are more susceptible than females,

b. it is not known whether the mechanism(s) that operate(s) in rats would operate in man under conditions of normal dosages, under conditions of very high dosages or when exposure begins *in utero*.

We are aware of an ongoing large scale long-term two generation study in rats sponsored by the Calorie Control Council at the International Research and Development Corporation. We understand this study is due for completion at the end of 1981 and we hope to see these results as soon as they are made available. These results may help to resolve some of the problems discussed above and therefore we are not recommending any further studies at this time. We also wish to see the results of any further analyses that may be carried out on the National Cancer Institute epidemiology study. We hope that the monitoring of cancer incidence, particularly bladder cancer incidence, and artificial sweetener consumption continues in order to detect any changes, which because of the latent period required for tumour development might not yet have become apparent. Finally we *recommend* that data be collected on the intake patterns for saccharin following the introduction of other new sweetening agents onto the market (see para 6). (References 58–142)

ii. Cyclamic acid and its sodium and calcium salts

Cyclamic acid and its sodium and calcium salts were removed from the list of permitted artificial sweeteners at the end of 1969, following reports of possible urinary bladder carcinogenicity in rats fed a 10:1 mix of cyclamate and saccharin (Price *et al*, 1970, published in full as Oser *et al*, 1975). Many long-term rat studies have been performed since with cyclamate, either alone or as a 10:1 mix with saccharin, to investigate this further. No significant increase in the incidence of urinary bladder tumours has been detected in any of these subsequent direct feeding studies in the rat that would support the earlier findings, and there is no evidence of increased incidence of urinary bladder tumours in other species following oral administration. The increased incidence of bladder tumours reported in mice after direct implantation of cyclamate-containing pellets into the bladder (Bryan *et al* 1970), and in rats fed cyclamate in the diet following previous instillation into the urinary bladder of a potent bladder carcinogen (*N*–methyl–*N*–nitrosourea) at doses previously shown by the authors to be just subcarcinogenic (Hicks *et al*, 1975) are not regarded as interpretable in terms of the human situation.

Although urinary bladder tumours have not been observed in mice following lifetime exposure to cyclamate in the diet, questions have been raised about tumours in other tissues in this species. Slight increases in multiple pulmonary tumours or hepatocellular adenocarcinoma were reported in mice of certain strains receiving cyclamate in the diet; however these increases were not observed consistently in all strains studied and various aspects of the study design and performance were inadequate, including details of the histopathological examinations (Rudali *et al*, 1969). Furthermore these findings have not been confirmed in any of the studies carried out subsequently. In one lifetime study the incidence of lymphosarcoma appeared to be increased in a dose-related manner in female mice, but this was accompanied by an equal but opposite effect in males. Furthermore the incidence of lymphosarcoma was within the normal range for that strain of mice and laboratory (Brantom *et al* 1972). In another study incorporating lifetime exposure of the P, F3b and F6a generations, an increased incidence of 'lymphosarcoma' involving the lymph nodes was reported in male mice receiving cyclamate alone, which was not dose-related and was not seen in females. However, there was no correlation between the reported involvement of lymph nodes and the spleen and therefore the classification of the lesion is doubtful (Kroes *et al*,1975). Thus we consider the apparent increases in lymphosarcoma in mice to be unrelated to exposure to cyclamate.

The results of many tests on cyclamate and its principal metabolites, mainly cyclohexylamine (CHA), have shown no clear evidence of any mutagenic potential. In particular, where positive effects have been seen in *in vivo* cytogenetic studies, the effects were restricted in most cases to chromatid breaks or gaps without evidence of chromatid exchange, which is a more reliable indicator of genetic damage.

The results of many of the epidemiology studies investigating artificial

sweetener use and human bladder cancer incidence described above (para 14i) can be said to relate equally to cyclamate and to saccharin, as before 1969 saccharin was most often used in a 1:10 mix with cyclamate.

It has been demonstrated that ingested cyclamate can be converted to CHA through the action of the gut flora, in both animals and man. Only that cyclamate which is unabsorbed and remains in the lower gut is available for conversion. Studies have shown that the proportion actually converted varies between individuals and from day to day in the same individual; in some human subjects the proportion of ingested cyclamate converted to CHA may be as much as 60% or more. The major toxic effect seen in direct feeding studies with CHA is that of testicular atrophy in the rat. Although the atrophy is accompanied by a marked decrease in weight gain and food consumption, it does not appear to be secondary to this, but to be a direct toxic effect of CHA itself. There is a single report of a slight adverse effect on testicular function in dogs, that was reversible after cessation of dosing. However there is no evidence of testicular atrophy in mice fed equivalent amounts of CHA over most of their lifespan nor in rats fed cyclamate itself although the degree of conversion of cyclamate to CHA was not determined in these latter studies. The relevance of this effect to the human situation is therefore uncertain.

