DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 107 and 184

[Docket No. FDA–2026–N–10832]

RIN 0910–AJ34

Infant Formula Nutrient Requirements

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or we) proposes to amend the regulations on nutrient specifications and labeling for infant formula as part of its phased, comprehensive review of infant formula nutrients. This action, if finalized, would amend the minimum and/or maximum levels of four required nutrients, change the unit of measure for certain nutrients, change the permitted source to meet one of the nutrient requirements, and amend the content of the required labeling. This action also includes a comprehensive assessment of four additional nutrients for which we conclude that the current required levels remain appropriate and reflect the best available scientific evidence on infant nutritional requirements and safe intake levels.

DATES: Either electronic or written comments on the proposed rule must be submitted by March 2, 2027.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of March 2, 2027. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov*. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov*.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked, and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2026–N–10832 for ''Infant Formula Nutrient Requirements.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov*. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf*.

Docket: For access to the docket to read background documents, the plain language summary of the proposed rule of not more than 100 words as required by the ''Providing Accountability Through Transparency Act,'' or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: *With regard to the proposed rule:* Carrie Assar, Office of Critical Foods, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–1453; or Barbara Little, Office of Regulation and International Programs, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–2378. *With regard to the information collection:* Christopher Colburn, Office of Operations, Food and Drug Administration, Three White Flint North 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–8758, *PRAStaff@fda.hhs.gov*.

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I. Executive Summary

A. Purpose and Coverage of the Proposed Rule

Under Operation Stork Speed, FDA is taking steps to enhance its efforts to ensure the ongoing quality, safety, nutritional adequacy, and resilience of the domestic infant formula supply (*https://www.fda.gov/food/infant-formula-homepage/operation-stork-speed*). As part of this effort, FDA conducted a scientific review of a subset of nutrient requirements for infant formula to ensure that infant formula provides adequate nutrition to support the growth and development of infants from birth through 12 months of age while avoiding excessive intakes that could pose health risks. This is the first comprehensive update and review of infant formula nutrients by the FDA since 1998 and part of FDA's strategic, phased approach to evaluating available scientific evidence for a comprehensive review of infant formula nutrients, as announced as part of Operation Stork Speed. This proposed rule assesses 8 of the 30 required nutrients in infant formula. The proposed rule, if finalized, would amend the minimum and/or maximum levels of four required nutrients—iodine, vitamin A, vitamin D, and manganese—and establish a maximum level for manganese. Additionally, the proposed rule, if finalized, would change the unit of measure for vitamin A and vitamin D, change the permitted source to meet the vitamin A requirement, and amend the content of the required labeling. This action also includes a comprehensive assessment of four additional nutrients—chloride, selenium, potassium, and sodium—for which we conclude that the current required levels remain appropriate. FDA intends to address the remaining infant formula nutrient specifications through subsequent proposed rules followed by one final rule covering all infant formula nutrient requirement changes. Lastly, the proposed rule, if finalized, would amend infant formula labeling requirements to change the unit of measure for vitamin A from International Units (IU) to microgram Retinol Activity Equivalents (µg RAE), and change the unit of measure for vitamin D from IU to micrograms (µg). The rule would also provide that vitamin A and vitamin D content may be voluntarily declared in IU in parentheses immediately following the declarations in µg RAE and µg, respectively.

Additionally, in accordance with the OMB ''Final Information Quality Bulletin for Peer Review'' (*https://www.federalregister.gov/documents/2005/01/14/05-769/final-information-quality-bulletin-for-peer-review*), FDA intends to conduct an external peer review on all influential scientific information used to inform development of any final rule.

B. Summary of the Major Provisions of the Proposed Rule

The proposed rule, if finalized, would:

- Increase the required minimum level of iodine in infant formula from 5 µg/100 kilocalories (kcal) to 15 µg/100 kcal and decrease the required maximum level of iodine from 75 µg/100 kcal to 50 µg/100 kcal;
- Change the unit of measure for vitamin A in infant formula from IU to µg RAE (1 IU retinol = 0.3 µg RAE);
- Decrease the required minimum level of vitamin A in infant formula from 250 IU/100 kcal (75 µg RAE/100 kcal) to 70 µg RAE/100 kcal (233 IU/100 kcal) and decrease the required maximum level from 750 IU/100 kcal (225 µg RAE/100 kcal) to 120 µg RAE/100 kcal (400 IU/100 kcal);
- Limit permitted forms of vitamin A that contribute to minimum and maximum vitamin A content from both preformed vitamin A and *beta*-carotene to preformed vitamin A only;
- Change the unit of measure for vitamin D in infant formula from IU to µg (1 IU = 0.025 µg);
- Increase the required minimum level of vitamin D in infant formula from 40 IU/100 kcal (1 µg/100 kcal) to 2 µg/100 kcal (80 IU/100 kcal) and increase the required maximum level from 100 IU/100 kcal (2.5 µg/100 kcal) to 3 µg/100 kcal (120 IU/100 kcal);
- Decrease the required minimum level for manganese in infant formula from 5 µg/100 kcal to 1 µg/100 kcal and establish a maximum level for manganese in infant formula of 50 µg/100 kcal.

C. Legal Authority

We are issuing this proposed rule consistent with our authority in sections 201(z), 403(j), 412(i), and 701(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(z), 343(j), 350a(i), and 371(e)).

D. Costs and Benefits

This proposed rule, if finalized, would update the nutrient specifications for infant formula to reflect the best available scientific evidence on infant nutritional requirements and safe intake levels. Vitamin D is a fat-soluble vitamin essential for calcium absorption, skeletal mineralization, and the prevention of rickets. Clinical symptoms of vitamin D deficiency include hypocalcemia (*i.e.,* low blood calcium levels), hypophosphatemia (*i.e.,* low blood phosphorus levels), tetany, and rickets. We quantify benefits to formula-fed infants from avoided healthcare costs associated with vitamin D deficiency-induced late-onset hypocalcemia. This approach captures the most severe and acute clinical manifestation of vitamin D deficiency and therefore represents a lower bound on the rule's total societal benefits. Additional benefits include reduced risk of inadequate iodine intake, excessive vitamin A exposure, and excessive manganese exposure in formula-fed infants; these benefits are described qualitatively. We quantify costs to infant formula manufacturers from relabeling, reformulation, and administrative costs associated with Before First Processing notification submissions. Additional costs would include FDA review costs associated with those submissions. We estimate that the annualized benefits over 10 years would range from $18.8 million to $171.7 million, with a primary estimate of $80.9 million, at a 7 percent discount rate and from $20.9 million to $191.0 million, with a primary estimate of $90.0 million, at a 3 percent discount rate. The annualized costs would range from $8.4 million to $31.7 million, with a primary estimate of $17.6 million, at a 7 percent discount rate and from $8.3 million to $31.6 million, with a primary estimate of $17.6 million, at a 3 percent discount rate.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/acronym	What it means
25(OH)D	25-hydroxy vitamin D.
AAP	American Academy of Pediatrics.
AI	Adequate Intake.
ALA	Alpha-linolenic acid.
AR	Average Requirement.
ARA	Arachidonic acid.
BMIC	Breast Milk Iodine Concentration.
BSSL	Bile-Salt-Stimulated Lipase.
CDRR	Chronic Disease Risk Reduction Intake.
CFR	Code of Federal Regulations.
CFSAN	Center for Food Safety and Applied Nutrition.
CI	Confidence Interval.
D–A–CH	German, Austrian, and Swiss Nutrition Societies.
DHA	Docosahexaenoic acid.
DRI	Dietary Reference Intake.
EAR	Estimated Average Requirement.
EFSA	European Food Safety Authority.
EFSA NDA Panel	EFSA Panel on Nutrition, Novel Foods and Food Allergens.
EPA	Eicosapentaenoic acid.
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition.
EU	European Union.
FAO	Food and Agricultural Organization.
FDA	Food and Drug Administration.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
FITS	Feeding Infants and Toddlers Study.
FR	**Federal Register**.
FSANZ	Food Standards Australia New Zealand.
GABA	Gamma-Aminobutyric Acid.
GUL	Guidance Upper Level.
HFP	Human Foods Program.
HHS	U.S. Department of Health and Human Services.
ICCIDD	International Council for Control of Iodine Deficiency Disorders.
iHMNutD	Interim Human Milk Nutrient Profile Data.
IOM	Institute of Medicine.
IQR	Interquartile range.
IU	International Unit.
Kcal	Kilocalorie.
Kg	Kilogram.
kJ	Kilojoule.
L	Liter.
LA	Linoleic acid.
LOAEL	Lowest Observed Adverse Effect Level.
LSRO	Life Sciences Research Office.
mEq	Milliequivalent.
mg	Milligram.
MILQ	Mothers, Infants, and Lactation Quality.
MIREC	Maternal-Infant Research on Environmental Chemicals.
mmol	Millimole.
MoH	Ministry of Health.
NASEM	National Academy of Sciences, Engineering, and Medicine.
ND	Not Determined.
NHANES	National Health and Nutrition Examination Survey.
NHMRC	National Health and Medical Research Council.
NOAEL	No Observed Adverse Effect Level.
Oz	Ounce.
PRA	Paperwork Reduction Act.
PRI	Population Reference Intake.
PRIA	Preliminary Regulatory Impact Analysis.
RAE	Retinol Activity Equivalents.
RDA	Recommended Dietary Allowance.
RE	Retinol Equivalents.
RfD	Reference Dose.
RFI	Request for Information.
RNI	Recommended Nutrient Intake.
Secretary	Secretary of HHS.
SE	Standard error.
TDS	Total Diet Study.
µg	Microgram.
UIC	Urinary Iodine Concentration.
UL	Tolerable Upper Intake Level.
UNICEF	United Nations Children's Fund.

Abbreviation/acronym	What it means
U.S.C.	United States Code.
USDA	U.S. Department of Agriculture.
VAD	Vitamin A Deficiency.
WHO	World Health Organization.
WIC	U.S. Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children.

III. Background

The Infant Formula Act of 1980 added section 412 of the FD&C Act, establishing requirements for infant formulas, including nutrient content requirements, and authorizing the Secretary of Health and Human Services (HHS) to revise these requirements. In the **Federal Register** of October 30, 1985 (50 FR 45106), FDA issued a final rule revising the infant formula nutrient requirements of the Infant Formula Act of 1980 (Pub. L. 96–359, 94 Stat. 1190), which was codified at § 107.100 (21 CFR 107.100). In 1995, FDA's Center for Food Safety and Applied Nutrition (CFSAN), now known as the Human Foods Program (HFP), contracted the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences to provide evidence-based recommendations on compositional requirements for infant formula, with Health Canada serving as a cosponsor. The assessment was conducted in consultation with expert scientists and professional organizations. The 1998 LSRO Panel report represents our last comprehensive review of the required infant formula nutrients although comprehensive updates to the nutrient requirements were not proposed after the report (Ref. 1). In 2015, we updated the table in § 107.100 to add the mineral selenium to the list of required nutrients and to establish minimum and maximum levels of selenium in infant formula (80 FR 35834, June 23, 2015). The table in § 107.100 specifies that infant formulas must contain 30 nutrients; the table specifies minimum levels for each nutrient and maximum levels for 10 of the 30 nutrients.

On March 18, 2025, HHS and FDA announced ''Operation Stork Speed,'' a set of actions and initiatives to expand options for safe, reliable, and nutritious infant formula for American families, including a comprehensive infant formula nutrient review (*https://www.fda.gov/food/infant-formula-homepage/operation-stork-speed*).

On May 14, 2025, FDA issued a Request for Information (RFI) as a first step in the comprehensive nutrient review process (90 FR 20475, May 14, 2025). Specifically, the RFI sought information that would help us determine whether there is a need to revise the existing nutrient requirements in § 107.100, taking into consideration any new scientific data or information related to infant formula nutrients, including international infant formula standards. The comment period closed on September 11, 2025.

IV. Legal Authority

Section 412(i) of the FD&C Act establishes requirements for the nutrient content of infant formula. Section 412(i) of the FD&C Act contains a table listing the required infant formula nutrients with respective minimum and, as applicable, maximum required levels. Section 412(i)(2) of the FD&C Act authorizes the Secretary, and by delegation the Commissioner of Food and Drugs (Commissioner), to revise the list of required nutrients and to revise the level of any required nutrient. In addition, section 412(i)(1) of the FD&C Act, as amended by the Food and Drug Omnibus Reform Act of 2022 (commonly referred to as FDORA (Pub. L. 117–328)), requires the Secretary, and by delegation the Commissioner, to review the table of required nutrients ''every 4 years as appropriate,'' taking into consideration ''any new scientific data or information related to infant formula nutrients, including international infant formula standards.'' The table of required nutrients is codified at § 107.100.

The nutrition information labeling requirements for infant formula are codified at § 107.10 (21 CFR 107.10). If finalized, the proposed rule would amend the label required in § 107.10(a)(2) to change the unit of measure for vitamin A in infant formula from IU to µg RAE and to change the unit of measure for vitamin D in infant formula from IU to µg. The rule would also amend § 107.10(b)(1) to provide that vitamin A and vitamin D content may be voluntarily declared in IU in parentheses immediately following the declarations in µg RAE and µg, respectively. ''Infant formula'' is defined as a food for ''special dietary use'' under section 201(z) of the FD&C Act. Under sections 403(j) and 701(e) of the FD&C Act for foods for special dietary uses, the Secretary, and by delegation the Commissioner, may prescribe regulations requiring information concerning the vitamin and mineral content of the food to be provided on the label to fully inform purchasers as to the value of the food for such uses. Thus, FDA has the authority to revise the statement of the content of nutrients required for infant formula labeling in § 107.10 under sections 201(z), 403(j), 412(i), and 701(e) of the FD&C Act. If the proposed revisions to § 107.10 are finalized, FDA will provide an opportunity for filing objections and requests for a formal evidentiary public hearing under 21 CFR part 12.

V. Description of the Proposed Rule

A. Scope

The proposed rule, if finalized, would apply to products that meet the statutory definition of ''infant formula'' in section 201(z) of the FD&C Act. Section 201(z) of the FD&C Act defines infant formula as ''a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.'' FDA regulations define an ''infant'' as a person not more than 12 months of age (21 CFR 105.3(e) and 106.3).

B. Approach and Assumptions Used in Scientific Assessments

The proposed rule evaluates eight of the 30 required nutrients in infant formula. For each nutrient, FDA reviewed the physiological role and health consequences of deficiency or excess, relevant nutrient reference values from major expert bodies, human milk composition data, international regulatory standards, and recent scientific evidence. This nutrient-by-nutrient approach culminates in an evidence evaluation and rationale section that explains FDA's basis for either proposing changes to current minimum and/or maximum specifications or concluding that existing levels remain appropriate.

In sections V.C through V.J of this document, we present FDA's nutrient-specific evaluations, including the scientific basis for proposed changes to minimum and maximum specifications and the rationale for maintaining current specifications where appropriate. These nutrient-specific

evaluations are based on comprehensive nutrient-specific assessments, which we reference herein and have included in the docket. As required by section 412(i)(1) of the FD&C Act, FDA considered scientific information and data since the last comprehensive review of infant formula in 1998 as well as infant formula nutrient requirements in international standards. FDA also reviewed and considered comments submitted in response to the RFI.

FDA conducted a comprehensive evidence scan of peer-reviewed literature using the PubMed database to identify English-language publications regarding chloride, iodine, manganese, potassium, selenium, sodium, vitamin A, and vitamin D. Searches were individually constructed to account for the distinct characteristics of each nutrient. The queries utilized specific Medical Subject Headings (commonly referred to as MeSH) and keywords focused on general pharmacokinetics, nutritional requirements, deficiency, and toxicity for human infants 0 to 12 months of age. To capture updated evidence, search parameters targeted literature published from the end of the previous 1998 LSRO report review periods through May 2026. This corresponded to search start dates of 1989 for manganese; 1992 for vitamin D; 1995 for chloride, potassium, sodium, vitamin A, and iodine; and 2015 for selenium, which corresponds to FDA''s final rule, ''The Addition of Minimum and Maximum Levels of Selenium to Infant Formula and Related Labeling Requirements'' (80 FR 35834, June 23, 2015). FDA considered study design among other factors when prioritizing the literature reviewed, which included meta-analyses, randomized controlled trials, clinical trials, and observational studies. While, for example, traditional literature reviews and case reports were generally excluded from the primary evidence scan used to evaluate nutrient specifications, FDA notes that such literature was incorporated where necessary to provide clinical, historical, or toxicological context. The population of interest focused on healthy, full-term infants. This target population included infants with low birth weight or who were small for gestational age but excluded preterm infants and those with conditions requiring specialized formulas. Finally, the selected outcomes prioritized evidence regarding minimum dietary requirements, maximum safe levels, clinical signs of deficiency or toxicity, and adverse nutrient interactions.

To evaluate nutrient reference values, FDA considered recommendations from several expert bodies, including the National Academies of Science, Engineering, and Medicine (NASEM), the European Food Safety Authority (EFSA), the Australian National Health and Medical Research Council (NHMRC)/New Zealand Ministry of Health (MoH), and the German, Austrian, and Swiss nutrition societies (D–A–CH). These organizations, utilizing expert committees, develop nutrient reference values, including Dietary Reference Intakes (DRIs), which are science-based benchmarks used to assess and plan diets for healthy populations. Grounded in rigorous expert review across multiple countries and methodologies, these values serve as appropriate inputs for evaluating both the adequacy and safety of nutrient intakes in infant populations.

Nutrient reference values developed by these expert committees include several types of recommendations: Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), Adequate Intake (AI), and Tolerable Upper Intake Level (UL). The EAR represents the average daily intake estimated to meet the needs of half of healthy individuals in each life stage. EFSA uses an equivalent term, Average Requirement (AR). The RDA is derived mathematically from the EAR (EAR plus two standard deviations) and is set to meet the needs of nearly all (97–98 percent) healthy individuals (Ref. 2); the Food and Agriculture Organization (FAO) of the United Nations/World Health Organization (WHO) and EFSA use equivalent terms: the Recommended Nutrient Intake (RNI) and Population Reference Intake (PRI), respectively (Refs. 3, 4). When insufficient scientific evidence exists to establish an EAR—and thus an RDA—an AI is established instead, based on experimentally derived intake levels or observed mean nutrient intakes in healthy populations (Ref. 2). The UL represents the highest average daily intake level likely to pose no risk of adverse health effects (Ref. 2). These reference values provide science-based benchmarks for assessing both the adequacy and safety of nutrient intakes in infant populations and are incorporated into each nutrient section if available.

FDA considered human milk composition data, where appropriate, as a primary source of evidence, recognizing that human milk serves as the gold standard for infant nutrition during, at minimum, the first 6 months of life, and that most nutrient AIs for infants are based on observed nutrient concentrations in human milk.[1] Mature human milk is the stage of lactation established approximately 2 weeks postpartum, following colostrum and transitional milk, and is characterized by a relatively stable nutrient composition compared with earlier phases (Ref. 5). For the purposes of FDA's review, human milk collected 21 days or more postpartum was considered mature. In addition, for the purposes of this review, FDA converted nutrient concentrations in human milk from per liter (L) to per 100 kcal using an assumed energy density of approximately 650 kcal/L for mature human milk. This value represents a well-supported midpoint estimate that is consistent with the range of values reported across multiple independent data sources and accounts for the natural variability in human milk energy content across lactation stages and populations (Refs. 6, 7, 8, 9, 10). FDA acknowledges that this value represents a midpoint within a range of plausible estimates and commits to updating this reference value as new, nationally representative data from North American populations become available. Therefore, FDA requests comment on the use of approximately 650 kcal/L in mature milk for calculations performed in this proposed rule including the references that were used to derive this value.

Two recent publications provide updated human milk nutrient composition data that were considered in this review, along with other relevant studies as discussed in the sections

[1] For the purposes of this notice of proposed rulemaking, FDA converted nutrient concentrations in human milk from per liter (per L) to per 100 kcal using an assumed energy density of approximately 650 kcal/L for mature human milk. This value represents a well-supported midpoint estimate that is consistent with the range of values reported across multiple independent data sources and accounts for the natural variability in human milk energy content across lactation stages and populations. The most directly applicable North American data are provided by the iHMNutD project, which reported a weighted mean energy density of 67.4 kcal per 100 grams (approximately 695 kcal/L) based on nine studies comprising 208 participants from the United States (Ref. 8). The MILQ study reported median energy density values that varied by lactation stage, with approximately 650 kcal/L at 18–31 days and stabilizing at approximately 597–602 kcal/L from 3–4 months onward, with a pooled median of approximately 607 kcal/L for 1–6 months (Ref. 10). A systematic review reported approximately 620 kcal/L for mature milk from exclusively breastfed infants aged 3–6 months (Ref. 9), and a probabilistic modeling study reported approximately 650 kcal/L for infants aged 1–3 months and approximately 617 kcal/L for infants aged 3–6 months (Ref. 6). The reference value of approximately 650 kcal/L is also consistent with the central reference value identified by EFSA, which served as the basis for EFSA's recommended permitted energy range for infant formula (Ref. 7). FDA acknowledges that this value represents a midpoint within a range of plausible estimates and commits to updating this reference value as new, nationally representative data from North American populations become available.

below. The Mothers, Infants and Lactation Quality (MILQ) study was designed to establish reference values for nutrient concentrations in human milk from well-nourished women with minimal nutrient supplementation and dietary fortification across geographically diverse populations. The study collected human milk samples from 1,242 women in Bangladesh, Brazil, Denmark, and The Gambia at multiple time points throughout the first 8.5 months of lactation (Ref. 11). Concentrations of macronutrients, water-soluble vitamins, fat-soluble vitamins, and minerals were quantified using validated analytical methods. Milk volume was measured simultaneously, enabling calculation of total nutrient transfer to the infant (Ref. 11). The other study developed interim human milk nutrient profile data (iHMNutD) for use in North American food composition databases through a literature synthesis of eligible North American data from three previously published systematic reviews covering the period 1980–2022 and one large Canadian biomonitoring study (Ref. 8). Data were restricted to mature milk from term-born infants collected within the first 6 months of lactation using nutrient-specific collection and analytical methods. Values were reviewed by subject matter experts and accompanied by data flags to communicate uncertainty where data were limited (Ref. 8).

FDA reviewed international infant formula standards and recommendations from Codex Alimentarius, the European Union (EU), Australia, New Zealand, Canada, and China, among others, to inform its assessment of appropriate nutrient specifications while also considering differences in methodology and regulatory philosophy. Codex Alimentarius and some non-U.S. countries use the term ''infant formula'' to refer to formula intended for infants 0–6 months of age and the term ''follow-on formula'' to refer to formula intended for infants 6–12 months of age. In the United States, there is not a regulatory distinction between formula intended for infants 0–6 months of age and formula intended for infants 6–12 months of age; both are considered ''infant formula,'' as defined in 21 CFR 106.3 and section 201(z) of the FD&C Act. We considered data on nutrient function and interactions, clinical outcomes associated with deficiency or excess intake, U.S. dietary intake data, and other evidence relevant to evaluating minimum and maximum nutrient levels in infant formula. Where relevant, FDA notes distinctions between maximums and guidance upper levels (GULs) established in some international standards. Unlike maximums, GULs apply to nutrients for which sufficient information for a science-based risk assessment is not available; rather, they are derived based on meeting nutritional requirements of infants and an established history of apparent safe use. In general, from a nutrition perspective, it is best that nutrient contents in infant formulas do not exceed GULs unless higher levels cannot be avoided (Ref. 12).

To estimate infant exposure to nutrients from infant formula, FDA assumed typical infant formula intakes of 0.78 L/day for infants 0–6 months of age and 0.6 L/day for infants 7–12 months of age, accounting for the introduction of complementary foods in the second half of infancy. These intake volumes are based on observed consumption patterns in breastfed infants and are consistent with the assumptions used by NASEM (Ref. 2) and similar to assumptions used by other expert bodies in establishing nutrient reference values. Assuming a standard infant formula energy density of 20 kcal/oz (676 kcal/L), these volumes correspond to approximately 527 kcal/day for infants 0–6 months of age and approximately 406 kcal/day for infants 7–12 months of age. FDA requests comment on all aspects of its assumptions to calculate the kcal consumed per day for infants 0–6 months of age and infants 7–12 months of age, including the assumption of the energy density of infant formula.

For certain nutrients, FDA also considered a high consumer scenario based on data from three cycles of the National Health and Nutrition Examination Survey (NHANES), using the 90th percentile of energy intake from infant formula among non-breastfed infants to evaluate potential nutrient exposures at the upper end of the consumption distribution (Refs. 13, 14, 15, 16, 17, 18). Evaluation of typical consumption scenarios (*i.e.,* mean, representing the average diet) informed the assessment of minimum specifications to ensure adequate nutrient intakes, while both typical and high-consumer scenarios informed the assessment of maximum specifications to ensure appropriate safety margins.

C. Chloride

The current requirements for chloride in infant formula are a minimum level of 55 milligrams (mg)/100 kcal and a maximum level of 150 mg/100 kcal (§ 107.100). Based on our analysis of scientific information and data since the 1998 comprehensive study of infant formula nutrients (LSRO Panel report), including infant formula chloride requirements in international standards, we conclude that the required chloride levels in § 107.100 remain appropriate.

1. Background

Chloride is an essential mineral that serves critical physiological functions in infants, including maintenance of acid-base balance, regulation of fluid and electrolyte homeostasis, and production of hydrochloric acid for digestion (Refs. 19, 20). Chloride works closely with sodium, potassium, and bicarbonate as electrically charged particles in body fluids to help regulate membrane electrical charge, facilitate nutrient absorption, and generate signals in muscles and nerves (Ref. 20). Chloride also helps keep mucus moist and fluid in the lungs and other organs through a process controlled by the Cystic Fibrosis Transmembrane Conductance Regulator channel; when this channel malfunctions, it causes cystic fibrosis (Ref. 20). Most dietary chloride intake comes from sodium chloride (*i.e.,* table salt) added to food during processing or at the table (Refs. 19, 20).

a. Health Consequences of Chloride Deficiency

A deficiency in chloride can result in metabolic alkalosis (*i.e.,* a condition in which blood becomes excessively alkaline) (Ref. 21). The most well-documented cases of chloride deficiency in the United States occurred during 1978–1979, when approximately 150 infants in the United States developed hypochloremic metabolic alkalosis after consuming improperly formulated soy protein-based infant formulas (Ref. 22). These formulas contained chloride levels as low as 1–2 milliequivalents (mEq)/L (approximately 5–11 mg/100 kcal) (Refs. 22, 23, 24), and symptoms were observed in some infants consuming formula with 5.1 mEq/L (approximately 27 mg/100 kcal) (Ref. 1). Infants with acute chloride deficiency exhibited a failure to thrive, lethargy, loss of appetite, and weakness. Other laboratory abnormalities included low blood and urine chloride levels with metabolic alkalosis, low blood potassium levels, and red blood cells in the urine (Refs. 24, 25). This public health incident helped lead to the enactment of the Infant Formula Act of 1980 (Pub. L. 96–359).

Long-term followup studies of the infants in the United States affected by the chloride deficiency crisis identified subtle neurodevelopmental effects in children who experienced severe

chloride deficiency during infancy, particularly affecting language skills (Refs. 22, 26).

b. Health Consequences of Excess Chloride Intake

Hyperchloremia is a condition in which blood chloride levels exceed the normal range. Hyperchloremia typically results from medical disorders or clinical treatments rather than dietary chloride intake, and excessive chloride consumption through infant formula or other food is unlikely to be a cause of hyperchloremia (Ref. 20).

In its 2005 assessment, NASEM found no research examining the consequences of chronic overconsumption of chloride in infants (Ref. 19). Available evidence regarding harmful effects of excess chloride consumption in infants remains sparse. FDA's review identified no significant new scientific evidence concerning adverse outcomes from excessive dietary chloride consumption during infancy since NASEM's 2005 report (Ref. 27).

