FrieslandCampina Domo: high quality ingredients for infant nutrition

Breast milk is the **best** nutrition for infants.

When breast milk is not or insufficiently available, we want to offer the very best alternative there is: **guaranteed safe** and the **highest quality** possible infant nutrition, because we believe:

Every child deserves to grow up healthy

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Content

- Background on HMO
- Scientific studies
- Application suggestion

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Research progress of 2’-Fucosyllactose in the next generation infant nutrition

Nov 1st 2018 | Beijing | China Nutrition and Health Food Association

Benfeng Sun | Sr.Technical Manager | FrieslandCampina Ingredients

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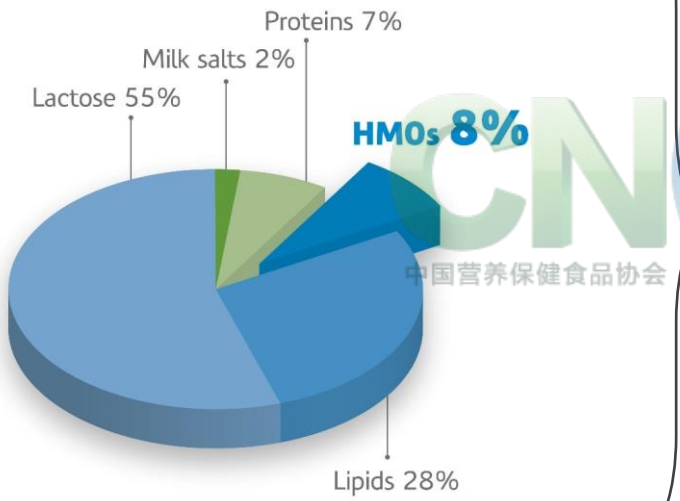
Human milk contains a high concentration of Oligosaccharides (HMOs)

Composition of human milk



HMOs in human milk

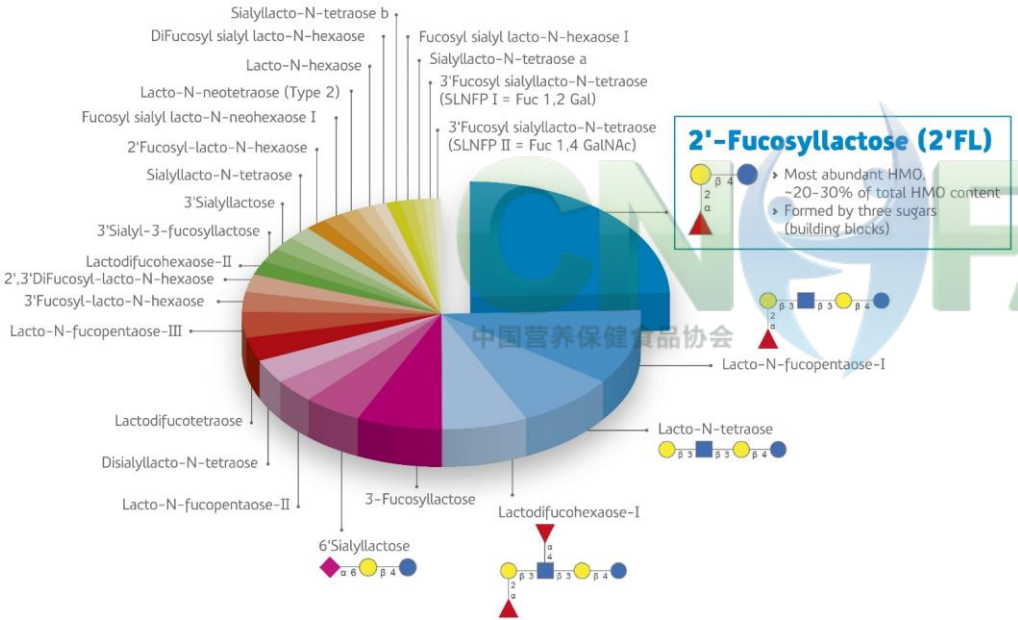
- HMOs are oligosaccharides (complex sugars)[1]
- Third largest component in mother's milk
- Concentration in milk: 10-15 g/l[2]
- Soluble fibers, indigestible by the infant
- Key role in protecting and promoting the health of newborn infants[2]
- Currently absent in infant formula[1]

