



Developing Consensus on Evaluations for Functional Ingredients in Infant Formula

From Human Milk Components to Clinical Evidence

A Workshop

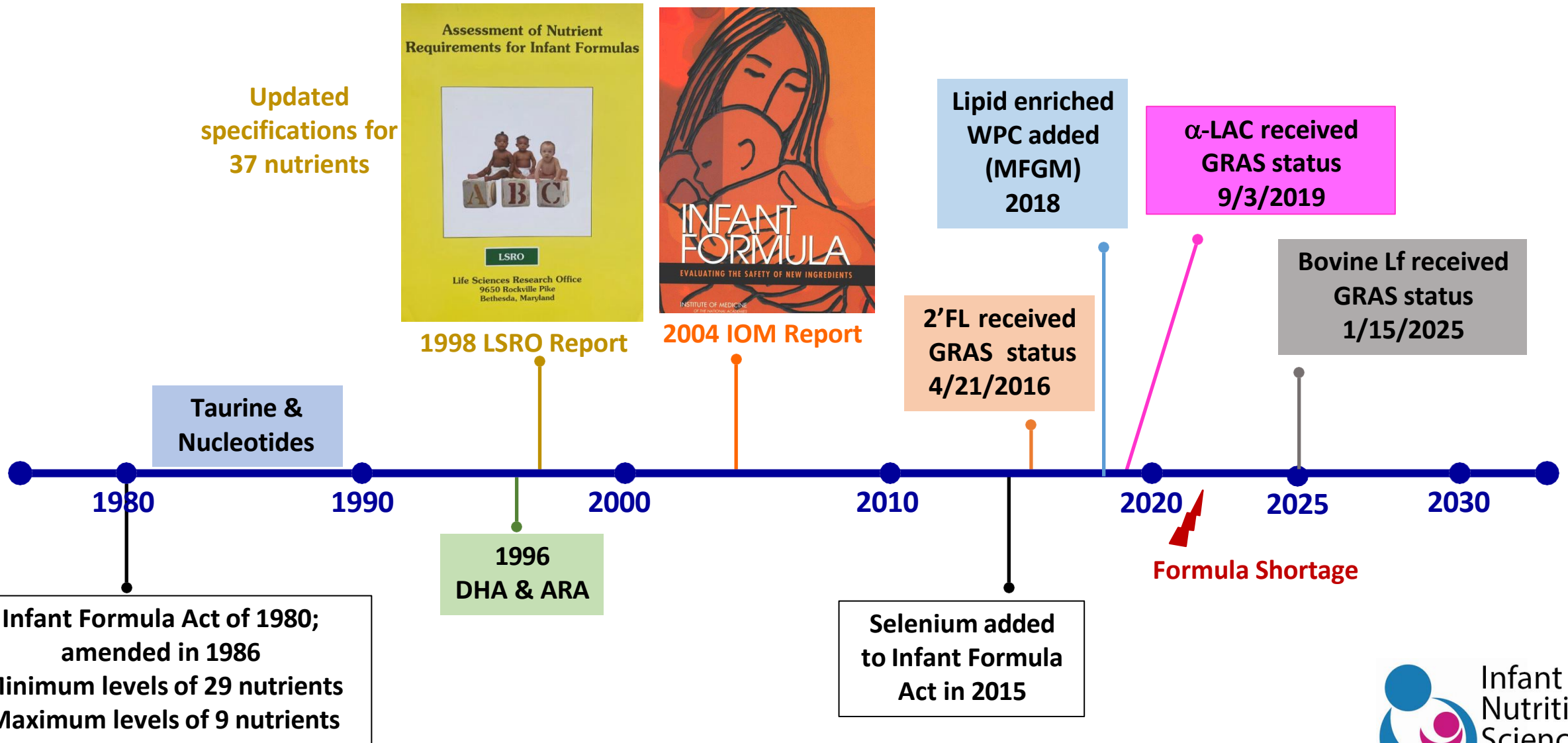


March 2-3, 2026



Infant
Nutrition
Science
Coalition

Setting the Stage: Regulatory and Formula Additions



Setting the Stage: DGAs, Workshops, NIH and NAM



Included B-24 mos, pregnancy and lactation

NIH-FDA Workshop

www.nature.com/pr
Pediatr Res 2023; 94: 420-422

COMMENT OPEN
 Science surrounding the safe use of bioactive ingredients in infant formula: federal comment

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www.jpeds.com • THE JOURNAL OF PEDIATRICS
WORKSHOP/SYMPOSIUM SUMMARY 2023; 255: 20-41

Summary of the Joint National Institutes of Health and the Food and Drug Administration Workshop Titled “Exploring the Science Surrounding the Safe Use of Bioactive Ingredients in Infant Formula: Considerations for an Assessment Framework”

Sharon M. Donovan, PhD¹, Steven A. Abrams, MD², Meghan B. Azad, PhD^{3,4}, Mandy B. Belfort, MD, MPH⁵, Lars Bode, PhD⁶, Susan E. Carlson, PhD⁷, David C. Dallas, PhD⁸, Kasper Hettling, PhD⁹, Kirsi Järvinen, MD, PhD¹⁰, Jae H. Kim, MD, PhD¹¹, Carlito B. Lebrilla, PhD¹², Michelle K. McGuire, PhD¹³, David A. Sela, PhD¹⁴, and Josef Neu, MD¹⁵

HM as a Biological Matrix

The American Journal of
CLINICAL NUTRITION
 A Publication of the American Society for Nutrition

MAY 2023 • VOLUME 117 • SUPPLEMENT 1

Breastmilk Ecology: Genesis of Infant Nutrition: BEGIN Project

This “Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN)” Project is a multidisciplinary effort to understand the biological system and human factors that impact the ecology of human milk. The project includes a report from “Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Working Group 1: Infant feeding”, a report from “Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Working Group 2: Infant feeding”, a report from “Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Working Group 3: Infant feeding”, a report from “Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Working Group 4: Infant feeding”, a report from “Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Working Group 5: Infant feeding”, and a report from “Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Working Group 6: Infant feeding”.

BEGIN Project

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Check for updates

OPEN ACCESS

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An expert panel on the adequacy of safety data and physiological roles of dietary bovine osteopontin in infancy

Stephen A. Fleming^{1*}, Sarah M. Reyes^{2*}, Sharon M. Donovan³, Olle Hernell⁴, Rulan Jiang⁵, Bo Lönnerdal⁶, Josef Neu⁷, Lawrence Steinman⁷, Esben S. Sørensen⁸, Christina E. West⁴, Ronald Kleinman^{9,10} and John C. Wallingford¹¹

NATIONAL ACADEMIES
 CONSENSUS STUDY REPORT

Challenges in Supply, Market Competition, and Regulation of Infant Formula in the United States

NATIONAL ACADEMIES
 CONSENSUS STUDY REPORT

Protein Quality and Growth Monitoring Studies
 Quality Factor Requirements for Infant Formula



The National Academies of
 SCIENCES • ENGINEERING • MEDICINE

CONSENSUS STUDY REPORT

Scanning for New Evidence on the Nutrient Content of Human Milk

A Process Model for Determining Age-Specific Nutrient Requirements

Report of a Meeting
 ASN

Am J Clin Nutr 2022; 115: 570-587

Assessing the safety of bioactive ingredients in infant formula that affect the immune system: recommendations from an expert panel

Emily A Callahan,¹ Talal Chatila,^{2,3} Richard J Deckelbaum,⁴ Catherine J Field,⁵ Frank R Greer,⁶ Olle Hernell,⁷ Kirsi M Järvinen,⁸ Ronald E Kleinman,^{9,10} Joshua Milner,¹¹ Josef Neu,¹² Kinga K Smolen,^{2,3} and John C Wallingford¹³



Stork Speed

Mission and Key Focus Areas

The Infant Nutrition Science Coalition (INSC) brings together scientific experts from **academia, government, and industry** to advance research on human milk and infant nutrition.

Comparative Composition



Examining comparative composition of human milk and formula and ensuring accurate data collection methods.



Physiological Effects

Understanding physiological effects of human milk and formula components and identifying valid preclinical models, including animal models and new alternative methods (NAMs).

Comprehensive Health Markers



Developing comprehensive infant health markers beyond traditional growth measurements.

The INSC is governed by a **tripartite** group of experts who provide strategic oversight and scientific guidance for all activities.