2. Nutrient Reference Values

a. NASEM (United States)

NASEM established AIs for chloride for infants in 2005 as part of its comprehensive report, *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (Ref. 19). NASEM established an AI of 180 mg/day for infants 0–6 months of age and an AI of 570 mg/day for infants 7–12 months of age. NASEM established these AIs based on the sodium content of human milk, assuming chloride adequacy in equimolar amounts to sodium, because most dietary chloride is consumed as sodium chloride. The calculation for infants 7–12 months of age accounted for the introduction of complementary foods at this age.

b. European Food Safety Authority (EFSA)

The EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) published a comprehensive Scientific Opinion on dietary reference values for chloride in 2019 (Ref. 20), in which it established an AI of 300 mg/day for infants 7–11 months of age. EFSA did not establish an AI for chloride in infants 0–6 months of age, but, through a comprehensive review of human milk studies from others of term infants in Western populations, the EFSA Panel determined an approximate midpoint of chloride concentration in mature human milk to be 400 mg (11.3 millimole (mmol))/L and estimated infant intake of 320 mg/day from exclusive breastfeeding.

The EFSA Panel also reviewed a study that calculated physiological requirements of chloride in infants and that recommended an intake of 120 mg/day throughout the first year of life. EFSA noted that the amount of chloride provided by human milk during the first 6 months of life (approximately 320 mg/day) is substantially higher than this calculated physiological requirement, suggesting either that the approach underestimates actual needs or that human milk provides chloride beyond minimal physiological requirements (Ref. 20).

c. D–A–CH (Germany, Austria, Switzerland)

In 2017, D–A–CH established an AI for chloride of 300 mg/day for infants 0–4 months of age, and 450 mg/day for infants 4–12 months of age (Ref. 28). Because intake data from complementary foods were unavailable, the 4–12 months value was extrapolated from the 0–4-month group's values, adjusting for differences in average body weight.

d. UL

Establishing a UL requires evidence from studies that test multiple levels of intake and identify the point at which adverse effects begin to occur; however, available data were insufficient to support such a determination for chloride in infants (Ref. 19). Consequently, neither NASEM (Ref. 19) nor EFSA (Ref. 20) established a UL for chloride in infants. In its 2005 assessment, EFSA observed that chloride consumption levels in European populations surpassed the amounts needed for normal physiological function (Ref. 29). EFSA also recognized that higher consumption of chloride in the form of sodium chloride correlated with increased risk of high blood pressure (Refs. 20, 29). Nevertheless, EFSA determined that the available scientific evidence was inadequate to establish a specific numerical value for an upper limit (Ref. 20). Similarly, NASEM noted that ''as with other nutrients, an intake of sodium or chloride markedly above the AI is not warranted'' (Ref. 19).

e. Comparison of International Recommendations

Table 1 shows the chloride AIs established by NASEM, EFSA, and D–A–CH.

TABLE 1—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF CHLORIDE

Organization	Year	Age range (months)	Adequate intake (mg/day)	Tolerable upper intake level
NASEM	2005	0–6	180	ND
		7–12	570	ND
EFSA	2019	7–11	300	ND
D–A–CH	2017	0–4	300	ND
		4–12	450	ND

ND: not determined.

The considerable variation in chloride recommendations across international expert bodies reflects fundamental differences in methodology and data sources (Ref. 27). Despite these methodological differences, all expert bodies used human milk composition as the primary basis for chloride AIs and assessed that there is insufficient evidence to establish a UL.

3. Human Milk Composition

Maternal diet and nutritional status do not affect how much chloride is present in human milk (Refs. 20, 30). Multiple studies have characterized chloride concentrations in mature human milk from mothers with term pregnancies. The direct measurements of chloride concentrations in mature human milk resulted in values ranging from 339 to 547 mg/L across individual study timepoints (Refs. 31, 32, 33, 34, 35) and a pooled weighted mean of 416 mg/L (n=5 studies and 139 participants) (Ref. 8) and reflect the natural variability observed in human milk.

The MILQ study (Ref. 36) provides comprehensive recent data on human milk mineral composition, from 1,242 women in Bangladesh, Brazil, Denmark, and The Gambia. The MILQ study

reported sodium concentrations, not chloride. In converting sodium to chloride on an equimolar basis, substantially lower values are obtained than with direct measurements of chloride in milk (Ref. 27).

The discrepancy suggests either that chloride and sodium may not be present in exactly equimolar amounts in human milk or that different analytical methods, study populations, or periods yield systematically different results. NASEM's approach of establishing chloride AIs based on equimolar conversion from sodium may underestimate actual chloride concentrations when based on sodium measurements alone (Ref. 27).

4. International Regulatory Standards for Infant Formula

Chloride specifications for infant formula vary among international regulatory bodies and expert organizations, though most align closely with Codex Alimentarius standards. The Codex Alimentarius Commission, a program that establishes internationally recognized standards, specifies a minimum of 50 mg/100 kcal and a maximum of 160 mg/100 kcal. These specifications apply to both infant formula (for 0–6 months of age) (Ref. 12) and follow-on formula (for 6–12 months of age) (Ref. 37). The EU, based on recommendations from EFSA (Ref. 7), specifies a minimum of 60 mg/100 kcal and a maximum of 160 mg/100 kcal (Ref. 38). The EU minimum assumes that infants 0–6 months of age consume 500 kcal/day and require 300 mg/day of chloride. Other countries have adopted or proposed to adopt specifications aligned with Codex Alimentarius, including Food Standards Australia New Zealand (Ref. 39), Health Canada (Ref. 40), and China (Ref. 41); however, China has different standards for follow-on formulas for infants 6–12 months of age (approximately 220 mg/100 kcal maximum for 6–12 months) (Ref. 42).

In its 1998 comprehensive review of infant formula nutrients, LSRO recommended a minimum of 50 mg/100 kcal and a maximum of 160 mg/100 kcal. The LSRO Panel based the minimum recommendation on the mean minus one standard deviation value for the chloride concentration of human milk, which was approximately 320 mg/L (48 mg/100 kcal) (Ref. 30), rounded up to 50 mg/100 kcal for the minimum specification. The LSRO Panel found no evidence to suggest that chloride is absorbed differently from infant formula compared to human milk, supporting the use of human milk composition data as the basis for the specification. For the maximum chloride content of 160 mg/100 kcal, the LSRO Panel based this on the 90th percentile of FDA analyses of infant formulas available at that time, rather than on safety concerns, as no evidence supported that excessive chloride intake caused adverse effects in children.

Table 2 shows the requirements and recommendations of these international regulatory bodies and organizations.

TABLE 2—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR CHLORIDE IN INFANT FORMULA

Organization	Age range (months)	Minimum (mg/100 kcal)	Maximum (mg/100 kcal)	Reference
U.S. Current Standards	0–12	55	150	21 CFR 107.100.
LSRO [1]	0–12	50	160	LSRO, 1998.
Codex Alimentarius	0–12	50	160	CXS 72–1981, CXS 156–1987.
EU	0–12	60	160	Commission Delegated Regulation (EU) 2016/127.
Australia [2]	0–12	50	159	FSANZ P1028.
Canada [3]	0–12	50	160	Health Canada, 2025.
China	0–6	50	159	GB 10765–2021.
	6–12	ND	218	GB 10766–2021.

[1] Recommended ranges.
[2] Values converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[3] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Chloride Intake

A 2006 analysis of electrolyte intake in infants from the 2002 Feeding Infants and Toddlers Study (FITS) reported mean chloride intakes of 290 mg/day for infants 4–5 months of age and 761 mg/day for infants 6–11 months of age based on equimolar conversion of sodium to chloride (Ref. 43). Mean intakes exceeded NASEM's AI for both age groups. For infants 6–11 months of age, chloride intakes ranged from approximately 50 percent of the AI at the 10th percentile (276 mg/day) to approximately 260 percent at the 90th percentile (1,493 mg/day). Although there are several limitations of the FITS study (Ref. 27), the FITS data nonetheless provide useful information demonstrating that most infants—whether breastfed or consuming infant formulas meeting current specifications—along with age-appropriate complementary foods, achieve chloride intakes that meet or exceed established AIs.

6. Evidence Evaluation and Rationale

Based on the review of available literature, NRVs, and international standards, we conclude that the current minimum level of 55 mg/100 kcal and maximum level of 150 mg/100 kcal for chloride in § 107.100 remain appropriate.

a. Maintaining the Minimum Specification of 55 mg/100 kcal

The current minimum required level of 55 mg/100 kcal of chloride provides a 2- to 11-fold margin above the deficiency-causing levels of 5–27 mg/100 kcal associated with the 1978–1979 chloride-deficiency crisis. Given the severity of the consequences of the chloride-deficiency crisis in 1978–1979 and the lack of functional biomarkers for chloride status (*i.e.,* early indicators of chloride inadequacy), we determine that the substantial margin is appropriate.

Although methodological variability exists in measuring chloride levels in human milk, human milk composition data support the current required minimum. The current minimum of 55 mg/100 kcal falls between and aligns well with direct chloride measurements in human milk (approximately 52 to 84 mg/100 kcal, with a pooled weighted mean of 64 mg/100 kcal) (Refs. 1, 8, 20, 28, 31 through 35). When chloride measurements are derived from converting sodium concentrations to chloride, the chloride measurements are far lower than direct chloride measurements, suggesting that chloride and sodium are not present in exactly equimolar amounts in human milk (Refs. 8, 27, 36). Given the uncertainty associated with chloride measurements

derived from converting sodium concentrations to chloride, the current minimum appropriately reflects direct chloride measurement data while providing a conservative safety margin.

The current minimum ensures that infant formula provides chloride intakes that pose low risk of deficiency relative to established AIs (Ref. 27). Our current specification of 55 mg/100 kcal falls within the international consensus range, and no compelling evidence from other jurisdictions suggests that lowering the minimum would provide any benefit. Doing so would reduce the safety margin above the established deficiency threshold without corresponding nutritional justification (Ref. 27).

b. Maintaining the Maximum Specification of 150 mg/100 kcal

The current maximum of 150 mg/100 kcal substantially exceeds the median human milk chloride content while maintaining a prudent upper limit for sole-source infant nutrition. No compelling evidence supports either raising or lowering this specification (Ref. 27).

Although expert bodies have not established a UL for chloride in infants due to limited data (Refs. 19, 20, 29), the absence of an established UL reflects insufficient dose-response data regarding adverse effects rather than confirmation that all intake levels are safe (Ref. 27).

The current maximum provides a substantial margin above the chloride content of human milk (Ref. 27). FDA's current maximum of 150 mg/100 kcal provides an additional conservative margin below both LSRO's recommendation and the international standard of approximately 160 mg/100 kcal.

History of use and available intake data support safety at the current maximum. The current maximum would provide 791 mg/day for a 0–6-month-old infant and 609 mg/day for a 6–12-month-old infant consuming typical daily infant formula intakes. These chloride amounts have not been associated with adverse effects in clinical use since the chloride requirements were established in the Infant Formula Act of 1980. An analysis of 2002 FITS data (Ref. 43) reported mean sodium intakes corresponding to estimated chloride intakes of 290 mg/day (4–5 months of age) and 761 mg/day (6–11 months of age), although these estimates included intake from all dietary sources, not solely infant formula.

We have considered whether raising the maximum to align with the international consensus of approximately 160 mg/100 kcal would be warranted and conclude that it is not necessary to ensure adequate infant nutrition. While such harmonization could provide modest additional manufacturing flexibility and align U.S. standards with international regulatory agencies, the difference between the current U.S. maximum and the international standard is relatively small (6.7% or 10 mg/100 kcal). No evidence suggests that the current maximum is inadequate, constrains appropriate formulation, or that chloride intakes between 150 and 160 mg/100 kcal provide nutritional advantages to infants beyond those achieved at the present maximum of 150 mg/100 kcal. Manufacturers have successfully met the current specification since the 1980s without reported difficulties. Therefore, we conclude that the slightly lower maximum provides an additional conservative margin without imposing undue manufacturing constraints (Ref. 27).

c. Consideration of the Evidence Base

We acknowledge several uncertainties in the evidence base that support maintaining the current specifications. There is wide variability in reported human milk chloride concentrations across studies (171–547 mg/L or approximately 26–84 mg/100 kcal for mature milk) primarily from discrepancies between direct chloride measurements and sodium-based estimates, lack of functional biomarkers for chloride status, and individual variability in infant requirements. Given these uncertainties, the serious consequences of dietary chloride deficiency, and the lack of evidence of adverse effects from current specifications, we believe a conservative approach is warranted and that the current required minimum level of 55 mg/100 kcal and maximum level of 150 mg/100 kcal should be retained (Ref. 27).

D. Selenium

At the time FDA initially established nutrient specifications for infant formula, selenium was not recognized as an essential nutrient and was not one of the nutrients required by statute in infant formula. However, in 1989, an RDA for selenium for infants 0–6 months of age was established (Ref. 44), and in 2000, AI levels and ULs were established for infants 0–6 and 7–12 months of age (Ref. 45). In 2015, FDA added selenium as a required nutrient in infant formula with a minimum of 2 µg/100 kcal and a maximum of 7 µg/100 kcal (see 80 FR 35834, June 23, 2015). Based on our analysis of the scientific information and data since the addition of minimum and maximum levels of selenium to the infant formula requirements in 2015, including infant formula selenium requirements in international standards, we conclude that the required selenium levels in § 107.100 remain appropriate.

1. Background

Selenium is an essential trace element for humans that functions largely through its incorporation into proteins known as selenoproteins. The known biological functions of selenium include defense against oxidative stress, regulation of thyroid hormone action, and regulation of the oxidation/reduction status of vitamin C and other molecules (Ref. 46). Selenium also provides protective effects against toxicity of certain elements—including arsenic, lead, cadmium, and mercury—by facilitating urinary excretion, reducing oxidative damage, and forming biologically inactive complexes with these elements (Refs. 45, 47, 48). Infant selenium status is influenced by geographic variation in the selenium content of soil and water, which shapes maternal selenium intake and, in turn, the selenium content of human milk. As a result, the selenium intake of breastfed infants varies by geographic location (Ref. 46).

a. Health Consequences of Selenium Deficiency

Keshan disease, a cardiomyopathy that occurs almost exclusively in children, has been associated with selenium deficiency. Keshan disease has been reported in areas of China where the population has severe selenium deficiency (Refs. 46, 49; 78 FR 22442 at 22443, April 16, 2013). Selenium deficiency has also been identified throughout the lifespan in those who receive long-term parenteral nutrition (*i.e.,* intravenous nutrition) not adequately supplemented with selenium. Deficiency signs and symptoms include macrocytosis, loss of skin and hair pigmentation, and, in severe cases, cardiomyopathy (Ref. 46).

b. Health Consequences of Excess Selenium Intake

Chronic selenium toxicity (selenosis) is rare but has been observed in adults consuming diets containing excess levels of selenium due to selenium supplementation (Ref. 46). Reported characteristics include hair and nail brittleness and loss, gastrointestinal upsets, skin rash, garlic breath odor, fatigue, irritability, and nervous system abnormalities. Acute selenium toxicity

is rare, and the few reports in the literature of acute fatal or near fatal selenium poisoning in adults occurred secondary to accidental ingestion of selenium (Ref. 45).

2. Dietary Reference Intakes

a. NASEM

In 2000, NASEM established AI and UL values for selenium for infants as part of its comprehensive report, *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (Ref. 45). NASEM did not find sufficient evidence to calculate an EAR for selenium for infants during the first year of life and, therefore, did not have a basis to set an RDA for selenium for infants. This contrasts with the 1989 Food and Nutrition board recommendation, which had established an RDA for infants extrapolated from adult values (Ref. 44). NASEM's 2000 report instead determined that, due to the lack of functional criteria of selenium status in infants to accurately reflect dietary intake, recommended intakes should be based on an AI reflecting observed mean intakes of infants fed principally with human milk.

NASEM established an AI of 15 µg/day for infants 0–6 months of age and an AI of 20 µg/day for infants 7–12 months of age. NASEM's basis for deriving an AI for the first 6 months of life was the average intake by full-term infants born to healthy, well-nourished mothers and exclusively fed human milk (Ref. 45). The AI for infants 7–12 months of age was derived from using the data of infants 0–6 months of age, extrapolated upward to account for increased body size and the introduction of complementary foods.

NASEM established a UL of 45 µg/day for selenium for infants 0–6 months of age by relying on the concentration of selenium in human milk, which is not associated with known adverse effects. The UL of 60 µg/day for infants 7–12 months of age was extrapolated to account for increased body size (Ref. 45).

b. EFSA

EFSA published dietary reference values for selenium in 2014 (AI) and 2023 (UL) (Refs. 50, 51). EFSA did not establish an AI for selenium in infants 0–6 months of age. For infants 7–11 months of age, EFSA established an AI of 15 µg/day (Ref. 49).

EFSA established ULs of 45 µg/day for infants 4–6 months of age and 55 µg/day for infants 7–11 months of age. EFSA acknowledged that there are no direct data to support derivation of a UL for infants; however, given that there is no evidence that infants are more susceptible to selenium toxicity than adults, the EFSA Panel considered it appropriate to extrapolate ULs from adults to infants (Ref. 51). The EFSA Panel noted that these ULs are consistent with human milk concentrations.

c. FAO/WHO

The joint FAO/WHO Consultation established RNI levels of 6 µg/day for infants 0–6 months of age and 10 µg/day for infants 7–12 months of age based on the selenium content of human milk from international surveys, which averaged 18.5 µg/L, combined with data on milk consumption by exclusively breastfed infants (Ref. 3).

d. D–A–CH (Germany, Austria, Switzerland)

In 2015, D–A–CH established an AI for selenium of 10 µg/day for infants 0–4 months of age, based on the selenium content of human milk. Values were adjusted for body weight to establish an AI of 15 µg/day for infants 4–12 months of age. No UL was determined (Ref. 52).

e. Australian NHMRC/New Zealand MoH

Australia and New Zealand established AIs and ULs in 2005 (Ref. 53). The AI of 12 µg/day for infants 0–6 months of age was calculated by multiplying the average intake of human milk (0.78 L/day) and the average selenium content in human milk of 15 µg/L based on several key studies (Refs. 54, 55, 56). The AI of 60 µg/day for infants 7–12 months of age was extrapolated from that of the younger infants on a metabolic weight basis, with considerations for the introduction of complementary foods.

The UL for young infants was based on the studies showing that a human milk concentration of 60 µg/L was not associated with adverse effects (Ref. 57). This gives a no observed adverse effect level (NOAEL) of 47 µg/day (7 µg/kg body weight).

f. Comparison of international recommendations

Table 3 shows the selenium AIs established by NASEM, EFSA, FAO/WHO, D–A–CH, and Australian NHMRC/New Zealand MoH.

TABLE 3—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF SELENIUM

Organization	Year	Age range (months)	Adequate intake	Tolerable upper intake level
NASEM	2000	0–6	15 µg/day	45 µg/day.
		7–12	20 µg/day	60 µg/day.
EFSA	2014 (AI)	4–6	ND	45 µg/day.
	2023 (UL)	7–11	15 µg/day	55 µg/day.
FAO/WHO	2004	0–6	6 µg/day *	ND.
		7–12	10 µg/day *	ND.
D–A–CH	2015	0–4	10 µg/day	ND.
		4–12	15 µg/day	ND.
Australian NHMRC/New Zealand MoH	2005	0–6	12 µg/day	45 µg/day.
		7–12	15 µg/day	60 µg/day.

Values established are RNI levels.

The substantial variation in selenium recommendations across international expert bodies reflects fundamental differences in methodology and data sources (Ref. 49).

3. Human Milk Composition

a. Selenium Concentration in Human Milk

Maternal diet and nutritional status affect the amount of selenium present in human milk. The average selenium content of mature human milk sampled between 2- and 6-months lactation appears to be relatively constant within a population group. However, selenium content in human milk varies greatly based on maternal selenium intakes, including variability in selenium soil content (Ref. 45).

There is wide interindividual variation in the selenium content of human milk, and the selenium content of hind milk (*i.e.,* milk at the end of an infant feeding) is greater than that of the fore milk (*i.e.,* milk at the beginning of the feeding). Studies report average selenium concentrations of mature human milk of 10 to 23 µg/L (with a range of 6 to 39 µg/L) (Refs. 45, 49).

b. Recent Data

The MILQ study (Ref. 36) reported a pooled median selenium concentration of 9 µg/L in human milk collected from mothers of infants 1–6 months of age, representing only 50 percent of the NASEM reference concentration of 18 µg/L used to establish the current AI. The study suggested that the current NASEM AI may overestimate selenium concentrations in human milk from well-nourished populations and called for updated recommendations informed by these study data (Ref. 36). The iHMNutD study reported a pooled weighted mean selenium concentration which converted to approximately 20.4 µg/L (Ref. 8). A 2019 study (Ref. 58) measured milk selenium concentrations in lactating Chinese women across three regions with varying selenium status. Among mothers with optimal selenium intake, the Beijing milk concentration was 27.8 µg/L; combined with an average milk volume of 0.55 L/day, this yielded a calculated AI of 15.29 µg/day for Chinese infants 0–3 months of age, consistent with the current Chinese AI of 15 µg/day for infants 0–6 months of age.

4. International Regulatory Standards for Infant Formula

Selenium specifications for infant formula vary among international regulatory bodies and expert organizations (table 4). The Codex Alimentarius Commission specifies a minimum of 1 µg/100 kcal and a GUL of 9 µg/100 kcal for infant formula (0–6 months of age) (Ref. 12), and a minimum of 2 µg/100 kcal and GUL of 9 µg/100 kcal for follow-on formula (6–12 months of age) (Ref. 37). The EU specifies a minimum of 3 µg/100 kcal and a maximum of 8.6 µg/100 kcal (Ref. 38). Other countries have adopted or proposed to adopt specifications aligned with Codex Alimentarius, including Food Standards Australia New Zealand (FSANZ) (Ref. 39), Health Canada (Ref. 40), and China (Refs. 41, 42).

The 1998 LSRO Panel report recommended a minimum selenium requirement of 1.5 µg/100 kcal and a maximum of 5 µg/100 kcal. The minimum value approximated the estimated value for the mean minus one standard deviation for the selenium concentration in human milk in countries in which selenium deficiency has not been recognized in breastfed infants. This recommended minimum level would provide an estimated 7.5 µg/day of selenium for young infants exclusively fed infant formula, an amount below the 1989 RDA (10 µg/day). The LSRO Panel was aware that there were disparities between some of its recommendations for nutrient levels in infant formulas and the 1989 RDAs; however, the history of use for a large population in which selenium deficiency had not been reported was regarded as a reasonable basis for recommending a minimum value for selenium in infant formula (Ref. 1; 78 FR 22442 at 22443, April 16, 2013).

The 1998 LSRO Panel report recommended a maximum selenium level for infant formula of 5 µg/100 kcal (33.5 µg/L). This recommendation was based on the upper limit of the range of selenium in human milk, which was considered to represent a history of use for a large population in which selenium toxicity had not been reported. The LSRO Panel report also indicated that, on a body weight basis, this level is far below the intake associated with the development of selenosis in adults (Ref. 1; 78 FR 22442 at 22444–22445).

Table 4 shows the requirements and recommendations of these international regulatory bodies and organizations.

TABLE 4—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR SELENIUM IN INFANT FORMULA

Organization	Age range	Minimum (µg/100 kcal)	Maximum (µg/100 kcal)	References
U.S. Current Standards	0–12 (months)	2	7	21 CFR 107.100.
LSRO [1]	0–12 (months)	1.5	5	LSRO, 1998.
Codex Alimentarius	0–6 (months)	1	9 (GUL)	CXS 72–1981.
	6–12 (months)	2	9 (GUL)	CXS 156–1987.
EU	0–12 (months)	3	8.6	Commission Delegated Regulation (EU) 2016/127.
Australia [2]	0–12 (months)	2	9 (GUL)	FSANZ P1028.
Canada [3]	0–12 (months)	1	9	Health Canada, 2025.
China	0–6 (months)	3	8.6	GB 10765–2021.
	6–12 (months)	2	8.6	GB 10766–2021.

[1] Recommended ranges.
[2] Values converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[3] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Selenium Intake

A randomized dose-response trial of healthy term infants from birth to 16 weeks of age fed infant formula containing selenium at three different concentrations and a breastfed reference group found that infants fed the formula containing a selenium level of 1.9 µg/100 kcal received sufficient selenium to meet their nutritional needs and that much of the selenium above the level of 1.9 µg/100 kcal was eliminated from the body (Ref. 59). An analysis of a randomized controlled trial investigating maternal selenium status during pregnancy and lactation in relation to infant birth outcomes across

898 mother-infant dyads in Guatemala, India, and Pakistan concluded that maternal selenium supplementation did not impact serum selenium concentrations in populations at high risk for deficiency, suggesting that supplementation may not overcome the impact of low dietary intake and the high demands of pregnancy and early lactation (Ref. 60). However, the authors noted that larger studies in high-risk regions are needed to further clarify the relationship between maternal selenium deficiency and infant outcomes (Ref. 60).

6. Evidence Evaluation and Rationale

Based on our review of available scientific data, information, and international standards, we conclude that the current minimum of 2 µg/100 kcal and maximum level of 7 µg/100 kcal for selenium in § 107.100 remain appropriate.

a. Maintaining the Minimum Specification of 2 µg/100 kcal

The current minimum of 2 µg/100 kcal is based primarily on two sources of evidence. First, NASEM's AI of 15 µg/day for infants 0–6 months of age, converted to an energy basis assuming 100 kcal/kg body weight/day intake, yields approximately 2.1 µg/100 kcal. FDA rounded this to 2 µg/100 kcal for the minimum specification (Refs. 45, 49). The current minimum provides adequate selenium to meet established AIs. For a 0–6-month-old infant consuming a typical daily infant formula intake, infant formula at the minimum specification provides 10.5 µg/day, which represents 70 percent of the NASEM AI of 15 µg/day (Refs. 45, 49). While this percentage may appear modest, it is important to note that the AI is based on the mean intake from human milk and is intended to meet or exceed the needs of nearly all individuals in the population (Refs. 45, 49). Second, the randomized dose-response trial described in section V.D.5 of this document provides direct clinical evidence supporting this minimum level, demonstrating that 1.9 µg/100 kcal was sufficient to achieve selenium status indicators comparable to breastfed infants (Ref. 59). Additionally, the current minimum also aligns well with international standards (Ref. 49).

Moreover, recent evidence from the MILQ study suggests that the pooled median total selenium intake from human milk is 7.3 µg/day from 1 to 6 months postpartum, representing only 49 percent of the NASEM AI (Ref. 36). This finding raises questions about whether the NASEM AI may overestimate infant selenium requirements, as the MILQ study population of well-nourished mothers and healthy, normally developing infants showed no evidence of selenium deficiency despite intakes well below the established AI. However, the current minimum specification of 2 µg/100 kcal, providing 10.4 µg/day, exceeds the MILQ median intake by 42 percent, offering a conservative margin of safety.

The minimum specification also accounts for potential differences in bioavailability. The U.S. minimum was established as a level providing sufficient amounts to account for potential differences in bioavailability among various infant formula types, including a conservative estimate of 50 percent relative bioavailability of selenium from soy protein-based formulas compared to human milk (Ref. 1). This conservative approach ensures that all formula types, regardless of protein source, provide adequate selenium.

Human milk composition data support the current minimum. The current minimum of 2 µg/100 kcal exceeds the estimated median value of 1.3 µg/100 kcal from the MILQ study by approximately 54 percent, providing a safety margin to account for population variability and potential differences in bioavailability (Refs. 36, 49). The MILQ study authors noted that the substantially lower concentrations as compared with NASEM estimates suggested that the differences may be due to maternal dietary selenium intake, which varies with regional soil selenium content (Ref. 36). The lower MILQ study values as compared with other studies may reflect populations with lower selenium intake rather than indicating that lower concentrations are adequate (Refs. 8, 36, 49, 58). Data from other well-nourished populations (Refs. 8, 58) support selenium concentrations closer to the NASEM reference value. The wide geographic variability in human milk selenium concentrations underscores the importance of maintaining a minimum specification that ensures adequacy across diverse populations and accounts for the serious health consequences of selenium deficiency, including Keshan disease (Ref. 49).

b. Maintaining the Maximum Specification of 7 µg/100 kcal

The current maximum is based on safety considerations. NASEM established a UL of approximately 7 µg/kg/day for infants 0–6 months of age, which approximates 7 µg/100 kcal (Ref. 45). The UL is defined as ''the highest daily intake level that is likely to pose no risk of adverse health effects in almost all individuals in a life stage group'' (Ref. 45). NASEM established this UL by relying on data on the concentration of selenium in human milk, which is not associated with known adverse effects.

