Consumers Union
NONPROFIT PUBLISHER OF CONSUMER REPORTS
101 Truman Avenue, Yonkers, New York 10703-1057
914-378-2000

Comments of Consumers Union At the FDA Nanotechnology Public Meeting
Break out Session on Prescription Drugs, including biological drugs,
animal drugs and over-the-counter (OTC) drugs, including Sunscreens
by Carolyn Cairns
Program Leader
September 8, 2008

Consumers Union appreciates the opportunity to comment once again on the need for FDA to regulate nano-engineered materials as unique substances, which may pose different biological risks than their larger counterparts. It has been 2 years since FDA's first public meeting on this issue and over a year since the Task Force report was issued. In the meantime many new products have reached store shelves with untested engineered nano-materials (ENMs). We hope FDA will use the results of this meeting to greatly accelerate regulatory efforts and that we won't be here two years from now, still waiting for action to be taken.

In my comments today I will discuss both what we do know about the unique hazards associated with nanomaterials, and what we yet need to know in order to ensure that their use in foods, drugs and cosmetics is safe. FDA's delay in making nano-specific safety testing a pre-requisite for approval impedes the development of critical analytical tools needed to characterize the presence, toxicity and fate of ENMs already in commerce. FDA should not approve nanoscale ingredients in the face of such ignorance, particularly for widespread, exposure-intensive applications of questionable medical benefit.

Consumers Union has been investigating potential risks and benefits from nanomaterials in consumer products for several years and our comments are based on our own research and tests of several nano-enabled products, including sunscreens. Our recommendations about the type of analytical data that FDA should be demanding for pre-market approval of new drugs and over-the-counter treatments can be summarized as follows:

1. Treat nano-materials as new across the board and drop Generally Recognized as Safe (GRAS) status for all nanoscale ingredients.
2. Require all nanomaterials to be characterized according to features known to impact safety (such as size, charge, shape and surface coatings and purity) using validated testing and standardized nomenclature.
3. Build product-specific risk analysis procedures to assess the direct and indirect impacts and fate of nanomaterials in the systems in which they will be used including their interactions with excipients.

4. Where results of product-specific exposure, toxicity and efficacy tests are available for safety analysis, ensure that they accurately reflect the true conditions in which the products will be used.

Question 1. Are there general parameters or screening tools by which to evaluate the likelihood that a particular material might have nanoscale-specific properties and to decide when and what sort of further evaluation might be warranted? Are there characteristics that FDA can use to broadly categorize materials with respect to their likelihood of having nanoscale-specific properties that warrant further review?

Generally, No. Substances are being manipulated at the nanoscale to achieve a wide range of changes in chemical and physical properties, the biological impacts of which will be unique to the specific changes made and the behavior and fate of engineered nanomaterials (ENMs) in the products in which they are used. As such, they all warrant further review. Therefore, FDA must require safety assessments in the form of new drug petitions for all ENMs, even if macro-scale versions of the substances have already entered the marketplace. We have said before that companies need to disclose to FDA and the public when they develop new materials with features at the nanoscale.[1] FDA should be regulating drugs not on a likelihood assessment, but based on detailed knowledge about the specific nanoscale properties of the materials in question.

We do know that nanoscale properties such as size, morphology and charge can greatly change toxicity. The Royal Society and other expert bodies have detailed some of the types of nanoscale features known to impact safety.[2][3] The tremendous increase in the ratio of surface area-to-mass of nanoscale materials, alone can greatly increase reactivity and toxicity, thereby calling into question the traditional mass-based approach to regulating exposure and predicting toxicity.[2] Therefore, FDA needs to mandate disclosure of new nanoscale ingredients, and regulate them as new.

