COMMITTEE PAPER FOR DISCUSSION

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

BOVINE LACTOFERRIN

Issue
The Committee is invited to consider two EFSA opinions for the above product and advise whether these opinions have addressed its initial concerns relating to the application. The Committee’s conclusions will help to inform the UK position on authorisation of this ingredient.

Background
1. Lactoferrin is an iron-binding glycoprotein of about 80kDa that that is naturally present in milk and other secretions. Bovine lactoferrin is isolated from cow’s milk and is a basic protein (isoelectric point pH 8.7) consisting of a single polypeptide chain of 689 amino acids.

2. In 2008 and 2010 the Committee reviewed two initial opinions for the authorisation of bovine lactoferrin as a novel food ingredient for use in a range of foods including infant formula. These applications were from a company called Biopole SA (Initial assessment carried out by the Belgian Competent Authority, ACNFP/90/P1) and DMV International (Initial assessment carried out by the Dutch Competent Authority, (ACNFP/98/P2).

3. Although both initial opinions generally supported the authorisation of bovine lactoferrin as a novel food ingredient, the Belgian report highlighted uncertainties in relation to the effect of heat processing when bovine lactoferrin is incorporated into infant formula and rejected its use as a preservative. Despite the broadly positive assessments a number of concerns were highlighted by the Committee and the UK subsequently objected to the marketing of both products. The UK objections are attached at Annex A.

4. In light of objections from the UK and other EU Member States, the European Commission asked the European Food Safety Authority (EFSA) to carry out an additional assessment on lactoferrin produced by DMV International. Around the same time a third application, from the Japanese company Morinaga Milk Industry, was submitted to the Irish Competent Authority. As there was an ongoing EFSA evaluation for lactoferrin, the Irish Competent Authority referred the Morinaga application directly to EFSA. The first application from Biopole SA has stalled as the company is understood to have ceased trading.
5. EFSA has recently issued two opinions for lactoferrin which conclude that bovine lactoferrin is safe for the proposed uses and use levels and these are attached at Annex B (DMV International) and Annex C (Morinaga). Members should note that EFSA considered both applications in tandem and its conclusions for DMV’s product similarly apply to Morinaga, which is produced using comparable production processes. Although the ACNFP has not reviewed the Morinaga product (see para 4) the Committee’s earlier concerns will similarly apply as both companies rely on the same set of safety data.

6. The Committee’s concerns and the view of EFSA in each of the areas are summarised in the table below.

<table>
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<tr>
<th>Summary of Committee’s Concerns(^1)</th>
<th>EFSA Response</th>
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<tr>
<td>Lactoferrin may affect iron availability. [raised in 2008 but not in 2010]</td>
<td>This aspect was not considered by the EFSA Panel.</td>
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<td>A single mutagenicity study is insufficient</td>
<td>EFSA regard the Ames test to be sufficient, given the nature of the novel ingredient (see Annex B p15).</td>
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<td>Is the rat is a suitable species for demonstrating the safety of the NI, 60% of bovine lactoferrin survives passage through the stomach. A study to demonstrate that a similar proportion survives intact in the rat would provide the necessary justification</td>
<td>No pilot study provided but EFSA accepted the applicant’s view that rats are a suitable species as they have been shown to absorb native lactoferrin (see Annex B p16).</td>
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<tr>
<td>Sub-chronic Study (1) 12 animals per sex per group is less than is recommended for food additives and related substances. Given that this product naturally raises questions about allergy and immune response it is surprising that the mesenteric lymph node was not sampled and/or weighed.</td>
<td>EFSA regarded the study to be robust and did not comment on the number of animals used (see Annex B p16-17).</td>
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<tr>
<td>Sub-chronic Study (2) The pancreas in males shows an increased incidence of islet fibrosis in all treated groups (4/12, 6/12, 6/12) compared with control (1/12)</td>
<td>EFSA Agreed with study authors that the fibrosis was not a result of lactoferrin and cited a published study which showed a relatively high incidence of spontaneous islet pancreas fibrosis in rats of a similar age to that used in the lactoferrin study (see Annex B p16-17)</td>
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\(^1\) See Annex A for full text
Committee Action Sought

7. The Committee is asked to consider the EFSA opinions and to advise whether it is satisfied that its previous concerns have been adequately resolved.

8. If not, the Committee is asked to highlight any remaining concerns and to advise on the likelihood and severity of adverse effects is bovine lactoferrin were to be authorised as a novel ingredient in the EU.

9. The Committee’s advice will help to inform the UK voting position on this application at the Standing Committee on the Food Chain and Animal Health.

Secretariat
September 2012

Annexes attached:

Annex A: Text of letters to the Commission setting out the ACNFP’s comments on the Belgian and Dutch Competent Authorities’ Initial Opinions.

Annex B: EFSA Opinions on the safety of Lactoferrin (DMV International)

Annex C: EFSA Opinions on the safety of Lactoferrin (Morinaga)
As the UK Competent Authority (CA), the Food Standards Agency has sought advice from the Advisory Committee on Novel Foods and Processes (ACNFP) on the initial assessment report prepared by the Belgian Competent Authority (CA) for the above product.

