Sustainable Clinical Research, Health Economic Aspects and Medical Marketing: Drivers of Product Innovation

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Abstract
Marketing-driven innovation in the field of pediatric nutrition, in particular in the infant formula segment is not sustainable. New benefits of products must be scientifically proven and safety and efficacy of new formulae established in clinical trials. The scientific innovation process of three infant formulae is described. Improvement in protein quality allowed to reduce the protein concentration in whey-based infant formula. Weight gain and BMI of infants fed those formulae corresponds to breastfed infants and is lower than in infants fed traditional formulae with higher protein concentration. A meta-analysis indicates associations between rapid weight gain in infancy and obesity later in life. If infants cannot be exclusively breastfed until 4–6 months of age, feeding low-protein formulae may contribute to positive long-term health outcome with potentially important health economic effects. A partially hydrolyzed whey based formula for prevention of allergic symptoms in children with hereditary risk for allergic diseases was developed more than 25 years ago. The most recent meta-analysis which included 15 randomized clinical trials indicates that the risk of all allergic diseases and atopic dermatitis/eczema is significantly reduced in infants at risk when the partially hydrolyzed formula is fed. The partially hydrolyzed formula had the same protective effect as casein-based high-degree extensively hydrolyzed formula. Because of substantial price differences between the two formulae, feeding the partially hydrolyzed whey formula is cost saving. Hypoallergenic claims can be made in many countries, and international nutrition committees have positively commented the preventive effect of those formulae. Acidified formulae have been widely used during the last decade in replacement feeding programs for infants whose mothers are HIV positive. The formula was innovated by improving whey protein quality and lowering protein concentration. The bacteriostatic properties of the new formula were proven in in vitro tests. Meta-analysis indicated that feeding the formula to immunocompromised infants resulted in growth similar to breastfeeding. The bacteriostatic effects of the acidified formula need to be
Introduction

Prenatal, early postnatal, and early childhood nutrition plays an important role for short- and long-term health. The short-term effects of inadequate nutrition are well documented both in developed and developing societies. In addition, there is a growing body of evidence showing that nutrition during the early life cycle may program endocrine, cardiovascular, and central nervous systems and induce epigenetic phenomena with long-term effects on health. Industry must continuously learn from research and try to add sustainable innovation to products once new health benefit areas have been clearly identified [1].

Innovation in the field of dietetic foods for infants and small children is a cumbersome process. In order to launch new products, in particular formulae for premature and term infants, safety and efficacy has to be established. Therefore, new product development in that segment requires a pharmaceutical project management which starts with preclinical evaluation and ends with clinical trials in the target group. The innovation process can take 5–10 years and is expensive. In the pharmaceutical industry, patent protection generally allows to market new drugs for several years, whereas in the baby food industry patent protection is poor and can be easily circumvented. Small and medium-sized companies have difficulties to compete in the innovation process and consolidation in the industry occurs. Finally, the extremely conservative regulatory environment in the field of formulae for low-birthweight and term infants [2–5] requires a novel food approach to add new ingredients and make product-related claims.

Marketing, on the other hand, would like to quickly push new products with nutritional benefits to the market. One typical example was the addition of DHA to infant formula. More than 15 years after introduction of the first formulae with DHA, science has evidence for benefits for low-birthweight infants [6]. The debate on benefits for term infants continues [7, 8]. However, companies put pressure on regulatory agencies to allow the addition of DHA and to make claims. Marketing in the meantime had done an ‘excellent’ job and convinced mothers via TV advertising, in particular in Asian countries that DHA in formula is important for long-term better brain performance, which is a typical example of ‘over-claiming’. Formulae with added DHA have a substantial price premium which parents have to pay. Therefore, mainly non-breastfed infants from higher social classes receive formulae fortified with DHA. With very limited scientific data, the baby food industry now also adds DHA to weaning food in jars, cereals and formulae for infants and children between 6–36 months of age. Key opinion leaders in pediatric nutrition

communicated to health care professionals, but also the risks if replacement feeding is not acceptable, feasible, affordable, sustainable, and safe for mother and infant.
and pediatricians who carefully follow the relevant literature should make up their mind if formulae and baby food with DHA are important for long-term health and performance and should be recommended.