Researchers at the University of Oregon and Oregon State University have made some progress in developing a database to begin to develop the most rudimentary toxicity screens.[4] However, far from being predictive, these tools are still being developed and the data are not sufficient or appropriate to draw any universal conclusions about structure-activity relationships. Given the number of variables that can be altered in the development and use of nanoscale materials, it's hard to see how broad generalizations about the safety of all combinations of nanoscale materials in products can be made. Further, tests characterizing nanomaterials in their pure form, may not predict the activity

---

[1] Consumers Union Comments to the Food and Drug Administration Regarding Use of Nanoengineered Materials, October 6, 2006.
[2] Royal Society and Royal Academy of Engineering, 2004, Nanoscience and Nanotechnologies, p.85-88.
[3] International Council on Nanotechnology, No.4, May 1, 2008, Towards Predicting Nano-bio Interactions: An International Assessment of Nanotechnology Environmental Health and Research Needs.
[4] Hutchison, JE, Greener Nanoscience: A Proactive Approach to Advancing Applications and Reducing Implications of Nanotechnology, ACSNano, Volume 2, No.3, 395-402, 2008; Nanomaterial Biological Interactions KnowledgeBase http://oregonstate.edu/nbi/pages/#

of such materials in product formulations. Thus, Consumers Union believes that all nanomaterials warrant detailed safety evaluations and FDA review, and should not be granted Generally Recognized as Safe (GRAS) status.

Question 2. What are the unique manufacturing features of products containing nanoscale materials and how should these be evaluated? Can nanoscale materials affect product formulation, components, excipients and processing?
Nanoscale materials, related contaminants, impurities and variability may affect the efficacy and toxicity of consumer products and other materials with which they interact. For example, nanoscale titanium dioxide used in sunscreens can be in the rutile or anatase forms, and it can be coated with aluminum or silica. These differences can affect reactivity and possibly toxicity, bioavailability and efficacy of formulations.[5] The recent finding that nanoscale titanium dioxide in sunscreen degrades metal surface coatings raises many concerns about the reactive nature of many nanomaterials. [6] The fact that under certain conditions some nanomaterials can change form (e.g. anatase to rutile TiO_2) or charge also raises many concerns about the stability of nanomaterials in these products.[7]

The reactive nature of many nanomaterials makes it difficult to ensure product purity or to know how nanoscale features are accounted for in product specifications. The expense and technical difficulty of analyzing nanoscale ingredients alone and in formulation make it unlikely that companies using them would do testing necessary to ensure purity, particularly if contamination does not significantly affect product functionality. For these reasons, FDA should insist that manufacturers establish and carry out detailed methods for characterizing nanoscale ingredients in the forms and formulations in which they are used.

The current FDA monographs for sunscreen active ingredients do not include any requirements for disclosure or control of such critical characteristics, nor do we know how much, if any of this detail is specified by suppliers or formulators.[8] Potentially misleading terms like "micronised" are not defined and yet are widely used in ways that confuse consumers about whether nanoscale materials are present in consumer products. Our tests of leading brands of sunscreens found nanoparticles (less than 100 nm in 2 or 3 dimensions) and/or nanostructured particles (less than 100 nm in one dimension) in every mineral-based sunscreen product we have tested. But few products provide any indication of the size or nature of the mineral, other than, in a few cases, use of the term "micronised."[9]

---

[5] Y.H. Tseng et al., Thermostability of TiO2 nanoparticles and its photocatalytic Reactivity at Different Anatase/Rutile Ratio. Paper presented at Nnaotech Nanotechnology Conference and Trade Show, 2006.
[6] Bakers, P., A. Branch, The Interaction of Modern Sunscreen Formulations with Surface Coatings, Progress in Organic Coatings 62(2008) 331-320.
[7] H. Shin et al., Crystallization Process of TiO2 Nanoparticles in Acidic Solutions. Chemistry Letters Volume 33 (2004), No. 10, p. 1382.
[8] Federal Register Volume 72, No. 165, Monday August 27, 2007.
[9] Consumer Reports, July 2007, Nanotechnology Untold Promise, Unknown Risks.

