RULEMAKING PETITION TO THE
UNITED STATES FOOD AND DRUG ADMINISTRATION
REQUESTING FDA TO REGULATE NANOMATERIALS IN INFANT FORMULA

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CENTER FOR FOOD SAFETY,
518 C Street, N.E.
Suite #200
Washington, D.C. 20002

and,

INTERNATIONAL CENTER FOR TECHNOLOGY ASSESSMENT
303 Sacramento St, 2nd Floor
San Francisco, CA 94111

Filed With:

JANET WOODCOCK,
in her official capacity as,
Acting Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Docket No. _____

February 14, 2022

PETITION FOR RULEMAKING REQUESTING FDA REGULATE NANOMATERIALS IN INFANT FORMULA

The undersigned submit this petition pursuant to 21 C.F.R. § 10.30, the Right to Petition Government Clause contained in the First Amendment of the United States Constitution,[1] and the Administrative Procedure Act (APA),[2] to request that the Commissioner of the Food and Drug Administration (FDA) amend regulations regarding nanomaterials in infant formula.

Nanotechnology and products containing manufactured and engineered nanomaterials have arrived and represent the crest of a product wave spanning many industries. A rapidly expanding universe of products containing nanomaterials is currently widely available, being sold to the public, and disposed of into the environment. These new materials can have fundamentally different properties from their bulk material counterparts—properties that also create unique human health and environmental risks—which create new oversight challenges for the regulatory agencies charged with protecting public health and the environment. Of unique concern is the use of engineered nanomaterials in infant formulas sold throughout the United States.

A recent study conducted by Arizona State University (ASU) found nanomaterials in infant formula manufactured by four infant formula companies: Gerber, Enfamil, Well Beginnings, and Similac.[3] The nanomaterials found were: nano-hydroxyapatite, nano-titanium dioxide, and nano-silicon dioxide.[4] Bulk scale hydroxyapatite is used as a calcium source, but can also be used to stabilize ingredients in formula mixture.[5] Through nanotechnology, hydroxyapatite can now be manufactured as nanoparticles to take advantage of properties at the nanoscale. Titanium dioxide is only approved as a food additive for whitening, but it is likely that the nano-titanium dioxide is used as a "brightener" for its reflective properties and as an anti-caking agent in infant formula.[6] Nano-silicon dioxide is used as a clearing agent in beer and wine, as well as a flow enhancing chemical, food additive, or coating. Again, it is likely that it is

[1] U.S. Const. amend. I.
[2] 5 U.S.C. § 553(e).
[3] Arizona State University researchers tested the same brands as they are sold in Europe and found that they did not contain the nano forms of these chemicals. Unpublished study discussed by Dr. Paul Westroff, ASU research director in conversation with Jaydee Hanson, March 10, 2020.
[4] S. Jared, P. Westerhoff, et al., *Detection and dissolution of needle-like hydroxyapatite nanomaterials in infant formula*, NanoImpact (2017), *available at* https://www.sciencedirect.com/science/article/abs/pii/S2452074816300805.
[5] International Osteoporosis Foundation, *Introduction to Bone Biology: All About Our Bones*, http://www.gunnalag.com/2012/04/19/international-osteoporosis-foundation-introduction-to-bone-biology-all-about-our-bones/.
[6] H. Shi, et al., *Titanium dioxide nanoparticles: a review of current toxicological data*, Particle and Fibre Toxicol. vol. 10 (2013), *available at* https://particleandfibretoxicology.biomedcentral.com/articles/10.1186/1743-8977-10-15.

being used as a flow agent in infant formula.[7] While the risks of these nanomaterials in infant formula are not well understood, existing studies about toxicity, chemical reactivity, and its greater capacity to penetrate biological membranes along with the fact that infants are particularly vulnerable to food safety risks due to developing immune systems, have indicated cause for concern.[8]

Recently, various agencies of the European Union have raised serious health questions about both the nano and the bulk forms of both hydroxyapatite and titanium dioxide. The EU Scientific Committee on Consumer Safety (SCCS) concluded that: "[D]epending on the manufacturing process, needle-shaped [hydroapatite] HAP nanoparticles may also be produced. The available information indicates that HAP-nano in needle-shaped form is of concern in relation to potential toxicity. Therefore, needle shaped HAP-nano should not be used in cosmetic products."[9] The SCCS has concluded that there is a basis for concern that the use of HAP-nano in cosmetic products can pose a risk to the consumer.[10]

Likewise, the European Food Safety Agency (EFSA) has raised concerns about one of the most common food additives, titanium dioxide, largely due to the nano scale material in the titanium dioxide.[11] EFSA's recent assessment based on thousands of studies that have become available since 2016 resulted in a conclusion from the EFSA's expert Panel on Food Additives and Flavourings that "titanium dioxide can no longer be considered safe as a food additive." This is because "[a]fter oral ingestion, the absorption of titanium dioxide particles is low, however they can accumulate in the body."[12]

In light of these concerns, the Food and Drug Administration (FDA) must exercise its authority under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure infant formulas are safe and meet certain nutritional requirements. FDA's existing regulations do not include screening or safety testing of nanomaterials or other potentially toxic synthetic ingredients. Petitioners respectfully request that FDA immediately take the steps necessary to properly regulate nano-hydroxyapatite and all other nanoscale ingredients as new ingredients in infant

---

[7] S. Dekker, et al., *Knowledge gaps in risk assessment of nano silica in food: evaluation of the dissolution and toxicity of different forms of silica,* Nanotoxicology (2013), *available at* https://pubmed.ncbi.nlm.nih.gov/22394279/.

[8] J. Moya, et al., *Children's Behavior and Physiology and How It Affects Exposure to Environmental Contaminants,* Pediatrics (2004), *available at* https://pediatrics.aappublications.org/content/113/Supplement_3/996.

[9] European Union Scientific Committee on Consumer Safety, *Opinion on the Safety of nanohydroapatite,* (March 2021), *available at* https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_246.pdf.

[10] *Id*.

[11] European Food Safety, *Titanium dioxide E171 no longer considered safe when used as a food additive,* Newsnote Newsnote (May 6, 2021), *available at* https://www.efsa.europa.eu/en/news/titanium-dioxide-e171-no-longer-considered-safe-when-used-food-additive.

[12] *Id*.

formulas pursuant to FFDCA and other applicable statutes. We urge that FDA prohibit all engineered nano ingredients until they are demonstrated to be safe for this vulnerable population. This legal petition provides both the blueprint and the legal impetus to take such regulatory actions.

ACTIONS REQUESTED

Petitioners request that FDA undertake the following actions with regards to nanomaterial products in infant formula:

1) Amend regulations directed at FDA's oversight of nanomaterial products including:
    a. An amendment to 21 C.F.R. § 106.3 including the production of engineered nanoparticles as an additional express example for what constitutes a "major change" in infant formula;
    b. An amendment of 21 C.F.R. § 106.140 to include specific reference to engineered nanoparticles as a reason to notify FDA of a change in infant formula that may adulterate the product;
    c. An amendment to the table set out in 21 U.S.C. § 350a(i) and in its regulations at 21 C.F.R. § 107.100(a) to include nanomaterials with defined maximum levels;
    d. An amendment of 21 C.F.R. § 106.3 to define terms necessary to regulate engineered nanomaterial products in infant formulas in accordance with the European Commission's definitions, *see* note 124;
    e. A revision of FDA's 2014 Guidance on Assessing Significant Manufacturing Process Changes[13] to expressly include infant formula; and
    f. An update to FDA's regulations based on the 2014 guidance.
2) Declare all currently available infant formulas containing engineered nanoparticles as adulterated and misbranded and require a recall under 21 C.F.R. § 107.200.
3) Amend 21 C.F.R. § 106.40(a) so as to expressly prohibit the use of the GRAS for nanomaterials in infant formula in accordance with FDA's rationale in the 2014 guidance document.
4) Declare engineered nanoparticles in infant formula an imminent hazard to human health under 21 C.F.R. § 2.5(a).

PETITIONERS

The **International Center for Technology Assessment (ICTA)** is located at 303 Sacramento Street, San Francisco, California 94111. Formed in 1994, ICTA seeks to assist the public and policy makers in better understanding how technology affects society. ICTA is a non-profit organization devoted to analyzing the economic, environmental, ethical, political, and social impacts that can result from the application of technology or technological systems.

