Specialised infant milks in the UK:

Infants 0-6 months

Information for health professionals

September 2019

FIRST STEPS NUTRITION TRUST

Specialised Infant Milks in the UK: Infants 0-6 Months. Information for health professionals. September 2019.

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This resource is provided for information only and individual advice on diet and health should always be sought from appropriate health professionals. We have attempted to provide accurate information on the current composition of specialised infant milks sold in the UK in this report and do so in good faith. However, composition, names and claims may change, so please refer to the specific manufacturers for up-to-date information.
When referencing this document please refer to the website for the most recent version

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First Steps Nutrition Trust

First Steps Nutrition Trust is a charity which provides evidence-based and independent information and support for good nutrition from pre-conception to five years of age.

Also available from First Steps Nutrition Trust (www.firststepsnutrition.org)

Breastmilk and Breastfeeding: A simple guide

Infant Milks in the UK: A practical guide for health professionals

Infant formula: An overview

Costs of infant milks marketed in the UK

Infant Milks: A simple guide to infant formula, follow-on formula and other infant milks

'Scientific and Factual?': A review of breastmilk substitute advertising to healthcare professionals

'Scientific and Factual?': A further review of breastmilk substitute advertising to healthcare professionals

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Acronyms

AD	Atopic dermatitis
ANS	Approval not sought
ARA	Arachidonic acid
BDA	British Dietetic Association
BfN	Breastfeeding Network
BMF	Breastmilk fortifier
BMI	Body mass index
BNF	British National Formulary
CCG	Clinical commissioning group
CMPA	Cows' milk protein allergy
COMA	Committee on Medical Aspects of Food and Nutrition Policy
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
DHM	Donor human milk
DH	Department of Health
DHA	Docosahexaenoic acid
EC	European Commission
EFSA	European Food Safety Authority
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
EU	European Union
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FSA	Food Standards Agency
FSG	Foods for Specific Groups
FSMP	Foods for Special Medical Purposes
GMDI	Genetic Metabolic Dietitians International
HCU	Homocystinuria
IBFAN	International Baby Food Action Network
IVA	Isovaleric acidaemia
LBW	Low birthweight
LCP	Long chain polyunsaturated fatty acid
LCT	Long chain triglyceride
LF	Lactose-free
LPP	London Procurement Partnership
MCT	Medium chain triglyceride
MEP	Member of the European Parliament
MMA	Methylmalonic acidaemia
MSUD	Maple syrup urine disease

MUAC	Mid-upper arm circumference
NA	Not applicable
NE	Niacin equivalent
NEC	Necrotising enterocolitis
NICE	National Institute for Health and Care Excellence
NK	Not known
NKH	Non-ketotic hyperglycinaemia
NS	Not stated
NSPKU	National Society for Phenylketonuria
OFC	Occipitofrontal head circumference
PA	Propionic acidaemia
PARNUTS	Foodstuffs for particular nutritional use
PKU	Phenylketonuria
RCN	Royal College of Nursing
RCPCH	Royal College of Paediatrics and Child Health
RE	Retinol equivalent
RNI	Reference Nutrient Intake
RTF	Ready-to-feed
SACN	Scientific Advisory Committee on Nutrition
THIN	The Health Improvement Network
TYR	Tyrosinaemia
UKAMB	United Kingdom Association for Milk Banking
UNICEF	United Nations International Children's Emergency Fund
VLBW	Very low birthweight
WHO	World Health Organization

1 Introduction

Breastfeeding and breastmilk

This report is about specialised infant milks, labelled for use under medical supervision and marketed for consumption by infants from 0-6 months of age.

First Steps Nutrition Trust strongly supports international and national recommendations that every mother in the UK should be supported to breastfeed her baby exclusively for the first six months of his or her life, and to breastfeed alongside the introduction of solid foods at about 6 months for at least one year, and for as long after that as the mother chooses.

The importance of breastmilk for babies who are born prematurely or with serious medical conditions requiring specialist care is universally acknowledged. We strongly support and applaud the many measures now being taken in neonatal units across the country to support and encourage women to provide their babies with breastmilk and to become breastfeeding mothers when they leave hospital. We also fully support the right for all families to be able to access donor human milk where this may be needed.

1.1 Why have we written this report?

This report is designed to support all those who want to know more about specialised milk products marketed in the UK for infants 0-6 months of age. First Steps Nutrition Trust strongly supports greater investment to support women to breastfeed through the Unicef UK Baby Friendly Initiative accreditation scheme in maternity, neonatal, university and community settings. All those who work within Unicef UK Baby Friendly accredited settings must carefully consider their role in the protection of infant and young child health by respecting the WHO *International Code of Marketing of Breast-milk Substitutes* and subsequent World Health Assembly resolutions designed to protect the health of all infants, young children and their families. As part of this commitment it is important that health workers can access independent information about infant milks rather than relying on manufacturer information. This report has been written to provide that independent information.

Working within the WHO Code does not mean that health professionals cannot obtain up-to-date information about products. We strongly encourage health workers to be critical when they are presented with information from sales representatives, to work together to ensure they can interpret clinical studies presented as evidence, and to consider setting up multi-disciplinary groups to manage information presented to them about specialised milks.

A useful guide for health workers, *Working within the International Code of Marketing of Breast-milk Substitutes: A guide for health workers,* can be downloaded from Unicef UK Baby Friendly Initiative at

https://www.unicef.org.uk/babyfriendly/wp-content/uploads/sites/2/2016/10/Working-within-The-Code-Guide-for-Health-Workers.pdf

A resource for dietitians on how they can work within the WHO Code can be accessed at: https://www.firststepsnutrition.org/working-within-the-who-code

The information in this report is not designed to replace specialist medical and professional support and care from a clinical team.

The aim is to provide an overview of products available and key information about these products, and to investigate some of the claims made in the context of what else is known or recommended by independent scientific bodies. We hope it will stimulate discussion and encourage health workers who require information about products to be *active* in obtaining the information they need from commercial companies, and not be *passive* recipients of marketing information.

First Steps Nutrition Trust provides information on infant milks that are sold over the counter in the UK in its regularly updated report *Infant Milks in the UK: A practical guide for health professionals* as well as a number of other reports which consider composition, claims, cost and safe use of infant milks. All publications can be found at www.firststepsnutrition.org/composition-claims-and-costs

Terminology

There are a number of names and terms used for infant milks. Some people call them 'breastmilk substitutes', while others prefer the term 'artificial milks' or 'formula milks'. The term 'breastmilk substitute' refers to all products that are marketed in a way which suggests they should replace breastfeeding, even if the product is not suitable for that purpose. This may include infant milk, baby foods, gruel, tea, juice, bottles, teats/nipples and related equipment. For clarity we use the following terms throughout this report:

What do we mean by infant milk?

We use the term 'infant milk' as an umbrella term for all milk-based or milk substitute based drinks provided commercially for infants.

What do we mean by infant formula?

We use the term 'infant formula' to mean a food that can meet all an infant's nutritional needs during the first six months of life and which complies with the regulations for infant formula.

What do we mean by specialised infant milk?

We use the term 'specialised infant milk' to mean a product which can meet all of the nutritional needs of infants as a breastmilk substitute in the first six months of life, and which complies with the regulations for infant foods for special medical purposes.

What do we mean by supplementary feeding or supplementation?

We use the term 'supplementary feeding' or 'supplementation' to mean an infant milk given to an infant under 6 months old, to supplement their intake of breastmilk.

1.2 What does this report contain?

This report provides information on specialised infant milks currently available in the UK, marketed as suitable for infants from birth to 6 months of age.

This information can be read alongside the report *Infant Milks in the UK* (available at www.firststepsnutrition.org), which provides information for health professionals on infant milks available to buy over the counter in the UK. This report provides background data on:

- the components of infant milk and evidence to support claims made for efficacy
- contaminants and additives in infant milks
- feeding guidelines, and
- information on making up infant milks safely.

For more detailed information on many of the medical conditions mentioned in this report, see *Clinical Paediatric Dietetics* (Shaw, 2015).

1.3 Current infant feeding guidance

With few exceptions, the World Health Organisation (WHO, 2003) and health departments across the developed and developing world recommend exclusive breastfeeding for the first six months of life, and continued breastfeeding alongside complementary foods to the age of at least 2 years. In developed countries, we recommend that mothers breastfeed throughout the first year and for as long after that as the mother-baby partnership wishes to do so. Almost all mothers can breastfeed successfully. The number of maternal or infant health conditions which justify temporarily or completely stopping breastfeeding are actually very few (WHO, 2009). Where mothers cannot, or choose not, to breastfeed, breastmilk substitutes are required and these can provide infants with the energy and nutrients they need to grow and develop. However, it is impossible to recreate breastmilk which is a bioactive fluid, and there are inherent differences between breastmilk and infant milk (Renfrew et al, 2012):

- The exact chemical properties of breastmilk are still unknown and cannot be reproduced.
- A mother's breastmilk changes in response to the feeding habits of her baby and over time and adjusts to the infant's individual growth and development needs.
- Infant milk does not promote neurological development as breastmilk does.
- Infant milk has no positive impact on maternal health.
- Breastmilk includes a mother's antibodies and many other defensive factors that help the baby avoid or fight off infections and gives the baby's immature immune system the benefit of the mother's mature immune system.
- Infant milk requires manufacturing, storage and delivery systems, which have inherent quality control problems.

Despite these benefits, whilst 69% of women exclusively breastfeed at birth in the UK, this falls to less than half (46%) by 1 week, around a quarter (23%) by 6 weeks, and only 1% by 6 months of age (McAndrew et al, 2012). Breastfeeding rates among babies who may be born too early, or with a medical condition, are thought to be even lower. When preterm infants leave hospital it has been suggested that only 34% are wholly breastfed and 19%

partially breastfed (McAndrew et al, 2012; Quigley and McGuire, 2014). Little data is available about the rates of breastfeeding of babies with other special needs at birth in the UK. The MOSAIC study reported breastfeeding rates among very preterm infants in eight European areas, and rates varied from 70% in an area of Italy to 20% in an area of France. In the UK area included in this study, 35% of infants were breastfed at discharge (Bonet et al, 2011). The authors also concluded from this study that breastfeeding rates for very preterm babies were correlated with overall national breastfeeding rates, suggesting that a breastfeeding-friendly environment, reflected by a high national rate, also favours this practice among very preterm babies. The economic benefits of increasing both kangaroo skin-to-skin care and breastfeeding in neonatal units was investigated by Lowson et al (2015). The intervention 'Getting it Right from the Start' within 18 neonatal units in the North of the UK increased breastfeeding rates in the two neonatal networks to 47-52%. As well as significant clinical benefits for infants, the economic benefits of this, primarily from reducing hospitalisation of infants. was estimated as anything up to £582,432 per year.

Unicef UK Baby Friendly Initiative accreditation is now available for neonatal units and it is likely that in units working towards accreditation that both breastmilk intake and breastfeeding rates within neonatal units and on discharge will rise. In summer 2019 10 neonatal units in the UK were fully accredited and many more were on their Baby Friendly journey.

1.4 Foods for special medical purposes (FSMP)

Whilst infant formula legislation regulates the labelling and marketing of products based on some aspects of the WHO *International Code of Marketing of Breast-milk Substitutes*, specialised infant milks – which fall under the regulations for foods for special medical purposes –currently do not. This means that promotional activities, gifts, sponsorship, health claims and advertising showing idealised images can be, and are, used to strengthen the overall company brand of products where there are specialised as well as standard products. From February 2020 new EU regulations (which the UK currently say they are adopting) will however restrict some of these activities.

The two biggest infant formula companies in the UK – Danone Nutricia Early Life Nutrition (Cow & Gate, Aptamil and Nutricia branded products), and Nestlé (SMA) – produce both standard and specialised infant milk. Some of these different types of over-the-counter and prescribable products share company branding, logos and marketing material and provide an opportunity for the companies to bypass WHO Code restrictions on labelling and marketing. The similarity of names and appearance between products can cause confusion among both health professionals and users and increase the risk that an infant might be given an infant formula which is not suitable to meet their needs and which may adversely affect their health.

Specialised infant milks must comply with the legislation on foods for special medical purposes (FSMP). Until a change in EU regulation in July 2016, the only safeguard in the WHO *International Code of Marketing of Breast-milk Substitutes* (World Health Organization, 1981) which applied to FSMP was a requirement to label all FSMP as for 'use under medical supervision'. New regulations will include changes to labelling, advertising and promotion of FSMP to parents, carers or health professionals in the UK. Whilst the new EU regulations under the Foods for Special Groups Directive come into force in 2016, companies have a

period of grace to make changes to products, and for FSMP for infants this is four years, with a compliance date set of 22 February 2020. More details of the new regulation and delegated act can be found in section 4. Whilst many specialised milks are available only on prescription, some FSMP are freely available for purchase over the counter by families. Infant milks bought over the counter do not require medical or risk assessment, so their suitability and appropriateness are unknown. With no continued medical supervision by a qualified health professional, safe use of an FSMP cannot be guaranteed, and for this reason First Steps Nutrition Trust strongly believes that no FSMP should be sold over the counter in the UK. More information and evidence for the call for infant FSMP products to be removed from the shelves of supermarkets, shops and pharmacies can be found on the Baby Feeding Law Group at:
https://static1.squarespace.com/static/5c6bb04a65a70771b7cbc916/t/5ce2e03b9cfe170001660eda/1558372412884/Removing_iFSMP_from_shelves_May19.pdf

1.5 Working within the WHO Code to protect breastfeeding and infant and young child health

All health professionals should know how to operate within the framework of the WHO *International Code of Marketing of Breast-milk Substitutes* and subsequent World Health Assembly resolutions. Health professionals are a particular target for formula companies, given their influence and proximity to parents, carers and other health workers.

"Health workers are the ideal conduit for promoting company products. They engender public trust and respect and have easy access to virtually all new mothers and babies. The 'halo effect' of having mothers associate the company brand with a health worker, be this a personal recommendation or simply a logo on a pen, is highly valued."

Unicef UK Baby Friendly Initiative.

Promotion may take the form of information and gifts given by sales representatives, invitations to events and outings, payment of conference fees, travel and hotels or the provision of tools to help in clinical practice. Infant feeding 'study days' are often run directly by formula companies, often focussing on areas associated with infant feeding difficulty, such as reflux or allergy, but in reality the events are primarily designed to promote the brand.

Formula companies frequently sponsor or donate to national nutrition and health conferences. Health professionals should be aware that education offered at these study days and conferences is funded by the marketing departments of formula companies and will focus on topics related to their agenda, and not necessarily topics of current clinical or public health importance. These events provide an opportunity to approach health workers directly, obtain their contact details and disseminate branded marketing materials, including stationery and sales literature. This may take the form of clinical case studies, funded medical research, or health professional guides on particular infant feeding issues such as weaning the allergic child, or managing constipation.

With this in mind, and in accordance with the WHO Code, the Unicef UK Baby Friendly Initiative recommends that health professionals should (Unicef UK Baby Friendly Initiative, 2019):

- Not promote breastmilk substitutes, bottles or teats to the general public, either as individual health professionals, or on behalf of a health facility.
- Not give free samples of breastmilk substitutes to pregnant women, new mothers or families.
- Not use educational materials supplied by and carrying formula company logos and brands.
- Not accept gifts or stationery carrying company logos and brands.
- Not attend study days funded by formula companies.
- Consider very carefully the implications of accepting invitations to speak at conferences, accepting awards or prizes, writing opinion articles or completing market research surveys for any event or publication that takes funding from companies that market breastmilk substitutes or from organisations that they fund.

World Health Assembly resolution 69.9[1] in 2016 explicitly stated that:

'Any donations to the health care system (including health workers and professional associations) from companies selling foods for infants and children represent a conflict of interest and should not be allowed'

And that

'Sponsorship of meetings of health professionals and scientific meetings by companies selling foods for infants and young children should not be allowed'

No-one wants to restrict health professionals' access to the information they need to make clinical decisions. It is perfectly reasonable to obtain product information needed by actively asking the company questions about a specific product's composition, and independently discussing this with colleagues after considering the evidence provided.

In the UK, Baby Milk Action monitors and collates reported violations of the WHO Code on behalf of the Baby Feeding Law Group and this is done internationally by IBFAN (International Baby Food Action Network). For an idea of how the multinational companies that manufacture infant milks 'break and stretch' the rules around promotion of their products and violate the WHO Code and WHA resolutions, a summary of activities in the UK can be found at: http://www.babymilkaction.org/monitoringuk17

For contact details for Baby Milk Action and IBFAN, see section 6.

1.6 Critical appraisal of infant feeding marketing information

It is important that health professionals can critically appraise published research, particularly when it relates to infant feeding, and guidelines on the nutritional assessment of infant formulas was published by the COMA panel in 1996 (Department of Health, 1996). They made a series of recommendations, many of which are not implemented, but which remain relevant today. Note that the term 'formula' is used below to describe all infant milks.

[1] http://www.who.int/nutrition/publications/infantfeeding/breastmilk-substitutes-FAQ2017/en/

The report provides some general principles when assessing infant formula, including the following:

- All modifications to infant formula should be assessed nutritionally.
- Studies should be founded on a systematic review of relevant existing information. All such reviews should be made publicly available.
- At the outset of a nutritional study there should be a clear hypothesis of functional or clinical benefit with defined selection criteria and outcome measures.
- All studies should be interpreted in the light of outcomes of healthy infants exclusively breastfed for 4-6 months+.

The report also makes recommendations about how studies should be conducted, and these, alongside tools that have been developed to support those who want to critically review scientific papers, can be helpful when health professionals are making these assessments. A useful set of critical appraisal checklists to evaluate different types of studies can also be found at https://www.sign.ac.uk/checklists-and-notes.html

Some research papers may have a conflict of interest regarding funding. A meta-analysis undertaken for *The Lancet* by their non-communicable diseases group found that the scientific literature had a systematic bias towards industry funding, with favourable conclusions four to eight times more likely when articles were exclusively sponsored by the food and drink industry compared with those that were not industry-funded (Lesser et al, 2007). A review of equivalent randomised trials found that industry-funded trials were almost three times more likely to report favourable results (Flacco et al, 2015).

There is no formal means to challenge information provided about infant milks in health professional literature, even when this is inaccurate, misleading or does not support current policy and guidance. It is important that health professionals see all advertising of infant milks in professional journals in that context. Two reviews of advertising of infant milks to health professionals can be found on the First Steps Nutrition Trust website: *Scientific and Factual? A review of breastmilk substitute advertising to healthcare professional (2016)* and *Scientific and Factual? A further review of breastmilk substitute advertising to healthcare professionals (2019)* These can be accessed at www.firststepsnutrition.org/working-within-the-who-code. Health professionals may be surprised at the lack of evidence for claims made in advertising, the misuse of evidence by companies when making claims, and the poor or non-availability of some data used to back up claims made.

Some NHS Trusts or Health Boards have taken steps to protect health workers by setting up systems where any marketing material is critically appraised by health professionals, either prior to, or to completely avoid, any potential industry contact with health workers. Appraised information can then be given to health workers independently to ensure a consistent and evidence-based message is disseminated across the workforce.

A short report highlighting *'Organisations funded by the breastmilk substitute industry'*, which also contains a list of useful sources of independent information can be accessed from The Baby Feeding Law Group website:
https://static1.squarespace.com/static/5c6bb04a65a70771b7cbc916/t/5d07df0ddac3c800012276e2/1560796942265/Websites_and_organisations_June19final.pdf

2 Infant feeding

2.1 Supporting all new mums to exclusively breastfeed

Health professionals, particularly midwives, paediatricians, neonatal nurses, health visitors, infant feeding leads, lactation consultants, GPs and dietitians, but also children's nurses, pharmacists and other health professionals who have contact with families in the early weeks and months of a baby's life – have a key role to play in ensuring that all women are supported to breastfeed their babies. This is also the case when a baby needs to spend some time in specialist care or may have a specific medical condition. Some health professionals (as well as mothers themselves) may choose to become accredited breastfeeding counsellors, and all those who work in healthcare facilities which are Unicef UK Baby Friendly Initiative accredited should take up any opportunities for training in breastfeeding support on offer. Health professionals should know where to access breastfeeding support in their local area. Properly commissioned and funded breastfeeding peer support programmes are effective, can be run at a low cost, and facilitate an increase in maternal and infant health and well-being as well as an increase in social capital (Department of Health, 2012).

Where there are concerns about a breastfed baby's nutrition and growth, it is important that the mother receives timely, skilled breastfeeding support before infant formula is considered or introduced, to prevent any unnecessary intervention. Each NHS Trust should have an Infant Feeding Team, and a Lead or Co-ordinator for Infant Feeding. As a general rule, anyone can refer to their services. There are also likely to be local breastfeeding counsellors, lactation consultants and breastfeeding peer supporters offering breastfeeding support at free drop-in breastfeeding groups and cafés, and several national charities offer telephone and online support from qualified breastfeeding counsellors (see section 6).

Despite an understandable sense of urgency when a mother and baby experience feeding difficulties, a referral to the Infant Feeding Team should always be sought for skilled breastfeeding support. The Infant Feeding Team will work with medical, nursing and health professionals as well as the mother and her supporters to do what is best for the mother and infant at that time. They will work with and support the mother, to help her to recognise feeding cues, position and attach her baby correctly, and comfortably optimise breastmilk intake so that she can become an exclusively breastfeeding mother. Whilst an infant gaining weight may be a short-term priority, the long-term health benefits and relationship-building associated with breastfeeding should never be underestimated.

Data from a large study in Denmark on factors impacting on breastfeeding of preterm babies reported that early initiation of breastmilk pumping within 12 hours postpartum increased breastfeeding rates (Marastrup et al, 2014). However, it is important to remember that the act of feeding is not just about the milk consumed, but also an opportunity for increasing the well-being of both mother and infant through close physical contact. The understanding and promotion of the development of a close and loving relationship between mothers and their

infants, however they are fed, is part of Unicef UK Baby Friendly Initiative standards (Unicef UK Baby Friendly Initiative, 2013).

Strategies to support breastfeeding before considering supplementing with formula might include:

- Minimising any separation between mother and baby and promoting plenty of skin-to-skin contact to increase the likelihood of feeding responsively on cue.
- Expert observation of a full breastfeed to ensure that a mother knows how to position and attach her baby comfortably to the breast and can feed effectively.
- Ensuring mothers are aware of the difference between active and non-active swallowing.
- Discussing typical colostrum appearance and volume to support a mother to have realistic expectations of what she can produce.
- Encouraging a mother to feed her baby more frequently to help optimise and maintain her breastmilk supply: at least eight times a day and at least once overnight.
- Supporting a mother to recognise when a baby is taking adequate breastmilk – for example, knowing the number of wet and soiled nappies to expect.
- Offering both breasts during a feed.
- Showing a mother how to hand-express her breastmilk to increase and maintain breastmilk supply. Depending on how much breastmilk a baby is taking, this may need to be up to 12 times in 24 hours, including once overnight, and may be assisted by keeping an expressing log to track progress, or by considering how much milk has been expressed over a period of hours – for example, 60ml over 2 hours – to estimate roughly how much breastmilk a mother might produce over a 24-hour period. N.B. The amount of breastmilk a mother expresses is not necessarily an indicator of how much milk is being produced, as some mothers may have a good breastmilk supply but may not be able to express similar volumes.
- Ensuring there are no problems with expressing technique or suboptimal use of equipment – for example, incorrect flange sizes, or over-aggressive pumping technique.
- Avoiding use of dummies and teats during establishment of breastfeeding.
- Exploring the possible use/availability of donor milk.

A number of initiatives are being used to encourage and support the use of colostrum and breastmilk in infants who may require special care. For example:

- ‘Prescribing’ colostrum for babies, to ensure this is prioritised among all staff in the neonatal unit.
- Giving colostrum packs to all new mums and ensuring staff can support mums at all times of the day and night to optimise their milk production.
- Charts to encourage a mother to aim for around 750-900ml of breastmilk per day, by day 10 of her infant’s life.
- Teaching early hand-expressing of breastmilk (within the first 6 hours of birth), and breast massage to stimulate the hormones involved in breastfeeding.
- Encouraging senior medical staff to have meaningful conversations with parents-to-be (where appropriate) and new parents, about the vital role they can play in the management of their infant’s health and well-being through providing colostrum and breastmilk.

- Ensuring easy access to breast pumps at all times, and full support to use them.

Unicef UK Baby Friendly Initiative offer guidance for neonatal units in their document http://www.unicef.org.uk/babyfriendly/wp-content/uploads/sites/2/2015/12/Guidance-for-neonatal-units.pdf

WHO guidelines set out the most appropriate feeding options in order of the benefit to the health and well-being of an infant in a step-wise fashion, starting with breastmilk which is of the greatest benefit and smallest risk to health, to breastmilk substitutes being of least benefit and the greatest risk to an infant's health (WHO, 2003). The order of benefit is:

1 Mother's breastmilk
2 Mother's expressed breastmilk
3 Donor breastmilk
4 Breastmilk substitute, i.e. standard infant formula or a specialised infant formula (used under medical supervision).

Economic analysis of health outcomes have reported that it may take as little as a few years, and in some cases only a year, for investment to help women to breastfeed to translate into cost savings in disease prevention (Renfrew et al, 2012). Data suggests that, if women exclusively breastfeeding were supported to continue until 4 months, this could save £11 million a year to the NHS due to the reduction in three childhood infectious diseases, and that by doubling the number of women currently breastfeeding for 7-18 months in their lifetime, the burden of breast cancer cases could be reduced and around £31 million saved (Pokhrel et al, 2014).

It is important to remember that supporting breastfeeding is not just a paediatric or neonatal speciality. A breastfeeding mother, or her child, who becomes unwell and requires medical or surgical treatment will also need the same skilled support and insight from staff in adult and child settings.

2.2 The importance of human milk for the premature infant

The evidence for the importance of human milk in preventing illness and infection in vulnerable low-birthweight infants is unequivocal. A review of human milk feeding in premature infants and necrotizing enterocolitis (NEC) reported that an exclusive human diet provides protection against NEC and that risk is particularly decreased if more than 50% of feeds are human milk (Cacho, Parker and Neu, 2017). Pre-term infants are susceptible to NEC due to the immaturity of their gastrointestinal and immune systems. An exclusive human milk diet compensates for these immature systems in a number of ways: lowering gastric pH, enhancing intestinal motility, decreasing epithelial permeability and altering the composition of bacterial flora (Maffei and Schanler, 2017).

A study by Patel et al (2013) also showed a dose-response relationship between human milk intake by very low birthweight infants and sepsis, leading to considerable long-term cost savings and beneficial outcomes in these infants. A study of very low birthweight infants (23-34 weeks and between 490g-1700g) showed that implementing an exclusive human milk diet led to a significant decrease in the incidence of NEC, decreased feeding tolerance,

decreased time to full feeds, shorter lengths of hospital stay and considerable cost savings (Assad, Elliott and Abraham, 2016). Evidence also suggests that human milk feeding in premature infants can play a protective role in preventing retinopathy, particularly severe retinopathy. (Zhou et al, 2015). Preterm babies show improved cognitive development, speech and jaw development, visual acuity and earlier discharge from hospital compared with babies fed preterm infant formula (Altman et al, 2009; Horta et al, 2007; Huston et al, 2014; Rønnestad et al, 2005).

Evidence also suggests that providing breastmilk for very low birthweight infants hospitalised in the neonatal intensive care unit helps mothers connect with their infants and that mothers' faith in the healing properties of their milk is a motivating factor for sustaining breastfeeding during what is an anxious and stressful time for families (Rossman et al, 2013). There is also considerable evidence of the substantial economic benefits associated with human milk feeds during critical periods of neonatal hospitalisation (Johnson et al, 2014).

2.3 Medications and breastfeeding

The British National Formulary frequently contraindicates the use of medications during breastfeeding as often there is simply no evidence to guide decision-making. Such trials cannot ethically be undertaken in breastfeeding women. However, there are frequently medication options which are safe and which allow women to continue to breastfeed.

The Breastfeeding Network (BfN) – a UK-based charity that supports breastfeeding mothers with evidence-based information – has a Drugs in Breastmilk Information Service Facebook page staffed by a registered pharmacist, breastfeeding supporter and trained breastfeeding volunteers. Contact details can be found in section 6. The Breastfeeding Network also has freely downloadable leaflets about the safety of specific medications during breastfeeding, which can be accessed at: www.breastfeedingnetwork.org.uk/detailed-information/drugs-in-breastmilk/

The BfN Drugs in Breastmilk Information Service can guide clinicians in managing the risks to the mother and infant's health and well-being of continuing medication during breastfeeding, versus the risks from introducing a breastmilk substitute. Individual questions can be answered via the facebook page www.facebook.com/BfNDrugsinBreastmilkinformation/

The NHS also runs a drugs in lactation advisory service (DILAS) and information about this service can be found at www.sps.nhs.uk/articles/ukdilas/ and in the further information section of this report in section 6.

LactMed, the US National Library of Medicine's Drugs and Lactation Database, holds evidence-based information on medication use during breastfeeding and can be accessed at: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm. It also has a mobile app called LactMed, which can be freely downloaded for Apple and Android users.

2.4 Donor human milk and milk banks in the UK

Where an infant cannot receive maternal breastmilk for whatever reason, pasteurised donor human milk is superior to breastmilk substitutes. Boyd et al (2007) did a systematic review looking at the impact of donor milk compared to breastmilk substitutes on outcomes in premature infants. They reported that formula-fed very low birthweight babies were at significantly increased risk of necrotising enterocolitis (NEC) compared with those fed exclusively on breastmilk. The ongoing incidence of NEC and related mortality and severity of morbidity among survivors make this finding important. In a response to the Boyd et al paper, Williams et al (2007) highlighted that at that time there was an incidence of 2.1 neonatal unit admissions per 1,000 live births, 65% of whom weighed under 1,500g at birth. Overall mortality was 22% but it was significantly lower in those fed human milk compared with those fed on formula (5% v 26%, $p<0.05$).

An updated Cochrane review by Quigley et al in 2019 considered the benefits of formula versus donor breastmilk for preterm or low-birthweight infants. They also concluded, from the twelve randomised control trials reviewed which met their criteria, that whilst formula milk increased short-term growth rates it was associated with a higher risk of developing NEC (Quigley et al, 2019).

European guidelines have been published by ESPGHAN (the European Society for Paediatric Gastroenterology, Hepatology and Nutrition) on the benefits and risks of using donor milk in preterm populations (Moro et al, 2015; Arslanoglu et al, 2013). In this report the committee concluded that:

- The major clinical benefit of using donor breastmilk is protection against necrotising enterocolitis and sepsis.
- Human milk banks are essential for providing safe donor human milk to vulnerable infants.
- The presence of a human milk bank does not compete with breastfeeding, but decreases use of formula and increases exclusive breastfeeding at discharge.

The UK Association for Milk Banking (UKAMB) supports and promotes accountable provision of safe, rigorously screened donor breastmilk for sick or preterm babies, and NICE guidance sets out, in greater detail, recommendations for recruitment and screening of milk donors, and handling and processing of donor milk (National Institute for Health and Clinical Excellence, 2010). The NICE website www.nice.org.uk/guidance/cg93 also includes key priorities for implementation and provides useful tools and resources. The guideline is due for review in 2019.

The British Association of Perinatal Medicine has published guidelines on the use of donor milk. *The Use of Donor Human Expressed Breast Milk in Newborn Infants. A Framework for Practice* (2016). Available at: www.bapm.org/resources/43-the-use-of-donor-human-expressed-breast-milk-in-newborn-infants-a-framework-for-practice-2016

There are currently 14 milk banks in England, 1 in Scotland and 1 in Northern Ireland. Milk banks collect, screen, store, process and distribute donated human breastmilk. Contact details for UK milk banks can be found in section 6. The availability of donor milk to an infant may not be dependent on the number of milk banks in an area: in Scotland and Northern Ireland infants have equity of access to donor milk and since September 2016 the

Southwest Neonatal Network Donor Milk Bank has been funded by NHS England and provides equity of access as the milk bank for the Southwest region. This is not currently the case in all areas of England and Wales. However there are some milk banks that undertake to provide donor milk to neonatal units irrespective of location and donor recruitment has become more widespread as a result of the support of the SERV and other volunteer 'blood bike' groups. Provision of donor human milk to infants is also not exclusively provided to infants on neonatal units with some milk banks supporting its use on post-natal wards and in certain circumstances within the community. See the UKAMB website for further information www.ukamb.org.

The Human Milk Foundation was set up in 2017 to provide additional donor milk through the Hearts Milk Bank, to support families in need of donor milk and to conduct research into human milk. Information can be accessed here https://humanmilkfoundation.org/

2.5 Supplementing the intake of breastmilk

Use of a supplementary infant milk requires careful consideration because of risks to both infant and maternal health and well-being through disturbing the breastfeeding relationship. This may potentially reduce a mother's breastmilk supply and her sense of self-efficacy. There are no UK guidelines on supplementing breastfed babies, but the Academy of Breastfeeding Medicine in the US has a clinical protocol for use in hospitals on the use of supplementary feedings in healthy term breastfed neonates (Kellams et al, 2017) and can be found here: https://abm.memberclicks.net/assets/DOCUMENTS/PROTOCOLS/3-supplementation-protocol-english.pdf.

Where infant milk is required, it is very helpful to ensure that a mother understands why this may be necessary, for how long it may be required and, where appropriate, what plans are in place to help support continued breastfeeding alongside infant milk feeding. This may include support for transition back to breastfeeding at a later date if this is feasible. If a breastmilk substitute is indicated – either because the first three feeding choices (mother's breastmilk, mother's expressed breastmilk, or donor breastmilk) have already been investigated and either partial or exclusive infant milk feeding is required; or because the mother or baby has a serious medical condition precluding breastfeeding – the correct choice of breastmilk substitute needs to be made, and infant formula should be considered before specialised infant milk.

2.6 Breastmilk fortifiers

Whilst breastmilk fortifiers (BMF) are not infant milks, they are commonly used as a dietary supplement when babies are born prematurely, particularly among those born at under 33 weeks. For babies over 33 weeks gestation, breastmilk in sufficient volume (220ml/kg/day) is considered nutritionally adequate, although some vitamin and mineral supplements may be needed (Shaw, 2015). We have included some information on BMF in this report since this has been raised in discussions as a topic that health professionals would like more information on.

Commercial representatives may offer free samples of breastmilk fortifiers and may believe these are not covered by the WHO Code. However, accepting any gift from a commercial representative is discouraged for those who work within the WHO Code, and breastmilk fortifiers share brand names with breastmilk substitutes

Breastmilk fortifiers have been developed to provide additional nutrients to expressed breastmilk, particularly protein, calcium, and phosphate as well as vitamins and trace minerals. A Cochrane review considering evidence for the role of breastmilk fortifier in enhancing growth (Kuschel and Harding, 2004) reported that, whilst supplementation of human milk with multicomponent fortifiers was associated with short-term increases in weight gain, and in linear and head growth, no effect on serum alkaline phosphatase levels was observed. The authors concluded that there were insufficient data to evaluate long-term neurodevelopmental and growth outcomes, although there appears to be no effect on growth beyond 1 year of life and insufficient evidence to be reassured that there are no deleterious effects. A further Cochrane review in 2016 (Brown et al, 2016) reported that multi-nutrient fortification of human milk for preterm infants was associated with small increases in length gain and head growth during neonatal admission. However the authors again report limited data of any benefit beyond infancy and that there is little consistent evidence of other potential benefits or harms of fortification including effects on risk of feeding or bowel problems.

There has been some debate in the literature about the efficacy of a fortifier produced from human milk in reducing the risk of necrotising enterocolitis (NEC) compared to one made from bovine milk (Embleton et al, 2013). Breastmilk fortifiers derived from human milk are made by a US company, Prolacta Bioscience. They are being used in clinical trials in the UK and the company say they are now actively working in the UK with a public affairs company called RPP to promote the products. A statement reviewing the evidence on the efficacy of these products is currently being prepared, but caution is needed before accepting the evidence provided by the company alone on the benefits of these expensive products, which are made from pooled breastmilk purchased from women in the US and elsewhere.

A review of the fortification of human milk for preterm infants acknowledges the challenge in providing adequate nutrition to very low birthweight infants and suggests three strategies for fortification (Radmacher and Adamkin, 2017).

1. Standard fortification: the most widely used strategy is based on the assumption that the human milk being fortified has a protein content of 1.5g/100ml. A fixed dose of fortifier is added to milk over the entire fortification period and does not account for any changes in the energy and nutrient content of the milk being fortified. Evidence suggests that variations in the nutritional content of human milk make this an imprecise method.

2. Adjustable fortification: this method uses serial measurements of the urinary nitrogen levels to assess protein nutrition and the amount of fortifier that might be required.

3. Targeted fortification: this method uses infrared spectroscopy to analyse human milk in real time and assess the additional energy, protein and nutrient needs. It has been shown that the nutrient profile of human milk varies between women and within the same woman and challenges assumptions that standard amounts of fortifiers are needed. Periodic human

milk analysis could be helpful in supporting the nutritional plan for each infant and prevent growth faltering in the critical NICU period.

The authors point out in this review that adding standard fortifiers to human milk, when it may be that protein is the nutrient that is needed, increases the amount of other nutrients and this may impact on osmolarity.

It is currently advised that BMF be added to the minimum amount of breastmilk possible, and that this is used before fortifying any more milk to avoid prolonged storage, since the BMF may impact on the breastmilk's immunological components (although this has yet to be quantified) (Shaw, 2015).

Osmolarity and osmolality

It should be noted that osmolarity and osmolality are expressed in different units, and when reading papers or comparing products it can be confusing if different figures are given.
Osmolality is the concentration of a solution in terms of osmoles of solute per kilogram of solvent, expressed as mOsm/kg.
Osmolarity is the concentration of a solution in terms of osmoles of solute per litre of solution, expressed as mOsm/L.

In the UK we provide information on the osmolality (mOsm/kg) of products, but not all products, even when marketed here, provide information on this. Studies from other areas frequently use osmolarity (mOsm/L) as a measure, so this needs to be considered when comparing recommendations.

The osmolality of human milk is about 300mOsm/kg but this can be increased when fortifiers, nutritional supplements or medications are added. The present guidelines of the American Academy of Pediatrics recommend that osmolarity should be no more than 400mOsm/L for breastmilk or infant formulae to minimise the risk factors for necrotising enterocolitis. In the UK it has been recommended that osmolality should be kept below a maximum of 500mOsm/kg in normal conditions but that this should drop below 400mOsm/kg in malabsorptive states (Shaw, 2015). A recent systematic review on milk feed osmolality looking at whether this caused adverse gastrointestinal events in newborn and low birthweight infants concluded that there was no consistent evidence that differences in osmolality in the range 300-500 mOsm/kg are associated with adverse events in neonates (Ellis et al, 2019). In this review they found seven studies which showed no difference in adverse events with varying feed osmolalities, one study that reported delayed gastric emptying with feed osmolality of 539mOsm/kg, one which reported higher NEC incidence with feed osmolarity of 650mOsm/L compared with a feed of 359mOsm/L, but one study that found that NEC incidence was higher with a lower osmolarity feed.

A study looking at the impact of breastmilk fortifier on osmolarity of human milk samples (in this study human milk had a median osmolarity of 297mOsm/L) reported that adding breastmilk fortifier increased osmolarity up to 436mOsm/L (95% confidence interval 431-441mOsm/L) (Kreissl et al, 2013). The authors noted that the increase in osmolarity observed in this detailed study was significantly greater than the increase claimed by the

manufacturer of the product they used, and urged caution in using fortifiers until a rate of feed has been established which will minimise feeding difficulties (suggested by them as 100ml/kg/day). The authors also noted that processing of milk impacted on osmolarity, with thawed breastmilk/fortifier mixtures showing the highest osmolarity. The paper, published by ESPGHAN, provides a detailed review of impacts on osmolality when a range of fortifiers and micronutrients are added, and discussion of these findings should be part of the decision-making process around the fortification of breastmilk.

