Dairy Goat Co-operative

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19th August 2021

To FSANZ: submissions@foodstandards.gov.au.

SUBMISSION

FSANZ Application A1190 Call for Submissions July 2021

2′-FL in infant formula and other products

Submitter:

[redacted]

Level at which submission authorised: authorised by Regulatory and Technical Liaison Manager

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Information regarding the submitter:

Dairy Goat Co-operative (N.Z.) Ltd, (abbreviated as 'DGC'), is a New Zealand manufacturer, developer and exporter of premium consumer packaged nutritional powders primarily for infants and young children. It is a leading New Zealand exporter, and services over 30 international markets via its marketing partner and joint venture relationships. The markets are located primarily in Asia, Europe and Oceania.

Introduction

The purpose of this application is to extend the current voluntary permissions for use of 2'-FL sourced from *Escherichia coli* K-12 to encompass 2'FL sourced from *Escherichia coli* BL21.

We appreciate the opportunity provided by this Call for Submissions to make comments on the conclusions reached by FSANZ and the proposed drafting variation developed for implementation. DGC is an associate member of the Infant Nutrition Council (INC) and has participated in the preparation of the INC submission. This submission focuses on aspects of particular concern for DGC. A key focus of ours is to constructively contribute to the development of regulations that are evidence-based, balanced and consistent and protect the safety of consumers without being overly prescriptive. We have concerns about some aspects

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of the drafting variation included in the CFS and propose amendments to improve consistency and to better future proof the FSANZ code.

Key points

A. Concerns that remain after the implementation of A1155:

The INC submission to this A1190 CFS spells out the industry concerns that remain after the implementation of A1155, in particular:

A. The labelling restrictions on use of terms like 'human milk oligosaccharides' and abbreviations like "HMOs' which are used in literature and widely used in other markets.
B. The non-permission for voluntary addition of 2'FL and LNnt to Formulated Supplementary Foods for Young Children, and consequently the inability to deliver the potential benefits of HMOs to young children via these products.
C. The negative impact of 1) and 2) above on export trade and the competitiveness of ANZ formula manufacturers in the global market.

We consider it is inconsistent that voluntary addition of inulin-like fructans and galacto-oligosaccharides is permitted to FSFYC but not voluntary addition of approved human identical milk oligosaccharides. Human milk (and other milks including goat milk) contains a complex mix of oligosaccharides. Inulin-like fructans and galacto-oligosaccharides provide some of the beneficial effects provided by HMOs but these ingredients do not confer all the benefits provided by the mix of HMOs in human milk. Until relatively recently HMOs were not commercially available but now production processes have been developed that allow the production of some human milk identical oligosaccharides, such as 2'-FL, it is non-sensical that these ingredients are not permitted in FSFYC.

In addition, DGC is concerned about the provision in 2.9.1-7 (2) which precludes the addition of 2'FL and 2 LNnt to formulas with inulin-like fructans and/or galacto-oligosaccharides which is out of step with regulatory developments in other markets and the research accumulating on formulas supplemented with both these types of oligosaccharides. For example, the review undertaken by Reverri et al, 2018, of clinical experiences of feeding infants formulas with added 2'FL includes coverage of some formulas with 2'FL and galacto-oligosaccharides or inulin-like fructans added

DGC would like reconsideration of these matters.

B. Concerns about the drafting variation for identity and purity provisions

DGC strongly recommends that there is more consideration of the proposed handling of the specifications for 2'FL sourced from *Escherichia coli* K-12 or *Escherichia coli* BL21 in Schedule 3.

Schedule 3 has evolved over time and we observe that there is an inconsistency of approach regarding the parameters covered in the identity and purity specifications included. None of the primary sources of specifications listed under S3-2 (Food Additive

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Specifications, FAO JECFA Monographs, Food chemicals Codex and Commission Regulation (EU) No 231/2012) includes microbiological parameters. Looking at the specifications provided within S3-5 to 42 there is an inconsistent approach to the inclusion of microbiological parameters. Likewise, Schedule 3-4 provides limits for heavy metals for substances not covered by the primary references listed in S3-2 yet heavy metal provisions are also included within some of the specifications.

We would like to reiterate the following points made in our submission to the 2nd CFS on A1155:

> "DGC is aware of the prospect of future applications in this area and is concerned about the impact of handling such future applications on FSANZ proposal workflow. It may be more efficient to amend the specifications listed in Schedule 3 such that they might accommodate at least some future developments. We recommend that the specifications in the EU Novel Foods List for microbial sources of these substances be considered.
>
> Further, in the interest of improving the consistency within the FSANZ Code, we recommend that more scrutiny is placed on the parameters that are appropriate to include in the specifications included in Schedule 3. Suppliers' specifications typically include more parameters than are needed for the purpose of substance identification and purity provisions. We have suggested amendments to the proposed drafting variation below with rationale provided in *blue italics*.