Steering Committee

- **Sharon M. Donovan**, PhD, RD (Co-Chair) – **University of Illinois Urbana-Champaign**
- **Paul Hanlon**, PhD, DABT (Co-Chair) – **Abbott Nutrition**
- **Lindsay H. Allen**, PhD – **USDA/ARS and UC Davis**
- **Douglas Burrin**, PhD – **USDA/ARS and Baylor College of Medicine**
- **Vanessa Castagna**, PhD – **SciPinion**
- **David Dallas**, PhD – **Moore Family Center, Oregon State University**
- **Cindy Davis**, PhD – **USDA/ARS**
- **Barbara Schneeman**, PhD – **UC Davis**
- **Cypress Lynx**, MPH – **ILSI U.S. and Canada**
- **Stephane Vidry**, PhD – **ILSI U.S. and Canada / ILSI Global**

INSC Activities

Scientific Roundtables

Forums to explore foundational scientific questions that support the workshop objectives and the key focus areas of the INSC.

Perspectives Paper

This paper will identify gaps in scientific knowledge through the perspectives of diverse stakeholders and frame the workshop discussion and provide background insights.



Hybrid Workshop

Scheduled for March 2-3, 2026, this workshop will feature a tripartite discussion to address critical considerations related to human milk and infant formula composition, function, and comprehensive markers of normal infant development.

Consensus Paper

As a result of the collaborative discussions at the workshop, the consensus paper will outline key takeaways and strategies for addressing identified gaps.



Beyond

Potential for multi-year initiative, informing scientific advancements in infant nutrition and closing the gaps in human milk science.

Learn more: inscoalition.org

Roundtable #1: Establishing Scientific Consensus



The objective of this workshop is to identify areas of **consensus and divergence**.

To support this objective, it is important for us to have a shared definition of what consensus means.

The INSC hosted a Roundtable to clarify what consensus means, and discuss different approaches to documenting consensus.

The key takeaways from that Roundtable to keep in mind during this workshop are:

- **Consensus is context-dependent.** What it means to have consensus depends on the question being asked and the data that is used to support it.
- **Consensus is not equivalent to unanimity.**
- **Structured, evidence-based methods reduce bias and build trust.**
- **Diverse expertise strengthens outcomes.**
- **Consensus is a process, not an endpoint.** Science is constantly evolving and never settled. Must remain open to revision as new evidence, methods, and perspectives emerge; scientific uncertainties should not be confused with a lack of consensus.

Workshop Planning Committee



- **Douglas Burrin, PhD – USDA/ARS and Baylor College of Medicine**
- **Vanessa Castagna, PhD – SciPinion**
- **David Dallas, PhD – Moore Family Center, Oregon State University**
- **Cindy Davis, PhD – USDA/ARS**
- **Kasper Hettinga, PhD – Wageningen University**
- **Berthold Koletzko, MD, PhD – Ludwig Maximilians Universität Munich**
- **Devon Kuehn, MD – ByHeart**
- **Sarah Maria, MS – Mead Johnson Nutrition**
- **Cypress Lynx, MPH – ILSI U.S. and Canada**
- **Stephane Vidry, PhD – ILSI U.S. and Canada / ILSI Global**

Workshop Structure – Pre-Workshop



- Panelists were blinded to each other and responded to **2 rounds of charge questions** (developed by Workshop Planning Committee) using the SciPinion platform.
- SciPinion generated a summary report of **consensus, divergence, and confidence levels** for each question, which was reviewed and analyzed by the Workshop Planning Committee.
- This report guides the session framing and moderated discussions.

Workshop Objectives

- The workshop will explore foundational scientific questions across three topic areas:
 - Human milk as a guide for considering the inclusion of components in infant formula
 - Preclinical models used to evaluate ingredients
 - Clinical endpoints for assessing the safety and suitability of ingredients
- The end goal is to identify areas of **consensus and divergence**, highlight **key evidence gaps and research needs**, and inform future **research prioritization**.

Key Definitions

- **Safety:** Reasonable certainty...that a substance is not harmful under the intended conditions of use [21 CFR 170.3]
- **Suitability:** Suitable as the sole source of nutrition with benefits similar to those observed in breastfed populations [CODEX CXS 72-1981, Sec. 3.2]
- **Optional Ingredient:** Non-nutrient ingredients intended to mimic the composition and biological activity of human milk; not considered essential nutrients [CODEX CXS 72-1981]
- **Function:** Exerts effects beyond nutrition; modulates biological systems or processes [Human Milk Model, 2026]
- **Benefit:** An outcome resulting from addition of a new ingredient whereby the infant receives a health and/or developmental benefit compared to formula without the ingredient [Callahan et al. 2022]

Roundtable #2: Defining Bioactive

“Bioactive” is a term that has been used to describe food ingredients that have a physiological effect in the consumer. The consequence of an ingredient being defined as “bioactive” can be context dependent.

Evaluation of safety

All food ingredients have the potential to produce physiological effects in consumers, and these physiological effects must always be considered when evaluating safety.

Defining an ingredient as “bioactive” does not change how the safety of an ingredient would be evaluated.

Justification for addition

Defining an ingredient as “bioactive” could inform the justification for adding an ingredient to infant formula.

- Essential nutrients are “bioactive” by nature.
- Functional ingredients should be “bioactive”, otherwise there would not be a purpose for their addition
- Technological additives do not need to be “bioactive”. Their justification is tied to an effect in the product itself.

Definitions: Infant formula ingredient categories



This workshop will utilize differentiation of infant formula ingredients into three categories based on the purpose of their addition:

- **Functional ingredients:** Ingredients that exert a functional effect on infant health incremental beyond a nutritive effect.
 - Examples: DHA/ARA, Lactoferrin, Oligosaccharides, Probiotics
 - **Functional ingredients is the term that will be used in this workshop instead of “bioactive” based on the outcome of Roundtable #2**
- **Essential nutrients:** Ingredients that provide energy or are needed for growth, development and maintenance of life. Absence in the diet will cause nutritional deficiency.
 - Examples: Macronutrients, Vitamins, Minerals
- **Technological additives:** Ingredients added for the purpose of providing a functional effect in the product itself.
 - Examples: Antioxidants, Stabilizers, Acidity regulators

Regulatory Steps for Novel Formula Ingredients



United States regulations (21 CFR 106) establish several requirements that apply to all infant formula products that include novel ingredients.

FDA Review of Ingredients

The FDA mandates that any novel ingredient must have undergone formal FDA review through the Food Additive or FDA GRAS Notification (GRN) process. Self-GRAS determination for novel infant formula ingredients is not permitted.

FDA confirms this during the FDA Infant Formula Review (IFN) process, where they confirm the authorization of all ingredients.

Clinical study (GMS)

An infant formula that includes a novel ingredient is required to have undergone clinical evaluation in a Growth Monitoring Study (GMS).

The parameters of the GMS are defined in the regulation including duration and endpoints (length, weight, head circumference).

Post-Market Surveillance

Infant formula manufacturers are required to maintain records of any complaints and are required to investigate and report to the FDA in the case there is a causal relationship between a particular formula and an adverse outcome.

This requirement applies to infant formula products that include novel ingredients.

Current Assessment Pathway



The FDA has two offices involved in the review of infant formulas and infant formula ingredients:

- **OFAS (Office of Food Additive Safety):** evaluates individual ingredient safety — GRAS Notification Program or Food Additive Petition Process
- **ONFL (Office of Nutrition and Food Labeling):** evaluates finished formula nutritional adequacy and quality factors — Growth Monitoring Study (infant clinical)

Neither office specifically evaluates whether an ingredient provides a function in infant formula that brings the formula closer to the physiological function of the gold standard for infant nutrition, human milk.