Guidance on using breastmilk fortifiers safely, prepared by Imperial College Healthcare NHS Trust, can be found in section 4.

Breastmilk fortifier comes in sachets, and currently there are two brands available: Cow & Gate Nutriprem Human Milk Fortifier, which is provided in 2.2g sachets of powder; and SMA Breast Milk Fortifier which comes in 1g sachets of powder. Both brands of BMF provide information on the impact of the BMF on the composition of breastmilk but give different values for breastmilk as they use different reference values. The nutrients in BMF, and the nutritional composition of breastmilk per 100ml with the addition of BMF, are shown in Table 1.

TABLE 1. The nutritional composition of breastmilk fortifiers for preterm and low-birthweight infants, suitable from birth

Nutrients per 100ml	Cow & Gate Nutriprem Human Milk Fortifier *	SMA Breast Milk Fortifier *	Cow & Gate data used for 100ml preterm breastmilk[1]	SMA data used for 100ml preterm breastmilk[2]	Preterm breastmilk (100ml) plus Cow & Gate Nutriprem Human Milk Fortifier	Preterm breastmilk (100ml) plus SMA o Breast Milk Fortifier
MACRONUTRIENTS						
Energy kcal	15	17.2	67	68	82	85.2
Protein g	1.1	1.4	1.6	1.6	2.7	3.0
Whey:casein ratio	50:50	100:0	NS	NS	NS	NS
Carbohydrate g	2.7	1.3	7.3	7.3	10.0	8.6
– of which lactose g	0	NS	7.3	7.3	7.3	NS
Carbohydrate source	Malto-dextrin	Malto-dextrin	Lactose	Lactose	Lactose, malto-dextrin	Lactose, malto-dextrin
Fat g	0	0.7	3.5	3.5	3.5	4.2
Added LCPs ARA	×	×	NA	NA	×	×
DHA	×	✓	NA	NA	×	✓
MCT	×	✓	×	×	×	✓
VITAMINS						
Vitamin A µg-RE	232	380	15	90	247	470
Vitamin C mg	12	20	4.4	4.4	16.4	24.4
Vitamin E mg	2.6	4.4	0.35	0.29	3.0	4.7
Vitamin D µg	5.0	4.0	0.2	0.2	5.2	4.2
Vitamin K µg	6.4	8.8	2.0	2.0	8.4	10.8
Thiamin (B_1) µg	130	160	8.9	9.0	140	169
Riboflavin (B_2) µg	170	200	27	27	200	227
Niacin µg (mg NE)	2300	1520	210	210	2500	1730
Vitamin B_6 µg	110	120	6.2	6.0	100	126
Vitamin B_{12} µg	0.2	0.2	0.02	0.02	0.2	0.22
Folic acid µg	30	40	3.1	3.1	33.1	43.1
Biotin µg	2.5	3.6	0.54	0.54	3.0	4.14
Pantothenic acid µg	800	800	230	230	1000	1030
MINERALS						
Calcium mg	66	76	25	25	91	101
Chloride mg	25	32	58	58	83	90
Copper µg	40	40	40	38	80	78
Iodine µg	11	16.8	17.8	17.8	28.8	34.6
Iron mg	0.0	1.8	0.09	0.09	0.09	1.89
Magnesium mg	5.0	4.0	3.3	3.3	8.3	7.3
Manganese µg	8.0	8.0	0.4	0.4	9.0	8.4
Phosphorus mg	38	44	14.5	14.5	52.5	58.5
Potassium mg	23	48	50	50	73	98

Nutrients per 100ml	Cow & Gate Nutriprem Human Milk Fortifier *	SMA Breast Milk Fortifier *	Cow & Gate data used for 100ml preterm breastmilk[1]	SMA data used for 100ml preterm breastmilk[2]	Preterm breastmilk (100ml) plus Cow & Gate Nutriprem Human Milk Fortifier	Preterm breastmilk (100ml) plus SMA o Breast Milk Fortifier
Selenium µg	1.7	3.7	2.4	2.4	4.1	6.12
Sodium mg	35	36.8	28	28	63	64.8
Zinc mg	0.61	0.96	0.37	0.37	0.98	1.33
ADDED INGREDIENTS						
Added antioxidants	✓	✓	NA	NA	✓	✓
Contains soya	×	×	NA	NA	×	×
Contains fish oil	×	✓	NA	NA	×	✓
Contains egg lipid	×	×	NA	NA	×	×
Suitable for vegetarians	✓	×	✓	✓	✓	×
Halal approved	×	✓	NA	NA	×	✓
Osmolality mOsm/kg			NS	NS	450	Approx. 390**

ARA = arachidonic acid
LCP = long chain polyunsaturated fatty acid
NA = not applicable
DHA = docosahexaenoic acid
MCT = medium chain triglycerides
NS = not stated

* The nutrients listed are for the amount of breastmilk fortifier that is recommended for addition to 100ml of breastmilk. For Cow & Gate this is 2 x 2.2g sachets of powder, and for SMA 4 x 1g sachets of powder. These values have been derived from the given composition per sachet added to the values for breastmilk and small differences may be due to rounding of values for product composition provided to us.

** Value given by SMA is for mature breastmilk (100ml) plus 4x1g sachets SMA Pro Breast Milk Fortifier.

1 Reference given by Cow & Gate as mean values found in:

Koletzko B et al. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev. Nutr. Diet, Karger 2014 vol 110: 304-305.

2 Reference given by SMA as:
Tsang R, Uauy R, Koletzko B, Zlotkin S (eds). *Nutrition of the Preterm Infant. Scientific Basis and Practical Guidelines*. Second edition. Digital Educational Publishing. 2005.

Protein supplements

Cow & Gate offers the only protein supplement for breastmilk fortification currently available on the market. This has been developed to provide additional protein for extremely low birthweight babies (less than 1,000g). The supplement may be added to either fortified expressed breastmilk or preterm infant milk where the protein content is less than the 3.6-4.1g/100kcal (4.0-4.5g/kg/day) as recommended by ESPGHAN (2010).

The ESPGHAN published paper by Kreissl et al (2013) on osmolarity of breastmilk with added fortifiers reported that additional protein supplementation increased the osmolarity of the breastmilk/fortifier mixture by 23.5mOsm/L per 0.5g step, up to a maximum of 605mOsm/L. We recommend that those who prescribe and use breastmilk fortifiers review the data in this study, as the authors urge caution when adding a variety of fortifiers and micronutrients to breastmilk, and also suggest that regular osmolarity measurements are taken to ensure that risks to infants are minimised.

The protein supplement comes in 1g sachets of powder. Information on the nutrients in the protein supplement and the impact of the protein supplement on the composition of breastmilk and Nutriprem 1 preterm formula milk per 100ml, are provided by Cow & Gate and are shown in Table 2.

TABLE 2. The nutritional composition of protein supplement for preterm and low-birthweight infants, suitable from birth

	Cow & Gate Nutriprem Protein Supplement (1g sachet)	**Cow & Gate Nutriprem 1** (100ml)	**Preterm breastmilk** (100ml) **with 4.4g Cow & Gate Breastmilk Fortifier** (2 x 2.2g sachets) **and Cow & Gate Nutriprem Protein Supplement** (1g sachet)	**Cow & Gate Nutriprem 1** (100ml) **with Cow & Gate Nutriprem Protein Supplement*** (1g sachet)
MACRONUTRIENTS				
Energy kcal	3.4	80	85.4	83.4
Protein g	0.82	2.6	3.5	3.4
Whey:casein ratio	50:50	60:40	NS	NS
Carbohydrate g	0.02	8.4	10.0	8.4
– of which lactose g	0.01	5.0	7.3	5.0
Carbohydrate source	NA	Maltodextrin, lactose, oligosaccharides	Lactose, maltodextrins	Maltodextrin, lactose, oligosaccharides
Fat g	0.001	3.9	3.5	3.9
Added LCPs ARA	×	✓	×	✓
DHA	×	✓	×	✓
MCT	×	✓	×	✓
VITAMINS				
Vitamin A µg-RE	0	361	247	361
Vitamin C mg	0	17	16.4	17
Vitamin E mg	0	3.6	3.0	3.6
Vitamin D µg	0	3.1	5.2	3.1
Vitamin K µg	0	6.0	8.4	6.0
Thiamin (B_1) µg	0	140	140	140
Riboflavin (B_2) µg	0	210	200	210
Niacin µg **(mg NE)**	0	2400 (3.2)	2500	2400 (3.2)
Vitamin B_6 µg	0	120	100	120
Vitamin B_{12} µg	0	0.29	0.22	0.29
Folic acid µg	0	35	33.1	35
Biotin µg	0	3.6	3.0	3.6
Pantothenic acid µg	0	880	1030	880
MINERALS				
Calcium mg	5.2	101	96.2	106.2
Chloride	0.7	86	83.7	86.7
Copper	0	80	80	80
Iodine µg	0	27	28.8	27
Iron mg	0	1.6	0.09	1.6
Magnesium mg	0.5	8.0	8.8	8.5
Manganese µg	2.0	10	10	12
Phosphorus mg	5.2	63	57.7	68.2

	Cow & Gate Nutriprem Protein Supplement (1g sachet)	Cow & Gate Nutriprem 1 (100ml)	Preterm breastmilk (100ml) with 4.4g Cow & Gate Breastmilk Fortifier (2 x 2.2g sachets) and Cow & Gate Nutriprem Protein Supplement (1g sachet)	Cow & Gate Nutriprem 1 (100ml) with Cow & Gate Nutriprem Protein Supplement* (1g sachet)
Potassium mg	12.3	82	85.3	94.3
Selenium µg	0.3	4.5	4.4	4.8
Sodium mg	7.8	70	70.8	77.8
Zinc mg	0	1.1	1.0	1.1
OTHER				
Added antioxidants	×	✓	✓	✓
Contains soya	×	✓	×	✓
Contains fish oil	×	✓	×	✓
Contains egg lipid	×	✓	×	✓
Suitable for vegetarians	✓	×	✓	×
Halal approved	×	✓	×	×
Osmolality mOsm/kg	40	345	490[1]	385[2]

* We have calculated these values based on those for each component as the details for Nutriprem 1 have not been updated in the manufacturer's version of this combination of products.
1 Calculated from Preterm breastmilk (100ml) plus Cow & Gate Nutriprem Human Milk Fortifier (Table 1) plus 40 mOsmol/kg H_20 per 1g of protein supplement powder as published by manufacturer.
2 Calculated from Cow & Gate Nutriprem 1 (100ml) plus 40 mOsmol/kg H_20 per 1g of protein supplement powder as published by manufacturer

ARA = arachidonic acid
DHA = docosahexaenoic acid
LCP = long chain polyunsaturated fatty acid
MCT = medium chain triglycerides
NA = not applicable
NS = not stated

2.7 Concentration of powdered infant milk to increase energy and nutrient content

There are no UK guidelines outlining how the concentrating of powdered infant milks should be undertaken to increase the energy and nutrient content by volume. However, this is common clinical practice in infant and child feeding.

The systematic review of infant milk feed preparation undertaken by Renfrew et al in 2003 noted that different scoop sizes and a lack of universal instructions make parental education on how to use infant milks in this way more complicated, and introduces risks during reconstitution, particularly when infants may change infant milk (Renfrew et al, 2003). For example, the specialised infant formulas in this report have scoops that vary in size from 4.2g to 7.0g. Some manufacturers do not state what the ratio of formula and water should be, only that it should be prepared using the 'prescribed number of scoops'.

Osmolality is normally maintained homeostatically at around 280-300mOsm/kg H_20 (Thomas and Bishop, 2007). It has also been recommended that osmolality should be kept below a maximum of 500mOsm/kg H_20 to prevent the development of necrotising enterocolitis and/or osmotic diarrhoea in normal conditions; this should drop to below 400mOsm/kg H_20 in malabsorptive states (Shaw, 2015).

A study by Steele et al measured the osmolality of powdered infant milks (Pepti-junior, Enfamil AR and Neocate) at three different concentrations, as well as a range of infant milks to which modular supplements (Thick & Easy, Thixo-D, Calogen, Super Soluble Duocal and Super Soluble Maxijul) were added. They found that it was possible to accurately predict osmolality after observing a linear relationship between osmolality and concentration of infant milk. The study authors also found that concentrating infant milks often resulted in an osmolality exceeding 400mOsm/kg H_20 (Steele et al, 2013). Of note, laboratory scales were used in the study and these gave more conservative results than the scoops that would be used conventionally in hospital and community settings; use of scoop as opposed to scales has been found to result in higher osmolality, suggesting that the osmolality of feeds made up in the hospital/community setting could be higher (Paxson et al, 1977).

There has been some discussion about how the concentration of powdered infant milks may lead to the prescribing of nutrients, whether purposefully intended or by accident, which may in some cases exceed tolerable upper limits set out in UK law. Of particular concern is the likelihood that concentrated formula may result in intakes of vitamin A that exceed the safe upper limit (SUL). Anyone over concentrating powdered infant formula should consider the changes to osmolality as well as the micronutrient intake and ensure that these are within safe levels.

2.8 Indications for specialised infant milk

There is a lack of evidence, and no published guidance, to support health professionals in assessing whether a breastfed baby genuinely requires supplementary milk. The decision to introduce a breastmilk substitute, including a specialised infant milk, must be taken with due consideration and understanding of the risks to the breastfeeding mother, her infant and the environment associated with this decision. Inappropriate or poorly supported introduction, use and ongoing assessment and management of specialised infant milk, either in tandem with breastfeeding or instead of breastfeeding, can have long-term adverse consequences, including impacting on a woman's belief and efficacy in her ability to feed her baby (Sachs and Dykes, 2006). Sachs and Dykes also highlight the lack of published recommendations to support health professionals or parents to make the transition back to breastfeeding once supplementary feeding is no longer required.

It is important to note that breastfeeding is rarely contraindicated and with skilled input can be carefully managed alongside dietary management of most conditions (WHO, 2009). For many sick babies – for example, preterm babies – breastfeeding is vital to their well-being, short-term transition to health, and longer-term health outcomes.

Clinical conditions, surgery and separation of mother and baby may warrant supplementation, but these need individual assessment and may not always lead to

cessation of breastfeeding or the introduction of a specialised infant milk. Expressed milk and donor human milk should always be considered as the next best options.

Whilst there are WHO guidelines which list the clinical conditions affecting the ability to breastfeed (WHO, 2009), in many countries such as the UK breastfeeding is now encouraged in all but a few rare conditions. The Academy of Breastfeeding Medicine in the US has a protocol on maternal and infant indications for supplemental feeding which may be of interest (Academy of Breastfeeding Medicine Protocol Committee, 2009).

2.9 Faltering growth

Specialised milks are often prescribed following referral to a dietitian or GP due to concern about growth and/or nutritional status. This is commonly after a period of slow weight gain or weight loss and nutritional screening.

National guidelines on faltering growth were published in 2017 (NICE, NG75, 2017[2]). This guidance makes a distinction between:

1) weight loss in the early days of life (which may occur in some babies due to natural fluid losses and which is markedly different in risk when compared with acute weight loss during early life when a baby is not clinically thriving and may require urgent or life saving help) and 2) faltering growth after the early days of life.

Where a baby loses more than 10% of its body weight in the early days of life, NICE recommends that health professionals:

- Perform a clinical assessment, looking for evidence of dehydration, or of an illness or disorder that might account for the weight loss
- Take a detailed history to assess feeding
- Consider direct observation of feeding
- Ensure observation of feeding is done by a person with appropriate training and expertise (for example, in relation to breastfeeding and bottle feeding)
- Perform further investigations only if they are indicated based on the clinical assessment

If infants lose more than 10% of their birth weight in the early days of life, or they have not returned to their birth weight by 3 weeks of age, health professionals should consider referral to paediatric services if there is evidence of illness, marked weight loss, or failure to respond to feeding support.

It is important that a specialised infant milk is only prescribed following detailed medical, growth and feeding assessments by trained health professionals. Breastfeeding mothers need support from qualified practitioners, and supplementary formula should only be introduced after a mother has been shown and knows how to build and/or maintain her breastmilk supply and how to feed comfortably and effectively. A formula should only be used for the period during which clinical concerns remain about a clinical condition (Health Development Agency 2005; Unicef UK Baby Friendly Initiative, 2012).The NICE 2017

[2] https://www.nice.org.uk/guidance/ng75

guidelines recommend that healthcare professionals should be aware that supplementary feeding with infant formula in a breastfed infant may help with weight gain, but often results in cessation of breastfeeding. Mothers may benefit from knowing that data shows that an infant's growth normally catches up by around 2 years providing that feeding difficulties have resolved (Hollén et al, 2014). Where supplementation is given to a breastfed baby health professionals should:

- Support the mother to continue breastfeeding
- Advise expressing breastmilk to promote milk supply and
- Feed the infant with any available breastmilk before giving any infant formula.

Feeding support, and in particular breastfeeding support, should be given before, during and after any intervention or care for faltering growth. It has been suggested that medical intervention, developmental delay, IQ deficits and difficulties with attachment behaviour associated with early slow weight gain might be reduced by greater health professional vigilance to identify and manage feeding difficulties (Hollén et al, 2014).

The position and point in time from which an infant starts to fall through weight centiles is important, and a common-sense approach can help avoid unnecessary intervention. For example, for an infant starting on the 9th centile for weight, a fall through one centile space is of significance, although an infant on the 91st centile might move through three centile spaces before provoking similar concern (Shields et al, 2012). The first six weeks of life tend to reflect a regression to a mean weight as babies are no longer influenced by placental function and the maternal uterine environment. After this time, growth patterns more reliably reflect independent infant growth.

The NICE guidelines suggest the following criteria as thresholds for concern for faltering growth:

- A fall across 1 or more weight centile spaces, if birthweight was below the 9th centile
- A fall across 2 or more weight centile spaces, if birthweight was between the 9th and 91st centiles
- A fall across 3 or more weight centile spaces, if birthweight was above the 91st centile
- When current weight is below the 2nd centile for age, whatever the birthweight

The guidelines also highlight the need to accurately plot weight, length (birth-2 years) and use common sense when differentiating between a small baby from small parents (determined by comparing an infants' length calculating mid-parental height centile) and an infant with concerning growth.

Faltering growth can be multifactorial and unclear, however preterm, babies with neurodevelopmental concerns and babies born to mothers with post-natal depression or anxiety have a greater risk of faltering growth. Ensuring these details are captured in a history is important.

Although the guidelines recommend asking parents or carers of infants to keep a record of food intake it is noteworthy that the best measure of how well breastfed babies are feeding is

output rather than input related. Monitoring urine and stool output alongside clinical signs and weight will give a more accurate picture of input.

As with all good clinical care, the guidelines require any intervention to have a clear rationale, treatment goals and plans for withdrawal once goals are reached so as to normalise the feeding experience as soon as is indicated or safe.

Evidence shows that infant growth charts are complex and require training to facilitate skilled interpretation. This is particularly pertinent where there are concerns about growth and weight, in order to avoid unnecessary intervention, parental anxiety and undermining of breastfeeding (Sachs et al, 2006; Wright et al, 2013). To meet this need, the Royal College of Paediatrics and Child Health has produced training and education resources in addition to guidance regarding the optimal frequency of growth monitoring (Royal College of Paediatrics and Child Health, 2013).

2.10 Appropriate prescribing

In the current economic climate it is important for NHS organisations to ensure that foods for special medical purposes are appropriately prescribed. Between 2006 and 2016, prescriptions of specialist formula milks for infants with cows' milk protein allergy (CMPA) increased by nearly 500% from 105,029 to over 600,000 a year (PrescQIPP, 2016) while NHS spending on these products increased by nearly 700% from £8.1m to over £60m annually (NHS Digital, 2017). The increased prescribing and spend in this area has been suggested as being due to industry influence on over-diagnosis and evidence for this was outlined by Chris van Tulleken in an article in the BMJ in December 2018 (van Tulleken, 2018).

Reasons for the increase in spend were also investigated by the NHS London Procurement Partnership (LPP)[3], a London-based NHS initiative which collaborates with NHS organisations and social enterprises to deliver savings and improvements to enhance patient care.

In London the reasons for the increase in spend were suggested as:

- The increasing cost and range of paediatric specialised nutrition products
- Inequities in dietetic provision across London which mean that infants/children may be started on an inappropriate feed for a prolonged period
- Greater focus on allergy and training by companies that sell specialised formula, leading to greater, but sometimes misdiagnosed, identification of cows' milk protein allergy
- Poor communication between the acute and public health/GP sectors of the NHS, leading to inappropriate prescription
- Inappropriate use of a product as a first-line infant milk
- Wastage from over-prescribing, and

[3] For further information on the London Procurement Partnership and (after registering) to access its annual report, data analysis and GP guides and prescribing templates, see the LPP website http://www.lpp.nhs.uk/. This requires an NHS account.

- Parental reluctance to change products.

As different NHS Trusts have different dietetic and GP service provision, so prescribing guidelines will vary by Trust, but in many places they have been produced by individual clinical commissioning groups (CCGs). The London Procurement Partnership (LPP) has produced unsponsored GP guides to help support GP decision-making with regards to re-challenging children with allergies, outlining appropriate prescribing volumes per month, providing templates to make sure that prescribing of specialised nutrition products contains all essential information (e.g. anthropometry, product name, unit size, daily dose, monthly volume, prescribing goal, and plans for review), and lists current prices of these products.

The LPP recommends five ways to address spend on specialised nutrition products:

1. Understanding local prescribing and cost data by liaising with medicines management teams.
2. Understanding local dietetic capacity and their referral criteria into primary, secondary and tertiary organisations.
3. Implementing appropriate prescribing initiatives to reflect local priorities, e.g. developing local feeding guidance, and auditing high-spending GP practices using Scriptswitch software.
4. Collecting outcome (clinical, experience, financial, output) data.
5. Sharing data with GP practices, dietetic departments and CCGs.

2.11 Specialised milks prescribed for infants with food allergy

One of the most widely used specialised infant milks categories covers milks designed for use when an infant has a hypersensitive reaction to a food component. This can be an immediate IgE mediated allergic reaction or a delayed non IgE mediated food allergy, and infants can have single or multiple food allergies.

It is estimated that the lifetime self-reported prevalence of allergy to common foods in Europe ranges from 0.1 to 6.0% (Nwaru et al, 2014). Although food allergies are more common in children than adults many children outgrow their allergies during infancy and childhood. Food allergies are caused by the immune system handling harmless proteins in certain foods as a threat. The immune system releases a number of chemicals, which trigger an allergic reaction. The most common types of food allergy in infants and children are: hen's egg, cows' milk, peanut, soy, wheat and fish.

NICE guidelines on food allergy in children (CG 116, 2014) outline common symptoms and assessment procedures for diagnosis. As the impact of being diagnosed with a food allergy can lead to a significantly reduced quality of life, it is vital, wherever possible, that normal physiological feeding continues with removal of the suspected allergens to protect the feeding experience as an infant develops.

An infant's allergic reaction may, however, be life threatening and in these cases treatment needs to be clear, accurate and delivered as quickly and safely as possible to reduce risk of further reactions and co-morbidities. The risks of giving formula to a breastfed baby however

may result in a higher incidence of allergy, and more severe allergy, so changing feeding regimes should be done with caution and support.

It has been reported however that cows' milk protein allergy can be over-diagnosed among children with food allergy symptoms. A study of 381 infants exhibiting a possible adverse reaction to cows' milk found that 243 of them (64%) were mislabelled with a cows' milk protein allergy (Elizur et al, 2013). Almost 30% of infants with mislabelled reactions presented within the first month of life, and nearly half presented in the first two months, compared with only 9% and 20% of infants with IgE-confirmed cows' milk protein allergy. Misdiagnosis was most common in the first few months of life where infants had atopic dermatitis and where parents were more highly educated. Most infants with cows' milk protein allergy will have symptoms affecting a number of organ systems and not just the skin and the authors recommend that better parental and physician awareness of the importance of objectively diagnosing milk allergy is required to avoid mislabelling of infants as being allergic to cows' milk.

NICE clinical knowledge summary on cows' milk protein management (NICE Cows' milk allergy CKS, 2015[4]) provides guidance on how to manage suspected or diagnosed cows' milk protein allergy. The first line of support is to encourage continued breastfeeding for breastfed babies and to advise the mother to exclude cows' milk protein from her diet and to consider prescribing a daily supplement of 1000 mg of calcium and 10 micrograms of vitamin D to the mother to prevent nutritional deficiencies.

Where infants are mixed fed or exclusively formula fed then an extensively hydrolysed formula (eHF) is tolerated by the majority of infants and children (90%) with cows' milk protein allergy. These formula (often called hypoallergenic formula) are based on cows' milk but the protein is extensively broken down into smaller peptides that are less well recognised by the immune system. For the very few infants with severe allergy or multiple food allergies an infant formula which contains fully broken down proteins in the form of amino acids (amino acid based formula) should be used.

It is important to note that soy protein–based formulas, partially hydrolysed infant formula, hydrolysed pre-term formula or infant formula made from goats' milk are ***not*** suitable breastmilk substitutes for cows' milk protein allergy treatment.

Many healthcare professionals who are involved in research and practice, or who sit on expert groups looking at diagnosis and management of food allergies in infancy, work with breastmilk substitute companies, and so there is considerable conflict of interest in this area of infant nutrition. Organisations such as Allergy UK and the British Society for Allergy and Clinical Immunology (BSACI, the UK's professional society of allergists), accept considerable funds each year from the formula industry (van Tulleken, 2018). Care therefore needs to be taken when reviewing papers and guidelines from organisations and individuals where there may be conflict of interest. Health professionals should, wherever possible, use information that is conflict of interest free, and avoid any training offered in this area which is sponsored by breastmilk substitute companies.

[4] https://cks.nice.org.uk/cows-milk-protein-allergy-in-children

Information about specific formula marketed for infants with allergies can be found in sections 3.12 and 3.13.

2.12 Current cost of specialised infant milks

The cost of specialised infant milks varies and there is an extremely wide price range. To enable a clearer understanding of price we have compared the cost of infant milks per 100ml of infant milk as consumed (see Table 3). We searched the British National Formulary (BNF) for Children, which is updated on a monthly basis, and took high street prices for those milks which are available to purchase over the counter in supermarkets and pharmacies. It should be noted that some products listed on manufacturer websites are missing from the BNF for Children and some products included in that report have been discontinued. Some prices were obtained directly from NHS Supply data.To act as a comparison to these prices, main brands of cows' milk based powdered infant formula for use in term babies cost between 10p and 24p per 100ml.

TABLE 3. The current cost of specialised milks per 100ml

Prices are correct as of August 2019, unless otherwise stated.

Category	Infant milks in this category	Price per unit (£)	August 2019 BNFC price unless otherwise stated	Package weight/ volume	Cost per 100ml formula (£)
Infant milks for preterm and low-birthweight infants	Cow & Gate Hydrolysed Nutriprem	£0.47	August 2019 NHS supply	90ml	£0.53
	Cow & Gate Nutriprem 1	£0.37	Aug 2019 NHS supply	70ml	£0.53
	SMA Gold Prem 1	£0.37	Aug 2019 NHS supply	70ml	£0.53
Infant milks for preterm infants post-discharge	Cow & Gate Nutriprem 2	£1.74	✓	200ml	£0.87
	Cow & Gate Nutriprem 2 (powder)	£10.37	✓	800g	£0.20
	SMA Gold Prem 2 (liquid)	£0.30	Aug 2019 NHS supply	90ml	£0.33
	SMA Gold Prem 2 (liquid)	£2.30	Express Chemist	200ml	£1.15
	SMA Gold Prem 2 (powder)	£6.99	Chemist.co. uk	400g	£0.24
High-energy infant milks suitable for term infants from birth	Abbott Nutrition Similac High Energy	£0.73	✓	60ml	£1.22
	Abbott Nutrition Similac High Energy	£2.44	✓	200ml	£1.22
	Nutricia Infatrini	£1.56	✓	125ml	£1.25
	Nutricia Infatrini	£2.49	✓	200ml	£1.25

Category	Infant milks in this category	Price per unit (£)	August 2019 BNFC price unless otherwise stated	Package weight/ volume	Cost per 100ml formula (£)
	Nutricia Infatrini	£6.77	✓	500ml	£1.35
	SMA High Energy	£0.34	Aug 2019 NHS supply	90ml	£0.38
	SMA High Energy	£0.60	Aug 2019 NHS supply	200ml	£0.30
Thickened (anti-reflux) infant milks suitable from birth	Aptamil Anti-Reflux	£12.99	Boots	800g	£0.21
	Cow & Gate Anti-Reflux	£10.49	Boots	800g	£0.17
	Hipp Combiotic Anti-Reflux	£11.00	Boots	800g	£0.18
	Mead Johnson Enfamil AR	£3.95	✓	400g	£0.13
	SMA Anti-Reflux	£12.00	Boots	800g	£0.19
Lactose-free infant milks suitable from birth	Aptamil Lactose Free	£6.99	Boots	400g	£0.22
	Mead Johnson Enfamil O-Lac	£5.28	✓	400g	£0.17
	SMA LF	£6.00	Boots	400g	£0.17
Soy protein based infant formula suitable from birth	SMA Wysoy	£12.95	Boots	800g	£0.20
Partially hydrolysed infant milks suitable from birth	Aptamil Comfort	£12.99	Boots	800g	£0.22
	Cow & Gate Comfort	£10.49	Boots	800g	£0.17
	Hipp Combiotic Comfort	£11.00	Sainsbury's	800g	£0.18
	SMA Comfort	£12.00	Boots	800g	£0.19
	SMA HA	£12.00	Boots	800g	£0.19
Extensively hydrolysed peptide-based infant milks suitable from birth	Abbott Nutrition Similac Alimentum	£9.44	✓	400g	£0.33
	Aptamil Pepti 1	£9.87	✓	400g	£0.34
	Aptamil Pepti 1	£19.73	✓	800g	£0.34
	Mead Johnson Nutramigen 1 with LGG	£11.21	✓	400g	£0.38
	SMA Althéra	£11.09	✓	450g	£0.33
Extensively hydrolysed peptide-based infant milks with MCT, suitable from birth	Aptamil Pepti-junior	£13.67	✓	450g	£0.39
	Mead Johnson Pregestimil LIPIL	£12.43	✓	400g	£0.42
	Nutricia Infatrini Peptisorb	£3.81	✓	200ml	£1.91
Amino-acid based	Mead Johnson Nutramigen Puramino	£23.00	✓	400g	£0.78

Category	Infant milks in this category	Price per unit (£)	August 2019 BNFC price unless otherwise stated	Package weight/ volume	Cost per 100ml formula (£)
infant milks for non-metabolic disorders, suitable from birth	Nutricia Neocate LCP	£29.56	✓	400g	£1.02
	Nutricia Neocate Syneo	£29.56	MIMS Aug 2019	400g	£1.09
	SMA Alfamino	£22.98	✓	400g	£0.79
Infant milks for disorders of protein metabolism, suitable from birth	Nutricia GA1 Anamix Infant	£42.17	✓	400g	£1.58
	Nutricia HCU Anamix Infant	£42.17	✓	400g	£1.58
	Nutricia Hyper LYS Anamix Infant	£42.17	✓	400g	£1.58
	Nutricia IVA Anamix Infant	£42.17	✓	400g	£1.58
	Nutricia Methionine Free TYR Anamix Infant	£42.17	✓	400g	£1.58
	Nutricia MMA/PA Anamix Infant	£42.17	✓	400g	£1.58
	Nutricia MSUD Anamix Infant	£42.17	✓	400g	£1.58
	Nutricia NKH Anamix Infant	not available	not available	400g	not available
	Nutricia PKU Anamix Infant	£37.08	✓	400g	£1.39
	Nutricia TYR Anamix Infant	£42.17	✓	400g	£1.58
	Vitaflo International PKU Start	not available	not available	400g	not available
Modified-fat infant milks for disorders of fatty acid metabolism, suitable from birth	Nutricia Monogen	£22.01	✓	400g	£0.92
	Vitaflo Lipistart	£21.28	✓	400g	£0.80
Modified carbohydrate infant milks, suitable from birth	Nutricia Galactomin 17	£18.21	✓	400g	£0.58
	Nutricia Galactomin 19	£47.94	✓	400g	£1.55
Infant milk for calcium intolerance, suitable from birth	Nutricia Locasol	£25.33	✓	400g	£0.83
Infant milk for the dietary management of liver failure, suitable from birth	Nutricia Heparon Junior	£23.47	✓	400g	£1.06
Infant milk for the dietary management of renal disease, suitable from birth	Nutricia Kindergen	£31.50	✓	400g	£1.58
	Vitaflo Renastart	£28.96	✓	400g	£1.45

Category	Infant milks in this category	Price per unit (£)	August 2019 BNFC price unless otherwise stated	Package weight/ volume	Cost per 100ml formula (£)
Infant milk for the dietary management of epilepsy, suitable from birth	Nutricia Ketocal 3:1	£31.98	✓	300g	£1.01

* Information taken from the British National Formulary for Children and prices at Boots the Chemist and online at Sainsbury's, correct as of August 2019 except where highlighted otherwise.

2.13 Long-term consequences of using specialised infant milk

Little is known about the long-term health effects for an infant consuming specialised infant milk. There is some evidence to suggest that being exposed to breastmilk rather than a breastmilk substitute may positively affect food choices and long-term health (Trabulsi and Mennella, 2012). Although there is some evidence to support potential adverse long-term consequences in some vulnerable infant groups, this is not conclusive (Langley-Evans, 2014). Clinical practitioners often need to make clinical judgements based on short-term outcomes, such as growth, brain development, or survival, which become more pressing than any potential long-term health risks which may include obesity, oral ill-health, metabolic syndrome and cardiovascular disease. Evidence is however accumulating that obesity risks become established in early life and a review looking at the impact of prenatal and postnatal growth on childhood obesity reported that the risk of obesity increased when there was rapid postnatal growth, and that this was greater when babies had been small at birth (Matthews et al, 2017).

The European Food Safety Authority (EFSA) in their *Scientific Opinion on the Essential Composition of Infant and Follow-on Formulae* made it clear that ingredients added to infant milks should be "*in amounts that are beneficial and that the addition of unnecessary ingredients are a burden on an infant's metabolism"* (EFSA, 2014). First Steps Nutrition Trust advocates the use of the precautionary principle in decision making around the use of milk products for infants, with potential risk always taken into consideration along with potential benefit. Where there is little evidence of long-term benefit, or potential harm, this should be made clear.

2.14 How much milk to use and how to make up milk safely

The First Steps Nutrition Trust report *Infant Milks in the UK* outlines UK guidelines on how much milk term infants require by age and can be used as a reference to accompany this report (available at www.firststepsnutrition.org/composition-claims-and-costs). Infants who require specialist medical care will have their nutrient needs monitored on an individual basis.

The First Steps Nutrition Trust report *Infant Milks in the UK* also discusses the risks associated with under- and over-concentration of powdered infant milks and considerations

around the water used when making up a feed, and outlines UK policy on how to make up feeds safely (Food Standards Agency, 2005; NHS, 2011; Department of Health, 2013).

Start4Life and Unicef UK Baby Friendly Initiative, have both produced guides to support safely making up infant milk. The Unicef UK Baby Friendly Initiative and Start4Life leaflet is aimed at parents.

The Start4Life and Unicef guidance, *Guide to Bottle Feeding*, can be accessed at: www.unicef.org.uk/babyfriendly/wp-content/uploads/sites/2/2008/02/start4life_guide_to_bottle_-feeding.pdf

The British Dietetic Association produce guidance on making up milks safely in hospital which can be accessed here: www.bda.uk.com/regionsgroups/groups/paediatric/sfu_guidelines

2.15 Making up feeds marketed as foods for special medical purposes

UK policy on how to make up powdered infant milks safely states that at least 1 litre of fresh water from the cold tap should be boiled in a kettle. Previously boiled water should not be used. The boiled water should be left to cool for no more than 30 minutes. This step should ensure that the water used to reconstitute the feed is at a temperature above 70°, which will kill most of the pathogenic micro-organisms that may be present in powdered formula milk (Food Standards Agency, 2005; NHS, 2011). In 2013, following concern over some manufacturers suggesting that their products be reconstituted at temperatures below 70°C, the Department of Health reiterated its position on the safe preparation of powdered infant and follow-on formula milks and also stated that:

"... we want to be clear that all standard, non-specialised infant formula and follow-on formulas, including those containing probiotics, should be prepared in-line with current best practice, regardless of the presence of any contrary instructions on the product, in order to minimise the risk of infection." (Department of Health, 2013)

The reconstitution of milks marketed as FSMP are therefore not subject to these recommendations and it is permissable that they may be reconstituted at lower temperatures. Not following guidance to reconstitute feeds at temperatures of at least 70°C puts vulnerable infants (e.g. preterm, low-birthweight, immunocompromised infants) with special medical needs at a greater risk of microbiological contamination, as powdered feeds are not sterile and may contain harmful bacteria such as *Cronobacter sakazakii*. However, it is the opinion of the regulators at the UK competent authorities that, as an FSMP will be used under 'medical supervision', a risk assessment can be made on an individual basis. We believe this needs further review and recommend that safety is a primary consideration when using any infant milk. This position has been re-iterated in BDA guidance for the preparation and handling of specialised feeds for infants in UK hospital settings, which sets out the conditions under which some infant milks may be reconstituted at temperatures lower than 70°C. The guidelines can be accessed at : www.bda.uk.com/regionsgroups/groups/paediatric/sfu_guidelines

It may be the case that products are used under medical supervision where they are only available on prescription but when a product is freely available over the counter we believe that greater caution is needed. First Steps Nutrition Trust recommends that FSMP are not sold over the counter but are, indeed, only used under medical supervision as must be stated on the label by law.

Table 4 shows milks marketed as FSMP where reconstitution is recommended at temperatures below 70°C and gives the rationale for the lower temperatures where this has been stated by the manufacturer. Some of the manufacturers we have contacted have not offered a rationale for lower reconstitution temperatures.

