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

## Statement on the role of hydrolysed cows' milk formulae in influencing the development of atopic outcomes and autoimmune disease.

### Background

1. Atopic conditions, including asthma, eczema, rhinoconjunctivitis and food allergy, appear to have increased in prevalence in recent decades in many countries, and are some of the commonest causes of chronic illness in children and young adults living in the UK (Gupta *et al*, 2004; Gupta *et al*, 2007; Venter *et al*, 2010; De Silva *et al*, 2014; Nwaru *et al*, 2014). This apparent increase in disease prevalence, combined with data from migration studies, suggests that early-life environmental factors may be important modulators of atopic disease risk. Similarly, the autoimmune diseases type I diabetes mellitus (TIDM) and Crohn's disease also appear to have increased in prevalence in some countries (Bach *et al*, 2002).

2. The FSA commissioned a systematic review of the published scientific literature on infant formulae containing hydrolysed cows' milk protein and their potential role in reducing the risk of infants and young children developing atopic outcomes and autoimmune disease. The review was conducted by scientists at Imperial College London.

3. The COT has been asked for their opinion on the systematic review, which will be used to guide the FSA in directing future policy and guidance on the use of hydrolysed infant formulae.

4. The COT enlisted the help of two external experts to help them in their considerations: Professor Ian Kimber, Chair of Toxicology at the University of Manchester and Programme Advisor to the FSA Food Allergy and Intolerance Research Programme and Dr Paul Turner, an expert in paediatric allergy and immunology from Imperial College London.

5. A glossary of terms is provided as Appendix 1 to this statement.

### Methodology of the systematic review

6. The review was designed to answer three questions:

a) Does the use of either extensively or partially hydrolysed cows' milk formula feeding, in place of either standard cows' milk formula or breast milk, influence children's future risk of developing atopic outcomes or autoimmune disease?
b) Does the extent of protein hydrolysis (i.e. partial versus extensive hydrolysis) in hydrolysed cows' milk formula influence children's future risk of developing atopic outcomes or autoimmune disease?

c) Does the fraction of cows' milk (whey versus casein) used to make a hydrolysed cows' milk formula influence children's future risk of developing atopic outcomes or autoimmune disease?

7. Databases searched were The Cochrane Library; EMBASE; LILACS; MEDLINE and Web of Science with the original searches run in July 2013 and updated in April 2015 for intervention trials and systematic reviews. PROSPERO was also searched for relevant systematic reviews.

8. Original research papers were included from any date up to April 2015. Original studies included randomised controlled trials (RCTs), quasi-RCTs, controlled clinical trials, prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies, other case-control studies and cross-sectional surveys. Both intervention and observational studies were identified during the review, but due to the large number of intervention studies available, observational studies were not included in the analysis. Intervention studies are considered to be more reliable, as variables between populations can be better controlled than in observational studies.

9. Studies of infants between birth and 12 months of age were included in the review. Studies were excluded where participation was limited to infants with a specific disease state, premature infants <32 weeks gestation or very low birth weight infants. Included interventions were:

(i) any extensively hydrolysed formula (eHF);
(ii) any partially hydrolysed formula (pHF);
(iii) any whey based hydrolysed formula;
(iv) any casein based hydrolysed formula;
(v) whey based eHF ;
(vi) casein based eHF ;
(vii) whey based pHF ;
(viii) casein based pHF ;
(ix) hydrolysed cows' milk formula not otherwise defined.

10. Non-cows' milk formulae, such as soya-based formula, were not considered in this review, but studies using other hydrolysed mammalian milk formulae would have been considered if they had been available. Comparators of interest were breast milk, hydrolysed or non-hydrolysed cows' milk formula or other mammalian milks.

11. The systematic review recorded the degree of hydrolysis as defined by the original study and the brand name where available, which was used to interpret the findings.

12. During the analysis, intention to treat data were used in preference to per-protocol, as is generally recommended for assessments of clinical effectiveness.

13. Outcomes of interest were chosen for their prevalence in children and young adults with minimum inclusion criterion of 1 in 1000 prevalence in the general population. Atopic outcomes comprised: asthma / wheeze; atopic eczema; allergic rhinoconjunctivitis (AR); food allergy; allergic sensitisation. Autoimmune outcomes comprised type 1 diabetes mellitus (TIDM); coeliac disease; inflammatory bowel disease (such as Crohn's disease or ulcerative colitis); autoimmune thyroid disease (such as Grave's disease or Hashimoto's thyroiditis); juvenile rheumatoid arthritis; vitiligo and psoriasis. Outcome data were analysed and presented within the age groups 0-4 years, 5-14 years and ≥15 years for all outcomes other than allergic sensitisation and TIDM, where outcome data were not divided by age.

14. Studies were quality assessed using the Cochrane Risk of Bias tool with an additional assessment of risk of conflict of interest (Cochrane; 2009). Risk of publication bias was assessed for meta-analyses that included at least 10 studies.

15. The evidence was graded using the GRADE system[1] where evidence was assigned one of four categories: HIGH, MODERATE, LOW or VERY LOW depending on the strength of evidence. The interpretation of GRADE evidence assessments is that for HIGH level assessments, further research is very unlikely to change confidence in the estimate of effect; for MODERATE evidence further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; for LOW level evidence, further research is likely to have a very important impact on confidence in the estimate of effect and is likely to change the estimate. For VERY LOW level evidence any estimate of effect is uncertain.