In conclusion, we consider that none of the direct feeding studies carried out in rats since the removal of cyclamate from the list of permitted artificial sweeteners (on the basis of Oser's results) has shown any increase in the incidence of urinary bladder tumours that would support the earlier findings. Furthermore, we do not consider there to be any association between lifetime exposure to cyclamate and carcinogenesis in the mouse.

We note that some of the unresolved problems associated with saccharin and urinary bladder tumours arising from the data of Hicks and others may also be applicable to cyclamate and therefore it is as a matter of prudence that we consider cyclamate to be only temporarily acceptable for use in food.

In view of the known conversion of cyclamate to CHA in man and the findings of testicular atrophy in the rat fed CHA itself in the diet we *recommend* that, for the time being at least, the intake of cyclamate should be restricted. There is also a need for assurance from research on the mechanism(s) involved that the production of testicular atrophy in rats by CHA is not indicative of risk to man. Thus for the present we *recommend* that the consumption of cyclamate be limited by restricting its use to certain designated food items and that consumption be monitored to enable determination of actual intakes in both the general population and in particular subgroups. (References 91, 92, 102, 124, 143–195).

iii **Sorbitol**

Sorbitol is currently permitted for use in food without restriction by the Miscellaneous Additives in Food Regulations, 1980. It has a long

history of use in the human diet, particularly in diabetic diets, without indication of significant harmful effects. Biochemical data indicate that sorbitol is only slowly absorbed from the gastrointestinal tract and that it is slowly acted upon by bacteria, properties which probably account for the diarrhoea experienced by subjects ingesting large quantities of sorbitol (50g or more daily). There are few conventional toxicological studies on sorbitol although it was used at a single dose level (20% of the diet) as an appropriate control for xylitol in two year studies in the rat and dog and in a multi-generation study (see below para 14v). Various effects were seen with sorbitol including adrenal medullary hyperplasia (see para 7). Because only one very high dosage level of sorbitol was used it is not possible to evaluate fully the significance of these effects for man. It is interesting to note that similar effects were seen in the same study in the animals receiving high doses of xylitol (see para 14v) and also in studies with animals receiving mannitol (para 14iv); this indicates a generalised non-specific cause for these effects. There are also data indicating that sorbitol, mannitol and xylitol alter mineral absorption and/or excretion, in particular of calcium. We *recommend* that these effects of sorbitol be investigated further (see paras 7, 8). We also *recommend* that data be collected on the intake patterns for sorbitol following the introduction of other new bulk sweetening agents onto the market (see para 6). (References 196–209, 221, 223, 224, 231, 232, 233)

iv. Mannitol

Mannitol is currently permitted for use in food without restriction, by the Miscellaneous Additives in Food Regulations 1980, although in practice it is not used as widely as sorbitol. It occurs extensively in nature in various vegetables and there is a long history of its clinical use for the induction of diuresis. Biochemical data indicate that mannitol is slowly absorbed from the gastrointestinal tract, thus probably explaining its laxative effects in subjects ingesting large amounts (10–20g or more daily) of mannitol. A recent long-term study with mannitol in female rats has indicated an increased incidence of adrenal medullary hyperplasia in treated animals, although the incidence varied between strains. There is also evidence that mannitol increases calcium and magnesium absorption and excretion. We *recommend* therefore that these effects of mannitol, which appear to be common to other bulk sweeteners, be investigated further (see paras 7,8) and that data be collected on the intake patterns of mannitol following the introduction of other new bulk sweetening agents onto the market (see para 6). (References 210–215)

v. Xylitol

Xylitol occurs widely in nature in a variety of fruits and vegetables and it is a normal intermediate in carbohydrate metabolism in animals and man, proceeding via the glucuronic acid-xylulose cycle and pentose phosphate shunt or by dehydrogenation to D-xylulose and subsequent phosphorylation to xylulose 5–phosphate. Xylitol has been subjected to extensive toxicological testing, with long-term studies in rats, mice and dogs, a multigeneration study

in the rat and metabolic and biochemical studies in animals and man. Sorbitol was included as an appropriate control in many of these toxicological studies. The data available indicate that exposure to high dietary levels of xylitol results in similar effects to those seen with sorbitol and mannitol, namely gastrointestinal disturbance, adrenal medullary hyperplasia (see para 7) and altered mineral absorption and/or excretion. We *recommend* therefore that these effects be investigated further (see paras 7,8) and that data be collected on the intake patterns of xylitol following its introduction onto the market (see para 6). (References 216–242)