Long-term development projects of three infant formulae, which have been available during the last 5 years, will be presented. One formula is a product mainly used in developing countries. Sustainable research has resulted in product development with short- and long-term health benefits for the infant. Furthermore, health economic aspects and responsible medical marketing of those products will be addressed.

Low-Protein Formula with Improved Protein Quality

There are three factors which stimulated the development of a new infant formula generation in the 1990s:

- First, new insights into the composition of breast milk: during the first months of lactation, the protein concentration in breast milk decreases considerably, reaching levels of around 9–11 g/l [9]. If the lactation period persists until 1–2 years of age, protein concentrations are still around 8–10 g/l [10]. Protein concentrations in infant formula were in the range of 15–20 g/l until the end of the last decade, and therefore substantially higher than in breast milk. This was due to differences in amino acid composition and the assumed lower digestibility. In addition, infants fed infant formulae which were on the market before 2000 had higher volumes of intake than breastfed infants, which resulted in protein intakes which were >50% higher than in breastfed infants [11].
- Second, detailed insights into early nutrition and growth: several cohort studies had indicated [12, 13] that formula-fed infants show higher weight gain than breastfed infants during the first months of life, and the discussion on potential associations between rapid weight gain during infancy and later risk of obesity started up.
- Third, studies on metabolic outcome in breast- and formula-fed infants: already in 1988, Axelsson et al. [14] published that a high level of protein intake during early infancy influences plasma amino acid concentrations, insulin secretion, and growth. Stimulation of insulin-like growth factor-1 could result in rapid weight gain and increase in adipose tissue [15].

In view of the insights on breast milk concentration and after intensive discussion with the authors of the studies which had indicated faster growth [12] and unfavorable metabolic outcome [14] in infants fed ‘high-protein’ formulae, it was decided in 1995 to develop a low-protein formula with improved protein quality [16]. Modification of the protein whey fraction resulted in lower threonine and higher concentrations of tryptophan, cysteine, arginine and histidine. An amino acid profile closer to breast milk and improved levels
of limiting indispensable amino acids allowed to reduce total protein quantity in the formula. After animal trials had indicated safety of the new formula, randomized clinical trials with the new whey-based ‘low-protein’ formula (casein:whey ratio 30:70) with 12 g protein per liter (1.8 g/100 kcal) were done in different parts of the world. Longitudinal growth studies indicated that weight and length gain of infants who were exclusively fed the ‘low-protein formula’ until 4 months of age were similar to breastfed infants. Two recent meta-analyses included the results of all randomized clinical trials and growth studies and confirmed the findings (fig. 1) [17]. Metabolic outcome, in particular plasma amino concentrations were close to breastfed infants [16], and insulin-like growth factor-1 concentrations were lower than in the infants.

**Fig. 1.** Weight-for-age and BMI at 4 months of age (z scores, WHO growth curves). Breastfeeding vs. low-protein formula. ANCOVA correcting by birth z score and gender (means, 95% CI). Adapted from Steenhout et al. [17.]
who were on ‘high-protein’ formulae [18]. The ‘low-protein’ formula was introduced in the years 2000 as starter (NAN 1®) and 2009 as follow-up formula (NAN 2®). In 2005 and 2009, a ‘low-protein’ hypoallergenic (NAN HA®) and acidified formulae (NAN Pelargon®, BIONAN®) were launched, respectively. Other formula companies have launched similar products during the last years.

