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Comments from the Natural Resources Defense Council on nanoparticles in sunscreens, cosmetics, and personal care products

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FDA proposed regulation

The U.S. Food and Drug Administration proposed a new regulation that sets standards for formulating, testing and labeling over-the-counter (OTC) sunscreen drug products with ultraviolet A (UVA) and ultraviolet B (UVB) protection. Our comments are directed to the proposed regulation to amend the existing over-the-counter (OTC) sunscreen rule published in 1999 that established regulations related to UVB light and mandated that OTC UVB sunscreen products be labeled with a SPF. FDA also is amending its existing 1999 rule to increase the SPF from SPF30+ to SPF50+. Additionally, the proposed rule:

- revises the existing SPF (UVB) testing procedures;
- allows new combinations of active ingredients; and
- asks for comments on the issue of nanoparticles.

Summary

An explosion of nanotechnology research has lead to a variety of promising new discoveries ranging from potential cancer treatments and energy production methods to the prevention of coffee stains, skin wrinkles, and bad hair days. While little is understood about the potential health and environmental implications of the widespread use of nano-sized chemicals, preliminary research indicates that there is cause for concern.

The Project on Emerging Nanotechnologies Consumer Product Inventory[1] identifies over twenty-five specific and generic nanotechnology sunscreens from the United States and abroad (search term 'sunscreen', December 2007). When reduced to very small sizes, titanium dioxide and zinc oxide continue to provide protection from ultraviolet light but without scattering light; thus, they can be applied to the skin as a clear, rather than white, cream, which is thought to be cosmetically advantageous. Companies are claiming that the nano-scale ingredients are 'micronized', which means that the chemical additive is ground down to a distribution of sizes that is likely to include particles of less than 100 nanometers (nm). In any case, though, it is clear that the 'micronized' chemicals are 'purposefully engineered to achieve size-dependent properties and functions' (see comments below on definition of nanotechnologies), and therefore should be considered by FDA as 'new for legal and regulatory purposes'. (See detailed comments below). This recommendation by NRDC was also made by Michael Taylor is his 2006 report, *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs* [2]

FDA must clarify its definition nanotechnologies

FDA has been wise about not limiting its definition of nanotechnologies and nano-enabled to a specific size range (FDA nanotechnology report, July 20007, p 6). However, the FDA will need to establish clear criteria for classifying nanomaterials, nano-intermediates, and nano-enabled products as "new" for legal and regulatory purposes and as "new" for safety evaluation purposes. Under the Federal Food, Drug and Cosmetics Act (FFDCA), 21 U.S.C, §§ 301 et seq., there are categories of products, such as cosmetics, that do not require pre-market notification or pre-market approval from FDA; however, with the increasing inclusion of nano-engineered particles in cosmetics, the assumption that cosmetics applied externally pose little safety concern no longer holds, As such, FDA must provide a clear guide to industry in determining whether a product poses a new safety question and how the Agency intends to exercise its authority. NRDC

[1] Project on Emerging Nanotechnologies. A nanotechnology consumer products inventory. http://www.nanotechproject.org/44

[2] *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs?,*[2] Michael R. Taylor (2006) Report available at http://www.nanotechproject.org/reports

recommends that this definition be capable of identifying all nano-enabled products, nano-intermediates, and nanomaterials where they are purposefully engineered to achieve size-dependent properties and functions. This would exclude accidental, natural, and incidental nanomaterials, but would capture nanomaterials and products containing nanomaterials that fall outside a rigid and unscientific definition based exclusively on size, if they are engineered specifically to take advantage of size-dependent properties and functions.

