

Compositional Requirements of Follow-Up Formula for Use in Infancy: Recommendations of an International Expert Group Coordinated by the Early Nutrition Academy

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Key Words

Infant feeding · Food standards · Infant food · Follow-up formula · Infant nutrition · Nutritional requirements

Abstract

The follow-up formula (FUF) standard of Codex Alimentarius adopted in 1987 does not correspond to the recently updated Codex infant formula (IF) standard and current scientific knowledge. New Zealand proposed a revision of the FUF Codex standard and asked the non-profit Early Nutrition Academy, in collaboration with the Federation of International Societies for Paediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN), for a consultation with paediatric nutrition experts to provide scientific guidance. This global expert group strongly supports breastfeeding. FUF are considered dispensable because IF can substitute for breastfeed-

ing throughout infancy, but FUF are widely used and thus the outdated current FUF standard should be revised. Like IF, FUF serve as breast milk substitutes; hence their marketing should respect appropriate standards. The compositional requirements for FUF for infants from 6 months onwards presented here were unanimously agreed upon. For some nutrients, the compositional requirements for FUF differ from those of IF due to differing needs with infant maturation as well as a rising contribution of an increasingly diversified diet with advancing age. FUF should be fed with adequate complementary feeding that is also appropriate for partially breastfed infants. FUF could be fed also after the age of 1 year without safety concerns, but different compositional requirements should be applied for optimal, age-adapted milk-based formulations for young children used only after the age of 1 year. This has not been considered as part of this review and should be the subject of further consideration.

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Background

The Food and Agriculture Organisation of the United Nations (FAO) and the World Health Organisation (WHO) jointly created the Codex Alimentarius Commission (CAC) in 1963, aimed at developing food standards, guidelines, and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme (www.codexalimentarius.net). The key goals are to protect the health and well-being of consumers, to ensure fair practices in the food trade, and to promote coordination of food standards work undertaken by international governmental and non-governmental organisations [1]. In the fall of 2012, Codex Alimentarius had 185 member nations and one member organisation covering 99% of the world's population [2]. Codex Alimentarius develops and publishes a large number of standards addressing food quality and safety that are of key importance for protecting public health and fair trade globally.

The Codex Standard 72 on Infant Formula was originally published in 1981, and a thoroughly revised version of this, i.e. *Standard for infant formula and formulas for special medical purposes intended for infants*, was adopted in 2007 [3]. The adoption of the updated standard was facilitated by recommendations on compositional requirements provided by an international expert group coordinated by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN, www.espghan.org) [1], which were largely adopted in the Codex standard.

In 1987, the CAC also adopted a standard for follow-up formula (FUF) [4]. FUF was defined in this Codex standard as 'a food prepared from the milk of cows or other animals and/or other constituents of animal and/or plant origin, which have been proved to be suitable for infants from the 6th month on and for young children'. [4]. However, the concepts and compositional data in this standard adopted in 1987, i.e. 25 years ago, do not correspond to those laid down in the recently updated Codex standard on infant formula (IF) [3] and current scientific knowledge [1]. Therefore, in 2010, the government of New Zealand proposed to the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) the need to discuss the revision of the standard for FUF, and the CCNFSDU agreed to consider this proposal [5]. In the following year (2011), the CCNFSDU noted support for the review of the FUF standard but, due to time constraints with the agenda, did not make a decision on whether or not such a review should be undertaken [6].

In 2012, New Zealand renewed the proposal for a review of the FUF standard [7].

In preparation for a possible review, the government of New Zealand asked the Early Nutrition Academy (ENA) to provide guidance on the compositional requirements for FUF for infants aged 6 months and older, based on current scientific and paediatric knowledge and in consultation with an international group of paediatric nutrition experts. The ENA is a non-profit society that was created by and represents the partners of international research projects funded by the European Commission and the Australian National Health and Medical Research Council (www.early-nutrition.org). The purpose of the society is to promote the knowledge of human nutrition in early life, to stimulate research in this and related areas of science, nutrition, and health, and to disseminate such knowledge at scientific meetings and elsewhere. The ENA, which represents a large number of researchers from universities across Europe, Australia, and the USA, was granted observer status at Codex Alimentarius in 2012 by the Executive Committee of the CAC.

The ENA, in close collaboration with the Federation of International Societies on Paediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN), ESPGHAN, and its other member societies, identified knowledgeable experts in the area of paediatric nutrition and health from all five continents and invited them to participate in an electronic exchange of information and in a physical meeting held on November 14–15, 2012, prior to the FISPGHAN World Congress on Paediatric Gastroenterology, Hepatology, and Nutrition in Taipei, Taiwan. Criteria for participation included expertise in paediatric nutrition and active contributions to international scientific societies or advisory bodies dealing with paediatric nutrition. Preference was given to experts that had already decided to attend the FISPGHAN World Congress in Taipei to avoid additional travel costs. In order to ensure that experts were in a position to provide objective and disinterested scientific advice, all participating experts submitted a written declaration of personal and non-personal (institutional) interests which were carefully reviewed and discussed. The expert participants are listed as authors of this manuscript. In addition, two observers from the government of New Zealand participated in the meeting in Taipei (Ms. Charlotte Channer and Ms. Jenny Reid). Based on a considered review of the available evidence and a thorough discussion, the expert group unanimously agreed on the conclusions reported below.

General Considerations and Definitions

The expert group strongly supports breastfeeding as the normal and ideal form of infant feeding, which should be actively promoted, protected, and supported [8–10]. Based on the results of an expert consultation [11], the WHO has recommended: ‘As a global public health recommendation, infants should be exclusively breastfed for the first 6 months of life to achieve optimal growth, development, and health. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to 2 years of age or beyond.’ [12].

Infants who cannot be fed at the breast, or should not receive breast milk for medical reasons (e.g. due to galactosaemia), or for whom breast milk is not available should receive IF that are intended to serve as a substitute for breast milk [5]. An IF serves ‘to satisfy, by itself, the nutritional requirements of infants during the first months of life up to the introduction of appropriate complementary feeding’ [3]. IF can continue to serve as a breast milk substitute for the entire duration of the first year of life and even beyond, although cow’s milk (or other suitable milks) can also be used in the second year of life [13, 14].