The current maximum substantially exceeds median human milk content while maintaining a prudent limit (Ref. 49). Although the current maximum is approximately 5.4 times the median human milk concentration from the MILQ study population, the studies conducted in mothers with optimal selenium intake (North American data) and from well-nourished populations (in China) reported reference values of approximately 3.1 µg/100 kcal and 4.2 µg/100 kcal, respectively (Refs. 8, 49, 58). Relative to these higher reference values from populations with optimal selenium intake, the current maximum of 7 µg/100 kcal represents approximately 2.3 times the North American median and 1.7 times the concentration in milk from optimally nourished Chinese mothers.

The current maximum is conservative compared to most international standards. The current maximum is lower than the Codex Alimentarius GUL, the FSANZ GUL, and the Health Canada, EU, and China maximums (Ref. 49). The LSRO recommendation of a maximum selenium level for infant formula of 5 µg/100 kcal was based on the upper limit of the range of selenium in human milk and represented a history of use for a large population in which selenium toxicity had not been reported. The current maximum is higher than the LSRO recommendation but aligns with the NASEM UL, reflecting a conservative approach based on safety considerations while providing additional manufacturing flexibility (Ref. 49).

History of use also supports safety at the current maximum. The current maximum has demonstrated safety in practice since the level went into effect in 2016. Manufacturers have successfully met the current specification since 2016 without reported difficulties, suggesting that the current maximum does not impose undue constraints.

c. Consideration of the Evidence Base

There is wide variability in reported human milk selenium concentrations across studies and geographic regions, reflecting differences in maternal selenium intake, which is highly dependent on regional soil selenium

content. There are limited recent data from U.S. populations specifically, methodological variability across studies, and uncertainty about bioavailability differences between infant formula types and human milk. Recent evidence suggests that populations at high risk of selenium deficiency may have higher needs during pregnancy and lactation that cannot be easily met through supplementation alone and that selenium status can decline substantially during lactation even with supplementation (Ref. 60). Given these uncertainties, the associated consequences of dietary selenium deficiency (*i.e.,* Keshan disease), the potential for selenium status to decline during lactation, and the lack of evidence of adverse effects from current specifications, we believe a conservative approach in maintaining the required minimum level of 2 µg/100 kcal and maximum level of 7 µg/100 kcal is warranted.

E. Iodine (Proposed § 107.100(a))

The current requirements for iodine in infant formula are a minimum level of 5 µg/100 kcal and a maximum level of 75 µg/100 kcal (§ 107.100). Based on our analysis of scientific information and data since the 1998 comprehensive study of infant formula nutrients (Ref. 1), including infant formula iodine requirements in international standards, we propose to amend § 107.100(a) to increase the required minimum to 15 µg/100 kcal and decrease the required maximum to 50 µg/100 kcal.

1. Background

Iodine is an essential micronutrient whose primary physiological role is as an essential component of the thyroid hormones that regulate protein synthesis, enzymatic activity, and metabolic processes critical to normal growth and development (Refs. 1, 61). In infants, thyroid hormones are particularly important for myelination of the central nervous system, which is most active in the perinatal period and during early postnatal development; iodine deficiency during this critical window can irreversibly impair neuromotor development (Ref. 62).

Iodine (I_2) refers to the elemental form, while iodide (I^-) is the reduced, ionic form that predominates in food, water, and the body. Most dietary iodine is rapidly converted to iodide in the gastrointestinal tract prior to absorption (Ref. 62). Infant formula and human milk contain iodine primarily in the iodide form. In regulatory and nutritional contexts, the term ''iodine'' is used conventionally to refer to total iodine intake regardless of chemical form, and this convention is followed throughout this document.

a. Health Consequences of Iodine Deficiency

Iodine deficiency disorders identified throughout the lifespan include intellectual disability, hypothyroidism, goiter, cretinism, and varying degrees of growth and developmental abnormalities resulting from inadequate thyroid hormone production (Ref. 62). Fetal iodine deficiency resulting in cretinism occurs in areas where endemic goiters exist, generally in association with iodine intakes less than 25 µg/day (Ref. 1). Infants are among the most vulnerable populations for iodine deficiency because their intrathyroidal iodine stores are small, daily thyroid hormone turnover rates per body weight are higher than at any other time of life, and they are entirely dependent on dietary iodine from human milk or infant formula (Refs. 61, 62). Deficiencies of vitamin A, selenium, or iron can exacerbate the effects of iodine deficiency (Refs. 61, 62).

b. Health Consequences of Excess Iodine Intake

High iodine intakes have been associated with thyroiditis, goiter, hypothyroidism, hyperthyroidism, and sensitivity reactions (Ref. 62). Excess iodine can be harmful to infants, particularly premature infants, because excretion mechanisms may be unable to accommodate high intake levels, potentially resulting in transient hypothyroidism (Refs. 1, 61).

2. Nutrient Reference Values

a. NASEM

NASEM established AI values for iodine for infants in 2001 based on the observed mean iodine intake of infants exclusively fed human milk (Ref. 62). NASEM established an AI of 110 µg/day for infants 0–6 months of age and an AI of 130 µg/day for infants 7–12 months of age. The AI for infants 7–12 months of age was extrapolated from the AI for younger infants using a metabolic weight ratio (Ref. 62). NASEM judged the UL to be not determinable for infants due to insufficient data on adverse effects and concern about the infant's ability to handle excess amounts (Ref. 62).

b. EFSA

EFSA published dietary reference values for iodine in 2014 (Ref. 63). EFSA did not establish an AI for iodine in infants 0–6 months of age, during which period exclusive breastfeeding is assumed to provide an adequate iodine supply. For infants 7–11 months of age, EFSA established an AI of 70 µg/day based on the urinary iodine concentration (UIC) threshold (100 µg/L) from school-age children, extrapolated to infants using age-adjusted urinary volumes and body weight. The EFSA Panel concluded that an iodine intake of 90 µg/day is adequate for the majority of infants, and, since there is no reason to assume that infants from birth to 6 months of age need more iodine than infants in the second half of the first year of life, an intake of 70 µg/day is adequate for the majority of infants from birth to 12 months of age (Ref. 63). EFSA did not establish a UL for iodine for infants.

c. WHO

WHO, together with the United Nations Children's Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD), established an RNI of 90 µg/day for children under 5 years of age (0–59 months) based on physiological evidence that positive iodine balance requires iodine intake of at least 15 µg/kg/day, approximating 90 µg/day for a 6-month-old infant weighing 6 kg (Refs. 64, 65). The recommended value supports normal thyroid hormone production without stressing the iodide trapping mechanism. While a UL for infants was not established, daily intakes exceeding 180 µg/day were not expected to provide additional health benefit and may be associated with impaired thyroid function. However, the Consultation set upper limits of probable safe intake for infants at 150 µg/kg/day (0–6 months of age) and 140 µg/kg/day (7–12 months of age) (Ref. 64).

d. D–A–CH (Germany, Austria, Switzerland)

D–A–CH established a reference value for daily iodine intake for infants of 80 µg/day for infants 0–12 months of age in 2025 (Ref. 66). This value represents a doubling of the previous D–A–CH reference value of 40 µg/day. According to the D–A–CH reference values, the updated iodine recommendation for infants differs methodologically from the previous reference value and allows the revised reference value to be expressed as a recommended intake rather than an estimated value (Refs. 61, 66). No UL was determined.

e. Australian NHMRC/New Zealand MoH

Australia and New Zealand established AIs for iodine in 2006 (Ref. 53). The AI for infants 0–6 months of age was calculated by multiplying the

average intake of human milk (0.78 L/day) by the average concentration of iodine in human milk (115 µg/L), consistent with the 2001 recommendation (Ref. 64), in addition to other studies, yielding an AI of 90 µg/day. The AI for infants 7–12 months of age was extrapolated from that of younger infants using a metabolic weight ratio, yielding an AI of 110 µg/day. No UL was determined (Ref. 53).

f. Comparison of International Recommendations

Table 5 shows the iodine AIs established by NASEM, EFSA, WHO, D–A–CH, and NHMRC/MoH.

TABLE 5—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF IODINE

Organization	Year	Age range (months)	Adequate intake (µg/day)	Tolerable upper intake level
NASEM	2001	0–6	110	ND
		7–12	130	ND
EFSA	2014	7–11	70	ND
WHO	2001	0–12	*90	ND
D–A–CH	2025	0–12	80	ND
Australian NHMRC/New Zealand MoH	2006	0–6	90	ND
		7–12	110	ND

*Values established are RNI levels.

The variation in iodine recommendations across international expert bodies reflects differences in methodology, data sources, and the timing of each review (Ref. 61). A key methodological difference across all bodies is the degree to which human milk iodine data are used as the primary reference. Unlike many other minerals, iodine in human milk is not homeostatically regulated (*i.e.,* automatically kept at a consistent level by the body) but directly reflects maternal iodine status and population-level iodine exposure. Consequently, human milk iodine concentrations vary substantially across populations and over time, and the choice of reference population for human milk data has a direct and substantial effect on the resulting AI (Refs. 36, 61, 67).

3. Human Milk Composition

There is wide variability in milk iodine concentrations across populations, driven by differences in national salt iodization policies, dietary patterns, geographic variability, and dietary supplement use (Ref. 61). Consequently, no single human milk iodine concentration can be considered universally representative. The large, multi-country MILQ study ultimately chose not to generate pooled iodine reference values or percentile curves because of this between-country variability, unlike its approach to other minerals (Ref. 36).

4. International Regulatory Standards for Infant Formula

Iodine specifications for infant formula vary considerably among international regulatory bodies and expert organizations (see table 6). The current U.S. specification of 5 µg/100 kcal (minimum) to 75 µg/100 kcal (maximum) is an outlier relative to international standards. Specifically, the U.S. minimum falls below the current minimum thresholds established by major international regulatory frameworks, while the U.S. maximum exceeds their corresponding upper levels.

Across the international regulatory frameworks assessed, minimum iodine specifications range from 10 to 15 µg/100 kcal, while maximum levels or GULs range from 29 to 60 µg/100 kcal. Codex Alimentarius, FSANZ, and Health Canada share identical specifications (10 µg/100 kcal minimum; 60 µg/100 kcal maximum or GUL) (Refs. 12, 37, 39, 40). China also has a maximum of 60 µg/100 kcal with a higher minimum of 15 µg/100 kcal (Refs. 41, 42). The EU specifies the narrowest range, with a minimum of 15 µg/100 kcal and a maximum of 29 µg/100 kcal (Ref. 38). The EU minimum was derived from EFSA's 2014 scientific opinion, which determined that a minimum iodine content of 14 µg/100 kcal (rounded up to 15 µg/100 kcal) is necessary for an infant consuming approximately 500 kcal/day to achieve an adequate intake of 70 µg/day (Ref. 7).

The 1998 LSRO Panel report recommended a minimum of 8 µg/100 kcal and a maximum of 35 µg/100 kcal (Ref. 1). The LSRO minimum was based on the then-current RDA for iodine of 40 µg/day for infants 0–6 months of age, which translates to 8 µg/100 kcal for a 5 kg infant consuming 100 kcal/kg/day (Ref. 44). Human milk was not used as the reference standard. Data obtained from iodine balance studies further support this level, estimating the dietary requirement at no more than 8.6 µg/kg/day (Ref. 1). The LSRO recommended maximum of 35 µg/100 kcal represented approximately the 75th percentile of FDA analyses of marketed formulas and was considered the lowest feasible value at the time (Ref. 1). The LSRO Panel considered the U.S. maximum of 75 µg/100 kcal to be too high.

Table 6 shows the requirements and recommendations of these international bodies and organizations.

TABLE 6—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR IODINE IN INFANT FORMULA

Organization	Age range (months)	Minimum (µg/100 kcal)	Maximum (µg/100 kcal)	Reference
U.S. Current Standards	0–12	5	75	21 CFR 107.100.
LSRO [1]	0–12	8	35	LSRO, 1998.
Codex Alimentarius	0–12	10	60 (GUL)	CXS 72–1981, CXS 156–1987.
EU	0–12	15	29	Commission Delegated Regulation (EU) 2016/127.
Australia [2]	0–12	10	60 (GUL)	FSANZ P1028.
Canada [3]	0–12	10	60	Health Canada, 2025.
China	0–12	15	60	GB 10765–2021, GB 10766–2021.

[1] Recommended ranges.

[2] Values converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[3] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Iodine Intake

The most direct evidence on iodine requirements in early infancy comes from a 2016 balance study in formula-fed infants 2–5 months of age (Ref. 68). The study found that zero iodine balance was achieved at approximately 70 µg/day and found iodine retention to be linear up to 300 µg/day with no evidence of down-regulation (Ref. 68). These findings led the authors to propose an EAR of 72 µg/day and an RDA of 80 µg/day, suggesting the current AI of 110 µg/day for infants 0–6 months of age may be set too high. The study also proposed a urinary iodine concentration threshold of approximately 125 µg/L as indicative of adequacy, slightly above the WHO cutoff of 100 µg/L (Ref. 68). An additional study to evaluate iodine status in settings with universal salt iodization supports these estimates (Refs. 61, 69).

Moreover, a 2022 secondary analysis of a randomized controlled trial (Ref. 70) provided independent corroboration of the proposed EAR. Median UICs were greater than or equal to 100 µg/L at all ages from 1 to 12 months, and more than 98 percent of infants met the proposed EAR of 72 µg/day. These findings support the appropriateness of the lower estimated iodine requirement derived from the 2016 balance study (Refs. 61, 68, 70).

These newer estimates are broadly consistent with established reference values. WHO, together with UNICEF and ICCIDD, established an RNI of 90 µg/day for children under 5 years of age (0–59 months) and identified a UIC of greater than or equal to 100 µg/L as indicative of adequate iodine nutrition, while noting that daily intakes exceeding 180 µg/day are not expected to provide additional health benefit (Refs. 64, 65). A narrative review of the literature from 1960 to 2007 proposed an iodine requirement of greater than or equal to 15 µg/kg/day (≥90 µg/day) for full-term infants (Ref. 71). Further, the 2016 balance study suggests that the true AR may sit somewhat below the established RNI, though the difference between the proposed RDA (80 µg/day) and the established RNI (90 µg/day) is modest, and both fall below NASEM's current AIs of 110 and 130 µg/day.

Studies conducted in populations with high environmental iodine exposure have documented adverse thyroid outcomes in infants and young children at elevated iodine intakes. A cross-sectional study documented subclinical hypothyroidism in 7.4 percent and elevated thyroglobulin in 15.8 percent of participants 6–24 months of age in a population with high environmental iodine exposure (Ref. 72). An observational study found that high iodine intakes were associated with subclinical hypothyroidism in 9 percent of children and elevated thyroglobulin in 13 percent at 3-year followup (Ref. 73).

The excess iodine exposures represented in these studies arise primarily from environmental sources and supplementation rather than from infant formula, and, in some cases, involve intake levels far exceeding those achievable through formula feeding alone. The studies were also conducted in populations with iodine exposure profiles markedly different from typical U.S. infants, limiting direct generalizability. Nevertheless, the thyroid and growth outcomes observed across these populations provide useful context for understanding the biological consequences of sustained elevated iodine intake in early infancy, a period of particular vulnerability to disruption of thyroid function (Ref. 61).

6. Evidence Evaluation and Rationale

a. Rationale for Increasing the Minimum Specification to 15 µg/100 kcal

The current minimum specification of 5 µg/100 kcal has not been updated since 1985 (50 FR 45106, October 30, 1985) and is no longer supported by more recently available scientific evidence. At this level, an infant 0–6 months of age would receive only approximately 26 µg/day of iodine, representing 24 percent of the NASEM AI of 110 µg/day (Ref. 62) and 29 percent of the WHO RNI of 90 µg/day (Ref. 65) (see table 7). An infant 6–12 months of age would receive approximately 20 µg/day at the current minimum, representing 16 percent of the NASEM AI of 130 µg/day and 23 percent of the WHO RNI of 90 µg/day. Intakes at both age groups fall below even the experimentally derived EAR of 72 µg/day (Ref. 68), representing 37 percent and 28 percent of that threshold for infants 0–6 months and 6–12 months of age, respectively, the most conservative available estimate of average iodine requirement. The 1998 LSRO Panel also recommended a higher minimum of 8 µg/100 kcal based on the then-current RDA of 40 µg/day for infants 0–6 months of age (Ref. 1).

TABLE 7—ESTIMATED DAILY IODINE INTAKE AT THE CURRENT AND PROPOSED MINIMUM SPECIFICATIONS EXPRESSED AS A PERCENTAGE OF NUTRIENT REFERENCE VALUES

Typical infant formula intake [1]	Energy intake from infant formula (kcal/day)	Estimated iodine intake (µg/day)	% NASEM AI	% WHO RNI	% Balance study EAR	% Balance study RDA
Current Minimum Specification (5 µg/100 kcal)						
0–6 months	527	26.3	24	29	37	33
6–12 months	406	20.3	16	23	28	25
Proposed Minimum Specification (15 µg/100 kcal)						
0–6 months	527	79.1	72	88	110	99
6–12 months	406	60.9	47	68	85	76

Reference values used: NASEM AI: 110 µg/day (0–6 months of age) and 130 µg/day (6–12 months of age) (Ref. 62); WHO RNI: 90 µg/day (0–12 months of age) (Ref. 65); 2016 balance study EAR (proposed): 72 µg/day; and 2016 balance study RDA (proposed): 80 µg/day (Ref. 68).
[1] Typical intake based on assumed formula consumption of 0.78 L/day (0–6 months of age) and 0.60 L/day (6–12 months of age) at 676 kcal/L.

FDA acknowledges that, at typical intake volumes, the proposed minimum of 15 µg/100 kcal does not fully meet the NASEM AI or WHO RNI for either age group, reflecting a challenge of setting a minimum specification for a nutrient with varying nutrient reference values among expert bodies. The NASEM AIs are based on the mean intake from human milk and are intended to reflect observed intakes in healthy populations rather than a minimum requirement threshold. The proposed minimum is intended to ensure an adequate iodine provision consistent with the best available evidence on iodine requirements in infancy (Ref. 61).

The current U.S. minimum of 5 µg/100 kcal is the lowest of any major regulatory jurisdiction. All other major international regulatory frameworks have established minimums of 10 to 15 µg/100 kcal: Codex Alimentarius, FSANZ, and Health Canada specify a minimum of 10 µg/100 kcal, while the EU and China specify a minimum of 15 µg/100 kcal (table 6). The proposed minimum of 15 µg/100 kcal aligns with the standards from the EU and China and represents a scientifically supported improvement over the current U.S. minimum.

Since the 1998 LSRO Panel report (Ref. 1), the evidence base has expanded substantially (see Refs. 68, 69, 70, 74) and consistently supports a minimum above the current 5 µg/100 kcal (Ref. 61). Additionally, a few comments in response to FDA's 2025 RFI on nutrient requirements for infant formula express support for increasing the minimum iodine level (90 FR 20475, May 14, 2025).

b. Rationale for Decreasing the Maximum Specification to 50 µg/100 kcal

The current FDA maximum of 75 µg/100 kcal has not been revised since 1985 (50 FR 45106, October 30, 1985). At this level, an infant 0–6 months of age consuming a typical daily infant formula intake would receive approximately 396 µg/day of iodine, and an infant 6–12 months of age consuming a typical daily infant formula intake would receive approximately 305 µg/day. These levels substantially exceed upper levels of probable safe intake (Ref. 75), as well as estimated intakes associated with subclinical thyroid dysfunction in several applicable studies (Refs. 72, 73).

The limitations of the current maximum are further illustrated by NHANES-derived estimates of energy intake from infant formula among high consumers (Refs. 13, 14, 15, 16, 17, 18). At the 90th percentile of energy intake from infant formula (836 kcal/day for infants 0–6 months of age and 794 kcal/day for infants 6–12 months of age), the current maximum of 75 µg/100 kcal would provide iodine intakes of approximately 627 µg/day and 596 µg/day, respectively.

These findings reinforce the need for a significant downward revision of the maximum specification, particularly given the absence of a formal UL for infants and the linear iodine retention observed across intake levels (Ref. 69). Because no UL has been established for infants by any major international expert body (Ref. 62), the safety margin between the current maximum and any established toxicity threshold cannot be precisely quantified, a significant limitation that further underscores the need for a decrease (Ref. 61).

As discussed in section V.E.5 of this document, other major international regulatory frameworks have established GULs or maximums substantially below the current U.S. maximum of 75 µg/100 kcal: Codex Alimentarius, FSANZ, Health Canada, and China specify a GUL or maximum of 60 µg/100 kcal, and the EU specifies a maximum of 29 µg/100 kcal (table 6). In 1998, the LSRO Panel report explicitly concluded that the current maximum of 75 µg/100 kcal was too high and recommended a maximum of 35 µg/100 kcal based on the 75th percentile of FDA analyses of marketed formulas at the time (Ref. 1). The proposed maximum of 50 µg/100 kcal represents a substantial reduction from the current maximum and falls within international consensus and available scientific evidence to reduce risk of excessive exposure while allowing manufacturing flexibility.

Since the 1998 LSRO Panel report, several lines of evidence have emerged that support reducing the maximum specification. A Technical Consultation document noted that daily intakes exceeding 180 µg/day are not expected to provide additional health benefit and may be associated with impaired thyroid function (Ref. 75). Consistent with this, studies conducted in populations with high environmental iodine exposure have documented adverse thyroid outcomes in infants and young children at elevated iodine intakes (Refs. 72, 73). A balance study (Ref. 68) further found that iodine retention was linear across all intake levels up to 300 µg/day, with no evidence of homeostatic down-regulation (*i.e.,* the body's ability to automatically reduce absorption or increase excretion to prevent excess buildup) at higher intakes, suggesting that infants do not have robust mechanisms to limit iodine retention at high intakes and that higher formula iodine concentrations may result in proportionally higher retention with uncertain long-term consequences. FDA considers that these findings, while derived from populations with environmental iodine excess rather than formula-fed infants, provide the best available evidence for understanding the biological consequences of sustained elevated iodine intake in early infancy and collectively support a significant downward revision of the maximum (Ref. 61).

At 50 µg/100 kcal, an infant 0–6 months of age consuming a typical daily infant formula intake would receive approximately 264 µg/day of iodine, and an infant 6–12 months of age consuming a typical daily infant formula intake would receive approximately 203 µg/day of iodine. Among higher consumers, NHANES-derived estimates of energy intake from infant formula indicate that, at the 90th percentile of energy intake from infant formula (836 kcal/day for infants 0–6 months of age and 794 kcal/day for infants 6–12 months of age), the proposed maximum of 50 µg/100 kcal would permit iodine intakes of approximately 418 µg/day and 397 µg/day, respectively (Refs. 13, 14, 15, 16, 17, 18, 61).

FDA acknowledges that these intakes exceed 180 µg/day, the level above which additional health benefits are unlikely (Ref. 75); however, they are below the probable safe upper limits of 150 µg/kg/day for infants 0–6 months of age (reference weight: 6 kg) and 140 µg/kg/day for infants 7–12 months of age (reference weight: 8.9 kg). Using the reference weights identified in the report, these correspond to absolute upper limits of approximately 900 µg/day and 1,246 µg/day, respectively (Ref. 64). In populations with excess environmental exposure to iodine, reports of subclinical hypothyroidism in infants and young children have been documented (Refs. 72, 73). However, the evidence from these studies is derived from populations with environmental iodine excess rather than routine feeding of formula-fed infants, and the generalizability of these findings to U.S. formula-fed infants is uncertain. Because no UL has been established for infants, the percentage of UL at the proposed maximum cannot be calculated: a significant limitation that FDA acknowledges. The proposed maximum reflects a conservative approach based primarily on international regulatory alignment, rather than a formally derived safety margin (Ref. 61).

F. Potassium

The current requirements for potassium in infant formula are a minimum level of 80 mg/100 kcal and a maximum level of 200 mg/100 kcal (§ 107.100). Based on our analysis of scientific information and data since the 1998 LSRO Panel report (Ref. 1), including infant formula potassium requirements in international standards, we conclude that the required potassium levels in § 107.100 remain appropriate.

1. Background

Potassium is an essential nutrient that serves critical physiological functions in infants, including regulation of cell volume, membrane transport, cardiac conduction, nerve signaling, and muscle contraction (Ref. 76). Most of the potassium in the body is found inside cells; potassium and sodium are interrelated and function together across cell membranes to regulate cell volume and membrane transport. Potassium also plays a role in regulating water and acid-base balance in the blood and tissues (Ref. 76). Potassium metabolism is tightly controlled over a wide range of dietary intakes, primarily regulated via the kidneys. Assessing potassium status is difficult because most potassium in the body resides inside cells, and no sensitive biomarker exists that can characterize the distribution of potassium requirements in healthy populations (Refs. 76, 77).

a. Health Consequences of Potassium Deficiency

Hypokalemia (*i.e.,* low blood potassium; serum potassium ≤3.5 mmol/L) can result from inadequate intake, excessive losses, or transcellular shifts in potassium. Hypokalemia from dietary inadequacy alone is rare in healthy individuals because the kidney efficiently conserves potassium at low dietary intakes (Ref. 77). Potassium depletion studies conducted in adults over short periods have shown that very low intakes (0–390 mg/day) can lead to hypokalemia. Inadequate potassium intake may also contribute to impaired glycemic control (Ref. 78). However, in clinical settings, hypokalemia is more commonly caused by abnormal losses of potassium (renal or gastrointestinal) or medications promoting transcellular shifts (Ref. 76).

b. Health Consequences of Excess Potassium Intake

In healthy individuals with normal kidney function, excess potassium is efficiently excreted and toxicity from dietary sources is unlikely. Hyperkalemia (*i.e.,* high blood potassium) is of greater concern in individuals with chronic kidney disease, diabetes, heart failure, adrenal insufficiency, or those taking certain medications. In addition, there is no evidence that high intakes of potassium cause hyperkalemia or other adverse effects in adults with normal kidney function (Ref. 77).

2. Nutrient Reference Values

a. NASEM

NASEM published DRIs for water, potassium, sodium, chloride, and sulfate in 2005 and published an updated report specific to sodium and potassium in 2019 (Refs. 19, 76). Because no EAR could be established due to the absence of a sensitive biomarker of potassium status and limitations in available balance study data, the committee established AI values for potassium in infants based on estimated potassium intakes from human milk (Ref. 76). The AI for infants 0–6 months of age was set at 400 mg/day, derived by multiplying the average human milk intake (0.78 L/day) by the average human milk potassium concentration (515 mg/L) from a meta-analysis of 15 studies focusing on the first 6 months of lactation. The AI for infants 7–12 months of age was set at 860 mg/day, based on estimated intakes from human milk plus an estimated potassium intake from complementary foods of approximately 600 mg/day, derived from NHANES 2003–2010 and FITS 2016 data (Ref. 76). The AI for infants 0–6 months of age is unchanged from the 2005 DRI report, while the AI for infants 7–12 months of age was increased from 700 mg/day (2005) to 860 mg/day (2019), reflecting updated estimates of complementary food contributions (Refs. 19, 76).

No UL has been established for potassium in infants. The 2019 NASEM committee concluded that ''there is insufficient evidence of potassium toxicity risk within the apparently healthy population to establish a potassium Tolerable Upper Intake Level (UL)'' (Ref. 76).

b. EFSA

The EFSA Panel established an AI of 750 mg/day for infants 7–11 months of age, extrapolated from the adult AI using isometric scaling and a growth factor (Ref. 79). No AI was established for infants 0–6 months of age. The EFSA NDA Panel estimated an approximate midpoint potassium concentration in mature human milk of 500 mg/L based on data from multiple studies of women from Western countries (Ref. 79).

c. D–A–CH

The D–A–CH reference values established estimated values of 400 mg/day for infants 0–4 months of age and 600 mg/day for infants 4–12 months of age. The authors based the 0–4-month estimate on an average human milk intake of 750 mL/day and a mean potassium content of 500 mg/L. They calculated the 4–12-month estimate by extrapolating from the younger group's value and adjusting for differences in reference body weight (Ref. 80).

d. Australian NHMRC/New Zealand MoH

NHMRC/MoH (2006) (Ref. 53) derived the AI for infants 0–6 months of age as 400 mg/day, calculated by multiplying the average human milk intake (0.78 L/day) by the average human milk potassium concentration (500 mg/L). NHMRC/MoH derived an AI of 700 mg/day for infants 7–12 months of age, calculated by assuming an average 0.6 L/day of human milk intake plus 440 mg/day from complementary foods.

e. Comparison of International Recommendations

Table 8 shows AIs of potassium for NASEM, D–A–CH, EFSA, and NHMRC/MoH.