TABLE 4. Infant milks where reconstitution is recommended at temperatures below 70°C, and the rationale for lower temperatures

Category	Manufacturer/ Product	Instruction	Rationale
Thickened (anti-reflux) infant milks suitable from birth	Aptamil Anti-Reflux[1]	Boil 1 litre of freshly run water. Leave kettle to cool for 45 minutes and no longer...	Unlike other formulae, this thickened feed mixes best in hand-hot water. DHSC and FSA aware
	Cow & Gate Anti-Reflux[1]	Boil 1 litre of freshly run water. Leave kettle to cool for 45 minutes and no longer...	Unlike other formulae, this thickened feed mixes best in hand-hot water. DHSC and FSA aware
	Hipp Combiotic Anti-reflux	Boil 500ml of freshly run water and leave to cool for 45 minutes.	Preparation of anti-reflux formulas is different from that for other formulas.
	Mead Johnson Enfamil AR[2]	Use boiled water left to cool to room temperature.	Not possible to make up at 70°C. DHSC notified
	SMA Anti-Reflux[1]	Boil fresh water, leave to cool no more than 30 minutes...add to sterilised bottle…cool bottle under cold running water or in a bowl or jug of cold water until lukewarm...add correct number of scoops of powder.	None given
Extensively hydrolysed peptide-based infant milks suitable from birth	Mead Johnson Nutramigen 1 with LGG[2]	Boil fresh water, measure into clean bottle, and cap. Cool down to room temperature.	To preserve the probiotic bacteria
Amino-acid based infant milks for non-metabolic disorders, suitable from birth	Nutricia Neocate LCP	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
	Nutricia Neocate Syneo	Boil fresh water for 5 minutes, pour the required amount of water into the sterilised bottle, and cool down to room temperature.	In order to preserve the *Bifidobacterium breve* M-16
Infant milks for disorders of protein metabolism, suitable from birth	Nutricia GA1, HCU, Hyper LYS, IVA, Methionine Free TYR, MMA/PA, MSUD, NKH,	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given

Category	Manufacturer/ Product	Instruction	Rationale
	PKU, SOD nd TYR Anamix Infant		
Modified-fat infant milks for disorders of fatty acid metabolism, suitable from birth	Nutricia Low Fat Module	Pour the prescribed quantity of warm, previously boiled water into a sterilised feeding bottle	None given
	Nutricia Monogen	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
Modified-carbohydrate infant milks suitable from birth	Nutricia Carbohydrate Free Mixture	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
	Nutricia Galactomin 17	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
	Nutricia Galactomin 19	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
Infant milk for the dietary management of calcium intolerance, suitable from birth	Nutricia Locasol	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
Infant milk for the dietary management of liver failure, suitable from birth	Nutricia Heparon Junior	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
Infant milk for the dietary management of renal disease, suitable from birth	Nutricia Kindergen	Boil fresh water, and cool for at least 30 minutes so that it feels warm to the wrist.	None given
Infant milk for the dietary management of epilepsy, suitable from birth	Nutricia Ketocal 3:1	Boil fresh water, and allow to cool to approx. 50°C.	None given

DHSC = Department of Health and Social Care FSA = Food Standards Agency

1 These infant milks are available over the counter without prescription.
2 These infant milks are available over the counter without prescription at pharmacies.

2.16 Compositional regulations relating to foods for special medical purposes

The current macro and micronutrient requirements for infant formula and follow-on formula are set out in EC/UK legislation (EU Commission Directive, 2006; Food Standards Agency, 2007) and Foods for Special Medical Purposes (EU Commission Directive, 1999).

In July 2016, the FSMP Directive was replaced by the Regulation on Foods for Specific Groups (FSG) (609/2013). This was adopted by the European Parliament, the European Council and the European Commission in June 2013. This directive contains new delegated acts relating to infant and follow-on formula and infant milks that are marketed as foods for special medical purposes. The new delegated act relating to foods for special medical purposes considerably strengthens the regulations that surround FSMP marketing and labelling and brings this in line with regulations for infant formula and follow-on formula.

Companies were given four years to change their products, and therefore at the present time composition and labelling of products is moving to the new regulations which DHSC tell us will still come into force in February 2020 regardless of the Brexit outcome.

Table 5 outlines current compositional standards for infant formula, follow-on formula, and foods for special medical purposes which remain applicable until February 2020. Table 6 outlines the new compositional requirements applicable from February 2020 with the changes highlighted in bold text.

TABLE 5. Macro and micronutrient requirements for infant formula, follow-on formula, and foods for special medical purposes applicable until February 2020.

	Infant formula		Follow-on formula		Foods for special medical purposes	
	Min/100ml	Max/100ml	Min/100ml	Max/100ml	Min/100ml	Max/100ml
Energy kJ	250	295	250	295	250	295
kcal	60	70	60	70	60	70
	Min/100kcal	Max/100kcal	Min/100kcal	Max/100kcal	Min/100kcal	Max/100kcal
Protein g	1.8	3.0	1.8	3.5	As per infant formula and follow-on formula values	
Carbohydrate g	9.0	14.0	9.0	14.0		
– of which lactose g	4.5	N/S	4.5	N/S		
Fat g	4.4	6.0	4.0	6.0		
Linoleic acid mg	300	1200	300	1200		
Linolenic acid mg	50	N/S	50	NS		
Prebiotic fibre g	NS	0.8[1]	N/S	0.8[1]		
VITAMINS						
Vitamin A µg-RE	60	180	60	180	60	180
Vitamin C mg	8	30	10	30	8	25
Vitamin E mg	0.5 [2]	5.0	0.5 [2]	5.0	0.5[2]	3.0
Vitamin D µg	1.0	2.5	1.0	3.0	1.0	3.0
Vitamin K µg	4	25	4	25	4.0	20
Thiamin (B_1) µg	60	300	60	300	40	300
Riboflavin (B_2) µg	80	400	80	400	60	450
Niacin µg (mg NE)	300	1500	300	1500	(0.8)	(3.0)
Vitamin B_6 µg	35	175	35	175	35	300
Vitamin B_{12} µg	0.1	0.5	0.1	0.5	0.1	0.5
Folic acid µg	10	50	10	50	4	25
Biotin µg	1.5	7.5	1.5	7.5	1.5	20
Pantothenic acid µg	400	2000	400	2000	300	2000
MINERALS						
Calcium mg	50	140	50	140	50	250
Chloride mg	50	160	50	160	50	125
Copper µg	35	100	35	100	20	120
Fluoride µg	NS	100	NS	100	NS	200
Iodine µg	10	50	10	50	5	35
Iron[3] mg	0.3	1.3	0.6	2.0	0.5	2.0
Magnesium mg	5.0	15	5.0	15	5.0	15
Manganese µg	1.0	100	1.0	100	1.0	100
Phosphorus[3] mg	25	90	25	90	25	90
Potassium mg	60	160	60	160	60	145
Selenium µg	1.0	9.0	1.0	9.0	1.0	3.0
Sodium mg	20	60	20	60	20	60
Zinc mg	0.5	1.5	0.5	1.5	0.5	2.4
OTHER						
Choline mg	7	50	NS	NS	7	50
Taurine mg	NS	12	NS	12	NS	12
Nucleotides mg	NS	5.0	NS	5.0	NS	5
Inositol mg	4.0	40	NS	NS	4	40
L-carnitine mg	1.2[4]	N/S	NS	NS	1.2[4]	NS

NS = not stated

See notes on next page.

Notes

1 Fructo-oligosaccharides and galacto-oligosaccharides (prebiotic fibre) may be added to infant milk. In that case their content shall not exceed 0.8g/100ml in a combination of 90% oligogalactosyl-lactose and 10% high molecular weight oligofructosyl-saccharose.

2 Vitamin E: 0.5mg/g of polyunsaturated fatty acids expressed as linoleic acid as corrected for the double bonds but in no case less than 0.5mg per 100kcal, and maximum 5.0mg/100kcal.

3 For products manufactured from soya protein isolates or in a mixture with cows' milk, minimum and maximum values for iron for infant milk are 0.45mg and 2.0mg respectively and for follow-on infant milk 0.9mg and 2.5mg respectively. For phosphorus, minimum and maximum values for both infant and follow-on infant milk are 30mg and 100mg respectively.

4 The L-carnitine concentration is specified only for infant milk containing protein hydrolysates or soya protein isolates.

Sources:

Infant Formula and Follow-on Formula (England) Regulations 2007.

EC Directive 2006/141/EC on Infant Formulae and Follow-on Formulae.

EC Directive 1999/21/EC on Dietary Foods for Special Medical Purposes 1999.

TABLE 6. Macro and micronutrient requirements for infant formula, follow-on formula, and foods for special medical purposes applicable from February 2020.

	Infant formula		Follow-on formula		Foods for special medical purposes	
	Min/100ml	Max/100ml	Min/100ml	Max/100ml	Min/100ml	Max/100ml
Energy kJ	250	**293**	250	**293**	250	295
kcal	60	70	60	70	60	70
	Min/100kcal	Max/100kcal	Min/100kcal	Max/100kcal	Min/100kcal	Max/100kcal
Protein g	1.8	**2.5**	1.8	**2.5**	As per infant formula and follow-on formula values	
Carbohydrate g	9.0	14.0	9.0	14.0		
– of which lactose g	4.5	N/S	4.5	N/S		
Fat g	4.4	6.0	**4.4**	6.0		
Linoleic acid mg	**500**	1200	**500**	1200		
Linolenic acid mg	50	**100**	50	**100**		
Docosahexaenoic acid (DHA)	**20**	**50**	**20**	**50**		
Prebiotic fibre g	NS	0.8[1]	N/S	0.8[1]		
VITAMINS						
Vitamin A µg-RE	**70**	**114**	**70**	**114**	**70**	180
Vitamin C mg	**4.0**	30	**4.0**	30	**4.0**	**30**
Vitamin E mg	**0.6**[2]	5.0	**0.6**[2]	5.0	**0.6**[2]	**5.0**
Vitamin D µg	**2.0**	**3.0**	**2.0**	3.0	**2.0**	3.0
Vitamin K µg	**1.0**	25	**1.0**	25	**1.0**	**25**
Thiamin (B_1) µg	**40**	300	**40**	300	40	300
Riboflavin (B_2) µg	**60**	400	**60**	400	60	450
Niacin µg (mg NE)	**400**	1500	**400**	1500	400	**3000**
Vitamin B_6 µg	**20**	175	**20**	175	**20**	300
Vitamin B_{12} µg	0.1	0.5	0.1	0.5	0.1	0.5
Folate µg-DFE[3]	**15**	**47.6**	**15**	**47.6**	**15**	**47.6**
Biotin µg	**1.0**	7.5	**1.0**	7.5	**1.0**	20
Pantothenic acid µg	400	2000	400	2000	**400**	2000
MINERALS						
Calcium mg	50	140	50	140	50	250
Chloride mg	**60**	160	**60**	160	**60**	**160**
Copper µg	**60**	100	**60**	100	**60**	120
Fluoride µg	NS	100	NS	100	NS	200
Iodine µg	**15**	**29**	**15**	**29**	**15**	35
Iron[4] mg	0.3	1.3	0.6	2.0	**0.3**	**2.5**
Magnesium mg	5.0	15	5.0	15	5.0	15
Manganese µg	1.0	100	1.0	100	1.0	**100**
Molybdenum µg	NS	**14**	NS	**14**	NS	**14**
Phosphorus[4] mg	25	90	25	90	25	**100**
Potassium mg	**80**	160	**80**	160	**80**	**160**
Selenium µg	**3.0**	**8.6**	**3.0**	**8.6**	**3.0**	**8.6**
Sodium mg	**25**	60	**25**	60	**25**	60
Zinc mg	0.5	**1.0**	0.5	**1.0**	0.5	2.4
OTHER						
Choline mg	**25**	50	NS	NS	7.0	50
Taurine mg	NS	12	NS	12	NS	12
Nucleotides mg	NS	5.0	NS	5.0	NS	5.0
Inositol mg	4.0	40	NS	NS	4.0	40
L-carnitine[5] mg	1.2	N/S	NS	NS	**1.2**	NS

See notes on the next page

Notes

1 Fructo-oligosaccharides and galacto-oligosaccharides (prebiotic fibre) may be added to infant milk. In that case their content shall not exceed 0.8g/100ml in a combination of 90% oligogalactosyl-lactose and 10% high molecular weight oligofructosyl-saccharose. Other combinations and maximum levels of fructo-oligoaccharides and galacto-oligosaccharides may be used provided their suitability for infants is demonstrated in Article 3 (3) (new regs).

2 Based on vitamin E activity of RRR-α-tocopherol.

3 Dietary folate equivalent 1µgDFE= 1µg food folate = 0.6µg folic acid

4 For products manufactured from soya protein isolates alone or in a mixture with cows' milk, minimum and maximum values for iron for infant milk are 0.45mg and 2.0mg respectively and for follow-on infant milk 0.9mg and 2.5mg respectively. For phosphorus, minimum and maximum values for both infant and follow-on infant milk are 30mg and 100mg respectively.

5 The L-carnitine concentration is specified only for infant milk containing protein hydrolysates or soya protein isolates.

Sources:

Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding

Commission Delegated Regulation (EU) 2016/128 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for food for special medical purposes

3 Specialised infant milks available in the UK

3.1 The composition of infant milks

The composition of infant milks sold over the counter in the UK is reviewed in the regularly updated First Steps Nutrition Trust report *Infant Milks in the UK* (www.firststepsnutrition.org/composition-claims-and-costs). Many of the components of specialised infant milks are the same as those in milks marketed for term infants. Please refer to the *Infant Milks in the UK* report for details of the ingredients commonly used in infant milks. Where there may be specific ingredients or sources of ingredients used in specialised milks, these are reviewed in the relevant sections in this report.

3.2 The specialised infant milk market in the UK

The specialised infant milk market is covered by several companies:

- Abbott Nutrition
- Aptamil (parent company Danone Nutricia Early Life Nutrition[5])
- Cow & Gate (parent company Danone Nutricia Early Life Nutrition)
- Hipp Organic
- Mead Johnson Nutrition
- Nutricia (Nutricia Advanced Medical Nutrition UK, parent company Danone Nutricia)
- SMA (parent company Nestlé)
- Vitaflo (parent company Nestlé).

There is a wide range of specialised infant milk products available on prescription in the UK, for a range of named conditions. The majority of specialised infant milks marketed for infants aged 0-6 months are nutritionally complete, but there are a growing number of nutritionally incomplete supplements or modules, particularly for specific macronutrients or fractions of macronutrients, such as amino acids. There has also been an increase in product ranges to include not only specialised infant milks and food supplements suitable for the first few months or year of life, but also for specialised infant milks for infants above 6 months of age. Products marketed for older infants and young children are not reviewed in this report.

5 Danone Nutricia Early Life Nutrition is the name used for the part of the larger Danone organisation that markets infant milks. In this report, for simplicity, we will continue to use Danone as the name for the producer of these infant milks.

3.3 Types of specialised infant milks available in the UK

This section describes the types of specialised infant milk currently available in the UK marketed for infants from 0-6 months.

Where we give information about specialised infant milks in this report, this information has been taken from the most recent website information or promotional material designed for health professionals or from conversations with consumer care lines or company staff. Whilst every attempt is made to give up-to-date information, it is advisable to check the dates of current datacards and refer to company websites to see if there has been any reformulation. All new or reformulated specialised milks to be sold on the UK market must be notified to a UK Government competent authority. Whilst neither the competent authorities, nor the manufacturers, will share with us data that is used for product notification, we encourage others to ask for this information.

Table 7 outlines the specialised infant milks available in the UK marketed for infants aged 0-6 months. Lactose-free, anti-reflux and comfort milks/partially hydrolysed infant milk available to purchase by parents and carers are included in this report as they are covered by regulations for foods for special medical purposes. We have also included soy-based infant formula, although this is covered by the Infant Formula Regulations (2007) since it may be suggested as a specialised formula.

TABLE 7. Prescribable and over-the-counter specialised infant milks available in the UK, suitable for infants aged 0-6 months

Category	Names of infant milks included in this category
Infant milks for preterm and low-birthweight infants	Cow & Gate Hydrolysed Nutriprem Cow & Gate Nutriprem 1 SMA Gold Prem 1
Infant milks for preterm infants post-discharge	Cow & Gate Nutriprem 2 SMA Gold Prem 2
High-energy infant milks suitable for term infants from birth	Abbott Nutrition Similac High Energy Nutricia Infatrini SMA High Energy
Thickened (anti-reflux) infant milks suitable from birth[1]	Aptamil Anti-Reflux Cow & Gate Anti-Reflux Hipp Combiotic Anti-reflux Mead Johnson Enfamil AR SMA Anti-reflux
Lactose-free infant milks suitable from birth[1]	Aptamil Lactose Free Mead Johnson Enfamil O-Lac SMA LF
Soy protein based infant formula suitable from birth	SMA Wysoy
Partially hydrolysed infant milks suitable from birth[1]	Aptamil Comfort Cow & Gate Comfort Hipp Combiotic Comfort SMA Comfort SMA HA
Extensively hydrolysed peptide-based infant milks suitable from birth	Abbott Nutrition Similac Alimentum Aptamil Pepti 1 Mead Johnson Nutramigen 1 with LGG SMA Althéra
Extensively hydrolysed peptide-based infant milks with MCT, suitable from birth	Aptamil Pepti-junior Mead Johnson Pregestimil LIPIL Nutricia Infatrini Peptisorb
Amino-acid based infant milks for non-metabolic disorders, suitable from birth	Mead Johnson Nutramigen Puramino

Category	Names of infant milks included in this category
	Nutricia Neocate LCP
	Nutricia Neocate Syneo
	SMA Alfamino
Infant milks for disorders of protein metabolism, suitable from birth	Nutricia GA1 Anamix Infant
	Nutricia HCU Anamix Infant
	Nutricia Hyper LYS Anamix Infant
	Nutricia IVA Anamix Infant
	Nutricia Methionine Free TYR Anamix Infant
	Nutricia MMA/PA Anamix Infant
	Nutricia MSUD Anamix Infant
	Nutricia NKH Anamix Infant
	Nutricia PKU Anamix Infant
	Vitaflo PKU Start
	Nutricia SOD Anamix Infant
	Nutricia TYR Anamix Infant
Modified-fat infant milks for disorders of fatty acid metabolism, suitable from birth	Nutricia Low Fat Module
	Nutricia Monogen
	Vitaflo Lipistart
Modified-carbohydrate infant milks suitable from birth	Nutricia Carbohydrate Free Mixture
	Nutricia Galactomin 17
	Nutricia Galactomin 19
Infant milk for the dietary management of calcium intolerance, suitable from birth	Nutricia Locasol
Infant milk for the dietary management of liver failure, suitable from birth	Nutricia Heparon Junior
Infant milks for the dietary management of renal disease, suitable from birth	Nutricia Kindergen
	Vitaflo Renastart
Infant milk for the dietary management of epilepsy, suitable from birth	Nutricia Ketocal 3:1

1 Some of these infant milks are not prescribable but have been included here as they are marketed as foods for special medical purposes and are therefore required to state ‘use only under medical supervision’ on the label.

3.4 Infant milks suitable for specific population groups

Parents and carers who may have access to specialised infant milks that have been imported to the UK from overseas should be strongly advised to use specialised infant milks which are known to comply with EC compositional and labelling regulations for foods for special medical purposes.

Specialised infant milk for vegetarians

Vegetarians avoid all meat and fish products and usually avoid ingredients that are sourced from slaughtered animals, such as gelatine and rennet. Whilst there is no legal definition of the term vegetarian, the Food Standards Agency identifies the legislation relevant to the use of the term and other legislation relevant to ingredient listing of animal products and provides advice on labelling foods as 'suitable for vegetarians' or 'vegetarian'. Additionally, the Vegetarian Society defines a vegetarian as: *"Someone who lives on a diet of grains, pulses, nuts, seeds, vegetables and fruits with, or without, the use of dairy products and eggs. A vegetarian does not eat any meat, poultry, game, fish, shellfish or by-products of slaughter.*" The Food Standards Agency guidance suggests that the term vegetarian should not be applied to foods that are, or are made from or with the aid of, products derived from animals that have died or have been slaughtered, or animals that die as a result of being eaten.

Specialised infant milks derived from cows' milk are generally not suitable for vegetarians due to the inclusion of fish oils and/or the use of the animal-derived enzyme rennet during the production process. Rennet, a by-product of animal slaughter, is used to separate curds from whey and, although vegetarian alternatives are available, manufacturers of infant milk do not typically use them. Infant milks derived from pork or meat protein or using pork enzymes during the manufacturing process (even though this this may not be present on the final foodstuff) are not suitable for vegetarians.

Not all manufacturers label formula milks as to their suitability for vegetarians. This may be due to the lack of a legal definition, or to confusion over the legislation relevant to labelling a product as suitable for vegetarians.

Specialised infant milk for vegans

Vegans avoid all products derived from animals. The only specialised infant milk that is suitable for vegans is the amino-acid based SMA Alfamino. Where a vegan mother requests or requires a top up or replacement for her own breastmilk for one or more infants in a neonatal unit then wherever possible donor breastmilk should be the first line of treatment before a highly specialised formula is used.

Halal and kosher specialised infant milk

Many specialised infant milks have sought approval for use by communities who require halal products. Many of those who choose a kosher diet will use specialised infant milks that are vegetarian or halal approved.

The term halal or 'permissable' can be applied both to ingredients and to the manufacturing process. The approval process tends to give halal approval status to the factory or

production facility to indicate that it has been inspected and approved to produce halal food, rather than to the product itself, so infant milks of the same brand which do not contain any haram or 'forbidden' ingredients may not all be halal approved (even if only the container size differs) if they have been made in different production facilities. For example, Danone's standard range of powdered infant milks are all halal, but none of the standard ready-to-feed infant milks are. Cow & Gate Nutriprem 2 is halal certified for the 900g powdered version and the 90ml serving, but not the 200ml serving. It is important that this is checked for each milk if it is a concern to the family seeking advice. We have asked for the halal status of all products but have not been provided with this information for a number of products and have assumed that it is not halal approved unless we have been specifically told it is.

Table 8 shows which specialised infant milks are suitable for vegetarians and vegans, and which are halal approved as at August 2019. Note that we have been unable to obtain information from manufacturers of any of the following milk categories on the suitability of these milks for special groups:

- infant milks for disorders of protein metabolism suitable from birth
- modified-fat infant milks for disorders of fatty acid metabolism, suitable from birth
- modified-carbohydrate infant milks suitable from birth
- infant milk for the dietary management of calcium intolerance, suitable from birth
- infant milk for dietary management of liver failure suitable from birth
- infant milks for dietary management of renal disease, suitable from birth
- infant milk for the dietary management of epilepsy, suitable from birth.

TABLE 8. Specialised infant milks suitable for vegetarians, vegans and those wishing to use halal products

Category of infant milk	Name of infant milk	Suitable for vegetarians	Suitable for vegans	Halal approved
Infant milks for preterm and low-birthweight infants	Cow & Gate Hydrolysed Nutriprem			✓
	Cow & Gate Nutriprem 1			✓
	SMA Gold Prem 1			
Infant milks for preterm infants post-discharge	Cow & Gate Nutriprem 2			✓[1]
	SMA Gold Prem 2			
High-energy infant milks suitable for term infants from birth	Abbott Nutrition Similac High Energy	✓		✓
	Nutricia Infatrini			✓
	SMA High Energy			
Thickened (anti-reflux) infant milks suitable from birth	Aptamil Anti-Reflux			✓
	Cow & Gate Anti-Reflux			✓
	Hipp Combiotic Anti-reflux			
	Mead Johnson Enfamil AR			
	SMA Anti-reflux			
Lactose-free infant milks suitable from birth	Aptamil Lactose Free			
	Mead Johnson Enfamil O Lac			
	SMA LF			✓
Soy protein based infant formula suitable from birth	SMA Wysoy	✓		✓
Partially hydrolysed infant milks suitable from birth	Aptamil Comfort			
	Cow & Gate Comfort			
	Hipp Organic Combiotic Comfort			
	SMA Comfort	✓		✓
	SMA HA			
Extensively hydrolysed peptide-based infant milks suitable from birth	Abbott Nutrition Similac Alimentum			
	Aptamil Pepti 1			
	Mead Johnson Nutramigen 1 with LGG			
	SMA Althéra			
Extensively hydrolysed peptide-based infant milks with MCT, suitable from birth	Aptamil Pepti-junior			
	Mead Johnson Pregestimil LIPIL			
	Nutricia Infatrini Peptisorb			
Amino-acid based infant milks for non-metabolic disorders, suitable from birth	Mead Johnson Nutramigen Puramino			✓
	Nutricia Neocate LCP	✓		✓
	Nutricia Neocate Syneo	✓		✓
	SMA Alfamino	✓	✓	

Note: Formulations can change, so check with manufacturer.

1 90ml and 200ml only, powdered product not certified.

3.5 Infant milks for preterm and low-birthweight infants

Key points

Preterm birth is defined as an infant being born before 37 completed weeks of pregnancy (gestational age). The WHO defines preterm birth as extremely preterm (below 28 weeks), very preterm (28 to less than 32 weeks), and moderate to late preterm (32 to 37 weeks). Support to provide breastmilk is of paramount importance in this population group

There are no published guidelines for optimal preterm nutrition in the UK. The cornerstone of preterm and low-birthweight nutrition is to mimic *in utero* nutrient accretion rates and prevent accumulated nutritional deficits, with the aim of achieving normal weight and length by the expected date of delivery. Three international guidelines, known as the ESPGHAN, Tsang and Koletzko guidelines, are used in UK clinical practice (Agostoni et al, 2010; Tsang et al, 2005; Koletzko et al, 2014).

There is a lack of consensus about how to achieve extra-uterine growth in the context of preterm care and morbidity, and whether such goals are optimal, or sometimes feasible. In practice many preterm infants experience growth failure or gain excessive weight due to fat deposition. Preterm and low-birthweight babies are particularly vulnerable to over- and undernutrition with poor short- and long-term health outcomes.

Human breastmilk is vital for preterm and low-birthweight babies as it confers immunological protection, improves neurodevelopmental outcomes, reduces risk of sepsis and necrotising enterocolitis (NEC), reduces readmissions in the first year post-discharge and has been shown, in long-term studies, to reduce poor long-term metabolic and cardiovascular outcomes. Human breastmilk is better digested and absorbed and is safer to feed than infant milk (American Academy of Pediatrics, 2012; Unicef, 2003) and it is often referred to as the 'best medicine' a preterm baby might receive.

Preterm infant milk has a higher energy, protein and carbohydrate content than breastmilk or infant formula and significantly higher levels of micronutrients and is often referred to in the preterm literature as 'enriched' infant milk. A Cochrane review found that higher protein intakes accelerates weight gain, but limited information is available on whether this impacts on long-term outcomes such as neurodevelopment (Fenton et al, 2014). Rapid postnatal catch up growth in babies small at birth has been linked to obesity in children and adolescents (Matthews et al, 2017).

Preterm infant milks are produced as a ready-to-feed liquid and are based on whey protein, skimmed milk, added sugars and a range of oils and fats to achieve an energy density of about 80kcal/100ml, compared to a term infant milk which has an energy content of around 66kcal/100ml.

This group of preterm infant milks is only available on prescription in the hospital setting. Successful transition to either breastfeeding or suitable infant milks available in the community after discharge from hospital will need advance planning, preparation and post-discharge monitoring.

Preterm birth is defined as an infant being born before 37 completed weeks of pregnancy (gestational age). The World Health Organisation defines preterm birth as extremely preterm (below 28 weeks), very preterm (28 to less than 32 weeks) and moderate to late preterm (32 to 37 weeks) (WHO, 2014). Being born too early is the leading cause of mortality in newborn babies in the UK and the second leading cause of mortality in children under 5 years of age (WHO, 2014). Preterm infants are often more unwell and medically unstable than other infant populations and need particularly close monitoring to avoid short- and long-term health complications.

There are highly varied nutritional practices around preterm feeding; these are reflective of the many unknowns that exist in preterm nutrition and the very varied morbidity associated with being born preterm. In preterm nutrition, the aim has been to feed sufficient nutrients to enable an infant to achieve a 'normal' weight and length by the estimated date of delivery, and to prevent or reverse nutritional deficiencies commonly observed in the preterm population. However, uncertainties concerning nutritional requirements remain, and whether feeding goals are appropriate and/or achievable and to what extent nutrients are absorbed are still debated. Other barriers that may stand in the way of normal feeding include infant and maternal morbidity, medical intervention or whether a preterm infant remains on the neonatal intensive care unit with specialised medical and breastfeeding support.

Growth failure is frequently observed in this population due to prescribed intakes not being achieved, interruptions to feeding plans, and morbidity associated with being born preterm. There has been debate in the US about what growth standards should be used for preterm infants (Fenton and Kim, 2013). It is widely accepted that no-one truly knows what the ideal growth of a preterm infant is, as feeding to these goals often results in weight and length gain but may be offset by an increased risk of cardio-metabolic disorders later in life.

It is frequently observed in the literature that preterm babies who are infant milk fed gain weight more quickly than breastfed babies, but it is not known to what extent this is because of relative overfeeding, the type of feeding (e.g. enterally fed via a feeding tube or via a bottle), or the style of feeding (e.g. *ad libitum* or controlled).

As is the case for term infants, colostrum is extremely important for a preterm infant and helps an infant transition from an intrauterine to extrauterine environment. Breastfeeding is one way that a mother of a preterm baby can be closely involved in her infant's care and if she wishes to breastfeed she should be supported with skilled help. Optimising the use of breastmilk in US neonatal intensive care units is covered in greater detail in a comprehensive review by the Academy of Breastfeeding Medicine (which was revised in 2016) and can be accessed here https://abm.memberclicks.net/assets/DOCUMENTS/PROTOCOLS/10-breastfeeding-the-late-pre-term-infant-protocol-english.pdf

Both the Unicef UK Baby Friendly Initiative and the Academy of Breastfeeding Medicine have produced protocols for choice of milk to be taken enterally. Using a step-wise approach, guidelines recommend starting with breastmilk from the breast, followed by expressed breastmilk, pasteurised donor human milk, and then artificial infant milk (Academy of Breastfeeding Medicine Protocol Committee, 2016; Unicef, 2003).

Preterm babies given breastmilk have been shown to have a significantly reduced risk of mortality and morbidity including sepsis, necrotising enterocolitis (NEC), chronic lung disease, and retinopathy of prematurity. Preterm babies show improved cognitive development, speech and jaw development, visual acuity and earlier discharge from hospital compared with babies fed preterm infant milk (Altman et al, 2009; Horta et al, 2007; Huston et al, 2014; Rønnestad et al, 2005). There is a growing body of evidence suggesting that low-birthweight infants fed breastmilk have better neurodevelopmental outcomes and lower incidence of late-onset sepsis, NEC and retinopathy of prematurity, and fewer re-hospitalisations in the first year (Underwood, 2013). This is in addition to the benefits observed in term breastfed infants by breastfeeding instead of infant milk feeding.

A Cochrane review comparing term or preterm infant milk versus donor milk (twelve trials, n=1,871) found that feeding with formula increased rates of growth during the hospital stay, but was associated with a higher risk of developing necrotising enterocolitis. Formula feeding was associated with a near-doubling of the risk of necrotising enterocolitis, but there was no evidence of an effect on all-cause mortality, or on long-term growth and neurodevelopment, (Quigley et al, 2019). Four trials compared standard term formula versus donor breast milk and eight compared nutrient-enriched preterm formula versus donor breast milk. Only the five most recent trials used nutrient-fortified donor breast milk. There are limited data from RCTs on the comparison of feeding with formula milk versus nutrient-fortified human milk. This limits the implications for practice from any review as nutrient fortification of human milk is now a common practice in neonatal care. Currently, four trials (involving more than 1100 infants) are ongoing internationally comparing donor milk and infant formula which can be included in future systematic reviews.

A recent systematic review (Walsh et al, 2019) of 7 trials and 590 infants (the authors noted the trials were all old and mostly industry funded) reported that nutrient-enriched versus standard formula for preterm infants does not reduce the time taken to regain birth weight but is associated with higher rates of weight gain and head growth (although not length gain) during neonatal unit stay after birth. A Cochrane review found that higher protein intakes accelerates weight gain but limited information is available on whether this impacts on long-term outcomes such as neurodevelopment (Fenton et al, 2014). Rapid postnatal catch up growth in babies small at birth has been linked to obesity in children and adolescents (Matthews et al, 2017).

A recent Cochrane review could not identify any trials (up to October 2018) comparing feeding preterm infants infant milk rather than their mother's own breastmilk (Dempsey & Miletin, 2019)).

Current guidelines

WHO guidelines on optimal feeding of low-birthweight infants highlight that many infants will thrive with a mother's breastmilk (WHO, 2006). Supplementation with additional micronutrients is dependent upon the exclusivity of feeding, age, weight and clinical condition of a preterm infant. In the UK, there are no national dietary guidelines for the feeding of preterm infants.

The WHO guidelines on preterm feeding state that, for infants born under 1.5kg there may be some evidence to warrant use of a preterm infant milk until the infant reaches 2.0kg in

weight, but for infants born at a weight of 1.5kg or above, the guidelines recommend that term infant milk is adequate for growth (WHO, 2006).

The WHO states that very low birthweight (VLBW) infants who cannot receive either their own mother's milk or donor milk should receive a preterm infant milk only if they fail to gain sufficient weight with term infant milk. Infant milk should be optimally delivered by cup or spoon in a responsive way to meet feeding cues, although a Cochrane review found that whilst cup-feeding significantly reduced no breastfeeding or partial breastfeeding by the time of discharge home, it increased length of stay by 10 days (WHO, 2006; Collins et al, 2008).

Three sets of guidelines (known as the Tsang, ESPGHAN and Koletzko guidelines respectively) have been published on the nutritional requirements of preterm infants (Tsang et al, 2005; Agostoni et al, 2010; Koletzko et al, 2014). Unlike term infants, preterm infants have variable higher growth demands. ESPGHAN guidelines report a higher nutritional requirement for energy, protein, calcium, potassium, sodium, phosphorus and fat-soluble vitamins than term infants. The guidelines differ in their focus, with ESPGHAN guidelines covering infants with a birthweight of 1.0-1.8kg while the Tsang guidelines cover infants from 1.0-2.5kg birthweight. Infants born at extremely low birthweights, i.e. under 1.0kg, are not addressed due to a lack of evidence, with the exception of protein requirements which ESPGHAN state are higher in extremely low birthweight infants. This has been used by SMA to make claims for their Gold Prem 1 formula (see below). A focus on lipids for preterm infants questioned whether higher doses of docosahexaenoic acid might be required until term (Lapillonne et al, 2013). New regulations will require all infant milks marketed as foods for special medical purposes to contain DHA from February 2020.

Products available

There are three specialised infant milks suitable from birth for preterm and low-birthweight infants. These are Cow & Gate Nydrolysed Nutriprem, Cow & Gate Nutriprem 1 and SMA Gold Prem 1. All are nutritionally complete for use from birth and are manufactured as a ready-to-feed (RTF) liquid (varying from 70-90ml preparations). These milks are only available in the hospital setting.

Preterm infant milks are labelled as suitable for a particular weight, i.e. current status, as opposed to birthweight or degree of prematurity at birth. Cow & Gate Hydrolysed Nutriprem is labelled for use in infants from 1.0-1.8kg and Cow & Gate Nutriprem 1 as suitable for infants from 1kg of weight. SMA Gold Prem 1 is marketed for preterm infants who are low birth weight and it is also claimed on the manufacturers website that this product is "*the only low birthweight formula that meets the ESPGHAN protein recommendations for feeding infants under 1 kg and up to 1.8 kg" .*

Nutritional composition

All of the infant milks for preterm and low-birthweight infants are predominantly whey-based and contain a blend of skimmed milk, lactose, added sugars, vegetable oils, medium chain triglycerides, long chain polyunsaturated fatty acids DHA and ARA, vitamins, minerals, trace elements and additions of inositol, taurine and choline. Cow & Gate products contain soya lecithin as an emulsifier, egg lipid and anhydrous milk fat.

The added sugars found in preterm infant milks include maltodextrin, which is a short chain glucose molecule often derived from corn, potato or rice starch, and which is added to Cow & Gate Hydrolysed Nutriprem and SMA Gold Prem 1. Glucose syrup is often added to increase the energy content and sweetness for palatability and is added to Cow & Gate Nutriprem 1. The use of, and health risks associated with consuming added sugars are discussed in more detail in the First Steps Nutrition Trust report *Infant Milks in the UK* (available at www.firststepsnutrition.org/composition-claims-and-costs).

A systematic review of randomised controlled trials investigating the effect of long chain polyunsaturated fatty acid supplementation on disease risk and neurodevelopment in preterm infants found no difference in NEC or sepsis rates (Smithers et al, 2008). The authors did find a significant increase in mental development but caveat this by saying that the two studies investigated had large effect sizes and confidence intervals. In another Cochrane review, no evidence of benefit or harm was found by adding LCPs to preterm infant milk (Schulzke et al, 2011).

A Cochrane review investigating infant milk with a high or low MCT content given over a week to exclusively infant milk fed preterm infants found eight randomised controlled trials (n=182). None of these reported any significant difference in short-term growth, gastrointestinal tolerance or NEC by MCT content (Nehra et al, 2003). The authors note that this may have been due to the short study duration of the RCTs. It should also be noted that the nutritional content and additions to a preterm infant milk in 2002 would differ from those of the present day. Long-term outcomes were not investigated.

A systematic review of nine small randomised controlled trials (RCTs) giving taurine supplementation to 189 clinically stable preterm infants born >30 weeks failed to show any benefit in improving growth (Verner et al, 2007). However, taurine is likely to continue to be added to preterm infant milks as they are to infant and follow-on milks, despite clarification from EFSA (2014) that there is no need to add taurine to infant milks. In a Cochrane review supplementary inositol was not found to result in important reductions in the rates of infant deaths, retinopathy of prematurity, intraventricular haemorrhage, bronchopulmonary dysplasia, NEC, or sepsis (Howlett et al, 2019). EFSA (2014) recommends the addition of inositol to all infant formula.

Studies quoted supporting manufacturer claims

The main health claim that specialised infant milks for premature and low-birthweight infants make is that they "*meet the particular nutritional requirements of this group*" or are "*tailored*" to meet preterm needs, i.e. that a specific nutrient or nutrients in these milks comply with the ESPGHAN, Tsang or American Academy of Pediatrics guidelines (Agostoni et al, 2010; Tsang et al, 2005).

All of the infant milks for preterm and low-birthweight infants contain concentrations of some vitamins and minerals that exceed the upper limit of the FSMP regulations (Table 8). Cow & Gate state in their marketing material that their formulations meet the ESPGHAN 2010 recommendations and contain long chain polyunsaturated fatty acids, nucleotides, vitamins and minerals to meet the requirements of growing preterm infants, which should reduce the need for additional nutrient supplementation. The currently available datacard for nutriprem 1 also includes a statement saying that it provides energy and nutrient levels which support

intrauterine growth rates with a lower volume intake than is required when either breastmilk or infant milk is used. This statement undermines breastfeeding and is not supported by evidence.

Cow & Gate have added anhydrous milk fat to their preterm formula milks. Their website claims that their formula is "*enriched with milk fat, to aid calcium and fat absorption, ease digestion and soften stools*" The clinical trials sponsored by Nutricia and used in support of these claims have previously been used to support the use of structured triglycerides in infant formula milks. Anhydrous milk fat, like structured triglycerides, has a greater proportion of the fatty acid palmitate esterified in the sn-2 position than the vegetable oils commonly used in infant milks. The studies by Carnielli et al 1996 and Kennedy at al, 1999 were conducted in term infants whilst Carnelli at al, 1995 was conducted in a very small number of preterm infants. All 3 clinical trials used test formulas containing the structured vegetable oil Betapol® and not anhydrous milk fat. The test formulas were not the same as those currently used in Cow & Gate preterm formula milks. EFSA (2014) reviewed all these studies in their expert review and reported that there was no benefit for infant health from the addition of palmitic acid predominantly esterified in the sn-2 position. A further study referenced (Quinlan et al,1995) looked at the difference in stool hardness between formula and breastfed infants and is not related to the use of anhydrous milk fat in preterm formula milks.

Cow & Gate Nutriprem also contains fructo and galacto-oligosaccharides. The Nutricia website claims that "*prebiotic oligosaccharides are proven to beneficially support gut health*" but no clinical trials are used to provide evidence of any beneficial health outcomes for the use of oligosaccharides in this formula.

