INSTITUTE FOR AGRICULTURE AND TRADE POLICY

To: Office of Food Additive Safety, U.S. Food and Drug Administration (FDA)

Re: Docket number: FDA-2011-D-0490

"[Draft] 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"[i]

Date: July 24, 2012

The Institute for Agriculture and Trade Policy (IATP) is a nonprofit, 501(c)(3) nongovernmental organization, headquartered in Minneapolis, Minn., with an office in Washington, D.C. Our mission states, "The Institute for Agriculture and Trade Policy works locally and globally at the intersection of policy and practice to ensure fair and sustainable food, farm and trade systems." To carry out this mission regarding "emerging technologies" in food, specifically the use of Engineered Nanoscale Materials (ENMs) in food ingredients and food-contact surfaces, IATP engages in research and advocacy activities.

Our most recent research publication, "International Standards for Trade of Nano-coated Produce?"[ii], outlines some of the challenges that the Codex Alimentarius Commission likely would face in elaborating standards on nano-coatings as food additives. IATP, as a member of the Transatlantic Consumer Dialogue's (TACD) Nanotechnology Working Group, has collaborated on resolutions presented to the U.S. government and the European Commission for discussion at TACD's Annual Meetings and at the Transatlantic Economic Council (TEC).[iii] TACD met most recently with U.S. and EC officials on June 5 at the State Department. Unfortunately, FDA was unable to send anyone to the nanotechnology break-out session of the meeting.

IATP is a co-plaintiff in the International Center on Technology Assessment (ICTA) et al lawsuit against FDA to compel FDA to respond to the May 2006 ICTA et al petition to regulate ENMs.[iv] Although IATP is disappointed in FDA's denial of the petition on April 20,[v] we welcome the opportunity to comment on the above-captioned draft guidance on the use of ENMs in food ingredients and food contact surfaces.

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General comment

The White House memo of June 9, 2011, "Policy Principles for U.S. Decision-Making Concerning Regulation and Oversight of Nanotechnology and Nanomaterials,"[vi] presents a very difficult challenge to FDA and other federal agencies with statutory environmental, health and safety (EHS) obligations. In addition to meeting these obligations by regulating nanotechnologies and ENMs according to "the best available science," the agencies are enjoined to promote "economic growth, innovation, competitiveness and job creation," according to President Barack Obama's executive order cited in the memo. The memo does not tell agency heads and administrators how to resolve possible conflicts between the science that informs the agencies' statutory EHS obligations and the economic imperatives for nanotechnology outlined in the memo.

However, there are strong indications that the current White House strategy for resolving these conflicts is to allow the Office of Management and Budget to block any rulemaking whatsoever on nanotechnologies and ENMs. OMB is reportedly responding sympathetically to industry lobbying that any rulemaking would "stigmatize" the technologies and endanger the government's promotion of and investments in nanotechnology as a source of economic growth.[vii]

FDA's recommendation to industry to consult with FDA about "significant change in manufacturing process"

In light of these political and industry pressures against regulation, IATP believes that FDA's draft voluntary guidance offers a non-prejudicial way for industry to consult with the agency about its applications of nanotechnologies to food ingredients and food contact surfaces under FDA's authority. We agree with the guidance recommendation that industry consult with the agency about each "significant change in manufacturing process for a food substance already in the market, irrespective of your conclusion about whether that change affects the safety or regulatory status of the food substance" (4). Given the change in properties that results from nano-sizing a material, and the increasing use of ENMs in food substances,[viii] IATP believes that all applications of ENMs to food ingredients and food-contact substances should require a pre-market safety assessment.

This belief notwithstanding, there are few peer-reviewed studies on the effects of chronic exposure to ENMs in the gastro-intestinal system to serve as a basis for a pre-market safety assessment, e.g., to determine whether safe Average Daily Intakes of ENMs in food substances can be set. A 2012 U.S. National Research Council report states, "little research progress has been made on some key topics, such as the effects of ingested ENMs on human health."[ix] FDA should commission, finance and publish such research as an urgent public health priority and a basis for regulation. FDA should solicit advice on criteria for prioritizing EHS research in food substances and food-contact substances and publish those criteria as part of an annual report

on FDA nanotechnology research. A General Accountability Office (GAO) review of 20 FDA-designated nanotechnology EHS research projects found nine of them not to be clearly directed to EHS objectives.[x] FDA should follow GAO's recommendations to improve and clarify its reporting of nanotechnology research.

