Superior
Health Council

FSMPs CONTAINING HUMAN MILK

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Federal Public Service Health, Food Chain Safety and Environment

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Superior Health Council

ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9751

FSMPs containing human milk

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides an expert opinion on FSMPs containing human milk.

This version was validated by the Board on
4 October 2023[1]

I INTRODUCTION AND ISSUE

FSMPs (*Food for Special Medical Purposes*) are notified to the FPS Public Health, Food Chain Safety and Environment, DG *Animals, Plants and Food* (DGAPF).

FSMPs are classified in the following three categories:

a) nutritionally complete foods with a standard nutrient formulation which, used in accordance with the manufacturer's instructions, may constitute the sole source of nourishment for the persons for whom they are intended;
b) nutritionally complete foods with a nutrient-adapted formulation specific for a disease, disorder or state of health which, used in accordance with the manufacturer's instructions, may constitute the sole source of nourishment for the persons for whom they are intended;
c) nutritionally incomplete foods with a standard formulation or a nutrient-adapted formulation specific for a disease, disorder or state of health which are not suitable to be used as the sole source of nourishment.

The DGAPF has received several reports of FSMPs containing human milk as an ingredient. The products are intended for (very) low-birth-weight preterm babies (preterm babies under 1250 g) as a supplement to or fortifier of the mother's own milk.

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

For the DGAPF, the formulation, presentation and intended use of these products raise many questions, on which the Superior Health Council (SHC) is asked to give its opinion:

- Is the safety of these products sufficiently guaranteed, given the manufacturing process and the analyses carried out?
- What microbiological risks are not covered by the manufacturing process?
- What are the health risks for the target group associated with variations in formulation due to the fact that the formulation of human milk develops according to the age of the child? Could standardised fortification prove insufficient to cover the nutritional needs of the target group?
- What are the health risks for the target group associated with a nutritional formulation that is inadequate for their needs?
- Does this product offer added value compared with other products on the market (infant milk for preterm babies classified as an FSMP)?
- Do the above products comply with the definition of an FSMP (Article 2.2(g) of Regulation (EU) No 609/2013)?
- How can milk traceability be ensured?
- Is there a risk that women who supply human milk to companies will be exploited?
- Given that human milk is not covered by the report on human tissue banks, are there any ethical constraints on the marketing of these human milk-based products?
- Could the marketing of these products have an impact on milk banks?
- Is it necessary to ban the use of human milk as a food ingredient?

II CONCLUSION

After careful study of the scientific literature and the files made available to it, the SHC does not support the marketing of FSMPs containing human milk for the following reasons:

1- Remunerating the "donation" of human milk (HM) risks putting the well-being of the breastfed child in competition with the socio-economic needs of the family.

2- Placing a human-milk substitute on the market could discourage mothers of preterm babies from actively pumping their milk to meet their child's needs. Likewise, it risks reducing HM donations to the breast milk collecting centres of neonatal units.

3- Placing a liquid fortifier on the market that partially replaces the daily volume of mother's own milk by 10–50% can only be a negative interference in the potential benefits of mother's own raw milk for the preterm baby.

4- In the case of an exclusive HM diet for preterm babies, recent studies do not show any benefit from fortification using HM-based liquid fortifiers, compared with the use of CM-based fortifiers. No positive effect has been demonstrated on the incidence of enterocolitis, late-onset neonatal infection, bronchopulmonary dysplasia, retinopathy or growth.

5- No studies have shown that the technological processes used to sterilise, concentrate and prepare both notified fortifiers and substitutes of human milk do not alter the bioavailability of nutrients, in particular with regard to the absorption of fats and minerals.

6- No satisfactory clinical study has demonstrated the good clinical and metabolic tolerance of either fortifiers or substitutes of human milk.

7- The use of FSMPs containing HM has not been shown to meet the increased needs of preterm babies as defined in the latest ESPGHAN recommendations.

8- In view of the lack of benefit in terms of both mortality and morbidity, and on the contrary the financial burden involved in using FSMPs containing human milk, it is impossible to envisage any advantage either for NIC departments or for institutions.