SMA Gold Prem 1 also claims to have a low osmolality of 308 mOsmol/kg in keeping with American Academy of Pediatrics (AAP) guidelines (Barness et al, 1976); that it is the only low birthweight formula that meets ESPGHAN protein recommendations for feeding infants under 1kg and up to 1.8kg and that it contains ESPGHAN compliant MCT levels of 39.5%

SMA previously claimed that the blend of lactose and glucose polymers present in SMA Gold Prem 1 "*help reduce osmolality and promote gastrointestinal tolerance"* and quotes two studies. The first study was published in 1981 and was based on an underpowered study of 11 healthy premature infants given glucose polymer and lactose tolerance tests finding no difference in glycaemic response (Cicco et al, 1981). The second was a paper published in 1965 concerning glycosidase activities of neonates (Auricchio et al, 1965).

Hydrolysed preterm formula

Cow & Gate Hydrolysed Nutriprem was launched in 2014 for use in infants from 1.0-1.8kg body weight who *"require a hydrolysed protein"*. The only claim made in the literature is that it may be helpful for infants who have compromised ability to break down or absorb whole proteins or who do not tolerate standard preterm infant milks. No studies are referenced to support this claim and it is not clear who may 'require' a hydrolysed formula.

Hydrolysed Nutriprem does not explicitly state that it can be used from birth, but Cow & Gate instead says that it can be used at a rate of 150-200ml/kg/day until an infant is 1.8kg-2,0kg.

The instructions for use section of the website for Hydrolysed Nutriprem includes a statement saying that the infant milk can be used *"to complement breastmilk, i.e. given as alternate feeds with breastfeeds, or prior to the availability of breastmilk".* This statement is somewhat misleading as it could sound as though breastmilk might require complementing with infant milk feeds. This undermines breastfeeding and particularly the use of colostrum and is not supported by evidence

There is no evidence supporting the use of hydrolysed infant milks in preterm infants and some evidence of potential harm. One small randomised controlled trial of 21 infants, born at 34 weeks or below and weighing up to1.5kg looked at the impact of either preterm infant milk or a hydrolysed preterm infant milk on growth and amino-acid excretion. The hydrolysed formula was associated with significantly slower weight gain ($p<0.045$) and lower mean change in z-scores for weight ($p<0.009$) and head circumference ($p<0.049$), and higher urinary excretion of amino acids at 14 days (Maggio et al, 2005). The authors suggest that this may mean that hydrolysed formulae have less nutritional value but this needs to be confirmed by larger studies. Hydrolysed feeds have also been suggested to reduce gastrointestinal transit time in preterm infants (Mihatsch et al, 2001).

Hydrolysed Nutriprem is not suitable for infants with cows' milk protein allergy. There is a risk that, because the product name contains the word 'hydrolysed', infants showing signs of an allergic reaction might be fed an inappropriate formula. The labelling of Hydrolysed Nutriprem states that the infant milk is only for use in infants from 1-1.8kg, which could confusingly suggest that younger/smaller babies have a particular requirement for a hydrolysed product.

Hydrolysed Nutriprem is ready to feed, must be shaken as the contents settle and discolour, and must be used within one hour of opening if bottle feeding. This therefore requires careful handling at a ward level to ensure safe feeding.

The nutritional composition and ingredients used in infant milks marketed for preterm and low-birthweight infants suitable from birth are given in Table 9.

TABLE 9. The nutritional composition of infant milks for preterm and low-birthweight infants, suitable from birth

Nutrients per 100ml	Cow & Gate Hydrolysed Nutriprem	Cow & Gate Nutriprem 1	SMA Gold Prem 1
INDICATIONS	Infants 1-1.8kg	Infants >1kg	Infants <1.8kg
MACRONUTRIENTS			
Energy kcal	80	80	80
Protein g	2.6	2.6	2.9
Whey:casein ratio	60:40	60:40	100:0
Carbohydrate g	8.4	8.4	8.1
– of which lactose g	5.0	5.0	3.7
Carbohydrate source	Maltodextrin, lactose	Maltodextrin, lactose, oligosaccharides	Maltodextrin, lactose
Fat g	4.0	3.9	4.0
Fat source	Sunflower, rapeseed, MCTs (coconut and palm oils) evening primrose oil, anhydrous milk fat, fish and single cell oils	Sunflower, rapeseed, MCTs (coconut and palm oils), evening primrose oil, anhydrous milk fat, fish and single cell oils	Rapeseed, sunflower and palm oils including MCTs and single cell oils
Added LCPs ARA	✓	✓	✓
DHA	✓	✓	✓
MCT	✓	✓	✓
LCP source	Fish oil and fungal/algal oils (vegetable source)	Fish oil and fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)
MICRONUTRIENTS			
Vitamins meeting regulations	Vitamins A, D, E and C, niacin (B_3) and folic acid higher than FSMP regulations	Vitamins A, D, E, niacin (B_3) and folic acid higher than FSMP regulations	Vitamins A,D, E, C and folic acid higher than FSMP regulations
Minerals meeting regulations	Selenium, sodium and iodine higher than FSMP regulations	Selenium and sodium higher than FSMP regulations	Sodium, potassium, phosphorus, iron and selenium higher than FSMP regulations
VITAMINS			
Vitamin A µg-RE	396	361	370
Vitamin C mg	22	17	20.8
Vitamin E mg	4.5	3.6	3.6
Vitamin D µg	3.1	3.1	3.7
Vitamin K µg	6.7	6.0	6.4
Thiamin (B_1) µg	170	140	140
Riboflavin (B_2) µg	210	210	200

Nutrients per 100ml	Cow & Gate Hydrolysed Nutriprem	Cow & Gate Nutriprem 1	SMA Gold Prem 1
Niacin µg (mg NE)	(3.0)	2400 (3.2)	1600
Vitamin B_6 µg	120	120	90
Vitamin B_{12} µg	0.15	0.29	0.23
Folic acid µg	35	35	40.6
Biotin µg	3.6	3.6	4.0
Pantothenic acid µg	880	880	800
MINERALS			
Calcium mg	97	101	116
Chloride mg	78	86	76
Copper µg	80	80	80
Iodine µg	27	27	28
Iron mg	1.6	1.6	1.8
Magnesium mg	8.0	8.0	8.3
Manganese µg	10	10	10
Phosphorus mg	55	63	77
Potassium mg	87	82	120
Selenium µg	4.5	4.5	4.8
Sodium mg	76	70	51
Zinc mg	1.1	1.1	1.2
ADDED INGREDIENTS			
Prebiotics	×	✓	×
Nucleotides	✓	✓	✓
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	✓	✓	×
Contains fish oil	✓	✓	×
Contains egg lipid	✓	✓	×
Suitable for vegetarians	×	×	×
Halal approved	✓	✓	×
Osmolality mOsm/kg	395	345	308

ARA = arachidonic acid
DHA = docosahexaenoic acid
FSMP = foods for special medical purposes
LCP = long chain polyunsaturated fatty acid
MCT medium chain triglycerides

3.6 Infant milks for preterm infants post-discharge

Key points

The growth and nutritional status of preterm infants post-discharge is very varied.

Older ESPGHAN guidelines (Aggett et al, 2006) recommend the use of a post-discharge infant milk enriched with protein, minerals, trace elements and LCPs at least until a post-conceptual age of 40 weeks, but possibly until about 52 weeks.

Two Cochrane reviews (Young et al, 2012, Young et al, 2016) are in conflict with this view, finding no evidence of beneficial growth outcomes at 12-18 months of age and not supporting the use of post-discharge infant milk. There are no long-term data to assess the effect of use of post-discharge infant milk on growth or long-term cardio-metabolic outcomes. A review of proactive breastfeeding support and feeding during the inpatient stay reported a reduced need for any specialised post-discharge feeding (Lapillone et al, 2013).

Two post-discharge preterm infant milks are available on prescription for use until 6 months corrected age, in liquid and powdered format. These infant milks are based on whey protein, skimmed milk powder, added sugars and a range of oils and fats including long chain polyunsaturated fatty acids, to achieve an energy density of about 75kcal/100ml, in comparison to a standard energy content of around 66kcal/100ml in infant milk.

ESPGHAN 2006 guidance suggested that infant milk fed infants should receive post-discharge infant milk with higher protein, minerals, trace elements and LCPs until 40 weeks post- conceptual age, and potentially up to 52 weeks post-conceptual age (Aggett et al, 2006). A Cochrane review of the effect of preterm versus term infant milk feeding on preterm infants identified 10 small, randomised controlled trials of variable methodological quality (n=762) but did not find consistent evidence for any effect on growth or long-term cardio-metabolic development might persist into later life (Young et al, 2012). A further review in 2016 (Young et al, 2016) reviewed 16 eligible trials involving 1251 infants and concluded again that that there is no evidence to support the use of post-discharge formula for preterm infants after hospital discharge to improve growth and development. Another systematic review however (funded and part-authored by Nutricia) reported that nutrient enriched diets after discharge showed no negative effects but frequently improved growth parameters at some point in the course of the study, in particular for boys (Teller et al 2016). .

A Cochrane review investigating growth and development of infants given a nutrient- and energy-dense post-discharge infant milk found little evidence of efficacy at up to 18 months post term compared with infants given a term infant milk (Henderson et al, 2007b). Another systematic review by Henderson et al (2007a) in the same year found no evidence of any trials comparing human breastmilk with post-discharge infant milk, so there are no scientific data to support and guide health professionals or mothers who might want to weigh up the risks and benefits of their feeding choices. The addition of complementary foods will confound the effects of any study examining post-discharge growth in preterm infants.

A review by Lapillonne et al notes that proactive breastfeeding support and feeding during the inpatient stay helps reduce the need for any specialised post-discharge feeding, and the authors concluded that the systematic use of nutrient-enriched post-discharge infant milks must be considered carefully (Lapillonne et al, 2013).

There are two infant milks for preterm infants post-discharge which can be prescribed to preterm infants following an inpatient stay: Cow & Gate Nutriprem 2 and SMA Gold Prem 2. RTF versions of these milks are for use only in a hospital setting. The powder format (900g pack) is recommended for use up to 6 months corrected age. SMA highlights that SMA Gold Prem 2 can also be used up to 6 months corrected age and "*as the sole source of nutrition until complementary feeding commences".*

Cow & Gate Nutriprem 2 and SMA Gold Prem 2 are enriched with energy (73 to 75kcal/100 ml) and protein (2g/100ml), and have higher proportions of vitamin A, calcium, iodine, iron, phosphorus, and zinc compared with standard term infant milk. Three references are given on the Cow & Gate website to support the use of post-discharge formula, all by the same author and all taken from the same Nutricia-funded study conducted in the 1990s in Newcastle. The formula used in this study was considerably higher in energy, protein, fat and carbohydrate than those now marketed (Cooke et al, 1998, 1999, 2001).

SMA highlights that Gold Prem 2 *"contains 100% whey, partially hydrolysed protein".* They also note that preterm infants are at a high risk of continued protein deficits on hospital discharge and that SMA Gold Prem 2 has higher protein than a standard formula. This reflects a change in the formulation and marketing of the product which previously had a slightly lower level of protein but was marketed as suitable for catch-up growth.

These infant milks are sometimes referred to as 'transitional infant milks' which provides a brand/marketing continuum in the same way that historical stage 1 (first), 2 (hungrier) and 3 (follow-on) infant milks did and allows cross-promotion of products across a wider age range. A risk associated with this is that low-birthweight infants may stay on specialised infant milk for longer than is necessary or desirable. This group of infant milks are higher in energy, protein, fat, LCPs, calcium, phosphorus, iron and vitamin A than term infant milks.

The promotional literature for Nutriprem 2 makes health claims about the infant milk *"containing prebiotic oligosaccharides (OS) specially formulated for preterm and low birthweight infants".* A systematic review and meta-analysis of the safety and efficacy of oligosaccharide supplementation of preterm infant milk found no decrease in NEC, late onset sepsis or quicker establishment of full enteral feeds but did find a significant increase in beneficial micro-organisms (Srinivasjois et al, 2013). There is no evidence that the addition of prebiotics, probiotics or synbiotics to infant formula have any benefits to health in term infants (EFSA, 2014).

The nutritional composition and ingredients used in infant milk marketed for preterm infants post-discharge are given in Table 10.

TABLE 10. The nutritional composition of infant milks for preterm infants post-discharge

Nutrients per 100ml	Cow & Gate Nutriprem 2 (powder)	Cow & Gate Nutriprem 2 (200ml RTF)	SMA Gold Prem 2 (powder)
MACRONUTRIENTS			
Energy kcal	75	75	73
Protein g	2.1	2.0	2.0
Whey:casein ratio	60:40	60:40	100:0
Carbohydrate g	7.5	7.5	7.7
– of which lactose g	5.9	5.8	5.3
Carbohydrate source	Lactose, oligosaccharides maltodextrin,	Lactose, oligosaccharides, maltodextrin	Lactose, maltodextrin
Fat g	4.0	4.0	3.8
Fat source	Sunflower, rapeseed, MCT oils from coconut and palm oil, evening primrose, anhydrous milk fat, fish and single cell oils	Sunflower, rapeseed, MCT from coconut and palm oil, evening primrose, anhydrous milk fat, fish and single cell oils	Sunflower, palm, rapeseed, and coconut oils including structured vegetable oils and single cell oils
Added LCPs ARA	✓	✓	✓
DHA	✓	✓	✓
MCT	✓	✓	×
LCP source	Fish oil and fungal/algal oils (vegetable source)	Fish oil and fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)
MICRONUTRIENTS			
Vitamins meeting regulations	Folic acid higher than FSMP regulations	Folic acid higher than FSMP regulations	✓
Minerals meeting regulations	✓	✓	✓
VITAMINS			
Vitamin A µg-RE	100	100	92
Vitamin C mg	12	12	12.8
Vitamin E mg	2.1	2.1	1.7
Vitamin D µg	1.8	1.7	1.2
Vitamin K µg	5.9	5.9	6.5
Thiamin (B_1) µg	90	90	100
Riboflavin (B_2) µg	150	150	190
Niacin µg	1900	1900	700
Vitamin B_6 µg	80	80	70
Vitamin B_{12} µg	0.25	0.23	0.24
Folic acid µg	20	20	13

Nutrients per 100ml	Cow & Gate Nutriprem 2 (powder)	Cow & Gate Nutriprem 2 (200ml RTF)	SMA Gold Prem 2 (powder)
Biotin µg	3.1	3.1	2.2
Pantothenic acid µg	600	600	700
MINERALS			
Calcium mg	87	87	80
Chloride mg	56	55	48
Copper µg	60	60	60
Iodine µg	22	22	17
Iron mg	1.2	1.2	0.8
Magnesium mg	7.2	7.0	8.6
Manganese µg	8.0	10	10
Potassium mg	78	77	77
Phosphorus mg	48	48	48
Selenium µg	1.7	2.0	2.0
Sodium mg	28	28	37
Zinc mg	0.9	0.9	0.9
ADDED INGREDIENTS			
Structured vegetable oils	×	×	✓
Prebiotics	✓	✓	×
Nucleotides	✓	✓	✓
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	✓	✓	×
Contains fish oil	✓	✓	×
Contains egg lipid	✓	✓	×
Suitable for vegetarians	×	×	×
Halal approved	×	✓[1]	×
Osmolality mOsm/kg	325	310	290*

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
MCT = medium chain triglycerides RTF = ready-to-feed

*Osmolality of Gold Prem 2 liquid is 296 mOsm/kg H_20

[1] Refers to both the 90ml and 200ml servings

3.7 High-energy infant milks suitable for term infants from birth

Key points

High-energy infant milk is often used in clinical practice when an infant's growth has been shown to be faltering. This is often initially observed when an infant does not follow their anticipated genetic growth potential on WHO growth charts, but these data need to be included as part of a global assessment of the infant's current and historical nutritional status.

Growth must be accurately plotted on the correct growth chart by health professionals who are appropriately trained to use such charts, and are qualified to interpret growth data, give parental feedback and agree interventions with parents or guardians which are supported by the evidence base for infant feeding.

It is important that health professionals know how to recognise true growth faltering in term infants and that, when a mother chooses to breastfeed, health professionals are able to provide effective support to optimise her breastmilk supply before considering high-energy infant milk, and know where to signpost a mother to qualified local or national breastfeeding support services.

High-energy infant milk has a higher energy, protein and micronutrient content and a higher protein:energy ratio than breastmilk or infant formula. It is marketed as suitable for term infants for promoting catch-up growth and weight gain. This composition is achieved by reducing the water content and by adding extra energy in the form of additional protein. These infant milks are based on whey protein, skimmed milk, added sugars and a range of oils and fats to achieve an energy density of about 100kcal/100ml, in comparison to an energy content of around 66kcal/100ml in infant formula.

There is little high-quality published evidence to demonstrate the efficacy of high-energy infant milks on weight gain and catch-up growth and some good-quality evidence that high-energy infant milk is no more effective than breastfeeding. Studies on the efficacy of high-energy infant milks for term infants appear to be primarily sponsored by infant milk companies.

It has been suggested that infant milk with a markedly higher energy density than breastmilk may increase total energy intake as appetite increases and leads to excessive weight gain in infants and potentially longer term impacts on weight.
The potential long-term impacts of using high-energy infant milk on later adiposity is of concern.

As with other foods for special medical purposes, use of high-energy infant milk requires ongoing medical review to ensure its use is clinically indicated and appropriately managed only for as long as is necessary, and that it does not interfere with timely complementary feeding to avoid longer-term feeding difficulties.

In 2007, the World Health Organization recommended protein and energy requirements for catch-up growth for malnourished infants based on observational studies of malnourished wasted (thin) infants (WHO/FAO/UNU, 2007). Supplementing energy alone does not enable catch-up growth in infants and children; additional protein is also required to achieve a gain in lean and fat body mass. The protein:energy ratio of the high-energy infant milk falls between 8.9 and 11.5% energy from protein to enable catch-up growth of between 10-20g/kg/day (WHO/FAO/UNU, 2007). This is higher than infant formula which provides about 8% and human breastmilk around 6% of energy from protein.

Examples of rates of weight gain in malnourished infants during catch-up as a function of protein and energy intakes, based on observed responses in malnourished wasted infants, are given in Table 11.

TABLE 11. Protein and energy needs for catch-up growth at different rates of weight gain

Rate of gain per day (g/kg/day)	Energy (kcal/kg/day)	Protein (g/kg/day)	Protein:energy (%)
5	105	1.82	6.9
10	126	2.82	8.9
20	167	4.82	11.5

Source: World Health Organization/Food and Agriculture Organization/ United Nations University (2007).

Practitioners are advised to use the NICE guidance on faltering growth (NICE NG75, 2017) reviewed in section 2.9.

Evidence for the use of high-energy formula is limited. One well conducted randomised controlled trial, sponsored by Farley Health Products (Heinz), studied catch-up growth in term small for gestational-age infants (n=471) who were breastfed or infant milk fed either a term or high-energy infant milk. The study found that, whilst length and occipitofrontal head circumference (OFC) increases were greater at 18 months in the group receiving high-energy infant milk, after adjustment for social class, maternal education and support, parental size, and infant's sex, size at enrolment, age at follow-up, and birth order, there were no significant differences in weight, length, or OFC between breastfed infants and either infant milk fed group (Fewtrell et al, 2001). This supports the notion that, when healthy term babies are born below the 10th centile, breastfeeding is perfectly adequate and breastfed babies will grow as well as specialised formula-fed babies. This study suggests there is no rationale for introducing high-energy infant milk to enable greater growth in breastfed babies.

There has been widespread debate about early catch-up growth and to what extent this may affect long-term health (Langley-Evans, 2014). It is not known how high-energy infant milks given for prolonged periods may affect future growth and risk of later metabolic conditions, particularly in preterm, low-birthweight and small for gestational age infants who have been observed to experience rapid catch-up growth, possibly due to use of specialised infant milk. A systematic review found that high protein intakes at 2-12 months of age and higher energy intake during complementary feeding were associated with a higher body mass index and

adiposity in childhood (Pearce and Langley-Evans, 2013). Another review linked obesity in children and adolescents who had been small babies with rapid catch up growth (Matthews et al, 2017). As strong evidence demonstrates that obesity can track from childhood into adulthood, it is important to ensure that high-energy infant milks are used with care (Freedman et al, 2001).

If high-energy infant milks are used, it is important that this does not interfere with the normal age-appropriate introduction of solid foods around 6 months of age.

There are three high-energy infant milks currently marketed in the UK: Abbott Nutrition Similac High Energy, Nutricia Infatrini, and SMA High Energy. There is a fourth high-energy infant milk, Infatrini Peptisorb (Nutricia), but as it is hydrolysed it is covered in the extensively hydrolysed peptide-based infant milk section (section 3.12). These are all prescription-only products, nutritionally complete from birth and are marketed as suitable for use in conjunction with complementary foods up to 18 months of age (or until an infant reaches around 8-9kg in weight). The maximum weight for infant milk cessation varies according to individual infant milks, which may be confusing to healthcare professionals and parents alike. For example, Similac High Energy states it is for use up to 8kg, whereas Infatrini is suitable up to a weight of 9kg. SMA High Energy does not state a weight limit for when the infant milk may no longer be needed, only an approximate age guide.

High-energy infant milk is an energy- and nutrient-dense infant milk – that is, it has more energy, protein, fat, carbohydrate and micronutrients per 100ml than human breastmilk and infant formula (99-101kcal/100ml vs. about 66kcal/100ml respectively). It is aimed at term infants with medically recognised higher energy needs including faltering growth, higher than average energy requirements and/or a need for fluid restriction. High-energy infant milks are only available as ready-to-feed infant milk.

The carbohydrate content of all the high energy infant milks comes from added sugars and lactose. The added sugars used include maltodextrin which like glucose syrup, is a starch hydrolysate. Maltodextrins can contain different mixtures of saccharides dependent on the degree of hydrolysis and the sweetness and acidogenicity of each depends on its composition (Hofman et al, 2016). Maltodextrin is the first ingredient (after water) in Similac High Energy formula, the second in Infatrini and the third in SMA High Energy and all three list maltodextrin before lactose in the ingredients lists.

Maltodextrin is frequently used in infant formula milks as it is cheap to produce and can help increase the energy content of infant milk, enabling manufacturers to make reductions in protein and fat content. Although used widely by the food industry, the role of maltodextrins in the development of dental caries is unclear. Studies in animals have shown that the incidence of dental caries was significantly higher in rats fed diets containing glucose syrup or maltodextrin than in those fed diets containing sugar and flour. The authors suggest that physiological differences between diets, such as viscosity, which impacts on the clearance time from the mouth, may be partly responsible for the increased caries incidence observed in rats consuming the maltodextrin and glucose syrup diets (Grenby and Mistry, 2000).

A recent literature review by Rezende and Hashizume (2018) concluded that available studies suggest that maltodextrins, although less potent than sucrose, can increase the acidity of the dental biofilm which may lead to the demineralisation of enamel. No studies

have evaluated the cariogenic potential of maltodextrin on dentin (Rezende and Hashizume, 2018). In order to evaluate the cariogenic potential of maltodextrin in infant milks, more studies of maltodextrins alone or with other sugars are required.

Further health concerns associated with consumption of added sugars include potential programming of sweeter taste preferences from a very early age and long-term chronic diseases. These are discussed in more detail in the First Steps Nutrition Trust report *Infant Milks in the UK* (available at www.firststepsnutrition.org/composition-claims-and-costs).

Although the iron content of the high-energy infant milks (around 1.0-1.2mg per 100ml) falls within the regulations for foods for special medical purposes (minimum of 0.5mg/100kcal and a maximum of 2.0mg/100kcal), it is much higher than the UK infant formula regulations, which permit a maximum of 1.3mg/100kcal. Research has shown that iron absorption is immature in the first nine months of life (Domellöf et al, 2002). Administering large doses may put an infant in danger of iron overload and poor growth possibly as a result of iron:zinc interactions which can reduce immunity and increase infections (Koletzko et al, 2005; Iannotti et al, 2006). See *Infant Milks in the UK* for further information on iron in infant milk.

Infatrini claims to be '*the complete package for faltering growth'* and claims it has '*clinically proven efficacy in catch up growth'*. The first reference given to support this refers to a randomised study, funded by Nutricia, which compared anthropometric, biochemical and haematological outcomes in infants fed Infatrini or an energy-supplemented modular infant milk based on Cow & Gate Premium with added Maxijul (a glucose polymer) and Calogen (a long chain fat emulsion) for a 6-week period (Clarke et al, 2007). The protein:energy ratio of the two infant milks was markedly different, with 10.4% of energy from protein in the Infatrini group vs. 5.5% in the modular group. This means that one of the arms of the trial did not meet the WHO protein:energy recommendation to enable catch-up growth and this is likely to have affected the study's outcomes (WHO/FAO/UNU, 2007). The second study referenced looks at the tolerance of infants to a high energy feed rather than efficacy (Evans et al, 2006).

The modular infant milk was lower than EC regulations require for protein, chloride and niacin composition. Both infant milks were lower than EC regulations require for manganese composition. The authors state that, despite subjects having a feeding target of 150-200kcal/kg/day, the RNIs for sodium, potassium, calcium and zinc were still not achieved in either group. Unfortunately, values for actual intake are not documented in the research, and there is no discussion of why this might have occurred. An increase in weight z-score was observed in both dietary groups, but skinfold measurements to determine whether the increase was due to greater lean body mass or was an increase in fat mass were not taken. No significant difference was observed in mid-upper arm circumference (MUAC), which is an indicator of muscle mass and a proxy of wasting. The glucose polymer supplemented group experienced a decrease in length z-score with no significant difference reported in the Infatrini group. The authors acknowledge that the study may have been underpowered (n=49). It is difficult, therefore, to accept this data as evidence that Infatrini is 'optimum' in its efficacy. A small study (n=30) found that introducing Infatrini at full strength vs. a 3-day graded introduction led to statistically significant increases in stool frequency but was otherwise well tolerated. The authors noted that introducing infant milk gradually may be advisable in infants under 12 weeks of age (Evans et al, 2006).

Similac High Energy's only claim regarding enhanced growth relates to the infant milk having more than 10% of energy from protein, but does not reference studies demonstrating the product's efficacy.

SMA claim that SMA High Energy is specifically designed to meet both the nutritional needs of infants with medically identified increased energy and nutrient needs and to promote digestion and tolerance. No studies are referenced to support the products efficacy in promoting catch-up growth, however, as with other high-energy infant milks, the protein energy ratio is in line with WHO/FAO /UNU, 2007 guidelines for catch-up growth. The protein component of SMA High Energy is partially hydrolysed whey and SMA claim that this supports shorter gastric emptying time making the formula easier to digest. This claim is supported by reference to a clinical trial which showed that in 8 healthy infants fed hydrolysed whey based formula, gastric transit time was reduced compared to infants fed human milk or standard non- hydrolysed whey or casein based formula milks (Billeaud et al,1990). It is however not clear how this translates into greater tolerance or easier digestion.

Data from a large randomised trial of healthy term infants given either a standard full-lactose non-hydrolysed cows' milk protein based infant milk or a 70% lactose, partially hydrolysed whey protein formula over 60 days reported that there was no difference in tolerance of intact compared to partially hydrolysed protein (Berseth et al, 2009).

SMA High Energy also contains structured vegetable oils which it claims promotes softer stools. This claim is supported by reference to a clinical trial sponsored by Nutricia in which healthy infants were randomised to receive either standard infant formula where 12% of the palmitate was in the sn-2 position or test formula where 50% of the palmitate was in the sn-2 position. The trial reported that infants consuming the high sn-2 formula passed more runny stools and fewer formed stools and that there was no difference in parental concern over stool hardness between the test and control group but that more parents of children who received the high sn-2 formula were concerned about runny stools. This trial also measured tolerance parameters reporting no significant differences in crying between groups and more mothers of children in the high sn-2 feeding group reporting colic at week 3 than in the control group. (Kennedy et al, 1999)

The only other reference SMA use to support claims around reduced intestinal irritability and diarrhoea, and tolerance and acceptability is from an abstract presentation at the 2014 Latin American Society of Pediatric Gastroenterolgy Hepatology and Nutrition. We have been unable to find the reference cited.

The nutritional composition and ingredients used in high-energy infant milks suitable for term infants from birth, marketed for faltering growth, are given in Table 12.

TABLE 12. The nutritional composition of high-energy infant milks suitable for term infants from birth

Nutrients per 100ml	Abbott Nutrition Similac High Energy	Nutricia Infatrini	SMA High Energy
INDICATIONS	Faltering growth, require fluid restriction, increased nutritional requirements	Faltering growth, require fluid restriction, increased nutritional requirements	Disease-related malnutrition, growth failure, malabsorption
MACRONUTRIENTS			
Energy kcal	100	101	100
Protein g	2.6	2.6	2.6
Whey:casein ratio	60:40	60:40	100:0
Carbohydrate g	10.1	10.3	10.0
– of which lactose g	4.8	5.2	5.8
Carbohydrate source	Maltodextrin, lactose, oligosaccharides	Maltodextrin, lactose, oligosaccharides	Maltodextrin, lactose
Fat g	5.4	5.4	5.5
Fat source	High oleic sunflower, soy, coconut and single cell oils	Rapeseed, sunflower, coconut, MCT oil from coconut and palm kernel oil, corn, single cell, butter and fish oils	Sunflower,palm, coconut, rapeseed, and fish oils, includes structured vegetable oils
Added LCPs ARA	✓	✓	✓
DHA	✓	✓	✓
LCP source	Fungal/algal oils (vegetable source)	Fish oil and fungal/algal oils (vegetable source)	Fish oil
MICRONUTRIENTS			
Vitamins meeting regulations	✓	✓	✓
Minerals meeting regulations	✓	✓	✓
VITAMINS			
Vitamin A µg-RE	100	81	100
Vitamin C mg	12	14	20
Vitamin E mg	2.0	2.1	2.3
Vitamin D µg	1.7	1.9	2.5
Vitamin K µg	7.0	6.7	9.0
Thiamin (B_1) µg	150	150	140
Riboflavin (B_2) µg	250	200	210
Niacin µg (mg NE)	1200 (1.98)	520 (1.2)	1000
Vitamin B_6 µg	90	110	90
Vitamin B_{12} µg	0.3	0.3	0.3
Folic acid µg	14	16	17
Biotin µg	4.5	4.0	2.8

Nutrients per 100ml	Abbott Nutrition Similac High Energy	Nutricia Infatrini	SMA High Energy
Pantothenic acid µg	440	800	940
MINERALS			
Calcium mg	80	100	100
Chloride mg	55	62	83
Copper µg	60	65	80
Iodine µg	16	18	19
Iron mg	1.1	1.2	1.0
Magnesium mg	9.0	9.0	11
Manganese µg	55	16	20
Phosphorus mg	42	50	60
Potassium mg	90	95	115
Selenium µg	1.9	2.2	4.5
Sodium mg	25	37	37
Zinc mg	0.7	0.8	1.1
ADDED INGREDIENTS			
Structured vegetable oils	×	×	✓
Prebiotics	✓	✓	×
Nucleotides	✓	✓	×
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	✓	✓	×
Contains fish oil	×	✓	✓
Contains egg lipid	×	×	×
Suitable for vegetarians	✓[1]	×	×
Halal approved	✓	✓	×
Osmolality mOsm/kg	333	360	392

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
MCT = medium chain triglycerides

1 Contains vitamin D synthesised from cholesterol, extracted from the grease in wool sheared from live sheep.

3.8 Thickened (anti-reflux) infant milks suitable from birth

Key points

Thickened infant milks are classified as foods for special medical purposes and should only be used under medical supervision (as must be stated on the label by law). Despite this recommendation these milks are sold over the counter in the UK in supermarkets and pharmacies. Thickened (anti-reflux) infant milks with added corn (maize) starch, potato starch or carob bean gum are marketed to manage reflux and regurgitation in infants.

NICE guidance published in January 2015 (National Institute for Health and Care Excellence, 2015a) and a NICE Quality Standard (QS112, NICE 2016) outline how gastro-oesophageal reflux should be diagnosed and managed in infants. Regurgitation is a common and normal occurrence in infants and does not usually need any investigation or treatment. Where (rarely) there are significant symptoms of frequent regurgitation with marked distress, thickener added to milk or a thickened formula is recommended for trial, only after a review of feeding history, and a reduction in feed volumes where appropriate or an increase in frequency of feeds, has been attempted.

Manufacturer guidelines on how to make up thickened infant milks are not in line with current recommendations for making up infant formula safely, since they suggest using cold or hand-hot water rather than water boiled and left to cool to 70^{O}C. Where these milks are prescribed, advice should be taken from a health professional on how to make them up appropriately.

Thickened infant milks are marketed as reducing gastro-oesophageal reflux (bringing up milk into the oesophagus) and vomiting or spitting up feeds in formula-fed infants. Whilst reflux does not generally result in health consequences and resolves spontaneously by about 3 months of age in the majority of cases, many parents seek remedies (Vanderhoof et al, 2003) and these milks have been developed to meet this actual or perceived need.

In the UK there are five thickened infant milks available: Aptamil Anti-Reflux (Danone), Cow & Gate Anti-Reflux (Danone), Enfamil AR (Mead Johnson), Hipp Combiotic Anti-reflux and SMA Anti-reflux (Nestlé). The on-pack nutritional information for Aptamil Anti-reflux and Cow & Gate Anti-Reflux suggests that the products have an identical composition. The whey:casein ratio of Aptamil Anti-Reflux, Cow & Gate Anti-Reflux and Enfamil AR are casein dominant with whey:casein ratios of 20:80. SMA Anti-Reflux is based on 100% hydrolysed whey protein whilst Hipp Combiotic Anti-reflux has a whey:casein ratio of 60:40. There is, as yet, no marketing information available on the Hipp Organic website to support the use of this product. Enfamil AR is generally not available over the counter.

Thickened milks are more dense than standard infant milks and therefore less likely to rise back up the oesophagus. The use of casein in anti-reflux milks has also been suggested to contribute to their efficacy. Many of the clinical trials examining the safety and efficacy of thickened milks have used predominantly casein based milks. The proposed method of action is that casein forms larger curds in the stomach and this is thought to result in fewer episodes of reflux (Ramirez-Mayans et al, 2003). It is also suggested that casein dominant

formula can result in slower gastric emptying compared to whey based formula milks (Ramirez-Mayans et al, 2003; Tolia et al.,1992). The role of delayed gastric emptying in the pathogenesis of gastro-oesophageal reflux in infants is considered to be controversial (Tolia et al.,1992) with some authors suggesting that delayed gastric emptying is more common in infants with symptoms of reflux, but this is mainly in populations with neurological disorders (Fonkalsrud, 1996; Fried et al, 1992).

It has been suggested that commercially prepared thickened infant milks have an advantage over thickeners added to milk at home as the latter type may lead to inconsistencies in composition (Ramirez-Mayans et al, 2003). Milk thickeners to add to milk include Instant Carobel (Cow & Gate), which uses carob bean gum as a thickening agent.

The thickening agent used in Enfamil AR is rice starch. Mead Johnson suggest that rice starch is the natural choice for thickening milks as it is typically used as a first weaning food. Whilst Ramirez-Mayans et al (2003) suggest that rice starch is associated with constipation, based on evidence from a study by where 3 out of 24 infants being fed milk containing 5% (5g/100ml) rice starch suffered constipation, Mead Johnson support the use of their product by reference to a study by Vanderhoof et al (2003) which concluded that Enfamil AR did not cause constipation. SMA Anti-Reflux is thickened with potato starch which they suggest is easily digested by infants and the thickening agent used in Danone products and in Hipp Combiotic Anti-reflux is carob bean gum, and it is suggested that this is not split by salivary amylase and therefore maintains the viscosity of the feed in the stomach (Wenzl et al, 2003).

Danone supports the use of its anti-reflux products by reference to clinical trials using its products. A prospective, double-blind trial in 20 infants reported that there was no change in the regurgitation frequency between groups receiving the thickened milk and the placebo group, but there was a significant decrease in the length of time of oesophageal acid exposure in the groups receiving the thickened milk (Vandenplas et al, 1994). In a further placebo-controlled crossover study in 14 healthy infants, the frequency and amount of regurgitation were reduced after consuming an infant formula thickened with carob bean gum, compared to when the infants were fed the same milk without thickener. However, there was no significant reduction in the occurrence or duration of acid gastro-oesophageal reflux. The decrease in regurgitation was thought to have resulted from the decrease in the number of non-acid gastro-oesophageal reflux episodes when thickened infant milk was consumed (Wenzl et al, 2003).

Nestlé relaunched SMA Staydown as SMA Anti-reflux in 2017. The updated formulation differs from its predecessor in a number of ways. It now contains less protein per 100ml, is based on 100%, partially hydrolysed whey rather than on 80% casein and the thickening agent has changed from pre-cooked corn starch to potato starch. Whilst use of SMA Staydown was supported by reference to clinical trials which showed reductions in the number of episodes of regurgitation in infants fed thickened casein based formula milks compared to those fed standard whey based formula milks (Moukarzel et al, 2007; Ramirez-Mayans et al, 2003; Xinias et al, 2003) the use of SMA Anti-reflux is supported by reference to abstracts from clinical trials. One of these is based on a hydrolysed whey based infant formula which also contains probiotics (Indrio et al, 2015) whilst the other is based on Nestlé milks thickened with potato/corn starch of undisclosed composition (Toporovski et al, 2013). SMA suggest on their website that:

'Whey dominant formulas containing partially hydrolysed protein accelerate gastric emptying time making the formula easy to digest'

Whilst some studies do suggest that gastric emptying is more rapid with hydrolysed whey based formula milks than with casein based milks, it remains unclear whether or not delayed gastric emptying contributes to reflux. It is also interesting to note that in a Nestlé sponsored study using NAN and NAN H.A products, Staelens et al,(2008), found no difference in the rate of gastric emptying between a partially hydrolysed whey protein formula and a standard whey based infant milk with intact protein. The authors of this study did highlight the fact that other differences between the test formulas may have influenced rates of gastric emptying.

All of the infant milks on the market are thickened with starches or gums and whilst some studies have shown that thickened infant milk can reduce regurgitation in some infants, systematic reviews of non-pharmacological and non-surgical therapies for gastro-oesophageal reflux in infants have concluded that thickened infant formulas do not appear to reduce measurable reflux, although they may reduce regurgitation (vomiting) (Horvath et al, 2008: Carroll et al, 2002).

A clinical trial including 60 infants and their carers which was designed to evaluate the efficacy of parental reassurance in combination with receiving three different types of infant milk: standard formula milk, infant milk thickened with rice cereal, or infant milk thickened with bean gum reported that regurgitation frequency was reduced in all of the three groups, and there was no significant difference in regurgitation frequency between the groups. All participating parents were reassured in the same way. The only significant difference between groups was that infants receiving infant milk thickened with bean gum experienced a greater increase in weight during the trial. The authors suggest that this effect may be due to the greater, although not statistically significant, decrease in regurgitation frequency in this group (Hegar et al, 2008).

The use of thickened milks in infants with simple reflux is not supported by the ESPGHAN Committee on Nutrition on the grounds that there is no conclusive information available on the potential effects of thickening agents on the bioavailability of nutrients and growth of children, or on mucosal, metabolic and endocrine responses (Aggett et al, 2002).
There is also very little evidence to suggest that these milks confer any benefits with respect to acid exposure of the oesophageal mucosa or bronchopulmonary complications of gastro-oesophageal reflux. It is suggested that, where infants have simple reflux and no complications, parents and carers require advice and information rather than a different type of formula (Aggett et al, 2002).