In 2007, ICTA spearheaded a coalition of international non-profit organizations working on nanotechnology that published a principles document, *Principles for the Oversight of*

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology.

Nanotechnologies and Nanomaterials. ICTA has also filed ground-breaking legal petitions on the human health and environmental risks of nanotechnology on behalf of a coalition of public interest organizations, including one in 2006 requesting FDA to regulate sunscreen composed of engineered nanoparticles and one in 2008 requesting EPA to regulate nano-silver products as pesticides.

The **Center for Food Safety (CFS)** is a nonprofit public interest organization that empowers people, supports farmers, and protects the earth from the harmful impacts of industrial agriculture through groundbreaking legal, scientific, and grassroots action. Our membership includes more than one million consumer and farmer supporters across the country who support organic food and farming, grow organic food, and regularly purchase organic products. A particular programmatic focus of CFS is protecting consumers from unsafe food additives, color additives, and food contact articles.

For example, CFS was a petitioner on Food Additive Petition No. 5A4810, which sought to prohibit the use of seven synthetic flavors that were found by the National Toxicology Program to induce cancer. FDA responded to that petition by removing the seven synthetic flavors from its approved food additives list. CFS was also a petitioner on Food Additive Petition No. 4B4809, which successfully led FDA to ban the use of unsafe long-chain perfluorinated compounds in food contact substances.

STATEMENT OF GROUNDS

I. Legal and Regulatory Background

A. First Amendment

Under the First Amendment to the U.S. Constitution, the people have a right "to petition the Government for a redress of grievances."[14] This right "is cut from the same cloth as the other guarantees of that Amendment, and is an assurance of a particular freedom of expression."[15] The Petition Clause ensures "that people 'may communicate their will' through direct petitions to the legislature and government officials."[16] The right to petition "extends to all departments of the Government."[17]

B. Administrative Procedure Act

Under the APA, CFS has the right to petition, as agencies must "give an interested person the right to petition for the issuance, amendment, or repeal of a rule."[18] Agency decisions "that [are] inconsistent with a statutory mandate or that frustrate the congressional policy underlying a

[14] U.S. CONST. amend. I.
[15] *McDonald v. Smith*, 472 U.S. 479, 482 (1985).
[16] *Id*. (quoting James Madison, 1 Annals of Cong. 738 (1789)).
[17] *Cal. Motor Transp. Co. v. Trucking Unlimited*, 404 U.S. 508, 510 (1972).
[18] 5 U.S.C. § 553(e).

statute" are impermissible.[19] The APA establishes the applicable standard for review of agency actions, which is whether the agency's decision was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law.[20] The APA requires an agency to "conclude a matter presented to it" "within a reasonable time."[21] Judicial review under the APA requires that "the reviewing court shall compel agency action unlawfully withheld or unreasonably delayed."[22]

C. Federal Food, Drug, and Cosmetic Act

Regulations regarding oversight over nanomaterial products, misbranding of infant formulas, and the GRAS process fall under the FFDCA. The Commissioner and FDA are responsible for ensuring the safety of infant formulas.

1. The Infant Formula Act

In 1980, Congress passed the Infant Formula Act (IFA), which added Section 412 to the FFDCA.[23] Under the IFA, an infant formula is considered adulterated unless it meets certain nutrient requirements and quality factors and is processed in compliance with good manufacturing practices and quality control procedures.[24] At least 90 days before marketing any infant formula, the manufacturer must first register it with FDA.[25] The registration submission must include the quantitative formulation of the infant formula, a description of any reformulation of the formula or change in processing, and assurances that the infant formula will not be marketed unless it meets nutrient requirements and quality factors and is processed in accordance with good manufacturing practices.[26]

After an infant formula is registered, if the manufacturer has knowledge that the infant formula may not provide the stated nutrient requirements or is otherwise adulterated or misbranded, the IFA requires the manufacturer to "promptly notify" FDA.[27] Once notified, FDA must make a determination as to whether the infant formula presents a risk to human health.[28] If

---

[19] *See, e.g., Ocean Advocates v. U.S. Army Corps of Eng'rs*, 402 F.3d 846, 858–59 (9th Cir. 2005).
[20] 5 U.S.C. § 706(2)(A).
[21] 5 U.S.C. § 555(b) ("[W]ithin a reasonable time, each agency shall proceed to conclude a matter presented to it."); id. § 706(1) ("The reviewing court shall . . . compel agency action unlawfully withheld or unreasonably delayed."); *id*. § 555(e) ("Prompt notice shall be given of the denial in whole or in part of a written application, petition, or other request of an interested person made in connection with any agency proceeding.").
[22] 5 U.S.C. § 706(1).
[23] *See* Infant Formula Act of 1980, Pub. L. No. 96-359, 94 Stat. 1190 (1980) (codified at 21 U.S.C. § 350a).
[24] 21 U.S.C. § 350a(a).
[25] 21 U.S.C. § 350a(c)(1).
[26] 21 U.S.C. § 350a(d)(1).
[27] 21 U.S.C. § 350a(e)(1).
[28] *Id*.

FDA determines that the infant formula does present a risk to human health, the manufacturer "shall immediately take all actions necessary to recall shipments of such infant formula from all wholesale and retail establishments," consistent with FDA's recall regulations and guidelines.[29]

2. FDA's Regulation of Infant Formula

According to FDA, "[t]he only substances that may be used in an infant formula are substances that are safe and suitable for use in infant formula."[30] This means that the only substances that may be used in infant formulas are those that are approved as food additives, those that are GRAS, or those that have been authorized by a prior sanction.[31]

After an infant formula is registered, if there is a "major change" in either the processing or formulation of the infant formula, it constitutes a "new infant formula" for which a new registration is required.[32] FDA defines "major change" in an infant formula as

> "any new formulation, or any change of ingredients or processes where experience or theory would predict a possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or any change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer."[33]

FDA then provides a non-exhaustive list of examples of infant formulas deemed to differ fundamentally in processing or in composition:

- Any infant formula produced by a manufacturer who is entering the U.S. market;
- Any infant formula powder processed and distributed by a manufacturer who previously only produced liquids (or vice versa);
- Any infant formula having a significant revision, addition, or substitution of a macronutrient (i.e., protein, fat, or carbohydrate), with which the manufacturer has not had previous experience;
- Any infant formula manufactured on a new processing line or in a new plant;
- Any infant formula manufactured containing a new constituent not listed in section 412 (i) of the [FFDCA], such as taurine or L-carnitine;
- Any infant formula processed by a manufacturer on new equipment that utilizes a new technology or principle (e.g., from terminal sterilization to aseptic processing); or
- An infant formula for which there has been a fundamental change in the type of packaging used (e.g., changing from metal cans to plastic pouches.[34]

---

[29] *Id*.
[30] 21 C.F.R. § 106.40(a).
[31] *Id*.
[32] 21 U.S.C. § 350a(c)(2)(B).
[33] 21 C.F.R. § 106.3.
[34] *Id*.

