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- This activity provides 1.0 contact hour(s) of nursing professional development.

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Today's evaluation form will ask you to inform us of any perceived bias in the presentation today.

What's new and what's coming in "Stork Speed"

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Objectives

- Recognize current marketing and regulatory issues related to infant formulas in the United States and Europe and the effect of operation “Stork Speed” on them
- Discuss the challenges involved in ensuring safe production and use of formulas in the US
- Recognize novel products for infant feeding entering the market including new infant formulas from Europe and Australia/New Zealand
- Identify pathways forward for the introduction of novel formulas in the US market for full-term infants

How are new formulas evaluated by the FDA?

- Growth monitoring studies
  - Generally monitoring is short term (e.g. 4-6 months)
  - Standards exclude including late preterms who are often fed standard formulas
  - Comparison is with current formulas, not human milk
  - Include some evaluation of adverse effects
  - Focus is on safety, not necessarily benefits to the new formula
- Animal protein study (PER)
  - Historical test used to evaluate growth based on protein source in laboratory rats
  - Inaccurate approach. Rats are not people. Alternatives used in other countries
  - Broad based safety evaluation comparison with current formula/product

Limitations in current approaches to evaluation of new formulas

- Virtually no data assessing cost/benefit
- Virtually no data related to interaction of bioactives, especially those in “different formulas”
- Information and data are not presented in a fashion useful to consumer or pediatricians
- Few data on meaningful clinical outcomes related to infection or allergy prevention/management
- Hard to connect common infant symptoms (e.g. colic) to specific components of human milk or formula