-> It is common nowadays to supplement infant formula with other prebiotic fibers, such as galacto-oligosaccharides (GOS)

[1]Bode (2012), [2]Bode (2015)

There is a wide variety of HMOs present in human milk

2'-Fucosyllactose is the most abundant HMO



HMO facts

- Currently, >200 different HMOs have been identified in human milk[1]
- 2'-FL is the most abundant HMO in human milk (20-30% of total HMO concentration)[2-9]
- Average 2'-FL concentration in human milk is 2-4 g/L[2-9]
- HMO composition is impacted by:
  - Genetics
  - Lactation stage
  - Environmental factors

[1]German (2008), [2]Bao (2007), [3]Chaturvedi (2001), [4]Kunz (2000), [5]Martin-Sosa (2003), [6]Newburg (2004), [7]Thurl (1996, 2010), [8]Wu (2010), [9]Asakuma (2007)

HMOs in milk depend on genetic background of the mother[1]

There is genetic variety in a number of genes involved in HMO synthesis:

- FUT2 = α1-2 fucosyltransferase
- FUT3 = α1-3/4 fucosyltransferase

Genotype mother	Enzyme missing	Main HMO missing from milk
$Se^+ Le^+$	-	-
$Se^+ Le^-$	FUT3	3-FL, LNFP-II
$Se^- Le^+$	FUT2	2'-FL, LNFP-I
$Se^- Le^-$	FUT2, FUT3	2'-FL, 3-FL, LDFT

Se = Secretor gene
Le = Lewis gene

Secretor vs non-secretor

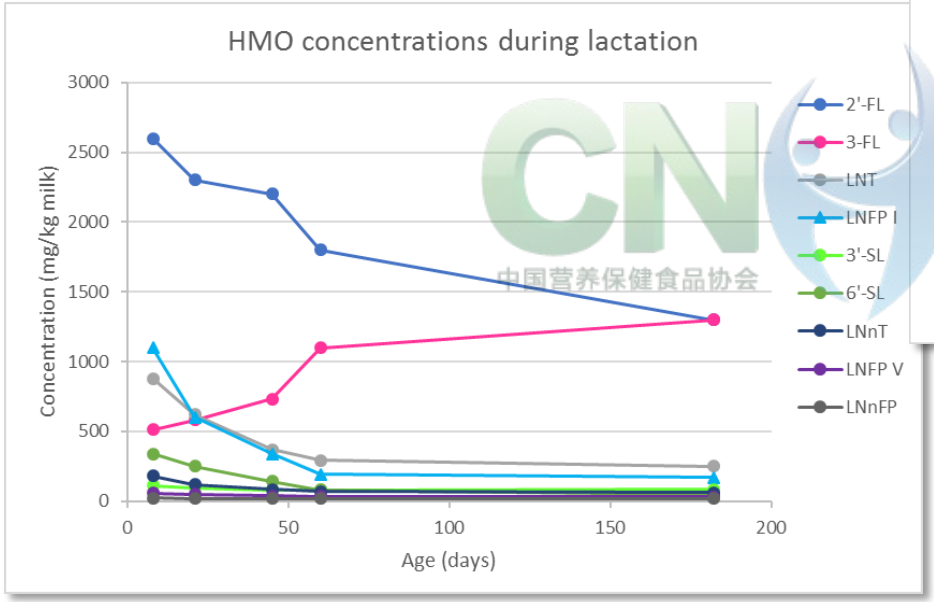
- Worldwide, roughly 80% of the population is secretor
- The % secretor does differ per region, e.g. 100% secretor in Mexico
- For China, the % secretor has been reported to be 78%[2,3]

