What can be expected from this technology

Manufacturing and supplying human milk oligosaccharides (HMO*) to contribute to the health and well-being of people around the world

There is a need for milk powder that is similar to breast milk

Q. Do you want a formula that is similar to breast milk*?

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage of Respondents Wanting a Formula Similar to Breast Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU (N=521)</td>
<td>92.5% No, 7.5% Yes</td>
</tr>
</tbody>
</table>

More than 90% of respondents want a formula that is similar to breast milk.

Greater variety of HMOs for larger population

The percentage of formulas containing HMOs is still low.*

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage of Milk Powder Containing HMOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>0%</td>
</tr>
<tr>
<td>2019</td>
<td>6%</td>
</tr>
</tbody>
</table>

Percentage of milk powder containing HMOs makes it available to more people.

Nutrients in breast milk

- Water
- Solid nutrients
- Lipids
- Lactose
- HMOs

The biggest difference between breast milk and formula is HMOs.

We still haven't covered HMOs in breast milk.**

Percentage of commercialized HMOs

- 2FL
- LNnT
- 6SL
- 3SL
- Commercialized 38%

A formula that is closer to breast milk.

* Abbreviation of “Human Milk Oligosaccharides”

* In-house data,
** Percentage accounted for by commercialized HMOs, 2FL and LNnT, out of breast milk HMOs
What can be expected from this technology

Manufacturing and supplying human milk oligosaccharides (HMO*) to contribute to the health and well-being of people around the world

<table>
<thead>
<tr>
<th>HMOs found to be valuable for the health of adults as well</th>
<th>Example of social issues to be solved: dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune stimulation</td>
<td><strong>Dementia</strong>: Approximately 50 million people worldwide suffer from dementia. Ten million people develop dementia every year. One of the major causes of disability and dependency among older people worldwide*.</td>
</tr>
<tr>
<td>Intestinal protection</td>
<td></td>
</tr>
<tr>
<td>Prebiotics</td>
<td></td>
</tr>
<tr>
<td>Maintenance and development of brain function</td>
<td></td>
</tr>
</tbody>
</table>

Recent years have seen the publication of an increasing number of functional studies on HMOs. In particular, the effects of 6SL & 3SL on brain function is attracting attention.

* Abbreviation of "Human Milk Oligosaccharides"
About this technology

Technology overview 1: using innovative biotechnology to establish a process for the mass production of HMO

Challenges of conventional technology

Existing production method: Chemical synthesis
- Expensive
- Complex process

What Kyowa Hakko Bio has made possible

Innovative production method: Fermentation
- Low-cost
- Simple process

Refining

Simple production method

Simple ingredients
- Sugars
- Materials for culture media

HMO-producing bacteria

Mass production

= enables large-scale production
About this technology

Technology overview 2: three types of HMO processes established thus far (2FL, 6SL, 3SL)

Strain Development

2′-fucosyllactose (2FL)-producing bacteria

6′-sialyllactose (6SL)-producing bacteria

3′-sialyllactose (3SL)-producing bacteria

Developing Production Process

Fermentation and purification process appropriate for 2FL

Fermentation and purification process appropriate for 6SL

Fermentation and purification process appropriate for 3SL

2FL product

6SL product

3SL product
Background of this technology (1): Kyowa Hakko Bio’s strain development

- **1956**: Developed the world’s first amino acid fermentation method
- **1990**: Developed biological production process for nucleic acids
- **2000**: World’s first microorganism-based HMO production process developed
- **2003**: *C. glutamicum* genome determined
- **2004**: Dipeptide synthase discovered

Technologies accumulated by Kyowa Hakko Bio

Applications filed for more than 14 HMO process patents

Technology for inducing high-yield production by microorganisms

Metabolic engineering

Technology for inducing the production of new substances by microorganisms

Genetic engineering

* A type of amino acid-producing bacteria
Developing a process suitable for the production of raw materials for products to be consumed by infants, which require high quality similar to pharma-grade products.

Fermentation process

The manufacturing process precisely controls the culture parameters of bacteria, which are sensitive to minute changes in raw materials and temperature, and controls impurities less than 0.1%.

Purification process

Our highly controlled refining process leverages our experience in pharmaceutical manufacturing, and is intended to ensure a steady supply of high-purity products.
Kyowa Hakko Bio is the first company in the world established an industrial-level production system for HMOs*

More than 140 citations since 2000**

We have been pursuing a competitive edge by applying for production process patents
- 2FL production process: employs one proprietary patented technology
- 6SL production process: employs six proprietary patented technologies
- 3SL production process: employs six proprietary patented technologies

6SL and 3SL are not yet supplied at industrial level

** Google Scholar
Future possibilities

Bringing more varieties of HMOs and their health value to the world

The presence of as many as 250 different HMOs has been reported in breast milk. Only two types, however, are commercially available in the world today.

We are researching production methods for more types of HMO than just the ones whose commercialization has been scheduled (2FL, 6SL and 3SL).

Bringing formula that resembles breast milk more closely to babies around the world.

Bringing the health value of breast milk to adults through health foods and beverages.