3. Petition Process under the FFDCA

FDA's regulations also provide for rulemaking petitions.[35] Once filed, FDA "shall furnish a response" to the petition "within 180 days" of its receipt.[36] FDA's response must either approve the petition, deny the petition, dismiss the petition if changes in law, facts, or circumstances render it moot, or provide a tentative response if the agency cannot reach a decision.[37]

II. Factual Background

A. Nanotechnology

Nanotechnology is a powerful new platform technology for taking apart and reconstructing nature at the atomic and molecular level.[38] The nanoscale is exceedingly tiny; it is the world of atoms and molecules, involving the manipulation of matter at the nanometer scale (nm), one billionth of a meter.[39]

"Nano" means more than just tiny manufacturing; every chemical element has characteristic, defined properties including color, hardness, elasticity, conductivity, melting temperature, etc. Put a different way, it is well-known that materials engineered or manufactured to the nanoscale exhibit radically different fundamental physical, biological, and chemical properties from bulk materials.[40]

One reason for these fundamentally different properties is that quantum physics comes into play at the nanoscale. [41] Another is that the reduction in size to the nanoscale results in an enormous increase of surface to volume ratio, giving nanoparticles a much greater surface area per unit of mass compared to larger particles.[42] Because growth and catalytic chemical reactions

---

[35] 21 C.F.R. § 10.30.
[36] *Id*. § 10.30(e)(2).
[37] *Id*.
[38] The National Nanotechnology Initiative (NNI) defines nanotechnology as the "understanding and control of matter at the nanoscale, at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale." NNI, *What It Is and How It Works*, https://www.nano.gov/nanotech-101/what; *see also* 15 U.S.C. § 7509(2).
[39] For illustration, a DNA molecule, which carries genetic information in the cell nucleus, is about 2.5 nm in diameter. A human hair is huge by comparison, between 80,000-100,000 nm wide. On a comparative scale, if the diameter of a marble was one nanometer, then the diameter of the Earth would be about one meter. NNI, *Size of the Nanoscale*, https://www.nano.gov/nanotech-101/what/nano-size.
[40] NNI, *What It Is and How It Works*, https://www.nano.gov/nanotech-101/what.
[41] Nanotechnology Now, *Nanotechnology Basics*, http://www.nanotech-now.com/basics.htm.
[42] Royal Society of Chemistry, *Nanoparticles* (2014), *available at* https://www.rsc.org/cpd/teachers/content/filerepository/frg/pdf/Nanoparticles.pdf. For example,

occur at the particle surface, a given mass of nanoparticles will have an increased potential for biological interaction and be much more reactive than the same mass made up of larger particles, thus enhancing intrinsic toxicity.[43] This enormous increase in surface area can change relatively inert substances into highly reactive ones. A material can then melt faster, absorb more, or simply become more explosive.[44]

Thus, to say that a substance is "nano" does not merely mean that it is tiny, a billionth of a meter in scale; rather, the prefix is best understood to also mean that a substance has the capacity to act in fundamentally different ways. Altered properties can include color, solubility, material strength, electric conductivity, and magnetic behavior.[45] For example, a gold wedding ring is yellow in color; but gold nanoparticles can appear red or purple.[46] Carbon (like graphite in pencil lead) is relatively soft; but carbon in the form of carbon nanotubes (nanoscale cylinders made of carbon atoms) is a hundred times stronger than steel.[47] An aluminum soda can does not burn; however, aluminum nanoparticles explode when used as rocket fuel catalysts.[48]

B. The Human Health and Environmental Risks of Nanomaterials

Just as the size and chemical characteristics of engineered nanoparticles can give them unique properties, those same new properties—tiny size, vastly increased surface area to volume ratio, high reactivity— can also create unique and unpredictable human health and environmental risks.[49] Swiss Insurance giant Swiss Re noted that:

---

a gram of nanoparticles has a surface area of a thousand square meters. Peter Montague, *Nanotechnology and the Precautionary Principle Imperative*, Multinational Monitor (Sept. 1, 2004), *available at* http://www.precaution.org/lib/06/montague_mm_040915.htm.

[43] *See, e.g.*, Seung Won Shin, et al., *Role of Physiochemical Properties in Nanoparticle Toxicity*, Nanomaterials (Basel) (Sept. 2015), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5304630/.

[44] *See, e.g.*, Michael Berger, *Explosibility of nanoparticles*, Nanowerk (Mar. 20, 2012), https://www.nanowerk.com/spotlight/spotid=24650.php.

[45] National Nanotechnology Institute, *What's So Special about the Nanoscale?*, https://www.nano.gov/nanotech-101/special.

[46] *Id*.

[47] National Nanotechnology Institute, *Explanation of the Carbon Nanotube Pencils* (Mar. 7, 2012), available at https://www.nano.gov/CNTpencils (click on "Explanation of Carbon Nanotube Pencils" link).

[48] A. Olivani, et al., *Aluminum Particle Size Influence on Ignition and Combustion of AP/HTPB/Al Solid Rocket Propellants*, RTO-MP-091, paper presented at the RTO AVT Specialists' Meeting on "Advances in Rocket Performance Life and Disposal" in Aalborg, Denmark (Sept. 23-26, 2002), https://www.sto.nato.int/publications/STO%20Meeting%20Proceedings/RTO-MP-091/MP-091-31.pdf.

[49] *See, e.g.*, A. Nel et al., *Toxic Potential of Materials at the Nanolevel*, 311 SCIENCE 622-27, 622, 623 Fig. 1 (2006); *see generally* Florini et al., *Nanotechnology: Getting It Right the First Time*, 3 NANOTECHNOLOGY L. & BUS. 38, 41-43 (2006).

> "[N]ever before have the risks and opportunities of a new technology been as closely linked as they are in nanotechnology. It is precisely those characteristics which make nanoparticles so valuable that give rise to concern regarding hazards to human beings and the environment alike."[50]

A growing number of peer-reviewed scientific studies have demonstrated the potential for nanomaterials to present serious toxicity risks for human health and ecosystems.[51] Manufactured nanomaterials move excessively through the environment and have the potential to enter living cells and the environment in ways never previously possible. For example, the human body absorbs nanomaterials more readily than larger sized particles and nanoparticles cross biological membranes that larger sized particles normally cannot, such as the blood-brain barrier.[52] In addition, research has shown that many types of nanomaterials can be toxic to human tissue and cell cultures, resulting in increased oxidative stress, inflammatory cytokine production, DNA mutation, and even cell death.[53]

Once loose in nature, these nanomaterials represent a new class of manufactured non-biodegradable pollutants. Nanomaterials' unique chemical and physical characteristics create foreseeable environmental risks, including potentially toxic interactions or compounds, absorption and/or transportation of pollutants, durability or bioaccumulation, and unprecedented mobility for a manufactured material.[54] Environmental impact studies have raised some red flags, including dangers from nanosilver to aquatic life; however, despite rapid nanomaterial commercialization, many potential risks remain dangerously untested due to the government's failure to prioritize and adequately fund environmental impact research.[55]

---

[50] Swiss Re, *Nanotechnology-Small Matter, Many Unknowns*, (2004), at 17, https://digitalcommons.wcl.american.edu/cgi/viewcontent.cgi?article=1347&context=sdlp.
[51] P.C. Ray, et al., *Toxicity and Environmental Risks of Nanomaterials: Challenges and Future Needs*, J. of Envtl. Science and Health (Feb. 9, 2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2844666/; Anastasia Georgantzopoulou, et al., *Ecotoxicological Effects of Transformed Silver and Titanium Dioxide Nanoparticles in the Effluent from a Lab-Scale Wastewater Treatment System*, Environmental Science & Technology (2018), *available at* https://classes.engineering.wustl.edu/eece534/2020-02-28_Discussion%20II_A_2018_EST_Ecotoxicological%20Effects%20of%20Silver%20and%20Titanium%20Dioxide.pdf; M. Peyravi, et al., *Toxicity of Nanomaterials in Plants and Environment*, chapter in Nanotechnology in the Life Sciences (Oct. 1, 2019), *available at* https://link.springer.com/chapter/10.1007/978-3-030-16379-2_13.
[52] M. Simko & M. Mattsson, *Interactions Between Nanosized Materials and the Brain*, Current Med. Chem. (Dec. 2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435026/.
[53] R. Wan, et al., *Cobalt nanoparticles induce lung injury, DNA damage and mutations in mice*, Particle and Fibre Toxicol. (Sept. 18, 2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604172/.
[54] *See, e.g.*, Md. N. Uddin, et al., *Engineered nanomaterials in the environment: bioaccumulation, biomagnification and biotransformation*, Envtl. Chem. Letters (2020), https://link.springer.com/article/10.1007%2Fs10311-019-00947-0.
[55] D. Biello, *Government Fails to Assess Potential Dangers of Nanotechnology*, Scientific American (Dec. 18, 2008), https://www.scientificamerican.com/article/government-fails-to-

In addition, nanomaterials' unique chemical and physical characteristics create foreseeable, yet unexplored, risks. For example, nanoparticles are the subject of vigorous drug research because of their ability to carry and deliver drugs to specific targets. But this same transport propensity could give nanoparticles the ability to carry toxic chemicals present in the environment.[56] The translocatory potential of nanomaterials that makes them commercially attractive for drug delivery could cause unintended consequences as nanomaterials are released into natural systems. Because of their tiny size nanomaterials may be highly mobile and travel further than larger particles in soil and water. Because nanoparticles tend to be more reactive than larger particles, interactions with substances present in the soil could lead to new and possibly toxic compounds.