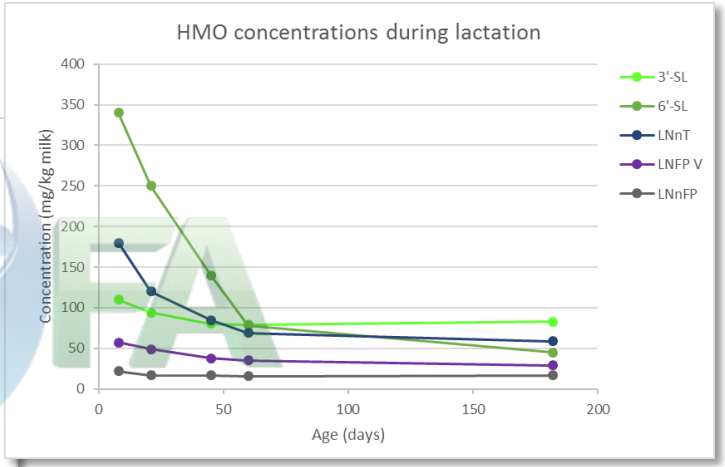
[2]Austin et al., 2016, [3]Guo et al., 2017

[1]Bode & Jantscher-Krenn, 2012

HMO concentrations in milk change during lactation

Maternal Infant Nutrition Growth (MING) study, Beijing, Suzhou and Guangzhou





- Most HMO decrease during lactation
- 3-FL concentration increases during lactation
- 3'-SL, LNFP V and LNnFP remain relatively stable

Austin et al., 2016

HMO key message

HMOs in human milk

- HMOs: Third largest component in mother's milk
- Composition:
  - There are >200 different HMO described in human milk
  - Most abundant HMO: 2'-FL
- Genetic variation determines HMO composition in human milk
- HMO concentrations change during lactation

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Content

- Background on HMO
- **Scientific studies**
- Application suggestion

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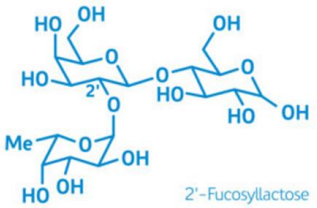
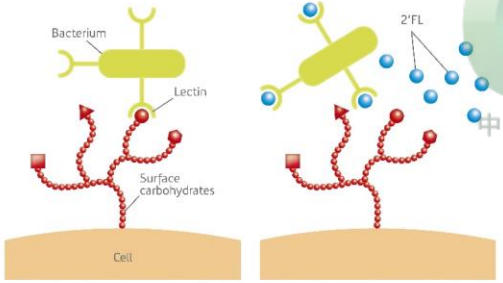
Health benefits described for 2’-FL



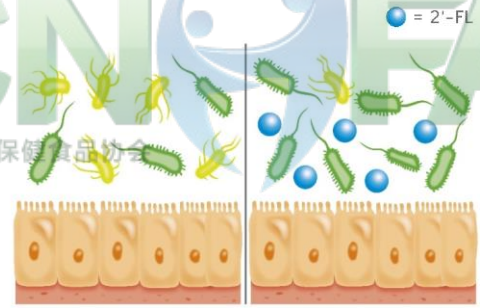
Multiple benefits described for 2’-FL, the most abundant HMO

1 Reducing risk of infections[1,2] (anti-microbial and anti-viral activity)



By serving as a **decoy receptor**, 2’-FL can inhibit binding and infectivity of pathogens

2 Stimulating growth of bifidobacteria[3]



By serving as a substrate, 2’-FL gives bifidobacteria a **competitive advantage for growth** in the gut

3 Other suggested health benefits of 2’-FL

- Reduction of the risk of allergy[4,5]
- Effects on gut maturation / gut barrier[6]
- Anti-inflammatory effects (e.g. NEC ↓)[7]
- Improving memory and cognition[8,9]

