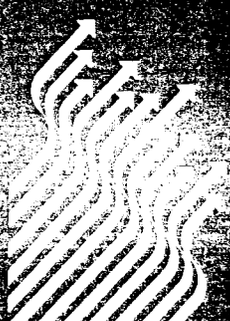
food - science technique

Reports of the Scientific Committee for Food

(28th series)



Report

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food — science and techniques

Reports of the Scientific Committee for Food

(28th series)

Report on infant formulae claimed to be 'hypoallergenic' or 'hypoantigenic'

(Opinion expressed on 9 December 1991)

Second Addendum concerning the essential requirements of infant formulae and follow-up milks based on cows' milk proteins and the minimal requirements for soya-based infant formulae and follow-up milks

(Opinion expressed on 9 December 1991)

Report on foods for particular nutritional uses whose sodium content has been modified Low sodium foods and salt substitutes

(Opinion expressed on 9 December 1991)

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A. LAFONTAINE
E. POULSEN
R. TRUHAUT

For his valuable and kind assistance to the "Report on infant formulae claimed to be 'hypoallergenic' or 'hypoantigenic'", the Scientific Committee for Food wishes to thank:

S. STROBEL The Hospital for Sick Children, London

Report of the Scientific Committee for Food on infant formulae claimed to be "hypoallergenic" or "hypoantigenic"

(Opinion expressed on 9 December 1991)

Terms of Reference

To advise on the minimum requirements of infant formulae based on protein hydrolysates presented as "hypoallergenic" or "hypoantigenic" products.

Introduction

1. Over the last years, the Committee adopted two reports on the minimum requirements of infant formulae and follow-up formulae based on cows' milk proteins [1] and soya proteins [2]. These reports have been supplemented by two addenda listing the nutritional substances which may be used in the preparation of these products [3,4].

2. Products based on high degree protein hydrolysates from different sources (primarily casein and/or lactoserum proteins) have been available for more than 40 years. They were and still are used mainly to treat various digestive disorders resulting from external pancreatic insufficiency, short bowel syndrome, enteropathies of various etiologies and proven allergy to cows' milk proteins. These products, which obviously belong to the category of "dietetic food for special medical use", are generally subjected to other modifications, especially in regard to their carbohydrate and fat content, in order to increase their efficacy in the treatment of gastrointestinal disorders and to prevent malnutrition [5-10].

3. Besides these classical semi-elemental diets for therapeutic use, new products based on hydrolysed proteins, presented as "hypoallergenic" or "hypoantigenic" formulae have been on the market since 1987 [11-13]. According to manufacturers, at present, they are sold in at least five EC member states, the USA and Canada [14]. They correspond to a more or less high degree hydrolysate. Due to the technological procedures used, these formulae have an at least 100 fold reduction of the major antigenic content compared with standard adapted milk formulae. This report deals with the above mentioned products and the conditions warranting the claims "hypoallergenic" or "hypoantigenic".

Definitions

4. The definitions and conversion factors used in the reports cited above [1,2] and in the first Report of the Scientific Committee for Food on the essential requirements for weaning foods [15] also apply in this report.

5. On the other hand, in order to avoid confusions as regards semantics, the following definitions have been adopted for this report:

Antigen:	A substance that can induce an immune response.
Allergen:	An antigen capable of inducing an allergic response.
Allergy:	Pathological clinical reaction after exposure to an allergen in persons already sensitized by a previous contact, irrespective of the underlying immunological mechanism.
Atopy:	Constitutional anomaly consisting of a hyperreactivity to environmental substances, connected with an altered IgE regulation.
Anaphylaxis:	Immediate hypersensitivity reactions (Type I of Gell and Coombs classification) involving the interaction of an antigen with IgE.
Tolerance:	Desirable clinical (and immunological) hypo-responsiveness after a food, bacterial or viral antigen are repeatedly administered via the oral route.
Food intolerance:	Undesirable reaction to a certain food or a specific ingredient of variable etiology (enzymatic deficiency, toxic, infectious, etc.) but where there is no known relationship with immunity.
Food allergy:	Clinical hypersensitivity reaction involving all arms of the immune system (humoral, IgE, IgG, IgA, etc.) and/or cellular mechanisms.
At risk infant:	Infants of one or two allergic parents and/or whose IgE level in cord blood exceeds 0.7 U/ml .

Documents consulted

6. In drafting this report, the Committee considered the data in the literature, the opinions adopted by the Committee on Nutrition of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) [16], the report of the Sub-Committee on Nutrition and Allergic Disease of the American Academy of Pediatrics [17] and the information provided by the Association of Dietetic Foods Industries of the EEC (IDACE), especially concerning the characteristics of products now on the market, the results of current experiences and conditions which allow the claim of "hypoallergenicity".

General Considerations

7. All dietary proteins, and especially cows' milk proteins, can cause various clinical disorders affecting virtually all organ systems. These can develop in the digestive tract in acute or chronic forms, in the respiratory system (asthma, spasmodic rhinitis), in the

skin (urticaria, atopic eczema, contact dermatitis) and include anaphylactic shocks, all of which are recognized allergic symptoms [18,19].

8. Allergy is one of the most significant morbidity factors in industrialized countries, affecting 20 to 35 % of the population [20,21]. The prevalence of food allergy itself varies according to statistics between 0.3 to almost 50 %. However, these extreme values are not realistic [22] and it is more reasonable to consider the prevalence of milk allergy as being around 2 to 7 % [23-25].

9. The risk of developing atopic disorders is approximately two times greater for infants where one parent or one brother or sister suffers from an allergy, compared with the normal population, and this risk is three times higher if both parents have allergic diseases [20]. Moreover, the risk of developing an atopic disease is much higher in infants in which the total IgE level in the cord blood is above 0.7 kU/L, compared with children in which the IgE level is below this value (52 % versus 13 %). The IgE level in cord blood is most frequently elevated in newborns with a family history of allergy [20,26]. Moreover, the risk of developing atopic disorders is around 3 in 4 (75%) for infants with an allergic family history and an elevated cord blood IgE level, while it is only 1 in 30 for infants without increased IgE level and no family history of allergy [27]. It is important to consider that around 3 % of infants are born to two atopic parents and that almost 10 % of newborns have an elevated IgE level at birth [28]. And finally, despite contrasting opinions [29], it seems to be established that the frequency of certain atopic disorders, especially asthma and allergic rhinitis, are increasing in industrialized countries [30,31], though, at the same time, it has not been shown that the frequency of other allergic food disorders is also increasing [19].

10. Oral ingestion of dietary proteins normally induces a condition of clinical tolerance. Without this fundamental phenomenon all feeding would quickly become impossible. This "non-response" when a food antigen is repeatedly administered must be distinguished from an active immunization process, in which cellular reactions take place and specific antibodies are produced in the presence of antigens and which, in a way, is the "normal" response of the organism to any antigenic attack. The characteristics of this tolerance acquisition process have been primarily studied in mice [32,33]. The type of reaction is related to the time of first antigen encounter. The early administration of ovalbumin to young mice induced sensitization, which was not observed when the same quantity of ovalbumin was given later. However, the chronic exposure to antigens after initial immunization modulates the immune response. Repeated doses seem to be more effective than a single ingestion for suppressing the hypersensitivity reaction. Repeated antigen feeds given to sensitized animals can induce a "secondary tolerance" [33]. Of course, it is difficult to extrapolate from baby mice to infants due to the differences in their digestive and immune-related developments. Nevertheless, it is conceivable that the digestive and immunological immaturity of newborns, as in baby mice, favors the stimulation of T-helper cells, so preventing the induction of tolerance by T-suppressor cells [33,34]. Within the framework of this hypothesis, it might be beneficial not to feed very young infants the highly antigenic proteins (e.g. cows' milk proteins) [35].

