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Cosmetic, Toiletry, and Fragrance Association

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September 19, 2006

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President & CEO

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Comments of the Cosmetic, Toiletry, and Fragrance Association Regarding the Scientific and Legal Issues Associated With Nanotechnology in Personal Care Products; Docket Number: 2006P-0210.

Dear Sir or Madam:

The enclosed comments are submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in response to the Citizen Petition submitted by the International Center for Technology Assessment and other parties entitled, *Petition to FDA to Amend its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically.* CTFA's comments are intended to provide the Association's views on the scientific and legal issues associated with the use nanotechnology in personal care products.

CTFA is the national trade association representing the cosmetic and personal care products industries. Founded in 1894, CTFA has almost 600 members whose businesses formulate, manufacture, distribute and market personal care products. Our members manufacture or distribute the vast majority of personal care products sold in the United States.

Respectfully submitted,

Elizabeth H. Anderson

Elizabeth H. Anderson
Executive Vice President –
Legal & General Counsel

cc: Charles Ganley, M.D.
Linda Katz, M.D.

Enclosures

2006P-0210 C2

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Comments of the Cosmetic, Toiletry, and Fragrance Association (CTFA) Regarding the Scientific and Legal Issues Associated With Nanotechnology in Personal Care Products

Submitted in Regard to Docket Number 2006P-0210: Petition to FDA to Amend its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically

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These comments are filed on behalf of the Cosmetic, Toiletry, and Fragrance Association (CTFA). CTFA is the national trade association representing the cosmetic and personal care products industries. Founded in 1894, CTFA has almost 600 members whose businesses formulate, manufacture, distribute and market personal care products. Our members manufacture or distribute the vast majority of personal care products sold in the United States.

I. Introduction

Nanotechnology offers enormous potential to enhance the lives of consumers through a wide array of applications, from medical products to industrial technology to personal care products. Already, nanotechnology has been used in numerous products that benefit consumers, including products subject to FDA's jurisdiction. Accordingly, CTFA supports continued scientific research and investigation into nanotechnology, and applauds FDA's efforts to bring together members of the concerned public to discuss scientific issues concerning nanotechnology. It is our hope that the agency's October 10, 2006 public meeting and the FDA Nanotechnology Task Force will assist the agency and the public in recognizing the enormous benefits to consumers from nanotechnology and understanding of the scientific principles involved. CTFA intends to be an active participant in this important public dialogue on nanotechnology.

These following comments, therefore, are intended to provide CTFA's views on the scientific and legal issues associated with the use nanotechnology in personal care products in advance of the October meeting and to respond to the Citizen Petition submitted by the International Center for Technology Assessment and other parties (Petitioners). As will be discussed more fully below, the Petitioners' citizen petition should be rejected on the basis of both the science and the law.

Petitioners essentially request that FDA (1) establish a separate regulatory regime specifically for products engineered by nanotechnology; and (2) demand that sunscreen products containing certain ingredients that are engineered by nanotechnology be withdrawn from the U.S. market. Neither of these contentions has merit.

First, FDA has no statutory authority to regulate nanotechnology as a technology. Since its inception, FDA's congressionally mandated authority has been limited to the regulation of products introduced into interstate commerce that meet the jurisdictional requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA). The FFDCA does not provide authority for FDA to regulate nanotechnology itself, divorced from specific products in or seeking to enter the market. Nor does the FFDCA impose different safety standards for products based on the technology they utilize. Accordingly, FDA has no authority to

impose different safety standards on products that use one particular technology. Moreover, FDA already comprehensively regulates the safety of medical and consumer products. Under the FFDCA, FDA has erected a complex and comprehensive regulatory system to safeguard the public health. This regulatory system has worked to ensure that, among other things, the food eaten by US consumers, the medical technology used by physicians and patients, and the personal care products used by countless citizens are all the safest in the world.

FDA's regulations and policies have always been driven by the most accurate science available. Petitioners, however, have provided no clear scientific justification for their claim that FDA must embark on a new regulatory system for nanotechnology. In fact, Petitioners' citizen petition mischaracterizes the scientific issues associated with nanotechnology. When the full body of scientific understanding of nanotechnology is considered, it is clear that FDA's existing regulatory authority is more than sufficient to ensure that medical and consumer products that utilize nanotechnology will continue to meet high standards of safety.

While nanotechnology is arguably a new technology, the challenges that it poses are familiar to FDA. In the past several decades FDA has witnessed a number of novel technologies that impact products regulated by FDA. These include, to name only two prominent examples, biotechnology and genetic engineering. Although each of these areas introduced new scientific principles and challenges, FDA's existing regulatory systems ensured that products engineered by those technologies were safe and effective. Nanotechnology is no exception. While nanotechnology may introduce additional scientific considerations for products engineered by that technology, FDA's existing regulations and policies are more than sufficient to account for the new issues.