At the end of the first decade of the 21st century, evidence-based medicine is strongly indicating that early infant feeding, weight gain during infancy and recently, protein intake with infant formulae are important for later health outcome. Meta-analyses and systematic reviews indicate that in comparison with breastfeeding, the consumption of high-protein formulae (only high-protein formulae were on the market when the studies were done) was associated with a 3–25% higher prevalence of obesity during childhood and adolescence [18–23]. Systemic reviews have also confirmed that high weight gain during infancy is associated with higher risk for later obesity [19, 24–26]. A recent randomized controlled clinical trial [27] compared weight for age, length for age, weight for length and BMI of infants fed ‘low-protein’ or ‘high-protein’ formulae between birth and 12 months of age. Growth of exclusively (at least until 3 months of age) breastfed infants was also presented. Infants fed the low-protein formulae at 6 and 12 months of age had lower weight for age, BMI and weight-for-length. At 24 months of age – i.e. 12 months after the formulae were discontinued – BMI and weight-for-length were still significantly lower in the children who had been on the ‘low-protein’ formulae. No significant differences between the infants fed the low-protein formulae and the breastfed control group were observed at any age. The authors speculated that lower protein intake in infancy might diminish the later risk of overweight and obesity.

We have only just began to look at health economic aspects of the impact of infant feeding practices – in particular breastfeeding and feeding formulae with ‘high’ – and ‘low-protein’ concentrations – on childhood, adolescent, and adult obesity. As indicated, breastfeeding is associated with lower risk, and duration of breastfeeding seems to play a role [21, 19]. Koletzko et al. [27] recently calculated that feeding low-protein formula compared with high-protein formula could be associated with a 13% lower risk of obesity in adolescence. The lifetime medical cost burden of obesity and implications for obesity prevention have been recently published by Finkelstein et al. [28]: the average lifetime attributable medical costs to obesity in the US (BMI >30) for 20-year-old adults is approximately USD 19,600, if degree of obesity, sex and ethnic differences are considered. Calculations of savings are presented (table 1) for two hypothetical scenarios. Adult obesity (rate in the US is 35% [29]) would be 1 or 13% lower in non-breastfed infants born in the US (4.3 millions [30]) if ‘low-protein’ formulae were provided. The annual economic burden would be reduced by USD 205 million and 2.67 billion, if obesity rates were 1 or 13% lower, respectively. This scenario is based on the assumption
that all infants on formula would receive low-protein formula and the results are nondiscounted for the purpose of discussion. Therefore, health authorities need to carefully analyze new incoming data on potential risk reduction of obesity through early infant feeding measures.

With the exception of the US, infant formula-producing companies are not allowed to communicate infant formulae directly to parents. Medical marketing should be very careful when already communicating ‘anti-obesity’ effects of low-protein formulae to healthcare professionals. However, the fact that low-protein formulae are closer to the reference breast milk and feeding of those formulae results in growth similar to breastfed infants can be communicated to all pediatricians who are interested in the long-term consequences of rapid infant weight gain.

**Hypoallergenic Infant Formula**

It is well documented in the literature that formula-fed infants with a documented hereditary risk for allergy are suffering more often from allergic disease than breastfed infants, in particular during the first years of life [31–33]. Early exposure to foreign protein, in particular cow’s milk protein can play an important role. In order to make infant formula hypoallergenic, it was necessary to test the technologic treatments which result in substantial reduction in the allergenicity of cow’s milk protein. Hydrolysis with proteases followed by heat treatment as well as hydrolysis followed by fractionation turned out to be practical ways of reducing milk protein antigenicity [34]. The taste of hypoallergenic formulae improved by further adapting the technology. Animal [35] and infant studies which are presented in a meta-analysis [33] then proved safety and efficacy of a 100% whey-based partially hydrolyzed formula (phF NAN HA®). Recently, safety of that whey-based phF with reduced protein content was confirmed by randomized controlled growth and metabolic outcome studies [18].