Keywords and MeSH *descriptor terms*[2]

Mesh terms*	Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Diet, Food, and Nutrition	Diet, Food, Nutrition	Voeding	Alimentation, Nutrition	Diät, Lebensmittel, Ernährung
Food, Specialized	Specialized food	Bijzondere voeding	Alimentation particulière	Spezialisierte Lebensmittel
Food safety	Food safety	Voedselveiligheid	Innocuité alimentaire	Lebensmittelsicherheit
Nutritional requirements	Nutritional requirements	Voedingsbehoeften	Besoins nutritionnels	Ernährungsanforderungen
Nutrition policy	Nutrition policy	Voedingsbeleid	Politique nutritionnelle	Ernährungspolitik
Legislation, Food	Legislation, Food	Wetgeving, voedsel	Législation, nutrition	Gesetzgebung
Premature birth	Premature birth	Premature geboorte of vroeggeboorte	Naissance prématurée	Frühzeitige Geburt
Human milk	Human milk	Moedermelk	Lait maternel	Muttermilch
Infant, newborn	Baby	Zuigeling	Nourrisson	Baby
Infant, premature	Preterm baby	Premature baby	Prématuré	Frühgeborenes Baby
Risk	Risks	Risico's	Risques	Risiken
Microbiology, risk	Microbiological risks	Microbiologische risisco's	Risques microbiologiques	Mikrobiologische Risiken
Ethics	Ethics	Ethiek	Ethique	Ethik

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.

III METHODOLOGY

After analysing the request, the Board and the Chair of the area NHFS (Nutrition and Health, including Food Safety) identified the necessary fields of expertise.

The assessment of the file was entrusted to the SHC NHFS permanent working group, in which the experts listed in the table under section VI were represented. The experts in this group filled out a general and ad hoc declaration of interests, and the Committee on Deontology assessed the risk of potential conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.
Both the Belgian Association of Neonatology (BVN/GBN) and the Federal Breastfeeding Committee (CFAM/FBVC) were heard.

Once the advisory report was endorsed by the NHFS permanent working group, it was ultimately validated by the Board.

[2] The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

IV ELABORATION AND ARGUMENTATION

List of abbreviations used

BPD	Bronchopulmonary dysplasia
GBN/BVN	*Belgische Vereniging voor Neonatologie* / *Groupement Belge de Néonatalogie* - Belgian Association of Neonatology
CFAM/FBVC	*Comité Fédéral de l'allaitement maternel* / *Federaal Borstvoedingscomité* - Federal Breastfeeding Committee
CI	Confidence Interval
CM	Cow's milk
DGAPF	DG Animals, Plants and Food
E	Energy
EN	Enteral Nutrition
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
FPS HFCSE	Federal Public Service for Health, Food Chain Safety, Environment
FSMP	Food for Special Medical Purposes
GA	Gestational age
HM	Human milk
LOS	Late-onset sepsis
NEC	Necrotising Enterocolitis
NHFS	Nutrition and Health, including Food Safety
NIC	Neonatal Intensive Care
RR	Risk Ratio
SHC	Superior Health Council
TPN	Total Parenteral Nutrition
UNICEF	United Nations Children's Fund
WHO	World Health Organization

1 Introduction

Human milk is the exclusive food of choice for all newborns.
For preterm babies, human milk is also the "gold standard", even if its formulation cannot meet the increased nutritional requirements of very premature infants. For preterm babies, their mother's own raw milk is the first choice for its high nutritional value, anti-infectious properties, etc.

In the absence of the mother's own milk, donated milk is the second choice, and needs to be checked for bacteriological and virological quality, and the absence of contaminants, drugs, medicines, etc. It is systematically pasteurised, which partially reduces both its nutritional and anti-infectious value.

Furthermore, the formulation of human milk varies greatly both between and within individuals, over time, depending on the duration of lactation, or during the same feed or extraction, which has led to the development of individual fortification techniques to promote growth.

Compared with mother's milk, cow's milk-based preterm milk significantly increases mortality and morbidity in preterm babies of low gestational age (GA).

Based on this data, neonatology departments have promoted breastfeeding and milk donation, as well as the development of in-house breast milk collecting centres.

The concept of industrialising mother's milk has been developed in the United States, by collecting surplus mother's milk from breastfeeding mothers in return for payment, and concentrating and processing it to make either liquid fortifiers or fortified substitutes for human milk, adapted to the nutritional requirements of very preterm babies. In the course of these developments, *Prolacta Bioscience* has filed no fewer than 12 patents:

- High fat human milk products: Patent number: 11122813 & 11419342
- Methods for obtaining sterile milk and composition thereof: Publication number: 20220232844
- Human milk products useful in pre- and post-operative care: Patent number: 11344041
- Microfiltration of human milk to reduce bacterial contamination: Patent number: 10506818 10820604
- Human milk permeate compositions and methods of making and using same: Patent number: 8927027
- Adulteration testing of human milk: Publication number: 20140272936
- Methods for testing milk: Patent number: RE48240 & 8628921
- Compositions of human lipids and methods of making and using same: Patent number: 8821878
- Nutritional compositions containing human milk oligosaccharides and method for using the same: Publication number: 20130059815
- Compositions of human lipids and methods of making and using same: Patent number: 8377445

- Method of producing nutritional products from human milk tissue and compositions thereof Patent number: 7914822
- Method for collecting, testing and distributing milk Publication number: 20070098863

These fortifiers and substitutes for HM meet the definition of an FSMP.

