

INFANT FORMULA: EVALUATING THE SAFETY OF NEW INGREDIENTS

Infant formulas are liquids or reconstituted powders fed to infants and young children to serve as substitutes for human milk. Infant formulas have a special role in the diet because they are the only source of nutrients for some infants and many receive infant formula at some time during their first year of life, often in combination with breastfeeding. Infancy is a uniquely vulnerable period of rapid growth and development and as such, feeding changes have the potential to impart benefit or harm in the short term, into early childhood, and even later into adulthood. Not all organ systems are fully mature at birth, and many are highly susceptible to environmental inputs as they undergo further development. Thus, measurements of safety parameters during infancy need to be equally or even more stringent than at other periods during the life cycle. The introduction of new ingredients to formulas must pose no or minimal risk to infants.

Existing guidelines and regulations for evaluating the safety of conventional food ingredients (e.g., vitamins, minerals) added to infant formulas have worked well in the past; however, they are not sufficient to address the diversity of potential new ingredients proposed by manufacturers to develop formulas that mimic human milk and do not adequately address the uniqueness of infants and infant nutrition. There is opportunity to address these limitations and standardize the safety assessment of ingredients new to infant formulas to ensure that the most vulnerable population members of our society, our infants, enjoy the safest possible food products.

The Committee on the Evaluation of the Addition of Ingredients New to Infant Formula was convened by the Institute of Medicine to provide U.S. Food and Drug Administration and Health Canada with a critical analysis of the current methods and to recommend tools and improved methods used to evaluate the safety of ingredients new to infant formula.

KEY QUESTIONS ADDRESSED:

General approach: How can one best ensure safety, considering the potential diversity of new ingredients that could be added to infant formula?

Preclinical tests: What kind of preclinical tests would be best indicators of possible harmful effects of a new infant formula? What animal models would one use whose response to food ingredients will be comparable to that of infants?

Clinical tests: What kind of clinical tests would be appropriate to examine if



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there is the potential for adverse effects when feeding a new formula to an infant? When are they needed? Under what circumstances will these tests be used? How will healthy growth in infants be assessed?

In-market monitoring: Once a new formula reaches the market, how does one follow its performance in infants? What kind of surveillance is needed to monitor that a new formula continues to be safe in the market?

RECOMMENDATIONS:

The committee recommends that for each new ingredient to be added to infant formula, the manufacturer establish balanced, qualified expert panels in consultation with the regulatory agency. Each expert panel will use decision-tree approaches to determine the kind of preclinical and clinical studies and in-market surveillance needed to ensure the safety of new ingredients by utilizing evidence-based approaches and high-quality scientific data.

Safety assessments of infant formulas need to be standardized (e.g. toxicity studies). A scientifically rigorous set of guidelines must also allow for flexibility since specific safety assessments must be targeted according to the nature of the ingredient.

The committee recommends that a distinct set of procedures that use an appropriate number and type of animal model at relevant developmental stages be included in preclinical studies. At least two animal models should be selected, and justification for the studies, as well as limitations, should be clear. The appropriate species, age, and safety factors should also be considered. Studies would include standard measures and/or in-depth measures for each organ system.

The committee recommends that growth studies should continue to be a centerpiece of clinical evaluation of infant formulas for the entire period when infant formula remains a substantial source of nutrients. Specific guidelines that define normal growth and establish a level of difference that represents a safety concern should be developed. In addition to growth studies, the committee recommends to test for effects on organ, immunological, and endocrinological systems and also to assess developmental-behavioral outcomes, including sensory-motor, cognitive development, temperament, and neural functions.

The committee recommends that the manufacturer implement an appropriate in-market surveillance strategy that is based on findings from preclinical and clinical studies and the potential for harm to infants.

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Infant Formula: Evaluating the Safety of New Ingredients is available for sale from the National Academies Press, 500 Fifth St. NW, Washington, DC 20001; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP's on-line bookstore at www.nap.edu. For more information about the Institute of Medicine, visit the IOM home page at www.iom.edu.

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