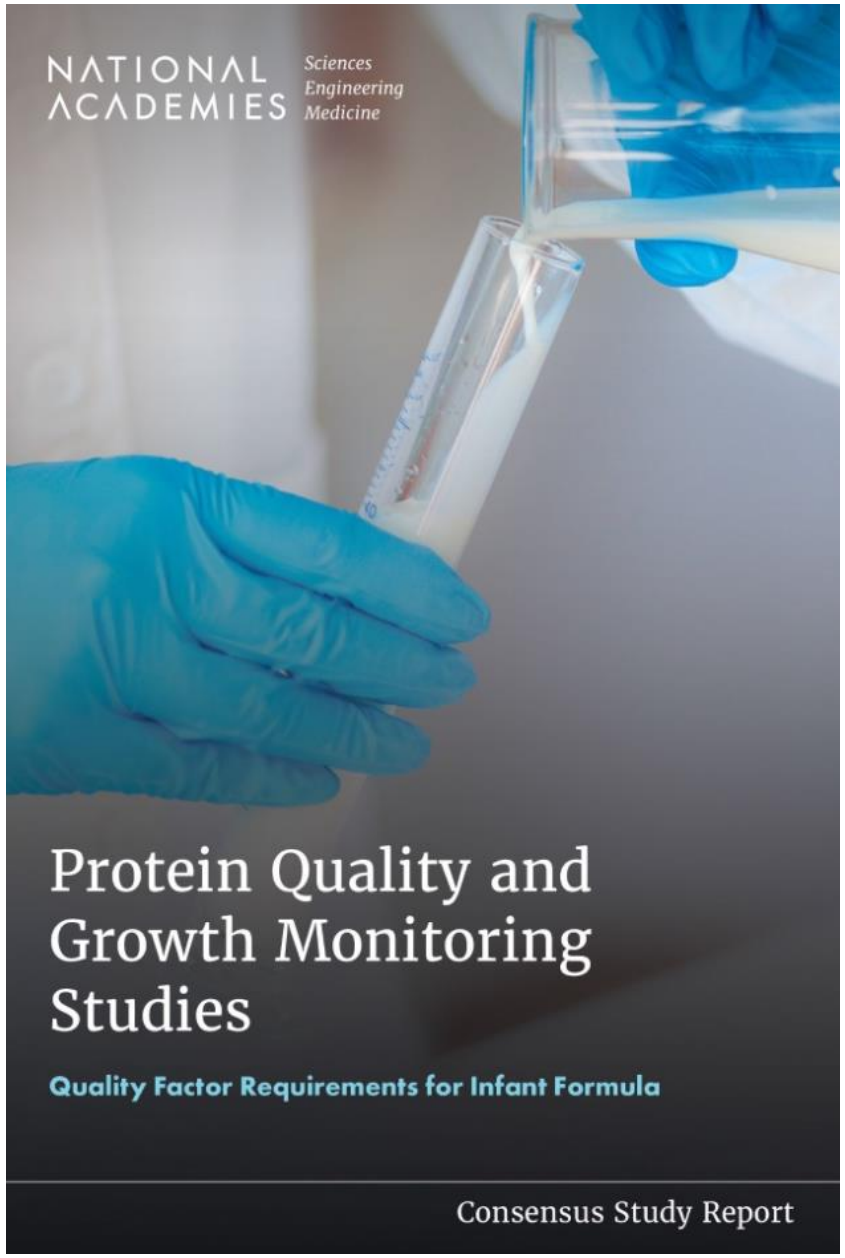
Study design issues

- Current study designs require enrollment prior to 14 days on all formula feeding, 6 study visits over about 15 weeks
- Concurrent formula group usually required but NOT a breast-fed control group
- Highly uncertain how intermediate data points are used by FDA in evaluating growth outcome
- Endpoint of 3 g/day growth difference does not use other anthropometry values, other approaches to body composition and is arbitrary
- Comparison with WHO/CDC curves also mandated but not clear how these data are used
- Safety outcomes are not clear (is normal spitting really an adverse event?)

Growth standard

Observations of 720 infants fed milk-based or isolated soy protein-based formulas and of 419 breast-fed infants indicated that the sex-related difference in rate of gain in weight from 8 to 112 days of age was 4.7 g/day for formula-fed infants and 3.6 g/day for breast-fed infants.[11] The difference in rate of gain between formula-fed and breast-fed infants during this age interval was 2.4 g/day for males and 1.3 g/day for females. On this basis, the Task Force recommends that a feeding-related difference in weight gain of more than 3 g/day over a 3 to 4 month period (although it is less than the sex-related difference) should be considered nutritionally significant.

From: Clinical testing of infant formulas with respect to nutritional suitability for term infants. AAP, CON, June 1988 and Nelson et al, 1989: https://www.sciencedirect.com/science/article/pii/0378378289900571



NASEM report: May 5, 2025

NASEM report: Protein efficiency

Conclusion 1: The committee concluded that the protein efficiency ratio (PER) is not the preferred method for assessing protein quality of infant formula.

Recommendation 1: The Food and Drug Administration should not use the protein efficiency ratio (PER) as the method for establishing the biological quality of protein of new infant formulas and should reconsider the need for the existing draft guidance on PER.

Recommendation 2: The Food and Drug Administration should adopt the human milk amino acid pattern as the reference pattern to assess the protein quality of infant formula.

NASEM report: Clinical studies

Recommendation 4: The Food and Drug Administration (FDA) should publish a single guidance document that describes: (1) the preferred design features of a growth monitoring protocol and explains how FDA uses required information in its evaluation that a formula supports normal physical growth, and the conditions under which alternative designs may be acceptable to FDA; and (2) guidance that outlines the conditions under which a growth monitoring study is needed. That guidance should take into account (1) whether the change in infant formula could reasonably affect growth, (2) if a new ingredient is normally found in human milk, (3) the extent to which prior studies have examined the effect of a new ingredient on growth, and (4) information about the effects of addition of the ingredient on the level of or bioavailability of a nutrient, whose deficiency over the course of the study would be manifested in reduced growth.