This is supported by NICE guidance in the UK (National Institute for Health and Care Excellence, 2015a) which outlines how gastro-oesophageal reflux should be diagnosed and managed in infants. The guidance reiterates that regurgitation is a common and normal occurrence in infants and does not usually need any investigation or treatment. Where, *rarely*, there are significant symptoms of frequent regurgitation with marked distress, thickener added to milk or a thickened infant milk is recommended for trial, only after a review of feeding history, and a reduction in feed volumes where appropriate or an increase in frequency of feeds has been attempted. This guidance has been reinterpreted through clever advertising and graphics by formula manufacturers to emphasise the use of a thickened formula in treatment of all types of regurgitation. Health professionals should note

that the guidance is clear that these formula are only recommended when there are significant symptoms of frequent regurgitation.

It is hoped that the NICE guidelines will support health professionals, including midwives, health visitors, GPs and hospital doctors, as well as lactation consultants, to provide consistent evidence-based support for anyone concerned about infant reflux and regurgitation. The guidance can be accessed at: https://www.nice.org.uk/guidance/

Thickened anti-reflux infant milks are foods for special medical purposes (FSMP) rather than infant formula and they should therefore be labelled with the statement: *'For use under medical supervision'.*

Currently, manufacturers suggest that these milks are made up with cold or hand-hot water, rather than with water boiled and cooled to 70^{o}C. This is because anti-reflux milk made up with water at 70^{o}C is likely to become lumpy. However, if the milk is made up with cold or hand-hot water, there is an increased risk of bacteria being present in the milk. We do not recommend that any milks are made up using water at a temperature of less than 70^{o}C unless the risks have been assessed by a medical practitioner.

The Department of Health has not asked manufacturers to change the instructions for making up these milks in line with recommendations for infant formula because the milks are foods for special medical purposes, but First Steps Nutrition Trust believes that as they are FSMP they should not be sold over the counter.

The nutritional composition and ingredients used in thickened (anti-reflux) infant milks suitable from birth are given in Table 13.

TABLE 13. The nutritional composition of thickened (anti-reflux) infant milks suitable from birth

Nutrients per 100ml	Aptamil Anti-Reflux	Cow & Gate Anti-Reflux	Hipp Combiotic Anti-reflux	Mead Johnson Enfamil AR	SMA Anti-Reflux
MACRONUTRIENTS					
Energy kcal	66	66	67	69	67
Protein g	1.6	1.6	1.4	1.7	1.3
Whey:casein ratio	20:80	20:80	60:40	20:80	100:0
Carbohydrate g	6.8	6.8	7.1	7.6	7.8
– of which lactose g	6.0	6.0	6.2	4.2	5.1
Carbohydrate source	Lactose, maltodextrin, carob bean gum	Lactose, maltodextrin, carob bean gum	Maltodextrin, carob bean gum, lactose	Rice starch, lactose, glucose syrup	Lactose, potato starch
Fat g	3.5	3.5	3.5	3.5	3.4
Fat source	Palm, rapeseed, coconut, sunflower and single cell oils and fish oil	Palm, rapeseed, coconut, sunflower and single cell oils and fish oil	Palm, rapeseed, and sunflower oils, fish and single cell oils	Palm olein, coconut, soya, high oleic sunflower oil and single cell oils	Sunflower, coconut and rapeseed
Added LCPs ARA	✓	✓	✓	✓	×
DHA	✓	✓	✓	✓	×
In approved ratio	✓	✓	✓	✓	N/A
LCP source	Fish oil and fungal/algal oils (vegetable source)	Fish oil and fungal/algal oils (vegetable source)	Fish and single cell oils	Fungal/algal oils (vegetable source)	N/A
MICRONUTRIENTS					
Vitamins meeting regulations	✓	✓	✓	✓	✓
Minerals meeting regulations	✓	✓	✓	✓	✓
VITAMINS					
Vitamin A µg-RE	50	50	70	62	68
Vitamin C mg	8.3	8.3	10	11.7	9
Vitamin E mg	1.0	1.0	0.8	0.92	1.2
Vitamin D µg	1.2	1.2	1.1	1.03	0.9
Vitamin K µg	4.5	4.5	5.0	5.5	5.1
Thiamin (B_1) µg	50	50	60	55	70
Riboflavin (B_2) µg	100	100	130	124	150
Niacin µg (mg NE)	(0.82)	(0.82)	670	(0.69)	700
Vitamin B_6 µg	50	50	40	41	50
Vitamin B_{12} µg	0.17	0.17	0.15	0.21	0.14
Folic acid µg	9.4	9.4	10	11	10.6
Biotin µg	1.5	1.5	1.7	2.1	1.5
Pantothenic acid µg	300	300	500	340	600
MINERALS					
Calcium mg	77	77	70	79	46
Chloride mg	52	52	45	55	50
Copper µg	40	40	45	45	60
Iodine µg	13	13	15	11.7	10
Iron mg	0.68	0.68	0.8	0.76	0.7

Nutrients per 100ml	Aptamil Anti-Reflux	Cow & Gate Anti-Reflux	Hipp Combiotic Anti-reflux	Mead Johnson Enfamil AR	SMA Anti-Reflux
Magnesium mg	5.1	5.1	5.5	5.5	6.8
Manganese µg	30	33	7.0	11	10
Phosphorus mg	43	43	38	44	26
Potassium mg	76	76	70	76	72
Selenium µg	1.3	1.3	1.5	1.93	2.4
Sodium mg	24	24	20	23	26
Zinc mg	0.59	0.59	0.6	0.69	0.7
ADDED INGREDIENTS					
Structured vegetable oils	×	×	×	×	×
Prebiotics	×	×	×	×	×
Nucleotides	✓	✓	×	✓	✓
Inositol	✓	✓	×	✓	✓
Taurine	✓	✓	×	✓	✓
Choline	✓	✓	×	✓	✓
L-carnitine	✓	✓	×	✓	✓
Added antioxidants	✓	✓	✓	✓	✓
Contains soya	✓	✓	×	✓	×
Contains fish oil	✓	✓	✓	×	×
Suitable for vegetarians[1]	×	×	×	×	×
Halal approved	✓	✓	×	×	×
Osmolality mOsm/kg	290	290	266	240	240

ANS = approval not sought
ARA = arachidonic acid
DHA = docosahexaenoic acid
LCP = long chain polyunsaturated fatty acid

1 Formula milks derived from cows' milk are generally not suitable for vegetarians due to the inclusion of fish oils and/or the use of the animal-derived enzyme rennet during the production process. Rennet is used to separate curds from whey and, although vegetarian alternatives are available, they are not used by all manufacturers.

3.9 Lactose free infant milks suitable from birth

Key points

Lactose-free infant milks are foods for special medical purposes and should only be used under medical supervision.

Primary and congenital lactose intolerance are clinical syndromes which can cause abdominal pain, diarrhoea, flatulence and/or bloating after ingestion of food containing lactose. These conditions are very rare in infants and require treatment with lactose-free infant formula under medical supervision.

There is no evidence that treating secondary lactose intolerance in infants following a bout of gastroenteritis is benefited by a lactose-free milk or that lactose-free milks are of any benefit in treating colic. Continued breastfeeding is always encouraged if a baby has gastroenteritis or colic.

There is a risk associated with feeding infant milks which have glucose as the carbohydrate source rather than lactose, as these milks have a greater potential to cause dental caries. Parents and carers using these milks are advised to avoid prolonged contact of milk feeds with their baby's teeth and ensure that they clean their baby's teeth after the last feed at night.

There may be further risks associated with using a lactose free milk as diets without lactose might have disadvantages for the composition of the infants' colonic microflora and colonic physiological function, and they may compromise calcium absorption.

In the UK, the lactose-free milks Aptamil Lactose Free and SMA LF are both marketed as suitable from birth and are widely available over the counter. A third product, Enfamil O-Lac, can be obtained through pharmacies.

The main difference between lactose-free and standard cows' milk based infant formula is that in lactose-free milk the carbohydrate is glucose rather than lactose. Lactose intolerance is a clinical syndrome which can cause abdominal pain, diarrhoea, flatulence and/or bloating after ingestion of food containing lactose. The underlying physiological problem is lactose malabsorption, which is caused by an imbalance between the amount of lactose ingested and the capacity of the enzyme lactase to hydrolyse it, and therefore the amount of lactose that can cause symptoms varies (Heyman et al, 2006).

Heyman et al (2006) identify the following different types of lactose intolerance:

- Primary lactose intolerance is caused by an absolute or relative lack of the enzyme lactase and is the most common cause of lactose malabsorption worldwide. It is known to be more prevalent among black and Asian populations but is extremely rare in infants.
- Secondary lactose intolerance results from injury to the small bowel such as might occur during acute gastroenteritis and persistent diarrhoea and is likely to be temporary.

- Congenital lactase deficiency is a rare condition in infants, in which the infant develops persistent diarrhoea as soon as any lactose, from human milk or formula, is introduced.
- Developmental lactase deficiency is observed among premature infants. Lactase production is deficient in the immature gastrointestinal tract until at least 34 weeks' gestation.

In the very rare cases of primary or congenital lactase deficiency lactose-free formula are necessary, but infants should be managed by a clinician. The continued use of breastmilk does not seem to have any adverse effects on preterm infants with developmental lactase deficiency (Shulman et al, 1995).

In the UK, the lactose-free milks Aptamil Lactose Free (Danone) and SMA LF (Nestlé) are widely available. Enfamil O-Lac is available through pharmacies. These milks are nutritionally complete for use from birth. SMA LF is presented as being suitable not only for infants with congenital lactase deficiency, but also for infants who have been diagnosed with lactose intolerance following a bout of gastroenteritis. It is also suggested to help in the dietary management of post-infectious diarrhoea in infants who are not breastfed. Aptamil Lactose Free is suggested as suitable for infants with primary or secondary lactose intolerance or those suffering from diarrhoea, bloating or wind caused by temporary lactose intolerance. Enfamil O-Lac is reported to manage both primary and secondary lactose intolerance and digestive problems such as colic, diarrhoea, bloating and wind associated with lactose intolerance.

In developed countries, the use of lactose-free milks as a treatment for acute gastroenteritis has been shown to have no clinical advantage over standard lactose-containing formula (Kukuruzovic and Brewster, 2002). The most recent ESPGHAN guidelines for the management of acute gastroenteritis in children (Guarino et al, 2014) suggest that there is weak evidence for the use of lactose-free milk for the treatment of acute diarrhoea in hospital settings, but that the routine use of lactose free milks in community settings is not recommended. Despite this assertion, in a multi-centre study conducted in 29 European countries in 2000, when doctors were asked, in a questionnaire, what they would recommend for an infant with acute diarrhoea, 36% said they would use normal lactose-containing infant formula, 35% would use lactose-free milk, and 19% would use a lactose and milk protein free product (Szajewska et al, 2000). This suggests there may be considerable confusion among health professionals about the treatment of temporary lactose intolerance in infants.

Lactose-free milks are also not recommended for the treatment of colic (NICE 2017). Some newer evidence also suggests that infants fed a lactose free formula will have higher blood glucose and some circulating amino acid levels after 120 minutes than infants fed standard infant formula, suggesting that lactose free formula may have a negative impact on the infant metabolism which require further investigation (Slupsky et al, 2017).

Lactose-free milk has a greater potential to cause dental caries. Lactose is a non-cariogenic sugar whereas the common replacement carbohydrate, glucose, is cariogenic (Bowen et al, 1997). It is therefore vital that parents using lactose-free milk follow advice to avoid prolonged contact of milk feeds with their baby's teeth and ensure that they clean their baby's teeth after the last feed at night.

There are further risks associated with the use of lactose free formula. Diets without lactose might have disadvantages for the composition of the infants' colonic microflora and colonic physiological function, and they might compromise calcium absorption (Ziegler& Fomon, 1983). Moreover, feeding lactose free diets from birth (for example, for preventive purposes), will cause false negative results of most neonatal screening tests for galactosaemia (Hðst et al, 1999).

The nutritional composition and ingredients used in lactose-free milks suitable from birth are given in Table 14.

TABLE 14. The nutritional composition of lactose free infant milks suitable from birth

Nutrients per 100ml	Aptamil Lactose Free	Mead Johnson Enfamil O-Lac	SMA LF
MACRONUTRIENTS			
Energy kcal	66	68	67
Protein g	1.3	1.42	1.4
Whey:casein ratio	0:100	20:80	60:40
Carbohydrate g	7.3	7.2	7.8
– of which lactose g	less than 0.006	less than 0.07	less than 0.007
Carbohydrate source	Glucose syrup	Glucose syrup, citrate	Glucose syrup
Fat g	3.5	3.7	3.4
Fat source	Palm, rapeseed, coconut, sunflower and single cell oils and fish oil	Palm olein, coconut, soya, high oleic sunflower and single cell oil	Sunflower, coconut and rapeseed oils
Added LCPs ARA	✓	✓	✓
DHA	✓	✓	✓
In approved ratio	✓	✓	✓
LCP source	Fungal/algal and fish oils	Fungal/algal oils (vegetable source)	Fish oils
MICRONUTRIENTS			
Vitamins meeting regulations	✓	✓	✓
Minerals meeting regulations	✓	✓	✓
VITAMINS			
Vitamin A µg-RE	55	63	80.5
Vitamin C mg	9.3	12.8	12.5
Vitamin E mg	1.2	0.86	1.5
Vitamin D µg	1.2	1.01	1.0
Vitamin K µg	4.5	10.1	5.3
Thiamin (B_1) µg	50	54	70
Riboflavin (B_2) µg	100	61	80
Niacin µg (mg NE)	(0.8)	(0.68)	750
Vitamin B_6 µg	40	41	50
Vitamin B_{12} µg	0.11	0.2	0.13
Folic acid µg	8.9	10.8	11.6
Biotin µg	1.8	2.0	1.5
Pantothenic acid µg	330	340	700
MINERALS			
Calcium mg	55	78	41.5
Chloride mg	41	53	45
Copper µg	42	51	50
Iodine µg	12	16.9	9.2
Iron mg	0.79	1.1	0.74
Magnesium mg	5.1	7.8	4
Manganese µg	34	41	15
Phosphorus mg	30	52	25

Nutrients per 100ml	Aptamil Lactose Free	Mead Johnson Enfamil O-Lac	SMA LF
Potassium mg	65	78	69
Selenium µg	1.6	1.42	1.7
Sodium mg	17	31	21
Zinc mg	0.56	0.68	0.53
ADDED INGREDIENTS			
Structured vegetable oils	×	×	×
Prebiotics	×	×	×
Nucleotides	✓	×	✓
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
L-carnitine	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	✓	✓	✓
Contains fish oil	✓	×	✓
Suitable for vegetarians[1]	×	×	×
Halal approved	×	NK	✓
Osmolality mOsm/kg	170	172	182

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NK = not known

1 Formula milks derived from cows' milk are generally not suitable for vegetarians due to the inclusion of fish oils and/or the use of the animal-derived enzyme rennet during the production process. Rennet is used to separate curds from whey and, although vegetarian alternatives are available, they are not used by all manufacturers.

3.10 Soy protein based infant formula suitable from birth

Key points

Soy protein based infant formula has protein from soya beans, and the carbohydrate source is maltodextrin. It contains no animal protein or lactose.

Concerns have been raised over the potential allergenic effect of soy protein based formula in infants at high risk of atopy and over the effects that the phyto-oestrogens present in soy protein based formula might have on future reproductive health.

Soy protein based infant formula have been shown to support normal growth and development in healthy term infants, the Chief Medical Officer has recommended that soy protein based formula should not be routinely used for infants under 6 months of age who have cows' milk protein allergy or intolerance.

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that the high levels of phyto-oestrogens present in soy protein based milks posed a potential risk to the future reproductive health of infants (Committee on Toxicity, 2003).

The carbohydrate source in soy based infant formula is maltodextrin rather than lactose so infants may need attentive mouth care as maltodextrin is associated with demineralisation of enamel (Rezende and Hashizume, 2018). Parents and carers using soy protein based infant formula are advised to avoid prolonged contact of milk feeds with their baby's teeth and ensure that they clean their baby's teeth after the last feed at night.

Advice in the UK is that parents and carers should always seek medical advice before feeding their infant soy protein based infant formula.

Soy protein based infant formula combine protein from soya beans with water, vegetable oils, maltodextrin and vitamins and minerals.

The amino-acid profile of soy protein is deficient in sulphur-containing amino acids, and soy protein based formula must therefore be fortified with the sulphur-containing amino acid L-methionine. Soy protein based infant formula are available both over the counter and by prescription and may be used from birth. They have sometimes been used for children who require an alternative to cows' milk based infant milks because they have an allergy or intolerance to cows' milk, or because they have a specific condition such as galactosaemia or galactokinase deficiency.

In a systematic review of clinical studies examining measures of infant health and development and comparing soy protein based infant formula with cows' milk protein based infant formula and/or human milk, Mendez et al (2002) concluded that modern soy protein based formula supplemented with methionine support normal growth and development in healthy term infants during the first year of life.

Soy protein based infant formulas have often been used as an alternative to cows' milk protein based infant milks in children with cows' milk protein allergy (CMPA). In a review of trials comparing the effect of prolonged feeding of soy protein based infant formula and of cows' milk protein based infant formula, meta-analysis found no significant difference in childhood asthma incidence, childhood eczema incidence or childhood rhinitis. The authors concluded that soy protein based formula cannot be recommended for allergy prevention or food intolerance in infants at high risk of atopy (Osborn and Sinn, 2006).

It is recognised that a proportion of children with CMPA are also allergic to soy protein. The Chief Medical Officer has recommended that soy protein based infant formula should not be used as the first line of treatment for infants under 6 months of age who have CMPA or cows' milk protein intolerance, as this is the period when they are most likely to become sensitised to soy protein (Chief Medical Officer, 2004). ESPGHAN recommends that soy protein based infant formula should not be used for infants under 6 months of age and that the use of therapeutic milks based on extensively hydrolysed proteins (or amino-acid preparations if hydrolysates are not tolerated) should be preferred to the use of soy protein formula in the treatment of cows' milk protein allergy (Agostoni et al, 2006).

Soy protein based infant formula contain much higher levels of phyto-oestrogens than formula based on cows' milk protein. Setchell et al (1998) estimated that infants aged 1 to 4 months who were fed soy protein based formula would receive 6-12mg/kg of body weight of phyto-oestrogens per day, compared to 0.7-1.4mg/kg of body weight per day for adults consuming soy protein based products. There has been very little research into the effects of consumption of phyto-oestrogens from soy protein based formula in very young infants. However, research in animals suggests that phyto-oestrogens can have detrimental effects on reproductive function, immune function and carcinogenesis.

In a review of the scientific evidence on soy protein based formula, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that the high levels of phyto-oestrogens present in soy protein based formula posed a potential risk to the future reproductive health of infants (Committee on Toxicity, 2003). A longitudinal study looking at 283 infants exclusively given soy protein based formula from birth suggests that girls may display different vaginal and uterine development in line with exogenous oestrogen exposure (Adgent et al, 2018). The impact this may have on development is yet to be established.

Potential links between soy infant formula and seizures in children with autism have been investigated (Westmark, 2014), with a hypothesis that phyto-oestrogens in soy protein based infant formula can contribute to lower seizure threshold. Whilst this study reports links using data from retrospective data collection and therefore cannot confirm an association, it reiterates the need for caution in the use of soy protein based formula in infancy.

The carbohydrate source in soy protein based infant formula is maltodextrin rather than lactose so infants may need attentive mouth care as maltodextrin is associated with demineralisation of enamel (Rezende and Hashizume, 2018). Parents and carers using soy protein based infant formula are advised to avoid prolonged contact of milk feeds with their baby's teeth and ensure that they clean their baby's teeth after the last feed at night.

The required composition of soy protein based infant formula is different to that of cows' milk based formula for a number of micronutrients including iron and phosphorus due to differences in bioavailability. Soy protein based formula are suitable for vegetarians but not for vegans.

Advice in the UK is that parents should always seek advice before feeding their infant soy protein based infant formula. The nutritional composition and ingredients in SMA Wysoy, the only soy based product on the market, are given in Table 15.

TABLE 15. The nutritional composition of soy protein based infant formula suitable from birth

Nutrients per 100ml	SMA Wysoy
MACRONUTRIENTS	
Energy kcal	67
Protein g	1.8
Carbohydrate g	6.8
Carbohydrate source	Maltodextrin
Fat g	3.7
Fat source	Palm, coconut, soya, sunflower and rapeseed oils
Added LCPs ARA	✓
DHA	✓
LCP source	Fungal/algal oils (vegetable source)
MICRONUTRIENTS	
Vitamins meeting regulations	✓
Minerals meeting regulations	✓
VITAMINS	
Vitamin A µg-RE	64
Vitamin C mg	12
Vitamin E mg	0.78
Vitamin D µg	1.7
Vitamin K µg	6.5
Thiamin (B_1) µg	50
Riboflavin (B_2) µg	130
Niacin µg	700
Vitamin B_6 µg	70
Vitamin B_{12} µg	0.2
Folic acid µg	15.2
Biotin µg	2.3
Pantothenic acid µg	440
MINERALS	
Calcium mg	68
Chloride mg	47
Copper µg	50
Iodine µg	14
Iron mg	0.65
Magnesium mg	7.6
Manganese µg	20
Phosphorus mg	50
Potassium mg	82
Selenium µg	2.5
Sodium mg	22
Zinc mg	0.52
ADDED INGREDIENTS	
Structured vegetable oils	×
Prebiotics	×
Nucleotides	×
Inositol	×

Nutrients per 100ml	SMA Wysoy
Taurine	✓
Choline	✓
Added antioxidants	✓
Contains soya	✓
Contains fish oil	×
Suitable for vegetarians	✓
Halal approved	✓
Osmolality mOsm/kg H_20	133

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid

3.11 Partially hydrolysed infant milks suitable from birth

Key points

Most infant milks containing partially hydrolysed proteins are marketed as 'comfort milks' and claim to be easier to digest and designed for the management of colic and constipation. One is marketed as preventing cows' milk protein allergy. All these milks are based on modified cows' milk with 100% whey protein.

No convincing evidence is presented by manufacturers to support the efficacy of these milks in preventing colic, wind or gastrointestinal discomfort. NICE clinical guidance is clear there is no infant formula solution for colic (NICE CKS, 2017) and NICE advise against a change in formula type. This position is further supported by a Cochrane review (Gordon et al, 2018) that found no convincing evidence that switching to a partially hydrolysed formula was effective in treating infantile colic. A more recent systematic review concluded that no randomised clinical trials have demonstrated the efficacy of partially hydrolysed formula in infantile colic and that there was a lack of evidence for other benefits too (Vandenplas et al, 2019).

A systematic review commissioned by The Food Standards Agency and published in the British Medical Journal in 2016 (Boyle et al, 2016) concluded that there was no consistent evidence that partially hydrolysed formula reduce risk of allergic disease. An ESPGHAN working group consensus (Vandenplas et al, 2016) also concluded that evidence on efficacy of partially hydrolysed formula on prevention of atopic disease is limited and also highlighted the lack of any evidence on potential negative long term metabolic consequences and outcomes of using these products.

Partially hydrolysed whey-based milks marketed as comfort milks

Most infant milks containing partially hydrolysed proteins are marketed as comfort milks which are 'easier to digest' and which the manufacturers claim are designed for the management of colic and constipation. In the UK there are four comfort milks available: Aptamil Comfort, Cow & Gate Comfort, Hipp Combiotic Comfort and SMA Comfort. They are all modified cows' milk formula based on 100% whey protein. All three products contain lactose at lower levels than those found in standard infant formula milks and all contain structured vegetable oils. Aptamil Comfort, Cow & Gate Comfort and Hipp Combiotic Comfort milks also contain non-digestible oligosaccharides and added starch for a thicker feed. Aptamil Comfort and Cow & Gate Comfort milks have an identical nutrient profile, and we believe they are the same product marketed under different names and at different prices.

No convincing evidence is presented by manufacturers to support the efficacy of these milks in preventing colic, wind or gastrointestinal discomfort. A recent Cochrane review (Gordon et al, 2018) found no convincing evidence that switching to a partially hydrolysed formula was effective in treating infantile colic. NICE clinical guidance is clear there is no infant formula solution for colic (NICE CKS, 2017) and NICE advise against a change in formula type. The NHS website only suggests practical and soothing strategies for colic

www.nhs.uk/conditions/colic/ (NHS, 2018). The EFSA review on infant formula composition (EFSA, 2014) reported no benefits for infants of the addition of prebiotic oligosaccharides or the use of palmitate in the *sn-2* position in infant formula which manufacturers make claims for in these formula

What claims are made, and what evidence is provided to support these claims?

Manufacturers support the claims made for their products by reference to clinical trials, but the trial data presented is often weak and many of the studies reported do not meet the criteria required to be considered for clinical evidence review. In most cases evidence is provided from just one study, and often these findings have not been supported by systematic expert evidence review.

SMA Comfort
SMA provide 4 references to support claims that SMA comfort is easier to digest, can prevent wind and leads to softer stools. The evidence given for the claim that milks with hydrolysed proteins are easier to digest comes from one small under powered study measuring gastric emptying in infants with and without reflux (Billeaud et al, 1990). The evidence that the addition of a structured fat blend aids stool softness and fat and calcium absorption curiously comes from a paper which was looking at the usefulness of a handheld diary to facilitate a parent questionnaire rather than a clinical trial (Yao et al, 2010). However the EFSA *Scientific opinion on the essential composition of infant and follow-on formulae* (2014) concluded that there was no convincing evidence for any beneficial effects from the fat blend palmitic acid predominantly esterified in the *sn-2* position that SMA use in their comfort milk.

One study from Italy is cited simply to give evidence for high numbers of infants having gastrointestinal problems in early life (Iacono et al, 2005) and a further study is quoted as evidence for infants having difficulty digesting lactose (Infante et al, 2011). This industry supported study looked at breath hydrogen in 20 2-6 week old formula fed infants with reported colic before, and after, treatment with a lower lactose formula. The formula used was not the same as SMA comfort, there was no reference group and the peer reviewers for this study had concerns about the data analysis. It is agreed in the UK that colic cannot be treated with a change in formula type (NICE CK, 2017)

Aptamil and Cow & Gate Comfort
Danone produces two comfort milks which have an identical composition: Cow & Gate Comfort milk and Aptamil Comfort milk. The Danone early life nutrition website provides evidence for both of these products: evidence is provided from 6 studies for Cow & Gate and the same 6 studies plus a further 7 studies for Aptamil comfort. The evidence provided by the same 6 studies for both milks provides evidence from three studies on the benefits of GOS/FOS prebiotic additions as stool softeners. Manufacturers use a number of single studies to support claims that there are benefits for the addition of prebotics to infant formula, for example the frequently cited study by Moro et al (2002) undertaken at the Numico (Danone) Research Centre. 90 healthy term infants were allocated to receive formula milk supplemented with oligosaccharides at a concentration of 0.4g/100ml or 0.8g/100ml or placebo, over a period of 28 days.

The infants receiving the formula milk supplemented with oligosaccharides showed a dose-dependent increase in the amount of *Bifidobacteria* in stools. However, this does not mean that there is any clinical benefit to the addition of oligosaccharides. All of the studies cited were included in the review by EFSA (2014) but were not accepted as evidence of any benefit from the addition of GOS/FOS to infant formula.

Both Cow & Gate and Aptamil comfort milk use two references on the use of structured fats to aid absorption of calcium. The studies by Carnielli et al (1996) and Kennedy et al (1999) are used to support claims that use of synthetic triglycerides with a higher proportion of palmitate in the *sn-2* position improves fat and calcium absorption, but EFSA included these trials in their expert review and concluded that using these structured fats did not offer any benefit (EFSA, 2014). In addition the Kennedy et al study reported that a number of parents reported concern about runny stools after feeding formula containing high *sn*-2 palmitate.

Both Aptamil and Cow & Gate comfort milk quote a study by Kanabar et al (2001) as evidence for benefit of formula with a lower lactose content in preventing flatulence and wind (Cow & Gate) or reduced likelihood of flatulence and intestinal discomfort (Aptamil). This study, funded by a company which produces lactase enzyme drops, was a small study with high drop our rates and levels of non-compliance. The study used lactase enzyme drops in infant formula or in a small amount of expressed breastmilk, not a reduced lactose formula in the trial and is therefore inappropriate as evidence in this context.

Aptamil Comfort milk also uses an additional reference to support comfort milk as preventing colic. This evidence comes from a clinical trial including 932 formula fed infants with minor feeding problems who attended a physician, funded by Numico (which is now part of Danone Nutricia group). All were given a new formula (but not one of the same composition as Aptamil comfort) and over time a reduction in the number of episodes and frequency of colic and regurgitation and an increase in the number and frequency of stools was reported. There was no control group or breastfed reference group, and it would be expected that these symptoms would decrease as infants developed. This weak observational study cannot be used to establish whether the amelioration of symptoms was due to the type of infant milk used (Savino et al, 2003). This reference has been heavily used by Cow & Gate in its print advertisements to health professionals to make the claim that *'95% of paediatricians reported an improvement in common infant feeding problems with a formula like Cow & Gate Comfort'.* More information about claims made in the health professional literature can be found in the report *'Scientific and Factual? A review of breastmilk substitute advertisments to health professionals'* which can be found at www.firststepsnutrition.org/working-within-the-who-code

Aptamil comfort milk also uses an additional 4 references to support its claims that galacto- and fructo-oligosaccharides(GOS/FOS) have a positive effect on intestinal microflora and have been shown to reduce the incidence of infections and need for antibiotics during the first 1-2 years of life (Moro et al, 2006, Arslanoglu et al 2007, 2008 and 2012). All of these studies (with the exception of Arslanoglu et al, 2012 which was a review follow up of the earlier studies) were included in the EFSA review where they concluded that the addition of prebiotics does not offer any benefit, and have been reviewed elsewhere in this report. An additional study funded by Numico (Bruzzeze et al, 2009) is also provided as evidence, but again this was considered as part of the evidence by EFSA which concluded that the addition of prebiotic oligosaccaharides offers no benefit to infants.

Hipp Combiotic Comfort
Hipp combiotic comfort milk (which unlike most other products in the Hipp range is not certified organic) claims that it has been specially developed with a reduced lactose content, hydrolysed protein, fibres and a special fat blend which makes it easier to digest than a standard infant formula. They provide no evidence to support these claims on the product page on their health professional website. In their additional learning resources in a factsheet about constipation they claim that infants presenting with symptoms of constipation may benefit from a specialist formula such as Hipp comfort and cite Kennedy et al (1999) already discussed above, and a paper by Quinlan et al (1995). This paper however looks at the difference in stool hardness between formula and breastfed infants and is not related to the use of a comfort formula. In the advice sheet on colic the claim is again made that Hipp comfort milk is suitable for the dietary management of colic, but no evidence is provided to support this.

Despite little evidence to support the claims that comfort milks can prevent colic, constipation and wind, and expert advice that this is not the case, weak regulation in the UK allows companies to make these claims on products freely available on supermarket and pharmacy shelves. We believe these claims both confuse families and undermine breastfeeding.

None of these partially hydrolysed formulas are available on prescription. A paper from a large randomised trial of healthy term infants given either a standard full-lactose non-hydrolysed cows' milk protein based infant milk or a 70% lactose, partially hydrolysed whey protein formula over 60 days reported that there was no difference in tolerance of intact compared to partially hydrolysed protein (Berseth et al, 2009). The authors noted that parents may mistake behaviours common in early infancy such as regurgitation and excessive crying as manifestations of intolerance to their infant milk and unnecessarily switch brands or types of milk.

Partially hydrolysed infant formula marketed as preventing cows' milk protein allergy

SMA HA was launched in November 2013 in the UK and was originally marketed as *"preventing 50% of eczema in infants from atopic families"* who used this as the sole formula from birth. These claims have now been changed and currently the milk is marketed as preventing cows' milk protein allergy in babies from atopic families.

Hydrolysed formulae are created by using enzymatic processes to break proteins naturally found in a food into smaller fragments. It is suggested that reducing exposure to intact allergens may prevent development of allergic diseases in infants and young children (Lowe et al, 2013). The development of atopic dermatitis (AD) or eczema is one of the allergic outcomes that has been extensively studied in infants and children in the first year of life. There have been many studies that have attempted to consider the role of early infant feeding on AD outcomes, in particular whether hydrolysed protein in formula can reduce the incidence in infants and children with family history of allergic disease.

Partially hydrolysed whey-based infant formula is cheap to manufacture and palatable to children compared to fully hydrolysed formula or partially hydrolysed casein formula (Lowe

et al, 2011). Nestlé originally promoted their NAN HA formula in 90 markets with the claim that it "*helps to reduce the risk of atopic dermatitis in infants".* However, this claim is made using evidence from one trial and using statements from paediatric groups which may not reflect more recent evidence and opinion in this area. Neither the US Food and Drug Administration (FDA) nor the European Food Safety Authority (EFSA) has approved this claim.

Most of the systematic reviews conducted reviewing evidence in this area highlight the lack of methodological rigour in many of the trials that have been carried out and the lack of consistency in study protocols which make clear conclusions difficult. A Cochrane review (Osborn and Sinn, 2006) reported that:

"There is no evidence to support feeding with a hydrolysed formula to prevent allergy in preference to exclusive breastfeeding. In infants at high risk for allergy who are unable to be completely breastfed, there is limited evidence that feeding with a hydrolysed formula compared to a cows' milk formula reduces allergies in babies and children, including cows' milk allergy. Concerns regarding quality of the evidence and consistency of the results indicates further studies are needed." (Osborn and Sinn, 2006).

In the UK, public health guidance from the National Institute for Health and Clinical Excellence (NICE) concluded from an extensive literature review that:

"*There is insufficient evidence that infant formulas based on partially or extensively hydrolysed cows' milk protein can prevent allergies*." (National Institute for Health and Clinical Excellence, 2008)

This public health guidance remained unchanged when the NICE guidance was reviewed in 2012.

The key evidence used to support the use of partially hydrolysed whey-based formula in the reduction of allergy in infancy in children from atopic families used in some statements and by commercial companies comes from the German Infant Nutritional Intervention Study (GINI) (von Berg et al, 2003, 2008) which randomised formula-fed infants into four groups and compared the incidence of a number of allergy symptoms. Data from this study is widely quoted as evidence that a partially hydrolysed whey-based formula prevented atopic dermatitis (AD) in the first year of life, but it is important to note that the difference in the number of children who completed the study and who were diagnosed with AD at 12 months was relatively small – 14.8% (n=38) in the cows' milk based formula group and 9.1% (n=22) in the partially hydrolysed formula group. Also, this study population had a high proportion of mothers exclusively breastfeeding in the first four months who were excluded from the study (42%). Some infants in the formula-fed groups were also receiving breastmilk, but this was not reported. Gender and family history are highlighted in this study as being of particular significance in AD development, suggesting that additional studies are needed to support these findings in other cohorts. In addition, the preferred intention to treat analysis failed to show any benefit of partially hydrolysed whey-based formula over cows' milk formula in this study (Lowe et al, 2011).

An Australian RCT published in 2011 (Lowe et al, 2011) considering the impact of a partially hydrolysed whey-based formula (NAN HA), a standard infant formula (NAN) and a soy

protein based (ProSobee) in infants who were formula-fed, partially breastfed or who moved from breastfeeding to formula feeding in the first four months of life, reported that there was no evidence that introducing partially hydrolysed whey-based formula reduced the risk of allergic manifestations, including eczema, in infants from atopic families and they concluded *"that partially hydrolysed whey based formula should not be used as a preventive strategy for infants at high risk of allergic diseases".*

In 2012 the Food and Drug Administration in the USA (Chung et al, 2012) produced a revised recommendation. The FDA concluded:

"There is little to very little evidence, respectively, to support a qualified health claim concerning the relationship between intake of partially hydrolysed whey based formula and a reduced risk of AD in partially breastfed and exclusively formula-fed infants throughout the first year after birth and up to 3 years of age."

In 2013 a 'review of systematic reviews' looking at evidence in prevention and aetiology of food allergy considered 14 systematic reviews in this area (Lodge et al, 2013) and again concluded that:

"There is insufficient evidence to conclude that the use of hydrolysed formula may reduce food allergy/sensitization when compared with standard formula in high atopy risk children."

The EFSA *Scientific Opinion on the Essential Composition of Infant and Follow-on Formulae* in 2014 stated that reducing the size of protein molecules cannot reduce the risk of allergy in infants from at-risk families (EFSA, 2014):

"The characterisation of protein hydrolysates by molecular weight of the protein cannot predict their potential to reduce the risk of developing allergic manifestations in genetically predisposed infants."

The Food Standards Agency commissioned a systematic review of the evidence on diet and allergy in the first year of life, which was published in 2016 (Boyle et al, 2016). This review concluded that:

"Overall there was no consistent evidence that partially or extensively hydrolysed formulas reduce the risk of allergic or autoimmune outcomes in infants at high pre-existing risk of these outcomes."

When the EU regulations change in February 2020 the claim that a hydrolysed infant formula can reduce the risk of cows' milk protein allergy will not be allowed unless new evidence demonstrating efficacy is submitted to a relevant competent authority from which further consideration would be given to how to adequately inform parents and caregivers about that property of the product.

Safety issues related to partially hydrolysed whey-based infant formula

There are safety concerns about partially hydrolysed whey-based infant formula since they are unsuitable for the *treatment* of allergy in infants. The FDA requires the following warning statement be displayed to indicate to consumers that partially hydrolysed infant formulas are

not hypoallergenic and should not be fed to infants who are allergic to milk or to infants with existing milk allergy symptoms.

"*Partially hydrolysed formulas should not be fed to infants who are allergic to milk or to infants with existing milk allergy symptoms. If you suspect your baby is already allergic to milk, or if your baby is on a special formula for the treatment of allergy, your baby's care and feeding choices should be under a doctor's supervision*."

The FDA concluded that the use of bold type is necessary, in light of the significant public health risk that would be created by the feeding of these formulas to infants who are allergic to milk or to infants with existing milk allergy symptoms. Manufacturer claims of a relationship between the consumption of partially hydrolysed whey-based formula and a reduced risk of developing AD could mislead consumers to think that these formulas are an appropriate choice for such infants.

The NHS makes the statement: "*Partially hydrolysed formulas aren't suitable for babies who have cows' milk allergy*." (NHS, 2016)

Any new partially hydrolysed formula made available to parents in the UK should therefore be required to carry a clear and bold warning on the label to this effect. Any promotion of partially hydrolysed whey-based formula milk products to health professionals must clearly warn of the risks associated with giving partially hydrolysed whey-based formula to infants and children with diagnosed cows' milk protein allergy or to infants showing symptoms of cows' milk protein allergy.

Data from a French longitudinal study of formula type and use has also highlighted potential risks of routine consumption of partially hydrolysed formula compared to exclusive breastfeeding or a non-hydrolysed formula. Despite some partially hydrolysed milks claiming that usage is associated with reduced risk of allergy, the study showed that use of a partially hydrolysed formula at two months of age was related to higher risk of wheezing at one year in at-risk infants and a higher risk of food allergy at two years of age both in at-risk and non-at-risk infants. Further studies looking at the risks associated with partially hydrolysed milks would be beneficial (Davisse-Paturet et al., 2019).

The nutritional composition and ingredients used in partially hydrolysed infant milks suitable from birth are given in Table 16.