The UK supports the view of the Belgian CA that additional studies are required in order to support the suitability of the novel ingredient (NI) in infant formula, and we also note that the use for premature infants and children with diarrhoea needs clarification in respect of Directive 1999/21/EC. The UK does not agree that allergy to lactoferrin is a minor concern, and we note that the NI should be labelled in a manner that includes reference to milk, thereby satisfying the regulatory requirements for food allergen labelling.

The levels of intake arising from the proposed uses of bovine lactoferrin appear to be markedly higher than its intake in existing foods and the UK is not convinced that the safety data provided are sufficient. The UK is therefore unable to support the authorisation of this product until we have received additional information on the following:

1. The consumption of the NI may effect iron availability as whilst bovine lactoferrin has the same iron binding capacity as the human variant but, apparently, does not show the same affinity to human intestinal receptors and is significantly more resistant to degradation in the stomach. The UK therefore requests assurance that more dietary iron does not remain associated with intact bovine lactoferrin and thus reduce iron (and other trace element) bioavailability as this could be of importance to individuals with marginal iron status.

2. The toxicological data package includes one negative Ames test which is adequate, although a full description is not provided. However a single mutagenicity study is insufficient and the applicant should provide data from at least three in vitro genotoxicity/mutagenicity assays for reassurance on this aspect of toxicity.

3. The UK questions whether the rat is a suitable species for demonstrating the safety of the NI, 60% of bovine lactoferrin survives passage through the stomach. A study to demonstrate that a similar proportion survives intact in the rat would provide the necessary justification for accepting rat data.

4. The UK notes that the 90-day study, with 12 animals per sex per group is less than is recommended for food additives and related substances. Whilst we note that the design is generally adequate, given that this product naturally raises questions about allergy and immune response it is surprising that the mesenteric lymph node was not sampled and/or weighed. We also note the following observations which were not picked up in the 4-week range-finding study:

   a. The death of a single high-dose animal from malignant lymphoma is surprising in a 90-day study and although a 1985 reference is cited as evidence that such tumours do occur in this strain it would have been more reassuring to see reference to current incidence in the animals form the specific source used.

   b. The pancreas in males shows an increased incidence of islet fibrosis in all treated groups (4/12, 6/12, 6/12) compared with control (1/12). This is not considered to be of concern by the authors but is difficult to ignore since it seems to be present at all doses. Evidence for a higher historic control incidence of such changes might provide some reassurance on this. However it is possible that we are seeing some interaction with normal pancreatic lactoferrin production and if this is the case it would be useful to review additional data on the chronic consequences of this and relevance to consumer exposure levels.
c. Thyroid weight and weight relative to body weight, is reduced in both sexes compared with the controls but only statistically significant in females. This is viewed to be within historical control values but as this occurs in change in both sexes additional confirmation is required.

5. The UK notes the involvement of lactoferrin in various aspects of reproduction and are of the view that this justifies a more thorough investigation of this aspect of toxicity.

(2) DMV International

UK response Sent 11 June 2010

As the UK Competent Authority under regulation (EC) 258/97 on novel foods and novel food ingredients, my Agency has consulted members of the Advisory Committee on Novel Foods and Processes (ACNFP) on this application and on the initial assessment report provided by the Dutch Competent Authority.

The Committee notes that the issues raised in response to the previous application for Bovine lactoferrin in September 2008 also apply to this application.

We are therefore unable to support the authorisation of this product until we have received additional information regarding:

1. Whether the rat is a suitable species for demonstrating the safety of this ingredient, as 60% of bovine lactoferrin survives passage through the stomach. A study to demonstrate that a similar proportion survives intact in the rat would provide the necessary justification for accepting rat data.

2. In the previous application, we noted that the 90-day study with 12 animals per sex per group is less than is recommended for food additives and related substances. The design is generally adequate, but given that this product naturally raises questions about allergy and immune response it is surprising that the mesenteric lymph node was not sampled and/or weighed.

We also noted the following observations which were not picked up in the 4-week range-finding study:

a. The death of a single high-dose animal from malignant lymphoma is surprising in a 90-day study and although a 1985 reference is cited as evidence that such tumours do occur in this strain it would have been more reassuring to see reference to current incidence in the animals form the specific source used.

b. The pancreas in males shows an increased incidence of islet fibrosis in all treated groups (4/12, 6/12, 6/12) compared with control (1/12). This is not considered to be of concern by the authors but is difficult to ignore since it seems to be present at all doses. Evidence for a higher historic control incidence of such changes might provide some reassurance on this. However it is possible that we are seeing some interaction with normal pancreatic lactoferrin production and if this is the case it would be useful to review additional data on the chronic consequences of this and relevance to consumer exposure levels.

c. Thyroid weight and weight relative to body weight, is reduced in both sexes compared with the controls but only statistically significant in females. This is viewed to be within historical control values but as this occurs in change in both sexes additional confirmation was required.

3. Lactoferrin is involved in various aspects of reproduction and this justifies a more thorough investigation of this aspect of toxicity.