[1]Morrow et al., 2004, [2]Weichert et al., 2013, [3]Yu et al., 2013, [4]Castillo-Courtade et al., 2015, [5]Sprenger et al., 2016, [6]Holscher et al., 2014, [7]Autran et al., 2015, [8]Vazquez et al., 2015, [9]Oliveiros et al., 2016

Diarrhea is a leading cause of death among children around the world, especially in the developing world

Percentage of deaths among children under age 5 attributable to diarrhea

WHO: 11% of child (0-5 yrs) mortality is caused by diarrhea

Unicef (2013), Liu (2012)

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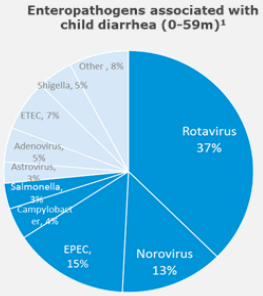
2'-FL helps prevent pathogen binding[1,2]

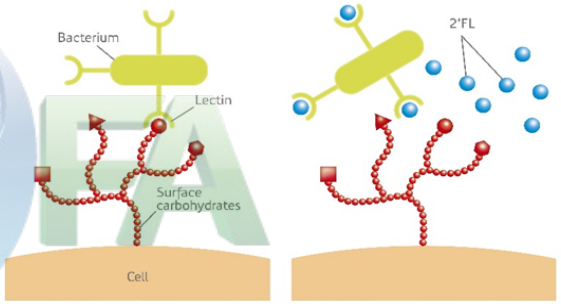
2'FL can reduce binding of pathogens associated with childhood diarrhea[1]

- Norovirus[2]
- Rotavirus[3]
- Enteropathogenic Escherichia coli[4]
- Campylobacter[4,5]
- Salmonella enterica serovar fyris[4]
- Pseudomonas aeruginosa[4]



[1]Lanata (2013), [2]Weichert (2016), [3]Triantis (2015), [4]Weichert (2013)

Mechanism for reducing the risk of infections
(e.g. Norovirus, *Campylobacter*)[1,2]



- 2'-FL is similar to carbohydrate structures on the gut cells of infants[3]
- Pathogens typically attach to these cell-bound structures to infiltrate the gut[3]
- 2'-FL serves as a decoy, thereby **preventing pathogen binding** to the intestinal wall[4]

[1]Morrow (2004), [2]Weichert (2013), [3]Weichert (2016), [4]Bode (2012)

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2'-FL reduces the risk of child diarrhea[1]

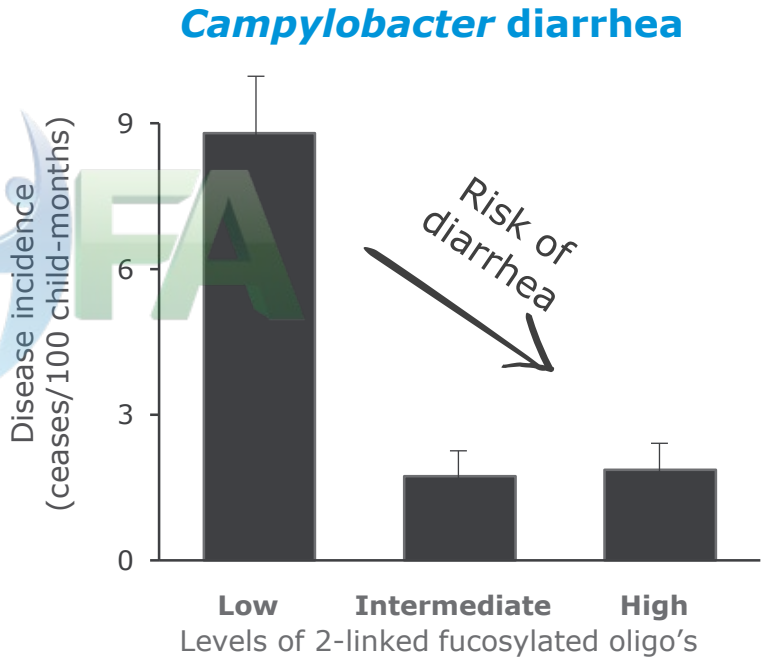
Objective

- Determine the association between maternal milk levels of 2-linked fucosylated oligosaccharides and prevention of diarrhea in Mexican infants (0-2 yrs).