C. Nanomaterials in Consumer Products: The Future Is Now

Nanotechnology and its material creations are no longer future predictions; they have arrived. Funding is astronomical, with over $31 billion in federally funded nanotechnology activities coordinated through the National Nanotechnology Initiative (NNI) since its inception in 2001.[57] Unfortunately, only a paucity of this robust federal funding—4% of the NNI's FY21 budget—was earmarked for environmental health and safety (EHS) research.[58]

1. Nanomaterials in infant formulas create new risks that cannot be inferred from bulk material counterparts or the testing of them.

Regulators, the public, and industry cannot rely on the existing knowledge of conventional chemicals to predict the properties and risks of nanomaterials. Just as the size and physical properties of engineered nanoparticles give them unusual properties of strength and reactivity, those properties also give them unpredicted risks, like increased toxicity,[59] due to modifications of physicochemical properties and extreme mobility, causing increased uptake and interaction with biological tissues.[60] Those same features that make engineered nanomaterials unique—small size, high surface area to volume ratio, high reactivity—can have negative

---

assess-dangers-of-nanotechnology/; Executive Office of the President, National Nanotechnology Initiative Supplement to the President's 2021 Budget, at 6 (Oct. 2020), https://www.nano.gov/about-nni/what/funding.

[56] S. Berkner, et al., *Nanopharmaceuticals: Tiny challenges for the environmental risk assessment of pharmaceuticals*, Envtl. Toxicol. and Chem. (Mar. 22, 2016), https://setac.onlinelibrary.wiley.com/doi/full/10.1002/etc.3039.

[57] Executive Office of the President, National Nanotechnology Initiative Supplement to the President's 2021 Budget, at 5 (Oct. 2020).

[58] *Id*. at 6.

[59] M. Gidwani & AV. Singh., *Nanoparticle enabled drug delivery across the blood brain barrier: invivo and in vitro models, opportunities and challenges*, Curr Pharm Biotechnol. (2014), https://pubmed.ncbi.nlm.nih.gov/24809717/.

[60] H. Shi, Magaye, et al., *Titanium dioxide nanoparticles: a review of current toxicological data*, Part Fibre Toxicol. (2013), https://doi.org/10.1186/1743-8977-10-15.

consequences for human health.[61] "The combination of effects can generate adverse biological effects in living cells that would not otherwise be possible with the same material in larger form."[62]

First, central to these health risk concerns is that humans have evolved mechanisms of protection against environmental agents; size is an important factor in the efficacy of these mechanisms. The exposure to engineered nanoparticles, having characteristics not previously encountered, presents new challenges to the normal defense mechanisms of, inter alia, the body's immune and inflammatory response systems.[63] Unlike larger particles, engineered nanoparticles have the unique ability to move from one area of the body to another, be absorbed by organs and tissues, and penetrate into cells. Research has highlighted movement from the lungs to the bloodstream,[64] the GI tract to other organs,[65] and the nose via olfactory nerves into the brain.[66] When inhaled, they reach all regions of the respiratory tract, and can move out of it via different pathways and mechanisms. When in contact with the skin, there is evidence of penetration of the dermis and subsequent translocation via the lymph nodes; and when ingested, systematic uptake can occur; when in the blood circulatory system, they can distribute through the body, and be taken up into the liver, spleen, bone marrow, heart, and other organs.

Second, the change in the physicochemical and structural properties of engineered nanoparticles can also be responsible for a number of material interactions that could lead to toxicological effects. There is a dependent relationship between size and surface area and nanoparticle toxicity; as particles are engineered smaller on the nanolevel, they are more likely to be toxic.[67] Once inside cells, they can interfere with cell signaling, cause structural damage, and

---

[61] C. Recordati, et al., *Tissue distribution and acute toxicity of silver after single intravenous administration in mice: nano-specific and size-dependent effects,* Part Fibre Toxicol. (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772516/.

[62] N. Andre, Xia, et al., *Toxic Potential of Materials at the Nanolevel,* Science (2006), https://pubmed.ncbi.nlm.nih.gov/16456071/.

[63] Y, Duan, et al., *Toxicological characteristics of nanoparticulate anatase titanium dioxide in mice,* Biomaterials (2010), https://www.sciencedirect.com/science/article/abs/pii/S0142961209010783?via%3Dihub.

[64] G, Oberdörster, et al., *Principles for characterising the potential human health effects from exposure to nanomaterials: elements of a screening strategy,* Particle Fibre Toxicology (2005), *available at* https://particleandfibretoxicology.biomedcentral.com/articles/10.1186/1743-8977-2-8.

[65] B. Belli, *Processed Foods and Food Packaging Already Contain Nanoparticles—Some of Which Could Be Harmful to Our Health,* The Environmental Magazine (Aug. 22, 2015), http://www.emagazine.com/includes/ print-article/magazine/9623/.

[66] G. J. Garcia, J.D. Schroeter, & J.S. Kimbell., *Olfactory deposition of inhaled nanoparticles in humans,* Inhalation toxicology (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4745908/pdf/nihms755292.pdf.

[67] M. Moreno- Horn, T. Gebel., *Granular biodurable nanomaterials: no convincing evidence for systemic toxicity,* Crit Rev Toxicol (2014), https://pubmed.ncbi.nlm.nih.gov/25257841/.

cause harmful damage to DNA.[68] Many relatively inert and stable chemicals, such as carbon, pose toxic risk in their nanoscale form.[69]

Third, beyond general risks associated with nanoparticle toxicity, available studies show how nanomaterials negatively affect the intestine and a potential correlation between Crohn's disease and microparticles in food.[70] Some data suggests that existing levels of nanoparticles up to a few hundred nanometers in size in processed food may be associated with rising levels of immune dysfunction and inflammation of the gastrointestinal tract.[71] Some specific nanoparticles, like silicon[72] and titanium dioxide can induce DNA damage in human intestinal cells.[73] Due to their size, nanoparticles can also transfer from mother to offspring, leading to brain damage, nerve system damage, and reduced sperm production in male offspring.[74]

Fourth, infants may be at greater risk of suffering health harms from nanomaterials because of their more vulnerable physiology. Early womb exposure, either direct or indirect, to toxicants can lead to irreversible damage, which can increase the risk of developmental harm and disease later in life. Direct developmental toxicity occurs from particles in maternal blood that cross the placental barrier and directly damage fetal tissues. Indirectly, nanomaterials present in maternal tissues might induce inflammation[75] which can reach the placenta and induce potential toxic effects on the fetus.[76] In mice studies, gestational exposure to nanomaterials impacted the

---

[68] V. K. Sharma, et al., *Organic-coated silver nanoparticles in biological and environmental conditions: fate, stability and toxicity,* Adv. Coll. Int. Sci. (2014), https://www.sciencedirect.com/science/article/abs/pii/S0001868613001735?via%3Dihub.
[69] *Id.*
[70] P. Ashwood, R. P. Thompson, and J.J. Powell., *Fine particles that adsorb lipopolysaccharide via bridging calcium cations may mimic bacterial pathogenicity towards cells,* Experimental Biology and Medicine (2007), https://pubmed.ncbi.nlm.nih.gov/17202591/.
[71] *Id.*
[72] Y. Yang, et al., *Survey of food-grade silica dioxide nanomaterial occurrence, characterization, human gut impacts and fate across its lifecycle*, Sci. Total Environ (2016), https://www.sciencedirect.com/science/article/abs/pii/S0048969716301644?via%3Dihub.
[73] B. Jovanović., *Critical review of public health regulations of titanium dioxide, a human food additive,* Integr. Environ. Assess. Manag. (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4309481/.
[74] K. Takeda., *Nanoparticles Transferred From Pregnant Mice to Their Offspring Can Damage the Genital and Cranial Nerve Systems,* Journal of Health Science (2009), https://jhs.pharm.or.jp/data/55(1)/55_95.pdf.
[75] P. Stapleton, et al., *Estrous cycle-dependent modulation of in vivo microvascular dysfunction after nanomaterial inhalation,* Reprod. Toxicol. (2018), https://pubmed.ncbi.nlm.nih.gov/29545171/.
[76] B. Dugershaw, et al., *Recent insights on indirect mechanisms in developmental toxicity of nanomaterials*, Particle and Fibre Toxicol. (2020), https://particleandfibretoxicology.biomedcentral.com/articles/10.1186/s12989-020-00359-x#citeas.