S3—40 Specification for 2′-O-fucosyllactose

For 2′-O-fucosyllactose (2′-FL), the specifications are the following:

(a) chemical name—–α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-D-glucopyranose;

(b) chemical formula—$C_{18}H_{32}O_{15}$;

(c) CAS number—41263-94-9;

(d) description— white to off white powder or agglomerates;

(e) ~~assay (water free) for sum of 2′-FL, lactose, difucosyllactose and fucose—not less than 96.0%;~~ *Not included in specifications for 2'FL from microbiological sources in EU Novel Food List.*

(f) assay (water free) 2′-FL—–not less than ~~94.0~~ 90%; *Lowest minimum applied in specifications for 2'FL from microbial sources in EU Novel Foods List.*

(g) D-lactose—–not more than ~~3.0~~ 5.0% *Highest maximum applied in specifications for 2'FL from microbial sources in EU Novel Foods List.*

(h) L-fucose——not more than ~~1.0~~ 3.0% *Highest maximum applied in specifications for 2’FL from microbial sources in EU Novel Foods lLst.*

(i) difucosyllactose——not more than 1.0%– *Refer to comment relating to (i) and (j) under (j).*

(j) 2’-fucosyl-D-lactulose——not more than 1.0% -*With regard to (i) and (j) we note that the two specifications for 2’FL from microbial sources in the EU Novel Foods List include provisions for different carbohydrates that may be present in small amounts. For the longevity of the specification we suggest that consideration is given to setting an upper limit for other carbohydrates.*

(k) ~~pH (20°C, 5% solution)——3.2 to 5.0~~ *Suggest deletion as not necessary; not included in nucleotide specs in S3, only included in one of the two specifications for 2’FL from microbial sources in EU novel foods list.*

(l) water——not more than ~~5.0~~ 9.0% *Highest maximum applied in specifications for 2’FL from microbial sources in EU Novel Foods List and also applied for LNnT in this list.*

(m) ash, sulphated——not more than 1.5%

(n) ~~acetic acid (as free acid and/or sodium acetate)——not more than 1.0%~~ *Suggest deletion as not necessary; not included in nucleotide specs in S3, only included in one of the two specifications for 2’FL from microbial sources in EU Novel Foods List.*

(o) residual proteins——not more than 0.01%

(p~~) lead——not more than 0.1 mg/kg~~ *Suggest deletion as default heavy metal criteria are covered by Schedule 3-4. We note that a maximum for lead is only included in one of the two specifications for 2’FL from microbiological sources in the EU Novel Foods list.*

(q) microbiological: *We suggest deleting the microbial parameters as these are not included in most of the specifications in Schedule 3. Further they are not consistent with the microbiological parameters for individual nucleotides listed is Schedule 3. If you look at the two sets of microbial criteria in the two specifications for 2’FL from microbial sources in the EU Novel Foods List these are very inconsistent.*

Alternatively, if it is preferred to retain some microbiological criteria then we recommend that these are aligned to the microbiological criteria for powdered infant formula in Schedule 27, Including the use of ‘not detected’ rather than ‘absent.’ The amendments below reflect this approach.

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(i) salmonella——not detected ~~absent~~ in 25 g

(ii) ~~total plate count——not more than 500 cfu/g~~

(iii) ~~enterobacteriaceae—— absent in 10 g~~

(iv) cronobacter (Enterobacter) sakazakii—— not detected absent ~~absent~~ in 10 g

(v) ~~listeria monocytogenes—— absent in 25 g~~

(vi~~)~~ ~~bacillus cereus——not more than 50 cfu/g~~

(vii~~)~~ ~~yeasts ——not more than 10 cfu/g~~

(viii) ~~moulds——not more than 10 cfu/g~~

(ix) residual endotoxins——not more than ~~10~~ 100 EU/mg *We suggest considering this amendment, 100EU/mg being the highest maximum applied in specifications for 2'FL from microbial sources in the EU Novel Foods List. "*

We have now compared the 2'FL specification currently in Schedule 3 for 2'FL sourced from *Escherichia coli* K-12 with the new additional specification proposed in the drafting variation in Annex to this submission for 2'FL sourced from *Escherichia coli* BL21. We note many inconsistencies between the two specifications (see Annex which shows these side-by-side). We propose the following changes:

A. To have only one entry in Schedule 3 for 2'FL from microbial sources which provides a single definition for 2'FLgiven that this compound is chemically and structural identical irrespective of source. We note that the EU takes this approach in its novel food list (EU2017/2470 consolidated to 16.05.2021). It includes one entry for 2'-Fucosyllactose (microbial source) and applies a definition including chemical name, chemical formula, CAS No. and molecular weight. The EU list then provides separate descriptions and purity provisions for the two microbial sources approved for use in specific applications. While the manufacturing processes for the two different sources are different we query whether it is warranted to have separate identity and purity provisions for them (see below).

B. Delete heavy metal parameters. Schedule 3-4 provides limits for heavy metals for substances not covered by the primary references.

C. Delete microbiological parameters based on arguments presented above. The microbiological limits specified for the two different sources are so significantly different this raises questions about the disparity.