Results

- High levels of 2-linked fucosylated oligosaccharides in human milk (among which 2'-FL) are associated with less diarrhea

2'-FL levels as % of total HMO:
Low: <29%
Intermediate: 29-37%
High: >37%



Morrow et al., 2004

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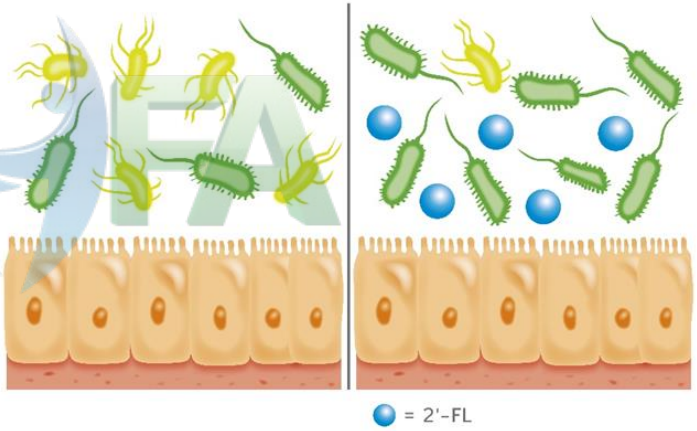
2’-FL stimulates the growth of Bifidobacteria (prebiotic effect)[1,2]

- Breastfed infant microbiota is typically rich in bifidobacteria[3]
- Infants fed breast milk lacking 2’-FL show delayed establishment of bifidobacteria in their gut microbiota[2]
- Beneficial bacteria in the gut metabolize HMO and grow[1]
- Pathogenic bacteria hardly metabolize HMO[1]
- Metabolites from bacterial HMO degradation create an environment that also **benefits the growth of desired bacteria[1]**



[1]Yu (2013), [2]Lewis (2015), [3]Harmsen (2000)

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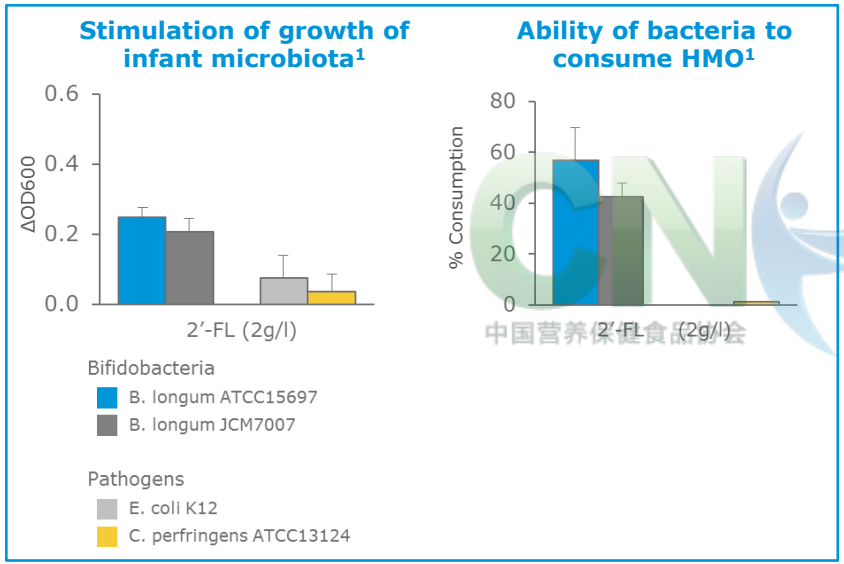
2’-Fucosyllactose stimulates growth of bifidobacteria[1]