11. Generally speaking, it is accepted that during the first weeks of life, infants are at a greater risk of developing food allergy and the early exposure to cows' milk increases this risk, not only with regard to allergic reactions to cows' milk proteins but also the development of allergy to other foods [36]. In a prospective study, it was shown that almost all of the infants diagnosed as having an allergy to cows' milk in the first year had received a cows' milk formula before the first month of life, and more than half before the age of one week [37]. Allergy to cows' milk proteins is observed rarely in infants who have been exclusively breast-fed during more than the first three months of life. A retrospective study of infants who developed an allergy to cows' milk revealed that although they were breast-fed up to the first three months, they had in fact received a

quantity of cows' milk equivalent to 0.4 - 3 g of β-lactoglobulin during the first days after birth [25]. However this information is contrasted by results of another randomized prospective study, in which the introduction of cows'milk proteins to infants during the first days after birth followed by breast-feeding, significantly reduced the incidence of allergic diseases at 18 months, compared with those not given cows' milk during the first days after birth. However, this difference was only observed when families at high risk, with two first degree relatives with atopy [38] were considered. The latter results are even more surprising considering that, in this connection, it is undoubtedly more dangerous to give cows' milk to newborns occasionally than regularly [25].

12. The theory that prolonged breast-feeding protects infants from the risk of subsequently developing asthma, eczema or other atopic diseases has long been controversial [18,39,40]. Ever since a constantly cited study was published in 1936 [41] which showed that, in a population of 20,000 infants, breast-feeding reduced the incidence of eczema by 7 times compared with artificial feeding, it has never been convincingly demonstrated that breast-feeding has a protective effect against atopy in a normal non-selected infant population. On the other hand, results from prevention studies in infants at risk (family history of allergy and/or elevated cord blood IgE level) are contradictory, supporting or rejecting the assertion that breast-feeding and a delayed dietary diversification reduce the risk of food allergy [40]. Some studies have even suggested an increase in the incidence of atopic diseases in infants exclusively breast-fed [18].

13. However, most of these are not randomized studies, thus creating biases especially with regard to recruitment of families. Moreover, they were not well controlled for a series of confounding factors, especially the age at which other foods besides milk are introduced, exposure to tobacco, air pollution, presence of pet animals (dogs, cats, etc.) and other environment-related variables [40]. In reality, mothers that breast-feed their infants over a longer period generally diversify the diet of their infants more progressively, less frequently request others to look after their infants and on the average smoke less than those mothers artificially feeding their infants. All of these factors may reduce the risk of sensitization [40,42]. Usually, these studies also have other weaknesses, especially the collection of *a posteriori* data, the absence of immunological investigations (e.g. the determination of specific IgE), inaccuracy regarding the duration of breast-feeding, the small sample size and the high number of dropouts [18,40,43]. Nevertheless, if the major problem of these studies is the absence of random assignment to one group or another – breast-feeding or artificial feeding – it must be recognized that, considering the advantages of breast-feeding, random sampling can pose ethical problems and may only be justifiable today in premature infants. In their case, an increased risk of allergic reactions can be balanced against the demonstrated advantages of using low birth weight infant formulae [44].

14. Since the decision whether to breast-feed an infant or not must be left up to the mother, it is essential to ensure that the groups are as comparable as possible regarding the identified confounding variables such as family history of allergy and the infants' IgE level at birth [45]. In studies where these precautions have been taken, exclusive breast-feeding during the first 4 - 6 months after birth and delayed introduction of other food significantly reduced the incidence of atopic diseases, especially eczema, and of the gastro-intestinal symptoms attributed to cows' milk up to the age of 12 to 36 months in infants at risk [26,44,45-47].

15. The protective effect of breast-feeding against eczema may be even more powerful if mothers exclude substances considered "allergenic" from their diet, especially milk products, eggs, peanuts and soya. In families at risk, a randomized trial revealed that at the age of 18 months, eczema was two times less frequent and less severe in breast-fed babies whose mothers followed an exclusion diet than in those whose mothers did not

modify their diet during the nursing period [45]. In another randomized study, the strict exclusion of milk, eggs and peanuts from the mother's diet during the last three months of pregnancy and during breast-feeding, the use of a casein hydrolysate to supplement breast-feeding or to replace it, if necessary, for up to 6 months of age and the exclusion of a number of common food products up to the age of 2 years, helped to significantly reduce the incidence of food allergic diseases such as atopic dermatitis, urticaria and gastro-intestinal disorders. On the other hand, the prevalence of allergic rhinitis and asthma was not modified by this dietetic manipulation [48]. However, no such favourable results were observed in other studies [49].

16. The effects of excluding food antigens from the mother's diet could be explained by the reduced passage of dietary substances into breast milk, such as β-lactoglobulin, bovine IgG, ovalbumin and wheat gliadin [25,50-54]. Various allergic disorders, including anaphylactic shock, have been observed in breast-fed infants where the mother consumed one of these antigens [55]. A correlation has been established between infantile colics and the consumption of cows' milk proteins by mothers [56]. However, many breast-fed infants suffering from eczema do not respond to maternal dietary manipulations [57] and a "hypoallergenic" diet for pregnant or breast-feeding females is not without risks if it is not accompanied by dietetic advice and appropriate monitoring [58].

17. Infant formulae based on soya proteins are suitable alternatives for cows' milk formulae in infants suffering from lactose intolerance or from galactosaemia. These formulae are also sometimes chosen by consumers who, for various reasons, do not wish to give their children products based on animal proteins [2]. On the other hand, they are often used in cases where there is suspicion or evidence of an allergy to cows' milk protein and for newborns and infants of families at risk, especially in the United States of America, where they represent almost 25 % of the infant-formula market [2,59,60]. However, there are very well documented reports of severe gastro-intestinal reactions in the form of vomiting, diarrhoea, weight loss, villous atrophy and even characteristic allergic symptoms as a result of feeding soya proteins. Moreover, intolerance associated with milk or soya proteins, or successive intolerance to these proteins, has been reported, especially when soya formulae have been prescribed for patients with acute gastroenteritis [2,60,61]. In some studies, almost one third of the infants allergic to cows' milk also reacted to soya [19,62,63] and, irrespective of the antigenic properties of soya, soya formulae are not considered any less allergenic than milk formulae [64]. The American Academy of Pediatrics has actually recommended that soya formulae should not be used to treat clinical allergic reactions to cows' milk proteins and/or to soya proteins [59] and, in line with the recommendations of ESPGAN [65], the Committee believes that less antigenic formulae (e.g. protein hydrolysates) should therefore be used in preference to soya formulae for infants who are allergic or who show signs of intolerance to dietary proteins [2].

18. The possibility of preventing symptoms of allergy in families at risk and in the population at large through the use of soya formulae has also been called into question. Even extremely well controlled studies have not revealed any difference in the development of an allergy that could be related to whether infants were given cows' milk or soya formulae [45,66-69], while a protective effect of breast-feeding [45,67-69] or casein hydrolysate [45] has been confirmed in all of the studies except for one [66]. Therefore, no reference should be made to the possible protective role of soya formulae with regard to allergy, which the Committee has already emphasized in a previous report [2]. Moreover, it must be noted that it is more difficult to exclude soya products than milk, from the diet of infants and young children because of the fact that soya is often added to products which are not assumed to contain it such as bread, sausages, etc.

19. The therapeutic efficacy of semi-elemental diets for treating proven enteropathy cases caused by cows' milk proteins and for infants with anaphylactic reactions to milk

products or other dietary proteins has already been proven [35,59]. Most of the studies were carried out with high degree casein hydrolysates (Nutramigen® and Pregestimil®, Mead Johnson) [7-9,48,70], with peptide sizes not above 1200 daltons molecular weight and which normally do not sensitize guinea pigs or induce anaphylactic reactions in them [71,72] even if it has been shown that these hydrolysates sometimes contain peptides which are large enough to be immunogenic in animals [73,74] and provoke allergic reactions in infants hypersensitive to dietary proteins [55,74,75,76]. The good tolerance and efficacy of a lactoserum hydrolysate (Alfaré®, Nestlé) have also been supported by a number of other publications [5,6,9,10] and anaphylactic reactions to this hydrolysate have only been rarely reported [6,77]. The published works on other high degree hydrolysed products based on casein (Alimentum®, Ross) [78-80], lactoserum proteins (Pepti Junior®, Nutricia) [81] or a mixture of soya proteins and beef collagen (Pregomin®, Milupa) [10], recently introduced onto the market, only involve a few cases and have often only been published in the form of abstracts, even if some of these products are used routinely with success to treat infants allergic to cows' milk.