Given FDA's budgetary limitations, IATP urges FDA to direct some of its research funding to build on work already done outside the United States, in order to enable premarket safety assessment of industry food products with ENMs. For example, a Dutch study has been able to determine consumer exposure to nano-silica in 27 commercialized food products. However, because the "mechanism of silicon absorption from the gastro-intestinal tract has not yet been clarified,"[xi] the Dutch researchers could not determine whether the exposure to nanosilica would be hazardous to human health, in the event that nanosilica bio-accumulates. FDA should prioritize research into this absorption mechanism, and indeed, the absorption mechanisms for all nano-metal oxides proposed for use in food substances and food-contact surfaces.

However, the challenges for FDA of evaluating industry claims about nanotechnology applications in food substances will extend beyond those of nano-toxicology. For example, Chinese researchers have discovered in animal testing that absorption of nano-silver may interfere with the replication of DNA molecules and can reroute molecular networks that could create genetic mutations.[xii] Nano-silver, among myriad other uses, is incorporated into food-packaging materials to kill pathogenic bacteria and thereby extend a food's shelf life.[xiii] However, nano-silver particles may migrate from the packaging material into the nano-wrapped food. The Chinese researchers said that the long-term effects of DNA interference from nano-silver are unknown and should be a priority for FDA's EHS research.

FDA does not have statutory EHS duties concerning food processing workers. Nevertheless, it should request that industry consultations on "significant manufacturing process changes" enable information sharing with the Occupational Health and Safety Administration (OSHA) on the industry manufacturing practices involving ENMs in food substances and food-contact surfaces. Such information would enable OSHA to expedite guidance to industry on protecting food processing workers who handle ENMs and might also inhale them. A recent study concluded, on the basis of analyses of pulmonary exposure, "we demonstrate that nanomaterials of distinct origin, morphology, physicochemical properties are able to induce protein citrullination" that may contribute to autoimmune disease, such as rheumatoid arthritis.[xiv] Among the nanomaterials is nano-silicon dioxide.

Given the many unknowns about the effects of ENMs in food substances on human health, it will be difficult for industry to demonstrate the safety of an ENM in a food substance under the provisions of the Food Drug and Cosmetic Act (FDCA) cited in the guidance, e.g., according to "the cumulative effect of the substance in the diet"(8). IATP is pleased that the draft guidance reminds industry that for food substances not Generally Recognized As Safe (GRAS) and commercialized without pre-market approval, FDA "can take enforcement action to stop distribution of the food substance and foods containing that food substance on the grounds that

such foods are adulterated because they are or contain an unlawful food additive" (8). IATP strongly urges FDA to retain this reminder in the final guidance and to use this authority in cases where industry violates the Titles pertaining to food in the FDCA by marketing food substances with ENMs that have not been FDA approved as safe for human consumption.

FDA's guidance to industry concerning nanoscale versions of food substances Generally Recognized As Safe

Per the aforementioned evidence, IATP agrees with this draft guidance advice to industry on ENMs in food substances: "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 pre-market review and approval by FDA, rather than to satisfy criteria for GRAS status" (19). We strongly urge FDA to retain this advice in the final guidance. Absent this guidance to industry, we share the concern of the General Accountability Office that "FDA's approach to regulating nanotechnology allows nanomaterials to enter the food supply without FDA's knowledge." [xv] Food processors might assume that food ingredients that they have determined to be GRAS in their macro-scale are likewise GRAS in their nano-scale. The assumption fills a regulatory vacuum, because FDA does not require industry to report its GRAS determinations to the agency. Under that assumption, industry would neglect to submit documentation on their use of ENMs in food substances and/or food-contact surfaces for a pre-market safety assessment. The unfortunate result of such neglect would be food substances with ENMs in commerce in likely violation of the FDCA.

Fortunately, the draft guidance forewarns industry that they cannot make their own determinations that ENMs in food substances are GRAS. As noted above, FDA recommends, but does not require, that industry consult with the agency concerning significant manufacturing process changes that include ENMs in food substances and food-contact surfaces. The guidance also forewarns industry that it can take enforcement actions to stop the distribution of food substances with unapproved additives, including ENMs.

However, in light of the depleted staffs and budgets for food inspection of FDA and the state agencies with which it works, it is not clear how effective, and indeed, dissuasive, such enforcement action will be. [xvi] Furthermore, FDA testing laboratories and state food inspection agencies lack both the ENM detection technologies, such as electronic tunneling microscopes, and trained personnel that would be required to gather evidence to demonstrate the need for enforcement actions.

IATP views the problem of inspection, testing and enforcement capacity as a broad one in U.S. federal agencies with EHS statutory obligations. [xvii] Nanotechnologies and ENMs present yet greater regulatory challenges for FDA and other agencies with EHS obligations and agencies

face political pressure to commercialize products with ENMs. We hope that FDA will not limit its learning about how to address these challenges to the U.S. regulatory literature.[xviii]

The final guidance cannot address, of course, such broad structural problems in a pre-market safety consultation. However, we believe that the aforementioned inspection, testing and enforcement capacity issues point to the need for FDA to discuss with industry and with the public FDA's plans for a program of post-market surveillance for any ENMs as food additives that the agency may approve for commercial use. Joint consultations with industry, scientists working in agri- and food nanotechnology, and interested members of the public could result in draft FDA guidance to industry on the post-market surveillance of ENMs in food substances and food-contact surfaces.