In vitro results on bifidogenic effect

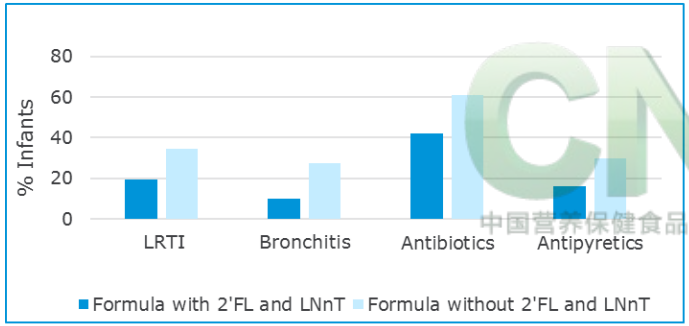
- 2’-FL stimulated the growth of *Bifidobacterium longum*, but not that of the pathogens *E. coli* and *C. perfringens*[1]
- Bifidobacteria utilized 2’-FL, whereas *E. coli* and *C. perfringens* did not[1]

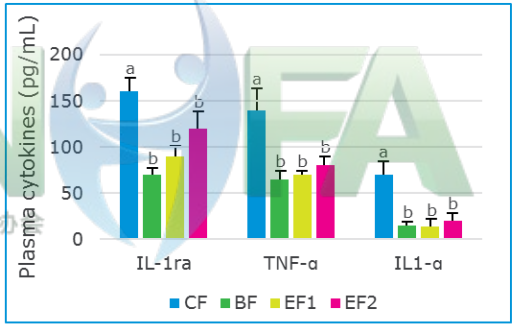
[1]Yu (2013)

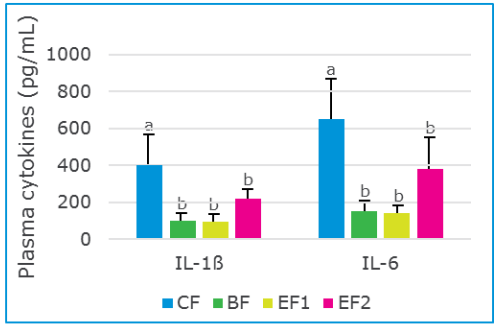
Clinical trial results with 2’-FL

2’-FL is safe and well tolerated

- Clinical trials in infants[1,2] and adults[3] have shown 2’-FL to be safe and well tolerated
- In addition, promising health effects have been found[2,4]







IF + 2’-FL and LNnT[2]:

- ↓ lower respiratory infections
- ↓ medication use

IF + 2’-FL[4]:

- Plasma inflammatory cytokines more closely resemble those found in breastfed infants

[1]Marriage et al., 2015, [2]Puccio et al., 2017, [3]Elison et al., 2016, [4]Goehring et al., 2016

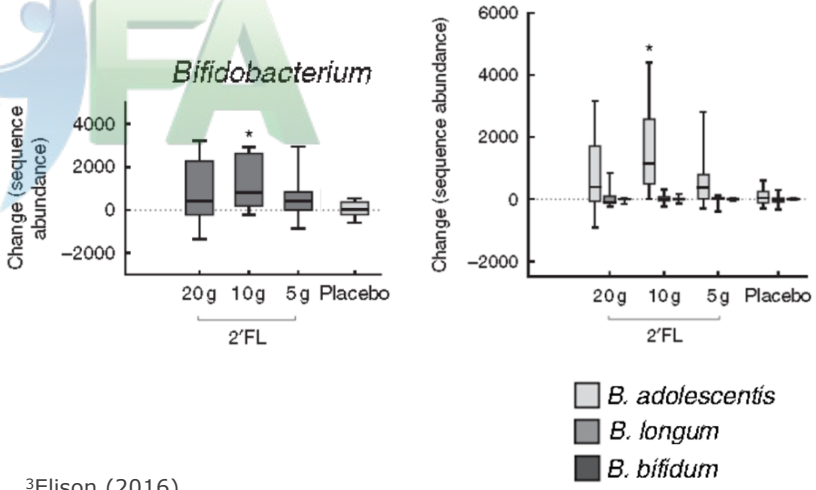
2’-Fucosyllactose stimulates growth of bifidobacteria[1,2]