- For the Humavant HM substitute:
  "nutritionally complete foods with a standard nutrient formulation which, used in accordance with the manufacturer's instructions, may constitute the sole source of nourishment for the persons for whom they are intended"

- For the Humavant R24, R26, R28 substitutes:
  "nutritionally complete foods with a nutrient-adapted formulation specific for a disease, disorder or state of health which, used in accordance with the manufacturer's instructions, may constitute the sole source of nourishment for the persons for whom they are intended"

- For the Humavant +4, +6, +8, +10, CR fortifiers:
  "nutritionally incomplete foods with a standard formulation or a nutrient-adapted formulation specific for a disease, disorder or state of health which are not suitable to be used as the sole source of nourishment"

2 Formulations of the FSMPs

2.1 Substitutes

Table 1. Macronutrient and electrolyte formulation of HM Humavant/100 ml substitutes

	H-HM	H - RTF 24	H - RTF 26	H - RTF 28	H - RTF 24	H - RTF 26	H - RTF 28
/100 ml		LMF/Prêt à l'emploi			LMF / prêt à l'emploi NL/BE		
E (kcal)	72	85	92	99	82	89	97
Fats (g)	4,1	4,7	5,4	6,0	4,5	5,1	5,8
Carbohydrates (g)	7,6	8,2	8,2	8,1	8,1	8,1	8,3
Proteins (g)	1,0	2,4	2,7	2,9	2,4	2,6	2,9
Na (mg)	8,9	58,6	61,4	66,2	56	60,7	64,8
Cl (mg)	29,5	77,1	77,1	77,1	64,3	68,3	75,5
K (mg)	42,9	88,5	91,8	99,9	83,2	90,1	98,1
Ca (mg)	26,2	126	136	146	123,8	134,3	144,9
P (mg)	13,0	67,5	72 ,8	79,2	66,8	71,7	78,9
Mg (mg)	3,1	7,1	7,7	8,4	7,1	7,7	8,4
Zn (µg)	130	800	800	900	750	820	910
Cu (µg)	20,4	85	82	93	79	80	87

The first H-HM substitute is a full-term HM substitute to be used to replace donated milk when the mother's own milk is insufficient, thus avoiding the use of cow's milk-based (CM) formula. Its nutrient content is very low in protein, sodium and minerals, requiring immediate fortification.

The other three substitutes have a theoretically more appropriate formulation, better suited to the needs of preterm babies. However, nutrient bioavailability has not been the subject of

clinical studies, and may have been altered in relation to fresh HM as a result of technical manipulation (e.g. via lipase or amylase activity). It is well documented that pasteurisation alone can alter the bioavailability of nutrients. In addition, the question arises as to which quantitative formulation is stated on these products, taking into account the great variability in the formulation of human milk. This information is not available in the documents submitted.

2.2 **Fortifiers**

Table 2. Macronutrient and electrolyte formulation of Humavant/100 ml fortifiers

	H+4 10ml *	H+4 20ml **NL+BE**	H+6 15ml *	H+6 30ml **NL+BE**	H+8 40ml *	H+8 40ml **NL+BE**	H+10 50ml	H+10 50ml **NL+BE**	H-CR 10ml
/100 ml	Fortifiant/à mélanger avec du lait maternel (*quantités fixées)								
E (kcal)	147	144	146	144	144	144	143	144	262
Fats (g)	9,5	9,3	9,7	9,3	9,5	9,3	9,4	9,3	25,7
Carbohydrates (g)	9,5	8,9	9,0	8,9	8,5	8,9	8,2	8,9	6,9
Proteins (g)	6,0	5,9	6,0	5,9	6;0	5,9	6,0	5,9	0,8
Na (mg)	231	179,3	160	131,3	135	110	134	93,3	6,3
Cl (mg)	298	112,2	213	102	176	91,8	193	81,6	/
K (mg)	263	246,2	192	189	156	155,7	179	135,6	29
Ca (mg)	519	474,2	358	343,6	276	275,9	284	221,2	61,9
P (mg)	276	265,5	192	189,5	147	143,2	151	120,7	19,6
Mg (mg)	29,5	29,5	22,3	22	16,8	16,5	17,4	13,8	2,8
Zn (mg)	6,0	3,2	4,0	2,3	3,3	1,9	3,2	1,6	0,3
Cu (µg)	440	311	290	245	230	184	250	158	28,1

