concluded from scarce, thus potentially unreliable, epidemiological data in complete MPO deficiency, remains to be defined.

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Effect of partially hydrolyzed whey infant formula and prolonged breast-feeding on the risk of allergic disease in high-risk children

To the Editor:

We reviewed with interest the article by Lowe et al.[1] The authors conclude the following: "Despite current dietary guidelines, we found no evidence to support recommending the use of pHWF [partially hydrolyzed whey infant formula] at weaning for the prevention of allergic disease in high-risk infants." As a sponsor of this study, Nestlé R&D feels obligated to make the following comments.

A 2006 Cochrane Review[2] on hydrolyzed formulas and allergy prevention assessed an unpublished 2-year report from the authors and excluded this trial from analysis because of "excess randomisation losses 238/620 (38%)." Nestlé R&D also assessed this report,[3] which stated that 238 infants received a "nonassigned" formula. This differs drastically from the 26 infants listed in the current article. This degree of nonadherence to formula allocation implies that a very large number of infants in all groups were exposed to intact proteins. This seriously jeopardizes any intervention aimed at reducing the risk of allergy with a hydrolyzed formula, and no statistical analysis can overcome this shortcoming.

In the current publication the first 97 infants were randomized to 2 formulas before the third one became available. In addition, 50% of subjects by 4 months and 39% by 6 months of age were still breast-feeding and did not receive their allocated formula. It is excellent that recommendations of prolonged breast-feeding were followed. In fact, the results could reflect a potential protective effect of breast-feeding in the whole study cohort. However, the low exposure to allocated formula coupled with prolonged breast-feeding introduces considerable bias, significantly decreasing the chances for identifying a difference caused by the formulas.

All clinical outcome measures were assessed through parental "telephone interview." No accepted diagnostic criteria for atopic dermatitis were used. There was no documentation of allergic disease between 2 and 6 years of age, leaving 4 of 7 years of follow-up undocumented. Also, documentation of allergic conditions for 6 to 7 years was done with a single telephone call at "6 or 7" years of age.

In summary, Nestlé R&D has significant concerns regarding the conclusions of this study, which is being published 21 years after its initiation and which, among other limitations, was single-blind, lacked strict diagnostic criteria, had high noncompliance rates, and had gaps in subject follow-up.

On the basis of a large body of evidence that includes studies of high quality, a number of professional organizations and expert groups[4,5] have concluded that use of certain hydrolyzed infant formulas, in particular partially hydrolyzed whey infant formula, has a role in the reduction of the risk of atopic disease, particularly atopic dermatitis. Also, 2 recent meta-analyses[6,7] confirm this benefit.

Safe alternatives to reduce allergic risk associated with intact cow's milk protein formulas are increasingly needed for infants who do not receive all the benefits of exclusive breast-feeding. The conclusions of a single study with the limitations mentioned above is of little consequence and should not affect current recommendations, which are in the interest of advancing infant health.

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Reply

To the Editor:

Dr Haschke[1] makes a number of incorrect claims related to our study.[2]

First, he states that exposure of children in the partially hydrolyzed whey formula (pHWF) group to intact cow's milk protein invalidates our findings.[1] As we state,[2] 69.1% of participants in the pHWF group received no exposure to intact cow's milk protein by 12 months of age. A sensitivity analysis, removing study participants who had been exposed, still showed no protective effect of pHWF for any of the allergic outcomes assessed.

Second, he states that the high rate of prolonged breast-feeding might reduce the benefit of pHWF. Our study only examined the effect of weaning to a formula after full or partial cessation of breast-feeding.[1] This is the usual context in which formula is introduced. It is valid for real-world application, particularly because the World Health Organization recommends that mothers should endeavor to breast-feed exclusively until 6 months of age.[3] Although the main results are presented from the intention-to-treat analysis (infants analyzed in the group to which they were assigned, regardless of actual exposure), as is current best practice (http://www.consort-statement.org/home/), we also performed extensive per-protocol analyses, which also did not identify a benefit of pHWF.[2]

The 2006 Cochrane review[4] excluded the Melbourne Atopy Cohort Study because of "excess losses" using an unpublished interim report, presumably provided by Nestlé. We cannot understand the claim that participant follow-up was low[1] when it was 92.7% at 2 years.[2] Disappointingly, we were not contacted to clarify the interpretation of the data.

Parent-reported eczema is a standard outcome in longitudinal cohorts of allergic disease. In our study frequent follow-ups were performed in early life,[2] when eczema is most likely to develop. Many nonvalidated definitions of eczema are used in children younger than 2 years.[5,6] The definition of eczema used in this study showed 85% sensitivity and 81% specificity when compared with trained-nurse assessment in an as-yet-unpublished validation study.[7]

The strengths of this ongoing study are the long-term follow-up, participant randomization and blinding to group of allocation, high follow-up rates, and performance of repeated skin prick tests. The short delay in pHWF availability did not materially influence study outcomes because the baseline characteristics remained balanced between the groups. Because of the difficulty in defining asthma/allergic rhinitis in early life, we analyzed outcomes at 6 to 7 years. The use of telephone interviews to ascertain the outcomes relevant to this article is standard practice.

The US Food and Drug Administration completed a review of this topic in May 2011, which was initiated by Nestlé's request to make a qualified health claim for pHWF (http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm256731.htm). The US Food and Drug Administration, which considered the meta-analyses cited by Dr Haschke,[1] concluded that "the relationship between feeding a 100 percent whey-protein partially hydrolyzed infant formula for the first 4 months of life and a reduced risk of atopic dermatitis throughout the first year of life and up to 3 years of age is uncertain."

We look forward to the integration of our trial into the body of evidence on this topic.

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