16. Sub-group analyses were carried out according to risk of bias, disease risk and study design. Meta-analyses were undertaken where 2 or more studies reported the same outcome for a given exposure. Where meta-analysis was deemed inappropriate due to differences in population, exposure/intervention or outcome; or where meta-analysis was not possible due to the nature of the data reported - individual study results were summarised within each report. Separate analyses were undertaken for each disease outcome, and for each intervention and comparator. The approach taken for the meta-analysis was inclusive, with data pooled for maximum statistical power, but examined for important sources of statistical or clinical heterogeneity. Results for randomised or quasi-randomised controlled trials were pooled separately from controlled clinical trials.

[1] Further information about GRADE can be found at: www.gradeworkinggroup.org/publications/Grading_evidence_and_recommendations_BMJ.pdf

17. Published systematic reviews were included within the search strategy for the review. Those systematic reviews that were considered to be high quality using revised AMSTAR[2] criteria were included in the systematic review report.

18. The contractors assessed the effect of hydrolysed formulae on a predefined list of atopic outcomes and autoimmune diseases. They did not merge different outcomes such as wheezing and eczema, type 1 diabetes mellitus and coeliac disease, or 'any atopic or autoimmune disease' due to concerns about clinical heterogeneity. In order to illustrate any population trends or changes in methodology, forest plots included in the report and in this statement have been ordered by publication date.

**Overall results of the systematic review**

19. Thirty seven intervention trials of hydrolysed formula were identified for inclusion in the systematic review, which included over 19,000 participants. Overall there were 29 randomised controlled trials (RCT), 5 quasi-RCTs (qRCT) and 3 Controlled Clinical Trials (CCT) describing atopic outcomes or autoimmune outcomes. Data on autoimmune outcomes were only available for TIDM. Thirty out of 37 studies were conducted in infants at high disease risk. Two plots showing a summary of treatment effects on different outcome measures using pHF and eHF; and a table containing the key findings including the GRADE assessment, can be found in Appendix 2. Overall there was no consistent evidence that hydrolysed formula influences risk of atopic or autoimmune outcomes, either positively or negatively.

20. Overall the risk of bias and conflict of interest was found to be high or unclear in most studies of allergic outcomes, but not autoimmune outcomes. There was evidence of publication bias in studies of eczema and wheezing.

21. There is no evidence to suggest that the age of assessment had a significant impact on the outcome measured, although there were more data available for outcomes in the first four years of life.

**Risk of eczema**

22. Twenty seven intervention studies were identified with over 5000 participants. All RCTs were conducted in children with a high risk of developing atopic outcomes. The majority of studies had a high or unclear risk of bias and a high or unclear risk of conflict of interest.

23. There was no evidence that the use of pHF in place of standard formula influences the risk of eczema in children aged 0-4 or aged 5-14 years.

[2] Further information about AMSTAR can be found at: http://amstar.ca/ and in Kung et al, 2010.

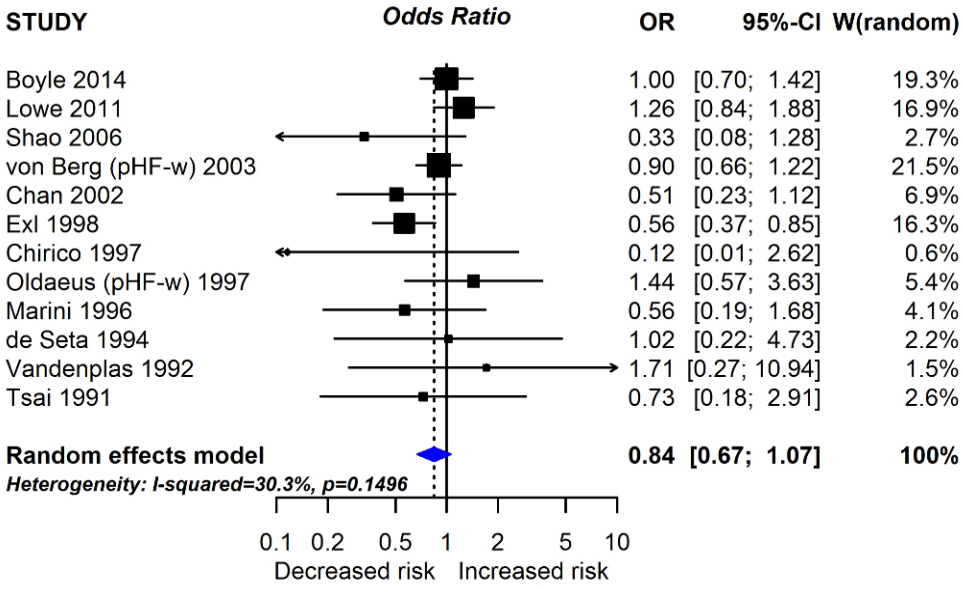


Figure 1: pHF vs Cow's milk for preventing eczema at 0-4 years – RCT/qRCT evidence

24. When data for eHF and pHF were pooled, analysis of 'any hydrolysed formula' versus cows' milk formula showed a reduced risk of eczema at age 0-4 years (RR 0.77; 95% CI 0.63-0.94), but not 5-14 years. This finding is based on meta-analysis of 16 studies and necessitated use of per protocol, rather than intention to treat, data from one large study (Von Berg, 2003). The analysis had high statistical heterogeneity, and there was evidence of publication bias.