TABLE 5—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF IODINE

Organization	Year	Age range (months)	Adequate intake (mg/day)	Tolerable upper intake level
NASEM	2019	0–6	400	ND
		7–12	860	ND
D–A–CH	2017	0–4	400	ND
		4–12	600	ND
EFSA	2016	7–11	750	ND

TABLE 5—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF IODINE—Continued

Organization	Year	Age range (months)	Adequate intake (mg/day)	Tolerable upper intake level
Australian NHMRC/New Zealand MoH	2006	0–6	400	ND
		7–12	700	ND

There is consistency across international bodies in the AI established for young infants (0–6 months of age). Divergence in AIs for older infants (7–12 months of age) across international bodies is primarily attributable to methodological differences in estimating potassium intake from complementary foods. EFSA used a different approach entirely, extrapolating from the adult AI using isometric scaling rather than observed infant intake data.

3. Human Milk Composition

Maternal dietary intake does not strongly influence human milk potassium concentrations (Ref. 76). Human milk potassium concentrations decline over the course of lactation (Ref. 79). Four sources informed the analysis of potassium concentrations in human milk: the 2019 NASEM meta-analysis (Ref. 76), the 2016 EFSA NDA Panel review (Ref. 79), the iHMNutD study (Ref. 8), and the MILQ study (Ref. 36).

In 2019, NASEM conducted a meta-analysis of 15 longitudinal and cross-sectional studies (1980–2017) and estimated mean potassium concentrations of 515 mg/L (95 percent confidence interval (CI): 472.76–557.81 mg/L) for the 0–6-month interval and 437 mg/L (95 percent CI: 367.89–505.22 mg/L) for the 7–12-month interval (Ref. 76). The 2016 EFSA Panel reviewed data from eight studies (1982–2012) and derived an estimate of approximately 500 mg/L as the midpoint concentration (Ref. 79). The iHMNutD study identified 10 eligible North American studies (1980–2024; total n = 905) and estimated a weighted mean potassium concentration of 573 ± 75 mg/L (Ref. 8). Additionally, the MILQ study, the most comprehensive recent data, reported a pooled median of 542 mg/L (interquartile range (IQR): 485–609 mg/L) from 1 to 6 months of lactation (Ref. 36).

Across all four sources, central estimates of potassium concentration in mature human milk ranged from approximately 500 to 573 mg/L (Refs. 8, 36, 76, 79). The NASEM estimate for human milk potassium content for infants 7–12 months of age (437 mg/L) (Ref. 76) was notably lower than the estimate for younger infants, consistent with the expected decline in potassium concentration over the course of lactation. While estimates derived from NASEM, EFSA, and the iHMNutD study show a degree of consistency, this convergence should be interpreted with some caution, as the three analyses draw from an overlapping body of foundational literature, particularly studies conducted in North American populations during the 1980s and 1990s (Ref. 77). The MILQ study (Ref. 36) provides broader geographic evidence consistent with the range of concentrations observed in North American estimates.

4. International Regulatory Standards for Infant Formula

The current U.S. minimum requirement for potassium aligns with the EU and meets or exceeds the minimum levels set by most other international bodies. The U.S. maximum of 200 mg/100 kcal exceeds most international standards, with only China's standard for infants 6–12 months of age (225 mg/100 kcal) surpassing it (see table 9).

In its 1998 comprehensive review, the LSRO Panel recommended a potassium range of 60–160 mg/100 kcal for infants 0–12 months of age. The recommended minimum was derived from the mean minus one standard deviation of potassium concentrations in mature human milk, with no evidence identified to suggest differences in potassium bioavailability between human milk and infant formula. The recommended maximum of 160 mg/100 kcal was based on the 90th percentile of FDA analyses of commercially available infant formulas at the time (Ref. 1).

Table 9 shows the requirements and recommendations of these international regulatory bodies and organizations.

TABLE 9—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR POTASSIUM IN INFANT FORMULA

Organization	Age range (months)	Minimum (mg/100 kcal)	Maximum (mg/100 kcal)	Reference
U.S. Current Standards	0–12	80	200	21 CFR 107.100.
LSRO [1]	0–12	60	160	LSRO, 1998.
Codex Alimentarius	0–12	60	180	CXS 72–1981, CXS 156–1987.
EU	0–12	80	160	Commission Delegated Regulation (EU) 2016/127.
Australia [2]	0–12	60	180	FSANZ P1028.
Canada [3]	0–12	60	180	Health Canada, 2025.
China	0–6	70	180	GB 10765–2021.
	6–12	75	225	GB 10766–2021.

[1] Recommended ranges.
[2] Values converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[3] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Potassium Intake

Several U.S.-based national dietary surveys have assessed potassium intake in U.S. infants and toddlers, consistently demonstrating that most infants meet or exceed established AIs for potassium. Data are available primarily from three iterations of FITS (FITS 2002, 2008, and 2016) (Refs. 43, 81, 82, 83) and from NHANES 2009–2012 (Ref. 84).

Mean potassium intakes for infants 0–6 months of age generally met or exceeded the AI of 400 mg/day. Mean intakes ranged from approximately 570 to 700 mg/day across datasets. At the 10th percentile, intakes ranged from

approximately 387 to 414 mg/day across FITS 2008 and FITS 2016, close to the AI, suggesting that most infants in this age group had potassium intakes at or above the recommended level.

Mean potassium intakes for infants 7–12 months of age consistently exceeded the current AI of 860 mg/day and ranged from approximately 1,085 to 1,225 mg/day across three FITS iterations and NHANES 2009–2012. The 10th percentile of usual potassium intake ranged from approximately 650 to 791 mg/day across available studies, falling below the current AI of 860 mg/day. While most infants had adequate intakes, a small proportion had intakes near or below the AI.

Several methodological limitations should be considered. Potassium intake estimates rely on proxy-reported 24-hour dietary recalls subject to recall bias. Human milk volumes were not directly measured but estimated using standardized assumptions, and some analyses excluded the youngest infants from intake modeling. The available data do not include information on health outcomes associated with potassium intake levels. As such, the extent to which current intakes translate to clinical outcomes cannot be determined from these data alone (Ref. 77).

6. Evidence Evaluation and Rationale

Based on the review of available scientific data, information, and international standards, we conclude that the current minimum level of 80 mg/100 kcal and maximum level of 200 mg/100 kcal for potassium in § 107.100 remain appropriate.

a. Maintaining the Minimum Specification of 80 mg/100 kcal

The current minimum of 80 mg/100 kcal is consistent with human milk potassium concentrations and provides potassium intakes that meet or exceed established AIs when applied to typical formula consumption patterns. The most current estimates of human milk potassium concentration range from approximately 77 to 88 mg/100 kcal (derived from 500 to 573 mg/L at a typical energy density of 650 kcal/L) (Refs. 8, 36, 76, 77, 79). The current minimum falls within this range.

Applied to typical formula consumption patterns, the current minimum provides potassium intakes that meet or exceed NASEM (2019) AIs for both infant age groups. For an infant 0–6 months of age consuming a typical daily infant formula intake, the minimum specification of 80 mg/100 kcal provides approximately 422 mg/day, which is 105 percent of the AI of 400 mg/day. For an infant 7–12 months of age consuming a typical daily infant formula intake, the minimum provides approximately 324 mg/day from formula alone. When combined with the estimated complementary food contribution of approximately 600 mg/day (Ref. 76), total intake would be approximately 920 mg/day, which is 107 percent of the AI of 860 mg/day. These calculations demonstrate that the current minimum supports adequate potassium intake across the first year of life (Ref. 77).

Population intake data provide contextual support for maintaining the current minimum. Across several large national surveys, mean potassium intakes for infants 0–6 months of age ranged from approximately 570 to 700 mg/day, and for infants 6–12 months of age ranged from approximately 1,085 to 1,225 mg/day, with all mean estimates exceeding the respective AIs (Refs. 43, 81, 82, 83, 84).

The current U.S. minimum is consistent with or above international regulatory standards. FDA considered whether the minimum should be lowered to 60 mg/100 kcal to align with Codex Alimentarius, FSANZ, Health Canada, and LSRO; however, lowering the minimum to 60 mg/100 kcal would reduce the daily potassium intake from formula for infants 0–6 months of age to approximately 78 percent of the AI, reducing the margin of adequacy for infants consuming formula as their sole source of nutrition. Maintaining the current minimum of 80 mg/100 kcal is supported by human milk composition data and U.S. population intake data and falls within the range of minimums set by international standards. FDA has not identified evidence that the current minimum is nutritionally insufficient or presents manufacturing challenges.

b. Maintaining the Maximum Specification of 200 mg/100 kcal

The current maximum of 200 mg/100 kcal was originally established based on the potassium content of cow milk, which was considered to represent a significant but tolerable burden on the kidneys for healthy infants with normal renal function (Ref. 85). After reviewing the available scientific evidence, FDA concludes that this maximum remains appropriate (Ref. 77).

No authoritative body has established a UL for potassium in infants (Refs. 1, 76, 77, 79). However, the current maximum of 200 mg/100 kcal has been in effect since the 1980 Infant Formula Act was enacted without documented adverse effects attributable to potassium intake from infant formula in healthy infants (Ref. 77).

The current maximum of 200 mg/100 kcal provides a substantial margin above the potassium content of human milk (approximately 77–88 mg/100 kcal), positioned at approximately 227–260 percent of the mean mature human milk potassium content on a per-calorie basis (Ref. 77). Applied to typical infant formula daily consumption, the current maximum would provide approximately 1,054 mg/day for an infant 0–6 months of age and approximately 812 mg/day from formula alone for an infant 7–12 months of age. These intakes substantially exceed the AIs but remain well below the levels associated with adverse effects in healthy infants with normal renal function (Refs. 1, 77).

Internationally, maximum specifications range from 160 to 180 mg/100 kcal for infants 0–6 months of age and up to 225 mg/100 kcal for infants 6–12 months of age, with the U.S. maximum of 200 mg/100 kcal falling within the upper portion of this range (see table 9). FDA considered whether the maximum should be lowered to align with the international consensus range and concludes that such a change is not warranted at this time. No UL has been established for potassium in infants, no documented adverse effects from dietary potassium intake at the current maximum have been identified, and lowering the maximum would reduce manufacturing flexibility without a demonstrated safety benefit. The LSRO Panel's recommended maximum of 160 mg/100 kcal was based on the 90th percentile of FDA analyses of infant formulas on the market at that time, rather than on safety concerns (Ref. 1). FDA also considered whether the maximum should be raised and concludes this is not warranted. No evidence was identified suggesting that higher potassium levels in infant formula would provide nutritional benefits (Ref. 77).

c. Consideration of the Evidence Base

FDA acknowledges several uncertainties in the evidence base. No sensitive biomarker of potassium status has been identified that can be used to assess adequacy at the population level (Refs. 76, 79). The AIs for infants are derived from observed intake data rather than experimental determination of requirements, and the AI for infants 7–12 months of age is sensitive to assumptions about complementary food contributions. Human milk potassium concentrations vary across studies, stages of lactation, and populations. Population intake data are based on proxy-reported dietary recalls not linked to health outcomes. Given these limitations, FDA considers that

maintaining the current specifications, which have a demonstrated history of safe use, is appropriate in the absence of compelling evidence for change (Ref. 77).

G. Vitamin A (Proposed §§ 107.10(a)(2), (b)(1), and 107.100(a) and (g))

The current requirements for vitamin A in infant formula are a minimum level of 250 IU/100 kcal (75 µg RAE/100 kcal) and a maximum level of 750 IU/100 kcal (225 µg RAE/100 kcal) (21 CFR 107.100). Based on our analysis of scientific information and data since the 1998 LSRO Panel report (Ref. 1), including infant formula vitamin A requirements in international standards, we propose to decrease the required minimum to 70 µg RAE/100 kcal (233 IU/100 kcal) and decrease the maximum specification to 120 µg RAE/100 kcal (400 IU/100 kcal) for vitamin A in infant formula in § 107.100(a). We also propose changes to the unit of measure from IU to µg RAE in § 107.10(a)(2), (b)(1), and § 107.100(a). Finally, we propose to change which forms of vitamin A may contribute to the minimum and maximum vitamin A content calculations from both preformed vitamin A and *beta*-carotene to preformed vitamin A only in newly established § 107.100(g).

1. Background

Vitamin A is a fat-soluble vitamin and essential nutrient that supports vision, immune function, cell growth and differentiation, and embryonic development (Ref. 86). These functions are especially critical during infancy, a period of rapid growth and immune system development. The term ''vitamin A'' encompasses preformed vitamin A (*i.e.,* retinol and retinyl esters) and provitamin A carotenoids such as *beta*-carotene, which the body can convert to active vitamin A. Infants are born with limited hepatic vitamin A stores even when mothers are well-nourished during pregnancy, making adequate postnatal intake from human milk or infant formula essential (Refs. 62, 86, 87, 88).

a. Factors Affecting Absorption

Preformed vitamin A absorption efficiency is generally 70–90 percent (Refs. 62, 87). However, exclusively formula-fed infants may absorb vitamin A less efficiently than breastfed infants because bile-salt-stimulated lipase (BSSL), which is present in human milk but absent from infant formula, facilitates hydrolysis of retinyl esters. Formula-fed infants rely solely on endogenous digestive enzymes for this process (Ref. 1). Unlike preformed vitamin A, the absorption and conversion of provitamin A carotenoids such as *beta*-carotene are far more variable (5–65 percent), depending on factors such as the food source, genetics, vitamin A status, and health status. The extent to which infants can absorb and convert *beta*-carotene to active vitamin A remains poorly understood (Refs. 62, 87, 89).

b. Health Consequences of Vitamin A Deficiency

Vitamin A deficiency (VAD) is a major public health concern in low- and middle-income countries, affecting an estimated 190 million preschool-age children globally (Ref. 90). Xerophthalmia is a well-documented consequence of VAD, encompassing a spectrum of ocular manifestations from night blindness to corneal ulceration and blindness (Refs. 87, 88, 91). VAD is also associated with increased morbidity and mortality from infectious diseases and impaired iron mobilization contributing to anemia (Refs. 62, 87, 91). In the United States and other high-income countries, clinical VAD is uncommon in healthy term infants receiving adequate nutrition, though infants with fat malabsorption disorders (*e.g.,* cystic fibrosis, cholestatic liver disease) are at elevated risk (Ref. 91).

c. Health Consequences of Excess Vitamin A Intake

Vitamin A is fat soluble and is stored primarily in the liver (Refs. 62, 87). Excessive intake of preformed vitamin A can cause hypervitaminosis A, a toxic condition caused by having too much vitamin A in the body. Provitamin A carotenoids are not associated with toxicity, because their absorption and conversion are downregulated at high intakes (Ref. 89). Acute toxicity in infants may manifest as bulging fontanelle, vomiting, irritability, and headache (Ref. 86). Chronic toxicity symptoms may include fatigue, loss of appetite, hair loss, bone pain, skin changes, and, in serious cases, liver damage, decreased bone mineral density, and increased intracranial pressure. In young children, doses as low as 450 µg/kg/day have been reported to cause hypervitaminosis A (Refs. 62, 88, 92).

2. Nutrient Reference Values

a. NASEM

NASEM established AIs for vitamin A in infants in 2001 based on the mean vitamin A intake of infants fed human milk, as no functional criteria of vitamin A status reflecting dietary response in infants have been demonstrated. The AI for infants 0–6 months of age was set at 400 µg RAE/day, derived from an average milk intake of 0.78 L/day and average human milk vitamin A concentration of 485 µg/L during the first 6 months of lactation. The AI for infants 7–12 months of age was set at 500 µg RAE/day, based on extrapolation from the 0–6-month AI plus estimated contributions from human milk and complementary foods. NASEM did not consider contribution of carotenoids in human milk in meeting the vitamin A requirement of infants (Ref. 61). The UL was set at 600 µg RAE/day for infants 0–12 months of age, derived from case reports of hypervitaminosis A in infants, with a lowest observed adverse effect level (LOAEL) of 6,000 µg/day and an uncertainty factor of 10 to account for the extrapolation from a LOAEL to a NOAEL. NASEM acknowledged this UL was deliberately conservative (Ref. 62).

b. EFSA

The 2015 EFSA Panel derived dietary reference values for vitamin A using a factorial approach (*i.e.,* multiplying together a series of known biological parameters) with pediatric-specific adjustments for body weight, liver/body weight ratio, and growth, yielding a PRI of 250 µg retinol equivalents (RE)/day for infants 7–11 months of age (Ref. 87). In 2024, EFSA proposed a UL of 600 µg RE/day for all infants 4–11 months of age, derived by allometric scaling from the adult UL (Ref. 89). EFSA noted that a UL of 500 µg RE/day for infants 4–6 months of age would be overconservative given that human milk secretion of retinol is estimated at 424 µg RE/day (midpoint concentration: 530 µg/L × 0.8 L/day) during the first 6 months of lactation (Ref. 89).

c. Australian NHMRC/New Zealand MoH

NHMRC/MoH derived AIs for vitamin A in infants based on human milk composition from a single multinational study (Ref. 53). The AI for infants 0–6 months of age was set at 250 µg retinol/day (as retinyl esters), based on an average human milk intake of 0.78 L/day and a retinol concentration of 310 µg/L. The AI for infants 7–12 months of age was set at 430 µg RE/day, based on an average human milk intake of 0.6 L/day (approximately 186 µg RE/day), plus an estimated 244 µg RE/day from complementary foods (including vitamin A from retinol and carotenoids). The UL for infants 0–12 months of age was set at 600 µg RE/day, derived from case reports of hypervitaminosis A in infants (Ref. 53).

d. FAO/WHO

The joint FAO/WHO Consultation estimated vitamin A requirements for infants from observed retinol intakes of breastfed infants in communities with good nutrition and no signs of deficiency (Ref. 3). Notably, due to insufficient data to derive mean requirements for any age group, the Consultation provided ''recommended safe intakes'' rather than true RNIs. The recommended safe intake for infants 0–6 months of age was set at 375 µg RE/day, based on an average human milk retinol concentration of approximately 1.75 µmol/L (503 µg/L × 0.75 L/day). The recommended safe intake for infants 7–12 months of age was increased to 400 µg RE/day, accounting for a decline in average milk intake to 0.65 L/day and increased mortality risk in vitamin A-deficient populations from 6 months of age onward (Ref. 3).

e. Comparison of International Recommendations

Table 10 shows the vitamin A AIs established by NASEM, EFSA, NHMRC/MoH, and FAO/WHO.

TABLE 10—VITAMIN A NUTRIENT REFERENCE VALUES

Organization	Year	Type of reference intake	Age range (months)	Value (per day)	Type of reference intake	Age range (months)	Value (per day)
NASEM	2001	AI	0–6 7–12	400 µg RAE 500 µg RAE	UL	0–12	600 µg RAE.
EFSA	2015 (PRI) 2024 (UL)	PRI	4–6 7–11	ND 250 µg RE	UL	4–11	600 µg RE.
Australian NHMRC/ New Zealand MoH.	2006	AI	0–6 7–12	250 µg retinyl esters. 430 µg RE	UL	0–12	600 µg RE.
FAO/WHO	2004	Recommended Safe Intake.	0–6 7–12	375 µg RE 400 µg RE	UL		ND.

1 µg RE = 1 µg retinol + 6 µg ß-carotene + 12 µg other pro-vitamin A carotenoids.
1 µg RAE = 1 µg retinol + 12 µg ß-carotene + 24 µg other pro-vitamin A carotenoids.

Authoritative bodies differ fundamentally on whether infant vitamin A requirements should be derived from observed intakes from human milk or through a factorial approach. NASEM (Ref. 62), FAO/WHO (Ref. 3), and NHMRC/MoH (Ref. 53) all used human milk composition, but the wide variation in mean retinol concentrations across studies explains why these bodies arrived at different values despite using the same general approach. None of the bodies reviewed incorporated provitamin A carotenoid contributions from human milk into reference values for infants 0–6 months of age due to unknown bioconversion efficiency in this age group. With respect to ULs, NASEM, NHMRC/MoH, and EFSA converged on 600 µg RAE/day or 600 µg RE/day despite different derivation methods, strengthening confidence in this value for evaluating maximum levels (Ref. 86).

FDA believes the NASEM AIs are the most appropriate choice for assessing minimum vitamin A requirements in infant formula, as they represent the most conservative estimates and best ensure that infant nutritional needs are met (Ref. 86).

3. Human Milk Composition

Vitamin A in human milk is present almost exclusively as retinyl esters in the lipid fraction of the milk (Ref. 93). Retinol concentration is highly dependent on fat content, is substantially higher in colostrum than in mature milk, and reflects both maternal vitamin A status and recent dietary intake (Ref. 93).

Three primary data sources inform FDA's assessment of vitamin A concentrations in mature human milk. These sources were selected based on recent publication dates, robust study designs, validated analytical methods, and inclusion of healthy, full-term mother-infant dyads (Ref. 86). A 2022 meta-analysis pooled data from 76 studies that used high-performance liquid chromatography-based retinol measurements totaling 9,171 samples across 33 geographically diverse countries (Ref. 94). Studies involving vitamin A supplementation were excluded. Country was identified as a significant source of variance (Ref. 94). The authors proposed the mean early mature milk concentration of 402.4 µg/L as the reference concentration for DRI revision in infants up to 6 months of age (Ref. 94). The MILQ study (Ref. 95) provides the most comprehensive recent data on retinol concentrations in human milk using validated analytical methods from well-nourished, unsupplemented populations across four countries. Median milk retinol concentrations were highest in early lactation (886 µg/L) and stabilized from 3 months onward (450–460 µg/L) (Ref. 95). The iHMNutD study reported a pooled weighted mean of 36.09 µg/100 g (approximately 372 µg/L) (Ref. 8); however, this value was based on a limited number of studies and participants, introducing uncertainty (Ref. 8).

FDA acknowledges several limitations relevant to the estimates from human milk studies that introduce uncertainty in cross-study comparisons, including small sample sizes, geographic variability, inconsistent collection protocols, and the absence of milk fat adjustment for retinol concentrations (see Ref. 86). Notwithstanding this, FDA considers that these three sources support a plausible range of approximately 370–460 µg/L (approximately 57–71 µg RAE/100 kcal) as the best current estimate of vitamin A concentration in mature human milk, with higher concentrations observed in early mature milk. This range informs FDA's proposed minimum vitamin A specification in infant formula.

4. International Regulatory Standards for Infant Formula

Vitamin A specifications for infant formula vary among international regulatory bodies and expert organizations, though most have adopted or proposed to adopt specifications that generally align with Codex Alimentarius standards (see table 11). The Codex Alimentarius specifies a minimum of 60 µg RE/100 kcal and a maximum of 180 µg RE/100 kcal for infant formula (for infants 0–6 months of age) (Ref. 12). For follow-on formula (for infants 6–12 months of age), Codex Alimentarius specifies a higher minimum of 75 µg RE/100 kcal with the same maximum (Ref. 37).

FSANZ and Health Canada specify the same maximum as Codex

Alimentarius but do not specify a higher minimum for infants 6–12 months of age, maintaining 60 µg RE/100 kcal for infants 0–12 months of age (Refs. 39, 40). The EU and China have higher minimums and/or lower maximums than Codex Alimentarius. The EU, based on recommendations from EFSA (Ref. 7), specifies a minimum of 70 µg RE/100 kcal and a maximum of 114 µg RE/100 kcal, applicable to both infant formula and follow-on formula (Ref. 38). The EU minimum of 70 µg RE/100 kcal was set to ensure that infants consuming approximately 500 kcal/day receive at least 350 µg RE/day (Ref. 7). The EU reduced the maximum from 180 µg RE/100 kcal to 114 µg RE/100 kcal (Ref. 96), resulting in a daily vitamin A intake of approximately 570 µg RE/day (assuming 500 kcal/day), just under the UL of 600 µg RE/day. China also specifies a lower maximum of 150 µg RE/100 kcal for infant formula (Ref. 41), although the maximum for follow-on formula is consistent with Codex Alimentarius (Ref. 42).

The LSRO Panel report recommended a minimum preformed vitamin A content of infant formulas of 60 µg RE/100 kcal and a maximum of 150 µg RE/100 kcal (Ref. 1), noting that a minimum above the estimated vitamin A concentration in human milk (approximately 30 µg RE/100 kcal) was appropriate to account for lower absorption efficiency in formula-fed infants due to the absence of BSSL (Refs. 1, 86).

Table 11 shows the requirements and recommendations of these international bodies and organizations.

TABLE 11—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR VITAMIN A IN INFANT FORMULA

Organization	Age range (months)	Minimum (µg RE/100 kcal)	Maximum (µg RE/100 kcal)	Permitted sources	Reference
U.S. Current Standards [1] [2].	0–12	75 (250 IU)	225 (750 IU)	Preformed retinol: retinol, retinyl acetate, retinyl palmitate (21 CFR 184.1930). *Beta*-carotene may be used in infant formula as a source of vitamin A (21 CFR 184.1245).	21 CFR 107.100.
LSRO [3]	0–12	60	150	Preformed vitamin A	LSRO, 1998.
Codex Alimentarius	0–6	60	180	Preformed retinol, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.	CXS 72–1981.
	6–12	75	180		CXS 156–1987.
EU	0–12	70	114	Preformed vitamin A	Commission Delegated Regulation (EU) 2016/127.
Australia [4]	0–12	59	180	*Retinol:* vitamin A (retinol), vitamin A acetate (retinyl acetate), vitamin A palmitate (retinyl palmitate), retinyl propionate. *Provitamin A: beta*-carotene.	FSANZ P1028.
Canada [5]	0–12	60	180	Retinol contents shall be provided by preformed retinol, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A.	Health Canada, 2025.
China	0–6	60	150	Vitamin A only includes preformed retinol, and does not include any carotene components when vitamin A is calculated and claimed.	GB 10765–2021.
	6–12 months	75	180		GB 10766–2021.

[1] Values converted from international units (1 IU = 0.3 µg RAE). See Section V.G.6.a, "Rationale for Changing the Unit of Measure from IU to µg RAE," for additional information on RE and RAE conversions.
[2] Vitamin A content may also be declared on the label in units of µg RE—when these declarations are made, they shall appear in parentheses immediately following the declarations in IU (21 CFR 107.10(b)(1)).
[3] Recommended ranges.
[4] Values were converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[5] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Vitamin A Intake

Several U.S.-based national dietary surveys have assessed vitamin A intake in U.S. infants and toddlers, including the FITS (FITS 2008 and FITS 2016) and NHANES (NHANES 2009–2012 and NHANES 2015–2020) (Refs. 81, 82, 84, 86, 97). Mean intakes for infants 0–6 months of age ranged from approximately 582 to 637 µg RAE/day, and for infants 6–12 months of age from approximately 669 to 794 µg RAE/day. Preformed vitamin A constituted 88 percent of total vitamin A intake for infants 0–6 months of age and 74 percent for infants 6–12 months of age, with the remainder derived from provitamin A carotenoids (Ref. 97). The proportion of infants with vitamin A intakes exceeding the UL ranged from 21 to 39 percent depending on study and age group (Refs. 81, 82, 84).

Important methodological differences must be considered when interpreting these data. Treatment of human milk varies substantially across studies. NHANES-based analyses exclude or cannot quantify human milk contributions, while FITS-based analyses estimate them through imputation. Infant dietary supplement inclusion differs across studies, and supplement use was reported in 8.8–23 percent of infants (Refs. 81, 82). Finally, carotenoid-derived vitamin A is disaggregated from preformed vitamin A only in one available study (Ref. 97), limiting comparisons of retinol versus carotenoid contributions.

Overall, the available studies support the conclusion that current vitamin A intakes in U.S. infants are adequate and that a significant proportion have

intakes approaching or exceeding the UL. It should be noted, however, that the available dietary intake data do not include information on health outcomes associated with vitamin A intake levels (Ref. 86).

