Comments of Consumers Union at FDA Nanotechnology Public Meeting
Breakout session on Food and color additives, including food contact substances

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The basic position of Consumers Union urges FDA to recognize that nanoscale particles exhibit novel properties and/or behaviors, compared to their larger counterparts, and raise unique safety concerns, so that a separate safety assessment must be required before such nanoscale particles/materials can be used for any food ingredient or packaging component that comes in contact with food. We, thus, agree with the recommendation of the UK Royal Society, and the European Commission's expert panel, which have stated that nanoparticles should be considered different that the normal size counterparts and separate safety assessments should be performed on them. Furthermore, FDA should require labeling of such ingredients immediately

1. **Can you identify specific classes of food ingredients or packaging components derived from or incorporating nanotechnology that you would identify as raising or not raising unique safety concerns and why?**

In general, no. Consumers Union believes that *any use of nanotechnology*, particularly the use of "engineered nanoscale materials" (ENM) (defined as a material purposefully manipulated at nanoscale that exhibits novel properties and/or behaviors as a result) for food and color additives, including food contact substances should require a full food additive petition (FAP) for the ENM, even if the macroscale version of the substance in questions has previously been granted a FAP. In other words, we want FDA to recognize that ENMs have the potential for structure-dependent health effects that are uniquely different than their larger counterparts and raise toxicity questions.

In this regard, we agree with the conclusions of the July 2004 report of UK Royal Society and Royal Academy of Engineering, which concluded, "We believe that chemicals in the form of nanoparticles and nanotubes should be treated separately to those produced in a larger form. Given the evidence that increased surface area can lead to greater toxicity per unit mass, regulation of exposure on a mass basis to nanoparticles and nanotubes may not be appropriate."[1] As a particle gets smaller and smaller, the ratio of surface area to volume/mass increases exponentially. Thus, the surface area of 100 grams of lead in a sphere 2.6 centimeters in diameter is 0.0002 m^2. If that particle size is reduced from 2.6 cm to 50 nm (nanometers), the total surface area is over 1,000 m^2 or 500,000-fold (or almost 6 orders of magnitude) greater. The drastically greater surface area means potentially greater reactivity with biological or chemical materials around them—such as increased reactivity with the immune system.

[1] Pg. 82 in Royal Society and Royal Academy of Engineering. 2004. "Nanoscience and Nanotechnologies: Opportunities and Uncertainties." At: http://www.nanotec.org.uk/report/chapter9.pdf

We already know that the for air pollution, the smaller size particles and their greater surface are typically more toxic than larger particles and can penetrate. In addition, the small size of nanoparticles (ENMs) means that they may be able to pass through membranes—evade the immune system[2] or pass through the blood-brain barrier or directly enter cells and their nuclei[3], etc. and travel to places that conventional scale materials cannot. Finally, ENMs can be of an intermediate size—larger than individual atoms and molecules, but smaller than other larger blocks of material—that causes them to have properties that can't be easily extrapolated from their component chemicals or the bulk substance. For all these reasons, **FDA should consider ENMs to be new materials with unfamiliar properties or a significant new use of a material**. **Existing food additive petitions, food contact notifications, or GRAS ("generally regarded as safe") determinations for macroscale materials should not be considered valid for versions made with ENMs**. Either way, **separate food or color additive petitions should be required**. At this point, given the new and unique risks posed by ENMs due to their small size and scientific unknowns associated with assessing their potential toxicology (e.g. increased toxicity per unit mass), ENMs should not be granted GRAS ("generally regarded as safe") status.

For "food contact substances" which meet the definition of "food additive" (e.g. indirect food additives), we note that Congress gave a streamlined pathway for approval of such substances, assuming that exposure would be relatively small (so rigorous safety review wouldn't really be necessary), requiring only a "food contact notification" (FCN) in place of the more rigorous food additive petition. However, the FDA can require a full food additive petition if it "determines that submission and review of a [food additive] petition . . . is necessary to provide adequate assurance of safety."[4] We believe that **FDA should state that due to the potential toxicity issues raised by ENMs used as food contact substances—basically due to their exponentially increased surface area to mass ration and greater surface reactivity which, in turn, could dramatically affect biological impacts—they are ineligible, as a class, for the FCN ("food contact notification") process, and that full food additive petitions are required.**