There are four complete fortifiers (HM+4,+6,+8,+10) plus a calorific fortifier composed mainly of HM lipids (H-CR). These liquid fortifiers partly replace mother's own milk: 10 or 20 ml for H+4, 15 or 30 ml for H+6, 40 ml for H+8 and 50 ml for H+10. These substitution volumes are not insignificant in view of the beneficial effects of the mother's own milk, which are directly proportional to the volume of milk administered.

The macronutrient formulation of these fortifiers is very similar. However, they differ greatly in terms of their electrolyte and mineral content, as well as Cu and Zn. The adequacy of formulations and the bioavailability of nutrients has not been specifically assessed in clinical studies, or has only been specifically assessed to a limited extent, and the file makes no mention of this.

The mineral formulation of these fortifiers differs from the limits imposed for FSMPs, both for electrolytes and minerals, assuming compliance with the strict formulation of these products. Nonetheless, it is important to remember that these liquid fortifiers are not intended for use on their own, but must be used in conjunction with human milk. In this sense, the formulations should be re-assessed taking into account the proportion of HM.

3 Presentation of FSMPs

All these products are presented in liquid form, frozen, and must be stored at a temperature below -20°C until use. After gentle thawing without heating, and homogenisation without shaking, these products can be stored in the refrigerator for up to 48 hours.

Finally, due to the need to fortify HM and given their liquid form, the use of Humavant products can only reduce the proportion of raw or pasteurised mother's own milk in the diet of preterm babies.

4 Claims and scientific data

4.1 Scientific literature

In support of the use of Humavant products, *Prolacta Bioscience* presents nine scientific articles suggesting the benefits of an exclusive human milk diet, excluding all animal products. It should be noted that these articles are a long way from representing all the data published, which is particularly regrettable and merits significant comment.

They suggest that an exclusive human milk diet using Humavant products not only reduces mortality and morbidity in very low-birth-weight preterm babies: necrotising enterocolitis, late-onset neonatal sepsis, bronchopulmonary dysplasia, retinopathy, etc., but also improves growth. Unfortunately, on analysis, these data have no real solid scientific basis.

The first study, by Sullivan et al. (2010), suggested a highly significant reduction in the incidence of necrotising enterocolitis in preterm babies weighing <1250 g receiving exclusively mother's own milk fortified with an HM-based fortifier, compared to those receiving HM fortified with a cow's milk-based fortifier or preterm milk (8/138 vs. 11/69; p=0.02). However, no significant differences were observed for other parameters: late-onset neonatal sepsis, bronchopulmonary dysplasia, retinopathy, duration of parenteral nutrition or growth.

The second study, by Cristofalo et al. (2013), was carried out in preterm babies weighing <1250 g whose mothers did not wish to breastfeed, and who were assigned randomly to receive either pasteurised HM fortified with an HM-based fortifier (HUM n=29), or a CM-based preterm milk (BOV n=24). In this study, only the incidence of enterocolitis (1/29 vs. 5/24; p=0.08) and the duration of parenteral nutrition over the entire study (27d vs. 36d; p=0.036) were significant and in favour of an exclusive HM diet.

The third study, by Abrams et al. (2014) reports a post hoc analysis of the first two studies. As mentioned above, these studies do not specifically assess the benefit of an HM-based fortifier vs. a CM-based fortifier in preterm babies receiving an exclusively HM-based diet, since they include in the reference group preterm babies receiving *exclusively* or *partly* preterm milk. Further analysis of the proposed results shows that if the population is divided into two groups, namely, according to the percentage of the diet received as milk formula (<10%, n=182 vs ≥10% n=78), both the duration of parenteral nutrition (p=0.02) and the incidence of late-onset neonatal sepsis (p=0.0001) or enterocolitis (6% vs 18%; p=0.001) were significantly lower in preterm babies receiving less than 10% of their diet as formula.

These results run counter to the initial hypothesis suggesting a major benefit from HM-based fortifier. However, they confirm the numerous previous studies demonstrating the protective effect of HM, and more specifically of mother's own milk, on the morbidity of preterm babies, and on the incidence of enterocolitis and late-onset neonatal sepsis in particular. Thus, this study in no way argues for a deleterious effect of the use of a fortifier containing hydrolysed or non-hydrolysed CM proteins in preterm babies receiving a diet excluding any preterm formula containing cow's milk proteins.

