European Food Safety Authority (EFSA) March 3, 2018
EFSA Scientific Committee

"Guidance on risk assessment of the application of nanoscience and nanotechnology in the food and feed chain: Part 1, human and animal health"

Comment on the Draft Public Consultation (Draft)

Submitted to: http://registerofquestions.efsa.europa.eu/roqFrontend/consultation/doc/105 and to SCER.PublicConsult.105@efsa.europa.eu

The Institute for Agriculture and Trade Policy (IATP) Europe appreciates this opportunity to comment on the Draft. IATP, a U.S. headquartered non-profit, non-governmental organization founded in 1986, opened the IATP Europe office in Berlin in 2017. IATP has participated in the Transatlantic Consumer Dialogue (TACD) since 2000 and, since 2016, has been the U.S. co-chair of the TACD Food Policy Committee. TACD presented resolutions on transatlantic cooperation in chemicals regulation, including nanomaterials, to the European Commission in 2013[1] and 2016.[2] IATP is one of seven NGOs and a labor union that in 2015 released a "Policy for Nanomaterials in Food and Food Packaging" addressed to companies employing nanomaterials.[3] In 2012, IATP submitted comments to the draft Food and Drug Administration Guidance for Industry on "significant new manufacturing changes," including those of nanotechnology, applied to food and food additives.[4]

*Overview: Comment on the Guidance Summary*

The legal status of this draft Guidance is contradictory. Here (lines 148-150) compliance with the Guidance is a "must." Elsewhere (e.g. 356-358) compliance is voluntary, i.e. "should," as with the U.S. Food and Drug Administration (FDA) Guidance on nanomaterials in food and feed, e.g: "FDA continues to welcome consultations with industry as an approach to ensuring that food developed using new technologies will be safe,"[5] (at 15). NGO testing of food products with nanomaterials, (e.g. nano-hydroxyapatite in infant formula[6]). and nano titanium dioxide in candy and pastry glazes[7], suggests that voluntary consultations with FDA have been absent or inadequate to secure industry cooperation. IATP urges EFSA not to emulate FDA's voluntary approach. Applicants to commercialize food and feed products with nanomaterials must demonstrate their compliance with the EFSA Guidance. The EFSA Management Board must make clear in a cover note to the Guidance that mandatory compliance with the Guidance is authorized by the 2018 revision to the Novel Food Regulation[8]. Even though the 2018 revision enables "generic authorizations," rather than applicant specific ones, manufacturers of nanotechnology-enabled food and feed still must comply with the Guidance to comply with the pre-market safety assessments required by the Novel Food law.

The study EFSA commissioned in 2014 shows that 55 nanomaterials were incorporated into foods, food supplements or food packaging already commercialized or intended to be commercialized

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in the Member States (lines 388-392). In May 2017, EFSA, other Commission agencies and Member States officials were beginning to discuss standardization of nanomaterial measurements and the reliability of those measurement results.[9] It appears that European food manufacturers commercialized novel foods with nanomaterials in advance of the 2018 revision of the Novel Foods Regulation, which appears to retroactively legalize that commerce. Nevertheless, EFSA must have the scientific capacity and legal authority to document publicly that "the scientific appropriateness of the [analytic] methods used are substantiated by the applicants" (lines 405-406). Absent that capacity and transparency of pre-market safety assessment, the legal concept of "generic authorizations" in the 2018 revision of the Novel Food Regulation will be read by consumer and environmental organizations as a regulatory loophole designed to expedite commerce, not to protect consumers or the environment. In the absence of the regulation of food and agri-nanotechnology, consumer organizations have had to use their scarce resources to detect nanomaterials in unlabeled food and cosmetic products.[10]

Nanoscience is the basis for a broad technological platform whose applications have many benefits. If EFSA, Member States and the food/feed industry do not wish nanotechnology to become the "new GMO," they must cooperate to transparently document applicant compliance with the Guidance. They must not replicate with nanotechnology the unhappy U.S. history of voluntary industry consultations and heavily-redacted commercialization applications for GMOs.