FUF have been previously defined by Codex Alimentarius as foods ‘intended for use as a liquid part of the weaning diet for the infant from the 6th month on and for young children’ [4], i.e. from the age of 6 up to 36 months. During the first year of life, both IF and FUF serve to substitute for breast milk; therefore, the marketing of both groups of products should respect the International Code of Marketing of Breast Milk Substitutes [15], the Global Strategy for Infant and Young Child Feeding [12], and World Health Assembly resolution WHA54.2 (2001). The expert group acknowledges that FUF are dispensable because IF can substitute for breast milk during the whole duration of the first year of life. However, currently FUF are widely used in many populations, and in some countries the large majority of infants receive FUF during the second half of the first year of life [7]. Therefore, it is recommended that Codex Alimentarius updates its FUF standard and provides guidance on the appropriate composition of FUF following currently available scientific information. FUF are meant to be used only in older infants after timely introduction of appropriate complementary feeding, with increasing amounts and diversity of complementary foods over time [12, 13]. While the global population recommendation of the WHO is exclusive breastfeeding for 6 months, introduction of complementary feeds during a range of ages

from the 5th to the 7th month has been considered an option for infants in affluent populations with high standards of hygiene and low risks of infection [16–18] and is widely practiced [19]. The expert group has provided recommendations for compositional requirements of FUF for use in infants generally from the age of 6–12 months, but not prior to the introduction of complementary feeding. The expert group considered that FUF must be able to serve as the dominant food source at the beginning of introducing complementary feeding when FUF may provide more than 90% of an infant’s energy intake. Therefore, in many aspects the recommended composition of FUF follows the current standard for IF [3]. The available evidence from studies addressing the specific nutrient needs of infants aged 6–12 months is more limited than for infants during the first months of life; however, there is evidence that the compositional requirements for FUF differ for some nutrients from those of IF due to differing needs with infant maturation as well as a rising contribution of an increasingly diversified diet with advancing age. The expert group based its recommendations on the concept that FUF will be fed along with complementary foods of adequate composition that would also suffice to meet the needs of a partially breastfed infant. Thus, FUF is not meant to compensate for inadequate complementary feeds, but rather appropriate complementary feeding regimens need to be supported in the interest of all infants, as per the norm of infants that are partially breastfed after the age of 6 months. FUF with a composition as recommended here could be continued for use after the age of 1 year without safety concerns. However, it is emphasized that different compositional requirements should be applied for optimal, age-adapted milk-based formulations for young children used only from the age of 1 year onwards. The expert group has not considered the specific nutritional requirements of young children (from the age of 12 months up to 36 months) as part of this review paper and acknowledges that the compositional requirements of such products (also referred to as ‘toddler milks’ or ‘growing-up milks’) [20, 21] should be the subject of further expert consideration.

Recommendations for FUF Composition

FUF is a food prepared from the milk of cows or other animals and/or other constituents of animal and/or plant origin that are suitable for infants from the timely introduction of complementary feeding onwards. The nutritional safety and adequacy of FUF and its components

Table 1. Proposed compositional requirements

Component	Minimum	Maximum	Guidance upper level
<i>FUF</i>			
Energy, kcal/100 ml	60	70	
Proteins			
Cow's milk protein, g/100 kcal	1.7*	2.5*	
Soy protein isolates, g/100 kcal	2.1*	2.5*	
Lipids			
Total fat, g/100 kcal	4.4	6.0	
Linoleic acid, g/100 kcal	0.3		1.4
α -Linolenic acid, mg/100 kcal	50	NS	
Ratio linoleic/ α -linolenic acids	5:1	15:1	
Lauric + myristic acids, % of fat	NS	20	
Trans fatty acids, % of fat	NS	3	
DHA ¹ , % of fat	NS	1.0*	
Erucic acid, % of fat	NS	1	
Phospholipids, mg/100 kcal			550
Carbohydrates			
Total carbohydrates, g/100 kcal	9.0	14.0	
Vitamins			
Vitamin A ² , μ g RE/100 kcal	60	180	
Vitamin D ₃ , μ g/100 kcal	1	4.5*	
Vitamin E ⁴ , mg α -TE/100 kcal	0.5 ³		5
Vitamin K, μ g/100 kcal	4		27
Thiamin, μ g/100 kcal	60		300
Riboflavin, μ g/100 kcal	80		500
Niacin ⁵ , μ g/100 kcal	300		1,500
Vitamin B ₆ , μ g/100 kcal	35		175
Vitamin B ₁₂ , μ g/100 kcal	0.1		1.5
Pantothenic acid, μ g/100 kcal	400		2,000
Folic acid, μ g/100 kcal	10		50
Vitamin C, mg/100 kcal	10		70
Biotin, μ g/100 kcal	1.5		10
Minerals and trace elements			
Iron (formula based on cow's milk protein), mg/100 kcal	1.1*	1.9*	
Iron (formula based on soy protein isolates), mg/100 kcal	1.3*	2.5*	
Calcium, mg/100 kcal	50		180*
Phosphorus, mg/100 kcal	25		NS*
Magnesium, mg/100 kcal	5		15
Sodium, mg/100 kcal	20		60
Chloride, mg/100 kcal	50		160
Potassium, mg/100 kcal	60		180
Manganese, μ g/100 kcal			100*
Iodine, μ g/100 kcal	10		60
Selenium, μ g/100 kcal	1		9
Copper, μ g/100 kcal	35		250
Zinc, mg/100 kcal	0.5		1.5
Other substances			
Choline, mg/100 kcal	7		150*
L-Carnitine, mg/100 kcal	1.2	NS	
Taurine, mg/100 kcal	NS	12	
Total added nucleotides, mg/100 kcal	0		10.8*

