COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of risks arising from the infant diet and the development of atopic and autoimmune disease: Systematic review C – part I – Hydrolysed formula and Risk of Allergic or Autoimmune Outcomes: a systematic review and meta-analysis (reserved business)

Introduction

1. The FSA has commissioned Imperial Consultants to conduct a systematic literature review of the published scientific evidence available on infant formulae containing hydrolysed cows' milk protein and their ability to reduce the risk of infants and young children developing atopic or autoimmune disease.

2. This systematic review has been conducted alongside three other systematic literature reviews conducted by Imperial Consultants and is referred to as systematic review C – part I. This review will not form part of SACN's infant feeding review and the COT is asked to provide a separate COT statement on Review C – part I. Review C part II (intervention studies) will be presented to the Committee at the same time as this review.

3. Systematic review C – part I is now complete and the results are presented to the Committee for discussion. Annex 1 contains the final report for systematic review C – part I. This item is to be discussed as reserved business and the annex withheld from publication on the FSA website because the results of systematic review C – part I have yet to be accepted for publication in a peer-reviewed journal.

4. Further background to this topic can be found in the cover paper for the COT discussion of Review A at their meeting in June (TOX/2015/18).1

Systematic review C – part I

5. The main purpose of systematic review C part I was to investigate the role of hydrolysed cows' milk formula feeding in place of either standard cows' milk formula or breast milk on a child's future risk of developing atopic or autoimmune disease. Allergic outcomes of interest were asthma, eczema, allergic rhinitis, allergic conjunctivitis, allergic sensitisation and total IgE; autoimmune outcomes of interest were type I diabetes mellitus, coeliac disease, inflammatory bowel disease,

[1] http://cot.food.gov.uk/cot-meetings/cotmeets/cot-meeting-30-june-2015

autoimmune thyroid disease (Grave's disease, or Hashimoto's thyroiditis), juvenile rheumatoid arthritis, vitiligo or psoriasis.

6. Cows' milk formula contains proteins from 14 kilo Daltons (kD, α-lactalbumin) in size, up to 67 kD (bovine serum albumin). In general, allergenic peptides are 10 to 70 kD in size with many in the 10 - 40kD range. There is no universally accepted definition of pHF (partially hydrolysed formula) and eHF (extensively hydrolysed formula). eHF is intended to have no peptides □□3 kD , and pHF is intended to have no peptides □□5kD. However, independent studies have found that pHF and eHF do not consistently meet these targets. pHF has been estimated to contain 15-20% peptides over the target size, and eHF up to 5%. Studies have shown both pHF and eHF are capable of eliciting immunological and clinical allergic reactions in a proportion of people who are allergic to cows' milk.

7. Therefore, for the purposes of this systematic review, hydrolysed formulae have not been pre-defined but definitions (if any) and trade names used in individual studies will be noted and used to interpret the findings.

8. Systematic review C part I aimed to address the following research questions:

- Does the use of either extensively or partially hydrolysed cows' milk formula feeding, in place of either standard cows' milk formula or breastmilk, influence children's future risk of developing atopic or autoimmune disease?
- Does the extent of protein hydrolysis (i.e. partial versus extensive hydrolysis) in a hydrolysed cows' milk formula influence children's future risk of developing atopic or autoimmune disease?
- Does the fraction of cows' milk (whey versus casein) used to make hydrolysed cows' milk formula influence children's future risk of developing atopic or autoimmune disease?

Results of systematic review C - part I

9. An overview of the results of systematic review C – part I is presented in Annex 1. The results of systematic review C – part I have been analysed according to disease outcome (i.e. eczema, wheeze, rhino-conjunctivitis, food allergy, allergic sensitisation, type I diabetes mellitus).

10. The final conclusions of systematic review C part I are detailed on page 125 and a summary table of the findings can be found on pages 134-135 of Annex 1.

11. Dr Boyle and Dr Garcia will attend the Committee meeting on the 8th September. They will present the results of systematic review C part I and address any questions the Committee may have. Dr Boyle hopes to submit a version of this work for publication in the peer reviewed literature and therefore the annexes will not be made publically available.

Questions on which the views of the Committee are sought

12. Members are invited to comment on systematic review C – part I and to consider the following questions:

i. Do Members consider that the review provides evidence of a link between exposure to eHF or pHF during the first year of life and subsequent development of atopic disease or autoimmune disease?

ii. Do Members consider that the review provides evidence of a link between the degree of hydrolysation of the proteins and subsequent development of atopic disease or autoimmune disease?

iii. Do Members consider that the review provides sufficient evidence for assessing the role of milk fraction (casein vs. whey) in hydrolysed formula consumed during the first year of life and subsequent development of atopic disease or autoimmune disease?

iv. If Members consider there is evidence to support a link in any of the above cases, they are asked to comment on whether this link applies to the general population, those at increased risk of developing atopic or autoimmune disease, or both.

v. Do Members have any other comments on systematic review C – part I or wish to raise any other matters arising from it?

Secretariat
August 2015

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The following annexes are attached to this report:

Annex 1 – Report on hydrolysed formula and the risk of allergic or autoimmune outcomes following a systematic review and meta-analysis.

Note: The Committee were provided with a pre-publication copy of the work of Imperial Consultants. This was received in confidence and will not be released when this paper becomes publicly available. As indicated, above the work will be submitted for publication following peer review.