A fourth study, Ghandehari et al. (2012), looks at the duration of parenteral nutrition by re-analysing data from previous studies from a particular statistical angle. It actually analyses "the probability or likelihood of needing TPN on any given day rather than the number of days on TPN." It suggests that this probability would have been 11% to 14% higher in the group given CM protein-based fortifiers or formula. This notion of "likelihood of use" is highly speculative, and would seem to include the days of parenteral nutrition required to treat enterocolitis.

A fifth multi-centre observational study, Hair et al. (2016), compares two cohorts of preterm babies weighing <1250 g born before and after the introduction of Humavant products, i.e. receiving a diet based partly on cow's milk (BOV) or exclusively on HM (HUM). A total of 1587 infants were included in the study. At the start of the study, the two groups were comparable. This cohort study suggests a significant reduction in mortality (17.2% vs. 13.6%; p=0.04), enterocolitis (16.7% vs. 6.9%; p <0.00001), late-onset neonatal sepsis (30.3% vs. 19.0%; p <0.00001), retinopathy (9% vs. 5.2%; p=0.003) and BPD (56.3% vs. 47.7%; p=0.0015) in preterm babies receiving an exclusive HM-based diet.
As mentioned above, this study does not specifically investigate the benefits of Humavant fortifiers versus hydrolysed or non-hydrolysed CM protein-based fortifiers, since it includes infants receiving CM-based formula in the CM group. This is a successive cohort study which does not exclude a bias resulting from improvements in care practices between the two periods. However, this study clearly demonstrates the benefits of promoting an exclusive mother's own milk or donated milk diet.

4.2 **Deleterious effects of a diet based on formula containing CM**

Numerous studies, meta-analyses and systematic reviews have documented the positive effects of a diet of mother's own milk or donated milk, all of which demonstrate the disadvantages of a diet containing CM-based preterm milk formula. The three most recent have been selected.

Table 3. Three systematic reviews demonstrating the disadvantages of a diet containing CM-based preterm milk formula.

Quigley M Cochrane Database Syst Rev. 2018 premature or low birth weight				
DM vs Formula	DHM	Formula	RR (IC)	p=
Regime exclusif	3/190 (1,56 %)	13/170 (7,65 %)	4,62 (1,47-14,56)	0,009
Suppl to OMM	27/612 (4,41 %)	44/633 (6,95 %)	1,56 (0,98-2,47)	0,061
Total	30/802 (3,74 %)	57/803 (7,1 %)	1,87 (1,23-2,85)	0,004
Miller Systematic Review 2018 premature ≤28 sem and/or average birth weight ≤ 1500g				
Excl HM vs PTF	6/555 (1,08 %)	34/438 (7,76 %)	0,22 (0,09-0,54)	0,0008
Any HM vs Excl PTF	102/2938 (3,47 %)	62/845 (6,15 %)	0,51 (0,35-0,76)	0,0009
High vs low dose HM^{rt}	32/583 (5,49 %)	50/533 (9,38 %)	0,54 (0,28-1,02)	0,06
High vs low dose HM^{Obs}	204/4242 (4,81 %)	363/4536 (8,0 %)	0,53 (0,42-0,67)	0,00001
Altobelli Systematic review 2020 Prematurés				
	n=	RR (IC)		p=
High vs low dose HM	2453	0,51 (0,31 - 0,85)		0,010
HM vs Mixed Feeding	1057	0,74 (0,59 – 0,94)		0,014
HM vs PTF obsv	6405	0,45 (0,32 - 0,62)		0,0000
HM vs PTF RT	1626	0,41 (0,42 - 0,93)		0,020
PTF vs Mixed	1672	1,37(1,13 - 1,65)		0,001

The Cochrane review by Quigley et al. (2018) clearly demonstrated the increased risk of enterocolitis in infants receiving exclusively cow's milk-based formula (see table above).

The meta-analysis by Miller & al. (2018) shows the beneficial effect of HM on the incidence of enterocolitis. It also shows the potential benefit in terms of late-onset neonatal sepsis and retinopathy. For enterocolitis in particular, it highlights that even partial feeding of mother's milk appears superior to an exclusive formula milk diet. The benefit of human milk is therefore dependant on the dose.

A more recent systematic review and meta-analysis by Altobelli et al. (2020) reiterates many of the results already included in previous articles, but also highlights the fact that an analysis of subgroups shows that the positive results are mainly found in preterm babies who received both mother's own milk and donated milk.