20. There is no randomized study which has addressed the preventive effects of a high degree hydrolysate with regard to atopy. The only recent study is one, already cited, in which Nutramigen® was used alone or as supplement to maternal feeding up to the age of 6 months, but the associated prolonged exclusion of cows' milk and of other highly antigenic products makes it difficult to determine which dietetic measure (i.e. single or combination), is responsible for the almost 40 % reduction in the prevalence of atopy at the age of 12 months [48].

21. A number of *in vivo* and *in vitro* tests have been or are being carried out by companies (Milupa in Belgium, France and Germany; Nutricia in the Netherlands; Nutripharm in France) that market infant formulae presented as "hypoallergenic" or "hypoantigenic" based on high degree hydrolysed milk, soya or beef collagen proteins, alone or as mixtures, like products traditionally used to treat cases of enteropathy with sensitization to dietary proteins. Up to now, no study putting forward favourable or unfavourable effects of these formulae on the prophylaxis of atopic diseases in infants at risk has been published in an international, peer reviewed journal.

22. On the other hand, there is a series of studies on the effects of a lactoserum protein trypsin hydrolysate with a lower degree than that of other hypoallergenic formulae but whose allergenicity is reduced by a complementary heat treatment [82]. All of the studies carried out with this product, sold in several EEC Member States under various Nestlé brand names and more recently in the United States and Canada (Good Start®, Carnation) involved groups at risk. Hereafter in this report, this product is referred to as HA formula, for "hypoallergenic" formula.

23. It has been first shown that the early administration of this HA formula during the first 5 days after birth in high risk infants did not lead to any abnormal reactions when reintroduced after 4 to 6 months of exclusive breast-feeding [11], while the inadvertent exposure to cows' milk under the same conditions induces sensitization in approximately one third of the infants [25]. Randomized and non-randomized preliminary studies have shown that there are practically no atopic symptoms at 4 months of age [12] or that atopy is 3 times lower [83] in infants fed a HA formula compared to those receiving classical infant formulae. In the Düsseldorf study (FRG), practically no difference was found at the age of 4 months between breast-fed infants whose mothers followed an exclusion diet and those fed since birth with a HA formula [83]. The retrospective analysis (data questionnaires) of several German studies revealed that the incidence of allergic symptoms at the age of 11 months in exclusively breast-fed infants was similar to that of infants exclusively fed with this HA formula during the first 5 days of life [84]. This was confirmed by a non-randomized study carried out in Italy involving more than 300

children. Here, it was reported that infants fed from birth with a HA formula, for whom the diversification of the diet had been delayed to the age of 6 months and who received a hypoallergenic diet up to the age of one year, had an cumulative incidence of allergy at the age of 1 and 2 years that was even lower than that of the breast-fed infant group, which in turn was 3 to 4 times lower than that of infants fed with cows' milk or soya formulae [47]. In the non-randomized Düsseldorf study, at the age of 6 months, infants fed with a HA formula also had an incidence of atopic symptoms which was about twice lower than that of breast-fed infants, partially confirming the results obtained in a reduced number of infants [85]. In this study, 32 % of the infants fed cows' milk formulae since birth developed atopic symptoms compared with 6.8 % in the HA-formula-fed group [86].

24. Two randomized, double-blind prospective studies show the protective effects of HA formulae against atopy in infants at risk. In the Canadian study, 72 infants were recruited into each of the following groups: HA formula, conventional cows' milk formula, soya formula or exclusive breast-feeding during more than 4 months. While, in the HA formula group, only 5 infants (i.e. 7.4 %) developed atopic symptoms during the first 6 months of life, 24 (35.8 %) and 25 (36.7 %) respectively of the infants fed cows' milk or soya developed such symptoms, especially eczema; the severity of the eczema was however not affected in the group fed with a HA formula and there was no significant difference in the severity of the other clinical symptoms in the 4 groups studied [87]. In the first group the favourable effect of the HA formula has been confirmed at the ages of 1 year and 18 months, the incidence of eczema and other allergy symptoms being 50 % lower than in the groups fed cows' milk or soya; no difference was observed between breast-fed infants and those fed the HA formula [88]. In the Brussels randomized study, 75 infants received one or two coded formulae, either a HA formula or a conventionally adapted formula during 6 months. The incidence of allergic symptoms was significantly reduced ($p < 0.001$) during this period if a hydrolysate was administered continuously (2/32 or 6.3 %) compared with the incidence in the group fed the adapted formula (14/35 or 40 %). At the age of 1 year, 7/32 (21.8 %) of the infants fed the hydrolysate developed atopic symptoms against 17/35 (48.6 %) in the group conventionally fed [89].

25. As has already been mentioned, acute anaphylactic reactions have been reported in highly sensitized subjects given high degree casein hydrolysates [55,74-76] or lactoserum proteins [6,77] for therapeutic purposes. Similar reactions have also been described with HA formulae. In all of these cases, HA formulae were used for infants suffering from acute allergy to milk and/or to soya but who tolerated high degree casein or lactoserum protein hydrolysates [10,90-92]. This suggests that HA formulae might induce anaphylactic reactions more often than high degree hydrolysates in infants suffering from hypersensitivity to dietary proteins [19]. It should be emphasized though that, according to manufacturers [82], this type of hydrolysates is not meant to be used in the treatment of these infants and that, to our knowledge, no acute accident has been reported when HA formulae were used as first line treatment.

26. "Hypoallergenic" infant formulae, whether high degree hydrolysates or HA formulae, have been used in Europe for many years. Hundreds of thousands of infants have been given them for several months and no unfavourable effects on their growth and development have been observed. Clinical files, prepared within the framework of an application for authorization to commercialize them in those EEC Member States where these products are sold, show that the weight and height, and head circumference of infants fed "hypoallergenic" formulae are comparable with those of breast-fed infants or those fed artificially with conventional formulae [13,93,94].

27. Informations provided by IDACE and manufacturers indicate that the apparent digestibility, protein efficiency ratio (PER) and the net protein utilization (NPU) of

different "hypoallergenic" or "hypoantigenic" formulae sold today are on a par with or higher than those of casein. The heat treatments used – pasteurization, ultra-high temperature treatment (UHT) – do not differ radically from those applied to standard infant milks, and lysin blockage is not greater than 15 % in HA formulae in which the antigenicity of lactoserum protein hydrolysate is reduced by means of ultra-high temperature treatment, known to increase the production of Maillard reaction products [95]. On the other hand, whenever lysinoalanine, which can reduce the bioavailability of zinc, has been searched for [82], no notable quantity has ever been found in HA formulae. Its control however is not related to the production techniques used but related to the starting material since lysinoalanine is formed mainly from phosphoserine, present in casein but not in lactoserum (whey) proteins, and the production of HA formulae does not facilitate its formation.

28. There is still very little information in the literature on the nutritional efficacy and metabolic tolerance of "hypoallergenic" formulae in general. All data published are concerning HA formulae. No difference has been found between breast-fed infants, infants fed with adapted formulae and those fed with HA formulae, with regard to total plasma proteins, prealbumin, retinol binding protein (RBP), transferrin, creatinine, calcium, phosphorus and IgG [94]. The total plasma amino-acid concentration was found to be similar in the three groups, at the age of 5 - 6 days and at the age of one month. The distribution of essential and non-essential amino-acids differs only slightly from one group to another, for an approximate 2-fold increase in the concentration of threonine in infants receiving lactoserum protein trypsin hydrolysate [93,94,96]. With the exception of threonine, the plasma amino-acid profile of HA formulae is therefore very close to that of breast-fed infants. Considering the immaturity of threonine metabolic pathways at birth [96], it should be investigated whether this increase in plasma levels is found at a later age. Be that as it may, threonine seems to be one of the less toxic essential amino-acids in rats and no toxic effect of elevated threonine levels in plasma has been observed in infants [96].