As for potential environmental impact of ENMs used in food contact substances (including indirect food additives), FDA regulations categorically exempt components of packaging materials from requirement of an Environmental Assessment (EA) under three conditions, when the substance is either: present in finished food-packaging material at not greater than 5 percent by weigh and is expected to remain with the finished food-packaging material through use by consumers; a component of a coating of a finished food-packaging material [e.g. like a can-liner, or pizza box liner]; or a component of another food contact substance intended for repeated use.[5] However, FDA does retain statutory authority to require an EA for any agency action that would normally be

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[2] http://nano.cancer.gov/news_center/monthly_feature_2006_sep.asp
[3] De Jong WH and PJ Borm. 2008. Drug delivery and nanoparticles: applications and hazards. *International Journal of Nanomedicine*, 3(2): 133-149. At: http://www.dovepress.com/articles.php?article_id=1836
[4] Section 409(b)(3) of the Federal Food, Drugs, and Cosmetics Act
[5] 21 CFR 25.32(i) and (j)

categorically excluded if available data indicate "extraordinary circumstances" that would make the exclusion unwarranted and if there was a significant impact on the environment[6]. **CU believes that use of ENMs in direct and indirect food and color additives creates an "extraordinary circumstance" that would negate the categorical exclusion** and so **FDA should require full EA and EIS (environmental impact statements) for all uses of ENMs, regardless of whether a categorical exclusion appears to apply**. For example, the categorical exclusion of a food contact substance (e.g. indirect food additive) if it's less than 5% by weight, may not be appropriate for ENMs. This exclusion is based on the notion that the exposure to the food contact substance (FCS) will be so low that harm would be minimal. However, this is based on behaviors of the FCS at the macro scale. If the FCS is produced at the nanoscale, the surface area—for the same quantity of material—could increase by 4 or more orders of magnitude, which could drastically alter the absorption or action of the compound. If activity or toxicity is based on surface area, then by making nanoscale versions of the FCS, you could inadvertently increase toxicity by several orders of magnitude, which means the regular assumption of "minimal exposure" due to low dose is incorrect. Thus, **FDA should require full EA and EIS (environmental impact statements) for all uses of ENMs, regardless of whether a categorical exclusion appears to apply**.

One potential class of food packaging substance that we are particularly concerned about is the use of FCS for microbiocidal purposes. An example would be the use of silver nanoparticles or silver ions for antimicrobial purposes. There are food containers that are impregnated with nanosilver that supposedly help keep food "fresher" by retarding microbial growth. Presently, for microbial biocides (e.g. antibiotics) in food packaging materials (e.g. indirect food additives), FDA requires a food additive petition when the FCS (food contact substance) use increases dietary exposure to the substance above 200 ppb (parts per billion). Given the uncertainties surrounded potentially toxicology of ENMs for such uses, **FDA should require full food additive petitions for any use of ENMs in FCS having biocidal activity, regardless of the exposure level in the diet.**

Since nano silver is being used for microbiocidal purposes in some many different products—at least 260 consumer products, according to petition sent to EPA, and signed by Consumers Union[7]—including food containers, slippers, socks, bandages, dietary supplements, **as part of the EA, FDA should require that human exposure to nano-silver from *all sources and products* be looked at together/collectively rather than separately, to get an idea of overall exposure, before granting a FAP for such use**. Since EPA has said they will regulate such products as pesticides, FDA should coordinate any such analysis with EPA.

In addition, the environmental impact of all that nano-silver being released into the environment should be considered as well. A full life-cycle analysis should be used. For example, for ENMs in packaging materials such as beverage liners or pizza box containers, what happens when those packages are recycled or discarded in the

[6] 21 CFR § 25.21
[7] http://www.icta.org/global/actions.cfm?page=15&type=364&topic=8

environment? In doing an EA based on a full life-cycle analysis, FDA should, where necessary, work in coordination with other agencies including the EPA and OSHA

3. What physical characteristics of food-related nanoscale materials are of greatest concern regarding the safety of dietary consumption?