Infant
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Perspectives Paper



Opportunities, Challenges, and
Key Questions

Perspectives Paper – Human milk as a model for next-generation infant formula: opportunities and challenges

- Need to make infant formula more similar to human milk to improve infant health outcomes
- **Opportunities:** Known differences between HM and IF
 - Macronutrient and bioactive differences
- **Opportunities:** Technologies to improve IF
 - Milk source
 - Milk processing
 - Milk component concentration
 - Novel ingredient production systems



Perspectives Paper – Human milk as a model for next-generation infant formula: opportunities and challenges



- **Challenges:** Implementing changes in IF composition
 - Selecting novel components & their concentration
 - Determining component synergies
 - Ingredient safety testing
 - As a standalone ingredient
 - Within the food matrix
 - Ingredient functionality testing



1 **Human Milk as a Model for Next-Generation Infant Formula: Opportunities**
2 **and Challenges**
3
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46

Perspectives Paper – Key Questions



Oregon State University
College of Health



- The scientific community needs to reach consensus on answers to key questions:
 1. What are the **key compositional and functional differences** in bioactive components between infant formula and human milk? **(Session 1)**
 2. How to establish **normative or reference ranges for functional human milk components** responsible for healthy infant development, given the inter-individual variability in human milk composition? **(Sessions 1 & 3)**
 3. Given the potential synergistic interactions among human milk components, how can infant formula be designed in the context of the knowledge that **human milk is a complex biological system**? **(Session 1)**

Comparative Composition



Examining comparative composition of human milk and formula and ensuring accurate data collection methods.

Perspectives Paper – Key Questions



Oregon State University
College of Health



4. Should novel human milk-like ingredients with possible function be examined via **additional tests to verify safety beyond traditional toxicology methods** and, if so, how? **(Sessions 2 & 3)**
5. Should infant formula with added novel ingredients with possible function be evaluated for **safety metrics beyond traditional growth non-inferiority studies**? If so, what additional measurements/metrics are needed to determine the impact of novel IF additions appropriately? **(Sessions 2 & 3)**



Physiological Effects

Understanding physiological effects of human milk and formula components and identifying valid preclinical models, including animal models and new alternative methods (NAMs).

Comprehensive Health Markers



Developing comprehensive infant health markers beyond traditional growth measurements.



Session 1

Human Milk as a Guide for Inclusion of Components in Infant Formula



Slido.com (#4190 806)



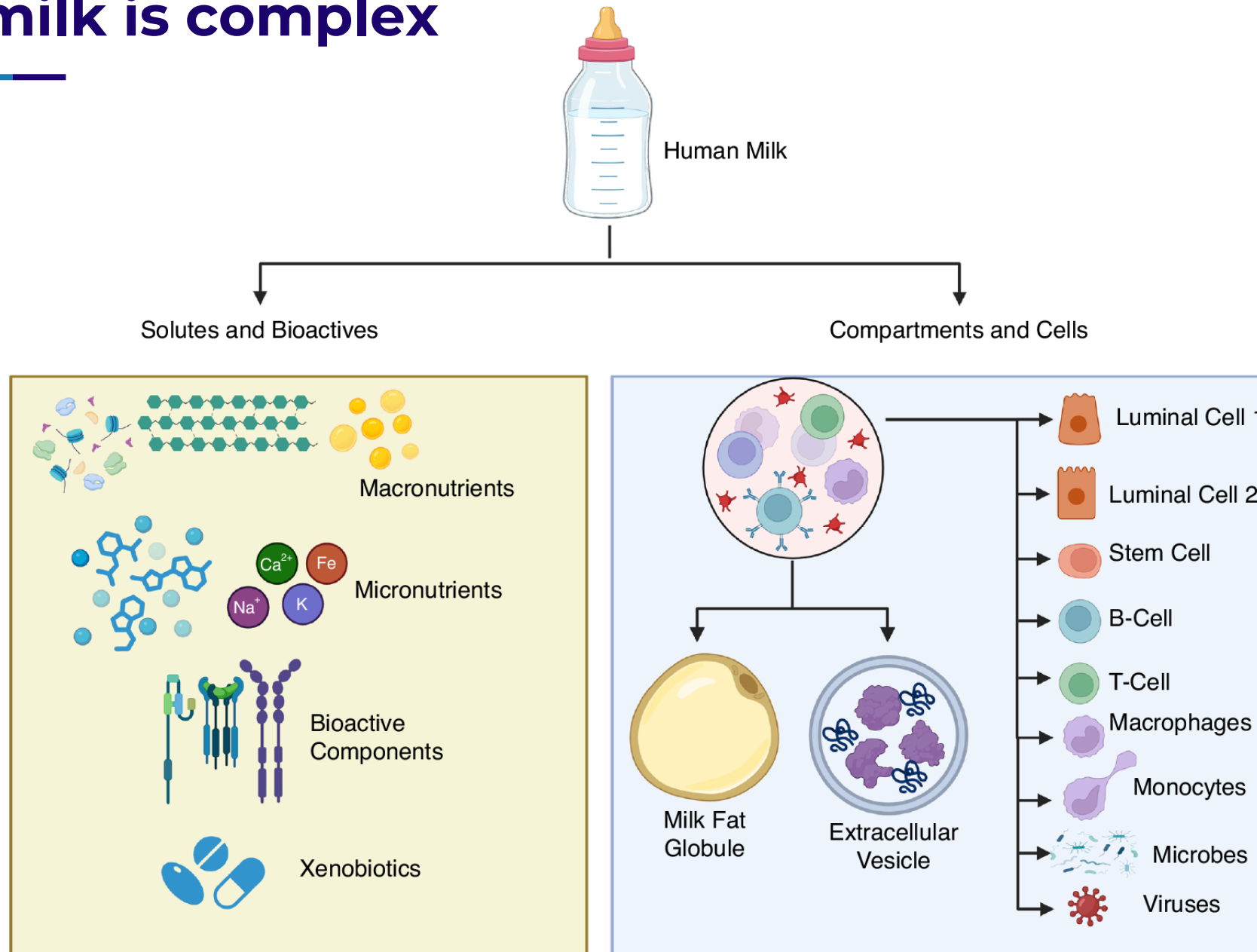
Focus of this Session 1

Current frameworks (GRAS, CODEX, IOM) may not address the specific challenge of functional ingredients.

Focus of this session:

- What scientific criteria should guide the inclusion of functional components in infant formula (IF), using human milk (HM) as reference:
 - Which components?
 - At what level?
 - In what form?

Human milk is complex

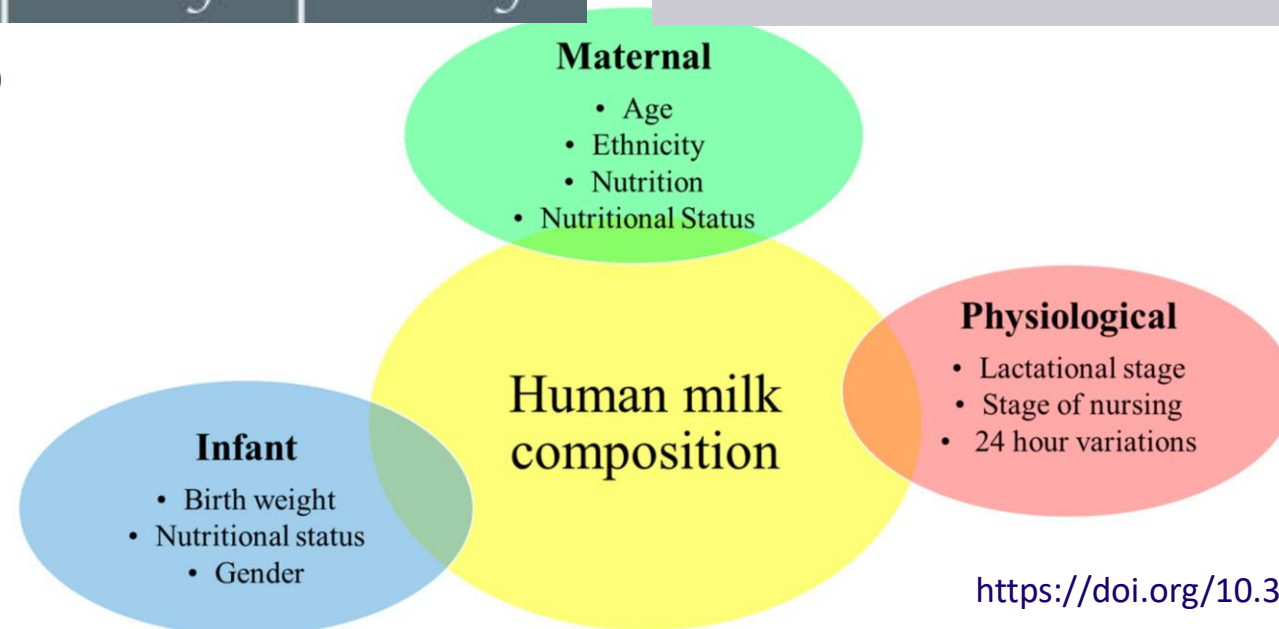


Human milk is dynamic



	Colostrum	Mature milk
Fat	10	35
Protein	20	10
IgA	5	1
Lactoferrin	5	1
Lactose	55	70