GRAS list materials should be reevaluated for safety where they are used not in conventional form, but in a form that is purposefully engineered to achieve size-dependent properties and functions

Under the FFDCA, materials that are "generally regarded as safe" (GRAS) are subject to much less stringent requirements. See e.g., 21 U.S.C. § 346a(k). For example, food additives, which generally would require pre-market review and approval from FDA, do not if they are identified as GRAS. See e.g. 21 U.S.C. § 321(s). To assure that nano-materials do not fall through this hole, any materials that are listed as GRAS in conventional form should be considered "new" for legal and regulatory purposes and be required to undergo reevaluation for safety and regulation when they are not in conventional form. Specifically, those materials that are in a form that is purposefully engineered to achieve size-dependent properties and functions should be considered "new" and not GRAS. If FDA fails to require this, then manufacturers may believe that they have no legal requirement to seek FDA pre-market review and approval, and thus FDA may not even be aware of the use of nanotechnologies in the product. This recommendation by NRDC was also made by Michael Taylor is his 2006 report, *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs* [3]

Nano-enabled products, nano-intermediates, and nanomaterials should be reevaluated for safety where they are used not in conventional form, but in a form that is purposefully engineered to achieve size-dependent properties and functions

Any materials should be considered "new" for legal and regulatory purposes and should undergo reevaluation for safety and regulation where they are used not in conventional form, but in a form that is purposefully engineered to achieve size-dependent properties and functions. This definition should include the use in sunscreens of micronized titanium dioxide and nano-scale zinc oxide. If FDA fails to require this reevaluation, then manufacturers may believe that they have no legal requirement to seek FDA pre-market review and approval, and thus FDA may not even be aware of the use of nanotechnologies in the product. This recommendation by NRDC was also made by

[3] *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs?,*[3] Michael R. Taylor (2006) Report available at http://www.nanotechproject.org/reports

Michael Taylor is his 2006 report, *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs* [4]

FDA must clarify that 'micronized' means nanomaterial

Where micronized titanium dioxide and nano-scale zinc oxide are used in over-the-counter sunscreens, FDA must clarify that this sunscreen is now a nano-enabled product, and contains nanomaterials that are 'new for legal and regulatory purposes'. These products should be reevaluated for safety and regulation. If FDA fails to clarify this, then public confidence in FDA's ability to monitor the safety of sunscreens will erode. This recommendation by NRDC was also made by Michael Taylor is his 2006 report, *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs* [5]

Failure to label, failure to warn

Nanoscale materials are already present in dozens of popular personal care products including anti-aging creams, sunscreens, shampoos, blushes, bronzers and other cosmetics that consumers apply to their skin daily. Unfortunately, there is little information available to the public about which products contain nanoscale ingredients and how, if even, these ingredients were tested for safety. Many manufacturers seem reluctant to disclose the presence of nanomaterials in their products, frequently using more appealing and ambiguous terms like 'ultra-fine' or 'micronized.' They also often fail to specify what the nanoscale material is, advertising that a product is 'made with nanotechnology' or with ingredients like 'novasomes' or 'nanocapsules.' Some manufacturers entirely omit any mention of nanoscale ingredients. Ironically, because of the lack of labeling laws, some companies are falsely claiming that their products are enhanced by nanotechnology, leaving consumers completely unable to make informed purchasing decisions.

Despite repeated requests from the public (for example, see citizens petition by Friends of the Earth and ICTA) FDA continues to fail to require mandatory labeling of consumer products that contain nanomaterials.

In stark and refreshing contrast to the FDA, the EU Directorate-General of Health & Consumer Protection (DG SANCO), Robert Madelin, is a strong and vocal advocate for the public's right to know what is in consumer products:

> "*When you tell me it's out there already, I get worried. I'm not stupid, but when you don't give me information than I am stupid. Companies are*

[4] *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs?,*[4] Michael R. Taylor (2006) Report available at http://www.nanotechproject.org/reports

[5] *Regulating the Products of Nanotechnology: Does FDA Have the Tools it Needs?,*[5] Michael R. Taylor (2006) Report available at http://www.nanotechproject.org/reports

> *hiding things because they think that the public doesn't need to know, or that companies don't want to talk about it until the definitions and testing standards are established. And, then, when things go wrong industry "will come crying to me and ask me to fix it" because industry "screwed up from the beginning."* [6]

NRDC strongly supports the comments of Madelin. The issue of consumer product labeling is about the public's right to know and to make informed choices. The arguments put forth by industry and FDA fall flat. Yes, we need to provide accurate information to the public, and yes, we need to develop standard definitions, testing methods, and health assessments. But, nanomaterials are already in hundreds of consumer products, including food packaging, without having undergone safety testing, and the public has a right to know. Regulators have an obligation to provide information, oversight, and public protection.