29. Experimental studies in 14 days old unweaned rats, which are an appropriate model for studying the absorption of calcium and trace elements in infants, have revealed that zinc, copper, manganese and calcium bioavailability values for HA formulae are similar to the values obtained with breast milk and much higher than those found for soya formulae [97], in which a low bioavailability can be attributed to the elevated phytate content in soya [98-100]. No difference was found between a HA formula and a casein-based high degree protein hydrolysate [97], although the zinc bioavailability was lower with non-adapted formulae (ratio lactalbumin/casein 20:80) than with formulae enriched for lactoserum proteins (60:40), the high degree of hydrolysis suppressing the inhibitory effect connected with the chelation of zinc with casein itself and with the high-molecular weight phosphopeptides formed during its digestion [98-100]. On the other hand, the binding of calcium with phosphopeptide derivatives of β-casein would favour its bioavailability by keeping it in solution, as proven by the slightly higher calcium retention with a non-adapted formula in rhesus monkeys aged 7-8 months. In this model, no significant difference was observed between a HA formula and a formula with a high lactoserum protein content. The worst results were obtained with the soya formula and the best results with breast milk. The absolute quantities of calcium absorbed are nevertheless identical irrespective of the formula tested, including breast milk, which suggests that the present level of calcium and phosphorus supplements in standard or hydrolysed infant formulae is adequate for a normal skeletal mineralization [101].

30. Nothing indicates that the replacement of intact proteins by a hydrolysate or a mixture of amino-acids in rats modifies trophic or morphological parameters, the mucosa protein content or the enzymatic activity of the brush border [102-104]. The surface unit absorption of amino-acids and small peptides was reduced without knowing whether this means a modification of the resistance of the unstirred aqueous layers or an alteration in the

transport system of amino-acids and peptides [104]. In any case, it is likely that these findings are of low physiological significance. Observations made in piglets concerning organ development, digestive enzyme activity and amino-acid digestibility have not revealed any major differences between animals fed with cows' milk, a formula based on hydrolysed cows' milk proteins and isolated soya proteins. Thus, it is unlikely that the replacement of intact proteins by hydrolysed proteins in infant formulae might cause major digestive disorders [105].

31. The "hypoallergenic" or "hypoantigenic" character of a formula can only be demonstrated by appropriate clinical tests. These tests must be preceded by a complete set of pre-clinical tests combining physico-chemical and immuno-chemical methods, in order to:

1) characterize the molecular properties of the hydrolysate to the extent that its residual antigenicity can be derived from these;

2) assess the actual reduction of antigenicity compared with that of the proteins used, by *in vitro* as well as by *in vivo* tests [17,82,106].

32. In general, the narrower the molecular weight distribution of a protein hydrolysate, the greater seems the probability that it will have a highly reduced residual antigenicity and thus, be potentially hypoallergenic [17]. However, sequences of 4 amino-acids have been recognized as immunogenic [19] and in practice, it is not possible to set an upper limit for the size of residual peptides, below which hypoallergenicity could be guaranteed, even if polypeptides with molecular weights lower than 5000 daltons are less immunogenic and oligopeptides are generally not [107]. Moreover, the techniques used do not permit to precisely define these molecular weights. The size of peptides obtained varies according to experimental conditions, so that a comparison of the hydrolysates among themselves is only possible if the analyses are carried out simultaneously under identical conditions [17].

33. Not all milk proteins have the same sensitivity to endopeptidases usually used to manufacture hydrolysates, i.e. trypsin and pancreatin. Alpha (α) and beta (β) caseins, β-lactoglobulin (LG) and α-lactalbumin (LA) are very sensitive to trypsin. A high degree hydrolysis of these proteins practically abolishes their capacity to sensitize (orally) or to provoke a reaction (intravenously) in guinea pigs sensitized to the starting proteins under discussion. On the other hand, immunoglobulins are more resistant and serum-albumin (BSA) is only slightly attacked, but they can be very rapidly denatured at ultra-high temperatures [95,97].

34. The sensitivity of proteins to heat varies according to the structure of the proteins. Lactoserum proteins, especially β-LG, are more sensitive than caseins. Nevertheless, even for lactoserum proteins, the temperatures to be reached and the heating time required to significantly reduce antigenicity can, owing to the Maillard reaction, unacceptably alter the nutritional value of products [108,109]. On the other hand, epitopes can appear which are not present in natural proteins [82]. Therefore, heat treatment alone cannot be used to produce good quality hypoallergenic formulae but it can be used together with selective hydrolysis to give more acceptable and tasteful products than high degree hydrolysates [82,95,107]. Finally, neither the degree of hydrolysis nor the extent of heat treatment alone should be used as a basis for defining the hypoantigenicity of a formula. Informations on the processes used should be systematically communicated to the responsible controlling authority, if necessary confidentially.

35. Several conditions should be fulfilled to ensure the hypoallergenicity of hydrolysed formulae. It is essential to check:

1) that the immunoreactive protein concentration is less than 1/100 of the protein content normally present in the starting materials used, and

2) that, using appropriate animal models, the oral administration of the formula does not induce sensitization (including anaphylactic shock or the development of antibodies detectable by passive cutaneous anaphylaxis tests) to major milk proteins, to other proteins present in the starting materials used or to residual peptides [14,106,110].

The quasi-absence of native proteins can be assessed by several techniques, e.g. electrophoresis on polyacrylamide gel (SDS-PAGE), immuno-precipitation reactions on agarose gel (immuno-diffusion, immuno-rocket electrophoresis) and ELISA or radio-immunological (RIA) techniques, the latter being both able to detect quantities of β-LG of the order of 10 ng/ml, i.e. 100 times lower than *in vivo* methods [106]. The decisive element in all the techniques used to determine an interaction between a hydrolysate and a preformed antibody (ELISA, RIA, etc.) resides nevertheless in the quality of the antiserum, and even if today it is the manufacturers' responsibility to rigorously define the properties of the antiserums used for their controls, it is recommended that reference standards be developed which can be used to compare products with one another and to establish indisputable limits [17].

36. Although tests of provoked passive or active anaphylaxis in animals and very sensitive measurements of the residual antigenicity of formulae must be carried out before any tests are performed involving human subjects, these techniques cannot be used for batch controls. Therefore, manufacturers should be recommended to carry out a number of tests on each batch, in particular those used to check the absence of significant quantities of high molecular weight polypeptides (e.g. on polyacrylamide gel) and the absence of immuno-diffusion precipitation [17,82] or even more sensitive and faster methods still being developed. In addition, it should be remembered that most of the immunological tests cited above only study anaphylactic responses, and that the study of cellular immunity may reveal cross reactions which differ from those detected by antibodies [111]. Finally, the Committee believes that *in vivo* and *in vitro* analyses of residual immunogenicity must also involve the final product (ready for use) and not only one or two of the major protein constituents of the product.

37. Considering the incidence of food allergy in the population at large and the reduction in the frequency of these symptoms expected from an antigen reduced diet, it is virtually impossible to show that a "hypoallergenic" or "hypoantigenic" formula has preventive effects in a non-selected population. Nevertheless, the conditions under which clinical tests must be carried out cannot be dissociated from the indications proposed by the manufacturers and from the properties claimed for each type of formula.

38. In line with the recommendations made by the Subcommittee on Nutrition and Allergic Diseases of the American Academy of Pediatrics, the Committee believes that the names "hypoallergenic" or "hypoantigenic" or any equivalent names (e.g. "with reduced antigenic activity") can only be used if the respective infant formula is well tolerated by infants with hypersensitivity to dietary proteins and whose hypersensitivity to milk proteins or other proteins entering the composition of the hydrolysate has been confirmed within two months before the test [17]. However, the Committee does not believe it justified from an ethical standpoint to use a double-blind placebo test for this demonstration, as recommended by the *ad hoc* Subcommittee mentioned above [17], but thinks that an open test is more appropriate in this case, provided that it involves a sufficient number of subjects, considering the fact that acute reactions are always possible in highly sensitized subjects, irrespective of the properties of the products and the manufacturing processes used (see points **19** and **25**).

39. In compliance with the provisions of article 6, paragraph 4 of Council Directive No 89/398/EEC, the labelling of these formulae and their presentation must not contain claims for any preventive or therapeutic properties. The claim the Committee recommends to be added to Annex IV of the Commission Directive of 14 May 1991 on infant formulae and follow-up formulae should only be authorized for formulae fulfilling the criteria stated in the annex of the present document. In addition to mandatory information and to the claim mentioned above, the labelling could also include usual contra-indications, especially for infants with hypersensitivity to proteins contained in the starting material of the product, and possible contra-indications regarding the combination with other foods (milk products, cereals, baby food in jars, etc.) [110].