25. The grade of evidence was found to be moderate for partially hydrolysed formula for the 0-4 years age group and very low for extensively hydrolysed formula in the same age group.

26. The review authors concluded that given the lack of studies with a low overall risk of bias and low risk for conflict of interest, evidence of publication bias and the lack of statistically significant findings in most analyses, there was no consistent evidence to support an association between infant feeding with a partially or extensively hydrolysed formula vs cows' milk formula and any change in eczema risk.

**Risk of wheeze and recurrent wheeze**

27. Twenty one intervention studies were identified with over 7000 participants. Almost half of the studies were considered to be at high risk of attrition bias or selection bias, and a quarter at high risk of conflict of interest.

28. Data for the outcome 'wheeze' were inconclusive, with pHF meta-analyses dominated by a multifaceted intervention study in which uptake of the intervention was very low, and a quasi-RCT with high risk of bias and conflict of interest; and eHF meta-analysis was not possible due to extreme heterogeneity.

29. There was no evidence that the use of pHF in place of standard formula influences the risk of recurrent wheeze in children aged 0-4 or aged 5-14 years.

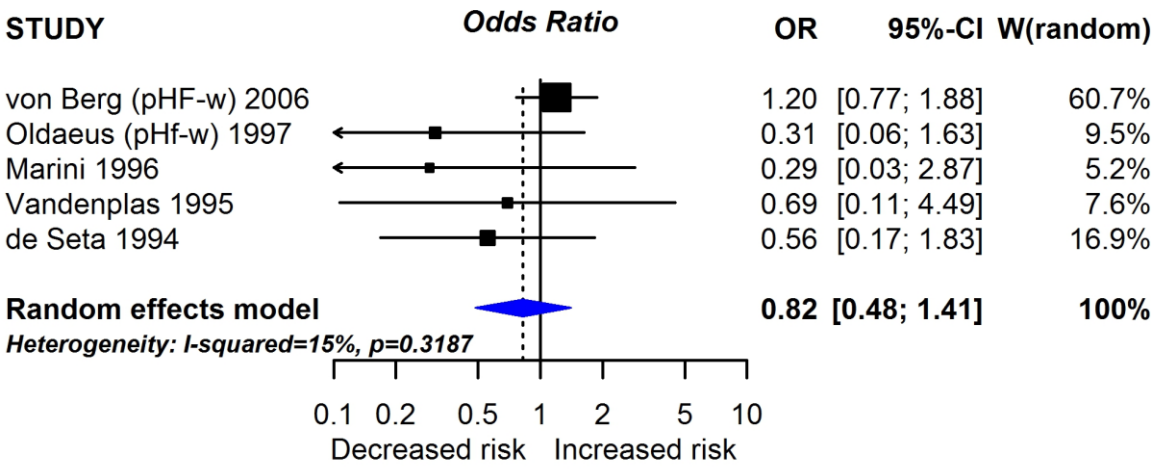


Figure 2: pHF vs cow's milk for preventing recurrent wheeze at 0-4 years.

30. There was no evidence that eHF in place of pHF or standard cows' milk formula influences risk of recurrent wheeze at aged 0-4 or aged 5-14 years. No significant associations were reported for lung function.

31. When data for eHF and pHF were pooled, analysis of 'any hydrolysed formula' versus cows' milk formula showed evidence of publication bias and no evidence of an effect on risk of recurrent wheeze.

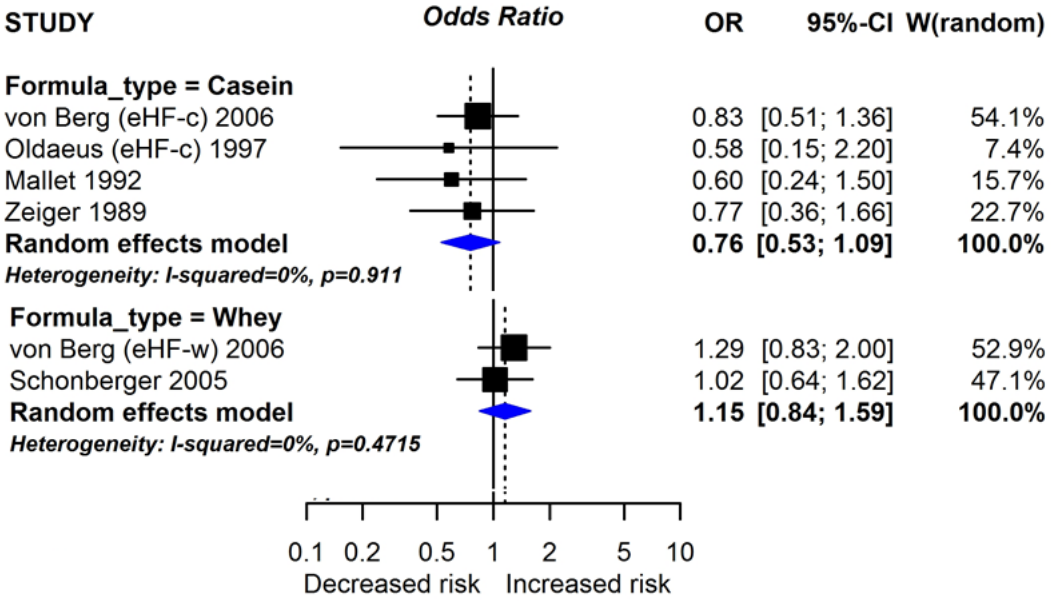


Figure 3: eHF vs cow's milk for preventing recurrent wheeze at 0-4 years.

