Department of Health

Report on Health and Social Subjects

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Guidelines on the Nutritional Assessment of Infant Formulas

Report of the Working Group on the Nutritional Assessment of Infant Formulas of the Committee on Medical Aspects of Food and Nutrition Policy

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Preface

I welcome this Report which will be of assistance to Government, industry and health professionals. It provides a guide to the standards of evaluation appropriate for today's infant formulas. In many circumstances good practices are already in place, but there are areas where I hope that more effective study designs will be developed. It is increasingly being recognised that nutrition and growth in early life have an impact on subsequent health and development. It is therefore important that comparative trials of infant formulas include larger groups of infants followed up for longer periods than is now generally the case.

The Working Group has considered only the nutritional assessment of infant formulas. I believe that the principles of assessment outlined in this report will also assist those who are designing studies to assess infant formulas from other perspectives, or to assess infant foods other than infant formula.

Sir Kenneth Calman
Chairman, Committee on Medical Aspects of Food and Nutrition Policy

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Acknowledgements

The Working Group is grateful for the written contributions submitted by the following organisations and individuals.

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Miss J Pick	Croydon.
Mr J T Winkler	Action and Information on Sugars, London.
Ms L H Foster	South Bank University, London.

1. Recommendations

A. General Principles (Chapter 5)

A1. All modifications to infant formulas should be assessed nutritionally.

A2. Studies should be founded on a systematic review of relevant existing information. All such reviews should be made publicly available.

A3. At the outset of a nutritional study there should be a clear hypothesis of functional or clinical benefit with defined selection criteria and outcome measures.

A4. Infant formulas which have been modified for other reasons than to provide a functional or clinical benefit should at the least be subjected to studies of acceptability.

A5. All studies should be interpreted in the light of outcomes of healthy infants exclusively breastfed for four to six months, rather than the composition of human milk. In the absence of adequate data, consideration should be given to including a breastfed reference group in studies.

A6. Reference datasets for common outcome measures for breastfed infants should be developed.

B. Study Design (Chapter 6)

B1. Appropriate pre-clinical studies should be performed for previously untested components of infant formula.

B2. Manufacturers, scientific and professional groups should, where possible, collaborate to minimise duplication and to enhance the size of studies.

B3. The views of all those to be involved in the study should be taken into account in designing it.

B4. A pilot study should be considered to provide the information necessary to design an adequate study.

B5. Nutritional, including metabolic, outcome measures should be justified as relevant to the modification under test.

B6. The need for continuing follow-up to two years of age or beyond, and the consequent ethical and practical implications, should be considered in all studies.

B7. There should be common features in the design of studies so that results from several different studies can be assessed together.

B8. In clinical trials, random allocation of infants to study groups should be used to minimise selection bias.

B9. Where possible investigators should be blind to the allocation of test and control formulas to minimise observer bias.

B10. Studies should be designed to have the statistical power to detect important effects on important outcomes, allowing for possible withdrawals of infants.

C. Conduct of the study (Chapter 7)

C1. All studies of infant formula should be approved by an appropriate human research ethics committee.

C2. Information about the purpose, design and outcome of the study should be offered to the infant's carers and to all professional staff who are responsible for the care of the participants.

C3. Studies to assess infant formulas should comply with the principles of Good Clinical Practice and Good Laboratory Practice.

C4. All infants in studies should be characterised with regard to factors known to influence the outcome measures.

C5. Data on all participants recruited should be as complete as possible whether or not they finish the study.

C6. The possibility of unpredicted adverse outcomes should be addressed by adequate clinical monitoring of the participants and by independent scrutiny of the accumulating data.

D. Data handling (Chapter 8)

D1. Results from clinical studies of infant formula, including those part-completed which have been abandoned, should be published.

D2. The statistical power of the study should be stated and the confidence limits of differences observed should be presented.

D3. The original records, with protection of the participants' confidentiality, should be preserved wherever possible and an anonymised data archive should be made publicly available.

D4. Consideration should be given to establishing a repository for information and data about trials of infant formula.

2. Introduction

2.1 Infant formulas have been developed to provide an adequate sole source of nutrition during the first half of infancy for infants not being breastfed. Thereafter, infant formula may be given as a drink as part of a mixed diet. Infants are nutritionally vulnerable specially because their rates of growth are greater than at any other age postnatally and the development of immature organs and systems needs a plentiful supply of nutrients.

2.2 At all ages metabolic adaptations occur in response to the supply of nutrients, and to the nature of the diet. For example, in adults, in order to maintain homeostasis, metabolic responses are modified if the availability of minerals such as calcium is altered. Infants are also responsive to diet although the physiological and metabolic adaptations are different from those of adults. Furthermore, maturing organs and systems may be modified permanently by events which have occurred at formative stages in their development including metabolic variations in response to nutritional status. This process, sometimes called programming, which is recognised in other mammals, may be equally important in humans, although still largely speculative[1]. Vulnerability of a developing infant to permanent changes in its internal programmes is likely to be limited to specific stages of development, whether intra- or extra-uterine, which vary from organ to organ. These changes may have long-term outcomes such that infant weight and rate of weight gain, both of which might reflect early nutrition, have been linked to health status in middle age[2,3].

2.3 The Committee on Medical Aspects of Food and Nutrition Policy (COMA), in 1980, acknowledged that the adequacy of artificial feeds should be assessed not only on nutrient content but also on bioavailability of nutrients and nutrient balance, and clinical and metabolic outcomes. The COMA report *Artificial Feeds for Young Infants*[4] stated that "assessment of the suitability and safety of an infant formula should include consideration of:

a. the ingredients used,

b. comparison with the proposed compositional guidelines,

c. laboratory tests and animal trials to assess nutritional adequacy and, for example, protein quality if appropriate,

d. feeding trials with human infants of appropriate age to provide evidence regarding acceptability, tolerance, nutritional adequacy and freedom from adverse effects,

e. metabolic studies when these are appropriate,

f. evaluation of any clinical or scientific information which suggests an association between the infant food or its constituents and disease, and

g. microbiological testing to ensure that the food is free from harmful organisms."

2.4 Since the publication of this report from COMA, there have been advances in the understanding of the biology of lactation including the composition of human milk, of its nutrient and non-nutrient factors and of their metabolic and physiological effects. There have also been manufacturing advances in understanding heat processing, the effect of modified raw materials, such as low-phytate soya protein, the exclusion of oxygen at certain stages during the manufacture, amongst others. The food manufacturers stand on the brink of a technical revolution as products of fermentation and/or genetic modification become available. At the same time, the range of outcomes related to nutrition, and the ability to evaluate them, has been extended. Established techniques such as those to assess cognitive and motor development have been refined. Many new techniques have been developed, for instance, x-ray absorptiometry to assess bone mineral density, doubly labelled water studies to measure energy expenditure in free living individuals, as well as improvements in the sensitivity and specificity of biochemical assays of body tissues.

2.5 In 1986, at the request of the United States Food and Drug Administration, the American Academy of Paediatrics convened a Task Force on Clinical Testing of Infant Formulas[5]. Its expert recommendations described the types of clinical studies appropriate to assess specific aspects of infant formula modification such as changes in protein mixture or source of calcium, as well as outcome measures such as gains in weight and indices of iron status. The report acknowledges that its recommendations would need to be reviewed both "as new or improved approaches to clinical testing of infants formulas are developed or as manufacturers develop new formulas quite unlike those that are now commercially available".

2.6 *Terms of Reference* COMA asked a Working Group to consider the principles that should underlie the nutritional assessment of infant formulas. A Working Group was set up with terms of reference

"To prepare guidelines for Government, industry and professionals on the nutritional assessment of modifications to infant formulas".

The Working Group, aware that prescriptive and detailed guidelines are quickly superseded, has concentrated on describing principles to guide those intending to assess infant formulas nutritionally. The guidelines expand on those set out by COMA in 1980[4] (para 2.3). They take account of developing expertise in designing clinical trials, in the ethics of non-therapeutic research, and in data handling, as well as the recent scientific developments described above (para 2.4).

