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Assessment of probiotics in infant formula and cereal based baby foods containing *Bifidobacterium lactis* Bb12 – update 2014

Opinion of the Panel on biological hazards of the Norwegian Scientific Committee for Food Safety

Assessment of probiotics in infant formula and cereal based baby foods containing *Bifidobacterium lactis* Bb12 – update 2014

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Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has appointed an ad hoc group consisting of both VKM members and external experts to answer the request from the Norwegian Food Safety Authority. The members of the working group are acknowledged for their valuable work on this opinion.

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Assessed by

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Background

The report «Assessment of benefits and risks in probiotics in processed cereal-based baby foods *Bifidobacterium lactis* Bb12» was published by the Norwegian Scientific Committee for Food Safety (VKM) in May 2010.

The Norwegian Food Safety Authority (NFSA) has, based on previous assessments by the VKM, prohibited the sale of certain processed cereal-based foods for infants and young children containing probiotics.

After receiving a notification of three cereal-based foods for infants and young children and one infant formulae supplemented with *Bifidobacterium lactis* (2012), the NFSA sent a request (draft sent in December 2012) to the VKM to assess the safety and suitability of the bacterial strain. The assessment should be based on the latest scientific documentation submitted by the notifier. The notifier has provided documentation concerning the bacterial strain, including a confirmation on the probiotic effect, in addition to documentation on the safety and suitability of the bacterial strain for infants.

The formal request for the assessment of the bacterial strain and the use for infants, was sent from the NFSA to the VKM in December 2013. This assessment is requested on the basis of the requirements of safety and suitability given in the legislation for cereal-based baby foods and infant formulae and in the legislation for foods for particular nutritional needs.

Terms of reference

Translated from Norwegian terms of reference:

- 1) Based on the latest documentation, - is there any new scientific knowledge that gives grounds for reconsideration of the conclusions concerning safety in the report “Assessment of benefits and risks of probiotics in processed cereal-based baby foods *Bifidobacterium lactis* Bb12” or are the conclusions in the report still valid?

The documentation from the notifier also deals with the suitability of the bacterial strain.

- 2) Are infant formulae and cereal-based foods for infants and young children supplemented with *Bifidobacterium lactis* suitable for infants (from birth)?

Information provided by the applicant 2013

The producer has provided updated and new information about the bacterial strain and safety using these products intended for infants and small children.

Assessment of the new information

“Assessment of benefits and risks of probiotics in processed cereal-based baby foods supplemented *Bifidobacterium lactis* Bb12” from 2010 answered a request from the Norwegian Food Safety Authority focusing on the age groups 4-6 months, 6-12 months and 1-3 years. However, the use of infant formula intended for newborns, supplemented with this probiotic, was neither asked by the NFSA nor assessed by VKM.

The notifier of the baby foods intended for infants and small children has provided information on three different cereal-based products intended for age-groups over 4 months and one infant formula intended for newborns, all supplemented with *B. lactis*. In its letter the company concludes that their products supplemented with *B. lactis* do not pose any health and safety risk.

Regarding health effect, we have already mentioned in our assessment (Halvorsen et al. 2010) that: “It is not the mandate of this report to evaluate the health claims related to the products as these health claims are assessed by EFSA.”

Our main conclusions regarding safety were as follows:

“No serious adverse events are reported, but neither has the effect of long-term intake of a single bacterial strain been studied. Furthermore, cereals supplemented with B. lactis Bb12 intended for infants and toddlers have not been studied regarding safety. We are not aware of any in vivo studies explicitly concerning the ability of B. lactis Bb12 to influence gene expression of epithelial cells”.

Furthermore, we were concerned regarding presence of antibiotic resistance gene against tetracycline (*tetW*) in the *B. lactis* Bb12. In the answer to the question from NFSA regarding antibiotic resistance gene in *L. lactis* Bb12, we concluded that:

“Consumption of probiotic microorganism B. lactis Bb12 that harbour gene encoding resistance against tetracycline (tetW) may increase the risk of the transfer of such genes to the resident microbiota and pathogenic bacteria and hence increase development of bacterial resistance. High similarity has been observed between tetW gene in bacteria of human and environment origin and B. lactis Bb12. This suggests the spread of tetracycline resistance gene (tetW) between bacteria of various origins. However, the transfer of tetracycline resistance gene (tetW) to other bacteria as a consequence of consumption of Bb12 has not been studied.”

As we have already mentioned in our assessment (Halvorsen et al. 2010) “It is important to note that the infant’s diet comprises a restricted variety of foods, which often are taken several times a day during a period of life when a stable intestinal flora is not yet established. The establishment of a normal intestinal microbiota takes at least two years and thus the intake of large numbers of probiotic bacteria in monoculture during the first years of life may greatly influence this process.”