32. The GRADE of evidence was considered to be moderate for the influence of pHF vs standard cow's milk formula on recurrent wheeze in 0-4 years and very low for eHF and the same outcome.

33. The review authors concluded that overall there was no consistent evidence to support an association between infant feeding with pHF or eHF and any change in risk of wheeze.

**Risk of allergic rhinoconjunctivitis**

34. Twelve intervention studies were identified with over 2500 participants. All studies were undertaken in populations at high risk of developing atopic outcomes. One third of studies were considered to be at high risk of bias, mainly due to attrition bias. Three quarters of studies had high or unclear risk of conflict of interest.

35. The pooled data showed an apparent reduction in risk of allergic rhinoconjunctivitis in children aged 0-4 years (but not aged 5-14 years) using pHF compared with cows' milk formula (RR 0.61; 95% CI 0.44-0.84). This was largely based on a multi-faceted intervention trial in which only 8% of participants in the intervention arm used the pHF formula they were allocated (Chan-Yeung, 2000). Analysis of any hydrolysed formula produced similar results, but these were also largely attributable to the Chan-Yeung et al (2000) study.

36. The review authors concluded that there was some evidence that a multi-faceted intervention trial incorporating environmental control measures as well as pHF may reduce risk of allergic rhinoconjunctivitis at age 0-4 (but not age 5-14), but the extent to which this can be attributed to pHF is very unclear. The review authors consider that other aspects of the intervention (such as reduced exposure to cigarette smoke and other environmental control measures) may have had a greater influence on the results of this study than the dietary interventions.

37. The review did not find any evidence to support that pHF or eHF alone influences the risk of allergic rhinoconjunctivitis, compared with standard cows' milk formula.

**Risk of food allergy and allergic sensitisation**

38. Thirteen and 19 intervention studies were identified with over 9500 and 5500 participants respectively for food allergy and allergic sensitisation. In both cases over 30% of studies were considered to be at high risk of bias, mainly due to attrition bias; over 70% were at high risk or unclear risk of conflict of interest.

39. No significant associations were reported in meta-analyses of eHF, pHF or any hydrolysed formula for the outcomes 'any food allergy' or food allergy to cows' milk at either 0-4 years or 5-14 years of age.

40. There was no significant difference in risk of 'any food allergy' with pHF (RR 1.73 95% CI 0.79, 3.80; $I^2$=42%) or eHF (RR 0.86 95% CI 0.26, 2.82; $I^2$=42%) compared with standard formula at age 0-4, nor for eHF at age 5-14.

There was also no difference seen in food allergy to cow's milk, egg or (pHF only) peanut.

41. The review authors concluded that no consistent evidence was found to support an association between use of hydrolysed formula and any change in risk of food allergy when compared to standard cows' milk formula.

42. Allergic sensitisation data were presented for the outcomes 'any allergen', cows' milk, hen's egg, peanut, food and aeroallergens. Skin prick test (SPT) and specific IgE data were used by studies to assess allergic sensitisation. Total serum IgE was reported in three studies.

43. No significant effects from meta-analyses or subgroup analyses were reported for pHF or eHF on allergic sensitisation to any allergen, cows' milk, peanut or aeroallergens

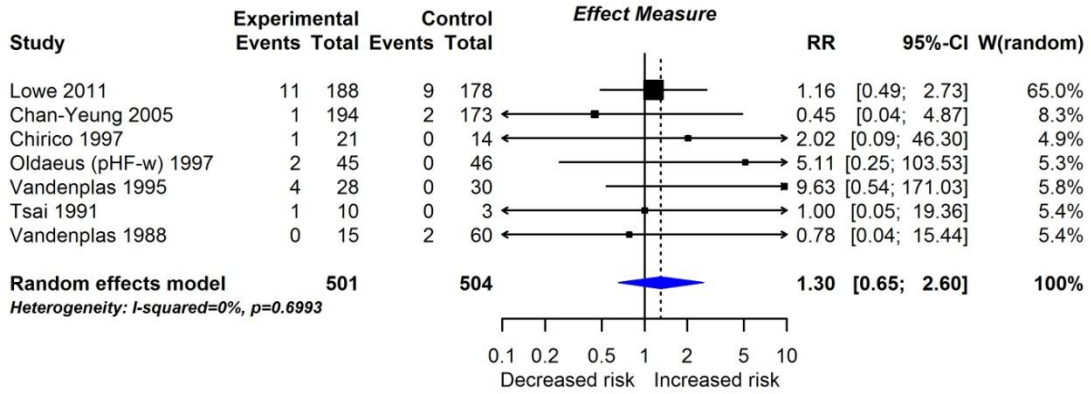


Figure 4. pHF and risk of allergic sensitisation to cow's milk.