Clinical results in infants

- 1.0 g/L 2’-FL and 0.5 g/L LNnT supplementation to infant formula shifted the stool microbiota closer to that of breastfed infants[1,2]

Clinical results in adults

- 2’-FL supplementation of adults (5, 10 or 20 g/day) increased *B. adolescentis* in the gut[3]

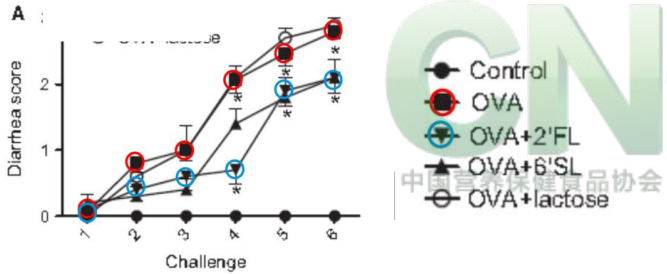


[3]Elison (2016)

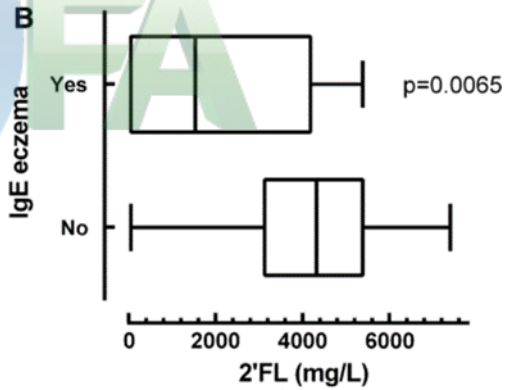
[1]Alliet (2016), [2]Alliet (Espghan, 2018), [3]Elison (2016)

Potential additional health benefits of 2’-FL
Allergy risk reduction

2’-FL reduced food allergy symptoms in a mouse model[1]



FUT2-dependent HMO (e.g. 2’-FL) reduced allergy risk (eczema) in infants at risk[2]



[1]Castillo-Courtade (2015), [2]Sprenger (2016)

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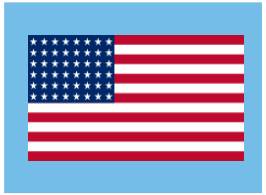
FrieslandCampina is submitting for regulatory approvals in the Infant Formula key markets



- Generally Recognized As Safe (GRAS)–FDA GRN No. 735–max 2.4g/L
  - https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=735
- FDA Notice | GRAS approval in April 2018

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- Novel Foods Application procedure–EUR-Lex-32017R2470-max 1.2g/L
- Approval on 2'-FL dossier October 2017. SE approved December 17

EC confirmation in May 2018

- https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R2470

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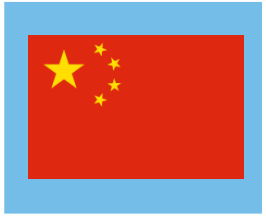


- National Health Committee
- Application of 2'-FL as nutritional fortifier
- Expert panel meetings held; Not decided yet whether link to EU or FDA dossier

Recommended dosage for 2'-FL in infant formula

The average human milk concentration of 2'-FL is 2 to 4 g/L[1-8], slowly declines during lactation to ~1.2 g/L[9]