should be based on scientifically accepted evidence. The expert group agrees with previously published comments that the adequacy and safety of dietary products for infants should be determined by a thorough evaluation of its effects on physiological, biochemical, and functional outcomes in infants [1, 22–24]. It also supports the conclusion that dietary products for infants should only contain components in amounts that serve a nutritional purpose or provide another benefit. Minimum and maximum values of nutrient contents in FUF are suggested here with the goal to provide safe and nutritionally adequate products that meet the nutritional requirements of generally healthy infants [1]. Guidance upper levels are proposed if the available evidence is considered insufficient for a science-based quantitative risk assessment in infants aged about 6–12 months. Minimum, maximum, and guidance upper level values refer to the total nutrient contents of products as prepared ready for consumption according to the instructions of the manufacturer. This expert group recommends that FUF contain per 100 kcal the nutrient contents as listed in table 1. This group recognizes that nutrient supply and status among infants and young children differs in various parts of the globe, particularly for micronutrients, and thus the requirements of specific nutrient contents in FUF might need to be set different from these recommendations in some countries or regions. In particular, the use and composition of FUF in different geographic areas should take into account national or regional micronutrient supplementation programs to avoid excessive intakes. Below we provide some comments which only address issues where recommendations for FUF are made that differ from the established compositional requirements of IF [1, 3].

NS = Not specified.

¹ The content of DHA (22:6n-3) shall be at least as high as the content of EPA (20:5n-3).

² 1 μ g RE (retinol equivalent) = 1 μ g all-trans retinol = 3.33 IU vitamin A. Retinol contents shall be provided by preformed retinol, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.

³ 1 mg α -TE (α -tocopherol equivalent) = 1 mg D- α -tocopherol.

⁴ The vitamin E content shall be at least 0.5 mg α -TE/g PUFA, using the following factors of equivalence to adapt the minimal vitamin E content to the number of fatty acid double bonds in the formula: 0.5 mg α -TE/g linoleic acid (18:2n-6); 0.75 mg α -TE/g α -linolenic acid (18:3n-3); 1.0 mg α -TE/g arachidonic acid (20:4n-6); 1.25 mg α -TE/g EPA (20:5n-3); 1.5 mg α -TE/g DHA (22:6n-3).

⁵ Niacin refers to preformed niacin.

* Levels that are different from those in the Codex Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants (Codex Stan 72-1981) [3].

Energy Density

Studies with current methodology have revealed an average energy density of human milk of about 65 kcal/100 ml [25, 26]. A dietary energy density markedly higher than typically found in human milk may increase the total energy intake and lead to a higher than desirable weight gain [1, 27]. A high weight gain of healthy children during the first 2 years is not desirable since it is associated with a markedly increased risk of later obesity and related diseases [12, 28, 29]. Therefore, the energy density of FUF should be the same as in IF, i.e. FUF prepared ready for consumption in accordance with the instructions of the manufacturer shall contain per 100 ml not less than 60 kcal (250 kJ) and not more than 70 kcal (295 kJ) of energy. This energy density is appropriate to support physiological weight gain in healthy infants who also receive adequate complementary feeding.

Protein

The average daily protein intake of breastfed infants at age 6 months has been estimated as 0.95 g/kg body weight [30]. Population reference intakes for the dietary protein intake per day calculated to meet the needs of basically all infants in the population with an adequate safety margin have been considered as 1.31 g protein/kg bodyweight at age 6 months and 1.14 g/kg at 12 months by the WHO/FAO/UNU [31] and by EFSA [32], whereas recent recommendations by some other bodies have set slightly lower dietary reference values of protein of 1.1–1.2 g/kg at 6 months [reviewed in 32]. To safely cover total protein needs at a daily energy intake of 80 kcal/kg, a protein supply of 1.31 g at 6 months would result in a protein density of 1.64 g protein/100 kcal, while a protein supply of 1.14 g at 12 months would result in a protein density of 1.43 g protein/100 kcal. It is recommended to set the minimum content of cow's milk protein in FUF at 1.65 g/100 kcal, based on a good protein quality with an adequate content of bioavailable essential amino acids. Consistent with the IF standard, protein content should be calculated based on the established nitrogen conversion factor of 6.25 [3].

High infant milk protein intakes during the first year of life that markedly exceed metabolic requirements were shown to lead to excessive weight gain which can increase the risk of later obesity and associated diseases [33–39]. Therefore, high milk protein intakes provided with formulae for infants should be avoided. While mature human milk at an infant age of 6 months provides about 5% of the energy content as protein, the protein content of mixed family foods and complementary foods is typically in the order of 15–20% of energy and most infants get-

ting complementary feeding have protein intakes far above the requirements [38–41]. We recommend that the maximum protein content in FUF should not exceed 150% of the minimum content, i.e. 2.5 g/100 kcal which equals about 10% of the energy content. This maximum protein content would also cover additional protein needs in case of catch-up growth.

Based on concerns of lower bioequivalence of soy protein isolate, the minimum protein content of IF based on soy protein isolates has been set in the IF standard at 1.25 times the minimum of cow's milk-based IF while the maximum levels set are the same [3], although the scientific evidence to justify this choice is limited. To achieve consistency with the IF standard, the minimum and maximum protein contents in FUF based on soy protein isolate should be set at 2.05 g/100 kcal and 2.5 g/100 kcal, respectively.

If proteins other than cow's milk and soy proteins are used in FUF, their suitability and adequate minimum and maximum amounts should be determined based on scientific evidence, including, where appropriate, clinical trials. Higher minimum protein levels than recommended for cow's milk protein may be needed for other protein sources to correct for potential lower contents of indispensable amino acids and potential lesser digestibility and biological value of the nitrogen content [42, 43]. Determination of the protein efficiency ratio in rats is of limited value for evaluating the suitability of proteins for infant feeding, and hence the protein efficiency ratio is not recommended for this purpose; rather the protein digestibility-corrected amino acid score (PDCAAS) should be considered [31].

The use of IF based on hydrolysed protein during the first 4–6 months of life was associated with risk reduction of infant and childhood allergy and infant cow's milk protein allergy in infants with a family history of allergy [44, 45]. There is no indication of a protective effect of the further use of hydrolysed protein in FUF during the second half year of infancy when complementary feeding usually provides intact proteins from cow's milk and other sources. Therefore, no value is provided here for hydrolysed protein in FUF.