Image credit: Amada44 / CC BY-SA 3.0

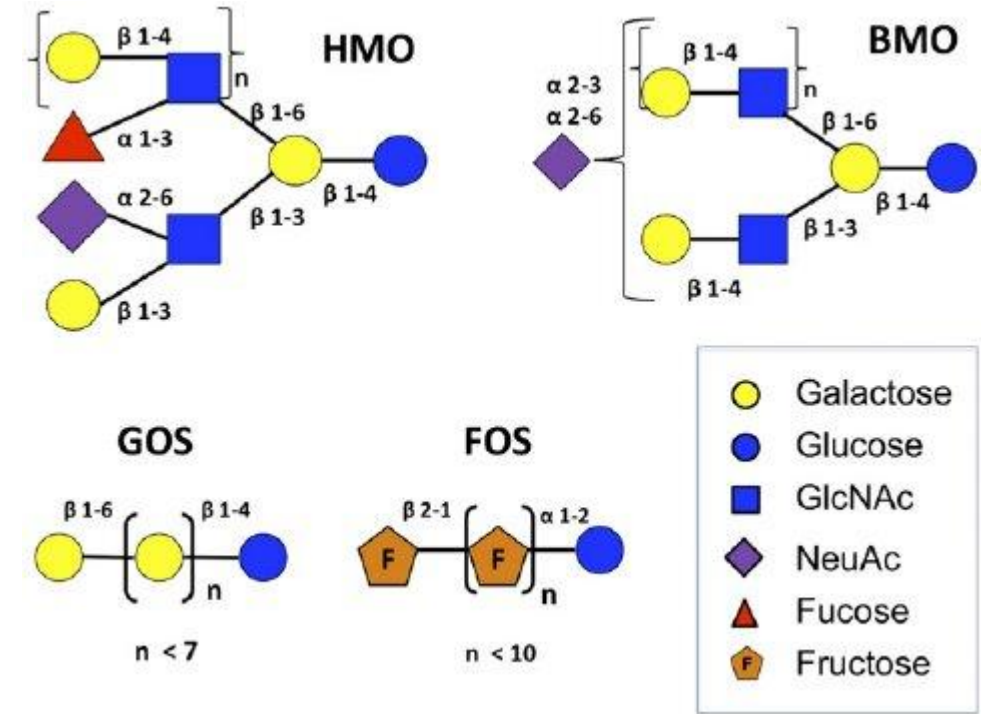
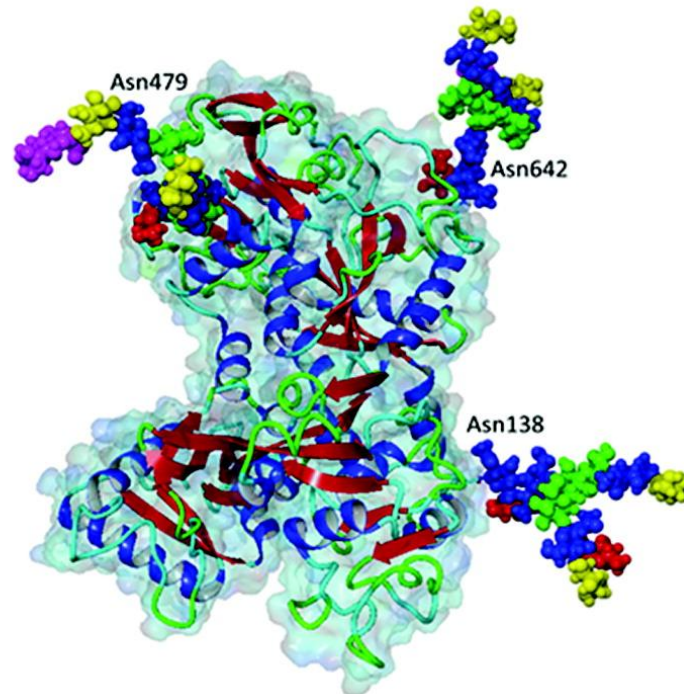
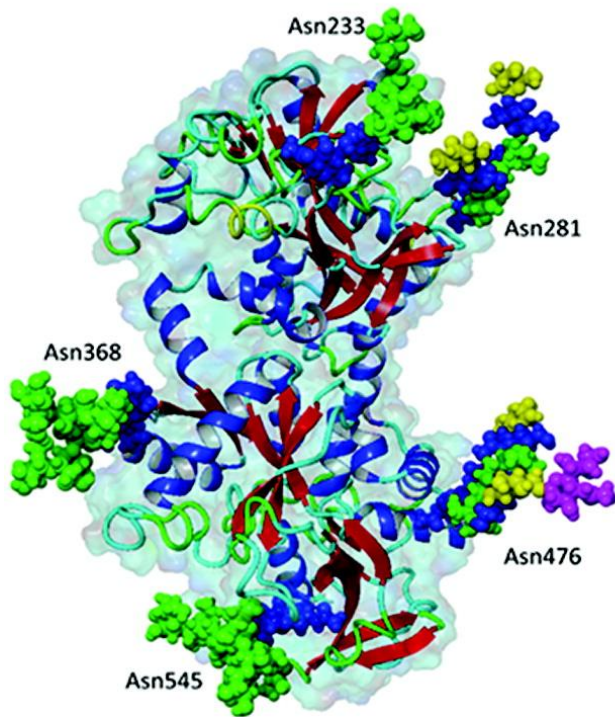


<https://doi.org/10.3390/nu10101379>

Human milk structures are unique

Bovine Lactoferrin

Human Lactoferrin



<https://doi.org/10.1139/bcb-2020-0106>

DOI: 10.3945/an.111.000455

Session 1 Panelists



- **Lindsay Allen**, USDA/ARS; UC Davis
- **Manki Ho**, Novonosis
 - Disclosure: Full-time employee at Novonosis. The content, remarks, and opinions presented here today are her own and do not reflect those of Novonosis.
- **Ashley Patterson**, Mead Johnson Nutrition
 - Disclosure: Employee of Mead Johnson Nutrition.
- **Tony Pavel**, Keller & Heckman
 - Disclosure: He/K&H represent a range of ingredient companies before the FDA, no specific conflict to disclose.

Thread 1: Which Functional Components to add?

Consensus target: can the panel reach agreement on:

- A set of scientific criteria for selection of functional components for potential addition to infant formula and whether different criteria apply for components similar to human milk vs those without a human milk analogue
- Whether presence in human milk constitutes independent scientific justification for inclusion or is mechanistic evidence required
- Whether a multi-tier classification framework, including “recommended” is scientifically preferable to the current binary structure of “optional” and “mandatory”

What should be the Criteria for Inclusion: Which Functional Components Belong in Infant Formula?

- **Q1:** What criteria, beyond safety, should guide the decision to pursue a human milk component for formula inclusion?
- **Q2:** Is a mechanistic rationale a scientific prerequisite, or can other outcomes data substitute for it?

S1T1.1 - Is mechanistic understanding of a functional ingredient important for selection as a candidate for addition to IF?

039

This is not a prerequisite for a candidate IF ingredient.



Only a prerequisite for ingredients that are functionally similar to HM components



Only a prerequisite for ingredients that are structurally similar to HM components



This should be a prerequisite for any functional ingredient



What should be the Criteria for Inclusion: Which Functional Components Belong in Infant Formula?

- **Q3:** In the survey, there seems to be support for a “Recommended” category, distinct from “Optional”. Do you agree, and what evidence would be needed to make that distinction?
- **Q4:** Should the standard of evidence for a non-human-milk component that achieves a human-milk-like outcome be higher than, equal to, or qualitatively different from the standard for a structurally identical or similar component?

S1T1.2 - What classification framework best fits novel functional ingredients in infant formula?