proper growth and development of the placenta[77] and increased the likelihood of fetal deformities and mortality.[78] In rat studies, oral exposure to nanomaterials crossed the placental barrier, making them transferable to the fetus[79] and leading to toxic effects.[80] The maternal inhalation of nanomaterials has also been found to impact placental development, functioning,[81] and the gestational endocrine vascular axis.[82] Indirectly, prenatal exposure to nanomaterials runs the risk of generating DNA damage in the fetal hippocampus,[83] resulting in behavioral deficits and neurodevelopmental disorders.[84] In ex vivo placental perfusion studies, most nanoparticles accumulated in the layer of placental tissue that mediates immunological, endocrine, metabolic, and protective functions.[85]

---

[77] L. Zhang, et al., *Gestational exposure to titanium dioxide nanoparticles imparts the placentation through dysregulation of vascularization, proliferation and apoptosis in mice*, International Journal of Nanomedicine (2018), https://www.researchgate.net/publication/322931896_Gestational_exposure_to_titanium_dioxide_nanoparticles_impairs_the_placentation_through_dysregulation_of_vascularization_proliferation_and_apoptosis_in_mice.

[78] *Id.*

[79] C. Teng, et al., *Size-dependent maternal-fetal transfer and fetal developmental toxicity of ZnO nanoparticles after oral exposures in pregnant mice*, Ecotoxicology and Environmental Safety (Oct. 30, 2019), https://www.sciencedirect.com/science/article/abs/pii/S0147651319307705?via%3Dihub.

[80] A. Guillard, et al., *Basal Ti level in the human placenta and meconium and evidence of a materno-foetal transfer of food-grade TiO2 nanoparticles in an ex vivo placental perfusion model*, Particle and Fibre Toxicol. (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7541303/.

[81] A. Alaeddin., *Maternal Titanium Dioxide Nanomaterial Inhalation Exposure Compromises Placental Hemodynamics*, Toxicol. Appl. Pharmacol. (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6422339/.

[82] E. Bowdridge, et al., *Maternal Engineered Nanomaterial Inhalation During Gestation Disrupts Vascular Kisspeptin Reactivity*, Toxicol. Sci. (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6542330/.

[83] S. Hawkins, et al., *Nanoparticle induced neuronal toxicity across placental barriers is mediated by autophagy and dependent on astrocytes*, University of Bristol (2018), https://research-information.bris.ac.uk/ws/portalfiles/portal/153977201/Manuscript_Hawkins_et_al_authors_manuscript.pdf.

[84] T. Notter, et al., *Prenatal exposure to TiO2 nanoparticles in mice causes behavioral deficits with relevance to autism spectrum disorder and beyond,* Translational Psychiatry (2018), https://www.nature.com/articles/s41398-018-0251-2.

[85] L. Aengenheister, et al., *Research on nanoparticles in human perfused placenta: State of the art and perspectives,* Placenta (Jan. 15, 2021), https://www.sciencedirect.com/science/article/pii/S0143400420304677.

2. Nanomaterials in infant formula and specific concerns

In 2016, Friends of the Earth commissioned independent laboratory studies on the use of engineered nanomaterials in baby formulas sold in the U.S. with a world-class technology research facility at Arizona State University.[86] These were the first ever laboratory studies focused on the detection of engineered nanomaterials in baby formulas marketed to the U.S. public.[87] The products tested were: Gerber Good Start Gentle, Gerber Good Start Soothe, Enfamil, Similac Advance OptiGRO (liquid), Similac Advance OptiGRO (powder), and Well Beginnings Advantage. The study revealed nano-sized structures and particles of potential concern within all formulas tested, including:

- Nano-hydroxyapatite in needle-like and non-needle-like form (nano HA),
- Nano-titanium dioxide (nano TiO_2), and
- Nano-silicon dioxide (nano SiO_2).[88]

Needle-like nano HA in infant formula is of global concern. Likely used as either a calcium source or to stabilize the ingredients in the formula mixture, the European Commission's Scientific Committee on Consumer Safety (SCCS) found the needle-like form of nano HA to be potentially toxic and advised it not be permitted in cosmetic products.[89] The ASU study found that needle-like nano HA dissolved faster in digesting fluids than larger bulk-sized hydroxyapatite.[90] Nano HA was also found to cause cell death in the liver and kidneys of rats.[91] A substance that has been found to cause cell death in the liver and kidneys of rats and which the SCCS advises against using in cosmetics should not be allowed in baby formula.

Titanium dioxide is approved for use as a whitener for food and beverage products. It is very biologically active and highly mobile in the body. A 2015 study found food-grade titanium dioxide, when engineered to the nanoscale, could be absorbed into the bloodstream. Further, nano TiO_2 has been shown to damage DNA,[92] disrupt the function of cells, interfere with the

---

[86] Friends of the Earth, *Nanoparticles in Baby Formula: Tiny new ingredients are a big concern*, at 4 (May 2016) ("FOE Report"), https://foe.org/resources/nanoparticles-in-baby-formula-tiny-new-ingredients-are-a-big-concern/.
[87] *Id*.
[88] *Id*.
[89] European Commission-SCCS, Opinion on Hydroxyapatite (nano), at 35 (Oct. 16, 2015), http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_191.pdf.
[90] J. Schoepf, P. Westerhoff, et al., *Detection and dissolution of needle-like hydroxyapatite nanomaterials in infant formula*, NanoImpact (2017), https://www.researchgate.net/publication/312414722_Detection_and_dissolution_of_needle-like_hydroxyapatite_nanomaterials_in_infant_formula.
[91] *Id.*
[92] B. Trouiller, et al., *Titanium Dioxide Nanoparticles Induce DNA Damage and Genetic Instability In Vivo in Mice*, Cancer Research (2009), https://cancerres.aacrjournals.org/content/69/22/8784.

defense activities of immune cells, and absorb fragments of bacteria and "smuggle" them across the gastro-intestinal tract, which provokes inflammation.[93]

Silicon dioxide is utilized as a "trickle and flow" aid in powdered food products, a clearing agent in wine and beer, a food additive, and a food coating. A study found nano SiO_2 in the livers of rats and mice after oral administration, showing it remains undissolved.[94] Further, nano SiO_2 was shown to enter the fetus via placental transfer.[95]

Overall, the presence of nanomaterials in infant formula poses unnecessary and unknown risks. Nanomaterials are more chemically reactive and bioactive than larger particles of the same chemicals. Due to their very small size, nanoparticles are able to enter cells, tissues, and organs, posing new toxicity risks. Infants may be at greater risk of suffering health harms from nanomaterials due to their more vulnerable physiology.[96]

D. FDA's Stance on Nanotechnology

FDA acknowledges that products it regulates likely utilize nanotechnology or contain nanomaterials and that such materials "can have chemical, physical, and biological properties that differ from those of their larger counterparts."[97] In 2007, FDA issued a task force report calling for the development of additional guidance documents to help ensure that public health and the environment are protected from this emerging industry.[98] Since 2007, FDA has finalized the following five guidance documents:

- Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives;

---

[93] P. Ashwood, et al., *Fine particles that adsorb lipopolysaccharide via bridging calcium cations may mimic bacterial pathogenicity towards cells*, Experimental Biology and Medicine (2007), 107, https://www.researchgate.net/publication/6597685_Fine_particles_that_adsorb_lipopolysaccharide_via_bridging_calcium_cations_may_mimic_bacterial_pathogenicity_towards_cells.

[94] S. Dekker, et al., *Knowledge gaps in risk assessment of nano silica in food: evaluation of the dissolution and toxicity of different forms of silica*, Nanotoxicology (2013), https://pubmed.ncbi.nlm.nih.gov/22394279/.

[95] S.C. Carreira, et al., *The toxicity, transport and uptake of nanoparticles in the in vitro BeWo b30 placental cell barrier model used within NanoTEST*, Nanotoxicology (Sept. 3, 2013), https://pubmed.ncbi.nlm.nih.gov/23927440/.