The recommended minimum content of indispensable and conditionally indispensable amino acids in FUF (table 2) is based on the data on amino acid content in human milk reference protein and the recommended minimum cow's milk protein content of 1.65 g/100 kcal, analogous to the approach adopted for IF [1, 3]. The expert group notes that new data on infant amino acid requirements are emerging [46–48], which may require revised

Table 2. Proposed values for minimum amino acid contents in FUF

Amino acid	g/100 g protein	mg/100 kcal
Cystine	2.1	34.7
Histidine	2.3	38.0
Isoleucine	5.1	84.2
Leucine	9.4	155.1
Lysine	6.3	104.0
Methionine	1.4	23.1
Phenylalanine	4.5	74.3
Threonine	4.3	71.0
Tryptophan	1.8	29.7
Tyrosine	4.2	69.3
Valine	5	82.5

FUF should contain per 100 kcal an available quantity of each of the amino acids listed at least equal to that contained in the reference protein, as shown in this table.

For calculation purposes, the concentrations of phenylalanine and tyrosine may be added together if the phenylalanine-to-tyrosine ratio is in the range of 0.7–1.5 to 1, and the concentrations of methionine and cysteine may be added together if the methionine-to-cysteine ratio is in the range of 0.7–1.5 to 1. It is noted that new data on infant amino acid requirements are emerging [46–48], which may require revised definitions of minimum contents of non-dispensable and conditionally indispensable amino acids in IF and FUF in the future.

definitions of minimum contents of non-dispensable and conditionally indispensable amino acids in IF and FUF in the future. Maximum levels of amino acid contents in FUF do not need to be set given that maximum levels of total protein are established.

Lipids

The lipid content and composition of FUF should generally follow the standards set for IF [1, 3]. A total fat content of 4.4–6.0 g/100 kcal equivalent to ~40–55% of the energy content similar to typical human milk values is recommended in order to allow for the same complementary feeding concepts to be applied for infants that are partially breastfed or partially fed IF or FUF. Also, the requirements for essential fatty acid contents should be similar to those set for IF [1, 3].

For some aspects of fat quality in FUF a precautionary approach is recommended in the absence of specific evidence for the second half of the first year of life; therefore, the established concepts for IF should be followed [3]. In consideration of the potential untoward effects of lauric acid and myristic acid on serum cholesterol and lipoprotein concentrations, the sum of both of these fatty acids

should not exceed 20% of the total fat contents. *Trans* fatty acids have no known nutritional benefit for infants, but may induce untoward biological effects. Commercial hydrogenated oils and fats should not be used in FUF. The *trans* fatty acid content of FUF should not exceed 3% of the total fatty acids, which allows for the use of reasonable amounts of milk fat from cows and other ruminant animals in FUF. Erucic acid has no known nutritional benefits for infants but was associated with potential myocardial toxicity in animals. Based on a precautionary approach, erucic acid contents acids in FUF should not exceed 1% of the total fat content.

The Codex standard for IF allows an optional supply of docosahexaenoic acid (22:6n–3, DHA) up to 0.5% of the fat content which must be matched with an at least equal supply of arachidonic acid (20:4n–6) [3]. The endogenous synthesis of DHA from the n–3 fatty acid precursor α -linolenic acid is limited in humans, and the degree of DHA synthesis varies considerably with inter-individual genetic differences in the fatty acid desaturase gene cluster [49, 50]. The provision of preformed DHA during the first year of life has been associated with benefits for visual and brain development and immune response, but other studies have not demonstrated benefit [51, 52]. Addition of DHA in an amount of 1% of the total fatty acids to formula for preterm infants has not led to untoward effects in a very large clinical trial [53, 54], and there is no reason to limit the content in FUF to a lower amount. During the first few months of life the ability to maintain arachidonic acid stores from endogenous synthesis increases [55]. Moreover, dietary preformed arachidonic acid is provided by a variety of complementary foods during the second half of the first year of life. The provision of oily fish with complementary feeds can provide high intakes of DHA with little supply of arachidonic acid, without any indication of adverse effects. In a randomized clinical trial, supplementation of infants with 500 mg/day of an n–3 fatty acid-rich tuna fish oil supplement providing DHA without appreciable amounts of arachidonic acid from the age of 6 months onwards did not show untoward effects [56, 57]. Therefore, it is considered unnecessary to set a requirement for added arachidonic acid in FUF that provides DHA. However, the expert group recommends limiting the content of eicosapentaenoic acid (20:5n–3, EPA), a direct metabolic competitor of arachidonic acid, to an amount not exceeding the content of DHA in FUF.

For IF fed from birth, a maximum phospholipid concentration of 300 mg/100 kcal (equivalent to about 2 g/l) has been set following the precautionary approach. For older infants at the age of FUF feeding, there are few con-

cerns regarding the provision of phospholipids with usual complementary feeds which provide considerable amounts of phospholipids. For example, infants will consume about 3.5 g phospholipids with one hen's egg. Research into the roles of phospholipids in human milk fat globules indicates potential benefits of adding certain phospholipids to FUF [58–60], in addition to solubilizing lipophilic compounds and acting as a source of long-chain polyunsaturated fatty acids. Therefore, a concentration of 550 mg/100 kcal (equivalent to about 3.5 g/l) is recommended as the guidance upper level.

Carbohydrates

Total carbohydrate contents in FUF equal to those set for IF are recommended. Lactose, glucose polymers, and precooked and gelatinized starches that are gluten free by nature are the preferred carbohydrate sources in FUF. Starches may provide up to 30% of the total carbohydrates. Fructose and sucrose are provided with complementary feeds and may also be provided with FUF, but in line with previous scientific evaluations it is recommended that the sum of saccharose (sucrose) and fructose should not exceed 20% of the total carbohydrate content in FUF [61], i.e. at a maximum carbohydrate content of 14 g/100 kcal no more than a maximum of 11.2 % of energy which is similar to the guidance provided by the WHO for the general population [62].

Vitamins

There is lack of sufficient evidence that would allow setting different compositional requirements for vitamins in FUF as compared to IF. Contents of lipid- and water-soluble vitamins in FUF equal to those set for IF are recommended, except for vitamin D.