040

(1/2)

Binary: optional / mandatory – with functional ingredients as optional category

 8 %

Binary: optional / mandatory – with functional ingredients as mandatory category

 8 %

Binary: optional / mandatory – with functional ingredients in either category depending on the evidence for benefit

 35 %

Tiered: optional / recommended / mandatory required based on evidence

 45 %

No — existing GRAS + growth trial framework is sufficient

 5 %

Thread 1: Which Functional Components to add?

Consensus target: can the panel reach agreement on:

- A set of scientific criteria for selection of functional components for potential addition to infant formula and whether different criteria apply for components similar to human milk vs those without a human milk analogue
- Whether presence in human milk constitutes independent scientific justification for inclusion or is mechanistic evidence required
- Whether a multi-tier classification framework, including “recommended” is scientifically preferable to the current binary structure of “optional” and “mandatory”

Thread 2: What Data Should Set Ingredient Levels?



Consensus target: can the panel reach agreement on:

- Whether mean human milk concentration should be a default starting point, an upper bound, or neither
- How variability in milk composition (between mothers, countries, lactation stages, etc.) should be used for determining levels

What human milk data should guide target levels for functional ingredients in infant formula?

- **Q1:** When using human milk data to set a target level for a formula ingredient, how should the field handle variability?
- **Q2:** Is a dual-level standard (minimum effective dose and maximum safe limit) scientifically appropriate and feasible for functional ingredients?
- **Q3:** Can human milk levels and the substantial variation between mothers be used as guidance for levels to move into preclinical and clinical studies to demonstrate safety?

S1T2 - When using human milk data to set a target level for a formula ingredient, how should the field handle variability (between mothers, countries, lactation stages, etc.)?

0 3 6

(1/2)

Use the global mean across all available data

 3 %

Use the median value to reduce the influence of outliers and skewed distributions

 33 %

Stratify data by relevant factors and set multiple targets

 56 %

Use the upper range of observed values to ensure adequacy for nearly all infants

 11 %

Do not use human milk composition directly

 11 %

Thread 2: What Data Should Set Ingredient Levels?



Consensus target: can the panel reach agreement on:

- Whether mean human milk concentration should be a default starting point, an upper bound, or neither
- How variability in milk composition (between mothers, countries, lactation stages, etc.) should be used for determining levels

Thread 3: Should Structure Match Human Milk?

Consensus target: can the panel reach agreement on:

- Which structural attributes require characterization and comparison to the human milk reference
- Whether sequence identity alone is sufficient for inferring biological equivalence, or whether functional activity confirmation is required

Thread 3: Should Structure Match Human Milk?

When adding a functional ingredient to infant formula, how closely must it match the structural form found in human milk?

- **Q1:** Is comparative structural analysis (amino acid sequence, glycosylation, etc.) a required prerequisite to functional demonstration, or can demonstrated functional activity in validated assays compensate for structural divergence?
- **Q2:** When working with structurally similar components, which study types should be required to demonstrate functional similarity?
- **Q3:** For a protein-based functional ingredient, structural differences from the native human milk form may affect functionality. What structural attributes require characterization before a novel form is considered suitable?

S1T3 - How important is structural identity to human milk for establishing suitability of a novel functional ingredient?

0 3 8

Critical — structural identity is required for biological equivalence

0 %

Important — functional activity data can compensate for structural differences

42 %

Secondary — demonstrated biological function matters more than structure

47 %

Not required — structural variation is acceptable if function is maintained

11 %

Thread 3: Should Structure Match Human Milk?

Consensus target: can the panel reach agreement on:

- Which structural attributes require characterization and comparison to the human milk reference
- Whether sequence identity alone is sufficient for inferring biological equivalence, or whether functional activity confirmation is required



Session 2

Preclinical Models for Evaluating Functional Ingredients

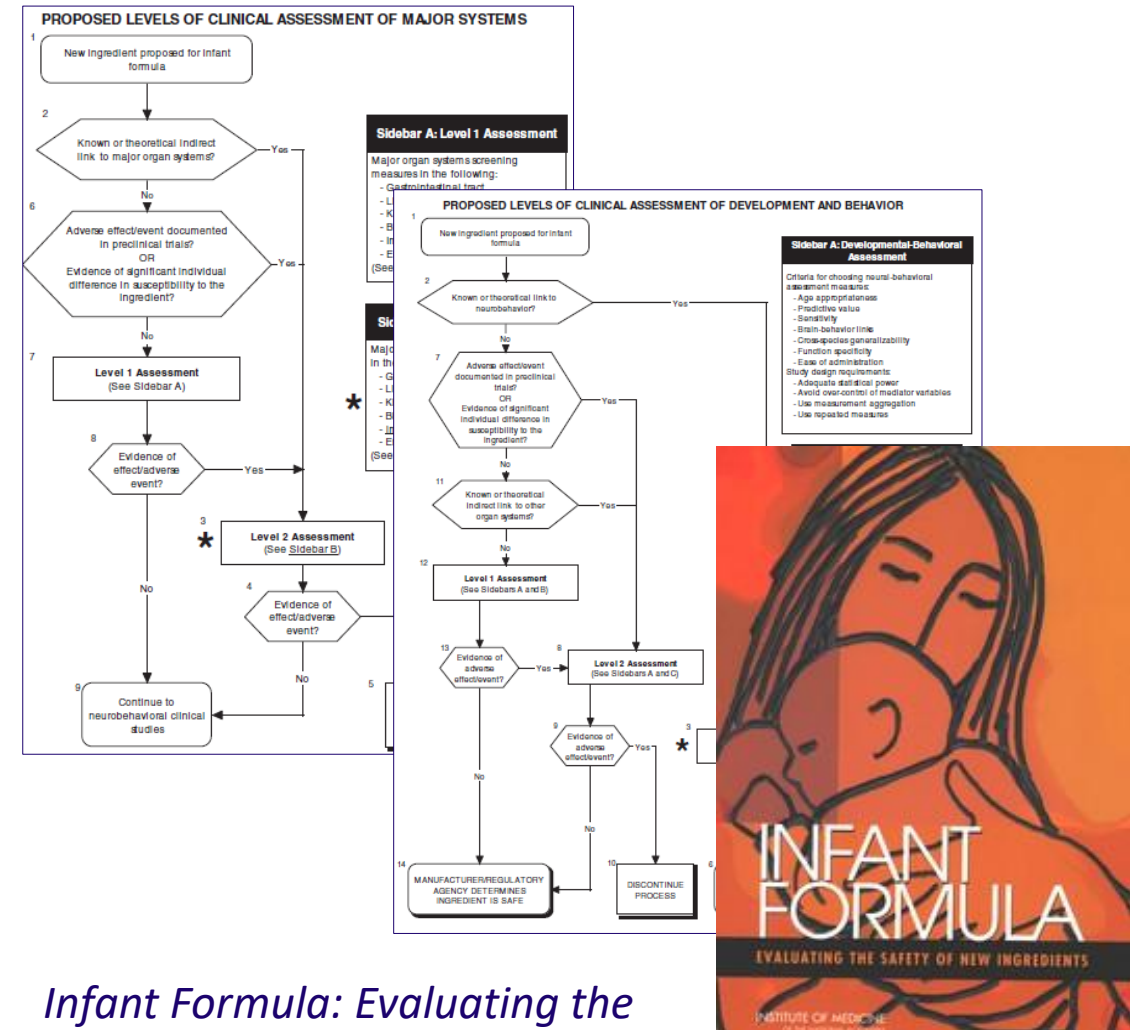


Slido.com (#4190 806)



Infant Formula Ingredient Safety: Why IOM 2004?

- ❑ In 2002, FDA and Health Canada to Institute of Medicine (IOM) to “review and identify gaps in methods currently used to assess the safety of ingredients new to infant formula.”
- ❑ A committee created hierarchical tools (decision trees) providing guidance to what evidence would be necessary to demonstrate the safety of broad range infant formula ingredients.
- ❑ Expert committee report 2004 lays out a systematic approach to the evaluation of the safety of novel infant formula ingredients, based on three major phases including preclinical, clinical, and post-market data assessment.



Infant Formula: Evaluating the Safety of New Ingredients (2004)


EFSA 2017: Infant Assessment Guidance

In 2017, the European Food Safety Authority (EFSA) published guidance on the safety assessment of substances in infant formula.

The EFSA guidance considers the same factors as the IOM guidance and provides a decision tree to guide selection of studies that would be needed to evaluate the safety of infant formula ingredients.

