Substitutes for breast milk for young infants have been developed from the milk of other mammals, through a variety of modifications, into the complex formulas that are available today. These developments resulted from improvements in the understanding of the chemical and nutrient composition of human milk and mammalian milks in general. Initially, the sole criterion for the adequacy of such formulas was the survival of infants fed on them. Subsequently, as the products became more refined, and their gross composition was modified to resemble more closely that of human milk, other factors such as linear and ponderal growth of the babies, and other anthropometric, biochemical, and metabolic factors were included in the evaluation of their effects (1). These criteria have often been measured over short periods of time (e.g., 1 to 3 months). However, it is now appreciated that early infant feeding may influence growth, development, and the incidence of gastrointestinal, respiratory, and allergic disease in early childhood (2–4) and, possibly, metabolism and health in later childhood and adulthood (4–8). Consequently, the nature of the evaluation of infant formulas and breast milk substitutes needs to be reviewed, focusing also on longer term nutritional and safety outcomes. The aim of this paper is to highlight the need for a systematic evaluation of nutritional and safety characteristics of dietary products for use in infants (e.g., infant formulas, follow-on formulas, dietary products for infants that are marketed as Foods for Special Medical Purposes [9] and other dietetic products for infants such as complementary foods). However, the Committee acknowledges that different criteria for nutritional and safety characterization may apply for products used as the sole and predominant food source, such as infant formulas and some Foods for Special Medical Purposes that are used as substitutes for breast milk or formula, compared with products that comprise only a minor portion of the total dietary intake, such as some complementary food.

Formulas are regarded as products intended to satisfy totally the nutritional requirements of infants during the first 4 to 6 months of life, and to contribute a major part of the nutritional requirements throughout the first year of life. The Directive on Infant Formulae and Follow on Formulae, published in 1991 (10), defines their basic composition, and it also permitted member states of the European Union to submit proposals for amendments to the composition of infant formulas. Since then, the inclusion of nucleotides, selenium, phospholipids, and long-chain polyunsaturated fatty acids has been allowed. Recently, a review of the evaluation of infant formulas was undertaken by a working group of the Committee on Medical Aspects of Food and Nutrition Policy of England and Wales (11).

The Committee on Nutrition supports the general concepts outlined in the report of the Committee on Medical Aspects of Food and Nutrition Policy of England and Wales, and agrees the following recommendations and comments are particularly important.

1. Although the composition of human milk can be a guide to that of infant formulas and breast milk substitutes, gross compositional similarity is not, in itself, an ideal determinant or indicator of the safety and nutritional adequacy of dietary products for infants. A
better approach is considered to be the comparison of outcomes in infants fed such products with those seen in healthy infants who have been breast-fed exclusively for 4 to 6 months. Unfortunately, such a reference group is not always readily available for comparative studies. The Committee on Nutrition supports the view that it would be in the general interest if research groups, and their respective sponsors, collaborated to compile datasets of common outcome measures from breast-fed babies. This information would then be available as a reference source for studies on the effects of infant formulas.

2. Appropriate clinical studies of nutritional and safety assessment should be performed particularly for components and combinations of components that have not been included previously in infant formulas and other dietary products for infants. Technological as well as compositional modifications to infant formulas should be assessed nutritionally as, for example, the Committee on Nutrition has recommended recently in the case of breast milk substitutes based on hydrolyzed protein sources (9).

3. The introduction of any modification to a formula or other dietary product for infants should be based on a systematic review of relevant, existing information. This review should enable the development of a clear hypothesis of the expected functional and clinical benefits that would derive from the proposed modifications. Furthermore, these reviews should be published or made publicly available in some form. Studies should be designed primarily to test these hypotheses, as well as to make general nutritional assessments.

4. Infant formulas or other dietary products that are modified for reasons other than to provide a novel functional or clinical benefit, or that are based on products already on the market should, at least, be subjected to studies of acceptability and of nutritional equivalence to the existing products. These studies should follow the same principles outlined herein, and the derived data should be available for archiving in a consolidated repository such as that proposed later.

5. All infants in clinical trials should be characterized with regard to factors that might affect the planned outcomes. Blind randomization with respect to the allocation of test and reference formulas is important, and all studies should comply with good clinical and good laboratory practices.

6. For all clinical trials, ethical approval and informed parental consent should be obtained, and these should be declared in the publication of the results.

7. It is important that the possibility of unexpected adverse outcomes be addressed by adequate clinical monitoring of participants, and by incorporating into the study design arrangements for the independent scrutiny of the accumulating data.

8. The general principles, design, execution, and data analysis of evaluative studies of infant formulas and other substitutes for breast milk need to be determined to detect relevant short- and long-term (i.e., in later childhood and adult life) outcomes. The design should consider from the outset the statistical power of the study, and the confidence limits of any differences found should be included in the published reports.

9. Preliminary pilot studies of the proposed study design are often useful to identify and to anticipate outcomes and issues that would inform definitive studies and enable protocols to be adapted, and would enable the views of the infants’ caregivers to be taken into account. This approach would be expected to enhance the cooperation of caregivers and the quality of the methodology of the subsequent definitive assessment.

10. Manufacturers and scientific, academic, and professional groups should collaborate to the extent of agreeing to an essential portfolio of data and outcomes, which will be recorded in all nutritional studies performed during early life. This will enable the later consolidation of information from individual studies into larger databases that will be appropriate for the assessment of long-term nutritional efficacy and safety, and will ensure detection of unanticipated outcomes of early feeding practices and dietary exposure.

11. A register of current trials should be established and, whenever possible, this information should be accessible to manufacturers and to clinical researchers. It should be used to reduce overlap between investigations, to avoid unnecessary replication of studies, and to encourage collaborative projects particularly in the evaluation of precompetitive modifications. Similar collaborations would facilitate the creation of cohorts that are large enough to enable follow-up of the studied infants through their childhood and into adulthood. It should be possible to achieve this without compromising intellectual property rights, commercial confidentiality, and competition between manufacturers.

12. Original study records, with protection of the participants’ confidentiality, should be preserved whenever possible. From these records an anonymous data archive should be made publicly available for retrospective epidemiologic assessment of associations with adverse and beneficial outcomes.

13. Many trials of infant formulas are not completed for a variety of reasons, and information from these as well as from some completed studies is not published. The results of such abandoned studies should at least be made available publicly, and to the consolidated database, together with the specific reasons for the cessation of the study. Similarly, the specific reasons why children withdrew from completed studies should be included in the published reports.

The ESPGHAN Committee on Nutrition advocates the systematic nutritional and safety evaluation of breast milk substitutes and other dietary products for infants for long- and short-term outcomes, and encourages those involved with infant care to promote the incorporation of these principles into their national regulatory processes. The Committee on Nutrition will be proposing, for general discussion, a list of core data that should be recorded in such studies. These guidelines may also provide a benchmark for the assessment of other dietary products, and they could be equally appropriate in the regulatory processes for the introduction of new Foods of Special Medical Purposes (9) and other dietary products designed for use in adults as well as in children.

REFERENCES