vi. Hydrogenated glucose syrup

Following ingestion hydrogenated glucose syrup is broken down at least partially to glucose and sorbitol. The laxative potential of this sweetener appears to be lower than that of an equivalent amount of free sorbitol, probably because a proportion of the total sorbitol derived from hydrogenated glucose syrup remains in the form of short chain polysaccharides. Short-term studies in the rat and dog, together with metabolic data, mutagenicity data and human tolerance studies do not contra-indicate the use of hydrogenated glucose syrup as a sweetening agent; however no long-term studies are available. In the light of the evidence that hydrogenated glucose syrup breaks down *in vivo* into glucose and sorbitol we do not consider it necessary to request long-term studies on the material itself at this time, nor to recommend that further work be performed along the lines of that requested above for sorbitol, mannitol or xylitol. However until the results of the work on sorbitol are available for evaluation we can only *recommend* that hydrogenated glucose syrup be classified as temporarily acceptable for use in food. We also *recommend* that data be collected on the intake patterns of hydrogenated glucose syrup following its introduction onto the market (see para 6). (References 243–257)

vii. Isomalt

Isomalt is produced by the enzymic transglucosidation of sucrose to isomaltulose followed by hydrogenation. It is broken down initially in the gastrointestinal tract to form sorbitol, mannitol and glucose, some of this breakdown occurring in the lower gut due to the action of the gut flora. Isomalt has some laxative effect when fed at high levels in the diet of animals and man. Short-term studies in the rat and dog do not indicate any signs of toxicity apart from a dose-related increase in bilirubin in the rat. Metabolic data in animals and tolerance studies in animals and man are also available. In the light of the evidence that isomalt breaks down *in vivo* into glucose, sorbitol and mannitol we do not consider it necessary to perform long-term studies on isomalt at this time, nor to *recommend* that further work be performed along the lines of that requested above for sorbitol, mannitol or xylitol. However we do *recommend* that within two years of the publication of this Report further information be provided on the effects of isomalt on bilirubin levels in the rat. Until these data and the results of the work on sorbitol and mannitol are available for evaluation we find isomalt only

temporarily acceptable for use in food. We also *recommend* that data be collected on the intake patterns of isomalt following its introduction onto the market (see para 6). (References 258–284)

15. **Summary of Recommendations**

i. We have made a number of recommendations in this Report, including those set out below:–

a. We would like to see the toxicological information submitted to us published in the scientific press (see para 2).

b. After a period to allow for new food manufacturing practices to develop and the market to stabilise following the implementation of new regulations, information should be collected to enable calculation to be made of intake levels in the general population and in special groups (see para 6).

c. A programme of work should be carried out on sorbitol, mannitol and xylitol to investigate further the effects seen following consumption of large amounts of these sweeteners, that may be linked to changes in vitamin B_6 status and oxalate metabolism, and/or mineral absorption and excretion (see paras 7,8).

d. Sweetening agents should not be added to normal foods for babies and young children; this does not preclude their use in such foods prepared for special dietary purposes (see para 9).

ii. We have classified the substances submitted to us in the following groups:–

GROUP A: aspartame
acesulfame potassium

GROUP B: saccharin and its sodium and calcium salts
cyclamic acid and its sodium and calcium salts
sorbitol
mannitol
xylitol
hydrogenated glucose syrup
isomalt

iii. Consideration of the safety-in-use of thaumatin has been deferred until the results of studies known to be in progress are available.

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APPENDIX III

GENERAL PURITY CRITERIA APPLICABLE TO PERMITTED SWEETENERS EXCEPT WHERE OTHERWISE PROVIDED BY SPECIFIC PURITY CRITERIA

Each sweetener shall not contain:

(a) more than 3 milligrams per kilogram of arsenic;
(b) more than 10 milligrams per kilogram of lead.

SPECIFIC PURITY CRITERIA APPLICABLE TO PERMITTED SWEETENERS

Acesulfame Potassium

Chemical name	potassium–3,4–dihydro–6–methyl–2,2,4–trioxo–2 λ^6, –1,2,3–oxathiazin–3–ide
Empirical formula	$C_4H_4KNO_4S$
Molecular weight	201.2
Description	white, odourless, crystalline powder or granules with an intensely sweet taste.
Content	not less than 99.0 per centum on a volatile matter-free basis
Volatile matter	not more than 1.0 per centum (determined by drying at 105°C to constant weight).
pH of a 1 per centum aqueous solution	not less than 6.5 and not more than 7.5.
Potassium acetate	not more than 0.5 per centum
Fluoride	not more than 30 mg/kg.