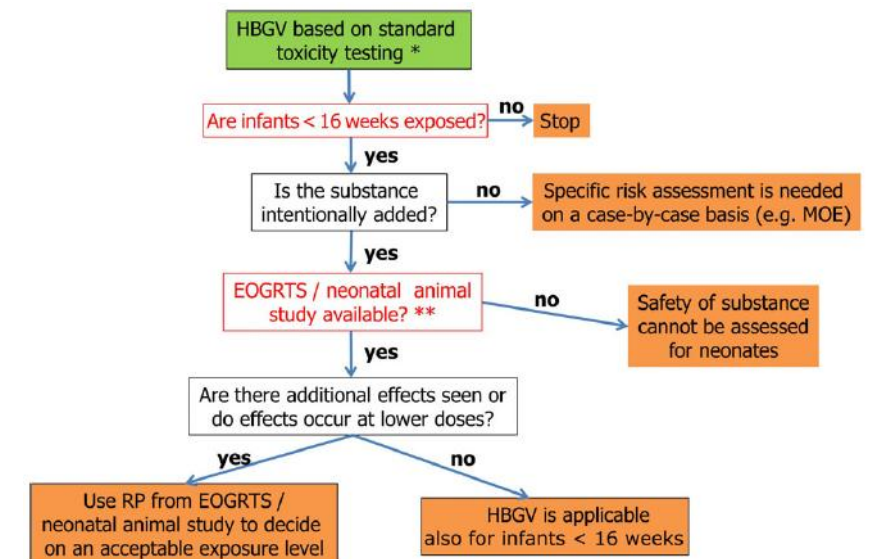
The guidance recommends standard food toxicology studies, with additional studies based on whether the ingredient is absorbed or not. The guidance also specifies that scientific justification can be provided to deviate from the recommended studies

SCIENTIFIC OPINION



ADOPTED: 26 April 2017
doi: 10.2903/j.efsa.2017.4849

Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age



Guiding Principles Infant Formula - IOM 2004

- ❑ Safety: Reasonable certainty...that a substance is not harmful under the intended conditions of use [21 CFR 170.3]
- ❑ Formula represents the sole source of 100% nutrition during 0-6 month life. Zero dietary buffer
- ❑ Infant biology represents immature system undergoing rapid development and growth
- ❑ Human milk is the gold standard for reference
- ❑ Goal new formula ingredients = close performance gap between breastfed vs formula fed infants



IOM 2004: Recommended Approach

The IOM 2004 guidance establishes a substance-specific, tiered approach that evaluates all available information to determine the appropriate studies needed to evaluate safety.

Within each of these four areas, the IOM guidance has a hierarchy of assessment, where a finding in an initial study triggers the need to conduct additional studies.

Characterization

- Ingredients must be fully characterized
- The properties of the ingredient guide study and endpoint selection

Pre-Clinical

- Standard toxicology studies inform whether the ingredient affects specific organ systems
- Evaluation of potential genotoxicity using validated methodology

Clinical

- Standard growth measurements
- Additional clinical measurements of organ system function
- Developmental/Behavioral evaluation

Post-Market

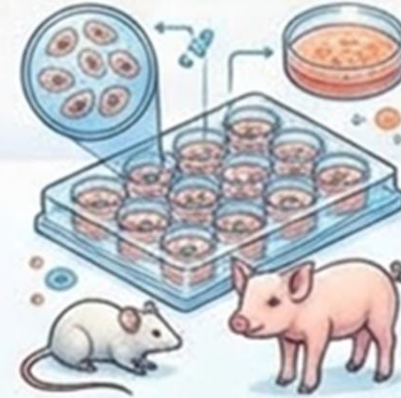
- Passive surveillance
- Review of the literature
- Active surveillance

IOM Two-Tier Classification



Tier 1: Standard

- GRAS Standard
- Chemical/stability tests
- Genotoxicity testing (Ames test, mouse lymphoma)
- Rodent sub-chronic toxicity 90-day
- ADME studies



Tier 2: Moderate

- Ingredient expected structure/function action
- Developmental/organ targeted action
- Neonatal pig/non-human primate
- Transcriptomic/microbiome
- New Approach Methodologies (NAM)

FDA GRAS Notifications for Infant Ingredients



GRAS Notification Database: 147 Notifications covering 46 unique infant formula ingredients

Micronutrients: 2 unique ingredients

- Amino acids: 1 (L-carnitine-L-tartrate)
- Essential vitamin: 1 (calcium L-methylfolate)

Macronutrients: 10 unique ingredients

- Fat: 6 (MCT, Corn oil, Canola oil, Milk fat, High 2-palmitic vegetable oil)
- Milk proteins: 10 (Goat milk, Goat whey, Whole cow milk)
- Mono- or Disaccharides: 2 (Goat lactose, N-acetyl-D-neuraminic acid)

Technological additives: 2 unique ingredients

- Additives: 3 (Sunflower lecithin, CITREM)

Functional ingredients: 32 unique ingredients

- Carotenoids: 2 (Lutein)
- Oligosaccharides: 21 (GOS, FOS, PDX)
- HMOs: 45 (2'-FL, 3-FL, 6'-SL, 3'-SL, LNT, LNnT, LNFP I, DFL)
- Fatty acids: 2 (DHA, ARA, Tuna oil)
- Probiotics: 32 (L. plantarum, B. breve, B. longum, B. bifidum, B. lactis, B. animalis, L. acidophilus, B. coagulans, L. paracasei, L. helveticus, L. fermentum, L. reuteri, L. rhamnosus, S. thermophilus)
- Postbiotics: 1 (B. coagulans)
- Proteins/Peptides: 3 (alpha-lactalbumin, lactoferrin)

FDA GRAS Notifications for Infant Ingredients



Majority of ingredients had this data
 Some ingredients had this data
 No ingredients had this data

Category	Human milk Equiv.	Infant clinical	General tox	Genotox	Piglet
Amino acid	Green	Green	Green	Green	Red
Essential vitamin	Green	Green	Green	Green	Red
Fat	Green	Green	Yellow	Red	Yellow
Milk proteins	Red	Green	Red	Red	Green
Mono- or Disaccharides	Green	Yellow	Yellow	Yellow	Red
Technological additives	Red	Green	Yellow	Green	Red
Carotenoids	Green	Green	Green	Yellow	Red
Oligosaccharides	Red	Green	Green	Yellow	Green
HMOs	Green	Red	Green	Green	Yellow
Probiotics	Red	Green	Yellow	Red	Red
Postbiotics	Red	Green	Green	Green	Red
Proteins/Peptides	Green	Green	Yellow	Yellow	Red

When multiple notifications exist for the same ingredient, scoring reflects the first successful notification

Session 2 Focus

- ❑ What non-clinical evidence is needed to establish that a novel functional ingredient is safe and suitable beyond what IOM Tier 1 requires?**
- ❑ When the IOM framework triggers a Tier 2 investigation because a functional ingredient has physiological activity, what is the appropriate pre-clinical model to use and what endpoints are necessary to show safety and suitability?**
- ❑ For a functional ingredient with physiological activity, is the combination of the GRAS preclinical package and the mandated infant growth trial sufficient evidence base for safety and suitability — or does the physiological activity itself create a category of scientific question that neither assessment was designed to answer?**

Session 2 Panelists



- **Sharon Donovan**, University of Illinois, Urbana-Champaign
 - Disclosure: *Scientific Advisory Boards*: ByHeart, Danone North America, National Dairy Council; *Grant Funding*: NIH, Nestlé Nutrition, Perrigo, Soy Nutrition Institute
- **Paul Hanlon**, Abbott Nutrition
 - Disclosure: Works for Abbott Nutrition, a manufacturer of infant formula products.
- **Dennis Keefe**, Exponent; FDA (*former*)
 - Disclosure: Consulting with Exponent LLC.
- **Claire Kruger**, Spherix Consulting Group
- **Caitlin Vonderohe**, Baylor College of Medicine
 - Disclosure: Research and salary supported by NIH (NIDDK/NHLBI), USDA/ARS, RW Morrison Trust, and Baylor College of Medicine. Student loans have been partially paid by an NIH Loan Repayment Award.
- **Laxmi Yeruva**, USDA/ARS; University of Arkansas for Medical Sciences

Thread 1: Safety and Suitability — What Does Each Require Preclinically? Consensus Target



Goal for this thread is to reach agreement on:

- Working definitions of what “safe” means in the preclinical context — and whether the GRAS standard plus the growth trial constitute sufficient scientific evaluation for physiologically active ingredients
- Working definitions of what “suitable” means in the preclinical context — what non-clinical evidence of physiological function is scientifically meaningful

Thread 1: Safety and Suitability — What Does Each Require Preclinically?