[96] The Royal Society & The Royal Academy of Engineering, *Nanoscience and nanotechnologies: opportunities and uncertainties* (July 2004), at 39, https://royalsociety.org/~/media/royal_society_content/policy/publications/2004/9693.pdf.

[97] FDA, *Nanotechnology Programs at FDA, available at* https://www.fda.gov/science-research/science-and-research-special-topics/nanotechnology-programs-fda.

[98] FDA, *Nanotechnology Task Force Report 2007* (July 23, 2007), https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force-report-2007.

- Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology;
- Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation;
- Safety of Nanomaterials in Cosmetic Products; and
- Use of Nanomaterials in Food for Animals[99]

It is the first guidance document that is of interest here. This guidance describes the factors that manufacturers should consider when determining the effects of a significant change in the manufacturing process for a food substance already in the market.[100] For purposes of this guidance, "food substance" refers to food ingredients that are food additives, substances that are GRAS, color additives, and food contact substances.[101] According to FDA:

> "We expect that there will be circumstances where *a significant manufacturing process change impacts the safety, the regulatory status, or both, of a food substance*. In such circumstances, a new regulatory submission may be necessary to clearly establish the conditions under which the food substance, manufactured by a new process, is safe and lawful. In the case of emerging technologies, a manufacturing process change may alter the identity or intended use of the food substance and a new authorization may be required . . . A *significant manufacturing process change of a food substance* already in the market can also affect the identity or conditions of use of a food substance, *rendering the use of the food substance not within the scope* of a food additive regulation*;* a GRAS listing or affirmation in our regulations; an effective food contact notification; or an existing determination of GRAS status."[102]

Thus, a significant manufacturing process change, such as the use of nanotechnology, which impacts the identity, safety, or conditions of use of a food substance renders that new substance adulterated.

---

[99] FDA, *Nanotechnology Guidance Documents*, https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-guidance-documents.
[100] FDA, *Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives*, at 4 (June 2014), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-assessing-effects-significant-manufacturing-process-changes-including-emerging. FDA published this guidance after CFS and FOE sued FDA for failure to take action on a 2006 rulemaking petition requesting FDA regulation of nanotechnology products generally and nano-sunscreens specifically.
[101] *Id*. at 5.
[102] *Id*. at 16 (emphases added).

E. Current Regulatory Measures on Nanomaterials in Infant Formula

Globally, different measures are being taken to address nanotechnology in infant formula. Nanoparticles in infant formula products are illegal in Australia, although independent testing in 2017 found nano HA in several Australian formula samples.[103] The EU employs the precautionary principle in its regulations for nanotechnologies. The EU is working towards a moratorium on novel foods containing nanomaterials and has implemented a nano-food labeling regime. In individual countries like France, Belgium, and Denmark, mandatory registries exist for nanomaterials. France, perhaps because of significant amounts of nano TiO_2 in all titanium dioxide, is banning the substance entirely.

In the U.S. there are no mandatory regulations or safety assessments required for nanomaterials used in food or consumer products. Manufacturers are not even required to list nanomaterial ingredients on product packaging. Thus, even though the ASU study revealed nanoparticles in five major infant formula products, no nanoparticles are listed on that packaging, deceiving consumers about the contents of the food they are feeding to their infants.

In 2016, Mars Incorporated agreed to remove all nano TiO_2 from its products following CFS's request that it do so.[104] Dunkin Donuts, Kraft, and McDonalds have also agreed to remove nanoparticles from their products.[105] But consumers in the U.S. cannot rely on individual companies to do the right thing, one company at a time; rather, it is incumbent upon FDA to take the necessary steps to protect the public from harm and especially to protect infants.

III. FDA Actions Requested Regarding Nanomaterial Products in Infant Formula

A. Enact New Regulations Directed at FDA Oversight of Nanomaterial Products in Infant Formula.

1. Undeclared nano-engineered versions of food substances contained in infant formula should be considered a major change necessitating registration of a new infant formula.

FDA must declare nano-engineered versions of food substances in infant formula a "major change" in infant formulas, requiring registration of new infant formulas. FDA's broad definition of "major changes" in an infant formula includes "any new formulation, or *any change* of ingredients or processes where experience or theory would predict a possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or *any change* that causes an infant formula to differ fundamentally in processing or in composition from any previous

---

[103] Scientific Committee on Consumer Safety (SCCS), Opinion on Hydroxyapatite (nano), at 18 (2016), http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_191.pdf.
[104] Ctr. for Food Safety, *Top Candy Company Mars Commits To Phasing out Harmful Nanoparticles From Food Products* (Oct. 27, 2016), https://www.centerforfoodsafety.org/press-releases/4550/top-candy-company-mars-commits-to-phasing-out-harmful-nanoparticles-from-food-products.
[105] *Id.*

formulation produced by the manufacturer."[106] This broad definition plainly includes the addition of nano-substances to infant formula, which change the composition. As such FDA should require manufacturers to register the formula as a "new infant formula."[107]

Additionally, while it already plainly qualifies, FDA should also amend 21 C.F.R. § 106.3 to include the production of engineered nanoparticles as an additional express example for what constitutes a "major change" in infant formula. FDA's regulations provide seven examples where an infant formula is deemed to differ fundamentally in processing or composition from what FDA has reviewed so as to constitute a "major change."[108]Although the production of engineered nanoparticles is already covered by some of these examples, it would bring regulatory clarity for FDA to specifically identify the production of engineered nanoparticles as a "major change" that results in a new infant formula requiring further registration.

FDA should also amend 21 C.F.R. § 106.140 to include specific reference to engineered nanoparticles as a reason to notify FDA of a change in infant formula that may adulterate the product.

2. Rigorous screening and safety testing of nanomaterials must be required.

Because FDA must require registration as a "new infant formula," FDA must also require that any infant formula marketed in the U.S. undergo rigorous screening or safety testing of nanomaterials or other potentially toxic synthetic ingredients. The FFDCA requires manufacturers to submit certain information to FDA whenever registering a "new infant formula."[109] This includes information about the quantitative formulation of the infant formula, a description of any reformulation or change in processing, assurances that the formula meets nutrient requirements, and assurances that the processing of the formula complies with good manufacturing practices.[110]

3. FDA must label nanomaterials on infant formula packaging.

Regarding nutrient requirements, FDA should update the table set out in 21 U.S.C. § 350a(i) and in its regulations at 21 C.F.R. § 107.100(a) to include nanomaterials with defined maximum levels. The FFDCA requires that infant formulas contain nutrients in accordance with the table set out in 21 U.S.C. § 350a(i) and provides FDA with authority to add nutrients to the table. FDA's broad definition of "nutrient" includes "any vitamin, mineral, or other substance or ingredient" that is required in accordance with the table in 21 U.S.C. § 350a(i) or by regulations issued under that section.[111] This plainly includes nanomaterials.

---

[106] 21 C.F.R. § 106.3 (emphasis added).
[107] 21 U.S.C. § 350a(c)(2)(B).
[108] 21 C.F.R. § 106.3 ("*Major change*").
[109] 21 U.S.C. § 350a(d)(1).
[110] *Id*.
[111] 21 C.F.R. § 106.3 ("*Nutrient*").

Inclusion of nanomaterials in the table at 21 C.F.R. § 107.100(a) would help ensure safety. This would require manufacturers to incorporate nanomaterials in their quality control procedures required by 21 C.F.R. § 106.91.[112] It would also require manufacturers to provide assurance that the formula complies with the nutrient content requirements of 21 C.F.R. § 107.100(a) whenever a manufacturer submits a notice for a new infant formula.[113]

4. FDA must establish regulatory definitions.

FDA's regulations set forth the steps that manufacturers must take in processing infant formula.[114] However, the current regulations do not establish definitions necessary to properly regulate engineered nanomaterial products, including the terms "nanotechnology," "nanomaterial," and "engineered nanoparticle."[115] FDA should amend 21 C.F.R. § 106.3 to define these and other terms it deems necessary to regulate engineered nanomaterial products in infant formulas.