2.7 *Meetings of the Working Group and external consultations* The first meeting of the Working Group was on 1 February 1995. Four meetings were held. Submissions were invited and contributions were received from those whose names are listed earlier. A meeting was held on 18 December 1995 between members of the Working Group and the Infant Formula Working Party of the Infant and Dietetic Foods Association to consider practical aspects of the matters addressed in this report. Comments on the report were provided by Mrs Cynthia Rickitt, National Breastfeeding Coordinator.

3. The development of guidelines for the composition of infant formulas

3.1 Successive UK Governments have stressed the superiority of breastfeeding. This policy has been based on advice from experts, particularly the Committee on Medical Aspects of Food and Nutrition Policy (COMA) of the Departments of Health. Its most recent report recommends:
"Breast milk provides the best nourishment during the early months of life. Mothers should be encouraged and supported in breastfeeding for at least four months and may choose to continue to breastfeed as the weaning diet becomes increasingly varied". "An infant who is not breastfed should receive infant formula or follow-on formula milk. Follow-on milk is not recommended as replacement for breastmilk or infant formula before six months"[6].

3.2 *Present-Day Practice in Infant Feeding (1974)* In 1974, COMA published its first statement on Present-Day Practice in Infant Feeding[7]. The expert group had been set up because of a progressive decline in breastfeeding. The report contained several recommendations concerning the encouragement of breastfeeding. Two subsequent national surveys of infant feeding practices showed a substantial increase between the years 1975-1980 in the proportion of women who were choosing to breastfeed their babies[8]. The report identified other problems including the then unsatisfactory composition of the cows' milk based artificial feeds, and difficulties in the preparation of feeds. The manufacturers responded by intensifying the search for safer and more easy to prepare artificial feeds which were subsequently made generally available.

3.3 *The Composition of Human Milk (1977)* Later, COMA asked a new expert group to report on The Composition of Mature Human Milk. A review of the literature failed to provide appropriate data on which to base a compositional profile of human milk in this country and the expert group advised the Department of Health and Social Security to set up its own study. Based on milk from women at about 5-6 weeks post delivery, the report, published in 1977, gave values for water, energy, total nitrogen, protein (and amino acid profile), fat (and as saturated, monounsaturated and polyunsaturated fatty acids up to carbon chain length 18), carbohydrate, non-protein nitrogen and cholesterol, as well as 12 vitamins and 15 minerals[9]. The report acknowledged its limitations including the absence of information about lactoferrin, immunoglobulins, enzymes, hormones, growth factors and living maternal cells. In the past 20 years, understanding of the composition and the nutritive, immunological and trophic functions of human milk and the physiology of lactation has increased[10].

3.4 Meanwhile the Food Standards Committee of the Ministry of Agriculture, Fisheries and Food was invited by Ministers to advise on the need for standards or for other controls on the composition and description of foods for infants and young children. In 1981 the Committee recommended that there should be legislation to ensure that only products approved as providing a sole source of nutrition for the young infant should be on sale[11]. It suggested that approval would be on the basis of pre-market scrutiny by an expert panel. However, before these recommendations could be taken forward, the European Commission tabled its own proposals for legislation to regulate the sale of these products (see Annex I). These European proposals took precedence.

3.5 *Artificial Feeds for the Young Infant (1980)* The COMA report Artificial Feeds for the Young Infant provided compositional guidelines for artificial foods intended as the sole source of nourishment for the healthy young infant[4]. The levels of nutrients it proposed were generally chosen to be in line with the average composition of mature human milk, as had recently been determined. However, some important differences were recommended because of differences in the bioavailabilities of nutrients from human milk and from cows' milk based manufactured products. It was acknowledged that there were likely to be further compositional changes to infant formulas in response to scientific and clinical advances. The Report pointed out the difficulty of confirming differences in outcomes where infants were fed formulas with comparatively small compositional variations.

3.6 *Present Day Practice in Infant Feeding (1988)* Following an update of the 1974 report[7] in 1980[12], a third report on Present Day Practice in Infant Feeding[13] made no recommendations for amendment of the 1980 nutrient composition guidelines for infant formulas[4]. However, it drew attention to findings that energy levels of human milk were lower than those reported in 1977 implying that infant formulas with energy levels towards the upper end of the recommended range provided energy in excess of average levels in human milk. The report pointed out that taurine was being added to infant formulas to match levels in human milk, which are higher than those in cows' milk. Sucrose and maltodextrins were being used as carbohydrates, particularly in formulas intended for lactose intolerant infants, and more children were being given products based on proteins other than milk, especially soya protein isolate. The fats used were usually blends of animal and vegetable fats with a higher proportion of unsaturated fatty acids than in cows' milk.

3.7 *The European Commission Scientific Committee for Food* In April 1983 the European Commission Scientific Committee for Food (ECSCF) published its First Report on the Essential Requirements of Infant Formulae and Follow-up Milks based on Cow's Milk Proteins[14] and in 1988 added compositional recommendations on the minimum requirements for those based on soya[15]. Its recommendations were broadly in line with the recommendations in the 1980 UK Government report Artificial Feeds for the Young Infant[4], with ranges based on minimum and maximum levels for specific nutrients. These reports, prepared by experts from members of the European Union, provide the basis for current

European[16] and UK legislation[17] on the composition of infant formulas. The statutory regulations are described in Annex I; they apply to the retail sale of infant formulas throughout the European Union. Products intended for research, which are not being marketed, are not so regulated and the responsibility for the welfare of the consumer rests with those conducting the research. If research indicates that a modification to infant formula offers public health benefits, Member States would be expected to submit evidence to the European Commission to enable assessment by the ECSCF with a view to possible amendment of the European Directive.

3.8 The Codex Alimentarius of the United Nations Food and Agriculture Organisation and the World Health Organisation also provides authoritative guidance. This body has published an internationally agreed standard for infant formula based on cows' milk or the milk of other animals or on other edible constituents of animal, including fish or plant origin, which have been proved to be suitable for infant feeding[18]. The standard is now being reviewed.

3.9 Special formulas have been developed to meet the nutritional needs of low birth-weight infants. A minority of infants, including those with metabolic disorders such as phenylketonuria, tyrosinosis and galactosaemia, cannot tolerate human milk or artificial milks used instead of human milk. The European report confirmed that "products intended for low birth-weight infants and for infants and young children suffering from nutritional metabolic disorders are excluded from its scope". The USA compositional regulations also exclude infant formulas for these categories of infant, and define them as "exempt infant formulas"[19].

4. The development of guidelines for assessing novel foods and novel food processes

4.1 The Advisory Committee on Novel Foods and Processes (ACNFP) in its report *Guidelines on the Assessment of Novel Foods and Processes*[20] states:

"A food may be novel as a result of the use of novel raw materials, novel processing or preparation techniques or novelty of its role in the diet. Novel food organisms or products derived from such organisms may result from recently developed techniques such as genetic modification or from more conventional plant and animal breeding techniques. It is unlikely that an all-embracing definition for novel foods and processes covering all eventualities can be derived and therefore the following definitions have been established:

- *Novel foods* are foods or food ingredients which have not hitherto been used for human consumption to a significant degree in the United Kingdom and/or which have been produced by extensively modified or entirely new food production processes.

- *A novel process* is a process which has not hitherto been used in the processing of foods."

4.2 Currently, foods in the UK are controlled under the Food Safety Act 1990. The 1991 report described a "decision tree" strategy for assessing novel foods or processes to enable clearance on public health grounds to ensure that there are no food safety reasons why the food should not be marketed in the UK. Novel foods or processes are considered individually to determine what information requirements are needed to achieve clearance. This scheme for giving clearance to foods and processes has operated under voluntary arrangements between Government and the food industry. There is a list of fifteen information requirements two of which particularly refer to human nutrition: "Nutritional evaluation" and "Human studies". These were the focus, in 1993, of an expert report from COMA, *The Nutritional Assessment of Novel Foods and Processes*[21]. Expanded guidance was given as a series of nutritional criteria that might be considered in assessing novel foods and processes. These are at Annex II. The ACNFP "decision tree" approach was updated and extended in 1995[22]. The current list of 15 information requirements is at Annex III; not all will be relevant to every product submitted for clearance and a flexible approach is encouraged.