6. Evidence Evaluation and Rationale

Based on the review of available scientific data, information, and international standards, we propose to decrease the current minimum specification for vitamin A from 75 to 70 µg RAE/100 kcal and to decrease the current maximum specification for vitamin A from 225 to 120 µg RAE/100 kcal in § 107.100. We also propose a change to the unit of measure for vitamin A in §§ 107.10(a)(2) and (b)(1) and 107.100 from IU to µg RAE. Finally, we propose a change to the form of vitamin A that may be used to meet the minimum and maximum vitamin A specifications in § 107.100 from both preformed vitamin A and *beta*-carotene to preformed vitamin A only in § 107.100(g) (see table 11).

a. Rationale for Changing the Unit of Measure From IU to µg RAE

Expert scientific bodies recommend expressing vitamin A intake in µg RAE rather than IU, as these weight-based units more accurately reflect the differing bioavailability and bioconversion of preformed vitamin A and provitamin A carotenoids. This approach has been widely adopted in dietary reference values and infant formula vitamin A specifications (tables 10 and 11). In the United States, vitamin A was expressed in RE in the 1989 National Research Council Recommended Dietary Allowances (Ref. 44). An RE is a standardized unit that captures how much bioavailable vitamin A the body derives from dietary sources. The RAE unit was introduced by the U.S. DRI Committee on vitamin A (Ref. 62) to reflect updated evidence on the bioavailability of provitamin A carotenoids. Under the RE system, 6 µg of *beta*-carotene was considered equivalent to 1 µg of retinol; under the RAE system, 12 µg of *beta*-carotene is required to yield 1 µg of retinol, meaning that the vitamin A activity attributed to provitamin A carotenoids is half the amount obtained when expressed in µg RAE compared to µg RE. Because preformed retinol contributes equally under both systems (1 µg retinol = 1 µg RE = 1 µg RAE), the practical effect of this change is that total vitamin A intake estimates are lower when carotenoid contributions are calculated using µg RAE rather than µg RE. The IOM recommended expressing vitamin A requirements in µg RAE rather than µg RE or IU to more accurately reflect the bioavailability of vitamin A from mixed diets and, accordingly, established the AIs for infants in µg RAE (Ref. 86).

In the United States, when included voluntarily on food (other than infant formula) and dietary supplement labels, vitamin A is declared in µg RAE following the recommendation from the NASEM Labeling Committee that the units of measure be consistent with the DRI (81 FR 33742 at 33912, May 27, 2016); 21 CFR 101.9(c)(8)(iv)) (Ref. 98). We are therefore proposing to change the units of measure for vitamin A in infant formula from IU to µg RAE, for consistency with both the DRI and U.S. nutrition labeling regulations for other foods. We believe this proposed change will benefit consumers, as it aligns the unit of measure for vitamin A in infant formula with that already used for general food and dietary supplement labeling in the United States, as well as infant formula labeling outside the United States. The IU may be voluntarily declared in parentheses immediately following the declaration in µg RAE, providing infant formula manufacturers with flexibility and supporting continuity for consumers accustomed to IU-based labeling. This change would also be more aligned with international regulatory standards. If only preformed vitamin A is permitted to meet the vitamin A requirement in infant formula, the adoption of µg RAE would not create a discrepancy with international organizations that use µg RE, since 1 µg RAE = 1 µg RE = 1 µg all-*trans*-retinol. The three units are numerically equivalent when applied solely to preformed retinol. FDA has developed a guidance document that provides detailed instructions to assist manufacturers in converting from IU to µg RAE (Ref. 99).

b. Rationale for Allowing Only Preformed Vitamin A To Meet Vitamin A Specifications

Current U.S. regulation allows *beta*-carotene to be used in infant formula as a source of vitamin A (§ 184.1245 (21 CFR 184.1245)). Other international expert bodies, aside from FSANZ, allow only preformed vitamin A as a source of vitamin A in infant formula (table 11). In its 1998 assessment, the LSRO recommended using only preformed vitamin A to meet the minimum requirements in infant formula (Ref. 1). NASEM did not include *beta*-carotene contributions when establishing the AI for vitamin A for infants because the bioconversion of carotenoids in milk and in infants is not known (Ref. 62). Because the efficiency with which infants convert *beta*-carotene to active vitamin A is unknown, relying on *beta*-carotene as a source of vitamin A in infant formula may put infants at risk of vitamin A deficiency if the assumed conversion does not occur as expected. Additionally, only preformed retinols are considered when establishing the UL for vitamin A, as provitamin A carotenoids are not known to cause vitamin A toxicity (Ref. 62). Thus, excluding *beta*-carotene from the calculated vitamin A content of infant formula would not increase the risk of vitamin A toxicity (Ref. 1, 62, 86). Therefore, FDA is proposing to amend § 107.100 to specify that vitamin A minimum and maximum levels must be met through preformed vitamin A only. *Beta*-carotene, if used in infant formula, shall not be considered to contribute to the required minimum and maximum levels of vitamin A in infant formula (proposed § 107.100(g)).

The use of *beta*-carotene in infant formula is addressed in § 184.1245(c)(2). FDA proposes to amend § 184.1245(c)(2) to list infant formula among the foods in which *beta*-carotene may be used at levels not to exceed current good manufacturing practice.

c. Decreasing the Minimum Specification From 75 µg RAE/100 kcal to 70 µg RAE/100 kcal

The proposed minimum specification of 70 µg RAE/100 kcal is supported by DRIs, human milk composition data, bioavailability considerations, manufacturing feasibility, and international standards, and provides an appropriate margin of nutritional adequacy for formula-fed infants. FDA relies on NASEM AIs as the most appropriate and conservative reference values for vitamin A requirements in infant formula. Notably, the AI is not equivalent to a minimum requirement, but rather it represents an intake assumed to be adequate based on observed intakes in healthy, breastfed infants (Ref. 62). At the proposed minimum, an infant 0–6 months of age consuming a typical daily infant formula intake would receive 369 µg RAE/day (92 percent of the NASEM AI of 400 µg RAE/day). For infants 6–12 months of age consuming a typical daily infant formula intake, the proposed minimum would provide 284 µg RAE/day from formula. NASEM estimated that complementary foods provide approximately 244 µg/day, yielding a combined intake of approximately 528 µg/day (106 percent of the NASEM AI of 500 µg RAE/day). FDA considers this level of intake adequate to meet the vitamin A needs of formula-fed infants 0–12 months of age, with a low risk of deficiency (Ref. 86).

Human milk composition data from multiple studies (Refs. 8, 94, 95) support a plausible range of approximately 370 to 460 µg retinol/L in mature human milk, corresponding to approximately 57 to 71 µg RAE/100 kcal. The proposed minimum of 70 µg RAE/100 kcal falls at the upper end of this range, indicating that formula-fed infants consuming formula at the proposed minimum would receive vitamin A at concentrations consistent with mature human milk from well-nourished populations. The proposed minimum also exceeds the LSRO recommendation of 60 µg RE/100 kcal and provides a buffer to account for potentially lower vitamin A absorption from formula due to the absence of BSSL (Ref. 86).

Lowering the minimum from 75 to 70 µg RAE/100 kcal also responds to manufacturing feasibility considerations. Manufacturers must account for nutrient degradation over shelf life, lot-to-lot variability in raw material potency, and inherent variation in blending and manufacturing processes when formulating infant formulas. In conjunction with the proposed maximum of 120 µg RAE/100 kcal, a minimum of 75 µg RAE/100 kcal would create an allowable manufacturing range of only 45 µg RAE/100 kcal. Reducing the minimum to 70 µg RAE/100 kcal widens this range to 50 µg RAE/100 kcal without compromising nutritional adequacy, reducing the risk of unintentional noncompliance during manufacturing (Ref. 86).

The proposed minimum of 70 µg RAE/100 kcal aligns with the EU minimum of 70 µg RE/100 kcal (Ref. 38); exceeds the Codex Alimentarius minimum for infant formula, the FSANZ minimum, the Health Canada proposed minimum, and the LSRO recommendation (all 60 µg RE/100 kcal) (Refs. 1, 12, 39, 40); and falls modestly below the Codex Alimentarius minimum for follow-on formula (75 µg RE/100 kcal) (Ref. 37). FDA's use of the NASEM AI as the primary reference value for assessing minimum requirements is consistent with the higher U.S. minimum relative to some international standards (Ref. 86).

FDA assesses that 70 µg RAE/100 kcal is consistent with available data on nutritional adequacy and appropriate as a minimum specification. At this level, estimated intakes for infants 0–6 months of age represent approximately 92 percent of the NASEM AI, within the 15 percent margin below the AI that has been used by other regulatory bodies to indicate low risk of nutritional inadequacy (Ref. 100).

d. Decreasing the Maximum Specification From 225 to 120 µg RAE/100 kcal

FDA's evaluation of the maximum is guided by the NASEM UL of 600 µg RAE/day for infants 0–12 months of age (Ref. 62), which is also supported by EFSA (Ref. 89) and NHMRC/MoH (Ref. 53). The NASEM UL was derived by applying an uncertainty factor of 10 to a LOAEL of 6,000 µg/day, identified from case reports of hypervitaminosis A in infants receiving supplemental preformed vitamin A.

At the current maximum of 225 µg RAE/100 kcal, estimated vitamin A intakes from infant formula substantially exceed the UL across all intake scenarios evaluated. U.S. dietary intake data from multiple national surveys consistently show that mean vitamin A intakes approach or exceed the UL and that 21–39 percent of infants have intakes above the UL (Refs. 81, 82, 84, 97). The current maximum also exceeds that of all other international regulatory standards, none of which permit a maximum above 180 µg RE/100 kcal.

FDA initially considered a maximum of 180 µg RAE/100 kcal, consistent with the Codex standard. However, at typical intake volumes, a maximum of 180 µg RAE/100 kcal would still result in estimated intakes from infant formula alone reaching 158 percent and 122 percent of the UL for infants 0–6 and 7–12 months of age, respectively, and as high as 251 percent and 238 percent of the UL among high consumers (90th percentile of energy intake from infant formula) (Refs. 13, 14, 15, 16, 17, 18). EFSA found that regular consumption of infant formula at the previously permitted maximum of 180 µg RE/100 kcal would result in intakes exceeding the UL (Ref. 7). In the interest of maintaining an adequate safety margin, particularly for high consumers of infant formula, FDA proposes a lower maximum of 120 µg RAE/100 kcal.

At the proposed maximum of 120 µg RAE/100 kcal, estimated vitamin A intakes from infant formula at typical volumes represent 106 percent and 81 percent of the UL for infants 0–6 and 7–12 months of age, respectively. Among high consumers (90th percentile of energy intake) (Refs. 13, 14, 15, 16, 17, 18), estimated intakes from infant formula alone reach 167 percent and 159 percent of the UL for the 0–6-month and 7–12-month age groups, respectively. While intakes exceed the UL under higher intake scenarios, the safety margin relative to the LOAEL improves substantially from approximately 2.9- to 3.2-fold at the current maximum to approximately 4.9- to 9.5-fold at the proposed maximum.

FDA acknowledges that no available data suggest that routine intake of infant formula at current vitamin A levels is associated with adverse events, and that U.S. dietary intake studies did not assess health outcomes associated with vitamin A intake levels (Refs. 81, 82, 84, 86, 97). Nevertheless, FDA considers it appropriate to limit unnecessary exposure to preformed vitamin A above the UL, particularly among high consumers.

The proposed maximum of 120 µg RAE/100 kcal falls within the range of international maximum specifications, which extend from 114 µg RE/100 kcal (EU) to 180 µg RE/100 kcal (Codex Alimentarius, Health Canada, and FSANZ) (Refs. 12, 37, 39, 40) and is below the LSRO recommendation of 150 µg RE/100 kcal (Ref. 1). The proposed maximum of 120 µg RAE/100 kcal is higher than the corresponding EU specification of 114 µg RE/100 kcal. This range is intended to provide manufacturers with sufficient operational flexibility to account for manufacturing overages, nutrient losses during processing, and shelf-life variability while ensuring appropriate vitamin A intakes across the U.S. infant population. FDA acknowledges that, despite a reduction of more than 46 percent from the current maximum, estimated vitamin A intakes among high consumers of infant formula may continue to exceed the UL at the proposed maximum. The safety margin relative to the LOAEL ranges from approximately 4.9- to 9.5-fold across intake scenarios evaluated (Ref. 86).

FDA acknowledges several important uncertainties in the evidence base underlying the proposed specifications for vitamin A in infant formula. The NASEM AI and UL were each derived from a limited number of studies with few participants, and the UL was deliberately set conservatively using a LOAEL rather than a NOAEL (Ref. 62). Human milk retinol concentrations vary substantially across studies, reflecting the influence of lactation stage, milk fat content, maternal vitamin A status, and geographic differences in diet and supplementation practices. The efficiency of vitamin A absorption from infant formula relative to human milk has not been precisely quantified, and the bioconversion efficiency of *beta*-carotene in infants remains unknown (Refs. 62, 95). Finally, none of the available U.S. dietary intake studies assessed health outcomes associated with vitamin A intake levels, limiting the ability to assess health outcomes at current intake levels. Given these

uncertainties, FDA has taken a conservative approach by only slightly decreasing the current minimum to preserve the margin of nutritional adequacy and implementing a large reduction in the maximum that is supported by the available safety evidence and falls within the range of current international maximum specifications (Ref. 86).

H. Sodium

The current requirements for sodium in infant formula are a minimum level of 20 mg/100 kcal and a maximum level of 60 mg/100 kcal (§ 107.100). Based on our analysis of scientific information and data since the 1998 comprehensive study of infant formula nutrients, including infant formula sodium requirements in international standards, we conclude that the required sodium levels in § 107.100 remain appropriate.

1. Background

Sodium is an essential nutrient. It plays a critical role in regulating extracellular fluid volume and blood pressure homeostasis, and it is important for the absorption of amino acids, small peptides, and monosaccharides (Refs. 76, 101, 102). Together with chloride and potassium, sodium maintains osmotic and acid-base balance between intracellular and extracellular compartments and is necessary for transporting solutes across membranes and generating electrical signals in the musculoskeletal and nervous systems (Refs. 101, 102, 103). Sodium also interacts with calcium, as increasing sodium intake has been shown to increase urinary calcium excretion, which may negatively affect bone health (Refs. 76, 101, 102). Approximately 95 percent of total body sodium is extracellular, and the body absorbs approximately 98 percent of dietary sodium consumed across a wide range of intakes (Refs. 76, 101, 102). There is no sensitive or specific biomarker for sodium status, as blood sodium concentrations are tightly controlled by homeostatic mechanisms (Refs. 76, 101, 102).

a. Health Consequences of Sodium Deficiency

Hyponatremia, defined as a sodium concentration in the blood less than or equal to 135 mmol/L, is rarely due to dietary sodium intake; rather, it is typically due to disturbances in free water balance and the hormonal regulation of that balance (Refs. 76, 101, 102). Low dietary sodium intakes are rare in healthy populations because sodium chloride and other sodium salts are ubiquitous in the food supply. Sodium intakes of infants who participated in the 2002 FITS exceeded the AIs (Ref. 43). There are also adaptive physiological mechanisms that reduce sodium losses in urine, feces, and sweat at low intakes, and the term-newborn kidney has sufficient renal absorption and excretion capabilities to minimize obligatory sodium losses (Refs. 1, 76, 101, 102).

b. Health Consequences of Excess Sodium Intake

Hypernatremia, defined as a blood sodium concentration greater than 145 mmol/L, is typically a consequence of dehydration rather than excessive sodium intake (Ref. 76). In adults, excessive sodium intake has been linked to elevated blood pressure and increased risk of cardiovascular disease (Refs. 76, 101, 102). It has been suggested that sodium intake during infancy may influence future blood pressure and taste preferences for sodium; however, the current evidence is insufficient to establish an upper limit of intake for this age group, and more research is needed (Refs. 76, 101, 102).

2. Nutrient Reference Values

a. NASEM

NASEM updated AIs for sodium in infants in its 2019 report, *Dietary Reference Intakes for Sodium and Potassium* (Ref. 76). The AI for infants 0–6 months of age was set at 110 mg/day, based on an estimated mean human milk sodium concentration of 140 mg/L and an assumed average consumption of 0.78 L/day. The AI for infants 7–12 months of age was set at 370 mg/day, based on approximately 70 mg/day from human milk (at 110 mg/L and 0.6 L/day) plus an estimated 300 mg/day from complementary foods. No UL was established for sodium in infants. In 2019, NASEM expanded its DRI model toward establishing DRIs based on chronic disease risk reduction intakes (CDRRs); however, NASEM was unable to establish a CDRR for infants. The absence of a sodium UL reflects an evolution in the DRI model's approach to characterizing risk rather than a change in the evidence regarding risks associated with excessive sodium intake (Refs. 76, 102).

b. EFSA

EFSA published a comprehensive scientific opinion on dietary reference values for sodium in 2019 (Ref. 101). Because insufficient data existed from which an AR could be derived, EFSA established an AI of 200 mg/day for infants 7–11 months of age based on upward extrapolation of the estimated sodium intake of exclusively breastfed infants during the first 6 months of life (midpoint sodium concentration of 150 mg/L and assumed milk transfer of 0.8 L/day = 120 mg/day), adjusted using the ratio of average energy requirements for infants 3 and 9 months of age. EFSA did not establish an AI for infants 0–6 months of age due to insufficient data. No UL was established for sodium in infants (Ref. 101).

c. D–A–CH

In 2017, D–A–CH established estimated values for sodium intake of 130 mg/day for infants 0 to under 4 months of age based on a mean mature human milk sodium concentration of 170 mg/L and an assumed average daily intake of 750 mL of human milk. For infants 4 months to under 12 months of age, the estimated value of 200 mg/day was derived from the 0–4-month value adjusted for differences in average body weight, as complementary food intake data from Germany were unavailable. No UL was established for sodium in infants (Ref. 28).

d. Comparison of International Recommendations

Table 12 shows the sodium AIs established by NASEM, EFSA, and D–A–CH.

TABLE 12—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF SODIUM

Organization	Year	Age range (months)	Adequate intake (mg/day)	Tolerable upper intake level
NASEM	2019	0–6	110	ND.
		7–12	370	ND.
EFSA	2019	7–11	200	ND.

TABLE 12—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF SODIUM—Continued

Organization	Year	Age range (months)	Adequate intake (mg/day)	Tolerable upper intake level
D–A–CH	2017	0–4	130	ND.
		4–12	200	ND.

All three expert bodies used human milk composition as the primary basis for infant sodium reference values, and none established a UL for sodium in infants (see table 12). The substantially higher NASEM AI for infants 7–12 months (370 mg/day) compared to EFSA (200 mg/day) and D–A–CH (200 mg/day) reflects a key methodological difference: NASEM incorporated estimates of sodium intake from complementary foods, while EFSA and D–A–CH applied body weight scaling or lacked complementary food intake data. All expert bodies acknowledged wide variability in reported human milk sodium concentrations across studies and populations, which complicates the derivation of precise reference values and underscores shared uncertainty in this area (Ref. 102).

3. Human Milk Composition

a. Sodium Concentration in Mature Human Milk

There is no clear correlation between maternal dietary sodium intake and human milk sodium concentrations (Ref. 104). Direct measurements of sodium concentrations in mature human milk across individual study timepoints ranged from approximately 82 to 297 mg/L, reflecting natural variability in human milk (Ref. 102).

b. Recent Data

The iHMNutD study, based on literature synthesis covering mature milk from 21 to 180 days postpartum, included 12 studies with 924 participants with applicable sodium data (Ref. 8). The pooled weighted mean sodium concentration was 14.73 ± 6.99 mg/100 g, which converts to approximately 152 ± 72 mg/L. Eleven of the 12 studies overlap with sources reviewed by EFSA (Ref. 101) and NASEM (Ref. 76) and are drawn from U.S. data sources. All studies with sodium data except the Maternal-Infant Research on Environmental Chemicals (MIREC) study were conducted before 2000, which was identified as a data limitation (Ref. 8).

The MIREC Study (Ref. 105) provides additional recent data from a large Canadian cohort. Samples were collected from 2007 through 2011, from 3.5 to 10 weeks postpartum. The geometric mean sodium concentration for the full sample set (n = 770) was 151 ± 70 mg/L, and for the DRI variable subset (n = 660) was 153 ± 71 mg/L. This study was included among the 12 studies evaluated in the iHMNutD study (Refs. 8, 105).

The MILQ study (Ref. 36) provides the most comprehensive recent data on human milk mineral composition. Median sodium concentrations were 140 mg/L at 1–2 months of age, 111 mg/L at 3–4 months of age, and 97 mg/L at 5–6 months of age, with a pooled 1–6-month median of 111 mg/L (IQR: 87–156 mg/L). Total daily median sodium intake from 1 to 6 months of age was 96.5 mg/day based on measured milk volumes (Ref. 36).

The pooled weighted mean of 152 mg/L reported by the iHMNutD study (Ref. 8) is broadly consistent with values from the MIREC study (151–153 mg/L) (Ref. 105) and converts to approximately 23 mg/100 kcal. The MILQ study pooled median of 111 mg/L corresponds to approximately 17 mg/100 kcal. Together, these values suggest a central reference range of roughly 17–23 mg/100 kcal as reflective of typical mature human milk composition (Ref. 102).

4. International Regulatory Standards for Infant Formula

Sodium specifications for infant formula are generally aligned among international regulatory bodies and expert organizations, and most are closely aligned with Codex Alimentarius standards. The Codex Alimentarius Commission specifies a minimum of 20 mg/100 kcal and a maximum of 60 mg/100 kcal for both infant formula (0–6 months of age) (Ref. 12) and follow-on formula (6–12 months of age) (Ref. 37). The EU, based on recommendations from EFSA (Ref. 7), specifies a minimum of 25 mg/100 kcal and a maximum of 60 mg/100 kcal (Ref. 38). Other countries that have adopted or proposed specifications aligned with Codex Alimentarius include FSANZ (20–59 mg/100 kcal) (Ref. 39) and Health Canada (20–60 mg/100 kcal) (Ref. 40). China specifies 30–59 mg/100 kcal for infants 0–6 months of age (Ref. 41) but has different standards for follow-on formula (6–12 months of age; see table 13) (Ref. 42).

In its 1998 comprehensive review, the LSRO Panel recommended a minimum of 25 mg/100 kcal and a maximum of 50 mg/100 kcal (Ref. 1). The LSRO Panel based the minimum on the 1989 RDA of 120 mg/day for infants less than 6 months of age, which for a 5-kg infant consuming 100 kcal/kg/day equates to 24 mg/100 kcal (rounded to 25 mg/100 kcal). The LSRO Panel was reluctant to use the mean minus one standard deviation approach typically applied to other nutrients due to high coefficients of variation in reported human milk sodium values. The recommended maximum of 50 mg/100 kcal was based on the 90th percentile of FDA analyses of infant formulas available at that time (Ref. 1).

Table 13 shows the requirements and recommendations of these international regulatory bodies and organizations.

TABLE 13—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR SODIUM IN INFANT FORMULA

Organization	Age range (months)	Minimum (mg/100 kcal)	Maximum (mg/100 kcal)	Reference
U.S. Current Standards	0–12	20	60	21 CFR 107.100.
LSRO [1]	0–12	25	50	LSRO, 1998.
Codex Alimentarius	0–12	20	60	CXS 72–1981, CXS 156–1987.
EU	0–12	25	60	Commission Delegated Regulation (EU) 2016/127.
Australia [2]	0–12	20	59	FSANZ P1028.
Canada [3]	0–12	20	60	Health Canada, 2025.

TABLE 13—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR SODIUM IN INFANT FORMULA—Continued

Organization	Age range (months)	Minimum (mg/100 kcal)	Maximum (mg/100 kcal)	Reference
China	0–6	30	59	GB 10765–2021.
	6–12	ND	84	GB 10766–2021.

[1] Recommended ranges.
[2] Values converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[3] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Sodium Intake

Reported sodium intakes in U.S. infants 0–12 months of age consistently met or exceeded the NASEM AIs across datasets reviewed, including two iterations of FITS (FITS 2008 and FITS 2016) and one cycle of NHANES (NHANES 2009–2012) (Refs. 81, 82, 84). For infants 0–5.9 months of age, FITS 2016 reported a mean usual sodium intake of 214 mg/day (10th–90th percentile: 107–347 mg/day), and FITS 2008 reported a mean of 175 mg/day for 0–5 months of age (10th–90th percentile: 138–240 mg/day), both exceeding the NASEM AI of 110 mg/day. For infants 6–11.9 months of age, mean usual sodium intakes were higher across all three surveys: FITS 2016 reported a mean of 400 mg/day (10th–90th percentile: 207–634 mg/day), FITS 2008 reported 528 mg/day (10th-90th percentile: 165–1,104 mg/day), and NHANES 2009–2012 reported 497 mg/day (10th-90th percentile: 163–946 mg/day), all exceeding the NASEM AI of 370 mg/day. In FITS 2016, approximately 49 percent of older infants exceeded the AI, and the wide 10th-to-90th percentile ranges observed across all surveys, particularly for the 6–11-month age group, indicate substantial variability in sodium exposure across the infant population.

Several methodological considerations must be factored in when interpreting these data. Human milk sodium content is relatively low and fixed by imputed volume rather than directly measured, so there may be limited precision when estimating sodium intakes in breastfed infants. All three studies rely on proxy-reported 24-hour dietary recalls, subject to recall bias. The statistical methods used to estimate usual intake distributions differ slightly across studies, though the approaches are designed to remove within-person variation and are broadly comparable. Additionally, the AI for sodium in infants is derived from estimated mean intakes from human milk in healthy, exclusively breastfed infants rather than from experimental dose-response data; consequently, exceeding the AI does not necessarily indicate risk of adverse health effects. Taken together, the data indicate that mean sodium intakes in U.S. infants meet or exceed the NASEM AIs across both age subgroups.

6. Evidence Evaluation and Rationale

Based on our review of available scientific data, information, and international standards, we conclude that the current minimum level of 20 mg/100 kcal and maximum level of 60 mg/100 kcal for sodium in § 107.100 remain appropriate.

a. Maintaining the Minimum Specification of 20 mg/100 kcal

The current minimum specification of 20 mg/100 kcal is supported by human milk composition data, intake-based reference value approaches, and international regulatory standards. Recent North American data from the MIREC study (Ref. 105) and the iHMNutD study (Ref. 8) converge on a central estimate of approximately 23 mg/100 kcal, while the multinational MILQ study (Ref. 36) suggests a somewhat lower value of approximately 17 mg/100 kcal, together defining a central reference range of approximately 17–23 mg/100 kcal for mature human milk sodium content. The reaffirmed minimum of 20 mg/100 kcal falls within this range. Applying the current NASEM AI of 110 mg/day using the same intake-based approach used by the LSRO yields an estimate of 22 mg/100 kcal, consistent with the North American central estimate and further supporting the current minimum (Refs. 1, 76, 102).

The current minimum requirement ensures that infant formula provides sodium intakes that pose a low risk of inadequacy relative to established AIs. For an infant 0–6 months of age consuming a typical daily infant formula intake, formula at the minimum specification provides 105 mg/day of sodium, which is 96 percent of the NASEM AI of 110 mg/day for infants 0–6 months of age. For an infant 0–4 months of age, this consumption level provides 81 percent of the D–A–CH AI of 130 mg/day for that age subset. For a 6–12-month-old infant consuming a typical daily intake of infant formula, the minimum specification provides 81 mg/day from formula, which is 22 percent of the NASEM AI of 370 mg/day, 40 percent of the EFSA AI of 200 mg/day for 7–11-month-old infants, and 40 percent of the D–A–CH AI of 200 mg/day for 4–12-month-old infants. However, for infants 7–12 months of age, estimated sodium intake from complementary foods of approximately 300 mg/day (Ref. 76) would contribute substantially to total sodium intake, bringing the total daily intake to approximately 381 mg/day, which is 103 percent of the NASEM AI (Ref. 102).

The current minimum aligns with international standards. The U.S. minimum of 20 mg/100 kcal is the same as Codex Alimentarius, FSANZ, and Health Canada but lower than the EU minimum of 25 mg/100 kcal as well as China's minimum of 30 mg/100 kcal. The current U.S. specification of 20 mg/100 kcal falls within this international consensus range, and no compelling evidence from other jurisdictions suggests that changing the minimum would provide any benefit (Ref. 102).

b. Maintaining the Maximum Specification of 60 mg/100 kcal

The current maximum provides a substantial margin above the central estimates of sodium content of mature human milk (approximately 17–23 mg/100 kcal) (Refs. 8, 36, 105). The LSRO Panel's 1998 recommendation of 50 mg/100 kcal as a maximum, although lower than the current specification, was based on the 90th percentile of sodium content in infant formulas available at that time, rather than on safety concerns, as the LSRO Panel found no evidence that excessive sodium intake caused adverse effects at these levels (Ref. 1). Finally, it is unclear if the difference between 50 and 60 mg/100 kcal reflects any functional significance, and the current maximum is aligned with international standards (Ref. 102).