FDA's mission begins with the "promot[ion] [of] the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."[116] With respect to food, FDA is charged with ensuring that food is safe.[117] Establishing the appropriate nomenclature for nanotechnology is a necessary prerequisite to enforcing, amending, and enacting appropriate agency regulation of nanotechnology products; regulators, the regulated industry, and the public must share a vocabulary. Formalizing FDA's nano-terminology will help foster interagency collaboration between FDA and other science-based agencies and will also help fulfill FDA's statutory mandate of fostering interagency collaboration.[118]

In addition to its own formal definition, FDA can gain insight from other agencies' nano-lexicon. For example, the NNI, the federal research and development program established to coordinate the multi-agency efforts in nanoscale science, engineering, and technology, in which FDA participates,[119] defines nanotechnology.[120] In addition, the U.S. Patent Office has defined a Patent Classification Class, Class 977, for Nanotechnology patents.[121] Congress defined

---

[112] *See, e.g.*, 21 C.F.R. § 106.91(a)(4) ("During the manufacturing process or at the final product stage, before distribution, each production aggregate shall be tested for all nutrients required to be included in such formula under §107.100 of this chapter . . .").
[113] 21 C.F.R. § 106.120(b)(5)(ii).
[114] 21 C.F.R. § 106.1(a).
[115] *See* 21 C.F.R. § 106.3.
[116] 21 U.S.C. § 393(b)(1).
[117] Id. § 393(b)(2)(A).
[118] Id. § 393(c).
[119] National Nanotechnology Initiative, *Nanotechnology Environmental and Health Implications (NEHI) Working Group*, https://www.nano.gov/nehi.
[120] National Nanotechnology Initiative, *What Is Nanotechnology*, https://www.nano.gov/nanotech-101/what/definition.
[121] Patent Class 977, Nanotechnology, Section I – Class Definition, reads: Nanostructure and chemical compositions of nanostructure;

nanotechnology in the 2004 Nanotechnology Research and Development Act.[122] Several national and international organizations have developed standard definitions for terms in nanomaterial science, including the International Association of Nanotechnology's Nomenclature and Terminology Subcommittee and the American National Standards Institute Nanotechnology Standards Panel (ANSI-NSP).[123] In 2011, the European Union defined "nanomaterial" as follows:

> "A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.
>
> In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.
>
> By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials."[124]

FDA's decision should correlate and be informed by these existing and developing national and international standards, although the EU's arbitrary distribution threshold of 50% of particles in the nanoscale is problematic, and the FDA's own request to review all materials that are smaller than 1000nm if their size makes a difference in the material functions should be incorporated into FDA regulations.

Device that includes at least one nanostructure;
Mathematical algorithms, e.g., computer software, etc., specifically adapted for modeling configurations or properties of nanostructure;
Methods of apparatus for making, detecting, analyzing, or treating nanostructure; and
Specified particular uses of nanostructure.
As used above, the term "nanostructure" is defined to mean an atomic, molecular, or macromolecular structure that:
Has at least one physical dimension of approximately 1-100 nm; and
Possesses a special property, provides a special function, or produces a special effect that is uniquely attributable to the structure's nanoscale physical size.
Patent Office Classification Definitions, Class 977, Nanotechnology (Oct. 2010), https://www.uspto.gov/web/patents/classification/uspc977/defs977.htm.

[122] 15 U.S.C. 7501 *et seq*.; *id*. § 7509 (definitions).

[123] Oberdorster et al., *Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy*, Particle and Fibre Toxicology 8, at 1.0 (2005); *see also* The Institute of Occupational Medicine, *Nanoparticles: An occupational hygiene review*, research report 274, at 9 (2004), https://www.hse.gov.uk/research/rrhtm/rr274.htm.

[124] European Commission, *Environment: Definition of a nanomaterial*, https://ec.europa.eu/environment/chemicals/nanotech/faq/definition_en.htm.

The following key definitions are used throughout the EU's document:

> Nanoscale
> Having one or more dimensions of the order of 100 nanometer (nm) or less.
> Nanoscience
> The study of phenomena and manipulation of materials at atomic, molecular, and macromolecular scales, where properties differ significantly from those at a larger scale.
> Nanotechnology
> The design, characterization, production and application of structures, devices, and systems by manipulating shape and size at the nanoscale.
> Nanoparticle
> A particle with at least one dimension smaller than 100 nm including engineered nanoparticles, ambient ultrafine particles (UFPs), and biological nanoparticles.
> Engineered/Manufactured Nanoparticle
> A particle of less than 100 nm engineered or manufactured by humans on the nanoscale with specific physicochemical composition and structure to exploit properties and functions associated with its dimensions and exhibits new or enhanced size-dependent properties compared with larger particles of the same material.
> Nanomaterial
> Any material that either contains a certain proportion of nanoparticles or consists exclusively of them.

Petitioners request that FDA amend its regulations at 21 C.F.R. § 3.2, or elsewhere where it deems appropriate, to include these necessary definitions.

5. FDA must revise its 2014 guidance to include infant formula.

FDA's 2014 guidance for assessing the effects of significant manufacturing process changes does not mention infant formula. FDA must clarify that infant formula is included in this guidance and clarify that the introduction of nanomaterials in infant formula constitutes a significant manufacturing process change. This should be inclusive with FDA's definition for what constitutes a "major change" in infant formula production.

B. Declare All Currently Available Infant Formulas Containing Engineered Nanoparticles as Adulterated and Misbranded and Require a Recall.

An infant formula is adulterated if it is not in compliance with FDA's nutrient or quality factor requirements or is not processed in compliance with good manufacturing practices and quality control procedures.[125] As explained above, the introduction of nanoparticles in infant formula constitutes a major change to these formulas for which new registration is required. This renders the formulas containing nanoparticles adulterated.

[125] 21 U.S.C. § 350a(a); *see also* 21 C.F.R. §§ 106.1, 107.1(c).

As a result, FDA must issue an order declaring that infant formulas containing nanoparticles are adulterated and require a recall of such adulterated products.[126] Under FDA's infant formula recall regulations, the agency must make a determination that an adulterated or misbranded infant formula presents a risk to human health.[127] That is the case here.

Infant formulas comprised of engineered nanoparticles are presented to the consumer based on the false assumption that such products are safe and effective based on scientific studies of bulk material counterparts of engineered nanoparticles. Further, as discussed in detail above, without further nano-specific safety research, such engineered particles represent a grave and untested "risk of illness or injury" to infants because of their novel properties and the associated dangers. Finally, a recall is required to protect health and welfare until proper study and testing of engineered nanoparticles can be completed and analyzed. Petitioners therefore request that FDA require a recall of all infant formula products containing engineered nanoparticles until the manufacturers of such products complete new food additive petitions that are approved by the agency and otherwise comply with the agency's relevant nanotechnology regulations.

Moreover, FDA should review whether the use of nano forms of chemicals in infant formulas has a health advantage for the infant. According to the lead author of the ASU study, infant formulas sold in Europe by Gerber, Similac, Well Beginnings, and Enfamil do not use nano ingredients.[128] There is no reason, then, that the same formulas sold in Europe cannot also be sold in the U.S. until FDA reviews the relevant safety data on formulas containing engineered nanoparticles and determines whether there are any health risks or benefits for the infant.

C. Preclude the Use of GRAS for Nanomaterials.

FDA must preclude the use of GRAS for nanomaterials because they are not "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe[.]"[129] To the contrary, FDA itself has recognized that, "[i]n the specific instance of nanotechnology, a food substance manufactured for the purpose of creating very small particle sizes with new functional properties likely would not be covered by an existing GRAS determination for a related food substance manufactured without using nanotechnology."[130] That is because "there are questions related to the technical evidence of safety as well as the general recognition of that safety, that are likely to be sufficient to warrant formal premarket review and approval by FDA."[131] Indeed, technologies like nanotechnology are so new "as to preclude a consensus among experts that the

[126] 21 C.F.R. § 107.200.
[127] *Id*.
[128] Personal communication between Jaydee Hanson and Dr. Paul Westerhoff, Arizona State University (Mar. 3, 2020).
[129] 21 U.S.C. § 321(s).
[130] FDA, *Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives*, at 20 (June 2014).
[131] *Id*.

use of a food substance manufactured using that technology is safe, thus precluding a determination that the use of the food substance is GRAS."[132] However, because the GRAS Rule permits manufacturers to self-certify chemical substances as GRAS without notice to FDA, FDA cannot readily monitor if manufacturers are complying with the non-binding guidance that precludes nanomaterials from being certified as GRAS.