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**Table 1.** Avoidable costs if ‘low-protein’ formulae protect from adult obesity

<table>
<thead>
<tr>
<th>Risk reduction</th>
<th>Avoided cases/year</th>
<th>Avoided cost/year, USD</th>
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<tr>
<td>-1%</td>
<td>10,490</td>
<td>205 million</td>
</tr>
<tr>
<td>-13%</td>
<td>136,370</td>
<td>2.67 billion</td>
</tr>
</tbody>
</table>

1 This scenario is based upon the assumption that all formula-fed infants would receive low-protein formula and the results are nondiscounted for the purpose of discussion. Calculated from Koletzko et al. [27] and Finkelstein et al. [28].
More than 25 years ago, the first cohort studies indicated that formula-fed infants with a documented hereditary risk of allergy (i.e. having an affected parent and/or sibling) might benefit from receiving a partially or extensively hydrolyzed formula (ehF). There are now 84 studies in the literature, among them 44 (15 randomized clinical trials) which involved one phF. There must be certainty regarding the choice of a hydrolyzed formula for allergy prevention as well as safety and efficacy of a particular hydrolyzed formula. Factors such as protein sources and method and degree of hydrolysis are important for clinical outcome.

Using clearly defined criteria, Szajewska and Horvat [36] included fifteen randomized clinical trials into their recent meta-analysis that compared the use of one phF with use of standard infant formula or extensively hydrolyzed bovine proteins (whey or casein). Incidence of all allergic diseases and atopic dermatitis/atopic eczema was the primary outcome variable.

This recent meta-analysis indicates reduced risk of all allergic diseases in favor of the phF compared with standard formula. At 3–6 months and at 12 months, administration of the phF compared with standard formula was associated with approximately 50 and 38% risk reduction, respectively. Seven and 12 infants needed to receive the phF to save one infant from allergic disease (NNT) at corresponding ages. The pooled results of data (5 trials) at 0–36 months of age indicated a significantly lower cumulative incidence of all allergic diseases.

Data from 5 trials [36] reported the effect of the phF on the cumulative incidence of eczema within a given period (0–3, 0–6, 0–18, 0–24 months, and 0 to 5–6 years). A consistent significant reduction in the risk of eczema in favor of the phF was shown in both fixed and random effects meta-analyses.

Five trials (table 2) [36] compared the effect of use of the phF versus an extensively hydrolyzed casein formula, and found no significant difference between the two groups for all allergic diseases and atopic dermatitis/eczema.

The preventive effect of feeding partially hydrolyzed whey-based formula is well documented, but health economic aspects have not been published so far. However, they are needed in order to be able to discuss reimbursement with health insurances. Cost of feeding the whey-based phF is easy to calculate – i.e. the price premium over regular formula is about 20–30%, but cost estimates for treatment of atopic dermatitis/eczema are needed to calculate a cost/benefit ratio.

Cost comparison between feeding (0–4 months) a partially hydrolyzed whey-based or an extensively hydrolyzed casein-based formula to non-breastfed or short-term (<3 month) breastfed infants at risk for development of allergy are presented for one European country (table 3). Meta-analysis had indicated that the two formulae are similar in their ability to prevent allergic manifestations and atopic dermatitis/eczema. The assumptions were
made based upon the number of births in France in 2007 [8], a breastfeeding rate of 53% in the first 3 months and percentage of infants at risk for allergy (23%) [37] who are not breastfed or breastfed <3 months and are therefore fed hypoallergenic formula, volumes of formula intake [38], and retail pharma prices per kilogram of the two formulae. The calculated cost length was 4 months with exclusive formula feeding. Even with these rather conservative assumptions, the cost difference between the two formulae can be estimated at EUR 34 million per year. Taking into consideration less conservative assumptions and that one fifth of the infants on ehF switch to amino acid-based formula with a much higher price, the cost difference can be estimated to be up to EUR 80 million per year.

Already in 1999, the EU regulation allowed to make a hypoallergenic claim for infant formula if clinical trials prove safety and efficacy of the formula. This claim was confirmed in the most recent EU directive on infant formulae. ESPGHAN/ESPCA[32] and more recently, the American Academy of Pediatrics [39] have made comments on hypoallergenic formulae. Therefore, medical marketing can communicate that the partially hydrolyzed whey-