NASEM report: Clinical studies

Conclusion 7: Conducting a research study in which a new formula is compared to an existing approved one, referred to by the term "concurrent control" as used in 21 CFR § 106.96(b)(5), is conventionally interpreted by investigators and FDA to mean the need for a randomized controlled trial (RCT). An RCT may be needed to demonstrate the absence of a negative effect on growth of infant formula–fed infants because of a change in formulation or processing of an infant formula. However, an RCT may not be needed under certain conditions, and suitable data could be generated in a single-arm study in which the growth of infants receiving the test formula is compared to the WHO/CDC growth standard.

Nutrient regulations: Macronutrients

TABLE F-1 Infant Formula Macronutrient Content Standards

		CODEX		US		AU/NZ		Canada		EU	
Macronutrient	Unit of Measurement	Minimum Level	Maximum Level	Minimum Level	Maximum Level	Minimum Level	Maximum Level	Minimum Level	Maximum Level	Minimum Level	Maximum Level
Calories	kJ/100ml	250	295	N/A	N/A	250	315[a]	N/A	N/A	250	293
	kcal/100ml	60	70	N/A	N/A	N/A	N/A	66.4	68	60	70
Protein	g/100 kcal	1.8	3	1.8	4.5	N/A	N/A	1.8	4	1.8	2.5
	g/100 kJ	0.45	0.7	N/A	N/A	0.45	0.7	N/A	N/A	0.43	0.6

Note high levels allowed for protein in the US and no specific regulation of energy density

Closer look: Macronutrients

- Carbohydrate source: Lactose used in most European formulas, even partial hydrolysates, per EU guidance
- Fat sources Use of whole fat milk as part of fat source in some formulas, seed oils are used in all formulas. No regulation requiring DHA or ARA in formula although all US registered formulas contain them

CHO source in formula

- One small study suggested possible issues with food enjoyment, fussiness at 2 years of age in infants who receive corn syrup solids (CSS) in formula
  - Groups also differed in protein source and the CSS group included soy and partial hydrolysates likely chosen due to fussiness
  - Note that “food enjoyment” was identical in all groups at 2 yrs
- Differences in microbiome also found based on CHO source
- Another study showed faster weight gain with non-lactose CHO in infants
- One study demonstrated lower glucose, higher insulin in babies after single feeding of CSS containing compared to lactose-based formula

Hampson, Hailey E et al.” *Nutrients* vol. 14,5 1115. 7 Mar. 2022, Jones RB, et al.. *Gut Microbes*. 2020;12(1):1813534, Kong et al J Nutr 2021;151:1572-80. Slupsky CM, et al. Sci Rep. 2017;7(1):3640

Increased rate of obesity with reduced lactose formula in California

Very recently a report in primarily Hispanic WIC clients suggested increased rates of obesity at 2 years in those fed lactose-reduced formula with CSS

Study participant age, y	RR[3]		
	Any CSSF	No CSSF	*P* value
Full sample			
2	1.10 (1.02, 1.20)	1.00 (ref)	0.02
3	1.08 (1.02, 1.15)	1.00 (ref)	0.01
4	1.07 (1.01, 1.14)	1.00 (ref)	0.01
Hispanic			
2	1.10 (1.01, 1.20)	1.00 (ref)	0.03
3	1.08 (1.01, 1.15)	1.00 (ref)	0.02
4	1.08 (1.02, 1.15)	1.00 (ref)	0.01

Anderson, Whaley and Goran, Am J Clin Nutr 2022;116(4):1002–9

Some specific issues: CHO effects on metabolism?

- Families (and internet commentators) often confuse CSS (glucose polymers) with high fructose corn syrup
- In Europe, CSS may be used only in non-organic formulas, nearly all formulas use lactose
- Clinical significance of current research not definitive but provide evidence for concern about use of lactose-reduced formula
- Of note, is that there are virtually no known or likely benefits of not using lactose as CHO source in infant formulas for term infants
- Even protein hydrolysates may consider using lactose except for infants with severe diarrhea

Seed oils!!!