Potential health risks from nanomaterials used in sunscreens and cosmetics

Laboratory and epidemiological studies report that some nanomaterials pose serious health risks. Occupational exposure to nano-zinc oxide at legal workplace limits caused adverse health effects in workers,[7] while inhalation of nano-titanium dioxide led to lung inflammation and lung scarring in rodents.[8] Computer simulations indicate that fullerenes (carbon buckyballs) have the ability to interact with cellular DNA.[9] Consumers using certain sunscreens or anti-aging (wrinkle) creams currently on the market give themselves a daily exposure to these potentially harmful nanoscale ingredients, while workers in certain industries inhale and handle these nanomaterials throughout the work week. (See Appendix A for toxicological summaries.)

Potential environmental risks from nanomaterials used in sunscreens and cosmetics

Nanomaterials also pose an environmental risk. Many are highly chemically reactive, are long-lasting, and have the capacity to linger in the environment. These characteristics could exacerbate any adverse ecological impacts of these same materials. Several studies have documented the potential for chemicals at the nanoscale to be much more damaging to plants and aquatic organisms than their normal-scale counterparts. For example, while

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[6] Jennifer Sass's blog. Europe vs. USA: labeling of nano-enabled consumer products. October 30, 2007. http://switchboard.nrdc.org/blogs/jsass/europe_vs_usa_labeling_of_nano.html

[7] J.M. Fine, et al., "Metal Fume Fever: Characterization of Clinical and Plasma IL-6 Responses in Controlled Human Exposures to Zinc Oxide Fume at and Below the Threshold Limit Value," *Journal of Occupational and Environmental Medicine*, Vol. 39, No. 8 (Aug. 1997), pp. 22-6.

[8] R.B. Baggs, J. Ferin, and G. Oberdorster, "Regression of Pulmonary Lesions Produced by Inhaled Titanium Dioxide in Rats," *Veterinary Pathology*, Vol. 34, No.. 6 (1997), pp. 592-7.

[9] X. Zhao, A. Striolo, and P.T. Cummings, "C60 Binds to and Deforms Nucleotides," *Biophysical Journal*, Vol. 89, No. 6 (Dec 2005), pp. 3856-62. Epub Spt. 23, 2005.

normal sized aluminum particles have no impact on stem cells, aluminum nanoparticles were shown to be toxic to mouse stem cells in lab studies.[10] Aluminum oxide nanoparticles stunted root growth in several important crop species including corn and soybeans, while the normal-scale aluminum at the same concentration had no effect.[11] Carbon fullerenes and nano-titanium dioxide both proved under some conditions to be much more toxic to aquatic life than their normal-scale counterparts under identical test conditions.[12] (See Appendix A for toxicological summaries.)

FDA's failure to use its regulatory authority puts the public at risk

NRDC recognizes the severe budget and resource constraints of the FDA to effectively oversee nanotechnologies, develop safety-testing protocols and detection methods, and expand in-house expertise. NRDC also recognizes the limitations of FDA's authorities to regulate sunscreens, cosmetics, and personal care products that contain nanomaterials. Nonetheless, the failure of FDA to exercise its existing authorities to implement even the basic oversight and regulation that is recommended in these comments will erode public confidence in FDA, compromise the reliability of nanotechnologies, and put public health at risk.

Relying on industry to self-regulate is a nightmarish abdication of existing FDA authorities. After analyzing over 200 voluntary programs, scientists Steffen Hansen and Joel Tickner published their findings about the necessary characteristics for developing successful voluntary programs.[13] According to the authors, the key elements of successful programs include the following: 1) Clear incentives to participate for various stakeholders (reduced costs, high publicity, agency guidance and technical assistance); 2) Signed commitments and periodical reporting; 3) Quality of information; 4) Transparency in design, reporting and evaluation (e.g. a clear baseline to measure development against; stakeholder involvement; public access to information to enhance their overall legitimacy); 5) Regulatory threat (threatening a harsher outcome, such as legislation, if a voluntary agreement is not reached).[14] Overall, the two scientists

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[10] L. Braydich-Stolle, et al., "In Vitro Cytotoxicity of Nanoparticles in Mammalian Germline Stem Cells," *Toxicological Science*, Vol. 88, No. 2 (December 2005), pp. 412-9. Epub July 13, 2005.