## Table 2. Whey phF vs. casein ehF preventive effect outcome

<table>
<thead>
<tr>
<th>Cases</th>
<th>Effect</th>
<th>Difference</th>
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<tbody>
<tr>
<td>0–12 months</td>
<td>1,137</td>
<td>0.98 (0.72–1.35)</td>
</tr>
<tr>
<td>0–18/24 months</td>
<td>164</td>
<td>0.90 (0.60–1.35)</td>
</tr>
<tr>
<td>0–36 months</td>
<td>1,137</td>
<td>1.03 (0.81–1.27)</td>
</tr>
<tr>
<td>0–5/6 years</td>
<td>1,137</td>
<td>1.05 (0.90–1.23)</td>
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**Eczema (cumulative incidence)**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Effect</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 months</td>
<td>1,137</td>
<td>1.06 (0.74–1.53)</td>
</tr>
<tr>
<td>18 months</td>
<td>164</td>
<td>1.12 (0.67–1.85)</td>
</tr>
<tr>
<td>36 months</td>
<td>1,137</td>
<td>1.13 (0.87–1.47)</td>
</tr>
<tr>
<td>5/6 years</td>
<td>1,137</td>
<td>1.17 (0.94–1.45)</td>
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Adapted from Szajewska and Horvarth [36].

## Table 3. Population-based cost comparison of non-breastfed infants at risk (France) receiving either whey phF or casein ehF (similar protective effects)

<table>
<thead>
<tr>
<th></th>
<th>Whey-based phF</th>
<th>Δ</th>
<th>Casein-based ehF</th>
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<tbody>
<tr>
<td>Cost of formula/kg, EUR[^1^]</td>
<td>24</td>
<td>33</td>
<td>57</td>
</tr>
<tr>
<td>Annual costs/year, millions of EUR</td>
<td>25</td>
<td>34</td>
<td>59</td>
</tr>
</tbody>
</table>

based formula can prevent allergic disease in children at risk and has a cost-benefit and taste advantage when compared with high-degree hydrolyzed casein-based formulae.

**Feeding Infants of HIV-Positive Mothers**

In non-breastfed infant populations exposed to suboptimal or compromised hygienic conditions, the risks to acquire gastrointestinal infections are substantially higher than in breastfed infants. Therefore, promotion of exclusive breastfeeding until 6 months of age and continuing breastfeeding beyond that age is key to reduce infant morbidity and mortality [40]. The WHO recommendations are embraced by almost all countries as well as by infant formula manufacturers. However, infant feeding choices are under discussion in a population of mothers, where HIV can be transmitted to the infant through breastfeeding. In such cases, WHO recommends [41] that HIV-infected mothers breastfeed exclusively for the first 6 months unless replacement feeding is acceptable, feasible, affordable, sustainable, and safe (AFASS) for mother and infants, and if replacement feeding is AFASS, avoidance of all breastfeeding by HIV-infected mothers should be recommended. In relation to feeding the infant at risk for transmission, particularly in the developing world, a setting associated with a much higher mother-to-child transmission (as high as 40%) than in developed world (<2%) [42], the implementation of current feeding recommendations, even when understood, may be hampered by ignorance and/or poor implementation of the recommendations [43–45]. Available evidence indicates that mixed feeding is the cultural norm, especially in Africa. In fact, exclusive breastfeeding is rarely practiced for 6 months, and is often discontinued much sooner. At best, more than half of the infants are exclusively breastfed for 6 months in only 28 countries in the world [46]. Even under study conditions, in most African countries duration of exclusive breastfeeding ranged only between 0.4 and 4.9 months of age [47, 48]. Best prevalence estimates of exclusive breastfeeding at 6 months of HIV-infected mothers under maximal support are reported to be up to 40% [48, 47]. Prophylaxis of mother-to-child transmission by giving the mother antiretroviral medications which are proven to be efficient [49, 50] has the potential to reduce transmission through breast milk. Antiretroviral prophylaxis to the breastfed infant is under evaluation, but the long-term effects for the children are not known [51, 52].