*General comment on the state of play of nanotechnology enabled product developer cooperation with authorities to enable robust risk assessment*

Perhaps the most poignant sentence of this mostly descriptive Draft is this one: “As a general principle, the test requirements stipulated in current EFSA guidance documents for conventional materials and EU legislation for various food and feed areas should be applied to a nanomaterial according to its intended use and should be followed,” (p. 9, 356-358). Guidance for industry documents have, by definition, no legal obligations nor are there penalties for not following the Guidance. For example, infant formula manufacturers suffered no legal consequences for failing to follow U.S. Food and Drug Administration (FDA) Guidance on nanomaterials in FDA-regulated food products. According to that Guidance, the manufacturers should have consulted with FDA before commercializing infant formula containing a nano-form of hydroxyapatite:[11] “FDA continues to welcome consultations with industry as an approach to ensuring that food developed using new technologies will be safe.”[12]

Even if you take the view that chronic exposure to nano-hydroxyapatite (nano HA) is below regulatory concern because the substance is soluble or because the manufacturer has determined hydroxyapatite to be Generally Recognized As Safe (GRAS), it is hard to imagine that FDA scientists would not want to read the manufacturers’ data on how the infant metabolizes the nano HA or whether the inhalation of the powdered formula poses risks to a child’s care givers or to workers manufacturing the formula. Indeed, FDA advised food manufacturers that, “At this time [June 2014], we are not aware of any food substances intentionally engineered on the nanometer scale for which here are generally available safety data sufficient to serve as the foundation for a determination that the use of a food substance is GRAS,” (*op cit.* pp. 15-16). This is, we hope, a persuasive analogy to illustrate that EFSA’s technical advice on risk assessment of a food or feed product containing Engineered Nanoscale Materials (ENMs) will be ineffective unless, and until,

manufacturers and product developers are required to follow the advice before putting nanotechnology-enabled food and feed products on the market.

The draft Guidance states, "The Scientific Committee considers that the application of this Guidance is unconditional for EFSA and for all parties submitting applications for the use of engineered nanomaterial under the food law," (p. 13, lines 541-543). IATP strongly agrees with the Scientific Committee. However, regrettably, the Scientific Committee's view does not have binding legal effect nor does it carry penalties for failure to comply. The EFSA management board should work with urgency to establish the Scientific Committee's view as a matter of EU-wide law.

To risk assess nanotechnology-enabled products, the cooperation of product developers is necessary. However, our TACD colleagues in Europe report that their testing of food and cosmetic products with nanomaterials shows that manufacturers are not even cooperating with the legal requirement to declare nanomaterials in four food (and five cosmetic) products.[13] The European Union at least provides consumer organizations with legal recourse for food manufacturer failure to follow nano-labeling law. In the United States, consumer organizations, in the absence of nano-specific risk assessment and regulation, have had to persuade food manufacturers to remove ENMs from their products or face reputational risk and possibly reduced sales for their branded products.[14]

The cooperation of product developers is necessary to generate robust exposure data to enable risk assessment of ENMs in their product matrices throughout the lifecycle of the products. As IATP commented on the draft strategic plant of the U.S. National Nanotechnology Initiative, "NNI agencies have failed to secure the cooperation of product developers to enable exposure scientists to provide regulators with validated data for Life Cycle Assessment (LCA) based risk assessments of products incorporating ENMs."[15] Past efforts (e.g. the nanomaterial stewardship program of the Environmental Protection Agency) to secure the voluntary cooperation of industry in a nanomaterials registry have not been successful.[16]

Regrettably, adequate European industry cooperation likewise has been lacking to enable robust risk assessment of ENMs, according to a December 15, 2017 statement from the European Chemicals Agency (ECHA): "In current situation, the authorities cannot verify whether registrants [to the REACH nanomaterials Annex] have demonstrated the safe use of nanomaterials throughout the supply chain or whether further regulatory risk management measures are needed. This may also have consequences in terms of market trust on nanomaterials. The realisation of the great opportunities that nanotechnology and nanomaterials may offer society, should go hand in hand with the transparent demonstration by industry of their safety and sustainability."[17] Notwithstanding the extensive technical and financial support that the Commission and Member States have given to nanotechnology product developers, the support has not been reciprocated with regulatory cooperation.

Nor do the Draft's references to EFSA's cooperation with the Organization for Economic Cooperation and Development (OECD) (line 432 *et* passim) provide assurance that the quality of data reported by governments to the OECD is adequate for robust risk assessment. An Institute for Occupational Medicine study, commissioned by three European NGOs, of 11,500 pages of raw

data about 11 ENMs provided to the OECD's Sponsorship Testing Program, concluded that the data provided was of little utility for risk assessment purposes.[18]