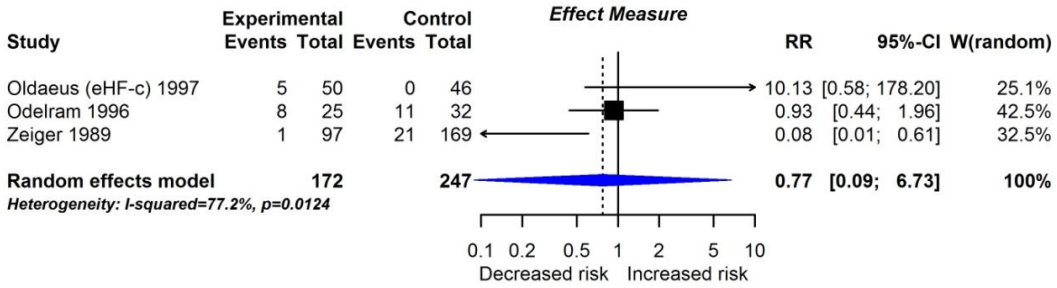


Figure 5. eHF and risk of allergic sensitisation to cow's milk.

44. The GRADE of evidence for the influence of pHF compared to standard cow's milk formula on the development of allergic sensitisation to cow's milk was moderate and for eHF was very low.

45. The review authors concluded that there was no consistent evidence to support an effect of hydrolysed formula upon allergic sensitisation. The GRADE of evidence is MODERATE for pHF, and VERY LOW for eHF, that there is no relationship with allergic sensitisation to cow's milk.

**Risk of type I diabetes mellitus**

46. Six intervention studies were identified with over 11,000 participants. Five of the six studies were considered to be at unclear risk of bias mainly due to unclear selection and/or assessment bias but five of six were at low risk of conflicts of interest.

47. A meta-analysis of eHF vs cows' milk formula showed no significant effects. No studies were identified that used pHF as an intervention.

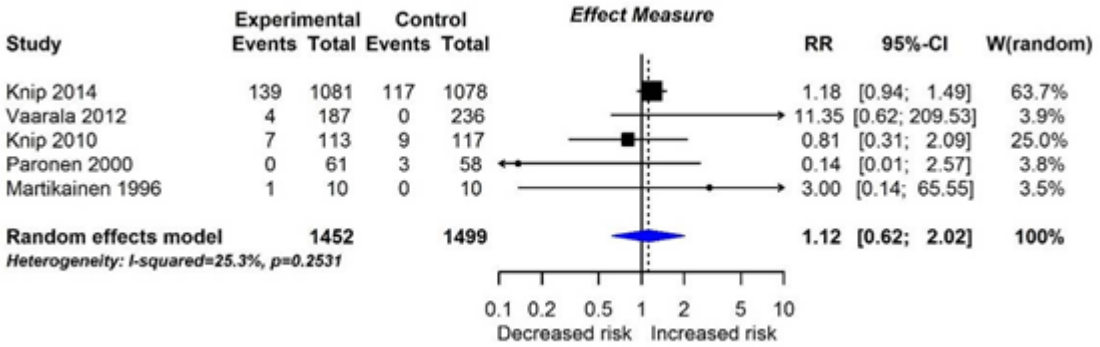


Figure 6: eHF vs cow's milk for preventing diabetes

48. The review authors concluded that the evidence does not support an association between the use of hydrolysed cows' milk formula and any change in markers of TIDM. The GRADE of evidence is HIGH.

**Findings from published systematic reviews and other reviews**

49. The systematic review commissioned by FSA identified one high quality systematic review by Osborn et al. (2006) in the published literature, which was a Cochrane review. Osborn et al. concluded that there was limited evidence to support a role for hydrolysed formula in reducing cows' milk allergy, and no evidence for an association with other specific atopic outcomes. They did however pool all allergic outcomes and find evidence that hydrolysed formula reduces risk of 'any allergic disease'. The conclusion regarding cow's milk allergy was based on a single study where the Cochrane review authors selected an outcome that was present in 30% of the control group and is therefore likely to be a poor measure of cows' milk allergy (Vandenplas et al., 1992). The systematic review commissioned by FSA identified 3 studies of pHF and 3 studies of eHF versus standard formula which reported cows' milk allergy and could be included in meta-analysis, including the study of Vandenplas et al., 1992. Taken together, they found no evidence to support the conclusions of Osborn et al. The authors of the systematic review commissioned by FSA did not consider it appropriate to pool all allergic and/or autoimmune outcomes together as 'any allergic disease' due to concerns about clinical heterogeneity.

50. The authors of the systematic review commissioned by FSA also highlight that their findings are not consistent with the conclusion of an independent Food and Drug Administration (FDA) review (FDA, 2012), which supported a limited

health claim that whey-pHF may reduce eczema in high risk infants. The authors of the FSA-commissioned systematic review suggested that the FDA conclusion might differ because the FDA utilised per protocol data from the Von Berg study in their analyses, since intention to treat data had not yet been published - and FDA did not include a more recent study by Lowe et al. (2011) which did not find a protective effect on eczema using the same formula.

**Conclusions of the systematic review**

51. The overall conclusions of the systematic review were as follows:

> "In this systematic review of hydrolysed formula for reducing risk of allergic or autoimmune outcomes, we found no clear evidence for a protective effect with respect to any of the outcomes studied. In general, relatively few included studies carried a low overall risk of bias and low risk of conflict of interest. In particular, the studies in relation to allergic outcomes commonly had unclear or high risk of overall bias, often due to post-randomisation exclusion of participants (attrition bias) and unclear or high risk of conflict of interest due support of the study or investigators by manufacturers of hydrolysed formula. We also found evidence of publication bias, at least in analysis of eczema and recurrent wheeze as outcome measures. This body of evidence should be viewed as pertaining to children at high risk of atopic outcomes or autoimmune disease, since these accounted for most studies and participants, and almost all analyses were dominated by the findings in high risk children. Thus the evidence base for use of hydrolysed formula in children at 'normal risk' of allergic or autoimmune outcomes is largely unexplored."

