

6. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. *Curr Med Res Opin* 2010;26:423-37.
7. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. *J Pediatr Gastroenterol Nutr* 2010;50:422-30.

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## Reply

### To the Editor:

Dr Haschke<sup>1</sup> makes a number of incorrect claims related to our study.<sup>2</sup>

First, he states that exposure of children in the partially hydrolyzed whey formula (pHWF) group to intact cow's milk protein invalidates our findings.<sup>1</sup> As we state,<sup>2</sup> 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.<sup>1</sup> 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.<sup>3</sup> 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.<sup>2</sup>

The 2006 Cochrane review<sup>4</sup> excluded the Melbourne Atopy Cohort Study because of "excess losses" using an unpublished interim report, presumably provided by Nestlé.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<sup>1</sup> when it was 92.7% at 2 years.<sup>2</sup> 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,<sup>2</sup> when eczema is most likely to develop. Many nonvalidated definitions of eczema are used in children younger than 2 years.<sup>5,6</sup> 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.<sup>7</sup>

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,<sup>1</sup> 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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## REFERENCES

1. Haschke F. Effect of partially hydrolyzed whey infant formula and prolonged breast-feeding on the risk of allergic disease in high-risk children. *J Allergy Clin Immunol* 2011;128:688-9.
2. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2011;128:360-5.e4.
3. World Health Organization. Complementary feeding. Report of the global consultation: summary of guiding principles. Available at: <http://www.who.int/topics/breastfeeding/en/index.html>. Accessed August 3, 2011.
4. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;(4): CD003664.
5. Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980;92:44-7.
6. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994;131:406-16.
7. Lowe A, Boyle R, Su J, Varigos G, Carlin C, Bennett CM, et al. Validation of definitions of eczema in infancy used in research. *Intern Med J* 2010;40:13.

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