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We propose that consideration is given to having just one specification included in Schedule 3 for 2'FL from microbial sources. The following draft specification is suggested:

Specification for 2′- fucosyllactose from microbial sources (from *Escherichia coli* K-12 or *Escherichia coli* BL21)

For 2′-O-fucosyllactose (2′-FL), the specifications are the following:

(a) chemical name——α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-D-glucopyranose;

(b) chemical formula—$C_{18}H_{32}O_{15}$;

(c) CAS number—41263-94-9;

(d) description— white to off white powder or agglomerates; or a colourless to slightly yellow liquid

(e) assay (water free) 2′-FL——not less than 90.0%;

(f) D-lactose——not more than 5.0%

(g) L-fucose——not more than 3.0%

(h) Difucosyllactose——not more than 5.0%

(i) For powder——not more than 9.0% water

(j) For liquid —solids -45% w/v (±) dry matter in water

(k) ash, sulphated——not more than 1.5%

(l) residual proteins——not more than 0.01%

Should microbiological parameters be included, please can any proposed uses of 'absent' be replaced by 'not detected.'

References:

Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods consolidated to 16.05.21. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02017R2470-20210516&from=DE

Reverri et al, 2018. Review of the Clinical Experiences of Feeding Infants Formula Containing the Human Milk Oligosaccharide 2'-Fucosyllactose. Nutrients, Oct 10(100: 1346. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6213476/

Some of the cited papers (all freely available):
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4645963/
https://academic.oup.com/jn/article/146/12/2559/4589986
https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.30.1_supplement.671.4

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ANNEX

Current specification in FSC (to be amended Specification for 2′- fucosyllactose sourced from Escherichia coli K-12 S3—40 Specification for *2′*-O-fucosyllactose

For 2′-O-fucosyllactose (2′-FL), the specifications are the following:

(a) chemical name—–α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-D-glucopyranose;
(b) chemical formula—$C_{18}H_{32}O_{15}$;
(c) CAS number—41263-94-9;
(d) description— white to off white powder or agglomerates;
(e) assay (water free) for sum of 2′-FL, lactose, difucosyllactose and fucose—not less than 96.0%;
(f) assay (water free) 2′-FL—–not less than 94.0%;
(g) D-lactose—–not more than 3.0%
(h) L-fucose—–not more than 1.0%
(i) difucosyllactose—–not more than 1.0%
(j) 2′-fucosyl-D-lactulose—–not more than 1.0%
(k) pH (20°C, 5% solution)—–3.2 to 5.0
(l) water—–not more than 5.0%
(m) ash, sulphated—–not more than 1.5%
(n) acetic acid (as free acid and/or sodium acetate)—–not more than 1.0%
(o) residual proteins—–not more than 0.01%
(p) lead—–not more than 0.1 mg/kg
(q) microbiological:
  (i) *salmonella*—–absent in 25 g
  (ii) total plate count—–not more than 500 cfu/g
  (iii) enterobacteriaceae—–absent in 10 g
  (iv) *cronobacter (Enterobacter) sakazakii*—–absent in 10 g
  (v) *listeria monocytogenes*—–absent in 25 g
  (vi) *bacillus cereus*—–not more than 50 cfu/g
  (vii) yeasts—–not more than 10 cfu/g
  (viii) moulds—–not more than 10 cfu/g
  (ix) residual endotoxins—–not more than 10 EU/mg

Specification proposed to be added: S3—45 Specification for 2′-fucosyllactose sourced from Escherichia coli BL21

For 2′-fucosyllactose (2′-FL) sourced from Escherichia coli BL21, the specifications are the following:

(a) chemical name—α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-Dglucopyranose
(b) chemical formula—C18H32O15
(c) CAS number—41263-94-9
(d) description—either a white to ivory powder, or a colourless to slightly yellow liquid
(e) 2′-FL—not less than 90.0%
(f) D-lactose—not more than 5.0%
(g) L-fucose—not more than 3.0%
(h) 3-fucosyllactose—not more than 5.0%
(i) difucosyllactose—not more than 5.0%
(j) fucosyl-galactose—not more than 3.0%
(k) glucose—not more than 3.0%
(l) galactose—not more than 3.0%
(m) water—not more than 9.0% for powder, not applicable for liquid
(n) solids—45% w/v (± 5%) dry matter in water, not applicable for powder
(o) ash, sulphated—not more than 0.5%
(p) residual proteins—not more than 0.01%
(q) lead—not more than 0.02 mg/kg
(r) arsenic—not more than 0.2 mg/kg
(s) cadmium—not more than 0.1 mg/kg
(t) mercury—not more than 0.5 mg/kg
(u) microbiological:
  (i) salmonella—absent in 100 g for powder, absent in 200 mL for liquid
  (ii) total plate count—not more than 10000 cfu/g for powder, not more than 5000 cfu/g for liquid
  (iii) coliform/enterobacteriaceae—absent in 11 g for powder, absent in 22 mL for liquid
  (iv) cronobacter sakazakii—absent in 100 g for powder, absent in 200 mLfor liquid
  (v) yeast and mould—not more than 100 cfu/g for powder, not more than 50 cfu/g for liquid
  (vi) aflatoxin M1—not more than 0.025 µg/kg
  (vii) endotoxins—not more than 10 EU/mg
  (Viii) GMO detection –not detected