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## **DIETARY PREVENTION OF ALLERGIC DISEASES IN INFANTS AND SMALL CHILDREN**

***Abstrakt:** This article provides information on the dietary prevention of allergic diseases in infants and young children*

***Keywords:** breast feeding; cow's milk allergy; food allergy; eczema; atopy; prevention; review; statements of evidence*

The role of primary prevention of allergic diseases has been a matter of debate for the last 40 yr. In order to shed some light on this issue, a group of experts from the Section on Pediatrics, EAACI (SP-EAACI) reviewed critically the existing literature on Dietary Primary Prevention of Allergic Diseases in Infancy and Early Childhood. Based on this review, three articles were published (1–3). Since the publication of this review, the first author (Chandra RK) of four of the papers included in part III has been accused of scientific fraud (4, 5). Based on an investigation at the University of Saskatschewan, it has been concluded that the published data in the papers by Chandra (6–9) cannot be verified. (The National, January 30, January 31 and February 1, 2006: <http://www.cbc.ca/national/news/chandra>). Three attempts were made by the SP-EAACI and the authors of another review on hydrolyzed infant formulae (10), to solicit information from the University of St. John where Chandra was based but without success. Inevitably, the original Cochrane meta-analysis on formulas containing hydrolyzed protein for prevention of allergy and food intolerance in infants was revised excluding the Chandra studies (11). The exclusion of these trials and inclusion of a new, large trial have resulted in changes to the Cochrane review conclusions (11). In contrast to the earlier Cochrane meta-analysis, the authors now conclude that: in high-risk infants who are unable to be completely breast-fed, there is limited evidence that prolonged feeding with a hydrolysed formula compared to a cows milk formula reduces infant and childhood allergy

and infant cows-milk allergy. In view of methodological concerns and inconsistency of findings, further large, well-designed trials comparing formulas containing partially hydrolysed whey, or extensively hydrolysed casein to cows milk formulas are needed. As emphasized by the expert group of SPEAACI (1), evaluation of hypoallergenic formula should be made per brand of hydrolyzed formula and not by source of protein (casein or whey) because the amount of residual protein may vary considerably between different hydrolyzed products, casein as well as whey hydrolysates, depending on the degree of hydrolysis. Unlike the previous Cochrane review on this issue (2003/2004), the members of the expert group of the SP-EAACI were guarded in their evaluation of the quality of the studies on primary dietary prevention by Chandra [see (3)]. However, we do not find that the exclusion of the two sets of trials by Chandra (6–9) demands a change of the recommendations regarding primary dietary prevention of allergic diseases (particularly food allergy/cows-milk allergy) in high-risk infants (3). We recognize the need to conduct a comprehensive systematic review using Cochrane methodology (11). Ideally, recommendations on primary dietary prevention should be based only on the results of randomized and quasi-randomized trials that compare the use of hydrolyzed infant formula to standard cows-milk formula (selection criteria in the Cochrane review). However, no sensible paediatrician would even contemplate attempting a randomized comparison with human milk as it would be totally unethical. Despite this, the authors of the Cochrane review (11) in their discussion appear to be suggesting that such trials are required. We should all accept that milk formulae will never be preferred to breast-feeding as considerations extend way beyond allergy.

In our opinion, mothers who are able to breast-feed should breast-feed, and there is no reason to supplement with formula-feeding when Occupational Medicine, Karolinska Hospital, Stockholm, Sweden, 20A.Z.- Kinderen, Free University of Brussels, Brussels, Belgium, 21Department of Environmental Health, Karolinska Hospital, Stockholm, Sweden Key words: breast feeding; cow's milk allergy; food allergy; eczema; atopy; prevention; review; statements of evidence Antonella

Muraro, Department of Pediatrics, University of Padua, Via Giustiniani 3 35128, Padua, Italy Tel.: +39 049 8213505, 06 + 39 049 8212538 Fax: +39 049 8213509 E-mail: muraro@pediatria.unipd.it Accepted 5 October 2007 Høst et al. 2 breast-feeding is sufficient. When developing recommendations on dietary primary prevention, high-quality systematic reviews of high-quality cohort studies should be included in the evidence base (3). The study type combined with assessment of the methodological quality determines the levels of evidence (12). It can be recommended to follow the recommendations on evaluation of methods in allergy prevention studies and definitions and diagnostic criteria of allergic diseases in the position paper by the SPEAACI (2). This review includes description of target group for dietary prevention, and methods and diagnostic criteria of atopic dermatitis, asthma and food allergy for prevention studies. In the Cochrane review, the primary outcomes were any allergy including asthma, atopic dermatitis, allergic rhinitis or food allergy. In many of the included studies, the diagnosis of allergy/ allergic disease was based on questionnaires. That is highly questionable. The authors seem to use the term food intolerance, which has been abandoned. Regarding updated definitions on allergy/atopy/allergic diseases – see recent guidelines (13). An important point regarding the diagnosis of food allergy is that many food allergies may be overlooked if the infants/children are not investigated at the time of onset of symptoms but only investigated at fixed time points. A diagnosis of food allergy cannot be made based on parental reports of symptoms and positive specific immunoglobulin E (IgE) or skin prick tests. It can only be based on controlled elimination and challenge procedures, in young children not necessarily DBPCFC [see (2, 14)]. Studies without use of strict diagnostic criteria and well-defined and verified outcome measures (apparent in more of the studies included in the Cochrane review) may confound the findings and make studies non-conclusive. Important factors regarding methodological quality are emphasized in the Cochrane review, such as adequate method of randomization, allocation concealment and blinding of treatment and blinding of measurement and evaluation of allergy. However, even studies meeting these demands on

methodological quality may be misleading and non-conclusive if adequate definitions, diagnostic criteria and outcome measures have not been used and followed. The authors of the Cochrane review have excluded studies where losses to follow-up are greater than 20%. This may raise the question whether this is correct. There are well-conducted studies with losses greater than 20% due to a careful description of drop-outs and reasons for drop-out. One study (15) has been excluded due to excess losses >20%, which is not correct according to data presented in the paper. The authors seem to be in favour of intention to treat analysis. However, this may not be the correct method in studies where the effect of a specific diet is evaluated. The reason for noncompliance to a diet may, for example, be due to parental refusal (e.g. due to unpalatability of a product) and not related to whether or not the infant tolerated the feeding with the product in question. Therefore, careful per-protocol analysis may be justified as well. Regarding randomization, the term quasi-randomization has been used for randomization according to date of birth and this form for randomization has been classified as not adequate. Presumably, the children or parents or doctors will not be able to influence this kind of randomization. In at least two studies (15, 16), allocation concealment was questioned in the Cochrane review though it has been described adequately in the papers. The review performed by the expert group of the SP-EAACI (3) only included studies published in peer-reviewed scientific journals in contrast to the recent Cochrane review (11), which also included a study published in an internal company report (Nestle' Internal Report 1992) (17), and another large study (18) published as a supplement to a scientific journal, which according to the publisher was not peerreviewed. The reason for inclusion of such studies seems questionable.

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