4.3 In assessing the safety of novel foods, including nutritional significance, the concept of *substantial equivalence* has been developed[23]. This is intended to be of practical assistance in proposing that traditional foods, accepted as safe in use, are the basis for comparison in the safety assessment of novel foods. This approach, while originally developed for foods which are, or are produced from, genetically modified organisms, may be applicable more widely. However further development of this concept will be needed before it can be applied to a complex food matrix, such as infant formula, where the interactions within the food are not fully predictable, and the food is the sole source of nutrition.

4.4 More recently the European Parliament and the Council of the European Union have drafted a Regulation concerning Novel Foods and Novel Food Ingredients which is now under negotiation. The Regulation is expected to describe statutory arrangements which are similar to the current UK voluntary scheme. Once this is agreed it will take priority over the arrangements described in para 4.2.

5. General principles for assessing an infant formula nutritionally

The Working Group recommends that

- **All modifications to infant formulas should be assessed nutritionally** (para 5.2).

- **Studies should be founded on a systematic review of relevant existing information. All such reviews should be made publicly available** (para 5.9).

- **At the outset of a nutritional study there should be a clear hypothesis of functional or clinical benefit with defined selection criteria and outcome measures** (para 5.10).

- **Infant formulas which have been modified for other reasons than to provide a functional or clinical benefit should at the least be subjected to studies of acceptability** (para 5.11).

- **All studies should be interpreted in the light of outcomes of healthy infants exclusively breastfed for four to six months, rather than the composition of human milk. In the absence of adequate data, consideration should be given to including a breastfed reference group in studies** (para 5.12).

- **Reference datasets for common outcome measures for breastfed infants should be developed** (para 5.12).

5.1 Modern infant formulas have been available for many years. Throughout this period changes have been introduced for different reasons. For example:

- **to achieve a compositional profile which compares more closely with human milk**, eg by adding ingredients not previously included such as carnitine or taurine or long chain fatty acids, or by adjusting the concentration of nutrients in the formula, for instance, increasing whey while decreasing casein in the protein fraction, or reducing energy levels;

- **to offer a product which is handled physiologically in a way which compares with the infant's handling of breast milk**, eg infant formulas contain little butterfat, because it is poorly absorbed: most of the lipid is of vegetable origin which is better absorbed, albeit not as readily as breast milk fats;

- **for some micronutrients, exceeding the levels in breast milk** with the intention of compensating for reduced bioavailability eg iron; or of providing a safety net where deficiencies continue to be reported, eg vitamin D;

- **to provide a product more suitable for infants with clinical disorders**, eg lactose free (or exclusion of other specific ingredients which the infant is unable to metabolise), or with partially or completely hydrolysed protein for infants who are allergic to whole cows' milk protein;

- **to offer a product which is more attractive or more easy to prepare**, eg changes to the additives used, or temperature changes to reduce Maillard reactions;

- **to use an alternative source** of raw ingredients.

5.2 It is acknowledged that infant formula does not offer the young infant the specific immunological and other benefits of breastfeeding. Many of the changes described above reflect the search for improved products, and infant formulas should continue to be developed to take account of the results of research. The Working Group believes that modifications to infant formulas should be nutritionally assessed. In the 1970s, National Dried Milk was given to many infants who were not being breastfed. When modern infant formulas were introduced as an alternative in the mid 1970s, the improvements they offered were relatively easy to confirm. Since then, modifications to the composition of infant formulas have continued. Trials to compare a new infant formula with others it might replace now generally need to be large and complex to have the statistical power to detect predicted moderate but important differences in outcomes.

5.3 Innovations to infant formulas may offer new concepts or may add new components, for example:

- cows' milk **protein may be hydrolysed** enzymically to varying extents with an expectation that it may be less allergenic than whole protein;

- nucleotides or selenium may be added as **ingredients not previously included**;

- **a novel food or process provides formula components**, for instance long chain polyunsaturated fatty acids from algal sources.

Infant formulas which incorporate new concepts or new components should be assessed nutritionally and clinically in line with the principles set out in the following chapters of this report. Such assessment will usually require a clinical study, but there may be exceptions. When an ingredient is added for the first time, it is important to evaluate both the new component itself and the infant formula containing the new component.

5.4 Ingredients for infant formulas may soon be prepared using innovations in food biotechnology including techniques involving genetic modification. Milk is unlike other foods in providing components, synthesised by the mother for the benefit of her young, which cannot be obtained by extraction from conventional food sources nor easily produced by conventional means in the laboratory. For example, human milk fat has several unique properties including its triacylglycerols structure, and its concentrations of long chain fatty acids such as docosahexaenoic acid and arachidonic acid. Many components of milk are species specific, thus bovine lactoferrin is different from human lactoferrin and cannot substitute for it. Novel techniques may provide a means for obtaining some of these ingredients if it is believed to be essential that they should be added; some components of human milk, such as living maternal cells, will never be synthesised. There are special considerations when the infant formula includes ingredients which are novel foods or which are produced using novel food processes. The COMA Panel on Novel Foods issued guidelines on the Nutritional Assessment of Novel Foods and Processes in 1993[21] (para 4.2) but set in the context of a diverse adult diet in which the novel food may feature occasionally. Ingredients which are novel foods or derived through novel processes and incorporated in infant formula are likely to make a more significant contribution to the diet. The young infant being fed infant formula has only one food which must provide for all nutritional needs, and, even after weaning, infant formula usually continues to provide a major part of the diet. Because of an infant's vulnerability and the risk of incurring adverse effects which may be life-long, safety, including toxicological considerations, must be the first priority.

5.5 Other changes which do not involve new concepts or new or novel components may also have significant effect on infant's nutrition.

- **Changing the composition of infant formula within the statutory compositional guidelines**

The statutory regulations for infant formula being marketed in the European Union are outlined in Annex I. However, it cannot be assumed that formulas which fall within the compositional requirements of these regulations will necessarily perform satisfactorily. The regulations allow latitude for variation in the permitted levels of ingredients so that diverse products can be prepared, all of which are legally acceptable. There is potential for individual nutrients to influence the absorption and metabolism of others, and the interactions in a complex material such as infant formula cannot be predicted with certainty. For example, no maximum value for calcium is specified and the minimum iron level (when iron is added) is 0.5 mg/100 kcal or 0.34 mg/100 ml at an energy density of 67kcal/100ml. Calcium may impair iron absorption and if it was proposed to market a formula with this low

level of iron and a high calcium content, for example 100 mg/100ml, it would be essential to assess iron bioavailability if the formula was to be used beyond the age of four months. A second illustration concerns a formula containing the minimum protein level permitted (1.8 g/100 kcal for modified cows' milk protein based formulas). At a usual energy density of 67 kcal/100ml, this is equivalent to 1.2 g protein/100 ml which may be only marginally adequate for the immediate neonatal period. Any increase in the proportion of the non-protein nitrogen in the whey protein used in the formulation, and/or any increase in heat processing, which might result in more heat damage to the protein, could result in a reduction in the level of biologically available protein. A final example concerns variations in the fatty acid pattern in infant formula. Several saturated fatty acids in formulas containing unmodified vegetable oils are generally not well absorbed by young infants: typical absorption of palmitic and stearic acids is 50-70 per cent, compared with approximately 85-90 per cent for oleic and linoleic acids. Since fat provides approximately 50 per cent of the energy content of infant formulas, the unabsorbed fatty acids represent a potentially significant energy loss. At present there are no limits in the infant formula regulations on the content of saturated fatty acids and it would therefore be possible to market a product which is less than optimum in providing energy.