Recent data show that a significant number of infants and young children in different parts of the world have a suboptimal or deficient vitamin D status [63–68] which has prompted efforts to improve vitamin D supply. The expert group recommends a higher maximum vitamin D content for FUF than previously established for in IF, which may contribute to improving vitamin D status and associated health outcomes. EFSA determined tolerable upper intake level (UL) for vitamin D of 1,000 IU for the whole duration of the first year of life while acknowledging a limited evidence base for the approach chosen [60]. In contrast, the Institute of Medicine determined an age-specific UL for vitamin D for infants aged 6–12 months of 1,500 IU/day [69]. Based on the latter, age-specific UL, and an assumed maximum FUF intake of 800 kcal/day, the recommended maximum value for vitamin D content in

FUF is 4.5 $\mu\text{g}/100$ kcal (180 IU/100 kcal). It is emphasized that vitamin D contents in FUF below this maximum value should be chosen in populations where additional vitamin D supplementation programs are implemented.

Minerals and Trace Elements

Iron

Body stores of iron present at birth cover most of the iron needs of healthy infants during the first half year of life, when iron absorption and dietary iron requirements are low [70]. In contrast, at the age of about 6 months endogenous body iron stores tend to be exhausted. At the age of 6–12 months, infants have high daily iron requirements of about 0.9–1.3 mg/kg body weight or about 8–11 mg/day [71–75]. To meet daily iron needs of 0.9 or 1.3 mg/kg body weight from FUF at an energy intake of 80 kcal/kg/day, an iron content of 1.1 or 1.6 mg/100 kcal, respectively, is required. The feeding of formula with an iron content of 1.9 mg/100 kcal from 6 to 12 months of age did not show adverse effects and was considered safe [76]. The expert group recommends an iron content in FUF based on cow's milk ranging from 1.1 to 1.9 mg/100 kcal. Since the bioavailability of iron in FUF based on soy protein isolates may be reduced by phytic acid content, a higher minimum iron content of 1.3 mg/100 kcal and a maximum content of 2.5 mg/100 kcal are suggested for FUF based on soy protein isolates, based on the same concepts as applied in the Codex IF standard [3].

Other Minerals and Trace Elements

The expert group recommends that FUF contain the same amounts of most other minerals and trace elements as set for IF, with the exception of calcium, phosphorus, manganese, and copper.

Infants aged 6–12 months have achieved a greater degree of renal maturation, and the UL of calcium of 1,500 mg/day is higher during the second half of the first year of life than for infants from birth to age 6 months [77]. Based on an assumed maximum intake of FUF of 800 kcal/day, a maximum level for the calcium content in FUF of 180 mg/100 kcal is recommended. No UL for phosphorus has been set by the Institute of Medicine and by EFSA, because there are no data relating to adverse effects of phosphorus intake for most of the first year of life except for a sensitivity of very young infants [78, 79]. Therefore, no maximum or guidance upper level for phosphorus is determined. Given that complementary foods can provide high and variable intakes of calcium and phosphorus, it is considered unreasonable to require a strict limitation of the calcium/phosphorus ratio in FUF.

The manganese content levels in IF are not based on firm evidence of quantitative requirements of infants but on human milk concentrations and indications of potential adverse effects of very high intakes in newborn animals [1]. During the complementary feeding period, variable and sometimes rather high supplies, e.g. from wheat, soybeans, sunflower seeds, and other seeds as well as nuts, occur, without any indication of untoward effects. No UL for manganese intake has been established [80]. The expert group sees no need to define minimum contents of manganese in FUF. Following the precautionary principle, a guidance upper level of 100 µg/100 kcal is recommended.

The liver toxicity of higher copper intakes is particularly high during the first few weeks and months of life [81–83], which has prompted setting of a guidance upper level of 120 µg copper/100 kcal for IF that can be fed as the sole source of nutrition from birth. At older infant ages, the infant liver appears to be far more resistant to the adverse effects of copper. In a controlled trial, the provision of about 2,000 µg Cu/day to infants from 3 to 9 months of age did not show any signs of adverse effects [84]. This intake would be equivalent to a daily intake of about 400 µg Cu/kg at the age of 3 months or about 500 µg Cu/100 kcal at an energy intake of 80 kcal/kg. Moreover, in infant rhesus monkeys, feeding a formula containing 6.6 mg Cu/l was not associated with any clinical evidence of copper toxicity [85]. Therefore, a guidance upper level for copper in FUF of 250 µg Cu/100 kcal is suggested.

Other Substances

Choline

The minimum choline content of 7 mg/100 kcal set for IF is also recommended for FUF. No major safety concerns exist and no adverse effects of higher choline intakes have been documented in infants. If an infant would consume 2 hen's eggs as part of complementary feeding it would get a choline supply in the order of 200–250 mg. A guidance upper level of 150 mg/100 kcal is proposed for FUF, in line with the proposed maximum phospholipid content of 550 mg/100 kcal, considering that a major part of added phospholipids may be provided as phosphatidylcholine.

Myo-Inositol

Myo-inositol can be readily synthesized in the human body, and there is no concern about toxicity with respect to usual intakes from food sources. Therefore, the expert group considers the setting of minimum a guidance of upper level for myo-inositol contents in FUF for older infants unnecessary.

L-Carnitine

Adoption of the established requirements for IF also for FUF is recommended.

Taurine

In line with previous expert consultations [2,3], the expert group sees no need for mandatory addition of taurine to FUF but recommends a maximum content of 12 mg/100 kcal.

Nucleotides

The addition of nucleotides to formulae for infants has been associated with proposed benefits of immune and antibody responses to vaccination, protection against diarrhoea, benefits for gut microbiota composition, and infant growth promotion [86–89]. Nucleotide concentrations in formula ranging from 1.9 to 10.8 mg/100 kcal have been evaluated [88]. Older infants that consume FUF are also exposed to nucleotide supplies from a variety of complementary foods and are considered less sensitive to conceivable untoward effects than neonates are. Therefore, a maximum nucleotide content of 10.8 mg/100 kcal is suggested.