History of use and available intake data also support safety at the current maximum. At typical daily infant formula intake volumes, the current maximum would provide approximately 316 mg/day for an infant 0–6-months of

age and 244 mg/day for an infant 6–12 months of age. Findings from the 2016 FITS reported mean sodium intakes of 214 mg/day (0–6 months of age) and 400 mg/day (6–11 months of age) (Ref. 82), although these estimates included intake from all dietary sources, including infant formula and complementary foods (Ref. 102).

Further, no upper limit or CDRR has been established for infants, and the current specification has not been associated with documented adverse effects in contemporary populations since 1980 when the Infant Formula Act was enacted. The evidence base for characterizing sodium intake-response relationships in infants remains limited, and findings derived from adult populations were extrapolated to children but not to infants (Ref. 76). This indicates that the current maximum level is sufficient to ensure nutritional adequacy in U.S. infants without adverse effects. The specifications are well-positioned within international regulatory consensus, and we find no compelling new evidence demonstrating functional benefits of modification or documented adverse effects at current levels (Ref. 102).

c. Consideration of the Evidence Base

We acknowledge several uncertainties in the evidence base that supports maintaining the current specifications. There is variability in reported mature human milk concentrations for sodium across studies (82 to 297 mg/L), lack of a sensitive or specific biomarker of sodium status and intake, and individual variability in infant requirements (Ref. 102). Nevertheless, FDA concludes that the totality of available evidence, including contemporary human milk composition data, alignment with international standards, and the longstanding history of use without documented safety concerns, supports maintaining the current minimum and maximum sodium specifications.

I. Vitamin D (Proposed §§ 107.10(a)(2), (b)(1), and 107.100(a))

The current requirements for vitamin D in infant formula are a minimum level of 40 IU/100 kcal (1 µg/100 kcal) and a maximum level of 100 IU/100 kcal (2.5 µg/100 kcal) (§ 107.100). Based on our analysis of scientific information and data since the LSRO Panel's 1998 comprehensive study of infant formula nutrients (Ref. 1), including infant formula vitamin D requirements in international standards, we propose to increase the required minimum to 2 µg/100 kcal (80 IU/100 kcal) and to increase the required maximum to 3 µg/100 kcal (120 IU/100 kcal) in § 107.100. We also propose to change the primary unit of measure from IU to µg in §§ 107.10(a)(2) and (b)(1) and 107.100.

1. Background

Vitamin D is a fat-soluble vitamin and essential nutrient important for calcium absorption, skeletal mineralization, and the prevention of rickets. The two major forms are vitamin D_2 (ergocalciferol), derived from plants and fungi, and vitamin D_3 (cholecalciferol), found in select animal-derived foods and synthesized in the skin with sunlight exposure. Both forms are also found in dietary supplements and fortified foods (Refs. 91, 106, 107). Vitamin D is generally present at low levels in human milk (Refs. 95, 106, 107, 108).

Vitamin D is recognized as a prohormone, as it undergoes two reactions before becoming biologically active. The first, occurring in the liver, produces 25-hydroxyvitamin D (25(OH)D; calcidiol), the major circulating form of vitamin D. The second, occurring in the kidney, converts 25(OH)D to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$; calcitriol), the metabolically active form (Refs. 91, 106). The main function of calcitriol is to increase plasma calcium and phosphate, which are required for the mineralization of bone and the development and maintenance of skeletal health (Ref. 106). Calcitriol also regulates gene expression in a wide range of tissues throughout the body through binding to the vitamin D receptor (Ref. 106).

Serum 25(OH)D concentration is an indicator of total vitamin D exposure, which includes vitamin D intake from food and supplements, as well as synthesis from sun exposure (Ref. 106). The 2011 DRI report for calcium and vitamin D notes that while serum 25(OH)D cannot be considered a validated health outcome surrogate, it allows comparison of intake or exposure with health outcomes (Ref. 106). The DRI committee's review of data suggested that relative to bone health, individuals are at risk of deficiency at serum 25(OH)D concentrations below 30 nmol/L (12 ng/mL); some, but not all, individuals are potentially at risk for inadequacy at serum 25(OH)D concentrations between 30 and 50 nmol/L (12 and 20 ng/mL); practically all individuals are sufficient at serum 25(OH)D concentrations of at least 50 nmol/L (20 ng/mL); and there may be reason for concern with serum 25(OH)D concentrations above 125 nmol/L (50 ng/mL) (Ref. 106). Consistent with NASEM's framework, the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society endorse a target serum 25(OH)D of greater than or equal to 50 nmol/L (20 ng/mL) for vitamin D adequacy (Ref. 91). Deficiency is generally defined as a concentration below 30 nmol/L (12 ng/mL) and insufficiency as 30–49 nmol/L (13–19 ng/mL) (Refs. 91, 106).

a. Health Consequences of Vitamin D Deficiency

Vitamin D deficiency results in inadequate skeletal mineralization. Clinical manifestations include hypocalcemia (*i.e.*, low blood calcium), hypophosphatemia (*i.e.*, low blood phosphorus), tetany (*i.e.*, involuntary spasms, muscle cramps, and twitching), rickets (a metabolic bone disease characterized by widening at the ends of long bones), rachitic rosary (a clinical and x-ray finding of bead-like swellings at the joints where the ribs meet the costal cartilage), skeletal deformities, lower limb deformities, and muscle weakness and pain (Refs. 91, 106). Because the periods of infancy and childhood represent critical windows of skeletal development, ensuring adequate vitamin D intake during these stages is essential to prevent these clinical outcomes, underscoring the importance of appropriate vitamin D in infant formula and early childhood nutrition. Serum 25(OH)D concentrations below 27–30 nmol/L are associated with increased risk of rickets when calcium intakes are limited (Refs. 106, 109, 110). No reports of clinical deficiency have been documented in infants receiving 400 IU/day of vitamin D, and this intake level generally maintains serum 25(OH)D above 50 nmol/L (Refs. 106, 108). Vitamin D deficiency may also manifest as hypocalcemic seizures. Although most commonly reported in breastfed infants, case reports have documented this outcome in formula-fed infants when compounding risk factors are present, including limited sun exposure, poor maternal vitamin D status during pregnancy, and low formula intake volumes (Refs. 108, 111, 112).

Populations at heightened risk for vitamin D deficiency include exclusively breastfed infants, infants with dark skin pigmentation, preterm infants, and infants with dietary fat malabsorption (Refs. 91, 106). Additional risk factors include reduced sunlight exposure, maternal vitamin D deficiency, sex, and having a mother who has given birth more than two times (Refs. 113, 114). A co-occurrence of multiple risk factors may substantially amplify risk (Ref. 113).

b. Health Consequences of Excess Vitamin D Intake

Excess vitamin D dietary intake can lead to hypervitaminosis D (*i.e.,* a toxic condition resulting from excessive vitamin D). In contrast, toxic levels of vitamin D do not occur from prolonged sun exposure, as thermal activation of previtamin D3 in the skin gives rise to multiple non-vitamin D forms that limit the formation of vitamin D (Ref. 106). Hypervitaminosis D leads to hypercalcemia (*i.e.,* high blood calcium) and hypercalciuria (*i.e.,* high urine calcium) and can eventually cause soft tissue calcification and renal and cardiovascular damage (Refs. 91, 106, 107). Symptoms of hypervitaminosis D in children are similar to those of hypercalcemia, including feeding difficulties, excessive or abnormal thirst and urine production, diarrhea, irritability, poor weight gain, and increased deep tendon reflexes (Ref. 1). In infants, excess intake for greater than 6 months may adversely affect linear growth (Refs. 106, 108).

c. Vitamin D_2 and Vitamin D_3: Bioavailability Considerations

Both vitamin D_2 and D_3 are permitted for use in infant formula. The structural difference between the two forms does not affect intestinal absorption or the reaction required for activation to calcitriol, the biologically active form of vitamin D (Ref. 106). The available scientific literature on the relative bioavailability and potency of vitamin D_2 compared with vitamin D_3 in humans presents mixed findings. The 2011 NASEM DRI report concluded that ''firm conclusions about different effects of the two forms of vitamin D cannot be drawn,'' while observing that ''it would appear that at low doses, D_2 and D_3 are equivalent, but at high doses, D_2 is less effective than D_3,'' in terms of raising the serum 25(OH)D concentration (Ref. 106). Data comparing the effects of vitamin D_2 and vitamin D_3 specifically in infants are limited. The EFSA NDA Panel, in its 2018 scientific opinion on the UL for vitamin D in infants, reviewed the available infant-specific evidence and concluded that ''the limited data available on infants . . . do not allow a conclusion to be drawn on whether there is a difference between vitamin D_2 and D_3 as regards their impact on serum 25(OH)D concentrations in infants'' (Ref. 115).

2. Nutrient Reference Values

a. NASEM

The 2011 NASEM DRI report established an AI for vitamin D of 400 IU (10 µg)/day for both infants 0–6 months of age and infants 6–12 months of age, as available data were insufficient to support derivation of an EAR for infants under 12 months of age (Ref. 106). This AI assumes minimal sun exposure contributing to vitamin D synthesis as well as adequate calcium intakes. Calcium and vitamin D are physiologically interdependent with respect to bone health outcomes, and an inadequacy in one may alter the body's handling of or response to the other (Ref. 106). Clinical studies have demonstrated that an intake of 400 IU (10 µg)/day is generally consistent with maintaining serum 25(OH)D concentrations above 50 nmol/L in infants, and no cases of clinical vitamin D deficiency have been reported at this level (Ref. 106).

The vitamin D AI for infants could not be derived from the nutrient content of human milk, as human milk does not provide a meaningful amount of vitamin D. Instead, the AI was based on evidence indicating that serum 25(OH)D ''above 30 nmol/L, and more likely closer to 50 nmol/L, appears to cover adequately the needs of the majority of the infants and support normal bone accretion'' (Ref. 106).

NASEM established separate ULs of 1,000 IU (25 µg)/day for infants 0–6 months of age and 1,500 IU (38 µg)/day for infants 6–12 months of age. The indicator selected for establishing these ULs was decreased linear growth. These ULs were derived from an NOAEL of approximately 1,800 IU (45 µg)/day established from mean intakes in a 1966 study, with an uncertainty factor of approximately 0.5 applied for infants 0–6 months of age to account for smaller body weight, and a 500 IU (12.5 µg)/day upward adjustment for infants 6–12 months of age to reflect their greater body mass and organ maturation (Ref. 116). NASEM acknowledged that decreased linear growth is a relatively insensitive endpoint and that dose-response relationships for adverse outcomes in infants are not well characterized (Ref. 106).

b. EFSA

In 2016, the EFSA NDA Panel established an AI for vitamin D of 10 µg/day for infants 7–11 months of age based on several trials conducted in mostly breastfed infants (Ref. 107). Two studies showed that supplementation with 10 µg/day of vitamin D_3 for at least 15 weeks led to achieved mean or median serum 25(OH)D concentrations of at least 80 nmol/L. This finding was consistent with conclusions from NASEM (Ref. 106) and recent trials that demonstrated that 10 µg/day of vitamin D_3 in primarily breastfed infants was adequate to achieve plasma/serum 25(OH)D concentrations of at least 50 nmol/L (Refs. 106, 107).

In 2018, EFSA revised the ULs for vitamin D in infants, establishing 25 µg/day for infants up to 6 months of age and 35 µg/day for infants 6 to less than 12 months of age. The EFSA Panel's systematic literature review of studies on four adverse health outcomes, specifically hypercalciuria, hypercalcemia, nephrocalcinosis (*i.e.,* abnormal deposits of calcium in the kidney tissue), and abnormal growth patterns, concluded that the available evidence on these endpoints was insufficient to derive a UL. The EFSA Panel instead used serum 25(OH)(D) concentration as an endpoint and concluded that a serum 25(OH)(D) concentration of 200 nmol/L or below is unlikely to pose a risk of adverse health outcomes in healthy infants. This value was not regarded as a toxicity threshold but rather as a conservative reference point from which the UL could be derived. The EFSA Panel estimated the proportion of infants expected to exceed this threshold at various intakes. The updated ULs apply to both vitamin D_2 and D_3, though the dose-response analysis was based predominantly on vitamin D_3 supplementation data (Ref. 115).

c. Australian NHMRC/New Zealand MoH

NHMRC/MoH established an AI for vitamin D of 5 µg/day for infants 0–12 months of age. This recommendation assumes little to no sunlight exposure. The AI is based on the lowest dietary intake of vitamin D that is associated with a mean serum 25(OH)D concentration above 27.5 nmol/L. While a minimal intake of 2.5 µg/day may be sufficient to prevent rickets in infants 0–6 months of age, the AI was set at 5 µg/day to provide an additional margin of adequacy, as many infants at the lower intake level may still present with 25(OH)D concentrations within the range associated with rickets when sunlight exposure is absent. NHMRC/MoH noted that several studies have demonstrated that 5 µg/day is adequate for older infants and for formula-fed infants (Ref. 53).

The UL for vitamin D for infants 0–12 months of age was set at 25 µg/day, based on a NOAEL of 45 µg/day with an uncertainty factor of 1.8. The uncertainty factor reflects the small sample sizes and the relative insensitivity of the endpoint used (linear growth) in the studies informing the NOAEL (Ref. 53).

d. FAO/WHO

The joint FAO/WHO Consultation established a RNI of 5 µg/day for vitamin D for infants 0–6 months and 7–12 months of age (Ref. 3). This value was derived using plasma 25(OH)D as the primary indicator of vitamin D status, with the goal of maintaining concentrations above 27 nmol/L, the threshold associated with normal bone health. The Consultation did not establish a UL for infants (Ref. 3).

e. Comparison of International Recommendations

Table 14 shows the vitamin D AIs established by NASEM, EFSA, NHMRC/MoH, and FAO/WHO.

TABLE 14—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF VITAMIN D

Organization	Year	Age range (months)	Adequate intake	Tolerable upper intake level
NASEM	2011	0–6	400 IU (10 µg)	1,000 IU (25 µg).
		6–12	400 IU (10 µg)	1,500 IU (38 µg).
EFSA	2016 (AI)	7–11	10 µg.	
	2018 (UL)	0–<6		25 µg.
		6–12		35 µg.
Australia NHMRC/New Zealand MOH	2006	0–6	5 µg	25 µg.
		7–12	5 µg	25 µg.
FAO/WHO	2004	0–6	5 µg*	ND.
		7–12	5 µg*	ND.

* Values established are RNI levels.

With respect to adequate intake, NASEM (Ref. 106) and EFSA (Ref. 107) both arrived at 10 µg/day (400 IU/day), while NHMRC/MoH (Ref. 53) and FAO/WHO (Ref. 3) established lower values of 5 µg/day. NASEM based its AI on evidence that serum 25(OH)D concentrations of approximately 50 nmol/L are sufficient to meet the needs of most infants (Ref. 106). EFSA similarly targeted 50 nmol/L as a minimum threshold but derived its AI from supplementation trials demonstrating achieved concentrations of at least 80 nmol/L at 10 µg/day and applied the value only to infants 7–11 months of age, without establishing a separate AI for younger infants (Refs. 107). By contrast, NHMRC/MoH and FAO/WHO both used a lower 25(OH)D threshold of 27–27.5 nmol/L to derive their respective values (Refs. 3, 53). With respect to ULs, NASEM (25–38 µg/day), EFSA (25–35 µg/day), and NHMRC/MoH (25 µg/day) all established infant ULs at or above 25 µg/day. Despite differing methodologies, all bodies that established a UL arrived at values within a similar range (Ref. 108).

3. Human Milk Composition

It is well established that human milk is generally not a meaningful source of vitamin D for infants. The MILQ study reported a pooled median antirachitic activity (*i.e.,* vitamin D activity to prevent or cure rickets) of 30.6 IU/L (approximately 0.765 µg/L; excluding Bangladesh, n = 1,461) in mature milk, representing only 61–77 percent of NASEM's estimated human milk vitamin D concentration of 40–50 IU/L (Ref. 95). The corresponding pooled median total infant intake from 1 to 6 months of age was 24.4 IU/day (0.61 µg/d), approximately 6 percent of the NASEM AI of 400 IU/day (Ref. 95). No eligible North American studies for total vitamin D in mature human milk were identified by the iHMNutD study. Only a single eligible North American study for 25(OH)D was identified (n = 21; mean: 0.13 µg/100 g; approximately 1.3 µg/L using the specific gravity of human milk of 1.031 g/mL). The authors cautioned that this 25(OH)D value is based solely on data from one study (Ref. 8). Globally, a 2026 systematic review similarly identified vitamin D as ''the nutrient most vulnerable to inadequacy among exclusively breastfed infants'' (Refs. 108, 117).

4. International Regulatory Standards for Infant Formula

International standards for vitamin D in infant formula are generally aligned with a minimum of 1 µg/100 kcal, with the exceptions of the EU and China (Refs. 38, 41, 42), which set higher minimums of 2 µg/100 kcal. Maximum specifications show somewhat greater variation, with the United States, Codex Alimentarius, the EU, and Canada sharing a common maximum of 2.5 µg/100 kcal for infants 0–6 months of age, while Codex Alimentarius, the EU, Australia, and Canada permit a higher maximum of 3 µg/100 kcal for older infants 6–12 months of age (Refs. 12, 37, 38, 39, 40, 118). China specifies a notably higher maximum of 5 µg/100 kcal for infants 0–12 months of age. Where rationale is provided, the allowance of a higher maximum for older infants reflects their greater tolerability for vitamin D, as evidenced by higher ULs established by NASEM for this age group, as well as their higher calcium requirements relative to younger infants (Refs. 40, 108).

In 1998, the LSRO Panel recommended a minimum of 40 IU (1 µg)/100 kcal and a maximum of 100 IU (2.5 µg)/100 kcal, based on long-standing use of the minimum in industrialized countries, elimination of nutritional rickets in formula-fed infants, and the 90th percentile of vitamin D content in commercially available formulas at the time (Ref. 1). In 2018, EFSA evaluated the safety of infant formula containing a maximum vitamin D content of 3 µg/100 kcal, the value established under Commission Delegated Regulation (EU) 2016/127 (Ref. 38). EFSA found that some high-consuming infants under 4 months of age could receive intakes approaching or exceeding the UL of 25 µg/day from infant formula alone. Following the assessment, the European Commission lowered the maximum vitamin D level for infant formula for infants 0–6 months of age from 3 µg/100 kcal back to 2.5 µg/100 kcal (Refs. 115, 118).

Table 15 shows the requirements and recommendations of these international bodies and organizations.

TABLE 15—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR VITAMIN D IN INFANT FORMULA

Organization	Age range (months)	Minimum (µg/100 kcal)	Maximum (µg/100 kcal)	Reference
U.S. Current Standards [1] [2]	0–12	1 (40 IU)	2.5 (100 IU)	21 CFR 107.100.
LSRO [3]	0–12	1	2.5	LSRO, 1998.
Codex Alimentarius	0–6	1	2.5	CXS 72–1981.
	6–12	1	3	CXS 156–1987.
EU	0–6	2	2.5	Commission Delegated Regulation (EU) 2019/828, amending Delegated Regulation (EU) 2016/127.
	6–12	2	3	Commission Delegated Regulation (EU) 2016/127.
Australia [4]	0–6	1	2.6	FSANZ P1028.
	6–12	1	3	
Canada [5]	0–6	1	2.5	Health Canada, 2025.
	6–12	1	3	
China	0–12	2	5	GB 10765–2021, GB 10766–2021.

[1] Values converted from international units (40 IU = 1 µg).
[2] Vitamin D may also be declared on the label content in units of µg cholecalciferol. When these declarations are made, they shall appear in parentheses immediately following the declarations in IU (21 CFR 107.10(b)(1)).
[3] Recommended ranges.
[4] Values converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[5] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Vitamin D Intake

A 2020 systematic review evaluating the effect of vitamin D supplementation in healthy, breastfed infants found evidence from six studies (n=334) indicating that supplementation at 400 IU/day was associated with a mean increase in serum 25(OH)D of 22.63 nmol/L (95 percent CI: 17.05 to 28.21) and a statistically significant reduction in the incidence of vitamin D insufficiency (serum 25(OH)D <50 nmol/L) (Risk ratio 0.57; 95 percent CI: 0.41 to 0.80) compared to placebo or no treatment (Ref. 119). The certainty of the evidence was rated as low to very low. This systematic review concluded that the evidence was insufficient to determine whether supplementation at this dose reduces deficiency (25(OH)D <30 nmol/L), improves bone mineral content, reduces the incidence of nutritional rickets, or affects growth (Refs. 108, 119).

A 2024 systematic review and individual participant data meta-analysis (120 studies; 5,412 participants), sought to identify a minimum serum 25(OH)D threshold associated with reduced risk of nutritional rickets in children under 4 years of age (Ref. 110). A key contribution of this analysis was its ability to account for the confounding effect of dietary calcium intake on the risk of rickets. When analyses were restricted to children with adequate calcium intake, the serum 25(OH)D threshold at which sensitivity and specificity for rickets were simultaneously maximized was approximately 28 nmol/L. When the full dataset was considered, this threshold increased to 40 nmol/L, reflecting the elevated vitamin D requirement in the presence of inadequate dietary calcium. The authors concluded that a minimum serum 25(OH)D concentration of approximately 28 nmol/L represents a low risk of nutritional rickets for most children with adequate calcium intake, a finding consistent with the positions of NASEM (Ref. 106) and other agencies in the development of vitamin D dietary reference values (Refs. 108, 110).

A 2024 meta-regression analysis examined the relationship between total dietary vitamin D intake and serum 25(OH)D concentrations in children under 4 years of age (Ref. 120). The analysis used a multilevel, multivariable dose-response approach and included 31 randomized controlled trials enrolling healthy children who received vitamin D supplements or fortified foods. Studies were excluded if they enrolled premature/low birth weight infants or children with conditions such as rickets (Ref. 120). The trials covered a wide range of total vitamin D intakes (0.6 to 57 µg/day), with a median of 11 µg/day. To translate the dose-response model into population-level intake recommendations, the authors simulated 100,000 individual serum 25(OH)(D) responses at each vitamin D intake level. The modeling demonstrated that a total daily vitamin D intake of 10 µg/day (400 IU/day) would maintain serum 25(OH)D above 28 nmol/L in 97.3 percent of young children, and that an intake of 35 µg/day (1,400 IU/day) would result in fewer than 1.5 percent of individuals exceeding a serum 25(OH)D concentration of 200 nmol/L, a NOAEL with respect to hypercalcemia and hypercalciuria. The authors acknowledged that the overall certainty of evidence was rated as low (Ref. 120).

U.S. dietary intake data indicate that inadequate vitamin D intake is common among infants across feeding types. Analysis of NHANES data found that only approximately 27 percent of U.S. infants met AAP guidelines for vitamin D between 2009 and 2016 (Ref. 121). Data from the 2016 FITS indicate that vitamin D was one of only two nutrients for which mean total intakes (including supplements) did not exceed the AI. Mean intakes were approximately 260 IU/day (6.5 µg/day) for infants 0–5.9 months of age and 296 IU/day (7.4 µg/day) for infants 6–11.9 months of age, with only 17 percent and 24 percent of infants in these respective age groups meeting the AI (Ref. 82). A longitudinal study of infants enrolled in the U.S. Department of Agriculture's (USDA) Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) found that despite the higher vitamin D intakes associated with formula feeding compared to breastfeeding, the proportion of formula-fed infants meeting the vitamin D AI ranged from only approximately 16–43 percent across time points (Ref. 122). Vitamin D supplementation was reported in only 4–5 percent of formula-fed infants.[2] Overall, only 16–36 percent of all WIC-enrolled infants, including those across all feeding types, met the vitamin D recommendation at any given time point (Ref. 122).

[2] WIC Program funds may not be used to purchase or issue dietary supplements, including vitamin D supplements.

6. Evidence Evaluation and Rationale

a. Rationale for Changing the Unit of Measure From IU to µg

Expert scientific bodies and international regulatory standards increasingly express vitamin D content in weight-based units (µg) rather than IU. Vitamin D specifications for infant formula currently must be expressed in IU (§ 107.10(a)(2)). In FDA's 2016 final rule revising the Nutrition and Supplement Facts labels, FDA replaced IUs with weight-based units for vitamin D on labels for conventional foods and dietary supplements, citing changes in understanding of vitamin activity and consistency with IOM DRI report units (81 FR 33742 at 33912). FDA considers that the same scientific rationale supports expressing vitamin D specifications for infant formula in µg, consistent with current labeling regulations, NASEM DRI values, and international infant formula standards. The conversion factor of 40 IU = 1 µg is universally accepted. FDA proposes to amend § 107.10(a)(2) to require that vitamin D specifications be expressed in µg with voluntary declaration of IU equivalents provided parenthetically, supporting continuity for healthcare providers and caregivers accustomed to IU-based expressions (Ref. 108). FDA also proposes to amend the table at § 107.100(a) to reflect the unit of measurement for vitamin D as µg rather than IU.

FDA proposes to express vitamin D specifications and label declarations for infant formula in micrograms of vitamin D, µg, encompassing both vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), rather than in micrograms of cholecalciferol alone. Currently, § 107.10(b)(1) specifies that vitamin D may be voluntarily declared on the label in units of µg cholecalciferol parenthetically following the declaration in IUs. Both vitamin D_2 and vitamin D_3 are currently permitted for use in infant formula individually or in combination (21 CFR 184.1950). Permitting declaration solely in µg of cholecalciferol would not accurately reflect the total vitamin D content of infant formulas containing vitamin D_2, either alone or in combination with vitamin D_3. As noted in section I.1.c of this document, the available scientific evidence of intake levels consistent with typical formula consumption does not demonstrate statistically significant differences in serum 25(OH)D response between vitamin D_2 and vitamin D_3, consistent with the conclusion of the 2011 NASEM report that ''it would appear that at low doses, D_2 and D_3 are equivalent'' (Ref. 106).

Accordingly, FDA considers that expressing vitamin D content as total µg vitamin D is scientifically appropriate, as it represents the combined antirachitic activity provided to the infant. This approach is also consistent with international infant formula standards, which specify and declare vitamin D content in terms of total vitamin D rather than by individual form (table 15), and with current U.S. nutrition labeling regulations for conventional foods and dietary supplements, which similarly declare vitamin D on a total basis in µg. Therefore, FDA proposes to amend § 107.10(a)(2) to require that vitamin D be expressed in µg. FDA also proposes to amend § 107.10(b)(1) to permit voluntary declaration in IU in parentheses following the declaration in µg, and to remove the option of expressing vitamin D in µg cholecalciferol.

b. Rationale for Increasing the Minimum Specification to 2 µg (80 IU)/100 kcal

Multiple independent assessments support 10 µg (400 IU)/day as an appropriate vitamin D intake for infants. NASEM established an AI of 10 µg/day for infants 0–12 months of age, EFSA independently arrived at the same AI for infants, and dose-response modeling predicted that this intake level would maintain serum 25(OH)D above 28 nmol/L in 97.3 percent of young children (Ref. 120). These independent assessments using different methodological approaches all support 10 µg (400 IU)/day as the basis for the minimum vitamin D specification in infant formula (Ref. 108).

U.S. dietary intake data suggest risk for inadequate vitamin D intake among U.S. infants (Refs. 82, 108, 121, 122). Although dietary intake data carry inherent measurement limitations, findings across these studies, conducted in both WIC and non-WIC populations using different methodologies, are consistent in suggesting that a substantial proportion of U.S. infants, including those who are formula-fed, are at risk of vitamin D intakes below the AI (Ref. 108).

At the current minimum of 1 µg (40 IU)/100 kcal, an infant 0–6 months of age consuming a typical daily infant formula intake would receive approximately 5.3 µg (211 IU)/day from infant formula, representing 53 percent of the NASEM AI of 10 µg (400 IU/day). To achieve the full AI at the current minimum, an infant would need to consume approximately 1,000 kcal/day from formula, a volume substantially exceeding typical intake for this age group. For infants 6–12 months of age consuming typical daily infant formula intakes, vitamin D intake at the current minimum would be approximately 4.1 µg (163 IU)/day, representing only 41 percent of the AI. FDA considers these intakes insufficient to reliably meet vitamin D needs in either age group.