**COT conclusions**

52. Members were impressed with the scope and rigorous methodology used in preparing this systematic review.

53. The COT concluded that the evidence available did not support the use of hydrolysed cow's milk formulae, either eHF or pHF, to influence the risk of developing allergic or autoimmune disease.

54. The Committee also agreed that the milk fraction used to produce the hydrolysed cow's milk formula (casein vs whey) did not influence children's future risk of developing allergic or autoimmune disease.

55. Members noted that the studies on TIDM were of a high quality and were less affected by bias and potential conflicts of interest than the studies on other allergic or autoimmune outcomes.

56. The Committee did not consider further research in this area to be of a high priority, given the evidence already available.

57. The COT felt that although the majority of data were derived from high risk groups, the conclusions from this report are likely to be applicable to a lower risk population.

58. The review has been published in the peer reviewed literature and has the following citation: http://www.bmj.com/cgi/doi/10.1136/bmj.i974

**COT Statement 2016/01**
**February 2016**

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**APPENDIX 1**

**Glossary of Terms and Abbreviations.**

This list defines the terms and abbreviations that appear in the Statement, as they have been used by the COT.

| | |
|---|---|
| **Allergen** | A substance capable of inducing an allergic immune response |
| | |
| **Allergic rhinoconjunctivitis** | Inflammation of nose and eye membranes caused by an allergic response and resulting in symptoms similar to the common cold |
| | |
| **Allergic sensitisation** | Typically associated with the production of specific IgE antibodies directed against harmless environmental antigens such as pollens, mites, milk, egg or peanut. There may also be an increase in the serum level of total IgE immunoglobulin. . Allergic sensitisation is strongly associated with atopic disease. |
| | |
| **Allergy** | Adverse health effects resulting from stimulation of a specific immune response |
| | |
| **AMSTAR** | Tool for assessing the methodological quality of systematic reviews |
| | |
| **Atopic dermatitis** | An allergic skin disorder, characterised by itching, eczematous skin lesions, and, often, a personal or family history of atopic diseases |
| | |
| **Atopy/atopic** | A genetic predisposition toward mounting IgE antibody responses. Atopy is associated with IgE-mediated allergic disease and, in practice, atopic individuals are commonly defined as those who exhibit sensitisation to two or more allergens |
| | |
| **Autoimmune disease** | A disease in which the immune system attacks healthy cells or tissues in the body leading to chronic disease. |
| | |
| **Eczema** | A group of skin conditions characterised by dry, red, flaky, itchy skin. The most common form of eczema is allergic or atopic eczema (also atopic dermatitis) |
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| **EMBASE** | An abstract and indexing biomedical database, which contains records from 1974 to present |
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| **Extensively** | Cow's milk formula which has undergone hydrolysis to |