- **Modifications to incorporate a new ingredient which has already been assessed but not in the specifications of the new brand of infant formula**

If a new ingredient, assessed in a specified product, is found to be nutritionally acceptable, other products, of different composition but also including the new ingredient, cannot necessarily be assumed to be nutritionally equivalent without further consideration, and assessment as appropriate. Varying the levels of these added components offers potential for differing interactions with other dietary constituents characterising the formula concerned. For example, if the outcome concerns faecal flora, the level of iron will be important and, as described above, other nutrients will have an effect on the availability of iron in the bowel.

5.6 Changes are also introduced to infant formulas for economic or technological reasons. For example, the raw material fat source may be changed in line with market forces, or the temperature during spray drying may be changed. The quality assurance applying within the factory should ensure that the product for sale has not been changed, for example, changes in the temperature during spray drying may affect the proportion of vitamin C which is lost during the processing, and appropriate compensation should ensure that vitamin C levels are consistent. In other circumstances, minor changes to the product are made for commercial reasons, for example so that companies can retail infant formulas which closely match products already on the market made by commercial competitors. For commercial and other reasons, hospitals may wish to change the infant formulas which are provided for their infant patients.

5.7 Manufacturers of infant formula need to be scientifically aware so that changes in their products, at whatever level, are only made after a responsible

consideration of the likely impact that the changes will have on the finished food. There should be an evaluation by appropriately qualified people of all changes to infant formulas, of any predicted nutritional consequences, and of how they should be assessed. The extent of the assessment that is required for a specific modification can only be determined on a case by case basis, formal clinical trials are not likely to be needed in every instance. It is not possible to define all current and future circumstances: in general, minor modifications are less likely to require comparative nutritional trials. However, any modification whether or not within the statutory regulations, which is hypothesised or claimed to have significant advantages, or which incorporates novel foods or is derived from novel food processes, should be subject to clinical trial. It is important that, within the bounds of commercial confidentiality, any changes to infant formulas should be overt so that the scientific community can contribute to continuing evaluation.

5.8 It has been suggested that infant formulas should be assessed as pharmaceuticals with a registered specification of the product and of the processes used in its manufacture. Because of the vulnerability of the population group and because of the crucial contribution nutrition in the early months of life makes to growth, development and health, some regulation of the composition of infant formulas is desirable. However, there are problems in regulating a food as a medicine, including its complexity. The balances of risk from giving a medicine, or from consuming a diet are different. A medicine is given to modify a disorder (itself carrying risks), whereas a diet is to maintain normal metabolism and growth. A medicine generally has one or few active principles, whereas infant formula is a complex matrix with individual nutrients acting individually or interacting with each other within the intestine and systemically. It is difficult to develop tests of the effects of changing isolated nutrients in the diet in a way that compares with tests of medicines. Nevertheless, it is increasingly being recognised that the methodology for assessing infant formulas can learn from the scientific rigour and disciplines of pharmaceutical testing. The Association of the British Pharmaceutical Industry has published guidelines which deal with the assessment of medicines[24]. They include Good Clinical Practice guidelines about the management of post marketing studies to assess efficacy and safety, and proper ethical and professional relationships between those collaborating in the study. Many of these can, in principle, apply equally to the assessment of infant formulas.

5.9 Before designing a study to assess a significant innovation or new concept, existing data should be reviewed systematically in a way that is comprehensive and objective, as is advocated for all research[25]. The important methodological criteria include avoidance of selection and observer biases, adjustment for potential confounding variables, definition of the outcome events and definition of feeding[26]. The systematic review seeks to identify all sources of data and to evaluate the merit of past studies and the degree of reliance that can be placed on their results. A review assists in defining more accurately the need for and scope of future investigations, what new studies are needed to fill gaps in knowledge or to validate earlier results, and what work should have a low priority because it is unlikely to contribute anything new to an already well researched field. Without this preliminary work, new studies run the risk of overlapping or leaving gaps in a

haphazard way, thus wasting time and resources, and putting participants to fruitless effort. The systematic review should be published as a contribution in its own right and also to clarify the basis for the design of the planned research[27]. In order to maintain confidentiality, commercial companies may wish to delay publication of the review until the research is completed.

5.10 An hypothesis to justify the innovation should be stated from the outset, including the characteristics of the infants for whom the new formula is intended. For most innovations the goal should be an hypothesised functional or clinical benefit based on defined outcome measures. For example, hypotheses might be that a new formula, if given for the first three months of life to infants born pre-term, will be associated with increased rates of weight gain, or, that the risk of allergic disease in bottle fed infants will be reduced if the new product is given exclusively for the first 16 weeks after birth. Studies designed simply to show that a new formula is no worse than the old formula are inadequate. A direct demonstration of benefit using traditional outcome measures such as length, weight, or blood nutrient levels may be difficult to achieve. There is a promising range of new techniques which focus on metabolic outcome measures, for example, new technologies that exploit advances in cellular biochemistry or stable isotopic tracer studies. Similarly, new techniques to assess neurophysiological status could supplement traditional motor and cognitive developmental monitoring. Alternatively, a proxy measure, such as a biochemical or clinical marker, or a change in intestinal microflora, might be an acceptable alternative. An example is the addition of nucleotides to infant formula: these are elements in human milk which might influence the microbiological flora of the infant gut and hence reduce the frequency of gastrointestinal infections. Demonstration of an effect on the faecal flora to a pattern that has separately been shown to be associated with a lower incidence of infection, might be a suitable proxy measure to show whether adding nucleotides reduces the risk of these infections. Where benefit is inferred from indirect outcomes such as this, longer term studies should, if possible, continue until it is confirmed directly that the innovation offers the benefit that has been hypothesised. When benefits are confirmed the Working Group recognises the importance of informing and educating both professionals and public about the modifications.

5.11 Where the infant formula has been modified for economic, technological or commercial reasons, it is not realistic to assess the products against a hypothesis of nutritional benefit, rather the hypothesis is that the new product is no less satisfactory than the product that went before. Nevertheless, consideration should, in all cases, include assessing whether the modification might have nutritional implications. It is also important to be assured that the new product is at least as acceptable to the intended consumers in regard to factors such as ease of preparation, readiness to consume, apparent ability to satisfy the infant's hunger, not causing stool changes, etc. As a minimum, acceptability trials with predefined outcomes, randomized, and including enough participants to give appropriate statistical power to the result should be conducted when new ingredients are used to provide macronutrients, the levels of the macronutrients are changed so that they are beyond previous experience, or when major changes are made to the manufacturing process.

5.12 Term infants being exclusively breastfed by healthy mothers for four to six months is the reference group for comparing alternative means of feeding (excluding infants with inherited metabolic disorders). But the allocation of infants to a breastfed feeding group cannot be achieved without selection bias because it is not ethical to ask mothers to give up their choice of how to feed their baby in favour of a random allocation to different feeding methods. It is also difficult to justify the ethics of recruiting infants into a breastfed group as part of a study which offers them, as individuals, no benefit. It should be considered whether a study can draw on sufficient reference data about breastfed infants from the literature. However, such data are so often inadequate, even for common outcome measures such as length and weight gain and body composition, that the development of reference datasets on breastfed infants should be considered.

5.13 Mature human milk has been a compositional model for infant formulas for 25 years in spite of inherent differences between it and infant formula (para 3.5). It is a living tissue with immunologically competent maternal cells, plasma proteins, maternal hormones, specific trophic factors and enzymes, and other active substances[6]. The composition of milk varies in time and between individuals depending on the age of the infant, the time of day, the volume produced, the mother's diet, etc. It is therefore difficult to evaluate the biological significance of differences in measures of outcome between a group of breastfed infants and groups of infants fed different infant formulas. Changes to infant formulas have mainly concerned nutrient composition but a manufactured product which, nutrient for nutrient, compares with human milk, may not offer the best formulation. It is difficult to justify modifying infant formulas by adding new components, such as urea, cholesterol, progesterone, etc, solely on the grounds that these substances are present in human milk and, *ipso facto*, might provide an improved product. On the contrary, several changes which improve infant formulas have resulted in compositional profiles which differ from that of human milk to provide products which the infant, nevertheless, handles physiologically in ways which match more closely the breastfed infant, such as using vegetable fats instead of animal fats.