Botswana, which has remarkable success in reducing mother-to-child transmission, has introduced replacement feeding (formula) in its preventive strategy [53]. Available evidence indicates that with adequate support, safe replacement feeding which meet the AFASS criteria can be successfully implemented in resource-limited settings [54]. Therefore, providing a formula with the highest possible safety margin during replacement feeding pro-
grams is a challenge for the industry. Already during the mid 1990s it became clear that a cow milk-based formula which was chemically acidified (NAN Pelargon®) became the preferred product in governmental and NGO-driven replacement feeding programs.

Before the introduction of modern infant formulae in the 1970s and 1980s, acidified formulae were very popular both in developing and developed countries. In countries where fermented milk products are part of the eating culture such as in Sub-Saharan Africa, acidified infant formulae are still very popular. Early clinical trials with the chemically acidified formula (pH <5) had resulted in lower gastric pH and a faster gastric transit time [55]. Randomized controlled clinical trials in Chile and France indicated lower incidence of gastrointestinal infections [56] and shorter duration of diarrhea [57]. Safety and efficacy of acidified formulae with and without the addition of the probiotic strain *Bifidobacterium lactis* have been documented [58, 59].

The acidified formula was never promoted by the company for replacement feeding programs. The widespread use and increasing demand since the mid-1990s prompted us to start a project to upgrade the formula according to the latest EU standards (e.g. low-protein whey protein formula similar to the formula described above) [4] and proof safety and efficacy in randomized clinical trials.

In the case of contamination due to poor hygienic settings, in a bottle of regular infant formula at 37°C in just 2 h the number of *Escherichia coli* germs can grow rapidly. The new acidified whey-based formula is characterized by an acidic pH value of 4.6–4.9, which ensures sufficient bacteriostatic activity of the formula without disturbing the organoleptic properties. Joosten and Lardeau [60, 61] confirmed the growth-restraining effect of the new acidified formula on pathogenic and putrefactive bacteria (fig. 2). In an in vitro study, three regular (soy-, whey-, and casein-based) and one acidified infant formula were artificially contaminated with eight different bacteria, including *Enterobacter sakazakii*, *Salmonella dysenteria*, *Salmonella typhimurium* and *E. coli* 0157:H7. The initial concentration of the bacterial strains was about 10³ CFU/ml of reconstituted formula. Growth of the different bacteria was monitored through counting before and after 3- to 6-hour incubation at 37°C. Most bacteria were growing rapidly in all non-acidified formulae, but growth was strongly suppressed in the acidified formula (fig. 2). Safety of the low-protein whey-based acidified formula was confirmed in three randomized controlled growth studies [17, 58, 59], which included both healthy and immunocompromised infants. The infants grew according to the WHO growth charts. The addition of the probiotic strain *B. lactis* to the formula resulted in better weight gain in the immunocompromised infants. The new formula now continues to be the preferred product for replacement feeding programs.

Comparing costs between two feeding methods in any given clinical setting (including HIV) is difficult, since actual costs, treatment delivery and
approaches, and other factors vary from country to country. Despite the hypothetical and real advantages of any feeding method, moral and ethical considerations mitigate against cost comparisons. Today, only a minority of eligible infants in most developing countries have access to antiretroviral medications. In order to change this, large investments are needed in infrastructure and personnel.

It is worthwhile to communicate the safety (bacteriostatic) aspects of the new acidified formula to governmental authorities and the medical community. Any other medical marketing of the formula in such sensitive environment would be inappropriate.
References

Discussion

Dr. B. Koletzko: You showed us in two studies the effects of formula acidified with fermentation on reducing diarrhea. I wonder whether you can really compare the effects of fermented formula to those of formula that is chemically acidified. Thus, allow me to ask whether the three studies that you performed in collaboration with Dr. Cooper and others have shown significant effects of the chemically acidified formula on diarrhea.

Dr. Haschke: In the growth studies with Dr. Cooper, we had infants during the first 4 months. We had both biologically acidified formulas and chemically acidified formulas in the study, and there was no difference between the two types of acidification.

Dr. B. Koletzko: In growth.

Dr. Haschke: In growth but also in disease outcome, so there is no difference.

Dr. B. Koletzko: So you found an effect of chemical acidification on diarrhea, that's my question.