Further Considerations

While the recommendations made here are based on current understanding of the available evidence, it is recognized that future scientific progress will necessitate revisiting and updating these compositional considerations. Modifications of FUF beyond established standards or the addition of other ingredients should be evaluated with regard to safety and possible benefits following current scientific standards, usually including clinical trials [1, 22–24]. Documentation of the safety of an ingredient or compositional concept in IF usually but not always can be extrapolated to FUF, whereas benefit usually should be demonstrated specifically for the age periods in which IF or FUF are used.

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J.B.v.G and B.Ko. are members of their respective National Breastfeeding Committees, and all authors declare to be strongly biased in favour of breastfeeding.

None of the authors reports a conflict of interest which would represent 'a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest', as defined by the US Institute of Medicine.

References

- 1 Koletzko B, Baker S, Cleghorn G, Neto UF, Gopalan S, Hernell O, et al: Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group. *J Pediatr Gastroenterol Nutr* 2005;41:584–599.
- 2 Codex Alimentarius: International Food Standards. 2012. <http://www.codexalimentarius.org>.
- 3 Codex Alimentarius Commission: Standard for infant formula and formulas for special medical purposes intended for infants. Codex Stan 72-1981, last revised 2007. Rome, Codex Alimentarius Commission, 2007.
- 4 Codex Alimentarius Commission: Codex standard for follow-up formula. Codex Stan 156-1987. Rome, Codex Alimentarius Commission, 1987.
- 5 Codex Alimentarius Commission: Report of the thirty-second session of the Codex Committee on Nutrition and Foods for Special Dietary Uses, Santiago, Chile, 1–5 November 2010. Rome, Codex Alimentarius Commission, 2011.
- 6 Codex Alimentarius Commission: Report of the thirty third session of the Codex Committee on Nutrition and Foods for Special Dietary Uses, Bad Soden am Taunus, Germany, 14–18 November 2011. Rome, Codex Alimentarius Commission, 2012.
- 7 New Zealand: Proposal to review the Codex standard for follow-up formula (Codex Stan 156-1987). Codex Committee on Nutrition and Foods for Special Dietary Uses, thirty-fourth session. Bad Soden am Taunus, 2012.
- 8 Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, et al: Breastfeeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2009;49:112–125.
- 9 Johnston M, Landers S, Noble L, Szucs K, Viehmann L: Breastfeeding and the use of human milk. *Pediatrics* 2012;129:e827–e841.
- 10 Kleinman R (ed): *Pediatric Nutrition Handbook*. Chicago, American Academy of Pediatrics, 2010.
- 11 World Health Organisation: The Optimal Duration of Exclusive Breastfeeding: Report of an Expert Consultation. Geneva, WHO, 2001.
- 12 World Health Organisation: *Global Strategy for Infant and Young Child Feeding*. Geneva, WHO, 2003.
- 13 ESPGHAN Committee on Nutrition, Agostoni C, Decsi T, Fewtrell M, Goulet O, Kolacek S, Koletzko B, et al: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:99–110.
- 14 American Academy of Pediatrics Committee on Nutrition: The use of whole cow's milk in infancy. *Pediatrics* 1992;89:1105–1109.
- 15 World Health Organisation: International code of marketing of breast-milk substitutes. Geneva, WHO, 1981.
- 16 EFSA Panel on Dietetic Products, Nutrition and Allergies: Scientific opinion on the appropriate age for introduction of complementary feeding of infants. *EFSA J* 2009;7:1423.
- 17 ESPGHAN Committee on Nutrition, Agostoni C, Decsi T, Fewtrell M, Goulet O, Kolacek S, et al: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:99–110.
- 18 American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology, Greer FR, Sicherer SH, Burks AW: Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183–191.
- 19 Schiess S, Grote V, Scaglioni S, Luque V, Martin F, Stolarczyk A, et al: Introduction of complementary feeding in 5 European countries. *J Pediatr Gastroenterol Nutr* 2010;50:92–98.