6. Guidelines for study design

The Working Group recommends that

- **Appropriate pre-clinical studies should be performed for previously untested components of infant formula** (para 6.1).
- **Manufacturers, scientific and professional groups should collaborate to minimise duplication and to enhance the size of studies** (para 6.3).
- **The views of all those to be involved in the study should be taken into account in designing it** (para 6.4).
- **A pilot study should be considered to provide the information necessary to design an adequate study** (para 6.6).
- **Nutritional, including metabolic, outcome measures should be justified as relevant to the modification under test** (para 6.7).
- **The need for continuing follow-up to two years of age or beyond, and the consequent ethical and practical implications, should be considered in all studies** (para 6.8).
- **There should be common features in the design of studies so that results from different studies can be assessed together** (para 6.9).
- **In clinical trials, random allocation of infants to study groups should be used to minimise selection bias** (para 6.11).
- **Where possible investigators should be blind to the allocation of test and control formulas** (para 6.12).
- **Studies should be designed to have the statistical power to detect important effects on important outcomes, allowing for possible withdrawals of infants** (para 6.14).

6.1 Preclinical studies are required for new components, not previously tested, which are to be added to infant formulas. These may be *in vitro* or in animals and should include studies of the absorption, metabolism and excretion of the new components as well as examination of the impact, if any, on physiological systems. Formal toxicological studies are essential. Studies may be conducted on adult volunteers before infants are given the new infant formula. Every effort should be

made to ensure that the results of preclinical studies, especially those to assess safety, are publicly available, even if the tests were incomplete or abandoned.

6.2 Following satisfactory conclusion of preclinical safety tests, clinical safety studies can proceed. These should be targeted to exclude plausible differences between index and control participants in outcomes chosen because of known or theoretical risks. For example, adding n-3 polyunsaturated fatty acids might influence the risk of bleeding or infection. Monitoring must be adequate to detect unexpected adverse outcomes and it is the professional responsibility of doctors and other health care staff to ensure that such outcomes are reported[28]. After the safety studies have been completed satisfactorily, the subsequent early clinical trials should incorporate safety outcome measures where possible. Longer term post-marketing studies, which are more usually observational and non-interventional, may be indicated to monitor an innovative infant formula as it is used by the infant population, and this practice may become more common as ingredients from novel sources are introduced. Post marketing surveillance may also be helpful to confirm the nutritional effect of the changes which have been introduced, particularly if large numbers of infants are needed to confirm a benefit.

6.3 In assessing a new infant formula it is usual for various clinical studies and trials to be indicated; they should be well designed and should include adequate numbers of participants. Infants, health professionals, and manufacturers all benefit if knowledge about an innovation to the standard design for infant formula is built up without delay or unnecessary expenditure. Cooperation between those involved is encouraged within the constraints of confidentiality. Health professionals should consider the likely benefits if more than one clinical centre participates in a coordinated project. In this way, a broader general database can be put together to enable detection of less common outcomes and adverse effects.

6.4 It is important when designing a study for the nutritional assessment of a new infant formula to take account of the views of all those involved in the study. Nutritionists and researchers might be the first to indicate from the results of scientific studies how infant formulas might be improved. For example, a clearer understanding of the long chain lipids in human milk, and of their function in growth and development, has suggested that there might be an advantage if they are included in infant formulas. Health care professionals such as health visitors, general practitioners and paediatricians who care for infants and who support their parents, are key investigators in any study. The manufacturers of infant formula should be fully included at all stages, as they need valid and relevant results to be confident that their new products are safe, and that any commercial activity is supported by well founded data.

6.5 Parents should be encouraged to contribute their perspective to the design of a study[29,30]. Health professionals may not always acknowledge the importance of parents' worries about possetting, taste, constipation, or preference to ensure that ingredients are "natural". If brushed aside, parents may introduce inappropriate home modifications when feeding their babies because the "experts" appear to be taking no notice. For instance, feeds may be diluted, other foods such as sugar or

rusks may be added to infant formula feeds, or less suitable alternatives perceived as more natural (such as unmodified, or even raw cows' or goats' milk) may be used inappropriately. To ignore parents is to risk losing the observations they alone can make from continual contact with their child.

6.6 Once the design for the study has been outlined, a pilot study will help to inform all those taking part and will allow the protocol to be refined. The procedures for the study can be assessed to ensure that they are practical and acceptable to parents, participants and investigators. Parents with no prior understanding of the issues are enabled, in this way, to make a more informed input after participating in a pilot study which has demonstrated the purpose and goal of the investigation. This may be particularly helpful where the infants to be studied come from a population group where communication with health professionals and scientists may be more difficult, for instance, a group defined by ethnicity or by educational achievements. At the same time, observations can be made of the numerical variance of selected outcomes to assist in determining the sizes of groups for the main study (para 6.14).

6.7 Outcome measures should be defined specifically for testing prior hypotheses. The measures chosen should be assessed for their accuracy, reproducibility, feasibility, contribution to safety assessment, and cost, and they should be relevant. The mere fact that an outcome can be measured easily, and with precision, and has always been measured, does not justify its inclusion unless it contributes to testing important hypotheses, or to a synthesis of study results with the results of other studies (para 6.9).

6.8 Most nutritional assessments of infant formula have focused on the first six months of life. Sometimes studies of the use of an infant formula are for short periods only, such as a few days. It is important to assess infant formula when used also for extended periods throughout infancy in the way formulas are used in practice. Continuing assessments as the child grows older are increasingly being seen as important, and some of the most fruitful nutritional research is based on long term follow-up of infants from birth[31,32]. Time intervals after the start of the study are described as immediate, early, medium term, and long term. Some outcome measures may be uniquely informative at a specific stage, for example, the ability to stand unaided, while other measures need to be repeated to establish trends, for example, length/height. The choice of outcome measures for each stage should be defined primarily by the need to test the hypothesis. When designing long term studies, early baseline measurements, for example, head circumference or blood levels of vitamin D, may be needed to interpret the significance of later observations. Although not always practical, studies should ideally be designed with the option of longer term follow-up, even if it is not intended to pursue this in the first instance. If the study is extended there are implications for maintaining contact with the participants, for data storage and for participants' confidentiality, and for the consents that are obtained at the time of the primary research. As the children mature, they will increasingly be able to choose for themselves whether to consent to continued participation.

6.9 Aggregating data from several studies may be the only way of achieving the statistical power needed to detect an important effect. It is reasonable to include a limited number of outcome measures, which have generally come to be regarded as routine, to assist the synthesis of the results with those from other studies. Examples of common core outcome measures are weight, length, haemoglobin level (where blood is being taken), timing of ability to sit unaided, and so on, depending to what age the study is designed to continue. From time to time, the outcome measures in common use should be reviewed to consider whether their inclusion continues to be justified. Such common observations, which give a degree of compatibility between studies, are valuable when examining long term outcomes into adult life even where this was not planned at the outset.

6.10 The study design should be appropriate to test the prior hypotheses effectively. A simple design without a comparator group may be appropriate for toxicological or other pre-clinical studies (para 6.1), or it may be the only option where protocols are very detailed and require a high level of commitment and motivation from the parents, for example, to examine physiological and metabolic processes. However, small observational studies like this have inadequate statistical power to detect subtle nutritional effects, are usually selective for the individuals recruited, and do not give results which can be generalised to a population of infants. Clinical trials of sufficient size which compare groups of participants fed on different infant formulas are the best way of detecting important differences in substantive outcomes. The population of infants to be studied will be defined by the hypothesis. For instance, a complex, short-term metabolic study may only be possible if the infants' parents have the time and education to cope with recording detailed observations. On the other hand, public health studies, where it is predicted that socio-demographic factors are likely to have an influence on the outcome, need to define a broader population group such as term born infants, excluding multiple births, and covering a whole population of births in a defined locality, or from a named hospital unit.