"Self-limiting levels of use": a regulatory concept that must be adapted to the novel properties and risks of ENMs

In the draft guidance, FDA assumes, on the basis of knowledge and experience, that industry will self-limit its use of certain food additives determined by industry to be GRAS, in order to ensure desired and marketable food product characteristics, e.g., palatability, nutrition objectives, texture, etc. The guidance reminds industry that according to FDA regulations for GRAS additives, good manufacturing practice requires that "The quantity of a substance added to food does not exceed the quantity reasonably required to accomplish its intended physical, nutritive or technical effect . . ." (8). FDA is well aware that industry's capacity to determine a safe level of use of ENMs in food and for the agency's capacity to monitor that level of use for additives that are not GRAS will pose many challenges. The exponentially greater surface-to-mass ratio of ENMs, compared to their macro-scale versions, requires a different set of metrics and good manufacturing practices.

As noted above, the current lack of peer-reviewed studies on the health effects of ingested ENMs means that nano-relevant metrics for food additives will not be agreed for some time. Metrics submitted by industry on a case-by-case basis for the programs outlined in Appendix 2 of the guidance should be subject to public review, and not classified as Confidential Business Information. The agency should organize public consultations for each ENM proposed for use as a food additive and invite submissions from the public, as well as from industry. In the meantime, the agency should assume that industry will have neither the knowledge nor technical capacity for "self-limiting" the use of ENMs to achieve the effects that FDA stipulates for GRAS food additives at the macro-scale.

Conclusion: pre-regulatory comparative technology assessment

The guidance advises industry that FDA regulations about the evaluation of industry information concerning the safety of food additives name "identity, purity, potency,

performance and usefulness" (10) as evaluative criteria. While all these criteria are important for the evaluation of safety, IATP believes that the criterion of "usefulness" gives FDA the authority and opportunity to discuss with industry whether a nano-scale version of a food substance is the optimal means to achieve a physical, nutritive or technical effect, relative to other possible means for doing so.

Lamentably, in the U.S. government, robust comparative technology assessment died with the Congressional decision in 1995 to shut down the Office of Technology Assessment, "a decision that one journalist at the time characterized as 'driving into the future with the headlights off'."[xix] As a result, there is no interagency clearing house on comparative technology assessment, so that government investments in, subsidies for and policy about nanotechnology respond to industry lobbying and political imperatives. In the absence of an OTA or an OTA function within EHS agencies, nanotechnology applications that could involve more than one agency lack any standards by which to judge whether the applications are optimal relative to the scientific risks and uncertainties of a particular application.

For example, research on the use of ENMs as soil additives for a variety of crops poses questions concerning the risks involved in the environmental fate of the ENMs and the persistence of the ENMs in foods processed from the crops.[xx] Let's say the technical objective of the nanotechnology application is more rapid seed germination or greater plant water retention. A pre-regulatory and pre-investment interagency process to evaluate the application might conclude that these technical objectives could be achieved by other means without the risks to human health and the environment that could result from chronic exposure to the ENMs in food processed from the crop or from ENMs in agricultural water run-off. Might it not be equally effective for a farmer to build the microbiotic health and water retention of the soil through composting and nutrient rich cover crops, rather than experimenting with a nano-soil additive?

However, in lieu of an interagency process of comparative technology assessment, under the regulatory criterion of "usefulness," the FDA could ask industry to show that it had evaluated other means to achieve an intended nutritional or technical effect and compared those means with the nanotechnology application it presents to the agency for pre-market safety approval.

Finally, IATP wishes to thank FDA for the opportunity to comment on the draft guidance. We look forward to participating in public consultations concerning issues discussed in this comment.

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[iii] http://tacd.org/index.php?option=com_docman&task=cat_view&gid=75&Itemid=40
[iv] http://www.centerforfoodsafety.org/wp-content/uploads/2011/12/1-Pls-Complaint.pdf
[v] http://www.icta.org/doc/Andrew%20Kimbrell-FDA-2006-P-0213-Citizen%20Petition.pdf
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[xiv] Bashir M. Mohammed et al, "Citrullination of proteins: a common post-transnational modification pathway induced by different nanoparticles *in vitro* and *in vivo*," *Future Medicine*, May 25, 2012. http://www.futuremedicine.com/doi/full/10.2217/nnm.11.177
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