- 20 Committee on Nutrition of the German Society of Pediatrics, Bohles H, Fusch C, Genzel-Boroviczeny O, Jochum F, Kauth T, et al: Composition and use of milk drinks for toddlers: updated recommendations of the Committee on Nutrition of the German Society for Paediatrics (in German). *Monatsschr Kinderheilkd* 2011;159:981–984.
- 21 Ghisolfi J, Vidailhet M, Fantino M, Bocquet A, Bresson JL, Briend A, et al: Cows' milk or growing-up milk: what should we recommend for children between 1 and 3 years of age? *Arch Pediatr* 2011;18:355–358.
- 22 Koletzko B, Ashwell M, Beck B, Bronner A, Mathioudakis B: Characterisation of infant food modifications in the European Union. *Ann Nutr Metab* 2002;46:231–242.
- 23 Koletzko B, Shamir R, Ashwell M: Quality and safety aspects of infant nutrition. *Ann Nutr Metab* 2012;60:179–184.
- 24 ESPGHAN Committee on Nutrition, Agostoni C, Aggett PJ, Agostini C, Goulet O, Hernell O, et al: The nutritional and safety assessment of breast milk substitutes and other dietary products for infants: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2001;32:256–258.
- 25 Wojcik KY, Rechtman DJ, Lee ML, Montoya A, Medo ET: Macronutrient analysis of a nationwide sample of donor breast milk. *J Am Diet Assoc* 2009;109:137–140.
- 26 Butte NF, King JC: Energy requirements during pregnancy and lactation. *Public Health Nutr* 2005;8:1010–1027.
- 27 Islam MM, Khatun M, Peerson JM, Ahmed T, Mollah MA, Dewey KG, et al: Effects of energy density and feeding frequency of complementary foods on total daily energy intakes and consumption of breast milk by healthy breastfed Bangladeshi children. *Am J Clin Nutr* 2008;88:84–94.
- 28 Stettler N: Nature and strength of epidemiological evidence for origins of childhood and adulthood obesity in the first year of life. *Int J Obes (Lond)* 2007;31:1035–1043.
- 29 Koletzko B, Beyer J, Brands B, Demmelmair H, Grote V, Haile G, et al: Early influences of nutrition on postnatal growth; in Gillman MW, Gluckman P, Rosenfeld R (eds): *Recent Advances in Growth Research: Nutritional, Molecular and Endocrine Perspectives*. Basel, Karger, 2012.
- 30 Fomon SJ: Requirements and recommended dietary intakes of protein during infancy. *Pediatr Res* 1991;30:391–395.
- 31 World Health Organisation/Food and Agriculture Organisation of the United Nations/United Nations University: Protein and amino acid requirements in human nutrition: report of a joint WHO/FAO/UNU expert consultation. Geneva, WHO, 2007, p 284.
- 32 EFSA Panel on Dietetic Products, Nutrition and Allergies: Scientific opinion on dietary reference values for protein. *EFSA J* 2012;10:2557.
- 33 Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, et al: Can infant feeding choices modulate later obesity risk? *Am J Clin Nutr* 2009;89:1502S–1508S.
- 34 Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, et al: Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. *Am J Clin Nutr* 2009;89:1836–1845.
- 35 Koletzko B, Brands B, Poston L, Godfrey K, Demmelmair H, Early Nutrition Project: Early programming of long-term health. *Proc Nutr Soc* 2012;71:371–378.
- 36 Oddy WH: Infant feeding and obesity risk in the child. *Breastfeed Rev* 2012;20:7–12.
- 37 Lonnerdal B, Chen CL: Effects of formula protein level and ratio on infant growth, plasma amino acids and serum trace elements. 2. Follow-up formula. *Acta Paediatr Scand* 1990;79:266–273.
- 38 Ohlund I, Hernell O, Hornell A, Stenlund H, Lind T: BMI at 4 years of age is associated with previous and current protein intake and with paternal BMI. *Eur J Clin Nutr* 2010;64:138–145.
- 39 Hoppe C, Molgaard C, Thomsen BL, Juul A, Michaelsen KF: Protein intake at 9 mo of age is associated with body size but not with body fat in 10-y-old Danish children. *Am J Clin Nutr* 2004;79:494–501.
- 40 Alexy U, Kersting M, Sichert-Hellert W, Manz F, Schoch G: Macronutrient intake of 3- to 36-month-old German infants and children: results of the DONALD Study – Dortmund Nutritional and Anthropometric Longitudinally Designed Study. *Ann Nutr Metab* 1999;43:14–22.
- 41 Butte NF, Fox MK, Briefel RR, Siega-Riz AM, Dwyer JT, Deming DM, et al: Nutrient intakes of US infants, toddlers, and preschoolers meet or exceed dietary reference intakes. *J Am Diet Assoc* 2010;110:S27–S37.
- 42 Schaafsma G: Advantages and limitations of the protein digestibility-corrected amino acid score (PDCAAS) as a method for evaluating protein quality in human diets. *Br J Nutr* 2012;108(suppl 2):S333–S336.
- 43 Davis TA, Nguyen HV, Garcia-Bravo R, Fiorotto ML, Jackson EM, Lewis DS, et al: Amino acid composition of human milk is not unique. *J Nutr* 1994;124:1126–1132.
- 44 Osborn DA, Sinn J: Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006:CD003664.
- 45 von Berg A, Filipiak-Pittroff B, Kramer U, Link E, Bollrath C, Brockow I, et al: Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). *J Allergy Clin Immunol* 2008;121:1442–1447.
- 46 Huang L, Hogewind-Schoonenboom JE, de Groof F, Twisk JW, Voortman GJ, Dorst K, et al: Lysine requirement of the enterally fed term infant in the first month of life. *Am J Clin Nutr* 2011;94:1496–1503.
- 47 Huang L, Hogewind-Schoonenboom JE, van Dongen MJ, de Groof F, Voortman GJ, Schierbeek H, et al: Methionine requirement of the enterally fed term infant in the first month of life in the presence of cysteine. *Am J Clin Nutr* 2012;95:1048–1054.
- 48 Elango R, Ball RO, Pencharz PB: Recent advances in determining protein and amino acid requirements in humans. *Br J Nutr* 2012;108(suppl 2):S22–S30.
- 49 Glaser C, Lattka E, Rzehak P, Steer C, Koletzko B: Genetic variation in polyunsaturated fatty acid metabolism and its potential relevance for human development and health. *Matern Child Nutr* 2011;7(suppl 2):27–40.
- 50 Gibson RA, Muhlhauser B, Makrides M: Conversion of linoleic acid and alpha-linolenic acid to long-chain polyunsaturated fatty acids (LCPUFAs), with a focus on pregnancy, lactation and the first 2 years of life. *Matern Child Nutr* 2011;7(suppl 2):17–26.
- 51 Campoy C, Escolano-Margarit MV, Anjos T, Szajewska H, Uauy R: Omega 3 fatty acids on child growth, visual acuity and neurodevelopment. *Br J Nutr* 2012;107(suppl 2):S85–S106.
- 52 EFSA Panel on Dietetic Products, Nutrition and Allergies: Scientific opinion on the substantiation of health claims related to docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and brain, eye and nerve development. *EFSA J* 2011;9:20–78.
- 53 Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis PG, Doyle LW, et al: Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. *JAMA* 2009;301:175–182.
- 54 Collins CT, Makrides M, Gibson RA, McPhee AJ, Davis PG, Doyle LW, et al: Pre- and post-term growth in pre-term infants supplemented with higher-dose DHA: a randomised controlled trial. *Br J Nutr* 2011;105:1635–1643.
- 55 Koletzko B, Sauerwald T, Demmelmair H, Herzog M, von Schenck U, Bohles H, et al: Dietary long-chain polyunsaturated fatty acid supplementation in infants with phenylketonuria: a randomized controlled trial. *J Inher Metab Dis* 2007;30:326–332.
- 56 Marks GB, Mihrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, et al: Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol* 2006;118:53–61.
- 57 Mihrshahi S, Peat JK, Marks GB, Mellis CM, Tovey ER, Webb K, et al: Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2003;111:162–168.
- 58 Lopez C, Menard O: Human milk fat globules: polar lipid composition and in situ structural investigations revealing the heterogeneous distribution of proteins and the lateral segregation of sphingomyelin in the biological membrane. *Colloids Surf B Biointerfaces* 2011;83:29–41.