5 The benefits of fortification with human milk

At present, only one Cochrane review by Prekumar et al. (2019) has been published, assessing the benefit of fortification with HM vs. fortification with CM, including only one randomised study, that of O'Connor et al. (2018), which included 127 preterm babies weighing <1250 g and receiving a diet of exclusively fortified HM, either with an HM-derived fortifier or a CM-based fortifier. It suggests that, compared with CM-based fortifiers, the use of an HM-based fortifier does not reduce the incidence of necrotising enterocolitis in preterm babies (RR 0.95, 95% CI 0.2 to 4.54; p=0.27). Similarly, no significant difference was observed in mortality, digestive intolerance, late-onset neonatal sepsis or bronchopulmonary dysplasia.

Since then, a second study by Eibensteiner et al. (2019) involving preterm babies weighing <1000 g fed HM fortified with an HM-based fortifier (n=96) or a CM-based fortifier (n=96) up to 32 weeks also failed to show a significant difference in morbidity between the two groups. The incidence of enterocolitis was 10% in the Humavant group versus 8% in the CM group. Only growth was significantly lower in the Humavant group (16.5 g/kg/d) than in the CM group (18.9 g/kg/d; p=0.009).

In 2022, the results of a new randomised study (Jensen et al., 2022) were presented in poster form. It shows that both mortality and morbidity are similar in preterm babies under 28 weeks' GA fed HM fortified with an HM-based fortifier (n=115) or a CM-based fortifier (n=114).

Finally, in a fourth study published in 2022, Gates et al. assessed a new HM-based fortifier from Medolac (n=37) in preterm babies under 34 weeks of age, and compared it with a previous group (n=49) receiving a CM-based fortifier. The results show a similar incidence of EN in both groups (2/37 vs. 3/49), whereas the incidence of BPD is significantly higher in preterm babies receiving the HM-based fortifier (11/37 vs. 10/49).

Table 4. Meta-analysis of four studies strictly assessing the influence of HM-based fortification (n=275) or CM-based fortification (n=271)

	HMF	CMF	p=	N	Weight
O'Connor 2018	3/64 (4,69 %)	3/61 (4,92 %)	0,80	125	0,198
Eibensteiner F 2019	10/96 (10,42 %)	8/96 (8,33 %)	0,62	192	0,304
Jensen GB 2022	8/115 (6,96 %)	9/114 (7,83 %)	0,79	229	0,362
Gates A 2022	2/37 (5,41 %)	3/49 (6,12 %)	0,89	86	0,136
Total	**21/275 (7,53 %)**	**23/271 (7,29 %)**	**0,91**	**632**	

These four studies, strictly assessing only fortification, suggest that in the original studies (Sullivan et al., 2010; Cristofalo et al., 2013; Abrams et al., 2014) it was indeed the use of CM-based preterm milk, and not fortification, that potentiated morbidity in very low-birth-weight preterm babies. However, due to the limited number of infants involved, larger randomised studies are still needed.

Finally, a fifth randomised study has just been published (Embleton et al., 2023). It includes preterm babies under 30 weeks of age receiving a diet of either HM (H+6), possibly supplemented with an HM-RTF 26 substitute (n=63), or mother's own milk fortified with a CM-based fortifier, possibly supplemented with a CM-based preterm milk (n=63). In this study, the authors report no difference in morbidity between the two groups (NEC, LOS, retinopathy, BPD), despite the partial use of a CM-based preterm milk.

Focusing on another area, the influence of fortification using Humavant products vs CM fortifiers on the microbiome of the preterm baby (Kumbhare et al., 2021) suggests that it is primarily the source of human milk (mother or donor) and not the type of fortifier that can influence the microbiome of the preterm baby. It also suggests that faecal calprotectin, a marker of digestive tract inflammation, is negatively correlated with the volume of mother's own milk received, but positively correlated with the administration of a Humavant fortifier, thus reinforcing the motivation to favour breastfeeding by the baby's own mother.

6 Comparison of *Prolacta Bioscience* data with current clinical practice

In studies assessing the benefit of HM-based fortifiers, the significance of NEC rates observed in the control group stands out. In fact, these rates appear to be much higher than those observed in neonatology departments. Rates of 16% to 21% have been reported in preterm babies weighing <1250 g fed on human milk fortified with a CM-based fortifier, or on preterm milk.

In Belgium, across all NIC units between 2011 and 2020, the rate of enterocolitis is 6.2% out of 10,203 preterm babies weighing <1500 g for a GA of between 24 and 31 weeks, (NICAUDIT, Belgium network). It is higher and stable in infants of between 24 and 27 weeks' GA, at 9.5%, but reduces significantly from 5.5% to 3.8%; p=0.031 between 2011–2015 (n=2917) and 2016–2020 (3817) in infants of between 28 and 31 weeks' GA.