In contrast, at the proposed minimum of 2 µg (80 IU)/100 kcal, an infant 0–6 months of age consuming a typical daily intake of infant formula would receive 10.5 µg (422 IU)/day from infant formula, representing 105 percent of the NASEM AI. For infants 6–12 months of age consuming a typical daily intake of infant formula, vitamin D intake at the proposed minimum would be approximately 8.1 µg (324 IU)/day, representing approximately 81 percent of the AI from formula alone. FDA considers this level of intake from infant formula to be sufficient to support meeting the AI when accounting for the typical patterns of formula feeding as well as complementary food contributions in older infants.

The proposed minimum of 2 µg (80 IU)/100 kcal aligns with or exceeds international standards (table 15). Both the EU and China specify a minimum of 2 µg/100 kcal for infant formula. Codex Alimentarius, Australia, Canada, and the LSRO Panel specify a minimum of 1 µg/100 kcal. The LSRO Panel noted that the 1 µg (40 IU)/100 kcal minimum had eliminated nutritional rickets in formula-fed infants and, noting that the RDA for vitamin D was 300 IU/day at that time, found no scientific justification to recommend a change (Ref. 1). The NASEM AI and the available U.S. dietary intake data indicate that the current minimum does not reliably support attainment of the AI across the range of typical infant formula consumption volumes. FDA considers that the proposed minimum of 2 µg (80 IU)/100 kcal more appropriately supports infants in meeting current nutrient reference values.

c. Rationale for Increasing the Maximum Specification to 3 µg (120 IU)/100 kcal

FDA's evaluation of the maximum is guided by the NASEM ULs of 25 µg (1,000 IU)/day for infants 0–6 months of age and 38 µg (1,500 IU)/day for infants 6–12 months of age. As discussed in section V.I.2.a of this document, NASEM used an endpoint of decreased linear growth (Ref. 106). NASEM noted that this endpoint is relatively insensitive and that newer data have not emerged to better characterize dose-response relationships or hypercalcemia risk in infants, representing a source of ongoing uncertainty (Ref. 106). EFSA established concordant ULs of 25 µg/day

for infants under 6 months of age and 35 µg/day for infants 6 to less than 12 months of age (Ref. 115). The modeling study similarly found that a daily intake of 35 µg/day would result in fewer than 1.5 percent of young children (under 4 years of age) exceeding serum 25(OH)D of 200 nmol/L (Ref. 120). The authors rated the overall certainty of evidence as low (Ref. 120). The convergence of assessments around similar ULs, despite differing methodologies, provides a consistent framework for evaluating the safety of the proposed maximum specification (Ref. 108).

i. Estimated Vitamin D Intakes at the Current and Proposed Maximum

At the current maximum of 2.5 µg (100 IU)/100 kcal, estimated vitamin D intakes from typical infant formula volumes represent approximately 53 percent and 27 percent of the ULs for infants 0–6 months of age and 7–12 months of age, respectively. Under a high-consumption scenario (*i.e.,* 90th percentile of energy intake from infant formula based on NHANES data from 2015–2023), these estimates increase to 84 percent and 52 percent of the ULs for the same age groups, respectively, from infant formula alone. At the proposed maximum of 3 µg (120 IU)/100 kcal, estimated vitamin D intakes at typical consumption volumes represent approximately 63 percent and 32 percent of the ULs for infants 0–6 months of age and 7–12 months of age, respectively (table 16). For high consumers, estimated intakes at the proposed maximum reach approximately 100 percent and 63 percent of the ULs for infants 0–6 months of age and 7–12 months of age, respectively. When complementary foods are also considered for infants 7–12 months of age, total estimated vitamin D intake reaches approximately 68 percent of the UL. Across all scenarios evaluated, estimated vitamin D intakes at the proposed maximum do not appreciably exceed the UL for either age group (Ref. 108).

TABLE 16—COMPARISON OF ESTIMATED VITAMIN D INTAKES FROM INFANT FORMULA ACROSS MAXIMUM SPECIFICATION LEVELS FOR INFANTS 0–6 MONTHS OF AGE AND 7–12 MONTHS OF AGE

Parameter	Current maximum (2.5 µg/100 kcal)	Proposed maximum (3 µg/100 kcal)
Infants 0–6 months of age		
Typical Intake Volumes		
Infant formula intake assumption	0.78 L/day at 676 kcal/L (527 kcal/day).	
Vitamin D from infant formula	13.2 µg/day	15.8 µg/day.
% of UL (25 µg/day)	53%	63%.
NHANES Data—High Consumers [1]		
90th percentile energy intake from infant formula	836 kcal/day.	
Vitamin D from infant formula	20.9 µg/day	25.1 µg/day.
% of UL (25 µg/day)	84%	100.3%.
Infants 7–12 months of age		
Typical Intake Volumes		
Infant formula intake assumption	0.6 L/day at 676 kcal/L (406 kcal/day).	
Vitamin D from infant formula	10.1 µg/day	12.2 µg/day.
% of UL (38 µg/day): Formula only	27%	32%.
NHANES Data—High Consumers [1]		
90th percentile energy intake from infant formula	794 kcal/day.	
Vitamin D from infant formula	19.9 µg/day	23.8 µg/day.
% of UL (38 µg/day): Formula only	52%	63%.
Vitamin D from complementary foods [2]	1.6 µg/day	1.6 µg/day.
Total vitamin D intake	21.5 µg/day	25.4 µg/day.
% of UL: Total intake	57%	68%.

[1] NHANES exposure estimates are based on the 90th percentile of energy intake from infant formula among non-breastfed infants aged 0–6 months (n = 235) and 7–12 months (n = 205), using NHANES data (Refs. 13, 14, 15, 16, 17, 18). Infants at the 90th percentile of energy intake from infant formula represent a high-consumption scenario and are used here to estimate upper-bound exposure to vitamin D from formula.

[2] Estimated vitamin D intake from complementary foods is incorporated into the 7–12-month exposure estimates only, reflecting the mean of reported complementary food intake among infants in this age group from the same NHANES cycles (Refs. 13, 14, 15, 16, 17, 18).

ii. Comparison With International Regulatory Standards

FDA's proposed maximum of 3 µg (120 IU)/100 kcal for vitamin D in infant formula is consistent with most international regulatory standards for follow-on formula for infants 6–12 months of age but exceeds most international standards for formula intended for infants 0–6 months of age. Codex Alimentarius, Australia, Canada, and the EU all permit a maximum of 3

µg/100 kcal for older infants (6–12 months of age), reflecting that age group's greater tolerability for vitamin D. The EU reduced its maximum for formula intended for infants 0–6 months of age from 3 µg/100 kcal to 2.5 µg/100 kcal following an EFSA safety assessment finding that some high-consuming infants in that age group may exceed the UL at the higher maximum. China specifies a notably higher maximum of 5 µg/100 kcal for all infants 0–12 months of age. The LSRO Panel's 1998 recommendation of 2.5 µg (100 IU)/100 kcal was based on the 90th percentile of vitamin D content in commercially available infant formulas at the time (Ref. 108).

Unlike most international frameworks, U.S. regulations do not distinguish between infant formula for infants 0–6 months of age and follow-on formula for infants 6–12 months of age. In the United States, all infant formulas must meet the nutrient specifications in § 107.100 and be suitable for infants from birth through 12 months of age. Accordingly, the proposed maximum of 3 µg/100 kcal would apply across the full infant age range, including younger infants 0–6 months of age who have a lower UL (25 µg/day) than older infants 7–12 months of age (38 µg/day) (Ref. 108).

iii. Safety Considerations for Younger Infants

EFSA's intake assessment for infants aged 0 to less than 4 months of age used high formula consumption values multiplied by median reference body weights, yielding estimated vitamin D intakes of approximately 19–25 µg/day at 1 month of age and 23–29 µg/day at 4 months of age. EFSA's approach, designed to characterize intake among high consumers in the context of European feeding practices, differs from FDA's exposure analysis, which is based on the 90th percentile of energy intake from infant formula among U.S. infants. EFSA's 2018 UL evaluation used a serum 25(OH)D concentration of 200 nmol/L as a conservative reference point rather than a toxicity threshold, predicting that 0–4 percent of infants under 6 months of age would exceed this level at intakes of 20–25 µg/day. FDA estimates that vitamin D intake among high-consuming U.S. infants 0–6 months of age at the proposed maximum is approximately 25.1 µg/day, which is at the NASEM UL. FDA considers this safety margin acceptable for younger infants, noting that the NASEM UL was derived from a relatively insensitive endpoint using a conservative uncertainty factor and that NASEM acknowledged limitations in the underlying evidence (Ref. 108). FDA is not aware of evidence of adverse effects at or near this level under current conditions of use. Nevertheless, FDA acknowledges residual uncertainty due to limited data on the dose-response relationship for adverse outcomes in infants 0–6 months of age and invites comment on whether a more conservative maximum should be considered for this age group.

iv. Manufacturing and Analytical Feasibility

The proposed maximum of 3 µg/100 kcal, paired with a proposed minimum of 2 µg/100 kcal, provides a manufacturing operating range of 1 µg (40 IU)/100 kcal. A 1 µg/100 kcal operating range between the minimum and maximum is intended to provide manufacturers sufficient flexibility to account for processing and shelf-life considerations while maintaining vitamin D intakes within a nutritionally appropriate and safe range across the U.S. infant population. Comments received in response to FDA's 2025 RFI on infant formula nutrient requirements support these manufacturing feasibility concerns (90 FR 20475). Multiple comments from industry stakeholders highlighted that vitamin D is a sensitive nutrient, since it degrades easily under certain conditions, with one reporting that it is less stable in the presence of protein hydrolysates or free amino acids, and that manufacturing variability and shelf-life losses necessitate formulating above the label claim, supporting the need for an adequate operating range between the minimum and maximum. Several of these comments recommended increasing the U.S. maximum to 3 µg (120 IU)/100 kcal, noting that the current U.S. maximum of 2.5 µg (100 IU)/100 kcal has proven insufficient to support manufacturing flexibility while reliably meeting the minimum label claim.

FDA's proposed range is also informed by considerations of analytical method performance and the ability to reliably verify regulatory compliance. A 2022 statistical assessment re-evaluated performance data from the multi-laboratory validation study of AOAC Method 2016.05/ISO 20636:2018, the current state-of-the-art analytical method for determining vitamin D content in infant formula. That study found that the narrower EU regulatory range of 2 to 2.5 µg/100 kcal presents significant compliance verification challenges: even when formula is accurately manufactured at the midpoint of that range (2.25 µg/100 kcal), approximately 18 percent of test results would be expected to indicate noncompliance due solely to analytical method variability (Ref. 123). In contrast, the Codex Alimentarius range of 1 to 2.5 µg/100 kcal was associated with a predicted noncompliance rate of less than 1 percent at the regulatory midpoint (Ref. 123). These findings indicate that maintaining the current maximum of 2.5 µg/100 kcal while raising the minimum to 2 µg/100 kcal is not analytically feasible using current validated methods (Ref. 123).

Applying the statistical methodology of the 2022 assessment previously discussed to the proposed 2 to 3 µg/100 kcal range, FDA estimates a predicted noncompliance rate of approximately 1.6 percent at the regulatory midpoint of 2.5 µg/100 kcal, assuming an average method reproducibility of 8.2 percent reproducibility relative standard deviation (Refs. 108, 123). FDA considers this to support the analytical feasibility of the proposed range and invites comment and data on analytical performance within the proposed range.

These manufacturing constraints also have direct nutritional implications. The AAP noted that, given manufacturing variability, shelf-life losses, and label claim requirements, it has proven difficult for infants to meet the full AI of 10 µg (400 IU)/day through typical infant formula intakes under the current allowable range, which the AAP characterized as too narrow. With label declarations commonly set at approximately 1.5 µg (60 IU) or 1.75 µg (75 IU)/100 kcal, manufacturers have difficulty ensuring that the label claim is maintained through end of shelf life without approaching or exceeding the current maximum of 2.5 µg (100 IU)/100 kcal, leaving only 25 to 40 IU/100 kcal of headroom for manufacturing overages (Ref. 91).

FDA acknowledges that the proposed range of 2 to 3 µg/100 kcal spans the same absolute width of 1 µg (40 IU)/100 kcal as the range the AAP described as insufficient. However, FDA considers that the proposed range addresses this concern not by widening the range, but by raising the minimum to 2 µg/100 kcal, which shifts the entire operating band upward, better positioning manufacturers to achieve label claims consistent with meeting the AI at typical consumption volumes. FDA invites comment on whether the proposed minimum-to-maximum range of 2 to 3 µg (80–120 IU)/100 kcal is sufficient to ensure that infants consuming typical volumes of infant formula can reliably meet the AI of 10 µg (400 IU)/day while addressing manufacturing variability and shelf-life losses. Specifically, FDA requests data and information on: (1)

whether the proposed 1 µg (40 IU)/100 kcal operating range is adequate to accommodate typical manufacturing overages and nutrient degradation over shelf life; (2) whether an alternative minimum or maximum should be considered, and if so, what scientific, technical, or operational data support such an alternative; and (3) whether the proposed maximum of 3 µg (120 IU)/100 kcal poses a risk of excessive vitamin D intake for infants 0–6 months of age (Ref. 108).

d. Consideration of the Evidence Base

FDA acknowledges significant uncertainties in the evidence base underlying its proposed vitamin D specifications for infant formula. The NASEM ULs were derived from a limited number of older studies using decreased linear growth, which it acknowledged as a relatively insensitive endpoint, and the dose-response relationship between vitamin D intake and adverse outcomes in infants is not well characterized (Refs. 106, 108). Additionally, differing consumption assumptions between FDA and EFSA led EFSA, but not FDA, to find that high-consuming infants under 4 months of age may exceed the UL at the proposed maximum of 3 µg/100 kcal. Exposure estimates do not account for vitamin D from sunlight. This is a conservative assumption with respect to the minimum specification, as any cutaneous vitamin D synthesis would supplement formula intake and reduce the risk of inadequacy. However, it is not conservative with respect to the maximum, as appreciable UV–B exposure would contribute to serum 25(OH)D concentrations beyond those estimated from formula intake alone.

Additionally, the estimates do not account for concurrent vitamin D supplementation. Currently, the AAP recommends that infants consuming less than 1,000 mL/day of infant formula receive routine vitamin D supplementation (Ref. 91). Thus, infants receiving both formula at or near the proposed maximum plus a vitamin D supplement could have total intakes that approach or exceed the UL, particularly among younger infants (Ref. 108). As an example, an infant 0–6 months of age consuming infant formula at the proposed maximum of 3 µg/100 kcal at approximately 780 mL/day would receive an estimated 15.8 µg/day from formula alone, and when combined with a standard 10 µg supplement, total intake would reach approximately 25.8 µg/day, marginally exceeding the UL of 25 µg/day (Ref. 108). FDA acknowledges this co-exposure scenario as a source of residual uncertainty and invites comment and associated data on the prevalence of concurrent formula feeding and vitamin D supplementation at volumes below the AAP threshold, and on whether additional labeling or guidance measures should be considered to address this scenario.

J. Manganese (Proposed § 107.100(a))

The current requirement for manganese in infant formula is a minimum level of 5 µg/100 kcal (21 CFR 107.100). There is no maximum level established. Based on our analysis of scientific information and data since the 1998 comprehensive study of infant formula nutrients (Ref. 1), including infant formula manganese requirements in international standards, we propose to decrease the required minimum level for manganese to 1 µg/100 kcal and establish a maximum level for manganese in infant formula of 50 µg/100 kcal in § 107.100.

1. Background

Manganese is an essential trace mineral found in all tissues and is required for normal amino acid, lipid, protein, and carbohydrate metabolism. Manganese functions as a cofactor for key metalloenzymes, including arginase, glutamine synthetase, pyruvate carboxylase, and manganese superoxide dismutase, supporting antioxidant defense, energy production, immune function, and neurological activity (Refs. 124, 125, 126). Manganese is integral to the synthesis of neurotransmitters, including dopamine, glutamate, and gamma-aminobutyric acid (GABA), that are essential for neural signaling and survival (Refs. 126, 127). During fetal and infant development, manganese is also essential for skeletal and connective tissue formation, as well as for carbohydrate, protein, and lipid metabolism during periods of rapid growth (Refs. 126, 127, 128).

Manganese concentrations and bioavailability differ substantially across infant feeding sources. Human milk contains relatively low manganese levels (approximately 3–10 µg/L), cow milk-based formulas contain intermediate concentrations (approximately 30–50 µg/L), and soy protein-based formulas contain the highest levels (approximately 200–300 µg/L)—up to 100 times that of human milk (Refs. 125, 126, 127). In infant formulas, manganese is present in the divalent form (*i.e.,* an oxidation state that allows for chemically bonding with two other atoms or groups), in contrast to human milk, in which it is predominantly in trivalent form, (*i.e.,* an oxidation state which can chemically bond with three other atoms or groups), resulting in less controlled absorption from infant formula (Refs. 126, 127). Iron status modulates manganese uptake, as both minerals share common transporters. Iron deficiency, the most clinically significant driver of manganese excess in infants, increases the amount of these shared intestinal transporters produced in cells and increases manganese absorption, while adequate iron stores reduce manganese uptake (Refs. 124, 126, 128, 129, 130, 131). Route of exposure also significantly influences manganese absorption, distribution, and tissue retention (Refs. 126, 132). The scientific literature lacks consensus on optimal biomarker selection for assessing manganese status (Refs. 126, 133).

a. Health Consequences of Manganese Deficiency

Acquired manganese deficiency in human infants is considered extremely rare given the manganese concentrations present in human milk, infant formula (Refs. 126, 127), and food, with no reported cases in the scientific literature to date (Refs. 125, 126). Animal models on manganese deficiency have documented impaired growth, skeletal abnormalities, neonatal ataxia (*i.e.,* an irreversible congenital defect characterized by a lack of normal coordination of movements and loss of equilibrium), impaired glucose tolerance, altered lipid and carbohydrate metabolism, and compromised immunity, as well as low red blood cell count, hemoglobin, and hematocrit (*i.e.,* the percentage of total blood volume made up of red blood cells) (Refs. 62, 126, 134, 135, 136, 137).

b. Health Consequences of Excess Manganese Intake

Although manganese deficiency data in humans are largely derived from animal studies, the primary concern for infants and children centers on the well-documented toxic effects of manganese excess (Refs. 126, 138). The developing brain is especially vulnerable to manganese imbalances, as manganese preferentially accumulates in the basal ganglia, and disruptions during critical neurodevelopmental windows can produce lasting alterations in dopamine and GABA metabolism (Refs. 126, 127). This vulnerability is compounded in neonates (*i.e.,* early infancy) by immature biliary excretion, the primary route of manganese elimination, limiting the infant's capacity to clear excess manganese. Potential adverse effects of excess manganese exposure

are discussed further, below, in section J.5 of this document.

2. Nutrient Reference Values

a. NASEM

NASEM established AI values for manganese for infants in 2001 (Ref. 62). For infants 0–6 months of age, NASEM established an AI of 3 µg/day based on the manganese content of human milk from well-nourished mothers (3.5 µg/L) and typical milk consumption patterns (0.78 L/day) and rounding, reflecting that no cases of manganese deficiency have been observed in full-term infants exclusively breastfed in the United States or Canada. The higher AI of 600 µg/day for infants 7–12 months of age accounts for complementary foods containing higher manganese concentrations than human milk (Refs. 62, 126).

b. EFSA

Due to insufficient evidence to establish an AR and, by extension, a PRI, the EFSA NDA Panel proposed an AI. For infants 7–11 months of age, the EFSA Panel determined an AI range of 0.02–0.5 mg/day (20–500 µg/day) (Ref. 139). This range accounts for the broad spectrum of manganese intake levels that appear to support adequate nutrition and is informed by several sources: upward extrapolation from manganese intakes in exclusively breastfed infants, observed manganese consumption in infants at 6 and 12 months of age, and values derived from extrapolating the adult AI through isometric scaling (Ref. 139). EFSA did not establish an AI for younger infants (Ref. 139).

c. Australian NHMRC/New Zealand MoH

NHMRC/MoH established an AI of 3 µg/day for infants 0–6 months of age, calculated by multiplying the average human milk intake (0.78 L/day) by the average manganese concentration in human milk (3.5 µg/L) and rounding. For infants 7–12 months of age, NHMRC/MoH established an AI of 0.6 mg/day (600 µg/day), which was derived using two methods. The first method used consumption estimates for infants at 6 and 12 months of age (0.071 and 0.08 mg/kg, respectively) (Ref. 140), which, applied to reference weights of 7 and 9 kg, yielded total manganese intakes of 0.5 and 0.72 mg/day (from human milk and complementary food). The second method used body weight adjustment to extrapolate from adult data, producing an estimate of 0.567 mg/day. As noted above, the AI for the 7–12-month age group is significantly higher than that for the 0–6-month group because human milk contains lower concentrations of manganese than the complementary foods introduced into older infants' diets (Refs. 53, 126).

d. UL

NASEM was unable to determine ULs in infants because of the lack of data on adverse effects in infancy and concern about infants' ability to handle excess amounts (Ref. 62). Similarly, NHMRC/MoH did not set ULs, noting that the gap between the oral exposure levels known to cause effects in humans and animals and the estimated intake from food is narrow (Ref. 53).

In 2023, the EFSA NDA Panel conducted an updated scientific opinion on the UL for manganese and concluded that a UL for manganese could not be established (Ref. 141). In the absence of adequate data to establish a UL, EFSA derived safe levels of intake based on observed dietary intakes among high consumers (95th percentile) as an indication of the highest level of intake at which there is reasonable confidence in the absence of adverse effects. For infants, EFSA adopted a conservative approach because of insufficient data to determine when manganese homeostatic processes become fully mature, calculating the average of all available 95th percentile estimates across countries for infants 4 months to less than 12 months of age. This yielded a ''safe level of intake'' of 2 mg/day (2,000 µg/day) for manganese intake from all dietary sources, including fortified foods and food supplements, for this age group. EFSA noted that this safe level of intake is more limited in application than a UL because the intake level at which the risk of adverse effects begins to increase is not defined (Ref. 141).

e. Comparison of International Recommendations

Table 17 shows the manganese AIs established by NASEM, EFSA, and NHMRC/MoH.

TABLE 17—ADEQUATE INTAKES AND TOLERABLE UPPER INTAKE LEVELS OF MANGANESE

Organization	Year	Age range (months)	Adequate intake (µg/day)	Tolerable upper intake level
NASEM	2001	0–6	3	ND.
		7–12	600	ND.
EFSA	2017	7–11	20–500	ND.
Australian NHMRC/New Zealand MoH	2006	0–6	3	ND.
		7–12	600	ND.

For the 0–6-month age group, NASEM and NHMRC/MoH assessed the manganese content of human milk combined with typical infant milk intakes and arrived at aligned AI values. EFSA did not establish a separate AI for this youngest age group based on the available information. All three bodies acknowledged that manganese deficiency has not been clinically observed in healthy, full-term, exclusively breastfed infants, which supports the human milk-based approach (Ref. 126).

For the 7–12-month age group, NASEM and NHMRC/MoH again converged on the same AI of 600 µg/day. EFSA used a different approach from NASEM and NHMRC/MoH, drawing on multiple methodologies, and proposed a range of 20–500 µg/day. EFSA's range-based approach reflects acknowledged uncertainty and captures the broad spectrum of intakes observed to support adequate nutrition, though its upper bound of 500 µg/day does not reach the 600 µg/day AI established by NASEM and NHMRC/MoH. The dramatic increase in AI values from the 0–6-month to the 7–12-month age group reflects the substantially higher manganese concentrations found in complementary foods relative to human milk (Ref. 126).

3. Human Milk Composition

Multiple studies have characterized manganese concentrations in mature human milk from mothers with term pregnancies. Across most study populations largely conducted outside of North America, reported manganese concentrations generally ranged from approximately 2 to 16 µg/L (Refs. 126, 142). One data source reported substantially higher manganese concentrations: a 1991 Philippines subcohort study reported approximately

39.55 µg/L (Ref. 143), which may have reflected either a positive bias in reported manganese concentrations or environmental contamination. FDA does not consider this dataset to be representative of the physiological range of manganese in human milk from the broader population (Ref. 126).

More recently, the 2024 MIREC study reported manganese concentrations in mature human milk from a Canadian pregnancy cohort, which is the largest published study of human milk mineral composition from a high-income country using methods meeting eligibility criteria for reference value development (Ref. 105). The average (±standard deviation) manganese concentration in human milk was approximately 1.99 ± 2.93 µg/L in the full dataset and 1.96 ± 1.74 µg/L in the subset of participants who met the DRI applicability criteria. These values were calculated as geometric means and converted to a volume-based measure using the density of human milk (1.032 g/mL). FDA considers these data to be a substantially stronger evidentiary basis for characterizing the physiological range of manganese in human milk from a North American population, as compared to the broader data set described above, based on sample size and population/location. Accordingly, FDA intends to rely primarily on these data to inform the minimum and maximum specifications for manganese in infant formula (Ref. 126).

4. International Regulatory Standards for Infant Formula

International regulatory bodies are largely aligned on manganese specifications for infant formula (table 18). Codex Alimentarius specifies a minimum of 1 µg/100 kcal and a GUL of 100 µg/100 kcal, applicable to both infant formula (0–6 months of age) and follow-on formula (6–12 months of age) (Refs. 12, 37). The EU specifies a minimum of 1 µg/100 kcal and a maximum of 100 µg/100 kcal (Ref. 38). Australia, Canada, and China have adopted or proposed specifications aligned with Codex, with the exception that China specifies a higher minimum of 3 µg/100 kcal for infant formula for infants 0–6 months of age (Refs. 39, 40, 41, 42). In 2005, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) International Expert Group recommended a minimum of 1 µg/100 kcal and a lower maximum of 50 µg/100 kcal, citing infants' underdeveloped excretory capacity and the risk of bioaccumulation (Ref. 144). In 1998, the LSRO Panel recommended a minimum of 1 µg/100 kcal and a maximum of 100 µg/100 kcal.

TABLE 18—INTERNATIONAL STANDARDS AND/OR RECOMMENDATIONS FOR MANGANESE IN INFANT FORMULA

Organization	Age range (months)	Minimum (µg/100 kcal)	Maximum (µg/100 kcal)	Reference
U.S. Current Standards	0–12	5	ND	21 CFR 107.100
LSRO [1]	0–12	1	100	LSRO, 1998
Codex Alimentarius	0–12	1	100 (GUL)	CXS 72–1981, CXS 156–1987
EU	0–12	1	100	Commission Delegated Regulation (EU) 2016/127
Australia [2]	0–12	1	100 (GUL)	FSANZ P1028
Canada [3]	0–12	1	100	Health Canada, 2025
China	0–6	3	100	GB 10765–2021.
	6–12	1	100	GB 10766–2021.
ESPGHAN [1]	0–12	1	50	ESPGHAN International Expert Group, 2005

[1] Recommended ranges.
[2] Values converted from per 100 kJ to per 100 kcal (1 kcal = 4.184 kJ).
[3] Reflects proposed compositional requirements for infant formula.

5. Recent Scientific Evidence on Manganese Intake

a. Evidence of Toxicity (Neurotoxicity)

There are two distinct exposure frameworks that often occur simultaneously or over extended periods: (1) aggregate exposure, which involves a single chemical received through multiple routes or pathways simultaneously; and (2) cumulative exposure, which involves multiple chemicals acting on the same target system (Ref. 145). In the case of infant manganese exposure, both frameworks are relevant. Exposure routes include infant formula, drinking water, prenatal transfer, and airborne sources (Ref. 126). Neurodevelopmental effects are modified by co-exposures to other metals and nutrients such as selenium, lead, arsenic, and iron (Refs. 130, 146, 147, 148, 149).

Manganese becomes neurotoxic at elevated levels, and infants represent a uniquely vulnerable population due to their immature biliary excretion, higher intestinal absorption rates, and developing blood-brain barrier (Refs. 124, 127, 147, 150). Evidence from multiple prospective cohort studies, reviews (Refs. 133, 146, 147, 148, 151, 152, 153, 154, 155), and risk assessments (Refs. 156, 157) consistently demonstrate that excess prenatal and postnatal manganese exposure is associated with deficits in cognitive, motor, language, and social-emotional development in children (Ref. 158). Both manganese deficiency and manganese excess impair neurodevelopment, making it challenging to define a single, universal toxicity threshold (Ref. 126). The threshold at which manganese transitions from beneficial to harmful varies across studies but has been identified at approximately 24–28 µg/L in maternal blood at delivery for psychomotor outcomes (Ref. 152) and at cord serum manganese concentrations greater than 9.1 µg/L for neonatal neurobehavioral deficits (Ref. 148).