40. In compliance with the provisions of article 6 paragraph 2 of the above mentioned directive, the technical files and all documents intended for medical experts could nevertheless mention the preventive properties of these products, provided that these have been properly established, be it to prevent transitorily or possibly permanently some atopic symptoms (eczema, asthma, spasmodic rhinitis, etc.) or more simply to prevent digestive symptoms resulting from an allergy to cows' milk proteins [110]. In this regard, the tests must have been carried out on infants at risk fed during at least 4-6 months with the respective formula, using a double-blind, randomized protocol including a standard infant formula [17].

41. Except for the modifications introduced during the formulation of the product and its production in order to guarantee its hypoantigenicity, infant formulae claimed to have "hypoallergenic" or "hypoantigenic" properties should satisfy all of the criteria of essential composition listed in Annex I of the directive on infant formulae and follow-up formulae. Their nutritional efficacy should also be demonstrated in all cases by a longitudinal study on weight and height development over at least 3 months, involving at least 20 babies born at full term and aged less than 1 month at the beginning of the study. Finally, the Committee believes that besides all the indispensable information on the properties of the hydrolysate and the procedures used (enzymes, molecular weight distribution, percentage of blocked lysin, PER, NPU, etc.), the information should be complemented, if necessary, by data on the plasma levels of albumin and short half-life proteins (prealbumin, RBP, transferrin), and on the plasma amino-acid profile.

Conclusions and recommendations

42. Exclusive breast-feeding in infants at risk during 4-6 months and a delayed introduction of foods other than milk significantly reduces the incidence of atopic symptoms, especially eczema, and of gastro-intestinal symptoms attributed to cows' milk, at least up to the age of 12 to 36 months.

43. Soya formulae cannot be considered less allergenic than milk formulae. In the absence of maternal milk, less antigenic formulae (e.g. protein hydrolysates) should be used for infants at risk, allergic infants and those showing clinical signs of intolerance to dietary proteins.

44. The therapeutic efficacy of high degree hydrolysates in cases of enteropathy caused by cows' milk proteins, and in infants showing anaphylactic reactions to milk products or to other dietary proteins has been well established. However, this does not completely exclude the possibility of anaphylactic reactions in highly sensitized infants receiving casein-based or lactoserum protein-based hydrolysates for therapeutic purposes.

45. The incidence of intolerance to dietary proteins is also significantly reduced in infants receiving a low degree lactoserum (whey) protein hydrolysate when its allergenicity has been reduced by an additional heat treatment. These HA formulae too can induce anaphylactic reactions in hypersensitive infants, perhaps more often than high degree hydrolysates, but, according to the manufacturers, they are not intended for therapeutic use in these infants and no adverse reactions have been reported when these formulae were used in the first instance or for a prophylactic indication.

46. The protective effect of HA formulae with regard to atopy has been demonstrated by prospective double-blind studies with infants at risk. The incidence of eczema and other allergic symptoms is similar as in breast-fed infants and two times less than in infants fed with cows' milk or soya infant formulae; this reduction continues at least up to the age of 12 to 18 months. Comparable results have been obtained with a high degree casein hydrolysate. This randomized study where the hydrolysate was used alone or as a supplement to breast milk up to the age of 6 months, a strict exclusion of various antigens from the mother's diet during the end of pregnancy and lactation periods and a delayed introduction of a number of common foods into the diet of the infants up to the age of 2 years is difficult to interpret because of the additional dietary modifications.

47. Infant formulae claimed to be "hypoallergenic" or "hypoantigenic" or those "with reduced antigen or allergen content" have been used in several Member States for years and no undesirable effects on the growth or development of infants have been observed. Their indications, which are not the purpose of this report, remain to be discussed. Some people are of the opinion that they must be reserved for infants at risk and/or for infants with clinical intolerance symptoms, and others believe that they are contra-indicated for infants suffering from acute reactions to their constituting proteins and that their main indication is prophylactic. Considering the information at its disposal, the Committee believes that it is premature to make any recommendation on this matter, as the indications of the products undoubtedly differ, depending on the raw materials and the processes used. The Committee also believes that, no matter what results are obtained with these products, the provisions of the WHO Code on the marketing of breast milk substitutes must be strictly respected, and that public authorities must ensure that commercial practices and the information provided to medical and health professionals do not in any way discourage mothers from breast-feeding their infants.

48. In any case, the Committee considers that manufacturers should guarantee that such products satisfy the following criteria to be able to claim an "hypoallergenic" or "with reduced allergen content" or "hypoantigenic" or "with reduced antigen content" status:

- the proteins must have been treated in such a way that the immunoreactive protein amount, measured with the appropriate methods (SDS-PAGE, immuno-diffusion, ELISA, RIA, or any other method with equivalent sensitivity), is lower than 1 % of that of nitrogen-containing substances in the formula;
- the criteria relating to protein given in the Annex of this report must be fulfilled. In addition, these formulae must satisfy all other relevant criteria regarding the essential composition of infant formulae as stipulated in Commission Directive 91/321/EEC on infant formulae and follow-on formulae;
- proof of the absence of any sensitizing character should be supported, before any clinical test, by a series of tests on laboratory animals under conditions where provocation tests show anaphylactic reactions in animals having received orally (or via other appropriate routes) the intact proteins from which the formula is derived;
- the clinical tests must have proven their tolerance in more than 90 % (confidence interval 95 %) of the infants suffering from a hypersensitivity to proteins from which the hydrolysate is made, unless the labelling and presentation of these formulae clearly mention that they are contra-indicated for such cases.

49. Their nutritional efficacy must have been demonstrated by means of clinical tests carried out according to recognized adequate protocols.

50. The labelling and presentation of these formulae should not mention any preventive or therapeutic properties. The technical files and documents intended for medical and health professionals can however mention their preventive properties, provided that these have been established by randomized, double-blind studies using the respective formula.

51. The manufacturers must keep at the disposal of the responsible authority all relevant information concerning the properties of the hydrolysate and the processes used.

Annex

Protein requirements for formulae manufactured from hydrolysed proteins

Minimum	Maximum
0.56 g/100 kJ (2.25 g/100 kcal)	0.7 g/100 kJ (3 g/100 kcal)

- The chemical index shall be equal to at least 80% of that of the reference protein (breast milk, as defined in Annex VI of Commission Directive 91/321/EEC).
- For an equal energy value the formula must contain an available quantity of each essential and semi-essential amino-acid at least equal to that contained in the reference protein (breast milk, as defined in Annex V of Commission Directive 91/321/EEC).
- The protein efficiency coefficient (PER) and net protein utilization (NPU) must be at least equal to those of casein.
- The taurine content shall be equal to at least 10 µmoles/100 kJ (42 µmoles/100 kcal) and the L-carnitine content shall be equal to at least 1.8 µmoles/100 kJ (7.5 µmoles/100 kcal).

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Second Addendum

(Opinion expressed on 9 December 1991)

to the Reports of the Scientific Committee for Food

concerning

the essential requirements of infant formulae and follow-up milks based on cows' milk proteins

(Opinion expressed on 27 April 1983)

and

the minimal requirements for soya-based infant formulae and follow-up milks.

(Opinion expressed on 9 December 1988)

Terms of reference

To advise on the addition of some nucleotides to the list of nutritional substances which may be added in the manufacture of infant formulae and follow-on formulae.

Introduction

1. The Committee has adopted up to now two reports on infant formulae and follow-on formulae based on cows' milk proteins and soya proteins [1,2]. It recently reconsidered its recommendations concerning the maximum level of vitamin D content of these products and approved a limited extension of the list of nutritional substances which may be added in their manufacture [3]. The second addendum to the above mentioned reports concerns the addition to infant formulae and follow-on formulae of nucleotides normally present in human milk and which are semi-essential compounds, especially during the first months of life.

Definitions

2. The definitions adopted in the above mentioned reports [1,2] and in the first report of the Committee on the essential requirements for weaning foods [4] have been retained.