6.11 Random allocation to comparative groups being fed different infant formulas will ensure that variations, which are known to be associated with the outcomes, such as parental height, mother's education, number of siblings, as well as those which are not known, are distributed without bias between the groups being compared . Parents must be informed about the nature and need for randomisation and about their freedom to withdraw their infant at any stage. It is crucial to ensure a high rate of acceptance by the individuals invited to participate if the results are to be generalized to the population being studied. It may be difficult to encourage a high rate of participation if the schedule for the study is complex or if it includes features that parents may wish to reject, such as blood sampling. To ensure high rates of participation, there may be circumstances where elements in the study design need to be sacrificed to lead to higher rates of agreement to participate. If the recruitment rate to the study is low, the justification for continuing may need to be reconsidered.

6.12 Although random allocation of infants to different feeding groups abolishes selection bias, other biases may not have been eliminated. If the parents know

which product their infant is receiving their behaviour or perceptions may be influenced differentially. To reduce this bias in what parents report, the feeds should be labelled only by a code to try to "blind" parents to which of the formulas their infant is receiving. Bias may also result if the infant's clinical adviser implies that one feeding regimen is better than another. Studies are "double blinded" where parents, researchers and clinical advisers, such as general practitioners, paediatricians and health visitors, are unaware of which product is being given to which infant. Double-blind randomized controlled trials are the most efficient means of assessing nutritional differences between infant formulas, and should, wherever possible, be the preferred methodology. Unfortunately, they are not always appropriate or attainable, for example, hydrolyzed infant formulas are recognisable by taste and smell.

6.13 There may be circumstances where cross-over studies are appropriate. All infants then receive both of the infant formulas being compared in a randomized sequence. Such studies may be designed to be double blind. The benefit of this type of study is that it involves fewer participants and it has a powerful statistical analysis. However, a drawback of a cross-over study is the possibility of a carry-over effect[33]. For instance, if the first formula gives slower weight gain, a subsequent formula might yield an unduly optimistic estimate of weight gain simply attributable to "catch-up".

6.14 The numbers of infants needed in each of the groups should be calculated taking into account both the sizes of differences between groups in outcome measures regarded as important, and the anticipated variability in these measures within each group. The larger the effect of an innovation on an outcome being measured, the fewer the participants needed in each group to achieve differences in outcome measures between the groups which are statistically significant. However, predicting the sample sizes needed may not be straightforward. There may be only a small effect from a modification to an infant formula because of interaction between nutrients which influence the outcomes, or because several measures, all of value in assessing clinical and nutritional status, may be needed. In spite of these uncertainties, attempts should be made to determine the required sample sizes using systematic reviews of whatever information is available and pilot studies (para 6.6).

6.15 Means to calculate sample sizes for binary, continuous, or ordered categorical outcomes to achieve a predetermined confidence and power for studies involving either equal or unequal group sizes have been described[34]. Most nutritional and metabolic studies of infant formulas would involve outcome measures of continuous variables such as weight. If a two-sided significance of 5 percent and a power of 80 percent is assumed, then a rapid means of calculating approximate sample sizes for such studies is given by the formula

$$n(\text{number per group}) = 16 \div d^2 .$$

d is the "standardised difference" between the two groups in the measured outcome which is thought to be clinically important; it is calculated as "effect" (judged as, for example, the clinically minimum difference accepted) divided by an estimate of

the standard deviation of the measurement in the group or population as a whole. If the study is designed to be long term, the numbers recruited at the start of the study should be large enough to ensure that the sample sizes remain adequate to detect significant differences even if a proportion of the participants have, for whatever reason, been lost during the course of the study. It is inefficient to do several incomplete and small studies, none of which provide reliable results. A well planned study may initially appear costly and the results may not be available quickly but in the longer term there are likely to be both cost and time savings.

7. Guidelines for the conduct of studies

The Working Group recommends that

- **All studies of infant formula should be approved by an appropriate human research ethics committee** (para 7.1).

- **Information about the purpose, design and outcome of the study should be offered to the infant's carers and to professional staff who are responsible for the care of the participants** (para 7.2).

- **Studies to assess infant formulas should comply with the principles of Good Clinical Practice and Good Laboratory Practice** (para 7.4).

- **All infants in studies should be characterised with regard to factors known to influence the outcome measures** (para 7.5).

- **Data on all participants recruited should be as complete as possible whether or not they finish the study** (para 7.6).

- **The possibility of unpredicted adverse outcomes should be addressed by adequate clinical monitoring of the participants and by independent scrutiny of the accumulating data** (para 7.7).

7.1 Research involving humans should be justified and should be conducted ethically. The Department of Health has issued guidance about NHS Local Research Ethics Committees (LREC) and recommends that all research protocols in the NHS be submitted for approval. Even if the research is outside the NHS, as are many trials of infant formulas, it is prudent to refer the protocol to the LREC for advice (Annex IV). Participants need to be assured that the time and effort to provide information, the discomfort of physical procedures, and the possibility of an adverse outcome, however minor, will have reasonable assurance of contributing to public knowledge and, ultimately, to communal benefit. Several UK bodies have published guidelines for the ethics of research in children (Annex IV). There are also local arrangements to consider the ethics of proposed research including the LRECs and ethics committees specific to individual research establishments whether public or private. Apart from the demand to protect the participants, it is also important to obtain prior ethical approval because, without it, several major scientific journals will not publish reports arising from the study.

7.2 It is the parent or lawful carer who decides whether the child will participate and who is required to give written consent. This action should be seen as the function of a trustee of the child's interest rather than as demonstrating rights over the child. It is good practice, as well as an ethical requirement, to explain the purpose and design of the study to the family participants and their right to withdraw the infant from the study at any time. It is particularly important to involve a parent throughout the study period to help to interpret the child's reactions and to achieve good compliance. Infants cannot articulate fears and causes of distress, which may include being handled by a strange adult, being cold, being in pain or hungry. Parents who have not yet registered their infants with a general practitioner should be encouraged to do so. The infant's general practitioner can only advise parents if fully informed (para 6.4). A written explanation about the trial, and named contact points for enquiries, should be available for the general practitioner, health visitor or other health professional who may be drawn into the research as, for instance, when asked to give clinical advice about a baby who is their patient and who is participating in a trial.

7.3 Arrangements for dealing with abnormalities found during the study should be in place from the outset. The researchers should agree the definitions of abnormality to trigger action when scrutinising the results from individual participants. These might include, for example, a level of lowest limit for haemoglobin, or a slower rate of weight gain than a preset reference rate. The participants and their professional advisers should be informed about the abnormal finding with an explanation. The research team may not include the professionals responsible for the participant's health care, and it is therefore crucial that good liaison is maintained with local professionals, especially the general practitioner and the health visitor. The researchers will generally be better informed about the science of the investigation and they have a duty to convey all the information needed so that the participant's family can be given the most appropriate advice. When the study is complete, it is good practice to tell the parents the main findings: feedback from parents can give fruitful insights.

7.4 Studies of infant formulas should comply with the principles of Good Clinical Practice and take account of the Declaration of Helsinki. The clinical investigator must be scientifically and professionally competent and must be aware of the principles and objectives of the trial. There should be adequate resources of time, staff and data recording equipment, and safeguards for confidentiality. The relationship between the manufacturer of the infant formula and the clinical investigator should not prejudice the latter's professional independence and does not preclude realistic payment for work done in the study. Further investigations should be in accord with Good Laboratory Practice to ensure that laboratory staff are appropriately qualified and that the equipment is reliable. The results of laboratory analysis should be monitored through a quality assurance scheme.