TABLE 16. The nutritional composition of partially hydrolysed infant milks suitable from birth

Nutrients per 100ml	Aptamil Comfort	Cow & Gate Comfort	Hipp Combiotic Comfort	SMA Comfort	SMA HA
MACRONUTRIENTS					
Energy kcal	66	66	67	67	67
Protein g	1.5	1.5	1.6	1.6	1.3
Whey:casein ratio	100:0	100:0	100:0	100:0	100:0
Carbohydrate g	7.2	7.2	7.1	7.1	7.8
– of which lactose g	2.7	2.7	2.7	3.9	7.8
Source of added carbohydrate	Glucose syrup, potato and corn starch, oligosaccharides, lactose	Glucose syrup, potato and corn starch, oligosaccharides, lactose	Maltodextrin, lactose, starch, oligosaccharides	Lactose, corn syrup solids, maltodextrin	Lactose
Fat g	3.4	3.4	3.5	3.6	3.4
Fat source	Structured vegetable oil, rapeseed, coconut, single cell, sunflower and fish oils	Structured vegetable oil, rapeseed, coconut, single cell, sunflower and fish oils	Structured vegetable oil, palm, rapeseed and sunflower oils	Structured vegetable oil, palm, soya, sunflower and coconut oils	Sunflower, coconut, rapeseed, arachidonic acid rich oil and fish oils
Added LCPs ARA	✓	✓	✓	✓	✓
DHA	✓	✓	✓	✓	✓
LCP source	Fish oil, fungal/algal oils (vegetable source)	Fish oil, fungal/algal oils (vegetable source)	Fish and single cell oils	Fungal/algal oils (vegetable source)	Fish oil, fungal/algal oils (vegetable source)
MICRONUTRIENTS					
Vitamins meeting regulations	✓	✓	✓	✓	✓
Minerals meeting regulations	✓	✓	✓	✓	✓
VITAMINS					
Vitamin A µg-RE	50	50	67	66	67
Vitamin C mg	9.3	9.3	10	9.0	9.0
Vitamin E mg	0.74	0.74	0.8	0.74	1.2
Vitamin D µg	1.2	1.2	1.1	1.2	0.9
Vitamin K µg	4.1	4.1	5.0	6.7	5.2
Thiamin (B_1) µg	50	50	60	100	70
Riboflavin (B_2) µg	100	100	100	110	160
Niacin µg (mg NE)	(0.85)	(0.85)	670	500	710
Vitamin B_6 µg	40	40	40	60	50
Vitamin B_{12} µg	0.14	0.14	0.15	0.18	0.14
Folic acid µg	9.3	9.3	10	11	10.6
Biotin µg	2.1	2.1	1.5	2.0	1.4
Pantothenic acid µg	360	360	500	350	630
MINERALS					
Calcium mg	49	49	60	42	45

Nutrients per 100ml	Aptamil Comfort	Cow & Gate Comfort	Hipp Combiotic Comfort	SMA Comfort	SMA HA
Chloride mg	41	41	45	43	50
Copper µg	40	40	45	30	60
Iodine µg	12	12	15	10	9.2
Iron mg	0.54	0.54	0.7	0.8	0.7
Magnesium mg	5.5	5.5	5.5	4.5	6.7
Manganese µg	8	8	8.6	10	10
Phosphorus mg	27	27	34	24	26
Potassium mg	75	75	70	65	76
Selenium µg	1.6	1.6	1.3	1.4	2.1
Sodium mg	20	20	20	16	26
Zinc mg	0.49	0.49	0.5	0.6	0.66
ADDED INGREDIENTS					
Structured vegetable oils	✓	✓	✓	✓	×
Prebiotics	✓	✓	✓	×	×
Nucleotides	✓	✓	×	✓	✓
Inositol	✓	✓	✓	✓	✓
Taurine	✓	✓	✓	✓	✓
Choline	✓	✓	✓	✓	✓
L-carnitine	✓	✓	✓	✓	✓
Added antioxidants	✓	✓	✓	✓	✓
Contains soya	✓	✓	×	✓	×
Contains fish oil	✓	✓	✓	×	✓
Suitable for vegetarians[1]	×	×	×	✓	×
Halal approved	×	✓	×	✓	×
Osmolality mOsm/kg	250	250	194	255	320

ARA = arachidonic acid
DHA = docosahexaenoic acid
ANS = approval not sought
LCP = long chain polyunsaturated fatty acid

1 Formula milks derived from cows' milk are generally not suitable for vegetarians due to the inclusion of fish oils and/or the use of the animal-derived enzyme rennet during the production process. Rennet is used to separate curds from whey and, although vegetarian alternatives are available, they are not used by all manufacturers.

3.12 Extensively hydrolysed peptide-based infant milks suitable from birth

Key points

Extensively hydrolysed infant milks are marketed primarily to be used in the dietary management of mild to moderate cows' milk protein allergy (CMPA). Some products are also marketed to manage multiple allergies, gastroenterological disorders such as malabsorption, inflammatory bowel disorder and short bowel syndrome, prolonged diarrhoea and cystic fibrosis. Some of these milks contain lactose and some have a proportion of their fat content as medium chain triglycerides (MCT).

Breastfeeding is the optimal way to feed a baby with cows' milk protein allergy, with individualised maternal elimination of all cows' milk protein foods and fluids and with adequate calcium and vitamin D supplementation to meet the mother's nutritional requirements during breastfeeding. NICE clinical guidelines on the management and treatment of cows' milk protein allergy provide clinical guidance on treatment of both suspected and confirmed cows' milk protein allergy (National Institute for Health and Care Excellence, 2015b).

This group of infant milks contains proteins which have been extensively broken down or hydrolysed. The hydrolysis process uses pork enzymes, making some milks unsuitable for those population groups who avoid pork products.

The use of high-profile health professionals working in allergy to promote brands is common in this area. When making clinical decisions, healthcare professionals should take note of whether guidelines or guides are sponsored by infant milk companies and should look for independent information wherever possible.

Breastfeeding remains the best way to feed an infant with IgE or non IgE mediated cows' milk protein allergy. Greater clinical success and cost savings can be made to the NHS by supporting breastfeeding wherever possible, and when clinically indicated, rather than immediately prescribing extensively hydrolysed infant milks. It is important also to safeguard the best interests of mixed fed infants, and successful breastfeeding will be achieved with skilled diet history taking and successful maternal elimination of cows' milk protein containing foods and fluids. In exclusively breastfed babies**,** the June 2015 NICE clinical knowledge summary on management of cows' milk protein allergy in infants advises breastfeeding mothers who exclude all dairy products from their diet to take a daily supplement of 1,000mg of calcium and 10 micrograms of vitamin D to prevent nutritional deficiencies (National Institute for Health and Care Excellence, 2015b) .

Clinical commissioning groups and local prescribing initiatives are likely to review products used to encourage cost savings through the use of cheaper infant milks as a first-line practice when cows' milk protein allergy is diagnosed. A cost comparison for different milks can be found in Table 3.

In the UK, NICE guidelines are available for the diagnosis and management of food allergy in children and young people (National Institute for Health and Clinical Excellence, 2011)

and additional support is available through the NICE clinical knowledge summary on confirmed cows' milk protein allergy highlighted above. UK guidelines for managing cows' milk protein allergy in primary care known as the iMAP guidelines have recently been rewritten with independent support (Fox et al, 2019) and information on this is available at https://link.springer.com/epdf/10.1186/s13601-019-0281-8?author_access_token=MHiNeTe8JNzsWHH29iKNNW_BpE1tBhCbnbw3BuzI2ROqeUkNL_DmjyCbkFVHW7hXWrYHNgFQDZn9wrwq8HmXvxuYEDKVOZ9WWdue29MF8X11E1tRGa72hZlU9r9_mjEHMR9CnN6HdtvOOElBqs6zWw%3D%3D

This updated guidance is available through the GP Infant Feeding Network website www.gpifn.org/imap. The updated guidance better supports breastfeeding and aims to reduce the over-diagnosis of cows' milk protein allergy that has been linked to previous versions of this guidance (van Tulleken, 2018).

ESPGHAN and an international working group which itself was funded by Nutricia, have published guidelines on the diagnosis and management of cows' milk protein allergy, depending upon whether infants are breastfed or infant milk fed (Koletzko et al, 2012; Vandenplas et al, 2007). They both recommend an extensively hydrolysed infant milk with proven efficacy in appropriate clinical trials. ESPGHAN note that, despite American and European guidelines recommending that extensively hydrolysed infant milks are tested in elimination challenge tests under double blind placebo controlled conditions in order to ensure, with 95% confidence, that they do not provoke allergic reactions in 90% of infants or children with diagnosed cows' milk protein allergy, this has not been undertaken by all manufacturers Høst et al, 1999). It is noted that a small percentage of infants and children diagnosed with cows' milk protein allergy who are given an extensively hydrolysed infant milk will continue to exhibit symptoms and may require a trial of an amino-acid based (elemental) infant milk. (An expert review by the Committee on Nutrition of the French Society of Paediatrics concluded that not all hydrolysates available on the European market have been subject to a detailed assessment of their nutritional efficacy, which is required by the regulations (Dupont et al, 2012).

Hydrolysed infant milks are heavily marketed to health professionals using allergy specialist dietitians and physicians via conferences, learning events and infant milk company branded recipe guides, parent guides, case studies, frequently asked questions and feeding tips. It is important that health professionals ignore marketing materials and consider the composition of each product, making independent assessments of evidence presented.

Milks currently marketed

There are seven different extensively hydrolysed peptide-based infant milks suitable from birth and all are approved by the Advisory Board for Prescribable Substances. All of the infant milks are powdered with the exception of Infatrini Peptisorb which is a ready-to-feed liquid. We have divided extensively hydrolysed milk into two groups to allow some comparison of products, and this categorisation is our own.

Extensively hydrolysed milks marketed primarily for use in the treatment of cows' milk protein allergy, which do not contain MCT:

- Abbott Nutrition Similac Alimentum

- Aptamil Pepti 1 (contains lactose)
- Mead Johnson Nutramigen 1 with LGG
- SMA Althéra (contains lactose).

Extensively hydrolysed milks marketed for severe and multiple allergies, disaccharide and whole protein allergy requiring peptide or amino-acid and MCT-based feeding:

- Aptamil Pepti-junior
- Mead Johnson Pregestimil LIPIL
- Nutricia Infatrini Peptisorb

Nutricia Infatrini Peptisorb is an extensively hydrolysed infant milk marketed for disease-related malnutrition, malabsorption, inflammatory bowel disease, short bowel syndrome and whole protein allergy. It has a significantly higher energy content than other milks in this category.

All of the extensively hydrolysed infant milks suitable from birth comply with EC regulations for foods for special medical purposes. There are no extensively hydrolysed infant milks suitable for vegetarians or vegans, or which are halal approved. All of this group of specialised infant milks are based on cows' milk protein.

Nutritional composition

This group of infant milks are composed of extensively hydrolysed proteins, fats, added vitamins, minerals and trace elements. They differ from infant formula in that they are processed to extensively, but not completely, break down the casein and whey present in the cows' milk protein using a combination of heat, enzymes (to break polypeptide chains), hydrostatic pressure and ultrafiltration. The hydrolysis of proteins is achieved using pork enzymes.

Infant milks with a molecular weight of <3,000 Da (daltons) can be categorised as hypoallergenic and hence considered suitable for use in the management of infants with cows' milk protein allergy. The molecular weight distribution of peptides within extensively hydrolysed milks vary. For example, Nutricia Pepdite report that in this milk 64% of peptides have a molecular weight of <1,000 Da, 34.2% of 1,000-5,000 Da and 1.8% of <5,000 Da. SMA Althéra claim that 99.3% of their peptides are <1,000 Da. In Similac Alimentum, 99% of the peptides are reported to be <1,500 Da.

Unlike infant formula which contain carbohydrate mainly in the form of lactose, this group of infant milks contain carbohydrate mainly in the form of maltodextrin or dried glucose syrup.

Of the milks which are milk-based, Aptamil Pepti 1, Aptamil Pepti-junior, Nutricia Infatrini Peptisorb and SMA Althéra are whey-based infant milks, whereas Abbott Nutrition Similac Alimentum, Mead Johnson Nutramigen 1 with LGG and Pregestimil LIPIL are casein-based infant milks.

A number of these infant milks contain added medium chain triglycerides (MCTs). MCTs are triglycerides with a chain length of 8-10 carbon atoms, e.g. C:8 to C:10. These types of fats are shorter than long chain triglycerides (LCTs), are relatively soluble in water and are

hydrolysed faster during digestion and absorption than LCTs. They are also metabolised using a different pathway to LCTs and enter the body via the portal venous system rather than the lymphatic system. MCTs are used therapeutically in infant milks for individuals with maldigestion, malabsorption and other gastroenterological conditions, such as short bowel syndrome.

Of the milks with added MCT 50% of the fat in Aptamil Pepti-junior and Nutricia Infatrini Peptisorb is composed of MCT, Mead Johnson Pregestimil LIPIL has 53% fat as MCT.

Manufacturer claims and evidence given to support them

One of the difficulties in reviewing evidence presented on the efficacy and use of infant milks marketed for management of cows' milk protein allergy and other allergies in infants, is that many of those who do research in this area, or who write clinical guidelines, are also employed or funded by the infant formula industry. We have looked at some of the evidence currently being used to support the claims made for some of the extensively hydrolysed infant milks, and we hope that awareness of how data is presented to health professionals will stimulate a more critical approach when reviewing advertising in this area. Reviews of advertising in the print media of some specialised infant milks can also be found in the publication '*Scientific and Factual?' A further review of breastmilk substitute advertising to health professionals*, available at https://www.firststepsnutrition.org/working-within-the-who-code.

Abbott Nutrition Similac Alimentum
Marketing material for Similac Alimentum claims to use "*striking images to create impact in a crowded marketplace*" and their marketing material suggests that "*some babies are in distress because they need an infant milk they will accept without fuss and that does not result in allergic reactions*". Abbott Nutrition claims that 96% of babies accept the infant milk and that it is "*safe*" and "*efficacious*", although the data they cite is 'on file' and only available as a handout in marketing literature. The first observational study they quote as evidence involved observing a single non-randomised group of 18 infants who were given formula for 15 days (Abbott Laboratories Ltd, 2013). The study found a significant improvement in weight for age z-scores but was not published in a peer-reviewed publication. A second larger study cited was conducted in 17 countries and investigated a total of 6,999 infants for 14 days. This study claimed a significant improvement in gastrointestinal parameters amongst infants given a new formula (Similac Advance) compared to older formula, but both groups did less well than breastfed infants in terms of stool softness and frequency. This study was undertaken in healthy as opposed to medically unwell infants and the product Similac Advance was launched around a decade before Similac Alimentum, so any gastrointestinal improvements cannot reliably be assigned to Similac Alimentum (Alarcon et al, 2002).

In 2014 Similac Alimentum, in print advertising, presented the case study of a baby, 'Jake', diagnosed with mixed IgE and non-IgE mediated cows' milk protein allergy, with no reference to any published evidence, yet making claims that having had Similac Alimentum for one day the baby in question was no longer crying and was "*sleeping like a baby*". The 2015 marketing campaign for this product focusses on an emotional advert showing a mother and infant sleeping, with very little text. They claim that the milk has proven efficacy. They quote one study from 1991 that looked at the safety of the use of a casein hydrolysate,

which does not qualify as a study of efficacy of outcome (Sampson et al, 1991), and one study that is ‘data on file’. The claim that the product is well tolerated is based on a small methodologically challenged Abbott-funded non-randomised prospective study of 25 infants with CMPA 4 months of age, on a 15-day trial of Similac Alimentum, with parent-reported outcomes (Borschel & Baggs, 2015). Overall, 50% of parents said they were very satisfied and 50% were somewhat satisfied with the study formula. The third claim made is that the formula is free of palm oil and palm olein and that this supports calcium absorption and bone mineralisation. This is supported with one reference to a study by Koo et al (2006). However, this review has been criticised as there was no breastfed reference group and there is known to be a large variation in normal bone mineral content in infants, which in itself may have no clinical significance. In the EU there are rules that govern the fatty acid composition of milks and it is the individual fatty acid profile rather than the source of fatty acids that is regulated.

Nutricia Aptamil Pepti 1

Aptamil Pepti marketing material claims that Pepti 1 is tolerated by 97% of infants with IgE mediated CMPA, and is clinically proven to relieve the symptoms of CMPA. The first of these claims is substantiated by reference to a small, company-funded study of 32 infants with proven cows’ milk protein allergy. After oral challenge with two extensively hydrolysed formula milks (including Nutrilon Pepti) and one partially hydrolysed formula milk, it was concluded that 97% of the 32 children tolerated Nutrilon Pepti (Giampietro et al, 2001). The second claim is substantiated by reference to a small company-funded study of 92 infants at risk of atopy who were fed a hypoallergenic infant milk with either added oligosaccharides or maltodextrin and observed for allergic manifestations (atopic dermatitis, recurrent wheeze, allergic rhinoconjunctivitis and urticaria) (Arslanoglu et al, 2012). The study found significantly fewer allergic symptoms at 2 and 5 years. Neither of these studies had a breastfeeding reference group against which to measure effect. Aptamil promote their infant milk as being the only extensively hydrolysed formula containing oligosaccharides and nucleotides, but neither of these substances are necessary additions to infant formula (EFSA, 2014).

Aptamil Pepti also contains lactose. The website claims that the presence of lactose benefits gut microbiota and aids calcium absorption. A very small clinical trial by Francavilla et al, 2012 is referenced to support the beneficial effects of lactose on gut microbiota. This cross over trial in which 16 infants were fed Nestlé Alfare without lactose for a period of two months followed by Nestlé Althéra with 3.8% lactose for further 2 months reported increasing total faecal counts of Lactobacillus/Bifidobacteria and decreasing counts of Bacteroides/Clostridia together with increasing median concentrations of short chain fatty acids in infants, when fed formula with lactose. No power calculations were performed for this study and modifications in diet that may have occurred over the course of the trial were not measured. The formula milks used were Nestlé milks with a higher level of lactose than that found in the Aptamil Pepti formula the trial is being used to support.

ESPGHAN, 2015 state that whilst lactose is considered to provide beneficial effects for gut physiology, including prebiotic effects and enhancement of calcium absorption, no specific need for lactose in young infants has been demonstrated (Koletzko et al, 2005).
In their 2018 print advertising campaign in professional journals Nutricia claim that Aptamil Pepti is "*the UK's most palatable eHF*". They support this claim by referencing a Nutricia-funded study. The research report referenced is unobtainable, however, a paper published

by the same author outlining this work references a taste test carried out on eHF's on the UK market. The study reported that Pepti 1 was ranked as most palatable by 77% of participants and that the HCPs in the study expected that good palatability would result in better acceptance. It was acknowledged that this does not prove that there is any link between HCP taste preference and child preferences for the same formula (Maslin et al, 2018). The study particpants were dietitians and GPs who all had prior experience of treating an infant with CMA, were recruited by market research agencies from their healthcare professional registers and 98% of whom had prior awareness of Aptamil Pepti 1. The study was funded by Nutricia.

The 2018 advertisement for Pepti 1 also suggests that it is *"The 1st step in the effective management of cows' milk allergy is extensively hydrolysed formula"* in any infant. The main body of the advertisement omits the fact that eHF is only the first line of treatment of CMA in infants who are formula-fed or mixed fed. The iMAP (an international interpretation of the Milk Allergy in Primary Care) guideline is used in support of this suggestion, however, the guideline recommends a trial of an eHF only for infants who are formula-fed or mixed-fed (Venter et al, 2017). Breastfeeding remains the primary recommendation for infant feeding (NICE, 2019).

SMA Althéra (Nestlé)

SMA Althéra is prescribable for dietary management of cows' milk protein allergy. SMA marketing material claims that Althéra has proven safety and efficacy sustaining normal growth by referencing a study of 75 nurses and 78 mothers in Sweden from 2011 that is 'held on file'. Advertising in 2015 focussed on the taste of Althéra and claim that "*95% of mothers prefer to feed their infant Althéra"* based on 'data on file'. They say it has a "*preferred taste"* and quote two studies to support this. The first (Niggemann et al, 2007) was a randomised prospective study in Germany funded by Nestlé of 65 infants, comparing the use of an extensively hydrolysed formula (Althéra) and an amino-acid based formula (Neocate). Interestingly, in this study they claim that Althéra has 99.7% of peptides <2,400 Da rather than the current claim of 99.3% <1,000 Da. Both formula were reported to be tolerated equally well and there were no significant differences in growth or allergy symptoms. This study was a tolerance study and does not provide any evidence as suggested to claim it has a preferred taste. The second is a poster presentation by Nestlé employees at an industry-funded conference (Rapp et al, 2013) which looked at how the level of hydrolysis in whey-based and casein-based milks affects sensory profile, using a panel of 11 adults. No results are presented to support their claim that the extensively hydrolysed whey-based formula was significantly less bitter, less salty and sweeter than a casein-based alternative.

The 2018 advertising campaign in the health professional literature implies that Althéra shows better clinical outcomes for symptoms resolution than other brands because it has a greater level of hydrolysis and consistently lower allergenic potential than other brands. This claim is based on the theory that the smaller Dalton size and low residual β-lactoglobulin present in Althéra, result in a product with a less allergenic profile, which therefore suggests that it may result in better clinical outcomes. The only clinical trial used to support this claim compared Nestlé Althéra with an amino acid based formula. This small clinical trial including 65 infants aged between 6 and 12 months showed that infants with CMPA tolerated the

Althéra formula milk to the same extent as the amino acid formula tested and showed similar outcomes in terms of skin, gastro intestinal and respiratory tract symptoms of allergy as infants fed the amino acid formula (Niggemann et al, 2007). The trial did not suggest that Althéra has a consistently low allergenic profile in terms of it's protein profile across batches and did not compare the outcomes achieved with Althéra compared to other extensively hydrolysed formula milks.

Mead Johnson Nutramigen 1 with LGG

Mead Johnson's extensively hydrolysed formula, Nutramigen LIPIL 1, was reformulated in 2015 to include a "unique probiotic", *Lactobacillus rhamnosus* GG (LGG). They claim that it "is clinically proven to relieve CMA symptoms affecting the skin and gastrointestinal tract", EFSA stated that there is no benefit in adding probiotics to infant formula or follow-on formula (EFSA, 2014). Mead Johnson claim that this formula is clinically proven to accelerate tolerance to cows' milk. The 2015 advertising campaign in the health professional literature used the slogan "*The express route to the end of cows' milk allergy"*. This claim was based on data from a prospective nonrandomised Italian trial of infants aged 1-12 months with CMPA who were already treated and free of symptoms and who were non-randomised to one of five treatment groups for 12 months to look at acquisition of tolerance to cows' milk (Canani et al, 2013). Two of the study arms used an extensively hydrolysed whey-based formula, one formula with LGG, one soya formula, one amino-acid based formula, and one a hydrolysed rice formula. The duration and exclusivity of breastfeeding between groups was not reported other than the proportion of infants per group breastfed for two months or more.

One of the main findings of the study was that infants with IgE mediated CMA were less likely than those with non-IgE mediated allergy to achieve tolerance after 12 months. The group receiving Nutramigen with LGG had the lowest rate of IgE mediated allergy. There were differences in the brand of infant milk consumed in each of the treatment groups. For example, within the amino acid-based formula group (n=33), three different brands of formula were consumed, but in the largest group (n=71), extensively hydrolysed casein based formula with LGG, only Nutramigen with LGG was consumed. Differences between brands may therefore have been masked, as brands were grouped according to category. The trial notably lacked a breastfeeding reference group to explore the effect of normal feeding on tolerance to cows' milk protein. As approximately half of infants with cow's milk protein allergy are known to outgrow this allergy at around 12 months, this may well also confound any conclusions regarding tolerance.

The authors concluded that the rate of acquiring oral tolerance was higher in the groups having either of the extensively hydrolysed formula and this was augmented by the addition of LGG, however, the study contains a large number of variables that could have impacted on the outcomes. Mead Johnson claim in their advertising that this milk is *"proven to have an average efficacy of 99%"* but in a footnote say that this claim actually refers to a different extensively hydrolysed product which does not have probiotics added. Again they also caveat the claims *"the only eHF clinically proven to accelerate time to tolerance*" and *"8 out of 10 infants are tolerant to cows' milk after 12 months use"* with the admission that these data come from the Canani et al, 2013 study reported above that compared an eHF with infant groups given soy, amino-acid and rice hydrolysate formula. Mead Johnson also claim that this is "*the world's leading CMA formula*" with evidence for this *'on file'*.

The 2018 advertising campaign in the health professional literature continues to use the 2015 claims and includes a further statement *"Help give her the ability to protect herself from future allergic manifestations".* The study used to support this implied claim is a clinical trial part sponsored by Mead Johnson, carried out between 2008 and 2014 (Canani et al, 2017). The infants included in the trial were aged between 1 and 12 months with a median age of 5 months, and the follow-up period was 36 months. Only infants with proven IgE mediated CMPA were included in the trial. Infants were randomised to receive either Nutramigen eHF with no probiotic or Nutramigen eHF with the probiotic *Lactobacillis rhamnosus* GG (LGG). Allergic manifestations and other food allergies were recorded at baseline and at 12 months, 24 months and 36 months. Skin prick tests and double-blinded, placebo-controlled food challenge tests were also performed at these visits to determine tolerance acquisition. The trial reported an absolute risk difference of -0.23 of any allergic manifestation during 36 months for Nutramigen with LGG compared to Nutramigen without probiotic. This means that, compared with eHF without probiotics, four subjects needed to be treated with eHF with probiotic for 36 months to prevent at least one allergic manifestation.

As highlighted previously, this trial relates only to children with IgE mediated cows' milk allergy. It is not clear from the trial data if the Nutramigen milks with LGG currently marketed are those used in the trial. No details of the duration or exclusivity of breastfeeding was provided except for the proportion of babies breastfed for more than two months, and there was no breastfed reference group. Parents were not blinded to the infant milk their child received and they recorded the amount of milk consumed daily. Health problems and allergic symptoms were recorded by structured interviews with parents. The interviews occurred at 12-month intervals or more frequently in individual children if advised by the GP. Although dietitians were employed to give advice on the cows' milk exclusion diet, the trial report did not appear to record compliance with the diet.

Mead Johnson have also financially supported studies in different countries that estimate the cost savings of using their Nutramigen eHF products with LGG in comparison to eHF products without LGG in different European countries and the US. The UK study by Guest and Singh, 2019 uses data on clinical outcomes from the previously mentioned Canani et al, 2017 study. Estimates of associated healthcare resource costs were derived from interviews with 4 UK GPs experienced in the management of patients with CMPA according to their local clinical protocol and NICE guidance (NICE, 2011). The data collected was used to populate a predictive statistical model that estimated the potential savings in healthcare costs that would be made by using eHF with LGG compared to eHF without LGG as the first line of treatment in infants with IgE mediated CMPA. The original study had a follow-up period of 3 years and the predictive model extrapolated potential savings to 5 years. This study reported that cost savings would be made on the basis of greater acquisition of tolerance and reduced allergic manifestations in infants fed Nutramigen LGG compared to those fed Nutramigen without LGG. No other brands were compared in the study. Nutramigen without LGG is no longer available in the UK and the study does not provide any evidence that Nutramigen with LGG is any more cost effective than eHF from other manufacturers.

The study has some major limitations including that the base data was taken from a study with some methodological limitations, as outlined previously. In addition, data on resource

use came from only 4 GPs in different UK locations. Local treatment protocols may vary and so it is not certain that the costs used were typical of other areas in the UK. The study fails to mention that breastfeeding remains the best way to feed an infant with IgE or non IgE mediated cows' milk protein allergy. Greater clinical success and cost savings can be made to the NHS by supporting breastfeeding wherever possible, and when clinically indicated. As this milk contains the probiotic *Lactobacillus rhamnosus GG,* instructions for making up this powdered infant milk include the use of cold water. This has caused some concern among health professionals, who recognise the risk associated with making powdered infant milk up with water at temperatures below 70^{o}C. The Food Standards Agency and the Department of Health regulators agreed, in a restricted correspondence and data review in 2015, that the milk can be sold in the UK with these instructions for making up the milk, but suggesting that claims for efficacy of this product contradict most other scientific reviews.

Safety of use

Infants receiving extensively hydrolysed infant milks may need attentive mouth care as some of the added sugars found in some of these infant milks are associated with the demineralisation of enamel (Rezende and Hashizume, 2018). The use of, and health risks associated with consumption of these types of carbohydrates is discussed in the First Steps Nutrition Trust report *Infant Milks in the UK* (available at: www.firststepsnutrition.org/composition-claims-and-costs).

The manufacturers of Aptamil Pepti-junior advise that Pepti-junior should not be used at full strength initially in infants with severe gut damage, but do not give evidence supporting this recommendation. Instead they recommend starting at half strength, working up to full strength in 2-3 days.

As there is so much marketing and promotion of products in this area, it is particularly important that health professionals know how to work within the WHO Code and to refer to recognised clinical guidance if suitable local prescribing guidance is not provided.

Table 17 shows the nutritional composition of extensively hydrolysed infant milks which do not have MCT added as part of the fat source, and Table 18 shows the composition of extensively hydrolysed infant milks with MCT.

TABLE 17. The nutritional composition of extensively hydrolysed (peptide-based) infant milks suitable from birth

Nutrients per 100ml	Abbott Nutrition Similac Alimentum	Aptamil Pepti 1	Mead Johnson Nutramigen 1 with LGG	SMA Althéra
INDICATIONS	Cows' milk protein allergy	Cows' milk protein allergy	Cows' milk protein allergy	Cows' milk protein allergy and/or multiple food protein allergies
MACRONUTRIENT				
Energy kcal	68	67	68	67
Protein g	1.9	1.6	1.9	1.7
Protein source	Milk	Milk	Milk	Milk
Whey:casein ratio	0:100	100:0	0:100	100:0
Carbohydrate g	6.6	7.0	7.5	7.3
– of which lactose g	0	2.9	0	3.8
Carbohydrate source	Maltodextrin, sucrose, modified corn starch	Maltodextrin, lactose, oligosaccharides	Glucose syrup, modified corn starch	Lactose, maltodextrin
Fat g	3.8	3.5	3.4	3.4
Fat source	High oleic safflower, MCT from palm kernel, coconut, soya and single cell oils	Palm, rapeseed, coconut, sunflower, single cell and fish oils	Palm olein, coconut, soya, high oleic sunflower and single cell oils	Palm, rapeseed, coconut, sunflower and single cell oils
Added LCPs ARA	✓	✓	✓	✓
DHA	✓	✓	✓	✓
LCP source	Fungal/algal oils (vegetable source)	Fish oil, fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)
MICRONUTRIENTS				
Vitamins meeting regulations	✓	✓	✓	✓
Minerals meeting regulations	✓	✓	✓	✓
VITAMINS				
Vitamin A µg-RE	61	53	61	79
Vitamin C mg	8.5	9.1	14.3	13
Vitamin E mg	0.9	1.0	0.9	1.5
Vitamin D µg	1.0	1.3	1.0	1.2
Vitamin K µg	5.4	4.7	8.9	7.3
Thiamin (B_1) µg	51	50	55	66
Riboflavin (B_2) µg	68	100	61	180

Nutrients per 100ml	Abbott Nutrition Similac Alimentum	Aptamil Pepti 1	Mead Johnson Nutramigen 1 with LGG	SMA Althéra
Niacin µg (mg NE)	(0.71)	(0.88)	(0.68)	860 (1.5)
Vitamin B_6 µg	41	40	41	53
Vitamin B_{12} µg	0.2	0.18	0.2	0.2
Folic acid µg	10	9.0	10.9	10
Biotin µg	3.0	2.2	2.0	1.6
Pantothenic acid µg	510	330	340	420
MINERALS				
Calcium mg	71	47	77	66
Chloride mg	54	40	65	40
Copper µg	50	40	51	55
Iodine µg	10	12	14.3	11
Iron mg	1.2	0.53	1.2	0.73
Magnesium mg	5.1	5.3	6.8	5.5
Manganese µg	5.0	9.8	41	4.8
Phosphorus mg	44	26	53	42
Potassium mg	71	81	83	70
Selenium µg	1.4	1.5	1.5	2.0
Sodium mg	30	20	32	20
Zinc mg	0.51	0.5	0.48	0.66
ADDED INGREDIENTS				
Prebiotics	×	✓	×	×
Probiotics	×	×	✓	×
Nucleotides	×	✓	×	×
Inositol	✓	✓	✓	✓
Taurine	✓	✓	✓	✓
Choline	✓	✓	✓	✓
Added antioxidants	✓	✓	✓	×
Contains soya	✓	×	✓	×
Contains fish oil	×	✓	×	×
Suitable for vegetarians	×	×	×	×
Halal approved	×	×	×	×
Osmolality mOsm/kg	274	280	280	281

ARA = arachidonic acid
DHA = docosahexaenoic acid
LCP = long chain polyunsaturated fatty acid
NA = not applicable
NK = not known

TABLE 18. The nutritional composition of extensively hydrolysed (peptide-based) infant milks with MCT, suitable from birth

Nutrients per 100ml	Aptamil Pepti-junior	Mead Johnson Pregestimil LIPIL	Nutricia Infatrini Peptisorb
INDICATIONS	Malabsorption from conditions such as short bowel syndrome, liver disease, chronic diarrhoea, post gastrointestinal surgery, feed intolerance	Allergy, malabsorption, maldigestion	Short bowel syndrome, malabsorption, inflammatory bowel disease, bowel fistulae, disease-related malnutrition, whole protein intolerance
MACRONUTRIENTS			
Energy kcal	66	68	100
Protein g	1.8	1.89	2.6
Protein source	Milk	Milk	Milk
Whey:casein ratio	100:0	0:100	100:0
Carbohydrate g	6.8	6.9	10.3
– of which lactose g	0.06	0	0.1
Carbohydrate source	Glucose syrup	Glucose syrup, modified corn starch	Maltodextrin, glucose syrup
Fat g	3.5	3.8	5.4
Fat source	MCTs, rapeseed, sunflower, palm, single cell oils, fish oil	MCTs, coconut, soya, high oleic sunflower oils and single cell oils	MCTs from coconut and palm kernel oil, rapeseed, sunflower, single cell oils and fish oil
With MCT oils (%)	✓(50)	✓ (55)	✓ (47)
Added LCPs ARA	✓	✓	✓
DHA	✓	✓	✓
LCP source	Fish oil, fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)	Fish oil, fungal/algal oils (vegetable source)
MICRONUTRIENTS			
Vitamins meeting regulations	✓	✓	✓
Minerals meeting regulations	✓	✓	✓
VITAMINS			
Vitamin A µg-RE	52	77	81
Vitamin C mg	9.3	13	12
Vitamin E mg	1.0	1.81	1.2
Vitamin D µg	1.3	1.25	1.7
Vitamin K µg	4.7	8.1	6.7
Thiamin (B_1) µg	50	54	150
Riboflavin (B_2) µg	100	61	150
Niacin mg NE	0.95	0.68	1.2
Vitamin B_6 µg	40	41	60

Nutrients per 100ml	Aptamil Pepti-junior	Mead Johnson Pregestimil LIPIL	Nutricia Infatrini Peptisorb
Vitamin B_{12} µg	0.18	0.2	0.41
Folic acid µg	8.9	10.8	15
Biotin µg	1.7	2.0	2.3
Pantothenic acid µg	330	340	450
MINERALS			
Calcium mg	50	78	80
Chloride mg	40	58	64
Copper µg	40	51	60
Iodine µg	12	14.2	15
Iron mg	0.77	1.22	1.0
Magnesium mg	5.1	7.5	8.0
Manganese µg	31	41	80
Phosphorus mg	28	51	40
Potassium mg	65	74	108
Selenium µg	1.8	1.49	2.0
Sodium mg	18	29	32
Zinc mg	0.5	0.68	0.9
ADDED INGREDIENTS			
Structured vegetable oils (beta-palmitate)	×	×	×
Prebiotics	×	×	×
Nucleotides	✓	×	✓
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	×	✓	×
Contains fish oil	✓	×	✓
Suitable for vegetarians	×	×	×
Halal approved	×	×	×
Osmolality mOsm/kg	210	280	350

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NA = not applicable NK = not known

3.13 Amino-acid based infant milks for non-metabolic disorders, suitable from birth

Key points

Amino-acid based infant milks contain protein in the form of individual amino acids and are marketed to be used in the dietary management of moderate to severe cows' milk protein allergy or multiple allergies. Amino-acid based infant milks are unlike other hypoallergenic infant milks in that they contain amino acids which are synthetically derived, as opposed to peptides originating from cows' milk, meat or soya as found in extensively hydrolysed formula.

These milks are about three times more expensive than extensively hydrolysed formula and are an area in which cost savings to the NHS can be made with use of appropriate prescribing.

Breastfeeding is the optimal way to feed a baby with cows' milk protein allergy, with individualised maternal elimination of cows' milk protein foods and fluids, and with adequate calcium and vitamin D supplementation to meet the mother's nutritional requirements during breastfeeding.

Amino-acid based infant milks are low in lactose or are lactose-free and contain maltodextrin or dried glucose syrup as the main carbohydrate source, meaning that oral care is particularly important for individuals being given these products.

The use of high-profile health professionals working in allergy to promote brands is common in this area. When making clinical decisions, healthcare professionals should take note of whether guidelines or guides produced by healthcare professionals are sponsored by infant milk companies and should look for independent information wherever possible.

Amino-acid based infant milks are unlike other hypoallergenic infant milks in that they contain amino acids which are synthetically derived, as opposed to peptides originating from cows' milk, meat or soya as found in extensively hydrolysed formula.

It is likely that infants with *moderate to severe* cows' milk protein allergy or multiple food protein allergy require breastfeeding mothers to have maternal dietary restriction of the identified allergens and/or the use of an amino-acid based infant milk.

As of December 2014, the EU Food Information for Consumers (EUFIC) Regulation came into force requiring 14 allergens on the regulatory list to be labelled on pre-packed foods, which includes infant milk. These are:

- celery (and celeriac)
- cereals containing gluten
- crustaceans, e.g. prawns, crabs, lobster, crayfish
- eggs
- fish

- lupin
- milk
- molluscs, e.g. clams, mussels, squid
- mustard
- nuts, e.g. almonds, walnuts, pecans, Brazil nuts
- peanuts
- sesame
- soybeans
- sulphur dioxide, a preservative found in some dried fruit.

This should be beneficial to women who want to continue to breastfeed but who may need to follow an exclusion diet of some kind, and full dietetic support should always be given for mothers to do this. Additional support will be needed so that breastfeeding women can manage their breastmilk supply if they have to have a period of expressing milk as they adopt dietary restrictions.

The Health Improvement Network (THIN) database holds data on 6 million anonymised UK patients entered by GPs and this has been found to be reflective of the UK population. A Mead Johnson funded study of 295 of these records examined the cost-effectiveness of giving infants under 1 year of age an extensively hydrolysed infant milk compared with an amino-acid based infant milk as a first-line treatment for cows' milk protein allergy. It found no significant differences in clinical outcomes between the two groups but did find a significant difference in 12-monthly cost to the NHS of £1,853 vs £3,161 per infant for the extensively hydrolysed and amino-acid based infant milks respectively (Taylor et al, 2012). The authors conclude that, in the absence of good-quality data demonstrating the superiority of one infant milk over another, extensively hydrolysed infant milks are cheaper and appear as effective in many cases.

A systematic review, undertaken in 2007 by Hill et al, examined the efficacy of amino-acid based infant milks in relieving symptoms of cows' milk protein allergy (Hill et al, 2007). They found six published randomised controlled trials, three of which were of good quality. Hill et al concluded that there was evidence of growth and tolerance of amino-acid based infant milks when compared with extensively hydrolysed infant milks, but noted a limited evidence base arising from small sample sizes, use of different infant milks, no evidence of alternatives to amino-acid based infant milks being used, and multiple outcomes which were often inconsistently reported.