Documents consulted

3. In drafting this opinion the Committee considered relevant scientific publications and information provided by the Association of Dietetic Food Industries of the EEC (IDACE) in particular concerning the specifications and the purity criteria of nucleotides.

Scientific background

4. Nucleotides are the basic building blocks of the nucleic acids RNA and DNA. They are comprised of one or more phosphate groups, of a pentose, either ribose or deoxyribose and a nitrogenous base. The nitrogenous bases are either purines (adenine, guanine, hypoxanthine or xanthine) or pyrimidines (uracil, cytosine or thymidine). Nucleotides are involved in other cellular functions such as in energy transfer or as modulators of enzyme activity [5].

   The purine and pyrimidine bases can be synthesized in the body from amino-acid precursors and can also be re-synthesized in the salvage pathway from catabolic intermediaries. The latter is the quantitatively more significant accounting for up to 90% of the purine bases. Certain tissues preferentially utilize the salvage pathway eg. the intestinal mucosa, bone marrow, hematopoietic cells such as leukocytes and erythrocytes. The *de novo* synthesis pathway and the salvage pathway are inversely related, the former being activated by the absence of nucleotides and the latter stimulated by their presence in the diet [6-8].

5. For certain cells such as lymphocytes or intestinal epithelial cells where growth and turnover can be rapid, dietary purines and pyrimidines can be considered as semi-essential. The rat's small intestine lacks the *de novo* synthetic pathway and the level of gut RNA falls on purine and pyrimidine deficient diets [9]. High density lipoproteins are increased in infants and experimental animals by nucleotide feeding and the elongation and desaturation of essential fatty acids are increased in neonatal infants and rats by dietary nucleotides [10].

   Iron bioavailability is influenced by inosine monophosphate (IMP) which is derived from the catabolism of adenosine monophosphate (AMP) [11,12]. IMP also plays a role in the T-cell mediated immune response [13] and nucleotides may be components of human milk that contribute to the enhanced immunity of the breast-fed infant [14]. In rats with 70% hepatectomy, liver regeneration is increased by intravenous administration of nucleotides. Intestinal recovery following diarrhoea may also be improved by dietary nucleotides [15].

6. Nucleoproteins, widely present in food, are digested by proteolytic enzymes to release nucleic acids. Pancreatic nucleases degrade nucleic acids into a mixture of mono-, di-, tri-, and polynucleotides. Intestinal alkaline phosphatase converts nucleotides to nucleosides releasing free phosphate, and nucleosidases convert nucleosides to the pentose and to free purine and pyrimidine bases [16,17]. Together, alkaline phosphatase, nucleotidases and nucleosidases generate a mixture of free purine and pyrimidine and nucleosides. It is in the latter form that they are absorbed by facilitated diffusion and by sodium dependent transporters [18].

7. Foods such as offal, sea-foods and dried legumes are especially rich in nucleotides. Cows' milk is low in nucleotides especially those based on cytosine and adenosine. It does, however, contain a high level of orotate. Both goat and sheep milk contain considerably more (four and five times respectively) nucleotide than cows' milk and colostrum contains more than mature breast milk [19,20].

8. Human milk is richer in nucleotides in comparison to cows' milk. Taking into account the total nitrogen content, nucleotides represent in human milk a higher percentage than in ruminant milks. As much as 30% of the total nitrogen in human milk is nonprotein nitrogen (about 5% in cows' milk) and soluble nucleotides contribute as much as 20% of the nonprotein nitrogen. As in other species, the nucleotide content of human milk decreases with advancing lactation, except for IMP which increases. There is variability in the levels of specific nucleotides which can be attributed to the individuals *per se* and also to the methods of sample preparation and analysis. The Committee has thus considered only the values obtained with the more recent techniques using HPLC and enzymatic methods.

9. Cytidine and uridine nucleotides represent the most important fraction of the total nucleotides in human milk. Total uridine derivatives reach an average up to 5.4 µmol/dl (range: 4.9 – 7.5) and total cytidine derivatives an average 3 µmol/dl (range: 2.2 – 4.9). The average for adenosine derivatives is 2.9 µmol/dl (range: 2.1 – 3.5) and that for guanosine derivatives is 0.8 µmol/dl (range: 0.6 – 1.3) [21]. AMP and CMP represent the majority of adenosine and cytidine nucleotides. Uridine monosphosphate (UMP) and guanosine monophosphate (GMP) are about 20 to 25% of total uridine and guanosine derivatives.

IMP is also present in human milk and no other inosine derivatives have been found. Orotate is practically absent in human milk.

10. Supplementation of infant formulae with nucleotides is authorized in Japan from 1965, in Spain from 1983 and in the United States from 1989. Only nucleotides in the form of monophosphate salts are used for supplementation, the total amount added being comprised between 2 and 5 mg/100 kcal in the marketed formulae. Considering the consumption of energy of young infants, the intake of nucleotides of those fed supplemented infant formulae is in the same order as that of breast-fed infants (11-18 mg/day) [9].

11. Until now, the Committee, like JECFA, has allocated an ADI not specified for 5'-ribonucleotides. Likewise the Committee has allocated an ADI not specified for specific nucleotides such as inosinic acid and its salts (E 630-633) and guanylic acid and its salts (E 626-629). Nevertheless studies on the effect of oral purines on serum and urinary uric acid of healthy hyperuricemic and gouty adult humans suggest that the purine derivatives

except those derived from guanine, increased serum uric acid concentrations [22]. So, several reports suggest that the maximum safe limit of ribonucleotides daily intake in the diet of adults would be 2 g, i.e. 30 mg/kg body weight [22]. The intake of nucleotides of breast-fed infants and of supplemented milk formulae is about 10 times less than the suggested maximum daily intake for adults.

Conclusions

12. There is not any sign of clinical deficiency which may be attributable to the lack of nucleotides in infant formulae. However it is well established that dietary nucleotides play a role in a number of physiological functions, namely lipid metabolism, immune response, tissue repair and possibly iron absorption. The exogenous supply of nucleotides may be important especially for those tissues with a high turnover.

13. Human milk has a specific nucleotide profile which differs from that of ruminant milks. The total nucleotides content in human milk ranges between 5 to 15 µmol/dl, i.e. approximately 2 to 6 mg/100 kcal. Thus the Committee considers that if infant formulae are supplemented with nucleotides it is advisable to supplement in the same order of concentrations as found in mature human milk.

14. There are no long term studies for infants fed nucleotide supplemented milk formulae. However, those products have been used in the United States, Japan and Spain for years and no deleterious effect has been reported. Therefore the Committee does not have any theoretical reason to think about negative effects of those formulae, at least within the range of nucleotide concentrations used until now.

15. A large number of children are still fed with infant formulae after 4-6 months of age. The amount of nucleotides likely to be added to either infant formulae or follow-on formulae would represent a very small proportion of the total intake of purine and pyridine bases in a diversified feeding pattern. The Committee considers that, while there would be no benefit to adding nucleotides to follow-on formulae, there is no reason to believe that this would have negative consequences, provided they are added at the same levels recommended for infant formulae.

16. Although human milk contains at least 12 acid soluble nucleotides, the opinion of the Committee is to limit the list to the following nucleotide-5'monophosphates: CMP, UMP, AMP, GMP and IMP, which are hydrolysed in the intestine and absorbed as nucleosides. Only the sodium salts of those nucleotides, easily soluble in water, should be authorized. The total concentration of those nucleotides in the ready to use products should be in the same order of magnitude as in human milk and in any case less than 5 mg/100 kcal. The maximum limit for each nucleotide should be:

CMP:	2.5	mg/100 kcal
UMP:	1.75	mg/100 kcal
AMP:	1.5	mg/100 kcal
GMP:	0.5	mg/100 kcal
IMP:	1	mg/100 kcal

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Report of the Scientific Committee for Food on foods for particular nutritional uses whose sodium content has been modified

(Opinion expressed on 9 December 1991)

Low sodium foods and salt substitutes

Terms of reference

To advise on foods for particular nutritional uses whose sodium content has been modified.