Aspartame

Chemical name	3–amino–*N*–(α–methoxycarbonyphenethyl)–succinamic acid; L–aspartyl–L–phenylalanine methyl ester
Empirical formula	$C_{14}H_{18}N_2O_5$
Molecular weight	294.3
Description	white, odourless crystalline powder with an intensely sweet taste.
Content	not less than 98.0 per centum on a volatile matter-free basis.
Volatile matter	not more than 4.5 per centum (determined by drying at 105°C to constant weight).
Specific rotation, $[\alpha]_D^{20°C}$	not less than +12.5° and not more than +17.5° (determined using a 4 per centum weight/volume solution on a volatile matter-free basis in 15M formic acid).
pH of a 0.8 per centum aqueous solution	not less than 4.0 and not more than 6.5.
Sulphated ash	not more than 0.2 per centum after ignition at 800±25°C.
5–Benzyl–3,6–dioxopiperazine acetic acid	not more than 1.5 per centum.

Hydrogenated Glucose Syrup

Description	clear colourless sweet-tasting aqueous solution of sorbitol, hydrogenated oligosaccharides and polysaccharides prepared by the catalytic hydrogenation of glucose syrup.
Content	on a dryweight basis the product has the following approximate composition: 4–*O*–α–D–glucopyranosyl–D–glucitol (50 per centum), hydrogenated higher polysaccharides (20 per centum), hydrogenated tri– to heptasaccharides (20 per centum) and free D–glucitol (7 per centum).
Dextrose equivalent	not less than 45 and not more than 48.
Solids content	not less than 74 per centum.
Reducing sugars	not more than 0.3 per centum on a dryweight basis, expressed as dextrose.
pH of a 40 per centum solution in water	not less than 5.0 and not more than 7.0.
Sulphur dioxide	not more than 10 mg/kg on a dryweight basis.
Sulphated ash	not more than 0.1 per centum after ignition at 800± 25°C, calculated on a dryweight basis.
Sulphate	not more than 0.01% on a dryweight basis, expressed as SO_4.
Chloride	not more than 50 mg/kg on a dryweight basis, expressed as Cl.
Nickel	not more than 2 mg/kg on a dryweight basis, expressed as Ni.

Isomalt

Chemical description	an approximately equimolar mixture of 6–*O*–α–D–glucopyranosyl–D–glucitol and 1–*O*–α–D–glucopyranosyl–D–mannitol
Empirical formula	$C_{12}H_{24}O_{11}$
Molecular weight	6–*O*–α–D–glucopyranosyl–D–glucitol ($C_{12}H_{24}O_{11}$): 344.3 1–*O*–α–D–glucopyranosyl–D–mannitol ($C_{12}H_{24}O_{11}.2H_2O$): 380.3
Description	white, odourless, crystalline, slightly hygroscopic solid with a sweet taste.
Content	not less than 98.0 per centum of 6–*O*– α–D–glucopyranosyl–D–glucitol and 1–*O*–α–D–glucopyranosyl–D–mannitol; each shall be present at a level of not less than 43 per centum (on a dry weight basis in each case).
Water	not more than 7.0 per centum (Karl Fischer).
Specific rotation, $[\alpha]_D^{20°C}$	not less than +91.5° (using a 4 per centum weight/volume aqueous solution).
Reducing sugars	not more than 1.5 per centum on a dryweight basis, expressed as dextrose.
D–Mannitol	not more than 0.5 per centum on a dryweight basis.
D–Sorbitol	not more than 0.5 per centum on a dryweight basis.
Ash	not more than 50 mg/kg after ignition at 800± 25°C, calculated on a dryweight basis.
Nickel	not more than 2 mg/kg on a dryweight basis, expressed as Ni.

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Xylitol

Chemical name	*meso*–xylitol
Empirical formula	$C_5H_{12}O_5$
Description	white, odourless, crystalline powder or crystals with a sweet taste.
Content	not less than 98.0 per centum on a volatile matter-free basis.
Volatile matter	not more than 0.5 per centum (determined by drying at 60°C over phosphorus pentoxide in vacuum for 4 hours).
Reducing sugars	not more than 0.2 per centum on a volatile matter-free basis, expressed as dextrose.
pH of 10 per centum acqueous solution	not less than 5.0 and not more than 7.0.
Other polyols	not more than 0.5 per centum singly and not more than 1.0 per centum in total on a volatile matter-free basis.
Ash	not more than 0.1 per centum after ignition at 800±25°C, on a volatile matter-free basis.
Nickel	not more than 2 mg/kg on a volatile matter-free basis, expressed as Ni.

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