Dr. Haschke: The study which I showed is a study after 6 months of age when the diarrhea time is starting up, one was in Chile and one was in France.
Dr. B. Koletzko: Allow me to add a comment regarding DHA. I fully agree with you that marketing of DHA formula, and also perhaps pricing of DHA-containing formula is hardly acceptable in many instances, but I would like to challenge your conclusion that we have no evidence for any effects of DHA in term formula. I want to cite the conclusions of the European Food Safety Authority who found that there is conclusive evidence for a cause-effect relationship between DHA intake in term infants and visual function development. The EFSA also concluded that the adequate DHA intake for infants and young children is 100 mg/day. Thus, while we do have a number of open questions and the IQ effects are overemphasized and not well based, we do have evidence for benefits of a DHA supply.

Dr. Haschke: I agree with you, I was just showing the meta-analysis. After so many years of research, this is the outcome. When health claims related to DHA will be submitted to EFSA they will be turned down. You are mentioning a transient effect on visual acuity; all other effects were rejected by EFSA. The European Food Safety Agency is very critical about DHA, but I agree with you that this one claim went through.

Dr. B. Koletzko: In their document concerning the requested claim on an effect of early DHA supply on cognitive development at 3 years, the EFSA pointed out that the evidence for the 3-year end point was not sufficient, but that they find a role of DHA in brain development and cognitive development.

Dr. Haschke: For me the main thing is that EFSA has rejected the claims. If they hadn't, the companies would have been trying to go over board, also in Europe. You must consider that due to the price positioning of these formulas in Asia, only children from the upper class have access. So there is a segmentation of the population which should not be there.

Dr. Cooper: Just to comment further on our studies. In each of the studies, there was a non-acidified standard formula, and we could show no difference in terms of incidence of diarrhea or any other morbidity as was shown in some of the other studies. Although, I don't think those were starter formulas. But I think there are two points to be made. The one is the studies were not powered for that outcome, and secondly because it was under study conditions, there was very close and ongoing education of the mothers in terms of preparation of the formula, and so from our studies we could not say that that had any effect on gastrointestinal infections, but whether it would happen in the field I don't think we would know in an unmonitored environment. However, our Health Department provides free milk for babies of HIV-positive mothers who elect not to breastfeed and have chosen the acidified formula. What Dr. Haschke didn't mention was perhaps the biggest advantage of the acidified formula, and that is that it doesn't taste good, it doesn't mix well in coffee and it’s more likely to end up in the baby's tummy than in the parents' tummies.

Dr. Gibson: You were talking about the balance between economic evaluation research and marketing. In the Economist this past week there has been a big article about Nestlé's commitment to R&D in health and wellness, trying to make it a health and wellness company. How does a company, given the marketing people are the main drivers from your perspective, take on board more research, how do you do that?

Dr. Haschke: I was part of the panel that was interviewed by The Economist. One of the factors we have clearly indicated is investing in research and development. Nestlé could show that during the last 10 years the effort dedicated to research for the whole company has been increased by 100%. There are certain segments of the company which are dedicated to nutrition like the Nestlé Nutrition company or the pet food company. Pet food is much more advanced in terms of health food than any other food. In the weight management for example, we have increased our research efforts by 400%. I am not giving you the absolute figures, investing in research means that
more scientific serious output can be expected. We have more resources to look at benefits which we have identified and we have more resources for long-term research. Similar approaches apply to pharma companies. We are not going in all fields of the area of nutrition. We have product segments like chocolate, but even here we look that the composition adheres to the standards. We have a clear policy in the company, and you can see that our company is in fact a producer of a lot of health products. If you look at micronutrient fortification, we are one of the biggest distributors of micronutrients. Yearly, 200 billion servings of fortified food are delivered to people, and among them there are 90 billion Maggi cubes. Maggi is a culinary product, but in many countries it’s a source of iodine.

**Dr. Gibson:** You made a big point here that the marketers are big drivers here. Has that been taken into consideration? How is the company going to get a reward out of this?