[11] L. Yang and D.J. Watts, "Particle Surface Characteristics May Play an Important Role in Phytoxicity of Alumina Nanoparticles, *Toxicology Letters*, Vol. 158, No. 2 (2005), pp. 122-32.

[12] S. Lovern and R. Klaper, "Daphinia Magna Mortailty When Exposed to Titanium Dioxide and Fullerene Nanoparticles," *Environmental Toxicology and Chemistry*, Vol. 25, No. 4 (Apr. 2006), pp. 1,132-7.

[13] Hansen SF, Tickner J. 2007. The Challenges of Adopting Voluntary Health, Safety and Environment Measures for Manufactured Nanomaterials: Lessons From the Past For More Effective Adoption in the Future. Nanotechnology Law & Business, 4(3). http://www.nanolabweb.com/index.cfm/action/main.default.viewArticle/articleID/211/CFID/1208156/CFTOKEN/40563212/index.html

[14] Discussed on Jennifer Sass's blog. Voluntary management of nano risks likely to fail. December 6, 2007. http://switchboard.nrdc.org/blogs/jsass/voluntary_management_of_nano_r.html

concluded that current voluntary programs overseeing manufactured nanomaterials have serious limitations.

The public does not trust the regulated industry to manage risk that it has created and neither should FDA.

Thank you for the opportunity to provide comments. We look forward to working with the FDA to increase the resources and authorities necessary for the Agency to protect human health by identifying and eliminating (or limiting) the risks associated with these new technologies.

APPENDIX A:

Selected Published Studies of Potential Risks of Nanoscale Materials in Sunscreens and Cosmetics

Nanomaterial	Cosmetic Applications	Health and Environmental Concerns
Carbon C60 (Buckyballs or Fullerenes)	Anti-aging (wrinkle) Creams	A study using detailed computer simulations suggested that, once inside body tissues, C60 could interact with cellular DNA, causing it to deform and almost surely preventing it from functioning normally. [15] This suggests that C60 may cause irreversible damage including cancer. If sperm and egg cells were to be affected, the damage could be inherited by the offspring of exposed individuals. Although C60 tends to be insoluble as single particles, it more often exists as crystalline aggregates. These aggregates have been reported to be toxic to bacteria, suggesting that they may have unintended impacts on ecosystems. [16] How the surface characteristics of C60, and all nanomaterials, are modified has been shown to greatly impact the material's toxicity, bioavailability, solubility, and other properties associated with toxicity.
Nano-titanium Dioxide (nano TiO_2)	Sunscreens, Lotions, Makeup	A 1992 study reported that rodents that inhaled nano-titanium dioxide (20 nm) for three months under conditions simulating occupational exposures (six hours a day, five days a week) had significantly more lung inflammation and scar tissue compared with those that inhaled larger titanium dioxide particles (250 nm).[17,18] Multiple laboratories have reported that nano-titanium dioxide particles are toxic to human and animal cells, and to aquatic organisms, in the presence of ultraviolet illumination (photoactivation), likely through the generation of toxic reactive oxygen species, making its use in sunscreen and skin cream unwise[19] Nano-titanium dioxide caused dose-dependent damage and death to water fleas, whereas at the same dose the conventional-sized chemical had no effect.[20]

[15] X. Zhao, A. Striolo, and P.T. Cummings, "C60 Binds to and Deforms Nucleotides," *Biophysical Journal*, Vol. 89, No. 6 (Dec 2005), pp. 3856-62. Epub Spt. 23, 2005.

[16] J.D. Fortner, et al., "C60 in Water: Nanocrystal Formation and Microbial Response," *Environmental Science and Technology*, Vol 1, No. 39 (June 2005), pp 4,307-16.

[17] G. Oberdorster, et al., "Role of the Alveolar Macrophage in Lung Injury: Studies with Ultrafine Particles," *Environmental Health Perspectives*, 97 (1992), pp. 193-9.