A German study compared safety and efficacy of an extensively hydrolysed formula compared with an amino-acid based formula in a small industry-funded prospective randomised controlled study with 65 infants with CMPA (Niggemann et al, 2007). The authors reported that growth and tolerance were the same when infants were given either milk, as were gastrointestinal symptoms and respiratory tract symptoms of allergy. A slight decrease in eczema was noted for infants fed the amino-acid based formula, but those on extensively hydrolysed formula had fewer episodes of vomiting and softer stools.

There is a considerable literature on the diagnosis and management of cows' milk and other food allergy in infancy, and we appreciate that we have only presented a few examples here. The management of any individual child requires expert clinical decision-making. Much of the guidance for diagnosing and managing cows' milk protein allergy is written by experts

who also work with formula companies, and we hope to provide more independent evidence in this area over time.

Products available

There are four amino-acid based infant milks for non-metabolic disorders available in the UK:

- Mead Johnson Nutramigen Puramino
- Nutricia Neocate LCP
- Nutricia Neocate Syneo
- SMA Alfamino.

All of these infant milks are manufactured as a powdered infant milk and are available on prescription. The greatest increase in spend on paediatric prescribable infant milks since 2006 has been in the hypoallergenic infant milk market.[6] In the current economic climate, clinical commissioning groups are reviewing ways to manage this by creating prescribing guidelines to ensure that these products are not used inappropriately or for longer than necessary.

These infant milks are nutritionally complete and contain amino acids, carbohydrate, fat, vitamins, minerals, trace elements and long chain polyunsaturated fatty acids (LCPs). Both Neocate LCP and Neocate Syneo contain nucleotides, for which EFSA found no evidence of benefit (EFSA, 2014). All four infant milks are compliant with EC regulations regarding foods for special medical purposes. SMA Alfamino is suitable for vegetarians and vegans.

Both Nutricia Neocate LCP and Neocate Syneo make reference to *"fast, effective*" resolution of symptoms in 3-14 days in a small trial of 25 infants who were given Neocate LCP for two weeks after symptoms did not resolve with a casein-based extensively hydrolysed infant milk. The study authors reported that symptom resolution was observed in 22 of the 25 subjects following a challenge with the casein-based infant milk after that period (Vanderhoof et al, 1997). A second small study referenced (de Boissieu et al, 1997) reported on 13 infants in France who had shown allergic symptoms to an extensively hydrolysed formula but tolerated an amino-acid based formula. Neocate Syneo was not given to infants in either study despite both being referenced in their promotion to health professionals.

Print advertising in 2015 claims that Neocate LCP is the "*Number 1 amino acid formula in the UK"* for which no evidence is given, and that it has superior palatability, with the evidence for this 'on file'. It also claims that this milk "*Enables growth"*, referring to the Niggemann et al study which showed equal growth and tolerance when either an amino-acid based or extensively hydrolysed formula is given (Niggemann et al, 2007), and a study by Isolauri et al (1995) which again showed that both extensively hydrolysed and amino-acid based formula led to adequate growth in infants with CMPA. The authors suggested that extensively hydrolysed formulas are safe and effective for most infants with CMPA, but that an amino-acid based formula may be preferable for infants with multiple food allergies. The print advert also claims that this product has an "*Optimal nutrient profile"* but simply references the current EU and Codex standards for foods for special medical purposes which do not specify an optimum profile, simply the range of values acceptable in law.

6 Data from LPP website http://www.lpp.nhs.uk/. Access requires an NHS account.

Nutricia Neocate Syneo has a similar nutritional composition to Neocate LCP but contains a prebiotic strain of fructo-oligosaccharides and a probiotic *Bifidobacterium breve* M-16V. Nutricia claim that Neocate Syneo can *"help rebalance gut microbiota dysbiosis".* They reference two papers for this claim which were both funded by Nutricia. The first of which (Candy et al, 2017) studied three groups of infants: a healthy exclusively breastfed group, a control group (who were given Neocate LCP) and a test group who were given Neocate LCP with added *Bifidobacterium breve* and a blend of fructo-oligosaccharides. The milk given to the test group was similar to Neocate Syneo but not identical. The infants in the test and control arm both had *"suspected"* CMPA and were given the formula for 8 weeks, during which time their CMPA may have resolved independently of the formula they were given. The infants in all three groups came from a range of different countries and were aged between 1.2 to 14.2 months old. . There were also twice as many caesarean-delivered babies in the control group than the test group. All of these factors were likely to affect their gut microbiota (Phillips, 2009; Odamaki, 2016; Wen & Duffy, 2017) and may have confounded the conclusions.

The study showed a shift in the faecal microbiota of infants on the milk containing pre- and probiotics (synbiotics) towards that of the breastfed infants but no change in gastrointestinal symptoms between the test and control group. They did not study gut microbiota directly but instead extrapolated the change in faecal microbiota to assume a shift in gut microbiota. In their promotion to health professionals, Nutricia also refer to a similar study (Burks et al, 2017) which looked at self-reported stool characteristics in those given a milk similar to Neocate Syneo. 81 out of 110 of the infants on either formula experienced an adverse event. The researchers found a similar decrease in symptoms for those taking an amino acid-based formula both with and without pre- and probiotics, suggesting that these added ingredients may not have any additional benefit. This corresponds with an ESPGHAN review in 2014 stating that there is *"insufficient data to recommend the routine use of probiotic- and/or prebiotic supplemented formulae"* while EFSA (2014) found *"no evidence that the addition of prebiotics, probiotics or synbiotics to infant formula has any benefits to health in term infants".*

Mead Johnson's online marketing material for Nutramigen Puramino includes a statement about the addition of 33% MCT oil to facilitate fat absorption and claims that *"Nutramigen PURAMINO is the same trusted and effective 100% hypoallergenic, amino acid-based infant milk as Nutramigen ARA",* making reference to a study in which an infant milk different to Nutramigen Puramino was used. However, they note that the milk used in the study did not contain MCT oil (Burks et al, 2008).

Safety of use

This group of infant milks contain dried glucose syrup as the main carbohydrate source, meaning that dental care is particularly important for individuals being given these products.

In recent years evidence has emerged suggesting a link between use of Neocate and the development of rickets and other types of metabolic bone disease (Abulebda et al, 2017; Gonzalez Ballesteros et al, 2017; Uday et al, 2018). This appears to be particularly common in children using Neocate rather than other elemental formulas (Creo et al, 2018).
Many of the published studies exploring this had small sample sizes. However, one of the larger studies, compromising of 102 children who were receiving Neocate via a tube, found up to 23% of them had a form of metabolic bone disease (Creo et al, 2018). Another study

identified fifty-one children across 17 institutions who had hypophosphatemia associated with elemental formula (most of whom were on Neocate). Skeletal radiographs demonstrated that 94% of these children had rickets, fractures or undermineralisation (Gonzalez Ballesteros et al 2017).

These studies suspected the cause to be deficient dietary supply or decreased gastrointestinal absorption of phosphate (Ang et al, 2018; Uday et al, 2018). These cases improved with supplemental phosphate or changing to a different elemental formula. However, in some cases, this treatment led to subsequent hypocalcaemia (Gonzalez Ballesteros et al, 2017; Akhtar Ali et al, 2019).

It is important to note that most of these cases were identified prior to October 2017 when Nutricia began adding dipotassium hydrogen phosphate to Neocate, however, Nutricia still advise routine monitoring of micronutrients and, in particular phosphate, for those on Neocate. Further research is needed to re-assess whether the safety of Neocate has improved.

The risks of the addition of probiotics to infant milks, such as Neocate Syneo, is not yet established. However, the Norwegian Food Safety Authority in 2014[7] has stated that a daily supply of a *"monoculture"* in *"large quantities over a prolonged period of time to age groups where the intestinal flora is still developing may therefore have unknown, but possible long-lasting adverse effects".* Nutricia also recommend that Neocate Syneo is prepared at room temperature. Please see Table 4 for more information.

The nutritional composition and ingredients of amino-acid based infant milks marketed for non-metabolic disorders, suitable from birth are given in Table 19.

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https://www.mattilsynet.no/language/english/food_and_water/Food_for_specific_Groups__FSG_/foods_for_infants_and_young_children_containing_probiotics.16873

TABLE 19. The nutritional composition of amino-acid based infant milks for non-metabolic disorders, suitable from birth

Nutrients per 100ml	Mead Johnson Nutramigen Puramino	Nutricia Neocate LCP	Nutricia Neocate Syneo	SMA Alfamino
INDICATIONS	Severe cows' milk protein allergy and multiple food allergy	Cows' milk protein allergy and multiple food protein intolerance	Cows' milk protein allergy, multiple food protein allergies, and other conditions where an amino acid-based diet is recommended.	Severe cows' milk protein allergy and multiple food allergy
MACRONUTRIENTS				
Energy kcal	68	67	68	70
Protein g	1.89	1.8	1.9	1.9
Protein source	Non-allergenic amino acids	Non-allergenic amino acids	Non-allergenic amino acids	Non-allergenic amino acids
Carbohydrate g	7.2	7.2	7.2	7.9
– of which lactose g	0	0	0	0
Carbohydrate source	Glucose syrup, modified tapioca starch	Dried glucose syrup	Dried glucose syrup	Glucose syrup, potato starch
Fat g	3.6	3.4	3.4	3.4
Fat source	High oleic sunflower, MCTs from coconut, palm kernel, soya and single cell oils	Non-hydrogenated coconut, high oleic sunflower, sunflower, canola and single cell oils	Palm kernel and/ or coconut oil, high oleic sunflower oil, sunflower oil, canola oil and single cell oils	Sunflower, rapeseed and esterified palm and single cell oils
– as MCT oils %	33	4	33	24
Added LCPs ARA	✓	✓	✓	✓
DHA	✓	✓	✓	✓
LCP source	Fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)
MICRONUTRIENTS				
Vitamins meeting regulations	✓	✓	✓	✓
Minerals meeting regulations	✓	✓	✓	✓
VITAMINS				
Vitamin A µg-RE	61	56	57	92
Vitamin C mg	8.1	7.1	7.3	10
Vitamin E mg	0.91	0.67	0.63	1.9
Vitamin D µg	0.85	1.2	1.2	1.0
Vitamin K µg	6.1	5.9	6.0	7.0
Thiamin (B_1) µg	54	70	80	70
Riboflavin (B_2) µg	61	70	80	150
Niacin µg (mg NE)	(0.68)	(1.4)	690 (1.5)	570 (1.3)

Nutrients per 100ml	Mead Johnson Nutramigen Puramino	Nutricia Neocate LCP	Nutricia Neocate Syneo	SMA Alfamino
Vitamin B_6 µg	41	70	80	53
Vitamin B_{12} µg	0.2	0.18	0.19	0.21
Folic acid µg	10.8	8.8	9.2	8.4
Biotin µg	2.0	2.6	2.7	1.8
Pantothenic acid µg	340	400	410	540
MINERALS				
Calcium mg	64	65.6	79.1	57
Chloride mg	58	53.3	54.4	58
Copper µg	51	60	60	56
Iodine µg	10.1	13.8	14.1	11
Iron mg	1.22	1.0	1.0	0.7
Magnesium mg	7.4	7.0	7.2	6.4
Manganese µg	17	30	30	7.0
Phosphorus mg	35	47.1	56	39
Potassium mg	74	72.5	74.2	79
Selenium µg	1.89	2.0	2.0	1.8
Sodium mg	32	26.1	26.6	25
Zinc mg	0.68	0.73	0.75	0.7
ADDED INGREDIENTS				
Structured vegetable oils (beta-palmitate)	×	×	×	×
Prebiotics	×	×	✓	×
Probiotics	×	×	✓	×
Nucleotides	×	✓	✓	×
Inositol	✓	✓	✓	✓
Taurine	✓	✓	✓	✓
Choline	✓	✓	✓	✓
Added antioxidants	✓	✓	✓	✓
Contains soya	✓	×	×	×
Contains fish oil	×	×	×	×
Suitable for vegetarians	×	✓	✓	✓
Suitable for vegans	×	×	×	✓
Halal approved	✓	✓	✓	×
Osmolality mOsm/kg	350	340	360	332.5

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
MCT = medium chain triglycerides NK = not known

3.14 Infant milks for disorders of protein metabolism, suitable from birth

Key points

Infants with inherited disorders of protein metabolism require specialist care. This section provides a brief overview of the products available, their nutritional composition and indications for use, but this information is not designed to replace specialist advice.

Infant milks for disorders of protein metabolism are available for a number of rare inherited metabolic disorders such as phenylketonuria (PKU), maple syrup urine disease (MSUD) and tyrosinaemia. Infants with inherited metabolic disorders will all require individualised clinical management and close medical supervision.

The breastfeeding of infants with inherited metabolic disorders is encouraged wherever possible as long as their biochemistry is within normal range and with ongoing close monitoring of blood biochemistry.

The National Society for Phenylketonuria (NSPKU) recommends that infants with PKU are breastfed where possible, as breastmilk is lower in phenylalanine than infant formula. Breastfeeding mothers will need specialist breastfeeding support and information to help manage any disruptions to breastfeeding during periods of illness or metabolic instability, and to protect breastmilk supply.

Infants presenting with abnormal blood biochemistry often need a period of specialised infant milk feeding, sometimes in combination with their usual breast and/or infant formula feeding, until they are metabolically stable.

Nutricia manufacture a range called Anamix Infant. Over recent years it has markedly increased its range of different infant milks for specific metabolic conditions by altering the infant milk's amino-acid content.

Current thinking and guidelines

Disorders of protein metabolism are rare but have a significant impact on an individual's nutritional requirements and can be catastrophic if untreated. These disorders are often genetically inherited and require lifelong dietary restriction of specific amino acids or groups of amino acids. All of these conditions are best managed by specialist metabolic services and health professionals. The most well-known example of this kind of disorder is phenylketonuria (PKU) which affects 1 in 10,000 infants in the UK. This equates to about 60-70 infants per year.

The breastfeeding of infants with inherited metabolic disorders is encouraged wherever possible as long as their biochemistry is within normal range and with ongoing close monitoring of blood biochemistry. A breastfeeding mother of an infant with an inherited metabolic disorder needs good breastfeeding and emotional support. There may be periods of disruption to breastfeeding, and support to express, store and optimise milk supply is

important. Disruptions to feeding may occur if infant blood concentrations of specific amino acids increase above target ranges. When infants are metabolically unstable, a period of using specialised infant milk free of the relevant amino acids will be indicated until blood biochemistry is back within range.

A brief description of some of the disorders of protein metabolism for which a specialised infant milk has been manufactured is given below.

Glutaric aciduria
Glutaric aciduria type 1 or GA1 is an autosomal recessive inherited organic acid disorder. It arises from a rare deficiency or absence of glutaryl-CoA dehydrogenase, an enzyme required to breakdown L-lysine, L-hydroxylysine and L-tryptophan. This deficiency leads to a build-up of glutaric acid, 3-hydroxyglutaric acid and sometimes glutaconic acids in the blood and urine. It can take until later infancy or toddlerhood to become symptomatic and is often precipitated by intercurrent illness or going without food for a period of time, which can provoke a metabolic crisis.

Dietary management focusses on avoiding long periods without food, reducing glutaric acid and 3-hydroxyglutaric acid by restricting dietary intake of lysine, and carefully monitoring protein intakes. The use of lysine-free, low-tryptophan infant milk before each breastfeed is suggested to reduce the amount of lysine provided by breastmilk to about 100mg/kg/day (Shaw, 2015).

Methylmalonia acidaemia (MMA) and propionic acidaemia (PA)
These two disorders are examples of organic acidaemias and have some shared biochemical and clinical characteristics.

MMA is caused by a defect in either methylmalonyl-CoA mutase-apoenzyme or a defect in 5'-deoxyadenosylcobalamin. There is a range of presentations from being responsive to treatment or causing life-threatening illness and both are associated with an increased mortality, and poor neurodevelopmental and physical outcomes. These will vary according to the severity of the condition and the speed with which symptoms are treated.

PA is caused by deficiency of the enzyme propionyl-CoA carboxylase.

Maple syrup urine disease (MSUD)
Maple syrup urine disease is a rare inborn error of metabolism caused by branched-chain alpha-ketoacid dehydrogenase deficiency and affects about 1 in 116,000 infants. It results in problems breaking down the amino acids leucine, isoleucine and valine found in dietary protein, and if untreated can lead to coma and permanent brain damage.

Dietary management of MSUD is to adopt a low leucine, isoleucine and valine diet, to regularly (weekly) monitor blood concentrations of leucine, isoleucine and valine and maintain these amino-acid concentrations within a safe specified range. Breastfeeding is to be encouraged should a mother wish to do so, unless her infant's blood leucine, isoleucine and valine concentrations fall outside of this range.

Phenylketonuria (PKU)
PKU is an autosomal recessive genetic disorder caused by a deficiency of the liver enzyme phenylalanine hydroxylase (PAH), which metabolises phenylalanine (Phe) to tyrosine. When this enzyme is deficient it leads to an accumulation of phenylalanine, and has a domino effect on other amino-acid related compounds leading to further metabolic abnormalities, and increases the risk of damage to the brain.

PKU management differs widely across Europe. European PKU guidelines offer recommendations for diagnosis, treatment and care in PKU (van Wegberg A et al, 2017). These suggest that treatment should be initiated before the age of 10 days to prevent neurological damage. Dietary treatment is the basis for PKU management and treatment should be for life. Blood Phe concentration should be monitored weekly up to 1 year of age to ensure it remains within a target range of 120-360µmol/l for PKU patients up to 12 years of age (van Wegberg A et al, 2017). In the UK, an expert panel agreed that a Phe concentration of 120-360µmol/l can be achieved by adopting a diet containing a "*protein substitute which is phenylalanine free (or at least very low in phenylalanine) and otherwise nutritionally complete with a composition sufficient to provide 100-120mg/kg/day of tyrosine and a total amino acid intake of at least 3g/kg/day in children under 2 years of age*" (Medical Research Council Working Party on Phenylketonuria, 1993).

The European PKU guidelines (van Wegberg A et al, 2017) make recommendations for total protein intake based on age-related safe levels of protein intake recommended by FAO/WHO/UNU, 2007 with an additional 40% from L-amino acid supplements. The guidelines refer to a number of observational studies in infants and adults that have investigated the Phe-free L-amino acid supplements dosage necessary for optimal growth in PKU that have shown mainly satisfactory growth if the total protein intake meets or is above the general population recommendations, however, in the referenced studies, national recommendations were commonly based on the FAO/WHO/UNU 1985 safe levels of protein intake which FAO/WHO/UNU 2007 reduced (in infants under 1 year by approximately 25 to 27%). No studies have examined growth in PKU at this level of total protein intake so the authors point out that these requirements should not be used until there is published data to support such a low protein intake in PKU.

Breastfeeding is encouraged where possible by the UK's National Society for Phenylketonuria (NSPKU), as breastmilk is relatively low in phenylalanine, with 46mg/100ml compared with 60mg/100ml in standard infant formula. It has been suggested in one study that breastfeeding may lower blood phenylalanine levels in children with PKU. Additionally, there may be a dose-response effect, with longer durations of breastfeeding leading to better biochemical control (O'Sullivan et al, 2013). The European PKU guidelines also state that in infants with PKU, breastfeeding in combination with a Phe-free infant L-amino acid formula should be encouraged. It is associated with long-term satisfactory blood Phe control and growth (van Wegberg A et al, 2017).

Tyrosinaemia
Tyrosinaemias are a group of inborn errors of metabolism. Hereditary Tyrosinaemia type 1 (HT1) is the most severe. HT1 is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase which is required for the final step in the degradation of tyrosine to fumarate or acetoacetate. When this enzyme is deficient abnormal accumulation of toxic intermediaries

can occur. If untreated this may lead to severe medical problems involving the liver, kidneys and brain. There are no European guidelines for the management of tyrosinaemia in infants. For more information on inherited metabolic diseases, the British Inherited Metabolic Diseases Group, a multidisciplinary group specialising in this area, has a website with further information and contacts (see www.bimdg.org.uk).

Products available

Powdered infant milks suitable from birth to 1 year of age are available for the dietary management of disorders of protein metabolism. These are all produced by Nutricia except for one product for the management of PKU which is produced by Vitaflo International (Nestlé).

There are currently two specialised infant milks suitable from birth and manufactured for use in infants with PKU, PKU Anamix Infant by Nutricia and PKU Start by Vitaflo International. Nutricia do not label their Anamix Infant range with details regarding suitability for vegetarians, vegans or halal consumers, nor is this information available on the Nutricia website. Health professionals should contact the manufacturer directly for these details in order to address dietary or cultural concerns.

There are no claims made by the manufacturers regarding this class of specialised infant milk. The names of the infant milks marketed for infants with other disorders of protein metabolism are given in Table 20.

TABLE 20. Types of infant milk available for disorders of protein metabolism, suitable from birth

Infant milk	For dietary management of	Free from
GA1 Anamix Infant	Infants with glutaric aciduria	Lysine (low tryptophan)
HCU Anamix Infant	Infants with B6 non-responsive homocystinuria or hypermethioninaemia	Methionine
Hyper LYS Anamix Infant	Infants with hyperlysinaemia	Lysine
IVA Anamix Infant	Infants with isovaleric acidaemia	Leucine
Methionine Free TYR Anamix	Infants with tyrosinaemia type 1	Methionine phenylalanine, tyrosine
MMA/PA Anamix Infant	Infants with methylmalonic acidaemia or propionic acidaemia	Methionine, threonine, valine (low isoleucine)
MSUD Anamix Infant	Infants with maple syrup urine disease	Leucine, isoleucine and valine
NKH Anamix Infant	Infants with non-ketotic hyperglycinaemia	Glycine
PKU Anamix Infant	Infants with phenylketonuria (PKU)	Phenylalanine
PKU Start	Infants with phenylketonuria (PKU)	Phenylalanine
SOD Anamix Infant	Infants with sulphite oxidase deficiency	Methionine, cystine
TYR Anamix Infant	Infants with tyrosinaemia	Phenylalanine, tyrosine

Nutritional composition

Infant milks for disorders of protein metabolism are not nutritionally complete as they have had one or more essential amino acids removed, due to the nature of the clinical condition they are formulated to manage.

Nutricia PKU Anamix Infant has 69kcal/100ml and contains protein in the form of amino acids, is phenylalanine-free, has carbohydrates mainly in the form of glucose syrup and some lactose, fat from a refined vegetable oil blend (sunflower, soya, coconut, canola), vitamins, minerals and trace elements. PKU Anamix Infant does not contain nucleotides but does contain added LCPs, derived from fungal/algal oils, prebiotics (from milk), inositol, taurine and choline. PKU Anamix Infant does not meet the EC regulations for the nutritional composition of foods for special medical purposes as the amount of selenium is higher than the maximum range as set out in the EC regulations for foods for special medical purposes. PKU Anamix Infant is suitable for the dietary management of phenylketonuria in infants from 0-1 year of age. Nutricia states that it can be used as a supplementary infant milk up to 3 years of age.

Vitaflo PKU Start has 68kcal/100ml and also contains protein in the form of amino acids, is phenylalanine-free, has carbohydrates mainly in the form of glucose syrup and some maltodextrin, fat from a refined vegetable oil blend (high oleic sunflower, coconut, rapeseed,

sunflower), vitamins, minerals and trace elements. PKU Start does not contain nucleotides but does contain added LCPs, derived from fish and fungal/algal oils, inositol, taurine and choline. PKU Start does not meet the EC regulations for the nutritional composition of foods for special medical purposes as the amount of selenium is higher than the maximum range as set out in the EC regulations for foods for special medical purposes. PKU Start is suitable for the dietary management of phenylketonuria in infants from birth. The nutritional composition and ingredients and the amino-acid profile used in some of the infant milks marketed for disorders of protein metabolism suitable from birth are given in Tables 21 and 22 respectively.

TABLE 21. The nutritional composition of infant milks for disorders of protein metabolism, suitable from birth

Nutrients per 100ml	Nutricia PKU Anamix Infant[1]	Vitaflo International PKU Start
INDICATION	Phenylketonuria	Phenylketonuria
Energy kcal	70[1]	68
Protein (amino acids) g	2.0 (2.3)	2.0
Carbohydrate g	7.5[1]	7.2
– of which lactose g	0.24	
Carbohydrate source	Glucose syrup	Glucose syrup and maltodextrin
Fat g	3.5	3.5
Fat source	High oleic sunflower, soya, non-hydrogenated coconut, canola, sunflower and single cell oils	High oleic sunflower, coconut, rapeseed, sunflower, fish and single cell oils
Added LCPs ARA	✓	✓
DHA	✓	✓
LCT %	97	
LCP source	Fungal/algal oils (vegetable source)	Fish and fungal/algal oils
MICRONUTRIENTS		
Vitamins meeting regulations	✓	✓
Minerals meeting regulations	Selenium higher than FSMP	Selenium higher than FSMP
MICRONUTRIENTS		
Vitamin A µg-RE	58.8	65
Vitamin C mg	7.4	8.6
Vitamin E mg	0.69	0.99
Vitamin D µg	1.3	1.6
Vitamin K µg	5.6	5.6
Thiamin (B_1) µg	80	60
Riboflavin (B_2) µg	80	70
Niacin µg (mg NE)	330 (1.1) [1]	470
Vitamin B_6 µg	80	60
Vitamin B_{12} µg	0.18	0.17
Folic acid µg	8.3	11
Biotin µg	2.7	2.7
Pantothenic acid µg	420	350
MINERALS		
Calcium mg	61.5	56
Chloride mg	53.3	51
Chromium µg	2.1	2.0
Copper µg	64.5[1]	60
Iodine µg	12.5	15
Iron mg	1.2	0.82
Magnesium mg	8.7	6.3

Nutrients per 100ml	Nutricia PKU Anamix Infant[1]	Vitaflo International PKU Start
Manganese µg	60	40
Molybdenum µg	1.8	2.3
Phosphorus mg	45	42
Potassium mg	75.2	71
Selenium µg	2.3	3.0
Sodium mg	28.7	27
Zinc mg	0.86	0.49
ADDED INGREDIENTS		
Prebiotics	✓	✖
Nucleotides	✖	✖
Inositol	✓	✓
Taurine	✓	✓
Choline	✓	✓
Added antioxidants	✓	✓
Contains soya	✓	✖
Contains fish oil	✖	✓
Osmolality mOsm/kg	**380**	**350**

ARA = arachidonic acid
DHA = docosahexaenoic acid
LCP = long chain polyunsaturated fatty acid
NK = not known
ANS = approval not sought
FSMP = foods for special medical purposes
LCT = Long chain triglycerides

1 GA1, HCU, Hyper LYS, IVA, Methionine Free TYR, MMA/PA, MSUD, NKH, PKU, SOD and TYR Anamix Infant milks vary mainly by their amino-acid profiles (see Table 18), with the exceptions of Hyper LYS, Methionine Free TYR and SOD which have a marginally lower copper content (60µg/100ml), and a marginally higher niacin content (1.2mg NE/100ml).

TABLE 22. The amino-acid profile of infant milks for disorders of protein metabolism, suitable from birth

Amino-acids (g) per 100ml	Nutricia GA1 Anamix Infant	Nutricia HCU Anamix Infant	Nutricia Hyper LYS Anamix Infant	Nutricia IVA Anamix Infant	Nutricia Methionine Free TYR Anamix Infant	Nutricia MMA/PA Anamix Infant
INDICATIONS	Glutaric aciduria	B6 non-responsive homocystinuria / hyper-methioninaemia	Hyperlysinaemia	Isovaleric acidaemia	Tyrosinaemia type 1	Methylmalonic acidaemia / Propionic acidaemia
ESSENTIAL AND CONDITIONALLY ESSENTIAL AMIINO ACIDS						
Arginine g	0.18	0.16	0.18	0.18	0.18	0.21
Cystine g	0.07	0.06	0.06	0.07	0.07	0.08
Histidine g	0.1	0.09	0.1	0.11	0.1	0.14
Isoleucine g	0.16	0.15	0.16	0.06	0.16	<0.007
Leucine g	0.27	0.25	0.27	nil added	0.28	0.32
Lysine g	nil added	0.17	nil added	0.16	0.19	0.21
Methionine	0.04	nil added	0.04	0.05	nil added	nil added
Phenylalanine g	0.12	0.11	0.12	0.12	nil added	0.14
Threonine g	0.13	0.12	0.13	0.11	0.14	nil added
Tryptophan g	0.01	0.05	0.05	0.04	0.05	0.06
Tyrosine g	0.12	0.11	0.12	0.12	nil added	0.14
Valine g	0.17	0.16	0.17	0.07	0.18	nil added
Aspartic acid g	0.15	0.14	0.15	0.15	0.15	0.19
Serine g	0.12	0.11	0.12	0.1	0.12	0.13
Glutamic acid g	0.02	0.02	0.2	0.02	0.21	0.02
Proline g	0.19	0.18	0.19	0.33	0.2	0.1
Glycine g	0.16	0.15	0.16	0.33	0.16	0.1
Alanine g	0.1	0.1	0.1	0.11	0.11	0.24
Carnitine g	0.002	0.002	0.002	0.002	0.002	0.002
Taurine g	0.005	0.005	0.005	0.005	0.005	0.005

Continued on next page

TABLE 22 continued. The amino-acid profile of infant milks for disorders of protein metabolism, suitable from birth

Nutrients (g) per 100ml	Nutricia MSUD Anamix Infant	Nutricia NKH Anamix Infant	Nutricia PKU Anamix Infant	Vitaflo PKU Start	Nutricia SOD Anamix Infant	Nutricia TYR Anamix Infant
INDICATIONS	Maple syrup urine disease	Non-ketotic hyperglycinaemia	Phenylketonuria	Phenylketonuria	Sulphite oxidase deficiency	Tyrosinaemia
ESSENTIAL AND CONDITIONALLY ESSENTIAL AMIINO ACIDS						
Arginine g	0.21	0.17	0.16	0.14	0.17	0.18
Cystine g	0.08	0.06	0.06	0.05	nil added	0.07
Histidine g	0.12	0.1	0.09	0.08	0.1	0.1
Isoleucine g	nil added	0.16	0.14	0.15	0.15	0.16
Leucine g	nil added	0.26	0.24	0.23	0.26	0.27
Lysine g	0.22	0.18	0.17	0.15	0.17	0.19
Methionine g	0.05	0.04	0.04	0.04	nil added	0.04
Phenylalanine g	0.14	0.12	nil added	nil added	0.11	nil added
Threonine g	0.16	0.13	0.12	0.15	0.13	0.13
Tryptophan g	0.06	0.05	0.05	0.05	0.05	0.05
Tyrosine g	0.14	0.12	0.22	0.22	0.11	nil added
Valine g	nil added	0.17	0.16	0.17	0.16	0.18
Aspartic acid g	0.18	0.16	0.15	0.22	0.16	0.15
Serine g	0.14	0.11	0.11	0.10	0.11	0.12
Glutamic acid	0.02	0.02	0.21	0.16	0.19	0.02
Proline g	0.23	0.18	0.17	0.15	0.18	0.2
Glycine g	0.19	nil added	0.14	0.21	0.15	0.16
Alanine g	0.12	0.1	0.09	0.08	0.1	0.1
Carnitine g	0.002	0.002	0.002	0.002	0.002	0.002
Taurine g	0.005	0.005	0.003	0.004	0.005	0.005

3.15 Modified-fat infant milks for disorders of fatty acid metabolism, suitable from birth

Key points

Two modified-fat infant milks are currently prescribable from birth: Nutricia Monogen and Vitaflo Lipistart., These infant milks have a high medium chain triglyceride (MCT) content to account for difficulties that infants with disorders of fatty acid metabolism have in digesting, absorbing or transporting long chain triglycerides (LCTs).

Nutricia Low Fat Module is a whey protein concentrate supplemented with free amino acids, carbohydrate, vitamins, minerals and trace elements with no added source of fat. It can be used for infants and children. It cannot provide complete nutritional support for children unless an additional source of essential fatty acids is used.

Dried glucose syrup is the main available carbohydrate so individuals who have infant milks from this range will require careful oral health care to prevent caries.

There are three products marketed to compensate for the difficulties that a very small proportion of infants have in digesting, absorbing or transporting long chain triglycerides (LCTs): Nutricia Monogen, Vitaflo Lipistart and Nutricia Low Fat Module. Nutricia Monogen and Vitaflo Lipistart have a high medium chain triglyceride (MCT) content derived from fractionated coconut oil of around 75-80% of total fat. Nutricia Low Fat Module is designed for use in infants with fatty acid oxidation disorders who are intolerant to MCT, and it can provide complete nutritional support in infants only when supplied with a source of essential fatty acids. The feeding guidelines for the Low Fat Module recommend the addition of a measured dose of walnut oil.

Medium chain triglycerides are molecules which contain carbon atoms linked into chains of 6-10 units, in comparison to LCTs which have chains of 12-18 units. They can be digested more readily by pancreatic enzymes, do not require bile acids for absorption, and can be absorbed directly into the portal vein. Large quantities of MCT can cause diarrhoea, which requires managing to avoid exacerbating the consequences of fat malabsorption, and accompanying malabsorption of vitamins and minerals (e.g. of iron, zinc, calcium, fat-soluble vitamins, folate, and vitamin B12). MCTs yield around 8.3kcal/g compared with LCTs which yield 9kcal/g and this is useful to consider when planning interventions. The n6:n3 ratio of Vitaflo Lipistart is 7.1:1 which is in line with ESPGHAN's recommendation of a range of 5:1 to 15:1 (Koletzko et al, 2005). The n6:n3 ratio of Nutricia Monogen is 4.2:1.

Vitaflo explain that this group of formulas were developed in line with the Genetic Metabolic Dietitians International (GMDI) guidelines for the dietary management of very long chain acyl CoA dehydrogenase deficiency (VLCADD) and other disorders of long chain fat metabolism (Genetic Metabolic Dietitians International, 2008). There appears to be no original published research concerning the safety or efficacy of these infant milks, with the exception of one paper on the use of Nutricia Monogen for infants with post-operative chylothorax (Cormack et al, 2004). This small study evaluated the response to Monogen treatment as defined by

the time required for resolution of chylothorax with no further need for surgery, and found that around four weeks of a Monogen or low-LCT diet was sufficient to avoid recurrence. Published papers covering the safety and efficacy of this group of formulas in disorders of fatty acid metabolism are lacking.

Nutritional composition

Both of the modified-fat specialised infant milks – Nutricia Monogen and Vitaflo Lipistart – are labelled as nutritionally complete with whey protein, carbohydrate, fat, vitamins, minerals and trace elements. Nutricia Low Fat Module is not nutritionally complete and contains a mixture of whey protein concentrate supplemented with free amino acids, carbohydrate, vitamins, minerals and trace elements. For Nutricia Low Fat Module and Vitaflo Lipistart the carbohydrate mainly comes from dried glucose syrup. For Monogen, the carbohydrate comes mainly from maltodextrin, and glucose syrup is also added. Vitaflo explain that the reason for the inclusion of glucose syrup is to replace lactose as a carbohydrate source as it *"offsets the increase in osmolality that replacing LCT with MCT brings about."* (Scott 2015, personal communication).

The fat content of Nutricia Monogen and Vitaflo Lipistart is mainly composed of medium chain triglyerides (MCTs), so that they are low in long chain triglycerides (LCTs). Nutricia Monogen markets itself as a low-fat infant milk with a fat content around half that of infant formula. Nutricia suggests that Monogen can be used for the dietary management of hyperlipoproteinaemia type 1, long chain fatty acid oxidation defects (LCFAODs), intestinal lymphangectasia, chylothorax or intractable malabsorption with steatorrhoea. They recommend monitoring and treating essential fatty acid status as infants may present with severe abnormalities depending on their clinical condition.

Lipistart (Vitaflo) has long chain polyunsaturated fatty acids (LCPs) arachidonic acid (ARA) and docosahexaenoic acid (DHA) added. The manufacturers suggest it can be used in LCT disorders, fat malabsorption and dietary disorders requiring a high MCT/low LCT infant milk. It is one of the few specialised infant milks to state explicitly in its preparation guidelines that water for infant milk should boiled and cooled and should remain at a temperature of at least 70ºC.

The mean protein content of these milks is around 50% higher (range 23%-69%) than standard term infant milk. Lipistart has a similar carbohydrate content to standard term infant milk, but Monogen has around 60% more carbohydrate and, therefore, also a higher energy content of 74.6kcal/100ml compared with around 69kcal/100ml for Lipistart.

It is noteworthy that dried glucose syrup is a major source of carbohydrate in the infant milks in this group. Dried glucose syrup is used as a carbohydrate source in MCT-rich products as this can offset the increase in osmolality that occurs as a result of replacing LCT with MCT. In this way, the use of dried glucose syrup is thought to reduce the risk of gastrointestinal intolerance. An infant receiving around 750ml of modified-fat infant milk would have an intake of around 69g of carbohydrate, mostly dried glucose syrup. The additional health risks associated with adding glucose syrup to infant formula are discussed in more detail in the First Steps Nutrition Trust report *Infant Milks in the UK* (available at www.firststepsnutrition.org/composition-claims-and-costs). Only Lipistart includes a recommendation to clean teeth regularly.

The vitamin C content of Lipistart is over double that of term infant milk and Monogen, but the rationale for this is unknown.

The nutritional composition and ingredients used in modified-fat infant milks for disorders of fatty acid metabolism suitable from birth are given in Table 23.

TABLE 23. The nutritional composition of modified-fat infant milks for disorders of fatty acid metabolism, suitable from birth

Nutrients per 100ml	Nutricia Low Fat Module	Nutricia Monogen	Vitaflo Lipistart
MACRONUTRIENTS			
Energy kcal	67.3	74.6	69
Protein g	1.6	2.2	2.1
Carbohydrate g	14.9	11.6	8.3
– of which sugars g	1.5	2.3	0.7
lactose g	0.16	1.3	0.17
Carbohydrate source	Dried glucose syrup	Maltodextrin, glucose syrup	Dried glucose syrup, maltodextrin
Fat g	0.14	2.2	3.1
Fat source	NA	MCT from fractionated coconut and/or palm oil, walnut oils and single cell oils	Coconut, palm kernel, soyabean oil and single cell oils
Added LCPs ARA	×	✓	✓
DHA	×	✓	✓
MCT %	×	84	81
LCT %	×	16	19
LCP source	NA	Fungal/algal oils (vegetable source)	Fungal/algal oils (vegetable source)
n6:n3	NA	4.2:1	7.1:1
Fatty acid profile g			
C_6 g	Negligible	0.01	0.015
C_8 g	Negligible	1.00	1.4
C_{10} g	Negligible	0.67	0.95
C_{12} g	Negligible	0.01	0.03
$C_{14:0}$ g	Negligible	0.01	0.03
$C_{16:0}$ g	Negligible	0.03	0.1
$C_{18:0}$ g	Negligible	0.01	0
$C_{18:1}$ g	Negligible	0.06	0.12
$C_{18:2}$ g	Negligible	0.15	0.17
$C_{18:3}$ g	Negligible	0.03	0.04
$C_{20:4}$ g	Negligible	0.01	0.03
$C_{22:6}$ g	Negligible	0.01	0.015
Other long chain fatty acids g	Negligible	0.01	0.05
MICRONUTRIENTS			
Vitamins meeting regulations	NA	✓	✓
Minerals meeting regulations	NA	✓	Copper marginally high

Nutrients per 100ml	Nutricia Low Fat Module	Nutricia Monogen	Vitaflo Lipistart
VITAMINS			
Vitamin A µg-RE	71.3	54.6	69.9
Vitamin C mg	8.1	10.1	20.3
Vitamin E mg	0.4	0.82	1.7
Vitamin D µg	1.2	2.0	1.4
Vitamin K µg	2.8	3.0	4.7
Thiamin (B_1) µg	50	60	90
Riboflavin (B_2) µg	80	80	120
Niacin µg (mg NE)	600 (1.5)	500 (1.3)	900 (1.5)
Vitamin B_6 µg	70	70	110
Vitamin B_{12} µg	0.17	0.11	0.23
Folic acid µg	5.1	11.4	15
Biotin µg	3.5	2.4	2.9
Pantothenic acid µg	360	370	440
MINERALS			
Calcium mg	44	60	73.7
Chloride mg	39.2	52.9	44.9
Chromium µg	1.4	1.8	2.0
Copper µg	61	60	70
Iodine µg	7.2	13.5	13.8
Iron mg	0.95	1.1	0.75
Magnesium mg	4.6	7.4	8.6
Manganese mg	0.06	0.06	0.06
Molybdenum µg	2.1	3.5	3.8
Phosphorus mg	31	36	53.9
Potassium mg	56.7	69.4	75.5
Selenium µg	1.5	1.9	2.4
Sodium mg	16.2	35.8	38.7
Zinc mg	0.68	0.76	0.71
ADDED INGREDIENTS			
Prebiotics	×	×	×
Nucleotides	×	×	×
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	×	×	✓
Contains fish oil	×	×	×
Osmolality mOsm/kg	270	240	180

ARA = arachidonic acid
LCP = long chain polyunsaturated fatty acid
MCT = medium chain triglyceride
DHA = docosahexaenoic acid
LCT = long chain triglyceride
NK= not known
NA = not applicable

3.16 Modified-carbohydrate infant milks suitable from birth

Key points

Two infant milks with modified carbohydrate content are manufactured for use from birth. These are Nutricia Galactomin 17 and Nutricia Galactomin 19.