**Dr. Haschke:** In the western countries you have the phenomenon of the discounters, where the food prices are low. If the consumer believes in the added value and if the food is recommended by health care professionals, this is a different story. We are heavily investing in our medical field force which is responsible worldwide for communicating medical or scientific product messages, and this is our main marketing drive in many countries. In most Asian countries you cannot go on TV and advertise.

**Dr. Ganguly:** I have a comment on the meta-analysis. We should view the meta-analysis results with respect to the population as there is a tendency to overestimate the results and extrapolate them to populations where the situation may be very different. For example, in India, where the majority of the population are vegetarian, there may be a role for DHA in term formulas as often the maternal diets are deficient in DHA. Studies that have been carried out in India have shown a benefit of adding fish oil to the maternal diet to decrease the incidence of low birthweight [1]. Therefore, adding DHA to term formulas in situations where maternal DHA intake is low may be justified.

**Dr. Solomons:** I would like to back that statement because what we have done so often is to use meta-analyses as universal truths. I always said that if you take the individual meta-analysis cases and their various positionings and overlap with zero, if they were well done they would be reproducible, that’s to say doing them again in the same setting you would find the same effect, and those with other effect doing them in the same place again you would find the same effect. For me, the meta-analysis weakness is that it seeks a worldwide mean for situational truths, and the situational truths are going to be more relevant to those situations than the worldwide average mean, so that’s why I applaud the kind of comment my colleague made.

**Dr. Haschke:** There is no gold standard. Meta-analysis is just another way to interpret studies which have a certain quality. I would like to pass this question onto either Dr. Makrides or Dr. Szajewska who have done many meta-analyses.

**Dr. Szajewska:** I fully agree with that, and very often the results of a meta-analysis are overinterpreted. People do not look into the details such as the population, interventions, comparisons, and outcome measures. In particular, they do not determine whether the outcome measures were similar and measured in the same way. I don’t think that it’s a problem with the meta-analysis. I think that very often it’s an overinterpretation of the results of the meta-analysis. Some people jump to conclusions without reading the details. As you said it Dr. Haschke, it’s not the gold standard; it’s one way of looking at the evidence, that’s it.

**Dr. B. Koletzko:** So, perhaps we should not draw the conclusion that a meta-analysis gives us the true answer, but a meta-analysis simply summarizes the available evidence in a systematic way.
**Dr. Szajewska:** A meta-analysis is not the way to make recommendations. It helps you like any systematic review in formulating recommendations, but that is not equal to making recommendations.

**Dr. Solomons:** The debate has to do with not seeing one’s country or oneself in the meta-analysis, and yet having to confront interpretations whatever they be of the meta-analysis. Now, there are arguments for why Bangladesh or Pakistan or Nepal or India are not represented in the meta-analysis. It has to do with cost, it has to do with placements, skilled people to do them. But to see that one is excluded for whatever reason from the meta-analysis profile, not seeing oneself there, is very likely to make one wary of any influence that they would make on one’s own possible policies in one’s own country. That’s what I think is the counter-interpretive argument of this tool.

**Dr. Makrides:** Just a couple of further comments to add to those made by Dr. Szajewska about meta-analyses. The conclusion of a meta-analysis is only as robust as the quality of the studies within the meta-analysis. It is important to have sensitivity analysis within meta-analyses to be able to understand the heterogeneity and the way things may be combined. For example, in meta-analyses involving LC-PUFA interventions it is legitimate to combine different sources because the biochemistry reacts in the same way, but it might not be appropriate to combine different sources of probiotics. Regarding the comment about generalizability to different population settings, that comes back to the nature of the individual studies that make up the meta-analysis. For example, the meta-analyses of LC-PUFA supplementation of infant formulas are largely extrapolable to industrialized societies, while other meta-analyses in the area of iron nutrition apply to both industrialized and semi-industrialized societies. So it is possible to tease out differential responses based on the characteristics of the population or the class of treatment through sensitivity analysis, and yes meta-analysis is a good tool to try to come as close to the truth as possible but there are issues with interpretation.

**Reference**