- 59 Gianni ML, Roggero P, Baudry C, Ligneul A, Morniroli D, Garbarino F, et al: The influence of a formula supplemented with dairy lipids and plant oils on the erythrocyte membrane omega-3 fatty acid profile in healthy full-term infants: a double-blind randomized controlled trial. *BMC Pediatr* 2012;12:164.
- 60 Zavaleta N, Kvistgaard AS, Graverholt G, Respicio G, Guija H, Valencia N, et al: Efficacy of an MFGM-enriched complementary food in diarrhea, anemia, and micronutrient status in infants. *J Pediatr Gastroenterol Nutr* 2011;53:561–568.
- 61 Koletzko B, Saris W, Flynn A, Palou A, Wal JM, Jackson A, Przyrembel H, Turck D, et al: Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. Brussels, European Commission, 2003.
- 62 World Health Organisation: Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation, January 28 to February 1, 2002. WHO Technical Report Series 916. Geneva, WHO, 2002.
- 63 Merewood A, Mehta SD, Grossman X, Chen TC, Mathieu J, Holick MF, et al: Vitamin D status among 4-month-old infants in New England: a prospective cohort study. *J Hum Lact* 2012;28:159–166.
- 64 Dawodu A, Wagner CL: Prevention of vitamin D deficiency in mothers and infants worldwide – a paradigm shift. *Paediatr Int Child Health* 2012;32:3–13.
- 65 Andiran N, Celik N, Akca H, Dogan G: Vitamin D deficiency in children and adolescents. *J Clin Res Pediatr Endocrinol* 2012;4:25–29.
- 66 Zhu Z, Zhan J, Shao J, Chen W, Chen L, Li W, et al: High prevalence of vitamin D deficiency among children aged 1 month to 16 years in Hangzhou, China. *BMC Public Health* 2012;12:126.
- 67 Bischoff-Ferrari HA: Vitamin D: role in pregnancy and early childhood. *Ann Nutr Metab* 2011;59:17–21.
- 68 Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, et al: Treatment of hypovitaminosis D in infants and toddlers. *J Clin Endocrinol Metab* 2008;93:2716–2721.
- 69 Committee to Review Dietary Reference Intakes for Vitamin D and Calcium: Dietary Reference Intakes for Calcium and Vitamin D. Washington, Institute of Medicine, 2010.
- 70 Domellof M: Iron requirements in infancy. *Ann Nutr Metab* 2011;59:59–63.
- 71 Institute of Medicine: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, National Academy Press, 2002.
- 72 World Health Organisation, Food and Agricultural Organisation of the United Nations: Vitamin and Mineral Requirements in Human Nutrition, ed 2. Geneva, WHO, 2004.
- 73 Austrian Nutrition Society, German Nutrition Society, Swiss Society for Nutrition Research, Swiss Nutrition Association (eds): Reference Values for Nutrient Intake. Frankfurt am Main, Umschau, 2002.
- 74 Nordisk-Ministerråd: Nordic Nutrition Recommendations 2004: Integrating Nutrition and Physical Activity. Copenhagen, Nordic Council of Ministries, 2005.
- 75 Australian Government: Nutrient reference values for Australia and New Zealand including recommended dietary intakes. Canberra, Commonwealth of Australia, 2006.
- 76 Walter T, Pino P, Pizarro F, Lozoff B: Prevention of iron-deficiency anemia: comparison of high- and low-iron formulas in term healthy infants after six months of life. *J Pediatr* 1998;132:635–640.
- 77 EFSA Panel on Dietetic Products, Nutrition and Allergies: Scientific opinion on the tolerable upper intake level of vitamin D. *EFSA J* 2012;10:2813.
- 78 Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, National Academy Press, 1997.
- 79 EFSA Panel on Dietetic Products, Nutrition and Allergy: Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) related to the tolerable upper intake level of phosphorus. *EFSA J* 2005;233:1–19.
- 80 Scientific Committee on Food, European Commission: Opinion of the Scientific Committee on Food on the tolerable upper intake level of manganese. Brussels, European Commission, 2000.
- 81 Araya M, Koletzko B, Uauy R: Copper deficiency and excess in infancy: developing a research agenda. *J Pediatr Gastroenterol Nutr* 2003;37:422–429.
- 82 Eife R, Weiss M, Barros V, Sigmund B, Goriup U, Komb D, et al: Chronic poisoning by copper in tap water. 1. Copper intoxications with predominantly gastrointestinal symptoms. *Eur J Med Res* 1999;4:219–223.
- 83 Eife R, Weiss M, Muller-Hocker M, Lang T, Barros V, Sigmund B, et al: Chronic poisoning by copper in tap water. 2. Copper intoxications with predominantly systemic symptoms. *Eur J Med Res* 1999;4:224–228.
- 84 Olivares M, Pizarro F, Speisky H, Lonnerdal B, Uauy R: Copper in infant nutrition: safety of World Health Organization provisional guideline value for copper content of drinking water. *J Pediatr Gastroenterol Nutr* 1998;26:251–257.
- 85 Araya M, Kelleher SL, Arredondo MA, Sieralta W, Vial MT, Uauy R, et al: Effects of chronic copper exposure during early life in rhesus monkeys. *Am J Clin Nutr* 2005;81:1065–1071.
- 86 Singhal A, Kennedy K, Lanigan J, Clough H, Jenkins W, Elias-Jones A, et al: Dietary nucleotides and early growth in formula-fed infants: a randomized controlled trial. *Pediatrics* 2010;126:e946–e953.
- 87 Singhal A, Macfarlane G, Macfarlane S, Lanigan J, Kennedy K, Elias-Jones A, et al: Dietary nucleotides and fecal microbiota in formula-fed infants: a randomized controlled trial. *Am J Clin Nutr* 2008;87:1785–1792.
- 88 Gutierrez-Castrellon P, Mora-Magana I, Diaz-Garcia L, Jimenez-Gutierrez C, Ramirez-Mayans J, Solomon-Santibanez GA: Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. *Br J Nutr* 2007;98(suppl 1):S64–S67.
- 89 Niers L, Stasse-Wolthuis M, Rombouts FM, Rijkers GT: Nutritional support for the infant's immune system. *Nutr Rev* 2007;65:347–360.