1. Dietary sodium in Europe

1.1 The sodium which is present in the diet as eaten has three distinct origins. The first one is represented by the sodium naturally present in foods and drinking water. Natural sodium content rarely exceeds values of 100 mg per 100 grams or 100 kcal (420 kJ) (see Table 2). The second source of sodium is represented by the salt (NaCl) which is added to foods, and as sodium salts of food additives, during various stages of their industrial processing and/or manufacturing. These food additive sources account for less than 10% of total sodium intake [22]. Processed foods tend therefore to be much richer in sodium than natural foods (see Table 1). The third source of dietary sodium is represented by the salt which is added to foods by the individual consumer during the domestic stages of preparation of the meals and/or at the table. This salt, being under the control of the individual consumer, is usually referred to as "discretionary" salt.

1.2 Total dietary sodium intake in the European region has been estimated to range between 3.5 and 5 g/day (9 to 12 g NaCl/day) [15]. The proportion of total sodium contributed by discretionary salt is not firmly established, but recent evidence suggests it may range between 20 and 40% of total sodium intake [16,18], although it has also been seen to drop down to only 2% [13,24]. This confirms that the major source of dietary intake of salt is currently from industrially processed foods [3,8,12]. The major sources of sodium are, for most countries, bread and other cereal and bakery products; the combined group of meats, fish, and eggs follows closely, and milk products come next (Tables 3 and 4).

2. Rationale for low salt intakes

2.1 Salt consumption, and sodium in particular, has been firmly linked to hypertension, both for its role in its pathogenesis and, even more so, for its treatment [7,9,10,21,25,28,29]. While there is a continuing controversy about the exact nature of the sodium-hypertension link, a large body of scientific evidence is available to show that high salt intakes are a necessary but not sufficient condition for inducing essential hypertension in all individuals (the Salt Hypothesis) [5]. On a population basis, it has been established that the habitual consumption of more than 6 g/day of salt is associated with an age-increase in blood pressure [15]. As for the hypertensive patient, the evidence shows that the blood pressure of most hypertensive falls following the reduction of their salt intakes [2,4,14,19]. The benefits of lowering blood pressure are further magnified by the concurrent reduction of the dependence on hypotensive drugs, which may have undesirable side effects.

2.2 On the basis of the above mentioned scientific evidence authoritative bodies have recommended that the total amount of dietary salt be maintained at about 5-6 g/day [1,27]. Such recommendations are addressed to the general public. However, it is recognized that genetically salt susceptible individuals and hypertensives will particularly benefit from low sodium diets, the salt content of which should range between 1 and 3 g/day.

3. Salt modified products

3.1 Individuals who wish or need to control the sodium content of their diet could do so by modifying certain habits and appropriately selecting common foodstuffs. Indeed the addition of salt during cooking or other meal preparation and at the table could be reduced. There are foodstuffs which naturally contain a low amount of sodium. Manufacturers, responding to expert recommendations and demand of the public, are marketing an ever increasing variety of common foodstuffs the sodium content of which is significantly less than in the past.

3.2 Dietetic products specially manufactured for the dietary management of certain conditions needing a well defined reduced Na content and clearly presented as such, comprise two distinct types:

a) sodium-modified foodstuffs to be consumed as such; and
b) sodium-modified salt substitutes which are added to foodstuffs during their preparation and/or at the table.

This report deals with these two types of products.

4. Overview of standards for low sodium products

4.1 Codex has established a standard for low sodium dietary foods and salt substitutes [6]. It describes these foods as being intended for special dietary uses by reason of their low sodium content and contemplates two categories, the low sodium and the very low

sodium products. For both, a three pronged definition is used, namely that the food be processed without adding salt, that the final sodium content be no more than half the amount contained in the normal-salt version, and that it does not exceed the threshold of 120 mg (low sodium) and 40 mg (very low sodium) per 100 g final product as consumed.

4.2 The U.S. regulation for sodium labelling [26] distinguishes four categories based on the sodium content per serving: sodium free (less than 5 mg), very low sodium (up to 35 mg), low sodium (up to 140 mg) and sodium reduced (with a 75% reduction over comparable normal product).

4.3 The regulation in the various EC member countries is very diverse and incomplete. In Italy an internal normative of the Ministry of Health is concerned with salt substitutes. Two types of salt substitutes are permitted, namely a low-sodium and an a-sodium salt substitute. No regulations exist for sodium modified foods. Spain, Germany, Belgium and France have specific regulations regarding sodium modified dietetic foods and salt, the amounts of sodium permitted and the various specifications varying modestly between countries. The UK, while not having specific regulations in this domain, has nevertheless clear recommendations. Most of these countries contemplate two categories of products, except for France and Belgium that specify the diverse sodium content for various food products, and the UK which considers three categories, sodium-reduced, -low, and -free.

5. Rationale for the recommendations

5.1 In making its recommendations the Committee based its rationale on the principle that consumption of low sodium dietetic foods, exclusively or in combination with low sodium common foods, should permit individuals with, or susceptible to developing hypertension to have a sodium intake approximately half of the amount recommended for the general population (i.e. 0.4 - 1.2 g Na/day or 1-3 g NaCl/day).

5.2 In agreement with Codex the Committee considers that it is necessary to adopt as an essential requirement for these products, a substantial reduction in their sodium content with respect to their common foodstuffs counterparts. The Committee has also considered that this principle of reduction of sodium with respect to the normal counterpart is without meaning if these reference foodstuffs are naturally low in sodium (i.e. less than 100 mg/100 g or 100 kcal or 420 kJ). A lower limit for the sodium content of the latter seems therefore justified as an additional criterium.

6. Definition of the categories

6.1 **The very low-sodium food** definition applies to special dietary foods whose final total sodium content is less than **40 mg/100 g** of the ready to consume product, and this final concentration is less than half the concentration present in its regular equivalent, whose initial sodium concentration must be higher than 100 mg sodium per 100 g or per 100 kcal (420 kJ), whichever of these is the lowest.

6.2 **The low-sodium food** definition applies to special dietary foods whose final total sodium content is less than **120 mg/100 g** of the ready to consume product, and this final concentration is less than half the concentration present in its regular equivalent, whose initial sodium concentration must be higher than 100 mg sodium per 100 g or per 100 kcal (420 kJ), whichever of these is the lowest.

6.3 **Salt substitutes** are divided into 3 categories corresponding respectively to products whose sodium content is less than 12 g/100 g of the salt mixture (sodium-reduced salt substitute), or less than 120 mg/100 g of the salt mixture (low-sodium salt substitute), or less than 10 mg/100 g of the salt mixture (sodium-free salt substitute). In sodium-free salt substitutes, potassium is most commonly used to replace sodium. The potassium content in these products should not exceed 30 g/100 g of the salt mixture in view of its reduced organoleptic acceptability and the risk of hyperkaliaemia in subjects with impaired renal function [5,20,23].

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Table 1: Sodium and salt in processed foods
of common use in Europe

Data expressed on the basis of net edible weight (mg/100 g) and of energy content (mg/100 kcal or mg/420 kJ)