Finally, it is clear that ENMs have the potential to interact adversely with other ingredients in the same product or with concurrently used products. FDA is aware of the research findings that indicate that mineral based sunscreens, which likely contain nanoscale forms of the minerals, increased dermal absorption of the insect repellant DEET.[10] FDA should require safety tests that characterize the impact of ENMs on absorption and toxicity of pesticides and other biologically active ingredients used in formulations with ENMs.

Question 3. What are unique physiochemical attributes of products containing nanoscale materials? How do they affect characteristics and performance of a product?

The nature of the properties of ENMs depends on how they are changed from their macroscale counterparts at the nanoscale. The increase in surface area that is created when a material is reduced to or created in the nanoscale often brings changes in reactivity. Shape, size charge, structure and surface coatings and functional groups are some of the basic characteristics recognized for their potential to greatly impact the fate and reactivity of materials in biological systems.[2] Smaller particles can evade the immune system[11] or pass through the blood-brain barrier or directly enter cells and their nuclei[12], etc. and reach parts of the body that conventional-scale materials cannot.

Additional concerns about ENMs relate to the end of product life. The accumulation of conventional pharmaceuticals in drinking water and environmental media has long been documented[13] and there is no reason to expect that nanoscale materials would be any different. In considering new product approvals involving nanoscale ingredients, FDA should evaluate the possible downstream impacts of their use to ensure that they do not threaten human or environmental health.

Question 4. What has been your experience to date with products containing nanoscale materials and/or have you avoided these products due to concerns about development and manufacturing of these products?

Our tests of nano-formulated sunscreens suggest that their performance varies considerably. Some products formulated with nanoscale titanium or zinc oxides performed well and others did not; none provided greater UVB or UVA protection than other sunscreens in our tests.[14]

---

[10] Brand, RM, L. McMahon, JL Jendrzejewski, AR Charron. 2007. Transdermal absorption of the herbicide 2.4-dichlorophenoxyacetic acid is enhanced by both ethanol consumption and sunscreen application. *Food Chem Toxicol* 45 (1):93-7; Gu,X, T Wang, DM Collins, S Kasichayanula, FJ Burczynski, 2005. In vitro evaluation of concurrent use of commercially available insect repellent and sunscreen preparations. *Br J Dermatol* 152(6):1263-7. Brand, RM., J Pike, RM Wilson, AR Charron. 2003. Sunscreens containing physical UV blockers can increase transdermal absorption of pesticides. *Toxicol In Health* 19(1):9-16

[11] http://nano.cancer.gov/news_center/monthly_feature_2006_sep.asp

[12] 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

[13] Kolpin, DW et al., Pharmaceuticals, Hormones and Other Organic Wastewater Contaminants in US Streams, 1999-2000: A National Reconnaissance, Environmental Science and Technology, 2002, March 15 36(6) 1202-11.

[14] Consumer Reports 2007, Sunscreens: Some are Short on Protection.

Many consumers have expressed concerns about the safety of ENMs in consumers products, including sunscreens. Because nanoparticles have different properties, their presence constitutes a "material fact" that should be disclosed to consumers. FDA should require mandatory labeling for all products that contain ENMs..

Question 5. What additional questions focusing on characterization and manufacturing aspects of products containing nanoscale materials should be addressed in this forum or brought to the attention of CDER?

Due to the variable and reactive nature of nanomaterials, it is particularly important that assays to evaluate exposure and toxicity of ENMs accurately reflect their conditions of use. For example, research shows that some nanomaterials can penetrate bent, burned or broken skin, but not intact skin. Assays to evaluate dermal absorption of ENMs should consider the effects of skin damage, pore size and hair follicles in assessing the integrity of skin as a barrier to ENMs. Likewise, tests that evaluate efficacy of all drugs and therapeutic treatments must take into account formulations and not rely exclusively on behavior of active ingredients alone in laboratory tests.

Finally, FDA should build and mandate the use of product-specific risk assessment procedures for ENMs that examine unique toxicity and exposure endpoints not likely to be detected with standard assays for conventionally sized materials. 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.[2,3,15]

---

[15] 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.