IATP greatly appreciates that EFSA has been able to deduce the use of 55 nanomaterials in food and feed products from the inventory that it commissioned in 2014.[19] These deductions provide the empirical basis for applying the selection of risk assessment techniques outlined in the draft Guidance. EFSA's Draft "recommends that the characterization of the nanomaterial is carried out at different stages, e.g. in its pristine state as tested and on the material as used in products and applications," (p.4, lines 158-160). This is an eminently logical recommendation, of course. However, industry characterizations of nanomaterials in their product and environmental and human health media matrices cannot be verified until EFSA and other regulatory authorities have authorized access to nanotechnology-enabled products and applications. As IATP wrote to the presidential Office of Science and Technology Policy regarding the NNI's 2015 co-sponsored workshop on Quantifying Exposure to Engineered Nanomaterials (QEEN)[20]:

> Several QEEN presenters identified an essential pre-requisite to the development of robust exposure data sets of ENMs in the human and environmental media of their use. Without the cooperation of nanotechnology and ENM product input developers, the research results of exposure studies of ENMs in their product matrices will not have regulatory validity, since exposure scientists are obtaining nanotechnology products for EHS [Environment Health and Safety] research outside of a regulatory process.[21]

Prominent exposure scientists told White House officials about the conflicting demands put on them by product developers who wanted faster throughput of data and validated methodologies to enable commercialization of their products while offering only "gray market" versions of those products for exposure assessment outside any regulatory framework.

We believe that a sustainable market for nanotechnology-enabled products, and particularly food and agri-nanotechnology products, cannot be based on a *de facto* industry self-regulation. Before draft Guidance "identifies the circumstances under which some requirements for **nanospecific data could be waived** [bold in the original]," the Guidance must specify compliance with the data submission requirements that must be satisfied before EFSA would consider granting such data waivers.

The updating of the Guidance should include an introductory section that places the principles and techniques of risk assessment in the broader risk analysis framework. Otherwise the Guidance may be read as a group of testing parameters and a decision-making procedure to enable product developers to avoid nano-specific testing and reporting to EFSA of those testing results and the risk assessments based on them.

*Comments on specific aspects of the Guidance*

The Guidance provides both Member States' and industry risk assessors with a great deal of useful, peer-reviewed information and decision-making criteria. The following comments are on issues raised in the Guidance but in need of further development.

Because measuring ENMs in food might result in damage to the measuring and characterizing instrumentation, food simulants are often used, as the Guidance notes, (p. 29, lines 996-997). However, one review article notes, "little is known about how the sample preparation impacts on the NP [nano-particle] characteristics, so it is difficult to know whether samples that have been prepared following a certain protocol produce data that are a realistic representation of NPs in their native environments."[22] The Guidance recognizes the analytical challenges of preparing a sample that is representative of the food matrix because they "contribute the largest uncertainty to the result. A critical issue in the sample preparation of the nanomaterial is the proper dispersion of particles. This issue is addressed in detail in 4.3.1," (p. 28, 994-996). Given the degree of analytic uncertainty and indeed, validity, that depends on the sample preparation, subsection 4.3.1 requires considerably more illustration of the degree of uncertainty according to which a food simulant is selected and prepared for incorporating which ENM. The links to NP dispersion protocols (p. 30, lines 1012-1017) is helpful. But this subsection requires more detail than a listing of techniques to distinguish incidental nanomaterials from ENMs and a sample listing of food simulants to use in sample preparation.

There is a disjuncture between the certainty of the Guidance's risk assessment decision-making tree (e.g. p. 35) and the unavailability of validated instrumentation with which to visualize ENMs in food or food simulants, a basic risk assessment step. A U.S. research team writes, "Well-validated imaging methods for characterizing inorganic- or organic-based nanomaterials in foods are not currently widespread, mostly due to the challenges of attaining informative data from complex matrices."[23] Despite this lack of well-validated imaging methods, a decision tree criterion for directing risk assessors to follow relevant EFSA guidance for conventional materials is a 'yes' answer to the question, "Does the material fully dissolve in the food/feed matrix?" (p. 35) If imaging methods for ENMs in food/feed are not well-validated, how is the risk assessor to determine that an ENM is fully dissolved? The discussion on uncertainty in the Guidance does little to clarify the utility of that decision-making question. Indeed, the Guidance may be avoiding the difficulty of visualizing the full dissolve of the ENM.

> When it is not possible to characterise the form in which the nanomaterial substance is present in food and/or feed applications, uncertainty in exposure assessment will be increased. This uncertainty could be reduced by characterisation of the nanomaterial in the food/feed or liquid food/feed products according to intended or existing applications, (p. 65, lines 2396-2398).