According to the “Guideline for evaluation of probiotics in food” (FAO/WHO 2002): “....the onus is on the producer to prove that any given probiotic strain is not a significant risk with regard to transferable antibiotic resistance or other opportunistic virulence properties.”

The *tet(W)* gene in *Bifidobacterium* seems to be integrated in the chromosome and its surrounding regions vary depending on the strain, but very often the gene is flanked by transposase target sequences or genes coding for transposase, an enzyme that catalyzes the movement of DNA fragments between different locations by recognizing specific target sequences, suggesting that, under adequate conditions, the gene could be transferred (Gueimonde et al. 2013). The presence of a tetracycline resistance gene, *tet(W)*, flanked by a putative transposase gene in *B. animalis* subsp. *lactis* was also confirmed in other strains of *Bifidobacterium* than Bb12 (Stahl&Barrangou 2012).

Among the data provided by the notifier, we could not identify any new studies regarding the **above mentioned concerns**.

As already mentioned, our assessment from 2010 did not include probiotic-supplemented infant formula intended for use by newborns. It seems likely that the same concerns as for the cereal-based products will be valid in this age group and possibly of even greater importance.

Among the literature provided by the notifier was also the position paper from 2011 of the ESPGHAN Committee on Nutrition (ESPGHAN 2011). Among their general conclusions are:

- (Conclusion 1): *“For healthy infants, the available scientific data suggest that the administration of currently evaluated probiotic-supplemented formula to healthy infants does not raise safety concerns with regard to growth and adverse effects”*.

But none the less:

- (Conclusion 5): *“In general, there is a lack of data on the long-term effects of the administration of formula supplemented with probiotics. Such data would be of particular importance if the effects persisted after the administration of the probiotics has ceased.”*

And concludes lastly;

- (Conclusion 6): *“Considering the above, the Committee does not recommend the routine use of probiotic-supplemented formula in infants.”*

Our view is in accordance with these conclusions.

Conclusion

The notifier has not provided data answering concerns in our assessment of *B. lactis* Bb12 (Halvorsen et al. 2010). We conclude that our concerns regarding safety have not been resolved and our conclusion from our assessment should be unchanged.

Konklusjon

Dokumentasjon fra melderer har ikke skaffet ny informasjon som kunne svare på bekymringer i VKMs vurdering av *B. lactis* Bb12 (Halvorsen et al. 2010). VKM konkluderer med at bekymringer angående sikkerheten ikke har blitt løst, og konklusjon fra vår vurdering bør være uendret.

Answer to the questions

1. Based on the latest documentation, - is there any new scientific knowledge that gives grounds for reconsideration of the conclusions concerning safety in the report "Assessment of benefits and risks of probiotics in processed cereal-based baby foods *Bifidobacterium lactis* Bb12" or are the conclusions in the report still valid?

Information about the bacterial strain and safety provided by the producer represents no new knowledge that would change the conclusions of the assessment conducted 2010.

2. Are infant formulae and cereal-based foods for infants and young children supplemented with *Bifidobacterium lactis* suitable for infants (from birth)?

The Panel on biological hazards (FG1), has adopted "Assessment of probiotics in cereal based baby foods containing *Bifidobacterium lactis* Bb12 – update 2014" and concluded that there is no new information that could change the conclusion of the assessment prepared in 2010:

"Use of commercially produced baby cereals are common in Norway, starting at an early age, and is particularly important for the establishment of bacterial flora in the gut and the development of the immune system.

According to the applicant a serving (25 grams) porridge powder contains 1×10^9 B. lactis Bb12 in monoculture. In the relevant age groups, the daily porridge intake is often larger than one serving, even in infants under 6 months. The daily exposure of B. lactis Bb12 from the products in question may therefore be $1-2 \times 10^9$ cfu for infants 4-6 months, and even greater in infants over 6 months. If a significant proportion of B. lactis Bb12 survives transport to the small intestine, this will result in a significant monocultur loads often several times a day. Prolonged exposure to B.lactis Bb 12 (1×10^9 cfu per portion) in monoculture for the youngest age groups (those under 12 months) may have previously unknown health effects.

The two lowest age groups, i.e. 4-6 months and 6-12 months, are in the most immature and vulnerable stage in terms of establishment of bacterial flora in the gut and the development of the immune system, and will therefore be the groups with the highest risk of any negative health effects from daily consumption of probiotics."

As the use of the infant formulae and processed cereal-based baby foods supplemented with *Bifidobacterium lactis* Bb12 was not assessed safe for the relevant age groups VKM concludes that the product is not suitable the same groups and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy (FG7) will not assess the issue further.

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