Galactomin 17 has a minimal lactose content and is designed for use in reduced lactose and galactose diets.

Galactomin 19 is a fructose-based infant milk and is for use in infants with glucose-galactose intolerance.

Nutricia Carbohydrate Free Mixture is a protein/fat supplement with no carbohydrates that can be used for infants and children. It cannot provide complete nutritional support for children unless an additional carbohydrate source is used.

Breastfeeding and feeding with cows' milk based infant milk are contraindicated for infants with galactosaemia, a genetically inherited autosomal recessive disorder, which is characterised by deficiency of the GALT or galactose 1-phosphate uridyl transferase enzyme. Classic galactosaemia is rare, being observed in about 1 in 44,000 UK infants per year (Pollitt et al, 1997). The UK has a galactosaemia register to collate data on this small population group; approximately 12-18 new individuals are added per year.

Galactosaemia leads to an accumulation of galactose, a sugar found in lactose, in the blood and other tissues, as the infant is not able to metabolise galactose to glucose. Galactosaemia is associated with increased neonatal mortality and morbidity (vomiting, diarrhoea, liver failure and sepsis) and long-term health outcomes are described in the literature. Infants diagnosed with the classic galactosaemia variant require a lifelong galactose exclusion diet.

In the case of infants with classic galactosaemia, it should be noted that a breastfeeding mother should be offered breastfeeding support and counselling from qualified practitioners to assist her with the physical discomfort and emotional impact of early, and perhaps unexpected, cessation of breastfeeding.

There are no official UK guidelines for the diagnosis and treatment of galactosaemia, however, a network of Galactosaemia experts from Europe and the USA (GalNet), have published a set of 40 recommendations for the diagnosis, treatment and follow-up of individuals suspected of having galactosaemia. Recommendation 4 states that:

'If classical galactosaemia is suspected in an infant, clinicians should immediately commence a galactose-restricted diet (soy-based, casein hydrolysate or elemental formula) without waiting for confirmation of the diagnosis.'(Welling et al, 2017)

The use of soya based infant formula for children aged under 6 months is controversial. In 2006 ESPGHAN made a statement about the use of soy infant milk, stating that soy infant

milk is indicated in galactosaemia. However, they caveat this by saying that raffinose and stachyose found in soy infant milk are hydrolysed by bacterial galactosidases in the gastrointestinal tract, which can increase galactose-1-P values in erythrocytes (Agostoni et al, 2006). In the UK, the Department of Health advises against using soy protein infant milk in infants under 6 months of age due to concerns about the phyto-oestrogen content and future reproductive health. The Committee on Toxicity states that soy infant milk should not be the first-line choice of infant milk for infants who have galactosaemia or galactokinase deficiency (Committee on Toxicity, 2003). The evidence for use of soy infant milk is discussed in more detail in the First Steps Nutrition Trust report *Infant Milks in the UK* (available at www.firststepsnutrition.org/composition-claims-and-costs

Amino-acid based (also known as elemental) formula milks are marketed to be used in the dietary management of moderate to severe cows' milk protein allergy or multiple allergies but may also be suitable for infants with galactosaemia as they do not contain lactose. These milks are however, very expensive and may be no more beneficial than other less expensive alternatives.

There are two infant milks marketed in the UK specifically for infants who need to avoid galactose in their diet, both are manufactured by Nutricia: Galactomin 17 and Galactomin 19. Nutricia states that Galactomin 17 is intended for use for infants requiring a lactose- and galactose-restricted diet. Galactomin 19 is aimed at infants who have glucose-galactose intolerance either primary or secondary to another disorder, but Nutricia do not specify which disorders this might include. Nutricia Carbohydrate Free Mixture contains no carbohydrate source. Nutricia states that it is also intended for use by infants and children with glucose-galactose intolerancebut can only provide complete nutritional support when supplied with an additional carbohydrate source such as fructose. As Nutricia Carbohydrate Free Mixture is free from any form of carbohydrate, it can also be used in the diagnosis of disorders of carbohydrate metabolism, such as monosaccharide intolerances and pyruvate dehydrogenase deficiency.

Galactomin 17 and Galactomin 19 are expensive infant milks to manufacture. There are other more cost-effective specialised infant milks which have a low lactose and therefore galactose content, or which are lactose- and galactose-free, which may be suitable in some cases. Table 23 shows milks that may be suitable for use in infants with galactosaemia and their associated costs. It is important to note that some lactose free milks do contain small amounts of lactose and some are whey based, or have a higher whey: casein ration, and therefore care should be taken when selecting an appropriate formula.

TABLE 24. The lactose composition of specialised infant milks for infants suitable from birth, compared with lactose content of infant formula

Category	Name of infant milk	Lactose content (g/100ml)	Protein source	Whey:casein ratio	Cost per 100ml
Infant formula	Average for three main brands	7.0	Milk	60:40	13p-18p
Lactose-free infant milks sold over the counter	Aptamil Lactose Free	<0.006	Milk	0:100	22p
	Mead Johnson Enfamil O-Lac	<0.07	Milk	20:80	17p
	SMA LF	<0.007	Milk	60:40	17p
Soy protein based infant formula	SMA Wysoy	0	Soya	NA	20p
Extensively hydrolysed peptide-base infant milks	Abbott Nutrition Similac Alimentum	0	Milk	0:100	33p
	Mead Johnson Nutramigen 1 with LGG	0	Milk	0:100	38p
Extensively hydrolysed peptide-base infant milks with MCT	Aptamil Pepti-junior	0.06	Milk	100:0	39p
	Mead Johnson Pregestimil LIPIL	0	Milk	0:100	42p
Amino-acid based infant milks	Mead Johnson Nutramigen Puramino	0	Non-allergenic amino acids	NA	78p
	Nutricia Neocate LCP	0	Non-allergenic amino acids	NA	£1.02
	Nutricia Neocate Syneo	0	Non-allergenic amino acids	NA	£1.09
	SMA Alfamino	0	Non-allergenic amino acids	NA	79p
Modified-carbohydrate infant milks	Nutricia Carbohydrate Free Mixture	0.01	Milk	0:100	NK
	Nutricia Galactomin 17	<0.01	Milk	0:100	58p
	Nutricia Galactomin 19	<0.01	Milk	0:100	£1.55

Nutricia Galactomin 17 has a very low lactose content and added long chain polyunsaturated fatty acids (LCPs) and nucleotides. The carbohydrate is almost exclusively glucose syrup.

Nutricia Galactomin 19 is a fructose-based infant milk with minimal lactose, galactose and glucose. Unlike Galactomin 19, Galactomin 17 does not have LCPs or nucleotides added. Glucose-galactose malabsorption is extremely rare and requires very close medical and dietetic management with rehydration plans in place to treat acute illness.

Neither product makes a recommendation about the need for regular dental care in their preparation guidelines, despite their modified-carbohydrate content.

The nutritional composition and ingredients used in modified-carbohydrate infant milks for disorders of carbohydrate metabolism suitable from birth are given in Table 25.

TABLE 25. The nutritional composition of modified-carbohydrate infant milks suitable from birth

Nutrients per 100ml	Nutricia Carbohydrate Free Mixture	Nutricia Galactomin 17	Nutricia Galactomin 19
INDICATIONS	Glucose-galactose intolerance either primary or secondary to another disorder or in diagnosis of other disorders of carbohydrate metabolism	Lactose- and galactose-restricted diets	Glucose-galactose intolerance either primary or secondary to another disorder
MACRONUTRIENTS			
Energy kcal	47	66	69
Protein g	2.0	1.3	1.9
Whey:casein ratio	0:100	0:100	0:100
Carbohydrate g	0.01	7.3	6.4
– of which sugars g	0.01	1.1	6.3
lactose g	0.01	<0.01	<0.01
Carbohydrate source	NA	Dried glucose syrup	Fructose
Fat g	4.24	3.5	4.0
Fat source	Palm, sunflower, rapeseed and coconut oils	Palm, rapeseed, coconut, sunflower, single cell and fish oils	Palm, sunflower, rapeseed and coconut oils
Added LCPs ARA	×	✓	×
DHA	×	✓	×
LCP source	NA	Fish oil, fungal/algal oils (vegetable source)	NA
MICRONUTRIENTS			
Vitamins meeting regulations	✓	✓	✓
Minerals meeting regulations	Manganese higher than FSMP regulations	✓	✓
VITAMINS			
Vitamin A µg-RE	80.5	55	74.2
Vitamin C mg	8.82	9.3	8.1
Vitamin E mg	1.06	1.2	0.98
Vitamin D µg	1.3	1.2	1.2
Vitamin K µg	5.74	4.5	5.3
Thiamin (B_1) µg	40	50	40
Riboflavin (B_2) µg	110	100	100

Nutrients per 100ml	Nutricia Carbohydrate Free Mixture	Nutricia Galactomin 17	Nutricia Galactomin 19
Niacin µg (mg NE)	0.63 (1.1)	430 (0.78)	580 (1)
Vitamin B_6 µg	40	40	40
Vitamin B_{12} µg	0.22	0.11	0.21
Folic acid µg	11.1	8.9	10.2
Biotin µg	1.64	1.8	1.5
Pantothenic acid µg	340	330	310
MINERALS			
Calcium mg	59	55	55
Chloride mg	44	41	40.8
Chromium µg	1.27	nil added	1.04
Copper µg	53	40	50
Iodine µg	7.7	12	7.1
Iron mg	0.55	0.79	0.5
Magnesium mg	6.7	5.1	6.1
Manganese µg	60	30	60
Molybdenum µg	2.62	nil added	2.4
Phosphorus mg	35	30	32.3
Potassium mg	65.4	65	60.2
Selenium µg	1.29	1.6	1.19
Sodium mg	22	17	20.4
Zinc mg	0.45	0.56	0.41
ADDED INGREDIENTS			
Prebiotics	×	×	×
Nucleotides	×	✓	×
Inositol	✓	✓	✓
Taurine	✓	✓	✓
Choline	✓	✓	✓
Added antioxidants	✓	✓	✓
Contains soya	×	✓	×
Contains fish oil	×	✓	×
Osmolality mOsm/kg	54	170	407

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NK = not known NA = not applicable

3.17 Infant milk for the dietary management of calcium intolerance, suitable from birth

Key points

One infant milk with a reduced calcium and vitamin D content for use from birth is manufactured by Nutricia and is called Locasol.

What little published evidence about the efficacy and safety of this type of infant milk exists is of limited use, as it appears to be mainly in the form of single case studies.

There appears to be very little published or high-quality data regarding the safety or efficacy of reduced-calcium infant milk. There is one Japanese case study in which a term 49-day old infant with familial hypercalcuria hypercalcaemia type 3 (FHH3) was given an unnamed reduced-calcium infant milk (2.6mg/100ml) for approximately two months after having received breastmilk and infant formula (Fujisawa et al, 2013). The study authors conclude that this infant milk improved the infant's suck and enabled catch-up growth, although other factors such as development could potentially account for the improvement in sucking behaviour, and the findings are very limited given that it was a single case study.

There are no current UK guidelines regulating management and treatment of calcium intolerance.

Nutricia Locasol is the only product marketed for the dietary management of calcium intolerance. It contains cows' milk protein, fats, carbohydrates, minerals, vitamins, trace elements and a reduced calcium and vitamin D content. The calcium content is around six times lower than that found in infant formula, and there is no vitamin D at all in Nutricia Locasol. There are no claims made by Nutricia about Locasol's efficacy.

Nutricia Locasol does not comply with EC regulations regarding foods for special medical purposes in that the calcium and vitamin D contents are below the minimum legal requirement for those micronutrients.

The nutritional composition and ingredients used in infant milk for the dietary management of calcium intolerance suitable from birth are given in Table 26.

TABLE 26. The nutritional composition of infant milk for the dietary management of calcium intolerance, suitable from birth

Nutrients per 100ml	Nutricia Locasol
MACRONUTRIENTS	
Energy kcal	66
Protein g	1.9
Whey:casein ratio	20:80
Carbohydrate g	7.0
– of which sugars g	6.9
lactose g	6.9
Carbohydrate source	Lactose, dried glucose syrup
Fat g	3.4
Fat source	Palm, sunflower, rapeseed and coconut oils
Added LCPs ARA	×
DHA	×
MACRONUTRIENTS	
Vitamins meeting regulations	Vitamin D lower than FSMP regulations
Minerals meeting regulations	Calcium lower than FSMP regulations
VITAMINS	
Vitamin A µg-RE	79
Vitamin C mg	7.9
Vitamin E mg	1.0
Vitamin D µg	nil added
Vitamin K µg	5.2
Thiamin (B_1) µg	40
Riboflavin (B_2) µg	100
Niacin µg (mg NE)	590 (1)
Vitamin B_6 µg	40
Vitamin B_{12} µg	0.2
Folic acid µg	10.5
Biotin µg	1.6
Pantothenic acid µg	300
MINERALS	
Calcium mg	<7
Chloride mg	60.3
Copper µg	40.6
Iodine µg	10.2
Iron mg	0.5
Magnesium mg	6.6
Manganese mg	0.05
Phosphorus mg	46

Nutrients per 100ml	Nutricia Locasol
Potassium mg	83.8
Selenium µg	1.5
Sodium mg	28.7
Zinc mg	0.4
ADDED INGREDIENTS	
Prebiotics	×
Nucleotides	×
Inositol	✓
Taurine	✓
Choline	✓
Added antioxidants	✓
Contains soya	×
Contains fish oil	×
Osmolality mOsm/kg	310

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NK = not known

3.18 Infant milk for the dietary management of liver failure, suitable from birth

Key points

Nutricia Heparon Junior is the only specialised infant milk available on prescription for the treatment of liver failure, suitable from birth.

It differs from infant formula in that its carbohydrate comes from dried glucose syrup, it includes MCT oil, branched chain amino acids and zinc, and is lower in sodium than infant formula.

Sodium in this product falls below the minimum EU FSMP requirement for sodium.

There appears to be no published data to support its efficacy or safety.

Paediatric liver disease is rare, occurring in one in 9,000-16,000 births (Baker et al, 2007). Baker et al note the small evidence base for dietary management of liver disease. Infants will often present with faltering growth, anorexia, fat malabsorption, jaundice and pruritus.

European guidelines, which include the input of the hepatology department at King's College Hospital, London, for use with infants with cholestatic liver disease before liver transplantation were published in 2007 (Baker et al, 2007). These give details of appropriate vitamin and mineral supplementation and make recommendations regarding the addition of MCT or LCTs. The study authors note that often MCT infant milks are less palatable and suggest using an infant formula in cases where infants do not accept the MCT infant milk. This raises an interesting point as it suggests that the clinical benefits of using specialised infant milk might be less important than the acceptance of the taste of the infant milk.

Heparon Junior is a nutritionally complete powdered infant milk for the dietary management of acute and chronic liver failure. There is only one such product available; no other manufacturers produce a liver-specific specialised infant milk.

Heparon Junior is composed of dried glucose syrup, skimmed cows' milk, 49% MCT, soya and canola oil, whey and casein, vitamins, minerals, and trace elements. Heparon Junior has a higher than average branched chain amino acid (30% of the protein content) and zinc content, and lower than average sodium content than infant formula.

The manufacturer recommends that some infants start on a lower concentration in order to build tolerance to the product, and increase to a concentration of 18%, i.e. 18g Heparon Junior powder made up to 100ml with water. The manufacturer requests that water is boiled before the infant milk is made up and that it is left for *"at least 30 minutes so that it feels warm to the wrist"* (Heparon Junior datacard, May 2014). UK guidance states that the temperature of the water should cool to no less than 70ºC which *"means in practice using water that has been left covered, for less than 30 minutes"*. The instructions for Heparon Junior, which state that water is left for *"at least 30 minutes",* implies that it is acceptable to leave it for longer, by which time it may be cooler and may increase the chances that an infant with liver failure could be exposed to harmful food-borne pathogens present in the powdered infant milk.

There appear to be no published trials or systematic reviews to validate this product's efficacy or safety.

The nutritional composition and ingredients used in infant milk for the dietary management of liver failure suitable from birth are given in Table 27.

TABLE 27. The nutritional composition of infant milk for the dietary management of liver failure, suitable from birth

Nutrients per 100ml	Nutricia Heparon Junior
MACRONUTRIENTS	
Energy kcal	86.4
Protein g	2.0
Whey:casein ratio	60:40
Carbohydrate g	11.6
– of which sugars g	2.9
lactose g	1.1
Carbohydrate source	Dried glucose syrup, lactose
Fat g	3.6
Fat source	MCT, soya and canola oils
Added LCPs ARA	×
DHA	×
Vitamins meeting regulations	✓
Minerals meeting regulations	Sodium lower than FSMP regulations
VITAMINS	
Vitamin A µg-RE	102
Vitamin C mg	10.4
Vitamin E mg	1.9
Vitamin D µg	1.7
Vitamin K µg	4.5
Thiamin (B_1) µg	60
Riboflavin (B_2) µg	100
Niacin µg (mg NE)	860 (1.4)
Vitamin B_6 µg	170
Vitamin B_{12} µg	200
Folic acid µg	9.9
Biotin µg	1.5
Pantothenic acid µg	430
MINERALS	
Calcium mg	91.6
Chloride mg	46.8
Copper µg	40
Iodine µg	9.9
Iron mg	1.3
Magnesium mg	7.0
Manganese mg	0.09
Phosphorus mg	49.9
Potassium mg	75.6

Nutrients per 100ml	Nutricia Heparon Junior
Selenium µg	2.4
Sodium mg	13.0
Zinc mg	1.3
ADDED INGREDIENTS	
Prebiotics	×
Nucleotides	×
Inositol	✓
Taurine	✓
Choline	✓
Added antioxidants	✓
Contains soya	✓
Contains fish oil	×
Osmolality mOsm/kg H_20	310 *

* Osmolality of 310mOsm/L is at 18% w/v dilution.

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NK = not known

3.19 Infant milks for the dietary management of renal disease, suitable from birth

Key points

Two specialised infant milks have been manufactured for infants with renal disease: Nutricia Kindergen and Vitaflo Renastart.

Labelling of these products shows that only Nutricia Kindergen can be used as a sole source of nutrition. Vitaflo Renastart can be used as a supplement despite having a similar nutritional composition.

Compositionally, in both infant milks the levels of levels of vitamin A, calcium, chloride, phosphorus and potassium all fall below current regulations for foods for special medical purposes. Any infant who is prescribed either of these specialised infant formulas requires close dietetic supervision to ensure that essential nutrients and/or micronutrients do not fall below individual estimated nutritional requirements. We have been contacted by professionals working in this area who have asked us to highlight that it might not be appropriate for some infants to have either of the renal formulas above at the recommended concentration.

Vitaflo highlights the need for careful oral health care when using Renastart. This is not always mentioned in other specialised infant milks containing added sugars.

There appears to be no published data to support efficacy or safety of either of these products.

Two powdered infant milks are suitable for use in infants with renal disease: Nutricia Kindergen and Vitaflo Renastart.

The Kindergen datacard states it can be used for infants with chronic renal failure where peritoneal rapid overnight dialysis (PROD) or continuous cycling peritoneal dialysis (CCPD) are required. Renastart states that it can be used for the dietary management of renal failure from birth.

Both manufacturers note that the vitamin A, calcium, chloride, phosphorus and potassium contents have been expressly reduced and their values for these nutrients are lower than the minimum levels required by EU regulations for foods for special medical purposes (see Table 5). Nutricia states that the reason for this is to manage the requirements of infants with chronic renal failure and that these micronutrients should be monitored and supplemented where required.

Despite both infant milks having a very similar nutritional composition, the manufacturers have made different statements as to their suitability as a sole source of nutrition. Nutricia have stated that Kindergen can be used either as a sole source of nutrition or as a supplementary infant milk. Renastart states that it is not suitable as the sole source of nutrition. The rationale for this statement is that, whilst Renastart contains all the nutrients

that would be included in a standard infant formula or a nutritionally complete paediatric feed, it contains lower levels of the nutrients mentioned above in order to compensate for impaired renal function. Vitaflo has told us that, although Renastart can be used exclusively for up to a few days during the acute phases of the disease until the electrolytes in plasma are lowered, it is typically used in conjunction with breastmilk or a standard infant formula or standard paediatric enteral feed.

Kindergen contains whey protein, carbohydrates, fat (from safflower, coconut and soybean oils), emulsifier, added antioxidants, added amino acids, vitamins, minerals and trace elements. Nutricia notes in its literature that Kindergen has a reduced phosphate and adjusted calcium level, and a higher sodium and fat content. This gives a calcium to phosphorus ratio of 1.2:1. Kindergen has over two times more sodium per 100ml than standard term infant milk (46.4mg/100ml vs. 16.7mg/100ml respectively). Kindergen has an energy content of 101kcal/100ml. This is accounted for by an increased fat and carbohydrate content which are both around one and a half times greater than infant formula.

Vitaflo Renastart has an almost identical composition to Nutricia Kindergen but does not highlight these variations compared with infant formula, or provide the rationale for their adjustment in their literature available on the company website. Guidelines on how to use Renastart and its comparison to standard infant formulas have been developed but are for health care professionals only and are not publicly available.

There are no studies quoted, nor any claims made, by the manufacturer regarding this type of specialised infant milk.

There may be risks to safe use, as published data regarding efficacy and safety are lacking and therefore there is no evidence base with which to guide specialist health professionals working in this area.

Vitaflo recommends regular teeth cleaning whilst using this product. Nutricia does not make a statement regarding this, although the carbohydrate is very similar.

The nutritional composition and ingredients used in infant milks for the dietary management of renal disease suitable from birth are given in Table 28.

TABLE 28. The nutritional composition of infant milk for the dietary management of renal disease, suitable from birth

Nutrients per 100ml	Nutricia Kindergen	Vitaflo Renastart
MACRONUTRIENTS		
Energy kcal	101	99
Protein g	1.5	1.5
Whey:casein ratio	100:0	98:2
Carbohydrate g	11.8	12.5
– of which sugars g	1.2	1.3
lactose g	0.2	0.12
Carbohydrate source	Dried glucose syrup	Dried glucose syrup, maltodextrin
Fat g	5.3	4.8
Fat source	High oleic safflower, non-hydrogenated coconut and soya oils	Palm, palm kernel, rapeseed, sunflower and single cell oils
Added LCPs ARA	×	✓
DHA	×	✓
LCP source	NA	Fungal/algal oils (vegetable source)
Vitamins meeting regulations	Low vitamin A	Low vitamin A
Minerals meeting regulations	Low calcium, chloride, phosphorus and potassium	Low calcium, chloride, phosphorus and potassium
VITAMINS		
Vitamin A µg-RE	26	25.6
Vitamin C mg	8.4	22.6
Vitamin E mg	0.56	0.6
Vitamin D µg	1.1	1.1
Vitamin K µg	5.1	6.0
Thiamin (B_1) µg	70	60
Riboflavin (B_2) µg	90	100
Niacin µg (mg NE)	920 (1.5)	1000 (1.6)
Vitamin B_6 µg	90	100
Vitamin B_{12} µg	0.18	0.2
Folic acid µg	16.4	17.2
Biotin µg	4.6	4.4
Pantothenic acid µg	300	400
MINERALS		
Calcium mg	22.4	22.6
Chloride mg	17	17.4
Copper µg	90	80
Iodine µg	7.0	16.4
Iron mg	0.96	1.0
Magnesium mg	11.0	10.6

Nutrients per 100ml	Nutricia Kindergen	Vitaflo Renastart
Manganese mg	0.09	0.02
Phosphorus mg	18.6	18.4
Potassium mg	24	23.4
Selenium µg	2.6	1.9
Sodium mg	46.4	48.4
Zinc mg	0.84	0.86
ADDED INGREDIENTS		
Prebiotics	×	×
Nucleotides	×	×
Inositol	✓	✓
Taurine	✓	✓
Choline	✓	✓
Added antioxidants	✓	✓
Contains soya	✓	✓
Contains fish oil	×	×
Osmolality mOsm/kg	215	225

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NK = not known

3.20 Infant milk for the dietary management of epilepsy, suitable from birth

The ketogenic diet, which is a diet high in fat (in the form of LCTs), low in carbohydrate and adequate in protein, is often used when drug treatment for epilepsy has not been successful. It is believed that trials of the ketogenic diet can result in fewer seizures or periods free of seizures. Metabolically, the diet mimics the starvation process by breaking down fat into ketone bodies which are then used preferentially by the brain to provide energy in the absence of glucose.

The ketogenic diet is recommended for GLUT 1 deficiency and pyruvate dehydrogenase complex deficiency.

Nutricia produces Ketocal 3:1 for the dietary management of epilepsy. This is suitable from birth to 6 months, either as a nutritionally complete infant milk or as a supplementary infant milk.

The ratio of 3:1 denotes 3g of fat to every 1g of protein and carbohydrate combined and describes a ketogenic diet therapy sometimes used in younger infants and children. As children age, the literature describes a 4:1 approach being adopted. There is evidence that around one-third of children treated with the ketogenic diet have more than 90% seizure control, and of these around 50% become seizure-free. An additional third observe a 50% reduction in seizures and the final third discontinue the diet due to difficulties with maintaining a diet requiring such close supervision and dietary restriction.

Ketocal 3:1 does not comply with EC regulations for foods for special medical purposes as it contains less niacin than the minimum EC requirement for this micronutrient.

The preparation instructions for Ketocal 3:1 do not comply with UK recommendations for the safe preparation of infant milk. UK Government recommendations state that water which is to be added to infant milk should boil and cool to no lower than 70ºC. Nutricia suggests that, when preparing Ketocal 3:1, water should be boiled and allowed to cool to 50ºC, or freshly boiled water should be mixed with cooled water to achieve a similar temperature.

The nutritional composition and ingredients used in infant milk for the dietary management of epilepsy suitable from birth are given in Table 29.

TABLE 29. The nutritional composition of infant milk for the dietary management of epilepsy, suitable from birth

Nutrients per 100ml	Nutricia Ketocal 3:1
MACRONUTRIENTS	
Energy kcal	66
Protein g	1.5
Whey:casein ratio	
Carbohydrate g	0.68
– of which sugars g	0.57
lactose g	0.55
Carbohydrate source	Lactose, dried glucose syrup
Fat g	6.4
Fat source	Palm, soya, sunflower and single cell oils
Added LCPs ARA	✓
DHA	✓
LCP source	Fungal/algal oils (vegetable source)
Vitamins meeting regulations	Niacin lower than FSMP regulations
Minerals meeting regulations	✓
VITAMINS	
Vitamin A µg-RE	49.9
Vitamin C mg	8.0
Vitamin E mg	0.75
Vitamin D µg	1.2
Vitamin K µg	5.3
Thiamin (B_1) µg	70
Riboflavin (B_2) µg	70
Niacin (mg NE	0.47
Vitamin B_6 µg	70
Vitamin B_{12} µg	0.13
Folic acid µg	13.3
Biotin µg	1.3
Pantothenic acid µg	270
MINERALS	
Calcium mg	79.6
Chloride mg	45.7
Copper µg	78.9
Iodine µg	11.8
Iron mg	1.1
Magnesium mg	10.0
Manganese µg	60
Phosphorus mg	53.1
Potassium mg	94.3
Selenium µg	2.0

Nutrients per 100ml	Nutricia Ketocal 3:1
Sodium mg	29.9
Zinc mg	0.78
ADDED INGREDIENTS	
Prebiotics	×
Nucleotides	×
Inositol	✓
Taurine	✓
Choline	✓
Added antioxidants	✓
Contains soya	✓
Contains fish oil	×
Osmolality mOsm/kg	100

ARA = arachidonic acid DHA = docosahexaenoic acid LCP = long chain polyunsaturated fatty acid
NK = not known

4 Instructions for making up breastmilk fortifier

Instructions for making up breastmilk fortifier (produced by Imperial College Healthcare NHS Trust[8]).

NB This is a guideline only and occasionally an individual plan will need to be made and documented

1. Wash hands

2. Clinell wipe a plastic tray, to be used as the area for milk preparation, and a BMF sachet, allow both to dry.

3. Collect milk and equipment – always use single use sterile bottles and syringes.

4. Wash hands and put on gloves.

5. Mix 1 sachet of BMF and 3ml expressed breast milk (EBM) in an expressing bottle; this will make a 4ml BMF concentrate. Use this bottle for storing the milk once fortified.

6. Ensure BMF is completely dissolved, may take a few minutes, use the tip of syringe if necessary.

7. It is best practice to fortify a maximum of 50mls and use before fortifying more to keep storage time to the minimum

8. Make up enough fortified milk to be used within a maximum of 12 hours, preferably less. Mix but do not shake vigorously as the fat globules are disrupted if milk froths.

   For 25ml fortified EBM: ½ strength = 1ml BMF concentrate and make up to 25mls
   Full strength = 2ml BMF concentrate and make up to 25mls

   For 50ml fortified EBM: ½ strength = 2ml BMF concentrate and make up to 50mls
   Full strength = 4mls BMF concentrate and make up to 50mls

9. Discard any unused BMF concentrate.

10. Label any unused fortified EBM with patient's details and time of milk preparation.

11. For milk storage & handling refer to relevant guideline

12. Store unused fortified milk in fridge and use within a maximum of 12 hours. If you calculate that you may have fortified milk stored for longer than 12 hours check with senior medical or nursing staff before discarding.

13. Discard gloves and wash hands. Repeat this process for each individual mother's milk

8 With thanks to Caroline King, Paediatric Dietitian, Imperial College Healthcare NHS Trust.

5 Infant feeding support and information

Helplines

National Breastfeeding Helpline
0300 100 0212
The helpline is staffed by volunteers from The Breastfeeding Network and The Association of Breastfeeding Mothers and is open from 9.30am to 9.30pm every day of the year. Support can be given in English, Polish and Welsh.

La Leche League GB
0845 120 2918

NCT Helpline
0300 330 0770

Useful organisations

The organisations listed below provide a range of information and resources on infant feeding.

Association of Breastfeeding Mothers
T: 08444 122 948
E: info@abm.me.uk
www.abm.me.uk
For breastfeeding information, a list of local support groups, and current breastfeeding news.

The Baby Café
www.thebabycafe.org
A charity that coordinates a network of breastfeeding drop-in centres and other services to support breastfeeding mothers across the UK and in other parts of the world.

The Baby Feeding Law Group www.bflg-uk.org
Works for the implementation of the WHO *International Code of Marketing of Breast-milk Substitutes* and subsequent, relevant World Health Assembly Resolutions into legislation in the UK.

Baby Milk Action
E: info@babymilkaction.org
www.babymilkaction.org

Best Beginnings
T: 020 7443 7895
www.bestbeginnings.org.uk

BLISS (The Premature Baby Charity)
T: 020 7378 1122
E: information@bliss.org.uk
www.bliss.org.uk
Provides support and care to premature and sick babies across the UK of the highest possible standard.

The Breastfeeding Network
T: 0844 120 0995
www.breastfeedingnetwork.org.uk
An independent source of support and information for breastfeeding women and those involved in their care.

Breastfeeding Network Drugs in Breastmilk Facebook page
https://en-gb.facebook.com/BfNDrugsinBreastmilkinformation/

Community Practitioners' and Health Visitors' Association (CPHVA)
E: infocphva@unitetheunion.com
http://unitetheunion.org/cphva

Drugs in Lactation Advisory Service (DILAS)
UKDILAS enquiry answering service is available from 09:00 – 17.00, Monday to Friday, excluding Bank Holidays
0116 258 6491 (Trent Medicines Information Centre)
0121 424 7298 (West Midlands Medicines Information Centre)
ukdilas.enquiries@nhs.net

European Food Safety Authority (EFSA)
www.efsa.europa.eu

Food Standards Agency (UK headquarters)
T: 020 7276 8829
E: helpline@foodstandards.gsi.gov.uk
www.food.gov.uk

GP Infant Feeding Network UK (GPIFN)
www.gpifn.org.uk

Hospital Infant Feeding Network (HIFN)
www.hifn.org

Human Milk Foundation
www.humanmilkfoundation.org

Institute of Health Visiting
www.ihv.org.uk

International Baby Food Action Network (IBFAN)
www.ibfan.org

La Leche League
T: 0845 456 1855 (General enquiries)
0845 120 2918 (24-hour helpline)
www.laleche.org.uk

Lactation Consultants of Great Britain (LCGB)
E: info@lcgb.org
www.lcgb.org

Local Infant Feeding Information Board
www.LIFIB.org.uk

Midwives Information and Resource Service (MIDIRS)
T: 0117 3706799
www.midirs.org

The Multiple Births Foundation
T: 0203 313 3519
E: mbf@imperial.nhs.uk
www.multiplebirths.org.uk

National Institute for Health and Care Excellence (NICE)
T: 0845 003 7780
www.nice.org.uk
For public health guidance on antenatal and postnatal care and nutrition and clinical guidance on a number of aspects of clinical care.

NCT
T: 0300 33 00 770
www.nct.org.uk
For information to support parents on all aspects of antenatal and postnatal care.

Neonatal Dietitians Interest Group (NDIG)
http://www.bapm.org/nutrition/information.php

NHS Information
www.nhs.uk

NHS Health Scotland
T: 0131 536 5500
www.healthscotland.com

Public Health Agency (Northern Ireland)
T: 028 9031 1611
www.publichealth.hsci.net

Public Health England
T: 020 7654 8000
www.gov.uk/government/organisations/public-health-england

Public Health Wales
www.publichealthwales.wales.nhs.uk

Royal College of Midwives
T: 020 7312 3535
www.rcm.org.uk

Royal College of Nursing
T: 020 7409 3333
www.rcn.org.uk

Royal College of Paediatrics and Child Health
T: 020 7092 6000
www.rcpch.ac.uk

Scientific Advisory Committee on Nutrition (SACN)
www.sacn.gov.uk

Unicef UK Baby Friendly Initiative
T: 0207 375 6030
E: bfi@Unicef.org.uk
www.babyfriendly.org.uk

United Kingdom Association for Milk Banking (UKAMB)
E: info@ukamb.org
www.ukamb.orgA charity that supports human milk banking in the UK.

World Health Organisation
www.who.int/health_topics/breastfeeding

6 Specialised infant milk companies

Abbott Nutrition
Infant milks produced:
- *Similac Alimentum*
- *Similac High Energy*

Abbott Nutrition
Abbott House
Vanwall Business Park
Vanwall Road
Maidenhead
Berkshire SL6 4XE
T: 01628 773 355
www.abbottnutrition.co.uk

Aptamil
Infant milks produced:
- *Aptamil Anti-Reflux*
- *Aptamil Comfort*
- *Aptamil Lactose Free*
- *Aptamil Pepti 1*
- *Aptamil Pepti-junior*

Aptamil
Newmarket House
Newmarket Avenue
White Horse Business Park
Trowbridge
Wiltshire BA14 0XQ
T: 0800 996 1000
www.eln.nutricia.co.uk

Cow & Gate
Infant milks produced:
- *Cow & Gate Anti-Reflux*
- *Cow & Gate Nutriprem Human Milk Fortifier*
- *Cow & Gate Comfort*
- *Cow & Gate Hydrolysed Nutriprem*
- *Cow & Gate Nutriprem 1*
- *Cow & Gate Nutriprem 2*
- *Cow & Gate Nutriprem Protein Supplement*

Cow & Gate
Newmarket House
Newmarket Avenue
White Horse Business Park
Trowbridge
Wiltshire BA14 0XQ
T: 0800 977 4000
www.eln.nutricia.co.uk

Hipp Organic
Infant milks produced:
- *Hipp Combiotic Comfort*
- *Hipp Combiotic Anti-reflux*

Hipp Organic Ltd
The Stable Block
Hurst Grove
Sandford Lane
Hurst
Reading
Berkshire RG10 OSQ
T: 0845 050 1351
E: inforequest@Hipp.co.uk
www.Hipp.co.uk
www.Hipp4hcps.co.uk

Mead Johnson Nutrition UK Ltd
Infant milks produced:
- *Enfamil AR*
- *Enfamil O-Lac*
- *Nutramigen 1 with LGG*
- *Nutramigen Puramino*
- *Pregestimil LIPIL*

Mead Johnson Nutrition UK Ltd
c/o Reckitt Benckiser
Wellcroft House
Wellcroft Road
Slough SL1 4AQ
T: 01895 230575
www.nutramigen.co.uk

Nutricia Ltd
Infant milks produced:
- *Anamix Infant range*
- *Carbohydrate Free Mixture*
- *Galactomin 17*
- *Galactomin 19*
- *Heparon Junior*
- *Infatrini*
- *Infatrini Peptisorb*
- *Ketocal 3:1*
- *Kindergen*

- *Locasol*
- *Low Fat Module*
- *Monogen*
- *Neocate LCP*
- *Neocate Syneo*

Nutricia Ltd
White Horse Business Park
Newmarket Avenue
Trowbridge
Wiltshire BA14 0XQ
T: 01225 751098
E: resourcecentre@nutricia.com
www.nutriciahcp.com

SMA Nutrition
Infant milks produced:
- *SMA Alfamino*
- *SMA Althéra*
- *SMA Breast Milk Fortifier*
- *SMA Comfort*
- *SMA Gold Prem 1*
- *SMA Gold Prem 2*
- *SMA HA*
- *SMA High Energy*
- *SMA LF*
- *SMA Staydown*
- *SMA Wysoy*

Nestlé Nutrition
1 City Place
Gatwick
RH6 OPA
T: 0208 686 3333
www.nestlehealthscience.co.uk
www.smahcp.co.uk

Vitaflo International Ltd
Infant milks produced
- *Lipistart*
- *Renastart*
- *PKU Start*

Vitaflo International Ltd
Suite 1.11
South Harrington Building
182 Sefton Street
Brunswick Business Park
Liverpool
L3 4BQ
T: 0151 709 9020
www.nestlehealthscience.co.uk

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