Regulatory and health-based thresholds for manganese exposure in infants have been established or proposed across studies and vary widely (Ref. 126). All current thresholds carry significant uncertainty, as they are largely extrapolated from animal studies or adult dietary data, and no threshold has been specifically validated for human infants across the full range of exposure routes and co-exposure conditions encountered in real-world settings.

Available evidence indicates that full neurological recovery from excess manganese exposure is unlikely when exposure is prolonged or occurs during critical periods of brain development (Refs. 126, 127, 133, 147, 159).

In addition to the limitations noted above regarding information about manganese toxicity, additional

limitations exist, such as study designs that preclude causal inference, the lack of a single validated biomarker, the potential for residual confounding by co-exposures, and inconsistent findings across studies and populations (Ref. 126).

b. Manganese Intakes From Water

Manganese occurs naturally in rocks, soil, groundwater, and surface water, with certain geographical regions in the United States exhibiting higher levels of manganese in the water (Ref. 160). Water manganese content is a significant consideration for formula-fed infants because water is used to reconstitute powdered and concentrated liquid infant formulas, and the total manganese intake reflects the contribution from water sources and infant formula. Powdered infant formulas, which represent most formula consumed by infants, require more water per unit volume than concentrated liquids, resulting in proportionally greater water-derived manganese intake. In a 2019 study, investigators analyzed data from 43,334 wells in the United States and estimated that 12.9 percent of groundwater samples exceeded the U.S. Environmental Protection Agency's Health Reference Level of 300 µg/L for manganese (Ref. 160). These findings were corroborated in a 2021 study at the state level, assessing water concentrations in Minnesota community public water systems, noting that 13 percent of U.S. groundwater samples exceeded this same threshold (Ref. 157). In the same 2021 paper, two additional international benchmarks applicable to the manganese content of water were highlighted: Canada's drinking water standard of 120 µg/L (Ref. 161) and a proposed WHO health-based guideline value of 80 µg/L (Ref. 162).

c. Manganese Intakes From Infant Formula

In 2019, a group of investigators measured manganese concentrations in infant formulas marketed in the United States and found ranges of 230–430 µg/L (36–65 µg/100 kcal) in cow milk-based formulas and 420–790 µg/L (64–120 µg/100 kcal) in soy protein-based formulas (Ref. 163). Researchers analyzing public drinking water in Minnesota and powdered infant formula samples also reported manganese concentrations of 69.8–291 µg/L and 306–531 µg/L for cow milk-based and soy protein-based infant formulas, respectively. Notably, the single amino acid-based formula included in the analysis contained the highest concentration at approximately 110 µg/100 kcal (Ref. 157). Based on these analyses, certain soy and amino acid-based formulas already exceeded the maximum specification of 100 µg/100 kcal set by other expert bodies (Ref. 126).

An important consideration is the combined exposure to manganese from both infant formula and drinking water used for reconstitution. When soy protein or amino acid-based formulas were reconstituted with water at the 95th percentile of Minnesota community water concentrations (562 µg/L), central tendency manganese intake estimates reached 156 percent and 213 percent, respectively, of the Minnesota Department of Health neonatal-based Reference Dose (RfD) (83 µg/kg/day) (Ref. 157). Upper-end estimates for all formula types, including cow milk-based formula, exceeded the RfD when reconstituted with water at the 95th percentile concentration (Ref. 157).

d. Manganese Intake

To characterize routine dietary manganese intakes among U.S. infants, FDA used food consumption data from the What We Eat in America/NHANES study covering 2017 to March 2020 (n = 332 infants 0–12 months of age) in conjunction with manganese concentration data from FDA's Total Diet Study (TDS) for fiscal years (FY) 2018–2020 (Refs. 164, 165, 166). Among infants 0–6 months of age (n = 169), the mean estimated daily manganese intake using mean TDS concentrations was 234 µg/day (10th percentile: 73 µg/day; 90th percentile: 601 µg/day). Among infants 7–12 months of age (n = 163), the mean estimated intake was 1,123 µg/day (10th percentile: 251 µg/day; 90th percentile: 1,991 µg/day) (Ref. 126).

6. Evidence Evaluation and Rationale

Based on the review of available scientific data, information, and international standards, we propose to decrease the current minimum specification for manganese in infant formula to 1 µg/100 kcal and to establish a maximum specification of 50 µg/100 kcal in § 107.100.

a. Rationale for Decreasing the Minimum Specification to 1 µg/100 kcal

At the current minimum manganese level, 5 µg/100 kcal, typical infant formula intakes provide approximately 26 µg/day and 20 µg/day for infants 0–6 months of age and 7–12 months of age, respectively. This represents 867 percent of the NASEM AI for infants 0–6 months of age (3 µg/day) and 3.3 percent of the AI for infants 7–12 months of age (600 µg/day). At the proposed minimum of 1 µg/100 kcal, the typical intake from infant formula is estimated to be 5.3 µg/day and 4.1 µg/day for infants 0–6 months of age and 7–12 months of age, respectively. These intakes exceed the AI for infants 0–6 months (176 percent AI) and would remain well below the AI for infants 7–12 months (0.7 percent AI). The notable discrepancy in AIs across the two age groups reflects variations in dietary exposure patterns (*i.e.,* older infants consuming complementary foods, which have higher concentrations of manganese) rather than a markedly distinct physiological requirement. Thus, FDA considers that manganese intakes at the proposed minimum of 1 µg/100 kcal are unlikely to present a risk of inadequacy for formula-fed infants in the 7–12-month age group (Ref. 126).

Manganese deficiency is rare in infants and has not been documented in healthy infants under normal dietary conditions. Cases of manganese deficiency are largely drawn from animal studies and rare genetic disorders affecting manganese transport. FDA considers that this limited evidence of deficiency under current intake conditions further supports the proposed reduction in the minimum specification (Ref. 126).

Central estimates of mature human milk manganese concentrations range from approximately 1.4 to 16 µg/L with recent North American data reflecting a mean concentration of 1.96 ± 1.74 µg/L (Ref. 105). Assuming an energy density of human milk of 650 kcal/L, the manganese content of human milk is approximately 0.3 µg/100 kcal based on the MIREC study (Ref. 105) mean, with the broader range of concentrations reported across studies corresponding to approximately 0.2 to 2.5 µg/100 kcal. The proposed minimum of 1 µg/100 kcal exceeds the mean manganese concentration of human milk on a per-kcal basis and remains within the range of concentrations reported across studies, providing a conservative margin above mean human milk concentrations (Ref. 126).

The current minimum of 5 µg/100 kcal exceeds all international standards assessed. The proposed minimum would align the U.S. minimum with international infant formula standards as well as recommendations from the LSRO Panel and ESPGHAN International Expert Group (table 18). Furthermore, the proposed decrease is supported by several comments recommending reducing or eliminating the minimum manganese requirement in response to FDA's 2025 RFI on nutrient requirements for infant formula (90 FR 20475, May 14, 2025).

b. Rationale for Establishing a Maximum Specification of 50 µg/100 kcal

Expert bodies, including NASEM and EFSA, have not established ULs for manganese in infants, citing insufficient dose-response data in human infant populations (Refs. 62, 141). Nevertheless, a substantial and growing body of evidence indicates that excess manganese exposure during infancy poses risks to neurodevelopment, and FDA considers that the weight of this evidence, along with the unique physiological vulnerabilities of infants and the aggregate nature of manganese exposure, supports establishing a maximum specification for manganese in infant formula (Ref. 126).

Manganese becomes neurotoxic at elevated levels, and infants represent a uniquely vulnerable population due to their immature biliary excretion, higher intestinal absorption rates, and developing blood-brain barrier (Refs. 125, 127). Evidence from multiple prospective cohort studies and reviews consistently demonstrates that excess prenatal and postnatal manganese exposure is associated with deficits in cognitive, motor, language, and social-emotional development in children (Refs. 133, 146, 147, 148, 151, 152, 153, 154, 155). FDA acknowledges that the dose-response relationship is complex and non-linear, that current health-based reference doses are largely extrapolated from neonatal animal studies rather than direct human infant data, and that causal inference from epidemiological literature remains limited by methodological constraints (Refs. 133, 156, 157). Nevertheless, FDA assesses that the consistency of associations across several independent cohorts, the biological plausibility based on manganese's known neurotoxic mechanisms, and the limited potential for full recovery from manganese-induced neurodevelopmental effects support a conservative approach to limiting manganese intake in infants.

Formula-fed infants may be exposed to manganese through several concurrent pathways, including infant formula, drinking water used to reconstitute powdered or concentrated liquid formulas, prenatal transfer, and inhalation (Refs. 147, 167). FDA considers that evaluating manganese intake from infant formula in isolation underestimates the total manganese burden experienced by formula-fed infants. As discussed in section V.J.5.b of this document, manganese occurs naturally in U.S. groundwater at variable concentrations (Ref. 160). Additionally, smaller community water systems, which comprise 97 percent of U.S. systems, have been shown to have significantly higher manganese concentrations than larger systems (Ref. 157). When infant formula is reconstituted with manganese-containing water, various combined contributions can result in total manganese intakes exceeding health-based reference doses (Refs. 126, 142, 155, 160).

At the proposed maximum of 50 µg/100 kcal, estimated manganese intakes from typical intake volumes of infant formula alone are approximately 264 µg/day and 203 µg/day for infants 0–6 months of age and 7–12 months of age, respectively, prior to any contribution from water or other sources (see table 19). Under a high-consumption scenario, defined here as the 90th percentile of energy intake from infant formula based on data from three NHANES cycles (Refs. 13, 14, 15, 16, 17, 18), these estimates increase to approximately 418 µg/day and 397 µg/day for the same age groups, respectively, representing approximately 139-fold and 66 percent of the respective AI values (see table 19). The proposed maximum continues to provide manganese well above adequacy thresholds while substantially reducing the formula-derived contribution to aggregate exposure.

TABLE 19—COMPARISON OF ESTIMATED MANGANESE INTAKES FROM INFANT FORMULA ACROSS MINIMUM AND MAXIMUM SPECIFICATION LEVELS FOR INFANTS 0–6 MONTHS AND 7–12 MONTHS OF AGE

Intake scenario	Estimated energy intake (kcal/day)	Proposed minimum (1 µg/100 kcal) (µg/day)	Proposed maximum (50 µg/100 kcal) (µg/day)	Codex alimentarius GUL (100 µg/100 kcal) (µg/day)
Infants 0–6 months of age				
Typical intake volume (0.78 L/day at 676 kcal/L)	527	5.3	264	527
NHANES 90th percentile	836	8.4	418	836
Infants 7–12 months of age				
Typical intake volume (0.60 L/day at 676 kcal/L)	406	4.1	203	406
NHANES 90th percentile	794	7.9	397	794

NHANES exposure estimates are based on the 90th percentile of energy intake from infant formula among non-breastfed infants 0–6 months (n = 235) and 7–12 months (n = 205) of age, using NHANES data (Refs. 13, 14, 15, 16, 17, 18). Infants at the 90th percentile of energy intake from infant formula represent a high-consumption scenario and are used here to estimate upper-bound exposure to manganese from infant formula.

Also, data from NHANES (2017–March 2020) and the TDS (2018–2020) suggest that infants may be routinely exposed to manganese at levels that substantially exceed the respective AIs for both age groups. This exposure accounts for all food sources, including complementary foods, infant formula, and human milk. FDA acknowledges that these estimates are subject to methodological limitations (Ref. 166) yet considers these intake data as contextual evidence in support of the proposed maximum.

Most major international regulatory bodies, including Codex Alimentarius, the EU, Australia, Canada, and China, have established a maximum or GUL of 100 µg/100 kcal (table 18). The LSRO Panel similarly recommended 100 µg/100 kcal (Ref. 1). FDA acknowledges this international consensus. However, FDA is concerned that this level may not fully account for aggregate infant exposure, particularly from drinking water used to reconstitute formula, or for the potentially higher absorption and retention of manganese in infants compared to the adults on whom adverse effect levels were based. FDA notes that the ESPGHAN International Expert Group reached a similar conclusion, recommending a maximum of 50 µg/100 kcal on the grounds that higher concentrations should be avoided given infants' immature

excretion mechanisms and the associated risk of bioaccumulation (Ref. 144).

Establishing a maximum specification for manganese in infant formula introduces manufacturing considerations that differ by protein source. Soy (*e.g.,* soy protein isolate) naturally contains high amounts of manganese, resulting in consistently higher manganese concentrations in soy protein-based formulas relative to cow milk-based formulas (Ref. 163). FDA acknowledges that the proposed maximum of 50 µg/100 kcal may represent the lowest technologically achievable level for soy protein-based formulas while maintaining adequate protein content. For cow milk-based formulas, which contain lower inherent manganese and for which manganese is typically added as a discrete ingredient (*e.g.,* manganese sulfate), greater formulation flexibility exists, and FDA does not expect that cow milk-based formulas would require formulation at or near the proposed maximum to meet nutritional requirements. It is also common for amino acid-based formulas to add manganese as a discrete ingredient, and FDA does not anticipate technological barriers to reformulation. FDA seeks comment on this proposed maximum, including data or information bearing on the feasibility of achieving lower manganese levels in soy protein-based infant formulas, which may include access to alternate sources of soy protein with lower manganese content.

c. Consideration of the Evidence Base

FDA acknowledges several important uncertainties in the evidence base supporting the proposed maximum. These include the absence of a validated UL for manganese in infants, the reliance on health-based reference doses extrapolated from neonatal animal studies, the lack of a single validated biomarker that captures total manganese body burden, the methodological limitations that preclude definitive causal inference regarding neurodevelopmental outcomes, variability in reported human milk manganese concentrations across studies, and the complexity of the dose-response relationship (Ref. 126). Despite these uncertainties, FDA is proposing to establish a lower maximum specification of 50 µg/100 kcal for manganese in infant formula (compared to 100 µg/100 kcal). FDA's recommendation is based on the weight of the available scientific evidence, including the consistency of associations between excess manganese exposure and adverse neurodevelopmental outcomes across independent cohorts, the unique physiological vulnerabilities of infants, and the aggregate nature of manganese exposure from multiple concurrent pathways, which together support a conservative approach to limiting manganese intake in this population.

VI. Proposed Effective/Compliance Dates

We intend that any final rule resulting from this rulemaking become effective 60 days after the date of the final rule's publication in the **Federal Register**. We propose a compliance date of 3 years after the effective date of the final rule completing our phased, comprehensive infant formula nutrient review to provide industry time to reformulate and relabel infant formula while recognizing the importance of updating the infant formula nutrient specifications. We invite comment on the proposed compliance date.

VII. Preliminary Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14192, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4).

Executive Orders 12866 and 13563 direct us to assess all benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. Rules are economically significant under section 3(f)(1) of Executive Order 12866 if they have an annual effect on the economy of $100 million or more; or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities. The Office of Information and Regulatory Affairs has determined that this proposed rule is a significant regulatory action under section 3(f)(1) of Executive Order 12866.

Executive Order 14192 requires that any new incremental costs associated with certain significant regulatory actions ''shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least 10 prior regulations.'' This proposed rule, if finalized as proposed, is expected to be an Executive Order 14192 regulatory action.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we cannot determine with certainty the magnitude of reformulation costs that small infant formula manufacturers would incur under this proposed rule, we find that the proposed rule may have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (Section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year.'' The current threshold after adjustment for inflation is $193 million, using the most current (2025) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Overview of Benefits, Costs, and Transfers

This proposed rule, if finalized, would update the nutrient specifications for infant formula to reflect the best available scientific evidence on certain infant nutritional requirements and safe intake levels. If finalized, the proposed changes to the nutrient specifications would generate benefits primarily through (1) reducing the risk of vitamin D deficiency in formula-fed infants and (2) reducing the risk of inadequate iodine intake, excessive vitamin A exposure, and excessive manganese exposure across the formula-fed infant population. The primary quantified benefit is avoided healthcare costs from vitamin D deficiency-induced late-onset hypocalcemia, with a primary annualized estimate of $80.93 million at a 7 percent discount rate and $90.04 million at a 3 percent discount rate. If finalized as proposed, benefits of this rule would begin accruing in 2031, following the proposed 3-year compliance period. Additional benefits from iodine, vitamin A, and manganese specification changes are described qualitatively. The primary present value of quantified benefits is $568.43 million at a 7 percent discount rate and $768.08 million at a 3 percent discount rate.

Costs are one-time and borne by domestic and foreign infant formula manufacturers in the compliance year. The primary annualized cost estimate is $17.64 million at a 7 percent discount rate and $17.57 million at a 3 percent

discount rate. The primary present value of costs is $123.86 million at a 7 percent discount rate and $149.86 million at a 3 percent discount rate.

This proposed rule is not expected to generate transfers. Table 20 presents the ROCIS summary of benefits, costs, and distributional effects of the proposed rule. All monetary values in table 20 are expressed in 2025 dollars.

TABLE 20—SUMMARY OF BENEFITS, COSTS, AND DISTRIBUTIONAL EFFECTS OF THE PROPOSED RULE

[Millions of 2025 dollars]

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered	
Benefits:							
Annualized Monetized ($millions/year)	$80.93	$18.79	$171.65	2025	7	2027–2036	
	90.04	20.90	190.98	2025	3	2027–2036	
Annualized Quantified	.....	.....	.....	.....	.....	.....	
	.....	.....	.....	.....	.....	.....	
Qualitative.							
Costs:							
Annualized Monetized ($millions/year)	17.64	8.35	31.70	2025	7	2027–2036	
	17.57	8.31	31.58	2025	3	2027–2036	
Annualized Quantified	.....	.....	.....	.....	.....	.....	
	.....	.....	.....	.....	.....	.....	
Qualitative.							
Transfers:							
Federal Annualized Monetized ($millions/year)	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
	From:			To:			
Other Annualized Monetized ($millions/year)	.....	.....	.....	.....	7	.....	
	.....	.....	.....	.....	3	.....	
	From:			To:			

Effects:
State, Local or Tribal Government:
Small Business:
Wages:
Distributional: Benefits are expected to accrue disproportionately to WIC-enrolled infants, who represent approximately 50 percent of formula-fed infants in the United States and are more likely to be exclusively formula-fed. Costs are borne by manufacturers.

In line with Executive Order 14192, in table 21, we estimate present and annualized values of costs, cost savings, and net costs over a perpetual time horizon. We estimate that this proposed rule would generate $7.08 million in 2024 dollars in annualized net costs at a 7 percent discount rate, discounted relative to year 2024, over a perpetual time horizon.

TABLE 21—EXECUTIVE ORDER 14192 SUMMARY TABLE

[Millions of 2024 dollars, discounted over a perpetual time horizon relative to year 2024 at a 7 percent discount rate]

	Primary estimate	Low estimate	High estimate
Present Value of Costs	$101.11	$47.85	$181.76
Present Value of Cost Savings	.....	.....	.....
Present Value of Net Costs	101.11	47.85	181.76
Annualized Costs	7.08	3.35	12.72
Annualized Cost Savings	.....	.....	.....
Annualized Net Costs	7.08	3.35	12.72

We request comment on our estimates of benefits, costs, and transfers of this proposed rule.

We have developed a Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 168) and at *https://www.fda.gov/about-fda/economics-staff/regulatory-impact-analyses-ria.*

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.32(n) that this action is of a type that does not normally have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). Collection of information includes any request or

requirement that persons obtain, maintain, retain, or report information to the Agency, or disclose information to a third party or to the public (44 U.S.C. 3502(3) and 5 CFR 1320.3(c)). The title, description, and respondent description of the information collection are shown under this section with an estimate of the annual reporting, recordkeeping, and/or third-party disclosure burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Infant Formula Nutrient Requirements.

Description: Finalization of this rule to amend regulations in 21 CFR part 107 for nutrient products would revise OMB control number 0910–0256 with regard to the scope of activity applicable to labeling of these products. At the same time, consistent with 5 CFR 1320.3(b)(1)(v), we estimate a de minimis one-time burden for *[a]djusting the existing ways to comply with any previously applicable instructions and requirements.*

Specifically, the proposed rule includes a mandatory unit change for vitamin A (from IU to µg RAE) and vitamin D (from IU to µg) that applies to all infant formula products regardless of whether nutrient levels change, such that all 326 UPCs would be subject to relabeling. We detail our estimates for this one-time reformulating cost here and in the PRIA. We note that we do not expect this to cause an ongoing increase in PRA burden above the current labeling requirements, but we seek comment on this assumption.

Relabeling costs were estimated using FDA's Labeling Cost Model (Ref. 169), updated to 2025 dollars. The model estimates per-UPC costs across labor, materials, inventory, and recordkeeping activities associated with a label change. All proposed label changes in this analysis are classified as minor changes, that is, changes confined to the Nutrition Facts panel that do not require multi-color redesign or modification of the principal display panel. The proposed changes, including updating declared values for vitamin D, vitamin A, iodine, and manganese and converting vitamin A and vitamin D declarations from IU-based to weight-based units, satisfy this definition.

The model distinguishes between coordinated and uncoordinated label changes. A coordinated change occurs when a manufacturer aligns a required regulatory label change with a planned voluntary relabeling cycle, avoiding prepress, design, and plate costs that would have been incurred regardless. An uncoordinated change occurs when a manufacturer must make a required label change outside of its normal voluntary cycle, incurring the full cost independently. Consistent with the model's empirical data showing that most products are voluntarily relabeled on a two-to-five-year cycle, we assume all label changes in this analysis are coordinated. Even under a coordinated change, manufacturers still incur administrative and recordkeeping costs associated with understanding the regulation, determining their response, and tracking the required change throughout the labeling process.

The estimated cost of a label change is $836 per UPC, with a 90 percent confidence interval between $226 and $1,942. We assume domestic and foreign entities incur the same per-UPC cost. Table 22 shows total estimated labeling costs by domestic and foreign origin.

TABLE 22—TOTAL LABELING COSTS

[2025$]

	Number of UPCs	Low	Primary	High
Domestic	291	$65,696	$243,392	$565,145
Foreign	35	7,902	29,274	67,973
Total	326	73,598	272,666	633,118

Domestic UPCs estimated as 89.2% of total UPCs, consistent with the ratio of domestic to total formulations.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, or the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. FDA solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XII. Request for Comments

We invite all interested persons to submit comments on any aspect of the proposed rule. In particular, we invite comment on the proposed changes to the minimum and/or maximum levels for iodine, vitamin A, vitamin D, and manganese; the proposal to establish a maximum level for manganese; the proposed changes to the unit of measure for vitamin A and vitamin D; the proposed change to the permitted source to meet the vitamin A requirement; and the proposed changes to the content of the required labeling. FDA also requests comment on maintaining the current required minimum and maximum levels in infant

formula for chloride, selenium, potassium, and sodium. Additionally, we invite comment on the following to further inform our phased, comprehensive infant formula nutrient review:

1. FDA is considering whether to require the inclusion of docosahexaenoic acid (DHA) and arachidonic acid (ARA) in infant formula. We invite comments supporting or opposing formal requirements for DHA and ARA, recommended minimum levels, ratios (*e.g.,* DHA:ARA ratio, amounts per 100 kcal), and any age- or formula type-specific considerations, along with scientific evidence supporting those recommendations.

2. FDA is considering whether alpha-linolenic acid (ALA) should be added as a required nutrient in infant formula given its role as an essential omega-3 fatty acid and precursor to longer-chain fatty acids such as DHA and eicosapentaenoic acid (EPA). If ALA were required, its ratio to linoleic acid (LA) would also need to be considered, as the two fatty acids compete for the same metabolic enzymes. We invite comments on the scientific evidence supporting or opposing a formal requirement for ALA and its ratio to LA, including any relevant clinical, epidemiological, or alternative data.

3. FDA is considering the minimum and/or maximum iron levels currently required in infant formula and will review emerging evidence regarding iron's role in neurodevelopment, gut microbiome development, and potential risks at higher intake levels. We invite comments on whether current levels should be maintained, increased, or reduced and on the scientific literature or international standards supporting those positions.

4. FDA is considering whether iron requirements in formula should differ for specific populations of infants (*e.g.,* infants 0–6 vs. 7–12 months of age, infants with socioeconomic and nutritional risk factors). We invite comments on evidence supporting differentiated iron requirements for these groups and how FDA should approach establishing population-specific standards.

5. FDA is considering whether L-carnitine should be required in infant formula given its role in fatty acid oxidation and energy metabolism. We invite comments on the current state of the science regarding L-carnitine's essentiality in infant nutrition and what evidence would support or oppose establishing a formal requirement.

6. FDA is considering whether the proposed minimum and/or maximum nutrient specifications for infant formula present any manufacturing, reformulation, or analytical feasibility challenges for manufacturers, and invites submission of any supporting data or information relevant to this determination.

7. FDA invites data and information on the variability of nutrient levels in tap water and bottled water in the U.S. and how such variability should be considered in establishing minimum and maximum standards for nutrients in infant formula, such as chloride.

8. FDA invites comment on our proposal to change the unit of measure from IU to µg RAE for vitamin A and from IU to µg for vitamin D, and on the potential impact of these changes on consumers' understanding of infant formula labeling.

XIII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

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List of Subjects

21 CFR Part 107

Food labeling, Infants and children, Nutrition, Reporting and recordkeeping requirements, Signs and symbols.

21 CFR Part 184

Food additives.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR parts 107 and 184 be amended as follows:

PART 107—INFANT FORMULA

■ 1. The authority citation for part 107 continues to read as follows:

Authority: 21 U.S.C. 321, 343, 350a, 371.

■ 2. Amend § 107.10 by:

■ a. In paragraph (a)(2):

■ i. Designating the table as table 1 to paragraph (a)(2); and

■ ii. In newly designated table 1, under ''Vitamins'' revising the entries for ''Vitamin A'', ''Vitamin D'', and ''Vitamin E''; and

■ b. Revising paragraph (b)(1).

The revisions read as follows:

§ 107.10 Nutrient information.

(a) * * *

(2) * * *

TABLE 1 TO PARAGRAPH (a)(2)

Nutrients	Unit of measurement
* * * * *	
Vitamins	
Vitamin A	Microgram Retinol Activity Equivalents.
Vitamin D	Micrograms.
Vitamin E	International Units.
* * * * *	

(b) * * *

(1) Vitamin A content may also be declared on the label in International Units, vitamin D content in International Units, vitamin E content in units of milligram alpha-tocopherol equivalents, and sodium, potassium, and chloride content in units of millimoles, micromoles, or milliequivalents. When these declarations are made, they shall appear in parentheses immediately following the declarations in microgram retinol activity equivalents for vitamin A, International Units for vitamin E, and micrograms for sodium, potassium, chloride, and vitamin D.

* * * * *

■ 3. Amend § 107.100 by:

■ a. In paragraph (a):

■ i. Designating the table as table 1 to paragraph (a); and

■ ii. In newly designated table 1, under the heading ''Vitamins'', revising the entries for ''Vitamin A'', ''Vitamin D'', ''Vitamin E'', and under the heading ''Minerals'' revising the entries for ''Manganese'', and ''Iodine''; and

■ b. Adding paragraph (g).

The revisions and addition read as follows:

§ 107.100 Nutrient specifications.

(a) * * *

TABLE 1 TO PARAGRAPH (a)

Nutrients	Unit of measurement	Minimum level	Maximum level
	* * * * *		
Vitamins			
Vitamin A	Microgram Retinol Activity Equivalents	70	120
Vitamin D	Micrograms	2	3
Vitamin E	International Units	0.7	
	* * * * *		
Minerals			
	* * * * *		
Manganese	Micrograms	1	50
	* * * * *		
Iodine	Do	15	50
	* * * * *		

* * * * *

(g) Vitamin A minimum and maximum levels shall be met through preformed vitamin A only. *Beta*-carotene, if used in infant formula, shall not be considered to contribute to the required minimum and maximum levels of vitamin A in infant formula.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

■ 4. The authority citation for part 184 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 371.

■ 5. Amend § 184.1245 by revising paragraph (c)(2) to read as follows:

§ 184.1245 *Beta*-carotene.

* * * * *

(c) * * *

(2) The ingredient is used in the following foods at levels not to exceed current good manufacturing practice: dairy product analogs as defined in § 170.3(n)(10) of this chapter; fats and oils as defined in § 170.3(n)(12) of this chapter; processed fruits and fruit juices as defined in § 170.3(n)(35) of this chapter; and infant formula.

* * * * *

Robert F. Kennedy, Jr.,

Secretary, Department of Health and Human Services.

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