[18] R.B. Baggs, J. Ferin, and G. Oberdorster, "Regression of Pulmonary Lesions Produced by Inhaled Titanium Dioxide in Rats," *Veterinary Pathology*, Vol. 34, No.. 6 (1997), pp. 592-7.

[19] T.C. Long, et al., "Titanium Dioxide (P25) Produces Reactive Oxygen Species in Immortalized Brain Microglia (BV2): Implications for Nanoparticle Neurotoxicity," *Environmental Science and Technology*, Vol. 40, No. 14 (2006), pp. 4,345-52.

[20] S. Lovern and R. Klaper, "Daphinia Magna Mortailty When Exposed to Titanium Dioxide and Fullerene Nanoparticles," *Environmental Toxicology and Chemistry*, Vol. 25, No. 4 (Apr. 2006), pp. 1,132-7.

Nano-zinc Oxide	Sunscreens, Lotions, Makeup	Because zinc oxide is also a common workplace air pollutant, its risks have been documented as metal fume fever. In a 1997 study designed to evaluate occupational exposures, 13 adults reported fever, cough, and fatigue after two hours of inhaling normal-scale zinc oxide fumes (100-1,000 nm diameter) at the workplace allowable limit)[21] A study of adult mice reported that gastrointestinal dosing with either nano-zinc oxide or larger particles resulted in much more severe symptoms in the nano-treated group, including lethargy, vomiting, diarrhea, and two deaths due to obstruction of the intestines by aggregated nano-zinc oxide.[22] In laboratory guinea pigs, inhalation of levels comparable to occupational exposure reduced lung function.[23]
Aluminum and Alumina (Aluminum oxide) Nanoparticles	Makeup	Normal-scale aluminum has been shown to disrupt bone formation, induce microcytic anemia, cause brain damage in patients w/ impaired kidney function, and impair parathyroid function.[24,25] In an *in vitro* assay, nanoscale Aluminum was toxic to mouse stem cells.[26] Alumina nanoparticles stunted root growth of corn, cucumbers, cabbage, carrots and soybeans within 24 hours of exposure through water.[27]

Note: For more detailed descriptions of these materials and current understanding of their potential risks please see the NRDC report released May 2007 titled, "Nanotechnology's Invisible Threat: Small science, big consequences. Available at www.nrdc.org/health/science/nano/nano.pdf.

[21] J.M. Fine, et al., "Metal Fume Fever: Characterization of Clinical and Plasma IL-6 Responses in Controlled Human Exposures to Zinc Oxide Fume at and Below the Threshold Limit Value," *Journal of Occupational and Environmental Medicine*, Vol. 39, No. 8 (Aug. 1997), pp. 22-6.

[22] B. Wang, et al., "Acute Toxicity of Nano- and Micro-scale Zinc Powder in Healthy Adult Mice," *Toxicology Letters*, Vol. 161, No. 2 (Feb. 2006), pp. 115-23.

[23] M. Conner, et al., "Lung Injury in Guinea Pigs Caused by Multiple Exposures to Zinc Oxide Mixed with Sulfer Dioxide in a Humidified Furnace," *Journal of Toxicology and Environmental Health*, Vol. 16, No. 1 (1985), pp. 101-114.

[24] A. Becaria, A. Campbell, and S.C. Bondy, "Aluminum as a Toxicant," *Toxicology and Inudstrial Health*, Vol. 18, No. 7 (Aug. 2002), pp. 309-20. Review.

[25] Y. Iwasaki, et al., "Uremic Toxin and Bone Metabolism," *Journal of Bone Mineral Metabolism*, Vol. 24, No. 2 (2006), pp. 172-5. Review.

[26] L. Braydich-Stolle, et al., "In Vitro Cytotoxicity of Nanoparticles in Mammalian Germline Stem Cells," *Toxicological Science*, Vol. 88, No. 2 (December 2005), pp. 412-9. Epub July 13, 2005.

[27] L. Yang and D.J. Watts, "Particle Surface Characteristics May Play an Important Role in Phytoxicity of Alumina Nanoparticles, *Toxicology Letters*, Vol. 158, No. 2 (2005), pp. 122-32.