Changes in the incidence of enterocolitis have also been reported in two publications, one in the United States (Stoll et al., 2015) and more recently in Scotland (Boele et al., 2020). The first concerns 34,636 preterm babies weighing <1500 g of 22 to 28 weeks' GA studied between 1993 and 2012. In this population, the incidence of enterocolitis was 7% in 1993, 13% in 2008 and then fell again to 9% in 2012. The second study reports an incidence of enterocolitis of 11% out of 948 preterm babies born between 24 and 28 weeks' GA between 2007 and 2016 in the southern part of Scotland. These values are significantly lower than the rates of the control groups in the *Prolacta Bioscience* studies. It should be remembered that the diet given in all the studies reported above consisted of mother's milk fortified with fortifiers, or of CM-based preterm milk, i.e. a diet similar to the control groups in the original *Prolacta Bioscience* studies.

7 Economic benefits

The technical files filed by the industry include studies suggesting a reduction in hospitalisation costs for infants receiving an exclusive human milk diet. These studies are essentially based on a reduction in morbidity and hospitalisation period, and appear to be speculative. Furthermore, they are based on healthcare systems that are very different to that in Belgium.

However, the cost of administering Humavant products to preterm babies remains challenging. The cost is generally estimated at €5,000 to €15,000 per patient, with Humavant products invoiced at around €6/ml. In Belgium, feeding is part of the ongoing treatment of patients, and there is no specific reimbursement for milk, as this is provided for free by mothers. The handling of the milk once it has been delivered to the departments is financed: verification, pasteurisation, fortifying, bottle-filling, etc. It should be noted that the use of Humavant products would also entail additional costs for storage facilities, deep-freezers, handling, etc.

The documents received report that the products are stable, provided that storage conditions are adequate. However, bacteriological safety could be compromised after thawing due to a relative loss of anti-infectious properties of donated HM, and it could be more susceptible to contamination than fresh human milk. There is little information available on this point.

8 Ethical issues

The studies put forward by the industry indicate a potential conflict of interest. They were financed by the company, which is not a problem intrinsically. However, several of the authors appear to be employees or consultants and are thus remunerated by *Prolacta Bioscience*. Similarly, some authors appear to be co-owners of patents filed by the company.

Prolacta Bioscience has received substantial investment capital to grow its activities. In the United States, HM "donor" mothers are remunerated according to the volume they donate. It is not clearly explained in the file submitted how these donor mothers are monitored. In Belgium, as in other European countries, surplus milk from donor mothers is supplied free of charge to milk banks, which are subsidised by the public authorities for their activities in the provision of the milk received, with the aim of promoting the use of HM. The commercial use of HM-based products raises ethical questions. Both UNICEF and the WHO condemn the marketing of HM. The marketing and export of products of human origin has been widely debated at European level, without any specific reference to human milk.
In 2017, UNICEF spoke out against an American company that was buying and exporting HM from impoverished regions of Cambodia. The Cambodian authorities have put an end to this activity. In France, the marketing and export of human milk is prohibited, and the management of human milk is restricted to recognised breast milk collecting centres. Humavant products should not be marketed.

Expanding the marketing of Humavant products to European countries and beyond risks the need for a huge increase in the paid collection of human milk, diverting it from its intended purpose: feeding one's own child.

In our countries, the marketing of Humavant fortifiers and above all human-milk substitutes also runs the risk of discouraging mothers of preterm babies, who are already troubled by their situation, from making the effort to breastfeed if they are guaranteed a commercial substitute. Moreover, why impose an arbitrary limit of 1250 g and not 1500 g, 2000 g, or 28 or 32 weeks? There is currently no scientific argument for setting a limit. How do you explain this limit to parents?

9 Responses to questions

In the DGAPF request, several specific questions were asked. The analysis above provides some answers.

1. Is the safety of these products sufficiently guaranteed, given the manufacturing process and the analyses carried out? Quality and safety information available at: https://prolacta.uk/product/quality-safety

In theory, checks on the donor mother are rigorous, according to the documentation provided by the industry via the DGAPF. However, given the expanding needs of the industry, this could lead to less selective collections. Technical handling procedures are well codified and have been the subject of numerous patents which have not been analysed in this report.

2. What microbiological risks are not covered by the manufacturing process?

The main microbiological risks are post-marketing in the maintenance of frozen stock and post-thaw handling of a product that has partly lost its anti-infective properties.