7.5 Common outcome measures such as growth rates, are influenced by multiple factors not just by the innovation under test. Birth weight, mother's education, household composition, and many others, modify outcomes and it is important to characterise all the infants invited to participate with regards to such

genetic, antenatal and environmental factors[35]. This will also help to determine the extent to which the infants who were included in the study are representative of the whole population from which they were drawn.

7.6 Data, in accord with the protocol, should be collected from all individuals who have been invited to take part, although realistically, for infants who did not finish the study, information is likely to be limited to participant characteristics. Where a study is incomplete for reasons such as changing the feeding regimen, outcome measures such as weight might continue to be recorded. The value of even limited data about infants who are invited, but who refuse to participate, has been stressed earlier, as allowing the investigation to assess the extent to which the sample is representative of the whole population and the findings can be generalised.

7.7 It is important to monitor the participants clinically throughout the study, and the accumulating data should be scrutinised to pick up unexpected adverse effects. If this is undertaken by the investigators, early trends of uncertain significance may bias later observations. Instead, a data monitoring committee convened by, but independent of, the investigators should be responsible for assessing the significance of adverse outcomes which have been observed and of advising the study team if there is a risk to the participants. Treatment may be indicated or the protocol for the study may have to be amended, or the study may need to be terminated.

8. The results: handling data and presenting findings

The Working Group recommends that

- **Results from clinical studies of infant formula, including those part-completed which have been abandoned, should be published** (para 8.1).

- **The statistical power of the study should be stated and the confidence limits of differences observed should be presented** (para 8.3).

- **The original records, with protection of the participants' confidentiality, should be preserved wherever possible and an anonymised data archive should be made publicly available** (para 8.4).

- **Consideration should be given to establishing a repository for information and data about trials of infant formula** (para 8.6).

8.1 All results should be made publicly available and, where possible, in forms which are accessible to the health professionals who advise parents. There should be an intention to publish the results in peer-reviewed professional journals, rather than journal supplements. Other ways of presenting data such as presentation at seminars or printing of special booklets, are less satisfactory. The report should describe the study methodology, the basis for recruitment of participants and details of those dropping out[36]. Comparative trials should report a range of variables such as birth weight, sex, social class of the family, etc, to confirm that selection to the feeding groups was unbiased and that the infants who have dropped out of the study have been random. Most trials of infant formula are intended to assess the products as they would be used by the general public. It may be helpful to compare the characteristics of the feeding groups with national characteristics, especially where the results inform the manufacturers prior to marketing the new infant formula.

8.2 It would be unethical not to analyse the results of research on human volunteers. There is a tendency for studies which show no difference between the groups being tested not to be published[37] and it is important that all data should be analysed and offered for publication. Negative results make a valid scientific contribution and protect future infants from being subjected to the same investigation. If the study gives results of uncertain significance, for instance, because the numbers of infants in the groups are too few it is still worth reporting such information as has been obtained although it is essential to outline the limitations of the study to avoid misinterpretation. If studies are discontinued before

they are complete, the researchers should attempt to make known any observations that have been collected, especially where these have contributed to the study being abandoned. There is a particular responsibility to inform if adverse factors were so worrying that to continue might place infants at risk. It is also worth describing reasons for halting a study when these are on methodological grounds. A suitable way to communicate the outcome of stopping a study prematurely might be in a letter to a professional journal.

8.3 The analysis should include results presented as absolute numbers. The statistical power of the study should be stated as well as the confidence limits of any differences observed. If the study lacks statistical power there may be scope for increasing the power of analysis by presenting together the results from the study with those from other studies with common features (para 6.9). The conclusions drawn from the study should address the clinical significance of statistically significant differences.

8.4 It is good practice to keep the records of the research, including ideally, hard copy of questionnaires, laboratory benchwork books, and so on. There must be effective safeguards for commercial and patient confidentiality. Information should also be preserved about manufacturing and production aspects of the feeds being tested and include, for example, the sources of the raw ingredients, information about compositional variations such as fatty acid profiles or sources and types of vitamins added, or additives incorporated during processing. Apart from allowing review of the study, the retention of such data provides a safeguard for all concerned in the study to evaluate unexpected legal or ethical challenges, or where it is suggested that a long-term observation in one or more participants might be associated with the formulas compared in the trial. Research documents, if retained, provide evidence to refute allegations of scientific fraud. Retaining these data need not be purely defensive, unexpected benefits which appear to be associated with the infant formula that was given may merit further investigation after the study has been completed[38].

8.5 Records of anonymised data sets of research studies are increasingly being made public. Survey data can be deposited at the Economic and Social Research Council Data Archive at the University of Essex, where they are held in electronic format. This Archive publicises the availability of the data and regulates access. This provides several opportunities: the data can be investigated to provide additional results or the study results may be synthesised with those from other studies. However, this Data Archive will not be appropriate for the data from all research trials and studies. Rather it offers a model of how data from human research can be preserved in the public domain and exploited to make the maximum contribution to advancing knowledge. The British Library has a similar scheme to hold data from toxicological studies and to enable public access.

8.6 The Working Group recommends that consideration should be given to establishing a repository for information about clinical trials of infant formula. As a minimum, protocols for studies could be lodged together with a record of the

stage the studies have reached[39] although commercial confidentiality and competition between manufacturers would need to be accommodated within any scheme for prospective registration of research. Wherever possible, this information should be accessible to manufacturers and to clinical researchers, and in turn should lead to less overlap of investigations and the encouragement of collaborative projects.

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Annex I. The Regulation of the Nutritional Aspects of Infant Formulas in the European Union

1. European Council Directive on Foodstuffs intended for Particular Nutritional Uses (1989)[1]

In 1989 the European Communities agreed a Council Directive which provided a framework for regulating foods specially designed to be used by persons with particular nutritional requirements. General food law enables the consumer to be protected against fraud concerning the nature of foods and their labelling. However, to meet the food needs for certain groups in the population, derogations to the general foods provisions may be needed to ensure appropriate composition and labelling to meet specific nutritional needs. Groups of foods to which this should apply were listed in the Directive and included "infant formulae", "follow-up milk and other follow-up foods", and "baby foods". The Directive also defines how these products shall be specified to enable their regulation. In particular, the specification may cover compositional criteria and nature of the product, the quality of the raw materials used, hygiene requirements and exclusive lists of permitted additives. The provisions regarding labelling, presentation and advertising also need to differ from those governing labelling of general foods in that the consumer needs to know the particular category of person for whom the product has been prepared ie infants. However, the labelling may not attribute properties for prevention, treatment, or cure of human disease. Directives for specific products may describe monitoring procedures to check that there is compliance with the regulation.

2. European Commission Directive on Infant Formulae and Follow-on Formulae (1991)[2]

The European Commission Directive on Infant Formulae and Follow-on Formulae was adopted on 14 May 1991. It laid down compositional and labelling requirements for infant formulae and follow-on formulae intended for use by infants in good health. It also provided for Member States to give effect to the principles and aims of the WHO/UNICEF International Code of Marketing of Breast-Milk Substitutes[3].

This Directive ensures that the only products marketed to satisfy the nutritional requirements of infants during the first 4-6 months of life are infant formulas. The composition is defined in terms of a range for energy, and nutrient ranges for protein, lipids and carbohydrates with several specifications and requirements for 13 vitamins and 10 minerals. The only accepted protein sources are cows' milk and soya. Six circumstances are listed where a claim may be made provided compositional criteria are met. These are:

- adapted protein
- low sodium
- sucrose free

- lactose only
- lactose free
- iron enriched.

This Commission Directive was brought into UK statute by the Infant Formula and Follow-on Formula Regulations 1995[4].