Safety and suitability are distinct constructs requiring different preclinical evidence. Does the existing regulatory baseline address both?

- **Q1:** The US regulatory pathway requires GRAS (safety/harm-detection) and a growth trial (nutritional adequacy). For an ingredient with documented physiological activity — immunomodulatory, microbiome-related, or neurological — is there a category of safety concern that neither was designed to detect?
- **Q2:** Functional ingredients are defined by their biological activity — simultaneously the basis for potential suitability and a potential mechanism of harm. How should the preclinical framework distinguish evidence for safety (harm-detection) from evidence for suitability (activity-confirmation and appropriateness)?

S2T1 - Is there a category of safety concern — specific to a functional ingredient's intended physiological activity — that the existing GRAS preclinical package was not designed to detect?

0 3 6

Yes — physiological activity-specific safety is a distinct scientific gap

 8 %

Possibly — depends on the ingredient's mechanism and activity domain

 53 %

No — IOM Tier 1 is sufficient for the safety of bioactive ingredients

 14 %

Unsure / insufficient data to judge

 25 %

Thread 2: The Mandatory Preclinical Package — What Is Required? Consensus Target

Goal for this thread is to reach agreement on:

- A provisional mandatory preclinical safety package with explicit scientific justification for each element — including acknowledgment of what each study does and does not establish relative to the GRAS standard
- The specific scientific criteria that elevate the neonatal piglet study from substance-specific-optional to substance-specific-required

Thread 2: The Mandatory Preclinical Package

— What Is Required?

What non-clinical studies should every novel functional ingredient be required to complete before the mandated clinical growth trial?

- **Q1:** The 90-day subchronic rat study commands near-universal endorsement but uses adult rodents at superphysiological doses and was not designed for neonatal-specific physiological systems. For an ingredient with physiological activity in neonatal GI, immune, or neurological systems — what can the 90-day rat study establish about the safety of that activity, and what does it leave unaddressed?
- **Q2:** One expert argued the neonatal piglet study should be mandatory, not substance-specific — on grounds that it is the best currently available model for the physiological systems most relevant to infant formula evaluation. The majority favored substance-specific designation. What specific scientific criteria should trigger the neonatal piglet study?

S2T2 - Should the neonatal piglet study be mandatory for all novel functional IF ingredients, or substance-specific?

038

Mandatory for all functional ingredients

3 %

Substance-specific — required when ingredient targets neonatal GI, immune, or neurological systems

55 %

Optional — case-by-case, not triggered by ingredient category

37 %

Not needed — GRAS preclinical package is sufficient

5 %

Thread 3: Model-to-Outcome Matching — Which Model for Which Outcome? Consensus Target

Goal for this thread is to reach agreement on:

- At least two or three provisional model-domain-endpoint pairings — e.g., the appropriate model for a triggered neurocognitive Tier 2 evaluation and for a microbiome suitability investigation
- What the IOM framework currently lacks and what a modernized version should specify

Thread 3: Model-to-Outcome Matching — Which Model for Which Outcome?

The IOM framework triggers Tier 2 investigations but specifies no model. Which preclinical model is appropriate for which physiological outcome?

- **Q1:** The IOM framework specifies that a Tier 1 signal can trigger a Tier 2 neurocognitive evaluation, but provides no guidance on which model is appropriate. Is the neonatal rat behavioral battery scientifically adequate, or does the neonatal piglet provide meaningfully more translatable data? And if the piglet returns a dose-dependent neurological signal — is that finding interpretable without reference data that does not yet exist?
- **Q2:** Should the field develop and publish a standardized model-to-outcome matching framework — specifying for each major physiological domain which model is appropriate, which endpoint set is required, and what standard of reference data exists for interpretation?

S2T3 - For a triggered IOM Tier 2 neurocognitive investigation, what is the most scientifically appropriate preclinical model?

0 2 5

Neonatal rat behavioral battery

8 %

Neonatal piglet (closest developmental parallel for GI-brain axis and brain growth)

84 %

Non-human primate

8 %

New approach method (NAM) — in vitro or organoid

0 %

Thread 4: When Is the Existing Framework Sufficient? Consensus Target

Goal for this thread is to reach agreement on:

- For safety — whether a clean GRAS preclinical package plus a clean growth trial together constitute sufficient clinical evidence for the physiological safety of a functional ingredient
- For suitability — whether the growth trial can support any functional or benefit claim, or whether all such claims require ingredient-specific clinical evidence with activity-matched endpoints

Thread 4: When Is the Existing Framework Sufficient?

A clinical trial is already required. The question is: is the mandated growth trial sufficient for physiologically active ingredients?

- **Q1:** For safety: the existing pathway requires GRAS preclinical data plus a non-inferior growth trial. For an ingredient with documented immunomodulatory activity in a neonatal piglet — is the combination of a clean GRAS package and a clean growth trial sufficient evidence that the ingredient’s physiological activity is safe? Or is safety of physiological activity a distinct question that neither assessment was designed to answer?
- **Q2:** For suitability: the growth trial demonstrates comparable growth and tolerance — it does not demonstrate that a functional ingredient’s intended activity is occurring or beneficial. For an ingredient with an intended microbiome or immune development claim: what clinical evidence is needed, and is it compatible with the growth trial design?

S2T4 - For a novel functional ingredient with documented immunomodulatory activity in a neonatal model: is GRAS preclinical data and a clean growth trial sufficient clinical evidence that the ingredient's physiological activity is safe?

Yes — sufficient if preclinical data is clean and growth trial passes

17 %

Probably — for most ingredients with modest physiological activity

9 %

No — safety of physiological activity requires activity-specific clinical endpoints

48 %

Depends entirely on the ingredient class and level of activity

26 %

Thread 5: Ingredient Interactions and Emerging Technologies

Consensus Target

Goal for this thread is to reach agreement on:

- Agreed criteria for when interaction studies are required, and the scientific unit of evaluation for reformulation scenarios
- A specific near-term validation milestone for neonatal intestinal organoid platforms — what evidence is needed for them to contribute to safety or suitability determinations

Thread 5: Ingredient Interactions and Emerging Technologies

When multiple bioactive ingredients co-occur in formula, and as new production technologies advance, how should the preclinical framework adapt?

- **Q1:** For a reformulation adding a novel functional ingredient to an existing product with multiple bioactive components: is the scientific unit of evaluation the novel ingredient alone, the novel ingredient in combination with existing bioactives, or the finished reformulated formula? Should the answer differ for safety vs. suitability questions?
- **Q2:** What validation evidence would be needed before a neonatal intestinal organoid assay could contribute meaningfully to a safety or suitability determination? Could a validated neonatal organoid platform eventually substitute for any component of the current IOM Tier 1 or Tier 2 package, reducing requirements for whole-animal studies?

S2T5 - For a reformulation adding a novel functional ingredient to an existing multi-ingredient formula, what is the appropriate scientific unit of evaluation?

0 2 9

The novel ingredient alone

3 %

The novel ingredient in combination with existing bioactives

0 %

The finished reformulated formula as a whole

79 %

Depends — no single unit appropriate across all IF ingredients

17 %



Session 3

Clinical Endpoints for Evaluating Safety and Suitability of Ingredients in Infant Formula



Slido.com (#4190 806)



Key Definitions

- **Safety:** Reasonable certainty...that a substance is not harmful under the intended conditions of use [21 CFR 170.3]
- **Suitability:** Suitable as the sole source of nutrition with benefits similar to those observed in breastfed populations [CODEX CXS 72-1981, Sec. 3.2]
- **Optional Ingredient:** Non-nutrient ingredients intended to mimic the composition and biological activity of human milk; not considered essential nutrients [CODEX CXS 72-1981]
- **Function:** Exerts effects beyond nutrition; modulates biological systems or processes [Human Milk Model, 2026]
- **Benefit:** An outcome resulting from addition of a new ingredient whereby the infant receives a health and/or developmental benefit compared to formula without the ingredient [Callahan et al. 2022]

Definitions: Infant formula ingredient categories



This workshop will utilize differentiation of infant formula ingredients into three categories based on the purpose of their addition:

- **Essential nutrients:** Ingredients that provide energy or are needed for growth, development and maintenance of life. Absence in the diet will cause nutritional deficiency.
 - Examples: Macronutrients, Vitamins, Minerals
- **Functional ingredients:** Ingredients that exert a functional effect on infant health incremental beyond a nutritive effect.
 - Examples: DHA/ARA, Oligosaccharides, Probiotics
- **Technological additives:** Ingredients added for the purpose of providing a functional effect in the product itself.
 - Examples: Antioxidants, Stabilizers, Acidity regulators

Regulatory Steps for Novel Formula Ingredients

United States regulations (21 CFR 106) establish several requirements that apply to all infant formula products that include novel ingredients.