Because of the GRAS Rule's deficiencies, in 2010 the Government Accountability Office ("GAO") issued a sharply critical report, *FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe*, GAO-10-246 ("GAO Report"). The GAO Report noted that since 1997, most GRAS determinations have been premised on the "common knowledge" of panels of industry experts, without any assurance that the panelists are independent and free of conflicts. The GAO report indicated that the GRAS Rule is especially concerning in the context of nanotechnology, because companies may conclude that engineered nanomaterials are GRAS without informing FDA.

For example, TiO_2 nanoparticles appear in food products from their use as a flow and reflecting agent. FDA approved bulk-scale TiO_2 as a color additive to whiten food; it has not approved nano-scale TiO_2 as a food or color additive, nor has it received notice of a GRAS determination, suggesting that it is being added to foods in a manner inconsistent with the law. Studies have shown associations between food-grade TiO_2 (in bulk- and nano-scale), and negative effects on both rat intestines[133] and human nutrient absorption.[134] Engineered nanomaterials are created through manipulation of particles at a molecular scale, which alters the physical properties of a substance without changing its chemical structure. Even when a substance such as TiO_2 is considered a safe additive at the bulk scale, it may have a unique effect on the human body at the nano scale. This is because nanomaterials can alter which toxic effects may occur and can also affect bioavailability of a substance by altering absorption, metabolism, or excretion.

There simply cannot be general recognition of safety for any food substance manufactured through the use of nanotechnology. Any such substances must go through FDA's premarket review so that the agency and the public have an opportunity to fully review and comment on any safety data.

Even in the absence of a rule prohibiting GRAS designation of nano-materials as a class, at a minimum FDA should prohibit the use of GRAS for nanomaterials used in infant formula because "[t]he only substances that may be used in an infant formula are substances that are safe and suitable for use in infant formula."[135] Under FDA's current regulations, this means that the

---

[132] *Id*. at 20-21.
[133] S. Bettini, et al., *Food-grade TiO_2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon*, Scientific Rep. (2017), https://www.nature.com/articles/srep40373.
[134] Z. Guo, et al., *Titanium dioxide nanoparticle ingestion alters nutrient absorption in an in vitro model of the small intestine*, NanoImpact (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604471/pdf/nihms846223.pdf.
[135] 21 C.F.R. § 106.40(a).

only substances that may be used in an infant formula are those substances that are used in accordance with the FDA's food additive regulations, are GRAS for such use, or are authorized by a prior sanction.[136] FDA should amend 21 C.F.R. § 106.40(a) so as to expressly prohibit the use of the GRAS for nanomaterials in infant formula in accordance with its rationale from its 2014 guidance document.

Due to the potential dangers created by early exposure to nanomaterials, the addition of nanoparticles in infant formula should be considered a change in processing or product reformulation under the FFDCA. Even changes in the engineering of the chemicals that produce "incidental nanomaterials" should be considered changes in formulation that require FDA approval as food additives. As such, the addition of nanoparticles should adhere to more regulatory measures before being considered safe for use in infant formula.

D. Declare Engineered Nanoparticles in Infant Formula an Imminent Hazard to Human Health.

FDA should declare that infant formula products containing engineered nanoparticles are an imminent hazard to the public health. Pursuant to FDA regulation, an imminent hazard to public health is considered to exist when the:

> "evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held."[137]

An imminent hazard "may be declared at any point in the chain of events which may ultimately result in harm to the public health," and "the occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists."[138]

Infant exposure to nanoparticles and other toxicants via placental transfer or infant formulas are of particular concern due to their weaker immune systems. Indeed, presently, the "biggest concern (regarding nanotechnology) is that free nanoparticles or nanotubes could be inhaled, *absorbed through the skin*, or ingested."[139]

To prevent injury, FDA needs to specifically consider the new and unique risks posed by the use of engineered nanoparticles in infant formula and incidental nanomaterials resulting from the production process, demand full health and safety dossiers on them, and test and regulate accordingly. While the FDA is researching these risks and reviewing this evidence, a moratorium on the infant formulations containing nanoparticles must be imposed.

---

[136] *Id*.
[137] 21 C.F.R. § 2.5(a).
[138] 21 C.F.R. § 2.5(a).
[139] Allianz Group, *Small Sizes That Matter: Opportunities and Risks of Nanotechnologies*, at 30, https://www.oecd.org/science/nanosafety/44108334.pdf (emphasis added).

ENVIRONMENTAL IMPACT

Pursuant to 21 C.F.R. § 25.3 l(a), (c), this petition qualifies for a categorical exclusion from the requirement that an environmental assessment be submitted.[140]

ECONOMIC IMPACT

According to 21 C.F.R. § 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following a review of this petition.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner which are unfavorable to the petition.

CONCLUSION

It is FDA's mission to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."[141] "There is almost unanimous opinion among proponents and skeptics alike that the full potential of nanotechnology requires attention to safety issues."[142] Regulatory agencies like FDA, with clear oversight mandates, can no longer postpone general safety evaluations of engineered nanomaterials by using the GRAS rule.

Moreover, engineered nanoparticles in infant formulas that are already in commercialization, are exposing and harming infants and should be given safety testing and regulatory priority. FDA can require companies to prove the safety of these products under the FFDCA. FDA has a different, higher statutory duty to ensure such products are safe, effective, and not misbranded and must assert its authority over the GRAS rule to protect the public health from the dangers of currently unlabeled and unregulated nanomaterial products in infant formula.

There is clear evidence that engineered nanoparticles including: needle-like and non-needle nano HA, nano TiO_2, and nano SiO_2 can induce developmental harm in infants. What is unknown is the extent to which these particles can cause harm. In order to fulfill its mandate to protect the public health, FDA cannot permit this safety experiment to play out without regulatory oversight, with possible tragic consequences.

---

[140] This does not mean petitioners agree that an application for, and the potential approval of, a new food additive application for a nanomaterial qualifies for a categorical exclusion.
[141] 21 U.S.C. § 393(b)(1).
[142] Nel, *supra* n. 50, at 622.

WHEREFORE, for the reasons contained herein, petitioners respectfully request that the Commissioner:

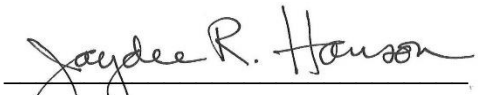
1) Amend regulations directed at FDA's oversight of nanomaterial products including:
    a. An amendment to 21 C.F.R. § 106.3 including the production of engineered nanoparticles as an additional express example for what constitutes a "major change" in infant formula;
    b. An amendment of 21 C.F.R. § 106.140 to include specific reference to engineered nanoparticles as a reason to notify FDA of a change in infant formula that may adulterate the product;
    c. An amendment to the table set out in 21 U.S.C. § 350a(i) and in its regulations at 21 C.F.R. § 107.100(a) to include nanomaterials with defined maximum levels;
    d. An amendment of 21 C.F.R. § 106.3 to define terms necessary to regulate engineered nanomaterial products in infant formulas in accordance with the European Commission's definitions, *see* note 124;
    e. A revision of FDA's 2014 Guidance on Assessing Significant Manufacturing Process Changes[143] to expressly include infant formula; and
    f. An update to FDA's regulations based on the 2014 guidance.
2) Declare all currently available infant formulas containing engineered nanoparticles as adulterated and misbranded and require a recall under 21 C.F.R. § 107.200.
3) Amend 21 C.F.R. § 106.40(a) so as to expressly prohibit the use of the GRAS for nanomaterials in infant formula in accordance with FDA's rationale in the 2014 guidance document.
4) Declare engineered nanoparticles in infant formula an imminent hazard to human health under 21 C.F.R. § 2.5(a).

In accordance with FDA regulations, petitioners request that FDA provide an answer to this petition within 180 days.[144]

Respectfully submitted,

Meredith Stevenson
Center for Food Safety
518 C Street, N.E.
Suite #200
Washington, D.C. 20002
Phone: (415) 826-2770
Email: mstevenson@centerforfoodsafety.org

[143] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology.
[144] 21 C.F.R. § 10.30(e)(2).



Jaydee Hanson
International Center for Technology Assessment
303 Sacramento St, 2nd Floor
San Francisco, CA 94111
Phone: (415) 826-2770
Email: jhanson@icta.org