This putative reduction in uncertainty is less based on an accurate and reliable exposure assessment than it is on the characterization of risk according to an already-existing application of ENMs to food. In our view, a risk assessment decision-making tree that incorporates uncertainty factors, including those based in instrumental limitations, should be included in the Guidance. IATP believes that conditional use registration should not be allowed for ENMs in food, feed and food packaging when it is not possible to characterize ENMs in food with a high degree of certainty.

Regarding the "Stepwise framework for nano-related hazard identification and characterization in food/feed" (p. 37), at the step in which the risk assessor is asked to consider, "Do these [oral toxicity study] results warrant further testing?" It is difficult for IATP to imagine a "no" to the

question if the ENM being tested was inorganic and there were "indications for slow elimination and distribution to specific tissues." This decision-making tree should be reconfigured to recognize the well-documented bio-persistence of nano-metal oxides and other inorganic nanomaterials that may be used in food or feed. As one review article stated, "the metal/metal oxide NPs presently have the highest potential to be ingested due to their increasing inclusion in dietary supplements and food conservation materials."[24] While the likelihood of ENM migration from food packaging polymers to the food packaged food may be low, EFSA should consider whether the decision-making tree for hazard characterization needs a second "branch" for inorganic ENMs.

The pressure to commercialize nanotechnology-enabled products should not be a deciding factor in use of "read across" methods of ENM toxicity data for risk assessment. The press release announcing a Commission-sponsored read across initiative, however, conveys that commercial pressure: "Industry has the ability to modify the chemical and physical characteristics of materials at the nanoscale leading to a wide array of nanomaterials (NMs) varying in size, morphology and surface characteristics. Due to financial, time and ethical considerations, safety testing of every unique NM for their potential adverse effects is virtually impossible. For these reasons, more efficient ways to obtain safety information are needed."[25] Notwithstanding the enthusiasm of the proponents of read across for expediting risk assessment and reducing the testing of ENMs according to read across toxicological predictive analytics, the EFSA Scientific Committee wisely states:

> There is considerable uncertainty (e.g. limited usability due to lack of data) on the value of read-across for risk assessment of nanomaterials. Owing to the current data gaps, the applicability of read-across to nanomaterials is limited and it is likely that experimental data (in vitro, in vivo) for read-across substantiation would be needed in a majority of cases . . . Whether a read-across justification is acceptable for waiving further (in vivo) testing is to be judged by EFSA on a case-by-case basis. (page 44)

EFSA would be doing both consumers and food and agri-nanotechnology product developers a great disservice by expediting risk assessment and circumventing in vivo and in vitro testing of ENMs by relying on *in silico* modeling of risks of ENMs in food and feed to human and animal health.

Last, but not least (for our purposes), EFSA poses a "Question to the public—request for input during the public consultation: Is there information from which we can derive guidance? This section may move to the recommendations if no more guidance e.g. on type of interactions and the type of assays, can be given," (p. 58, lines 2111-2113). A response to this question should be holistic, covering all ingested ENMs, and not just those ingested from the intentional incorporation of ENMs in food and feed.[26] For example, consideration should be given to measure human exposures derived from the "roots and shoots" studies of agricultural plants that take up nano-forms of metal oxides from water treat residues ("biosolids" in the term of the U.S. Environmental Protection Agency) used as fertilizer.[27] The absence of pre-treatment standards for industrial effluents with nanomaterials, e.g. from liquid phase synthesis products, and the lack of water plant technology to agglomerate ENMs ensures that biosolids fertilize agricultural crops with inorganic ENMs.

*Conclusion*

IATP hopes that these brief comments aid EFSA in finalizing this Guidance. We look forward to having the opportunity to contribute comments in a public consultation on Part 2 of the Guidance, regarding environmental health impacts.

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[3] https://www.iatp.org/sites/default/files/Nano%20Policy%2020150309.pdf

[4] https://www.iatp.org/files/2012-07-24-IATPCommentToFDA-Nanotechnology.pdf

[5] https://www.fda.gov/downloads/Cosmetics/GuidanceRegulation/GuidanceDocuments/UCM300927.pdf

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[7] https://archive.asyousow.org/our-work/environmental-health/nanomaterials/

[8] https://ec.europa.eu/food/safety/novel_food/legislation_en

[9] https://ec.europa.eu/food/sites/food/files/safety/docs/novel-food_nanomaterials_in_food_20170503_sum.pdf

[10] E.g. https://www.quechoisir.org/action-ufc-que-choisir-nanoparticules-dissimulees-9-plaintes-de-l-ufc-que-choisir-contre-des-fabricants-de-produits-alimentaires-et-de-cosmetiques-n50840/

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