FDA Review of Ingredients

The FDA mandates that any novel ingredient must have undergone formal FDA review through the Food Additive or FDA GRAS Notification (GRN) process. Self-GRAS determination for novel infant formula ingredients is not permitted.

FDA confirms this during the FDA Infant Formula Review (IFN) process, where they confirm the authorization of all ingredients.

Clinical study (GMS)

An infant formula that includes a novel ingredient is required to have undergone clinical evaluation in a Growth Monitoring Study (GMS).

The parameters of the GMS are defined in the regulation including duration and endpoints (length, weight, head circumference).

Post-Market Surveillance

Infant formula manufacturers are required to maintain records of any complaints and are required to investigate and report to the FDA in the case there is a causal relationship between a particular formula and an adverse outcome.

This requirement applies to infant formula products that include novel ingredients.

Current Assessment Pathway



The FDA has two offices involved in the review of infant formulas and ingredients:

- **OFAS (Office of Food Additive Safety):** evaluates individual ingredient safety — GRAS Notification Program or Food Additive Petition Process

Is the ingredient harmful under its intended conditions of use?

- **ONFL (Office of Nutrition and Food Labeling):** evaluates finished formula nutritional adequacy and quality factors — Growth Monitoring Study (infant clinical)

Does the finished formula support normal and comparable physical growth?

Neither office specifically evaluates whether an ingredient provides a function in infant formula that brings the formula closer to the physiological function of the gold standard for infant nutrition, human milk.

Session Focus



When a functional ingredient actively modulates a developing biological system — are current assessment tools designed to detect the full spectrum of potential consequences?

Session 3 Panelists



- **John Colombo**, University of Kansas
 - Disclosure: Consulted with several companies that manufacture products supporting maternal and infant nutrition, advising them on the nature of developmental processes in cognition and neurocognition, the interpretation of developmental outcomes, and the choice and configuration of developmental outcomes in clinical trials. His laboratory has also received funding to collaborate on or carry out industry research. Nestle Nutrition, Mead Johnson Nutrition/Reckitt, Ingenuity Foods, and Fonterra Brands (past).
- **Susan Dallabrida**, SPRIM PRO
- **Mona Eskander**, Health Canada (*former*)
 - Disclosure: Retired official from Health Canada and is currently the owner of Mona Eskander Consulting INC, an independent clinical and regulatory consulting firm in infant nutrition. She is speaking in her personal capacity and has no current financial conflicts related to the content of this workshop.
- **Leanne Redman**, Pennington Biomedical Research Center; University of Sydney
 - Disclosure: Past PI of growth trials sponsored by Abbott Nutrition and Nestle; PI of grants on maternal and infant nutrition sponsored by NIH; Past advisor to a2 milk, Bobbie, and One Willow.
- **Alan Ryan**, Clinical Research Consulting; FDA (*former*)
- **Barbara Schneeman**, UC Davis (*emeritus*); FDA (*former*)

Thread 1: Is There a Scientific Gap?

Do current safety assessment frameworks capture all potential consequences of adding an ingredient with physiological activity to infant formula?

Consensus Target:

- Whether a scientific gap exists between current assessment approaches and the potential consequences of physiologically active functional ingredients
- What category of concern that gap represents, if any

Thread 1: Is There a Scientific Gap?

Do current safety assessment frameworks capture all potential consequences of adding an ingredient with physiological activity to infant formula?

- **Q1:** Is there a category of safety concern — neither toxicological harm nor growth failure — that current assessment tools were not designed to detect for functional ingredients with physiological activity?
- **Q2:** What types of biological activity — if present — would the current GRAS and growth-study pathway be unlikely to detect?
- **Q3:** When a functional ingredient mirrors a human milk constituent at similar concentrations, does that provide meaningful safety reassurance — or does formula delivery introduce scientific uncertainty that milk-constituent status does not resolve?

S3T1 - Do you think current infant formula safety assessment frameworks are designed to detect safety signals from non-nutritive ingredients with physiological activity?

0 3 6

Yes, fully



Partially



No, there is no gap



I am not sure



Thread 1: Consensus Target

Has the panel reached alignment on:

- Whether a scientific gap exists between current assessment approaches and the potential consequences of physiologically active functional ingredients
- What category of concern that gap represents, if any

Thread 2: Ingredient or Formula?

What is the appropriate unit of evaluation — the functional ingredient in isolation, or the ingredient as delivered within the formula matrix?

Consensus Target:

- Conditions under which a standalone ingredient trial would — or would not — provide adequate evidence for safety and benefit evaluation
- What a minimum evidence package for small and start-up manufacturers should include

Thread 2: Ingredient or Formula?

What is the appropriate unit of evaluation — the functional ingredient in isolation, or the ingredient as delivered within the formula matrix?

- **Q1:** When evaluating physiological safety concerns, is the primary unit of evaluation the isolated ingredient or the ingredient within the formula matrix? Does the answer depend on the ingredient's mechanism of action or biological target?
- **Q2:** Does a functional ingredient's relevant biological activity change meaningfully when delivered in a formula matrix versus in isolation? Does this vary by ingredient category?
- **Q3:** If a functional ingredient were evaluated as a standalone supplement — regardless of whether the infant is breast- or formula-fed — what are the scientific trade-offs of decoupling ingredient evaluation from the formula context?

S3T2 - Which study design provides stronger evidence for evaluating a functional ingredient's safety?

0 2 9

A randomized infant formula trial



A standalone supplement trial in breastfed infants

0 %

Both are needed; neither alone is sufficient

3 %

It depends on the ingredient

10 %

Thread 2: Consensus Target



Has the panel aligned on:

- Conditions under which a standalone ingredient trial would — or would not — provide adequate evidence for safety and benefit evaluation
- What a minimum evidence package for small and start-up manufacturers should include

Thread 3: When Does Biology Trigger Evaluation?



What level of physiological activity should trigger deeper pre-market clinical evaluation — and how should that threshold be calibrated?

Consensus Target:

- The scientific principles that should govern a tiered evidence framework for physiologically active ingredients
- The threshold evidence types (in vitro, animal, mechanistic) that should elevate evaluation requirements
- What makes such a framework scientifically credible and practically usable

Thread 3: When Does Biology Trigger Evaluation?



What level of physiological activity should trigger deeper pre-market clinical evaluation — and how should that threshold be calibrated?

- **Q1:** The IOM 2004 framework was designed for nutrients — does it provide a workable structure for functional ingredients with physiological activity? Where does it break down?
- **Q2:** New approach methodologies — gut organoids, neonatal immune cell systems, in silico models — are advancing. For which scientific questions could these substitute for human infant data, and where is there no substitute?
- **Q3:** A principled tiered framework must be proportionate — calibrated to the nature and magnitude of scientific uncertainty, not set uniformly high. How should the scientific community balance rigor with proportionality?

S3T3 - At what point should demonstrated physiological activity in a functional ingredient trigger a higher tier of clinical evaluation?

0 3 2

At the earliest sign of in vitro biological activity

0 %

When animal or mechanistic data suggest a plausible developmental effect

81 %

Only if there is a proposed health claim

6 %

The current case-by-case approach is sufficient

13 %

Thread 3: Consensus Target

Has the panel identified:

- The scientific principles that should govern a tiered evidence framework for physiologically active ingredients
- The threshold evidence types (in vitro, animal, mechanistic) that should elevate evaluation requirements
- What makes such a framework scientifically credible and practically usable