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|---|---|
| **hydrolysed formula (eHF)** | ensure no peptides are ≥ 3kD. |
| | |
| **Food allergy** | An adverse reaction to a food or food component that is mediated via immunological mechanisms |
| | |
| **GRADE** | A systematic approach to making judgements about quality of evidence and strength of recommendations |
| | |
| **IgE antibody** | One of five classes of human immunoglobulin. IgE is involved in allergy and anaphylaxis as well as protecting against parasitic infection |
| | |
| **LILACS** | A comprehensive index of scientific and technical literature of Latin America and the Caribbean |
| | |
| **MEDLINE** | The US National Library of Medicine's bibliographic database that contains references to journal articles in the life sciences. It holds citations from 1950 to present |
| | |
| **Partially hydrolysed formula (pHF)** | Cows' milk formula which has undergone hydrolysis to ensure no peptides are ≥ 5kD. |
| | |
| **PROSPERO** | International prospective register of systematic reviews |
| | |
| **PubMed** | PubMed is a service of the US National Library of Medicine that includes over 18 million citations from MEDLINE and other life science journals for biomedical articles back to the 1950s |
| | |
| **Sensitisation** | Immunological priming to an allergen such that the sensitised subject may exhibit an adverse reaction following subsequent encounter with the same allergen |
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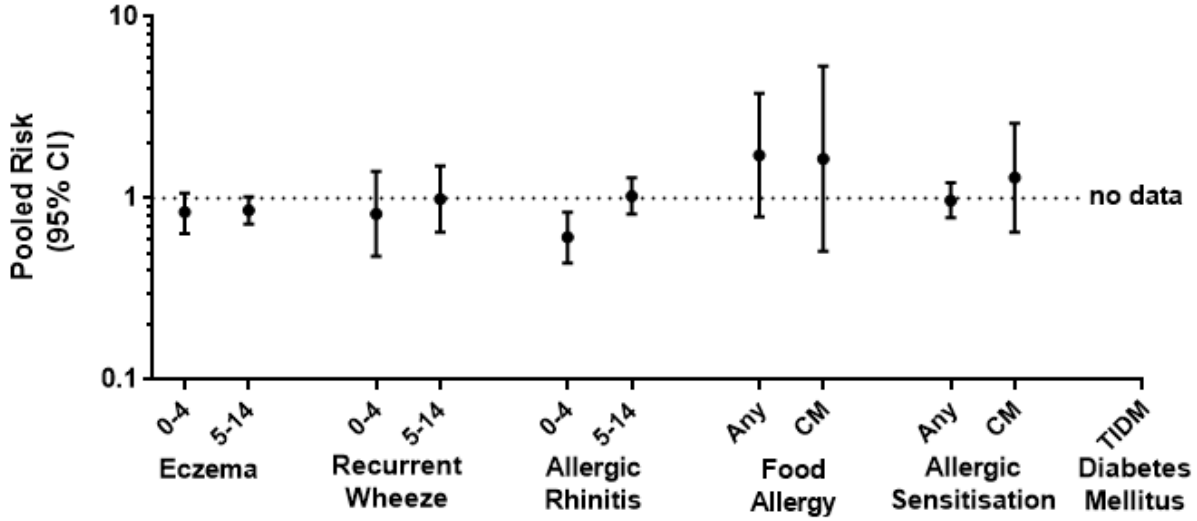
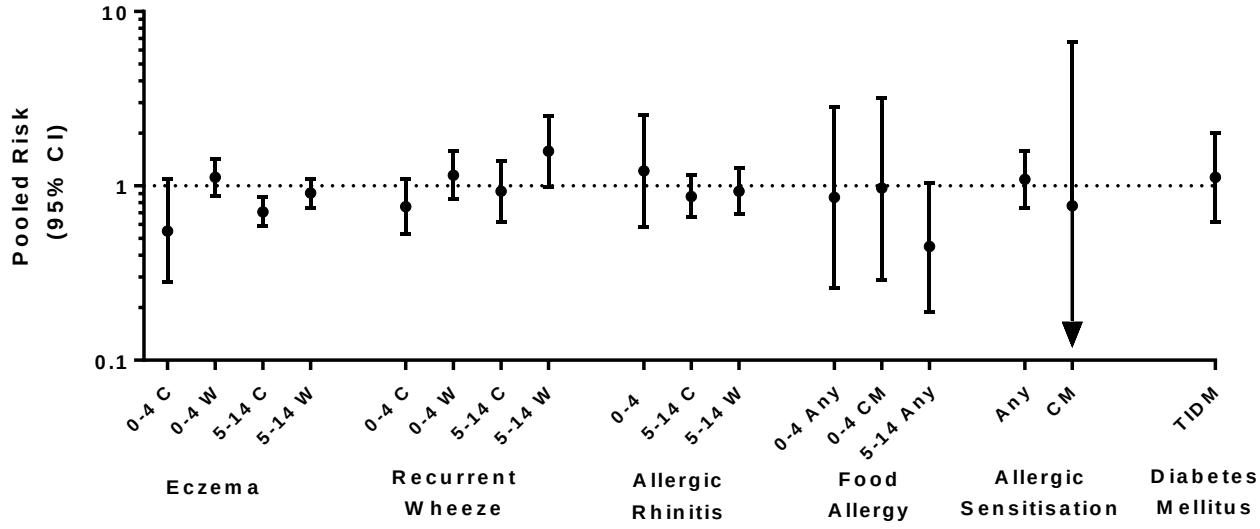
| **Skin prick test (SPT)** | A test to determine whether an individual has an IgE mediated immune response to a specific inhalant or food allergen. |
| | |
| **Type I Diabetes Mellitus** | An autoimmune disease where the immune system attacks pancreatic cells which produce insulin |
| | |
| **Wheeze** | A high-pitched whistling sound during breathing. It occurs when air flows through narrowed breathing tubes. Asthma is commonly defined as recurrent wheeze. |

**APPENDIX 2A:** Summary of treatment effects of hydrolysed formula on different outcome measures. Data shown are mean (95% CI) risk ratios (AR aged 0-4; food allergy; allergic sensitisation; TIDM) or odds ratios (all other outcomes) for partially hydrolysed formula compared with standard cow's milk formula.




**APPENDIX 2B**: Summary of treatment effects of hydrolysed formula on different outcome measures. Data shown are mean (95% CI) risk ratios (AR aged 0-4; food allergy; allergic sensitisation; TIDM) or odds ratios (all other outcomes) for extensively hydrolysed formula compared with standard cow's milk formula.




C = casein-dominant formula; W = whey-dominant formula; Any = sensitisation or allergy to any allergen; CM = sensitisation or allergy to cow's milk. TIDM = Type 1 Diabetes Mellitus.