	as mg/100g		as mg/100kcal or mg/420 kJ		Category * Sodium density
	Sodium	**NaCl**	**Sodium**	**NaCl**	
Brie cheese (27.9% fat) [a]	1117	2840	310	790	H
Camembert (22.3% fat) [a]	970	2467	320	820	H
Cheddar (32.2% fat) [a]	675	1717	160	420	H
Parmesan [a]	704	1790	180	450	H
Butter (salted) [b]	750	1907	100	260	MH
Margarine (standard) [a]	101	257	10	30	L
Corned beef [a]	833	2118	550	1390	H
Fried bacon [b]	1820	4628	370	930	H
Ham, canned [a]	1200	3052	630	1600	H
Ham, raw, smoked dried [a]	1400	3560	350	900	H
Pork pie [b]	720	1831	190	490	H
Sausage roll [b]	550	1399	110	290	MH
Sausage (bockwurst) [a]	700	1780	240	610	H
Herring, in tomato sauce [a]	526	1338	250	640	H
Salmon, canned [a]	540	1373	300	770	H
Salmon in oil [a]	4070	10350	1410	3580	H
Sardine in oil [a]	505	1284	210	540	H
Tuna in oil [a]	361	918	120	300	MH
Potato flakes, dried [a]	160	407	50	130	ML
Potato fried slices [a]	450	1144	80	210	MH
Potato fried sticks [a]	720	1831	140	360	H
Salad cream [b]	840	2136	270	690	H
Vegetable soup [b]	500	1272	1350	3440	H
Oxo cubes [b]	10300	26193	4500	11440	H
Asparagus, canned [a]	355	903	3550	9030	H
Spinach, canned [a]	170	432	1420	3600	H
Beans french, canned [a]	275	699	4580	11660	H
Pea, canned, drained [a]	211	537	750	1920	H
Tomato, canned [a]	9	23	150	380	H
Tomato juice [a]	5	13	30	80	L
Cornflour [d]	52	132	10	40	L
Pop Corn [e]	1940	4933	430	1080	H
Macaroni, raw [d]	11	28	traces	10	L
Macaroni, canned, cheese sauce [d]	560	1424	410	1030	H
Ravioli, canned, tomato sauce [d]	490	1246	700	1780	H
Pizza [d]	540	1373	220	550	H
White bread (average) [d]	520	1322	220	560	H
Wholemeal bread (average) [d]	550	1399	260	650	H
Rusk (cracker) [a]	263	669	70	180	ML
Corn flakes [d]	1110	2823	310	790	H
Muesli Swiss style [d]	380	966	100	270	MH
Rice Krispies [d]	1260	3204	340	870	H
Weetabix [d]	370	941	110	280	MH
Digestive biscuits plain [d]	600	1526	130	320	H
Semi sweet biscuits [d]	410	1043	80	230	MH
Sponge cake butter [d]	360	915	70	190	ML
Fruit cake [d]	250	636	70	180	ML
Madeira cake [d]	380	966	100	250	MH
Teacakes [d]	270	687	90	230	MH

Table 2: Sodium and salt in natural/unprocessed foods of common use in Europe.

Data expressed on the basis of net edible weight (mg/100 g) and of energy content (mg/100 kcal or /420 kJ)

	as mg/100 g		as mg/100 kcal or mg/420 kJ		Category * Sodium density
	Sodium	NaCl	Sodium	NaCl	
Human Milk [a]	16	41	23	57	L
Cows' milk (3.5% fat) [a]	48	122	72	182	ML
Cream (30% fat) [a]	34	86	10	30	L
Egg (chicken) [a]	144	366	86	219	MH
Meat (meat only) [a]	57	145	50	127	ML
Herring, raw [a]	117	298	53	134	ML
Salmon, raw [a]	51	130	25	60	L
Sardine, raw [a]	100	254	74	188	ML
Tuna, fresh [a]	43	109	18	45	L
Apple [b]	2	5	4	11	L
Orange [b]	3	8	9	22	L
Potato [a]	3	8	4	10	L
Asparagus [a]	4	10	29	73	L
Beetroot [c]	84	214	420	1068	H
Spinach [a]	65	165	433	1102	H
Beans, fresh [a]	2	5	5	14	L
Tomato [a]	6	15	35	90	L
Rice [b]	6	15	2	4	L
Flour, whole [b]	3	8	9	22	L

* Sodium density categories on the basis of NaCl mg/100 kcal:

- L = low <110 mg/100 kcal
- ML = medium low 110-210 mg/100 kcal
- MH = medium high 210-310 mg/100 kcal
- H = high >310 mg/100 kcal.

a Souci SW, Fachmann W & Kraut H, (1986). *Food composition and nutrition tables 1986/87.* 3rd ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart.

b Paul AA & Southgate DAT, (1978). *McCance and Widdowson's The composition of foods,* 4th ed., London: HMSO.

c Carnovale E & Miuccio F, (1990). *Tabelle di composizione degli alimenti.* Istituto Nazionale della Nutrizione. Roma.

d Holland B, Unwin ID & Buss DH, (1988). *Cereals and cereal products, The third suppl to McCance & Widdowson's The composition of foods, 4th ed.,* London, Royal Soc. Chem. & MAFF.

e Watt BK, Merill AL, (1975). Composition of foods. *Agricultural Handbook n°8.* Agricultural Research Service USDA, Washington.

Table 3: Sodium content of total diet

(in grams/day/*pro capita*)

and percent contribution from specified food groups

	Germany [1]	Finland [2]	Britain [3]	America [4]
	(as percent of total)			
Cereal & cereal products	34	20	40	29
Egg, meat & fish	34	15	29	14****
Milk & milk products	11	11	7**	10
Fats	1	10	16*	6
Veg. & fruits	4	1	6***	11
Sugar, candy, beverages & salt added in food prep.	16	43	-	30
	(in grams/day/*pro capita*)			
Total	**2.86**	**4.20**	**2.60**	**6.69**

* Included cheese, cream and ice cream
** Only milk
*** Only vegetables and roots
**** Excluded eggs

1 Docum. IDACE (1988).

2 Pietinen P, (1982). Estimating Sodium Intake from Food Consumption Data. *Ann. Nutr. Metab.* **26**: 90-99.

3 Bull BN, Buss DH, (1980). Contributions of foods to sodium intakes. *Proc. Nutr. Soc.* **39**: 30A.

4 Shank FR, Kang Park Y, Harland BF, Vanderveen JE, Forbes AL and Prosky L, (1982). Perspective of Food and Drug Administration on dietary sodium. JADA, **80**: 29-35`.

Table 4: Consumption of sodium from specified food groups in Italy (mg/day/*pro capita*) and as percent of their contribution to total intake *.

	mg/d/*pc*	%
Cereals & cereal products	833	28.5
Milk & dairies	369	12.6
Cured meats (hams, sausages, etc)	245	8.4
Meat & fish	107	3.7
Vegetables, fruits & pulses	98	3.3
Eggs	33	1.1
Beverages	20	0.7
Ready meals	16	0.5
Fats	16	0.5
Processed fish	16	0.5
Biscuits & cake	14	0.5
Seasonings & sauces	6	0.2
Baby foods	3	0.1
Salt added in food preparation	1147	39.3
Total diet	**2922**	**100.0**

* Cialfa F, Unpublished data on 10.000 households.

Table 5: Sodium content of regular and low sodium processed foods*

	Na content mg/100 g		
	Regular	Low salt or sodium reduced	Saltfree or no added salt
Cereal products			
Whole wheat bread	450	200	24
Multigrain	460	200	#
Breakfast cereals	190	#	14
Crackers	1000	540	#
Crispbread	530	#	62
Spreads			
Butter	700	340	19
Margarine	700	400	6
Peanut butter	500	#	18
Snackfoods			
Cashewnuts	400	#	18
Peanuts	500	240	10
Potato chips	400	360 ◊	26
Soups			
Chicken	380	200	100
Chicken noodle	450	240	#
Tomato	350	180	36
Mushroom	310	150	
Canned vegetables			
Canned peas	290	#	4
Canned tomatoes	280	#	15
Tomato sauce	1000	#	26
Tomato paste	530	#	40
Tomato juice	280	#	7
Canned fish			
Pink salmon	410	#	110
Tuna	400	#	82

* From Greenfield *et al.*, [11]

◊ Labelled as lightly salted

\# Not available.

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The Scientific Committee for Food was established by Commission Decision 74/234/EEC of 16 April 1974 (OJ L 136, 20.5.1974, page 1) to advise the Commission on any problem relating to the protection of the health and safety of persons arising from the consumption of food, and in particular the composition of food, processes which are liable to modify food, the use of food additives and other processing aids as well as the presence of contaminants.

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

The Secretariat of the Committee is provided by the Directorate-General for Industry of the Commission. Recent Council directives require the Commission to consult the Committee on provisions which may have an effect on public health falling within the scope of these directives.

The present report deals with **infant formulae claimed to be 'hypoallergenic' or 'hypoantigenic'** (opinion expressed on 9 December 1991), a **second addendum to the Reports of the Scientific Committee for Food concerning the essential requirements of infant formulae and follow-up milks based on cows' milk proteins and the minimal requirements for soya-based infant formulae and follow-up milks** (opinion expressed on 9 December 1991), and a **report on foods for particular nutritional uses whose sodium content has been modified — low sodium foods and salt substitutes** (opinion expressed on 9 December 1991).