- They are in infant formulas in order to provide EFA in proper ratios. Some TODDLER formulas don't always have them, but use coconut oil and palm olein in place of them (fruit and vegetable oils, not true seed oils)
- Small variations and decreases in amount based on use of whole milk fat, but not a large decrease. About ¾ of the fats in these formulas derives from vegetable sources
- This is a deflection and confusion, nothing to do with country of origin or quality and safety of an infant formula. There is no evidence that seed oils are harmful in infant formulas.

Need education about this stuff: Maybe Dr. Grok?

Today's focus is on seed oils. Look in your fridge; you'll probably see them hiding everywhere – even in "healthy" items, from organic humus to artisanal oat milk. Today, almost everyone is falling victim to hidden inflammatory oils, which are wrecking our health.

These seed (or vegetable) oils include canola, corn, soybean, grapeseed, safflower, peanut, palm, and cottonseed. Look at almost any label, and you'll almost certainly see one of them.

https://calleymeans.com/2024/01/02/scan-the-label-for-seed-oils/

Hi Grok: Is palm olein in infant formula a seed oil?

Palm olein is not a seed oil. It's a liquid fraction derived from palm oil, which is extracted from the fruit of the oil palm tree (*Elaeis guineensis*). Seed oils come from seeds like canola, sunflower, or soybean, while palm olein is from the fleshy part of the palm fruit. In infant formula, palm olein is often used to mimic the fat profile of breast milk, particularly its palmitic acid content, though its use is debated due to potential effects on calcium absorption.

DHA

- DHA is not a required ingredient in US formulas but is found in ALMOST all currently marketed ones. “The average DHA content of all formula purchased in US was: 12.6 mg/100 kcal. This DHA concentration is far below the minimum required DHA concentrations of infant formula (Stage 1) set by the European Commission of 20 mg/100 kcal” (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10143847/)
  - I tend to support the European view, but this is not settled science
  - DHA should always be given in appropriate ratio with ARA to ensure growth
  - More common for European formulas to use fish oil as a source, in US mostly use algal source. Not clear which is better/safer but probably doesn’t matter as mercury contamination of fish oil used in formulas is likely very minimal

Other nutrient issues: Minerals

TABLE F-3 Infant Formula Minerals and Trace Elements Content Standards

		CODEX		US		AU/NZ		Canada		EU	
Minerals and Trace Elements	Unit of Measurement	Minimum Level	Maximum Level	Minimum Level	Maximum Level	Minimum Level	Maximum Level	Minimum Level	Maximum Level	Minimum Level	Maximum Level
Calcium	mg/100 kcal	50	N/A	60	N/A	N/A	N/A	50	N/A	50	140
	mg/100 kJ	12	N/A	N/A	N/A	12	N/A	N/A	N/A	12	33.5
Phosphorus	mg/100 kcal	25	N/A	30	N/A	N/A	N/A	25	N/A	25	90
	mg/100 kJ	6	N/A	N/A	N/A	6	25	N/A	N/A	6	21.5
Calcium/ Phosphorus Ratio	N/A	1:1	2:1	1.1:1	2:1	1.2:1	2:1	1.2:1	2:1	1:1	2:1
Magnesium	mg/100 kcal	5	N/A	6	N/A	N/A	N/A	6	N/A	5	15
	mg/100 kJ	1.2	N/A	N/A	N/A	1.2	4	N/A	N/A	1.2	3.6
Iron	mg/100 kcal	0.45	N/A	0.15	3	N/A	N/A	0.15	N/A	0.3	1.3
	mg/100 kJ	0.1	N/A	N/A	N/A	0.2	0.5	N/A	N/A	0.07	0.31

Closer look at iron

Table 1

International regulatory bodies requirements for iron and DHA in infant formula.