**APPENDIX 2C**: Summary table of key findings with GRADE of evidence assessment.

| GRADE of evidence assessment | | | | | | | | Summary of findings | |
|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Other considerations** | **Relative risk** | **GRADE of evidence** |
| **Intervention: Partially hydrolysed formula vs standard cows' milk formula**<br>**Outcome: Eczema at age 0-4**<br>**Study design: RCT or qRCT** | | | | | | | | | |
| 12 studies | 11 RCT<br>1 qRCT | Serious<br><br>11 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest | Not serious<br><br>I2=30.3%, study estimates varying from 0.33 to 1.44; subgroup analysis suggests difference by study design or population | No | Not serious<br><br>95% CI for OR do not exclude a clinically important effect, but exclude very large effect sizes and significant harmful effects | No.<br><br>NB Significant risk when pHF and eHF data are combined.<br>Egger's P<0.05 | All RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease | **OR = 0.84**<br>**(0.67, 1.07)** | ⊗⊗⊗○<br>**Moderate** |
| **Intervention: Extensively hydrolysed formula vs standard cows' milk formula**<br>**Outcome: Eczema at age 0-4**<br>**Study design: RCT** | | | | | | | | | |
| 6 studies<br>7 interventions | 6 RCT | Serious<br><br>5 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest | Serious<br><br>I2=74.4% for analysis of casein-eHF; 0% for whey-eHF. Study estimates varying from 0.18 to 1.26 | No | Serious<br><br>95% CI for OR do not exclude large beneficial or harmful effects | Not tested (n<10)<br>NB Significant risk when pHF and eHF data are combined.<br>Egger's P<0.05 | All RCTs were undertaken in populations at high risk of eczema due to family history of allergic disease | **Casein eHF**<br>**OR = 0.55**<br>**(0.28, 1.09)**<br><br>**Whey eHF**<br>**OR = 1.12**<br>**(0.88, 1.42)** | ⊗○○○<br>**Very Low** |
| **Intervention: Partially hydrolysed formula vs standard cows' milk formula**<br>**Outcome: Recurrent wheeze at age 0-4**<br>**Study design: RCT** | | | | | | | | | |
| 5 studies | 5 RCT | Serious<br><br>4 studies with high or unclear overall risk of bias, all studies with high/unclear risk of conflict of interest | No<br><br>I2=15.0%, study estimates varying from 0.29 to 1.20 | No | Not serious<br><br>95% CI for OR do not exclude a clinically important effect, but exclude very large effect sizes | Not tested (n<10)<br>NB Significant risk when pHF and eHF data are combined.<br>Egger's P<0.05 | All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease | **OR = 0.82**<br>**(0.48, 1.41)** | ⊗⊗⊗○<br>**Moderate** |
| **Intervention: Extensively hydrolysed formula vs standard cows' milk formula**<br>**Outcome: Recurrent wheeze at age 0-4**<br>**Study design: RCT** | | | | | | | | | |
| 5 studies<br>6 interventions | 5 RCT | Serious<br><br>5 studies with high or unclear overall risk of bias, all studies with | Serious<br><br>I2=74.4% for analysis of casein-eHF; 0% for whey-eHF. Study | Not serious<br>2 studies used multifaceted interventions | Not serious<br><br>95% CI for OR do not exclude a clinically important effect, but | Not tested (n<10)<br>NB Significant risk when pHF and eHF data are | All RCTs were undertaken in populations at high risk of allergy due to | **Casein eHF**<br>**OR = 0.76**<br>**(0.53, 1.09)**<br><br>**Whey eHF** | ⊗○○○<br>**Very Low** |

| GRADE of evidence assessment | | | | | | | | Summary of findings | |
|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Other considerations** | **Relative risk** | **GRADE of evidence** |
| | | high/unclear risk of conflict of interest | estimates varying from 0.18 to 1.26 | | exclude very large effect sizes | combined. Egger's P<0.05 | family history of allergic disease | **OR = 1.15 (0.84, 1.59)** | |
| **Intervention: Partially hydrolysed formula vs standard cows' milk formula**<br>**Outcome: Allergic sensitisation to cows' milk at any age**<br>**Study design: RCT** | | | | | | | | | |
| 7 studies | 7 RCT | Serious<br><br>6 studies with high or unclear overall risk of bias, and high/unclear risk of conflict of interest | No<br><br>I2=0%, study estimates varying from 0.44 to 9.63 | Not serious<br><br>2 studies used multifaceted interventions | Not serious<br><br>95% CI for RR do not exclude a clinically important effect, but exclude very large effect sizes | Not tested (n<10) | All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease | **RR = 1.30 (0.65, 2.60)** | ⊗⊗⊗○<br>**Moderate** |
| **Intervention: Extensively hydrolysed formula vs standard cows' milk formula**<br>**Outcome: Allergic sensitisation to cows' milk at any age**<br>**Study design: RCT** | | | | | | | | | |
| 3 studies | 3 RCT | Serious<br><br>All studies with high or unclear overall risk of bias, 2 studies with high/unclear risk of conflict of interest | Serious<br><br>I2=77.2%, study estimates varying from 0.08 to 10.13 | Not serious<br><br>1 study used a multifaceted intervention | Serious<br><br>95% CI for RR do not exclude large effect sizes | Not tested (n<10) | All RCTs were undertaken in populations at high risk of allergy due to family history of allergic disease | **RR = 0.77 (0.09, 6.73)** | ⊗○○○<br>**Very Low** |
| **Intervention: Extensively hydrolysed formula vs standard cows' milk formula**<br>**Outcome: Type 1 Diabetes Mellitus at any age**<br>**Study design: RCT** | | | | | | | | | |
| 5 studies | 5 RCT | Not serious<br><br>All studies had low or unclear overall risk of bias, 4 studies had low risk of conflict of interest | Not serious<br><br>I2=25.3%, study estimates varying from 0.62 to 2.02 | No | Not serious<br><br>95% CI for RR do not exclude a clinically important effect, but exclude very large effect sizes | Not tested (n<10) | All RCTs were undertaken in populations at high genetic risk of TIDM, and 4 of 5 studies used casein eHF | **RR = 1.12 (0.62, 2.02)** | ⊗⊗⊗⊗<br>**High** |