3. Amendments to the 1991 Commission Directive

Member States of the European Union may submit proposals to the European Commission for amendment of the 1991 Commission Directive; these might relate to composition, nature, labelling claims, presentation, or marketing. The matter is then put to the European Commission Scientific Committee on Food (ECSCF) and an expert opinion is agreed. Since 1991, the ECSCF has provided an opinion on infant formulas claimed to be "Hypoallergenic" or "Hypoantigenic"[5]. The ECSCF has also considered nucleotides, lipids, especially long chain polyunsaturated fatty acids, selenium[6,7], and new labelling requirements which acknowledge the European Community Labelling Reference Values[8]. Amendments have now been agreed by Member States to the 1991 Directive in relation to the specific areas that have been considered by the ECSCF[9] and these changes will need to be reflected in national legislation within a stipulated period.

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Annex II Guidance on assessment of novel foods and processes [1]

General principles

1. Novel foods and food processes have the basic attribute of their novelty. They may or may not be intended as a substitute for an existing food, but in either case they must be considered in as broad a context as possible.

2. The starting point for assessment of novel foods should normally be a comparison with an existing food. Novel foods should be at least as safe, and, if possible, safer than comparable foods if such foods exist.

3. The assessment of novel foods and food processes should identify potential advantages and disadvantages from their introduction to the food supply, taking account of their composition, likely contribution to the diet and any particular preparation or cooking requirements.

4. A history of safe use if available from elsewhere in the world, should be incorporated into the nutritional assessment. However the adequacy in the database needs to be taken into account in the consideration.

5. Novel foods should be considered both in the context of the whole diet and the human response to that diet, and in the context of the responses of potentially vulnerable groups such as children and pregnant or lactating women. The overall diet should be safe, wholesome and nutritious.

6. Foods derived from genetically modified sources should be assessed in a similar manner to those produced by conventional techniques.

7. Where clearance is limited to use in a specified food product or range of products, if a further use is subsequently proposed, then the novel food should be submitted for re-evaluation.

8. The inclusion of a novel food in the diet should not lead to a change in the diet such that the likelihood of disease is increased. These effects may be of two forms:

   i. direct metabolic or other actions on pathophysiological processes;

   ii. relationships and interactions between nutrients, and between nutrients and known toxicants, likely to be present in the diet.

Nutritional criteria

To include:

1. the dietary significance of the novel food;

2. the nutrient content of the diet as eaten containing the novel food, and the content of any antinutritional constituents (such as trypsin inhibitors) that may be introduced into the diet with the novel food;

3. the bioavailability of the nutrients in the novel food itself, the food's possible effects on other components of the diet, such as the mineral content, and any implications of possible changes that might be induced in the gut microflora;

4. the effects of the novel food on the bioavailability of nutrients from other foods in the diet;

5. the quantitative effects and/or dose response relationships of the novel food in relation to gut and systemic functions.

Reference

[1] Department of Health. *The Nutritional Assessment of Novel Foods and Processes.* London: HMSO, 1993. Report on Health and Social Subjects:44.

Annex III Guidance on the types of information likely to be required when assessing novel foods and novel food processes [1]

I. Evidence of previous human exposure.

II. Intake and extent of use.

III. Technical details of the process.

IV. Product specification.

V. Nutritional assessment.

VI. History of the organism.

VII. Characterisation of derived strain in comparison with the parent strain.

VIII. Toxicological assessment.

IX. Human data.

X. Effect of the genetic modification on the known properties of the parent organism.

XI. Genetic stability of the modified organism.

XII. Site of expression of any novel genetic material.

XIII. Transfer of the novel genetic material.

XIV. Assessment of a modified organism for survivability, replication and colonisation/ amplification in the human gut.

XV. Safety information.

Reference

[1] Department of Health. *Guidelines on the Assessment of Novel Foods and Processes.* London: HMSO, 1991. Report on Health and Social Subjects:38, as amended by *A structured approach for the safety assessment of novel foods and processes: Revision to Chapter 4 of the ACNFP Guidelines.* July 1995.

Annex IV Children involved in Research - Ethical Considerations

1. British Paediatric Association Guidelines 1980

The British Paediatric Association (BPA) first issued guidelines to aid ethics committees considering research involving children in 1980[1]. Four premises were adopted.

i. That research involving children is important for the benefit of all children and should be supported and encouraged and conducted in an ethical manner.

ii. That research should never be done in children if the same investigation can be done in adults.

iii. That research that involves a child and is of no benefit to the child is not necessarily unethical or illegal.

iv. The degree of benefit resulting from the research should be assessed in relation to the risk of disturbance, discomfort or pain - the risk/benefit ratio.

Further, it divided research into **non-therapeutic research** where the procedure is of no benefit to the subject but may benefit the health and welfare of other children or adults, or where the procedure is of no benefit to the subject but may add to basic biological knowledge, and **therapeutic research** where the procedure is of potential benefit to the subject.

2. In forming an ethical judgement about a procedure undertaken for research purposes the guidelines acknowledge that it might be (i) no more than part of the ordinary care of an infant; (ii) involves the non-invasive collection of samples eg hair, faeces, cord blood; (iii) invasive, such as blood sampling, but representing a minor extension of normal treatment, eg taking an additional quantity of blood during venepuncture; (iv) or an invasive procedure purely undertaken for research proposes. In all cases it was considered that where there was no benefit to the subject of the research, the level of risk involved in any of the procedures should not be greater than minimal. To quote from the BPA guidelines "Risk, in this context, means the risk of causing physical disturbance, discomfort or pain, or psychological disturbance to the child or his parents, rather than the risk of serious harm, which no ethics committee would countenance in any case".

3. Royal College of Physicians of London: Research on Healthy Volunteers

The Royal College of Physicians of London published a detailed report about Research on Healthy Volunteers in 1986[2]. This considered particularly the means of carrying out a research project in regard to the recruitment and safeguards for subjects, consent and confidentiality aspects, and referral for approval by an ethics committee.

4. NHS Local Research Ethics Committees (LREC)

Government provided guidance in 1991 about ethics committees established locally to advise on the ethics of proposed research projects being undertaken within the National Health Service[3]. LRECs may also be asked to advise on the ethics of studies not involving NHS patients, for example by private sector companies, Research Councils or universities and the guidance encourages these approaches.

As a minimum the LREC will need to know:

i. has the scientific merit of the proposal been properly assessed?

ii. how will the health of the research subjects be affected?

iii. are there possible hazards and, if so, adequate facilities to deal with them?

iv. what degree of discomfort or distress is foreseen?

v. is the investigation adequately supervised and is the supervisor responsible for the project adequately qualified and experienced?

vi. what monetary or other inducements are being offered to the NHS body, doctors, researchers, subjects or anyone else involved?

vii. are there proper procedures for obtaining consent from the subjects or where necessary their parents or guardians?

viii. has an appropriate information sheet for the subjects been prepared?

5. British Paediatric Association Guidelines 1992

The BPA reviewed its guidelines in 1992[4]. The opening sentence states that "Medical research involving children is an important means of promoting child health and wellbeing". To encourage good, ethically sound research in childhood each project should

- have an identifiable prospect of benefit to children;
- be well designed and well conducted;
- not be undertaken primarily for financial or professional advantage;
- involve a statistically appropriate number of subjects;
- eventually be properly reported.

These guidelines also state that a project "should not simply duplicate earlier work".

6. While the 1980 BPA guidelines classified the degree of risk as "negligible", "minimal" or "more than minimal", in 1992 the descriptors of risk were "minimal", "low" or "high". In regard to blood sampling the guidelines acknowledge that some children are upset by the prospect of a needle puncture and most children dislike the pain of the procedure even when it is generally short lived. In the case of children who are very upset or frightened, blood sampling increases to low risk rather than minimal risk. In such cases there is a responsibility both on the parent, or other carer, and on the health professional to take note of the child's reluctance, and to desist. Blood sampling in non-therapeutic research is nowadays more acceptable because the equipment for taking blood has been improved and in many cases is designed specifically for the category of subject in the study - particularly important for infants. The degree of pain and the potential for trauma have been reduced substantially by employing personnel skilled in taking blood from children. As a result the risk of blood sampling, for most subjects, is minimal [5].

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