Regulatory Body	Age (Months)	Formula Type	Minimum	Maximum
Iron (mg/100 kcal)				
Food and Drug Administration	0–12	All	0.15 [1]	3.0
European Commission	0–6	Non-Soy-Based	0.3	1.3
	6–12	Non-Soy-Based	0.6	2.0
	0–6	Soy-Based	0.45	2.0
	6–12	Soy-Based	0.9	2.5

Who is right about iron??

Evidence supports European, not US approach

Adolescents who received iron-fortified formula as infants from 6 to 12 months of age at levels recommended in the US had poorer cognitive outcomes compared with those who received a low-iron formula. (Gahagan et al)

S. Gahagan, E. Delker, E. Blanco, R. Burrows, B. Lozoff, Randomized controlled trial of Iron-Fortified versus Low-Iron Infant Formula: developmental Outcomes at 16 years, J Pediatr 212 (2019) 124–130, e1.
And M. Domellof, C. Braegger, C. Campoy, V. Colomb, T. Decsi, M. Fewtrell, et al., Iron requirements of infants and toddlers. J Pediatr Gastroenterol Nutr, 2014 58 (1) (2014) 119–129.
[19] E.F.S.A. NDA Panel, (EFSA Panel on Dietetic Products Nutrition and Allergies). Scientific opinion on the essential composition of infant and follow-on formulae, EFSA J 12 (7) (2017) 3760.

Other issues related to new formulas

- Equity issues
  - If novel products including bioactives lead to improved clinical outcomes, should they always be included in WIC versions?
  - Do we need to reassess the Infant Formula Act/FDA guidance list and levels of nutrients regulated?
  - Most of the recently imported formulas have bioactives, will they continue to be available to WIC recipients?
- Concerns re: sourcing and contamination including environmental issues
- Effects on shelf life, transport, mixing characteristics
- Specific risks associated with preterm or immunocompromised infants

Goat milk-based formula?

- Allowed in Europe based on EFSA review of literature. Also allowed in antipodean countries (Aus/NZ)
  - Several recently imported infant formula in US use goat-milk protein
  - One study in 2014 found similar growth, biochem outcomes, no allergy or other noted benefits of goat's milk-based formula
- Additional study in 2015 found similar results, no benefit in crying, stool patterns
- No safety concerns. All are fully folate-fortified
- Currently have 3 infant formulas in use in the US that are goat milk-protein based and registered with FDA (one permanent, two pending permanent registration)

Zhou et al British Journal of Nutrition 2014, 111, 1641–165 ,
Xu M, Wang Y, Dai Z, Zhang Y, Li Y, Wang J. Food Nutr Res. 2015 Dec 10;59:28613.

Vegan protein formula

- Formula approved in Australia (also sold in other Asian countries) using pea and rice protein source
  - Approval in UK/Europe appears pending
  - Not clear if seeking registration in US (the FDA does not publish pending requests)
- A rice base formula is also marketed in EU countries
  - Regulatory status a bit unclear, but appears to be approved as a special nutritional product (hydrolyzed rice protein) https://www.sciencedirect.com/science/article/pii/S0929693X19300570
  - An important distinction is that specialized formulas in the EU are categorized as: “Foods for special medical purposes (FSMPs)” not as infant formulas and require an indication for their use, although it does not appear that this has any strict enforcement in many EU countries

Organic/GMO free

- European and some US formulas often contain organic designation which may have different meanings
- Organic label dictates non-GMO; however non-GMO label does not dictate organic ingredients
- Toxic exposures can occur from a variety of aspects of any type of formula production
- No strong evidence of risk to limited GMO exposure that may occur in some (esp soy) non-GMO-free formulas
- Substantial added costs to some of these designations, but families often choose them
- FDA needs to continuously work to establish standards for all infant nutrition products for potentially toxic exposures

de Mendonça Pereira BF, et al. Compr Rev Food Sci Food Saf. 2020 Jul;19(4):1378-1396