The two characteristics of greatest concern are the fact that the materials are nanoscale and that the materials/particles can exist in free form (and may be coated) or can migrate from packaging into food. The fact that nanoscale materials can have orders of magnitude more surface area than regular scale materials is most worrisome. Greater surface area means potentially greater reactivity, and, as the Royal Society reported, "evidence that increased surface area can lead to greater toxicity per unit mass." We agree with the Royal Society that this potentially greater toxicity per unit mass for nanoparticles means that should be viewed differently than normal size particles. The example of 100 grams of lead is instructive here, as discussed earlier. If toxicity were solely based on surface area, reducing to a nanosize can increase toxicity more than 100,000 fold. Thus, what were previously considered small quantities, and thus of little toxicological concern, can become a concern if the particles are nanosized. **Thus, thresholds for toxicity testing may need to be reduced for ENMs**. At present, FDA's toxicology guidance uses a dietary concentration of 50 parts per billion (ppb) as the trigger for toxicity testing of food contact substances. Given the uncertainties with ENMs, we feel that **FDA should require full food additive petitions for any use of ENMs in FCS, regardless of the exposure level in the diet.**

The potentially greater surface area also means potentially greater bioavailability of ENMs as food additives or ingredients, which could mean greater toxicity. Take lycopene, for example. A company, NutraLease Inc., has an encapsulation technology, called "Fortifying nanovehicles" (FNVs), that it uses to increase the bioavailability of various compounds, including lycopene. NutraLease present data showing that lycopene FNVs can deliver up to 3 times the amount of lycopene in the bloodstream compared to eating fresh tomatoes[8]. FDA recently approved a lycopene product for use as a color additive, but it is unclear if a lycopene FNV could be used under this condition. We would hope not. Though lycopenes benefits have been well documented, a maximum tolerable upper limit for lycopene has not been established and it is unclear what, if any harmful effects might occur at high doses attained with the nanoengineered form.

Another characteristic of ENMs that causes a nano-specific toxicology issue in addition to surface area and reactivitys that their The smaller size of some nanoparticles makes them able to bypass the immune system and enter cells directly through the cell membranes and so to be able to persist and accumulate in the body.

5. **Are the current FDA Redbook toxicological endpoints and array of toxicity tests used sufficient to describe the toxicity for their nanoscale counterparts, or must new endpoints and assays be considered? Are you aware of any other toxicity tests not**

[8] Nutralease. At: http://www.nutralease.com/t_experiments.asp

presently in wide use that may be more suitable? Are their toxicity tests that could be used to bridge data on macroscale ingredients to their nanoscale counterparts?

Present toxicological endpoints and toxicity tests will probably be inadequate to sufficiently describe the toxicity of ENMs. At present basic questions exist about the ability to adequately characterize and measure nanoparticles and their properties. Even the ability to accurately measure the size of some ENMs is sorely lacking. It is known that nanoparticles/ENMs may change their surface charge or particle-size characteristics depending on their chemical context, which greatly complicates any toxicology testing, as the ENM may behave in one way when part of the packaging material, and in a different way when it has migrated into the food matrix of the packaged item. Thus, the toxicology tests must be based on the substance that the consumer will be exposed to, which, in turn, must be related in a reliable, reproducible way to the identity of the FCS (food contact substance). Thus, the methodology and validation for the migration studies may be affected. Additional toxicology tests could include techniques for determining accumulation of ENMs in various tissues or protocols to understand the transformation of ENMs in the body. There are so many unanswered questions in this area that FDA must put more funding into answering such questions.

However, several expert working groups, including ones involving many different sectors of the government, have recommended that nano-scale materials need additional or modified testing to characterize their unique absorption, distribution, metabolism and elimination mechanisms that enable greater contact with specific organs, tissues, cells and proteins and potentially greater overall body burdens than conventional substances. FDA should consider requiring a battery of tests that includes those that expert working groups recommend, such as tests for oxidative stress, C-reactive protein, platelet aggregation and other immune and inflammatory responses, GFAP (a biomarker for neuro-toxicity) and genetic toxicity.[9]

7. **How can FDA better communicate issues of regulatory status and safety of food ingredients and packaging components derived from nanotechnology to the public and industry?**

FDA should be more open and transparent in this area. To gain public confidence, FDA should announce that it will recognize that ENMs constitute novel materials that they must therefore undergo a full food or color additive petition before being used as either a direct or indirect (e.g. part of food packaging) food additive. FDA should also say that all ENMs should undergo an EA prior to approval.

Most importantly, FDA should also announce that it will require labeling for all products that contain ENMs. Because nanoparticles have different properties, their presence constitutes a "material fact" that should be disclosed to consumers.

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[9] US DHHS, National Toxicology Program, National Science Foundation, US Environmental Protection Agency, US Air Force, Office of Sponsored Research, University of Florida, "Final Report: Workshop on Developing Experimental Approaches for the Evaluation of Toxicological Interactions of Nanoscale Materials," November 3-4, 2004. AND European Commission Scientific Committee on Emerging and Newly Identified Health Risks, "modified opinion on The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies," adopted 10 March, 2006.