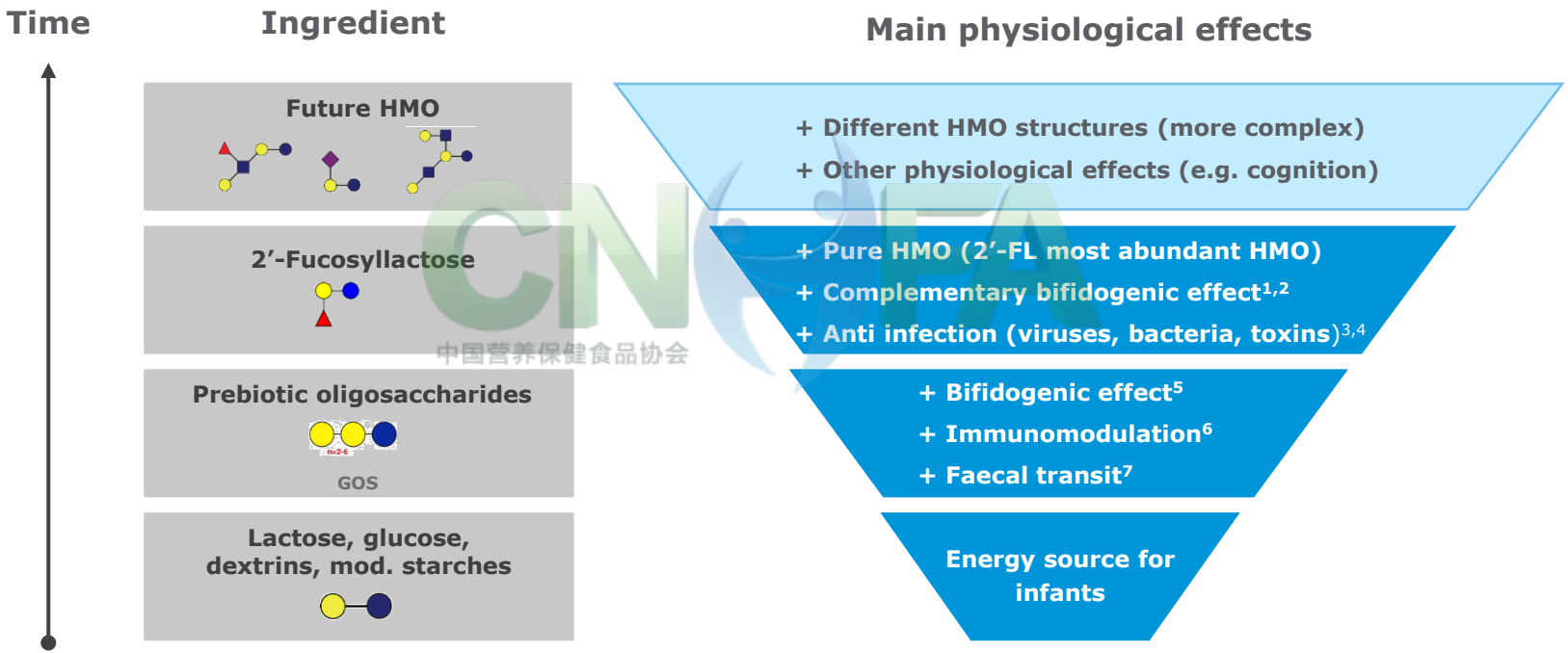
1 g/L's well tolerated and can contribute to reduced respiratory infections and antibiotics use[10-11].Higher than 2 g/L can reduce risk of infection and allergy[12-13].

Currently no evidence for a health benefit of lower levels than 1 g/L. Regulatory approved 2'-FL are max 1.2 g/L in EU[14] and max 2.4 g/L in USA[15]

Based on scientific studies and clinical trials, We recommend to apply a dosage of 2'-FL between 1 and 2 g/L in infant formula.

Reference: [1]Bao (2007), [2]Chaturvedi (2001), [3]Kunz (2000), [4]Martin-Sosa (2003),[5]Newburg (2004), [6]Thurl (1996, 2010), [7]Wu (2010), [8]Asakuma (2007), [9]Austin (2016), [10]Marriage (2015), [11]Puccio(2017), [12]Morrow (2004), [13]Sprenger (2016),[14]EUR-Lex-32017R2470-EN, [15]FDA GRN No. 735.

Achieving the leading position on GOS and HMO



[1]Bode (2009, 2012), [2]Lewis (2015), [3]Morrow (2004), [4]Weichert (2013), [5]Ben (2004), [6]Eiwegger (2010), [7]Sierra (2014)

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Thanks for your attention

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