A2 milk

- A2 milk refers to milk from cows who naturally genetically make A2 casein protein. Single amino acid difference from A2 beta-casein. Claimed to be more similar to human milk casein, less “toxic” metabolites. Data are not compelling in adults
- Limited studies NOT in infants suggest better tolerance to A2 protein
- Unaware of ANY studies in neonates/infant formula fed infants comparing A2 vs others
- US produced and international formulas have included A2-only milk
- Controlled trials would be valuable to assess A2 milk, however, it is not a substantial cost issue and not harmful

Sheng X, Li Z, Ni J, Yelland G.. J Pediatr Gastroenterol Nutr. 2019 Sep;69(3):375-382.

A few other variations of note

- Postbiotics after bacterial fermentation producing bioactives
- Clean label designation
- Whole cow milk fat instead of vegetable fat is common, BUT some vegetable fat is generally included to achieve needed essential fatty acid levels
- Sourcing of DHA/ARA using non-hexane purified algal source
  - Some European formulas use fish oil, but generally most formulas use algal sourced DHA
- Absence of emulsifier – no carrageenan in European formulas per EFSA regulations
- Note that many of these are found in recently imported formulas

Operation Stork Speed

The FDA uses its authorities, both longstanding and newly granted, to uphold the safety, nutritional adequacy and resilience of infant formula and the infant formula supply. The FDA is:

- Starting the nutrient review required by law by issuing a Request for Information in the coming months to start the first comprehensive update and review of infant formula nutrients by the FDA since 1998
- Increasing testing for heavy metals and other contaminants in infant formula and other foods children consume
- Extending the personal importation policy
- Encouraging companies to work with the FDA on any questions regarding increased transparency and clearer labeling
- Communicating regularly with consumers and industry stakeholders as significant developments occur to ensure transparency, including information regarding nutrients and health outcomes
- Collaborating with the National Institutes of Health and other scientific bodies to address priority scientific research gaps regarding short- and long-term health outcomes associated with formula feeding in infancy and childhood across the lifespan

The FDA remains committed to infant formula safety and nutritional quality and is taking all actions to ensure the U.S. infant formula supply ranks best in the world.

https://www.hhs.gov/press-room/operation-stork-speed.html

FDA meeting on Stork Speed: June 4, 2025

Meeting held at FDA with scientific experts
Discussed a range of formula related topics from RFI put out by FDA
Also covered issues of marketing
Video available: https://www.youtube.com/live/MmE6rlMJdwA

RFI from FDA about nutrients closed 9/11/2025. Next steps unclear?

Preprints available:

https://www.preprints.org/manuscript/202508.0225/v1 (Abrams, S.; Brenna, J.; Clemens, R.; Cohran, V.; Du, N.; Gilbaugh, A.; Goran, M.; Guild, A.; A Kerner, Jr, J.; B Knudsen, T.; Krishna, S.; Sentongo, T. FDA Expert Panel on Infant Formula "Operation Stork Speed" June 2025: Part 1, Nutrient Considerations. *Preprints* **2025**, 2025080225.)

https://www.preprints.org/manuscript/202508.0369/v1

https://www.preprints.org/manuscript/202508.0257/v1

Full remarks by me (35 minutes): https://www.youtube.com/watch?v=Q1NdGp8VVWU

Are European formulas “better” than American ones? Parents ask!

- Confused question: All formulas are “global” with raw materials sourced globally (e.g. vitamin premixes)
- US currently imports many formulas registered by FDA produced in Europe as well as Australia/NZ with FDA registration and supervision
- Standards can be different, but characteristics (e.g. whole milk fat inclusion) sought be some families are found in these formulas more often than in US based formulas. There isn’t anything special that you can’t obtain via FDA registered formulas from both US and other countries
- Use of non-FDA registered formulas is problematic, may not be safe and should be discouraged

Questions?

Post your Questions in the Q&A !

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