3. What are the health risks for the target group associated with variations in formulation due to the fact that the formulation of human milk develops according to the age of the child? Could standardised fortification prove insufficient to cover the nutritional needs of the target group?

The main risks are linked to the reduction in the volume of mother's own milk received by the infant, due to the replacement volume required for the liquid fortifier. The nutritional and anti-infective properties of raw HM are superior to those of pasteurised HM, which in turn are superior to those of donor milk. At present, few departments are able to provide personalised fortification, and this is limited to macro-nutrients.

4. What are the health risks for the target group associated with a nutritional formulation that is inadequate for their needs?

Today, postnatal malnutrition is relatively common, and mainly due to the fragility of very preterm babies. The introduction of Humavant products should not alter this risk. Nonetheless, some studies suggest that the growth achieved during the period of Humavant product use may be lower than that achieved with individualised fortification.

5. Does this product offer added value compared with other products on the market (infant milk for preterm babies classified as an FSMP)?

A distinction must be made between the various products:

- ***Fortifiers,*** *which do not appear to have any nutritional advantages over FSMP fortifiers (**no scientific proof is provided by the firm, as demonstrated above**), and have the major disadvantage of their cost, at €6/ml, and the fact they are in liquid form.*
- ***Human-milk substitutes,*** *fortified or non-fortified, could be an advantageous replacement for preterm milks classed as FSMPs, but their cost is a disadvantage, as is the risk of running counter to policies promoting breastfeeding.*

6. Do the above products comply with the definition of an FSMP (Article 2.2(g) of Regulation (EU) No 609/2013)?

Although fortifiers could fall under §3 and substitutes under §1 and §2, their status as an FSMP is clearly in question, given that no nutritional benefits have been demonstrated and that various risks have been identified with the marketing of these products. The status of these products is the responsibility of the FPS Public Health, on the basis of this scientific report.

7. How can milk traceability be ensured?

In the same way as for other FSMP products.

8. Is there a risk that women who supply human milk to companies will be exploited?

Yes, as seen in Cambodia. There is a risk that paying for milk will divert it from its original purpose. On the other hand, it's a little reminiscent of the wet nurses of centuries past.

9. Given that human milk is not covered by the report on human tissue banks, are there any ethical constraints on the marketing of these human milk-based products?

Human milk remains a human product, and its marketing and export diverts it from its original purpose. There is a risk that the infants of donors will be harmed by this trade. In Belgium, donating milk is free. Wouldn't this provision become obsolete if these foreign products were marketed?
In France, anonymous donated milk is considered a health product of human origin, delivered only on medical prescription, and only by structures authorised to collect, process and distribute donated milk: breast milk collecting centres.

10. Could the marketing of these products have an impact on milk banks?

There could certainly be a reduction in the incidence of breastfeeding of preterm babies, as well as an impact on the donation of milk, which might no longer appear necessary given that a commercial product presented as 'equivalent' would have appeared on the market.

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VI COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Stefaan DE HENAYW**; the scientific secretaries were Florence BERNARDY and Michèle ULENS.

ANDJELKOVIC Mirjana	Toxicology, chemical residues and contaminants	Sciensano
BERGER Nicolas	Food consumption surveys	Sciensano
DE BACKER Guy	Preventive medicine, public health, epidemiology	UZGent
DE HENAUW Stefaan	Public health nutrition	UGent
GOYENS Philippe	Paediatric nutrition	ULB
HUYGHEBAERT André	Food chemistry and technology	UGent
MAINDIAUX Véronique	Nutrition and dietetics	HE Vinci - Institut Paul Lambin
NEVEN Loes	Health promotion, food and health	Gezond Leven
RIGO Jacques	Paediatric nutrition	ULiège
SEEUWS Carine	Dietetics, food composition	Nubel
VANDEVIJVERE Stefanie	Nutrition and public health	Sciensano
VANSANT Greet	Food and health	KULeuven

The following groups were heard:

- **Belgian Association of Neonatology,**
- ***Comité Fédéral de l'allaitement maternel / Federaal Borstvoedingscomité* - Federal Breastfeeding Committee,**

and share the opinion of the SHC.

The following administrations were heard:

DARIMONT Amandine	Regulatory nutrition	FPS HFCSE
DECLOCK Dominique	Food supplements and cosmetics	FPS HFCSE
LAQUIERE Isabelle	Regulatory nutrition	FPS HFCSE
TAQUET Magali	Nutrition policy	FPS HFCSE
STORMS Tom	Food supplements	FPS HFCSE

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