Second, Petitioners' claim that certain sunscreen products must be withdrawn from the market is equally unfounded. In making this meritless claim, Petitioners ignore the fact that personal care products are among the safest products that FDA regulates. Product and ingredient safety are ensured by existing stringent government oversight and a history of successful industry self-regulation.[1] The current regulatory regime, therefore, provides FDA with ample authority to address the potential risks and benefits of nanotechnology in personal care products. In addition, a review of the scientific literature confirms that micronized particles utilized in personal care products do not pose a safety risk. Accordingly, imposing a different regulatory regime on personal care products utilizing nanotechnology would be contrary to public health and consumer

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[1] The cosmetic industry takes pride in its long history of self-regulation. Examples of CTFA self-regulatory programs include the voluntary establishment registration and product ingredient registration by member companies; the establishment of the Cosmetic Ingredient Review, an independent scientific panel charged with assessing the safety of cosmetic ingredients; and numerous technical guides and databases relating to cosmetic safety and regulation. CTFA's self-regulatory programs are not only effective, but they also save government resources.

welfare, and would be unsupported by FDA's statutory authority over personal care products. Simply stated, the ingredients used in personal care products are safe, provide clear benefit and enhance the lives of consumers.

The two product ingredients that Petitioners single out are no exception. Petitioners claim that sunscreens that utilize titanium dioxide or zinc oxide engineered by nanotechnology must be recalled for the market. Everyday, countless consumers use products containing these ingredients to protect themselves from the damaging effects of ultraviolet radiation. Titanium dioxide and zinc oxide have a long history of safe use as sunscreen ingredients. The medical literature demonstrates that products engineered through nanotechnology contain these ingredients are safe for consumers. Scientific data demonstrates that when applied to the skin, these ingredients do not create new toxicity concerns. Accordingly, Petitioners' request would result in consumers being denied access to unquestionably beneficial products without any scientific justification.

CTFA's comments, therefore, will address the following issues.

- First, the comments will provide an introduction to nanotechnology, demonstrating that there is, in fact, substantial disagreement even as to the definition of nanotechnology.

- Second, FDA's existing regulatory systems for several categories of personal care products will be discussed, including OTC drugs, cosmetics, and color additives. In addition, we address how these regulatory systems have provided FDA with ample tools to regulate the safety of another new technology that presented essentially the same issues as nanotechnology -- bioengineered foods.

- Third, we review the scientific literature investigating the toxicity of nanomaterials, which demonstrates that contrary to Petitioners' claims, there is no scientific consensus that nanomaterials present unique safety issues such that existing paradigms cannot adequately assess the safety of nanomaterials. In fact, there is scant evidence demonstrating that topical application of products containing nanomaterials present any new safety issues.

- Fourth, the comments will address the regulation of zinc oxide and titanium dioxide, two sunscreen ingredients manufactured by nanotechnology processes. The voluminous scientific record associated with these products, along with numerous findings of safety by other international scientific bodies, demonstrates that contrary to Petitioners' claims, there is no safety concern regarding these ingredients. In fact, FDA has regulated products containing these ingredients for decades, and

the available scientific evidence demonstrates that the introduction of nanotechnology does not alter the safety profile in any meaningful way.

- Fifth, the comments address the adverse effect that would result if FDA were to adopt a different regulatory system for products containing nanotechnology ingredients.

- Sixth, we respond to each of the Petitioners' specific comments to demonstrate why each unquestionably should be denied.

II. What is Nanotechnology?

Though Petitioners request sweeping regulatory changes based on whether a product contains ingredients that fall under the scope of the term "nanotechnology," Petitioners themselves admit that the term "nanotechnology" is not well defined. Various organizations have established different definitions for nanotechnology based on particle size, the manufacturing process, the properties of the material, etc.[2] The term "nanotechnology" may be used to

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[2] For example, the Center for Responsible Nanotechnology defines nanotechnology as:

> [E]ngineering of functional systems at the molecular scale. This covers current work and concepts that are more advanced. In its original sense, 'nanotechnology' refers to the projected ability to construct items from the bottom up, using techniques and tools being developed today to make complete, high performance products.

http://www.crnano.org/whatis.htm

The National Science Foundation defines nanotechnology as:

> Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometer range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size. The novel and differentiating properties and functions are developed at a critical length scale of matter typically under 100 nm. Nanotechnology research and development includes manipulation under control of the nanoscale structures and their integration into larger material components, systems and architectures. Within these larger scale assemblies, the control and construction of their structures and components remains at the nanometer scale. In some particular cases, the critical length scale for novel properties and phenomena may be under 1 nm (e.g., manipulation of atoms at ~0.1 nm) or be larger than 100 nm (e.g., nanoparticle reinforced polymers have the unique feature at ~ 200-300 nm as a function of the local bridges or bonds between the nano particles and the polymer).

http://www.nsf.gov/crssprgm/nano/reports/omb_nifty50.jsp

describe a wide array of technologies and applications, some of which have been used for decades and others that are new and emerging; each of which presents its own set of potential risks and benefits.

Examples of nanotechnology applications include:

- advanced drug delivery systems
- medical diagnostics
- advanced laser technology
- nanostructured catalysts
- systems on a chip
- chemical sensors
- wear-resistant coatings[3]

Some descriptions of nanotechnology include materials that have been used in personal care products for many years. These include fine grades (also called "microfine" or "ultrafine") of titanium dioxide and zinc oxide that are used in

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The Los Alamos National Laboratory defines nanotechnology as: "the creation of functional materials, devices, and systems through control of matter on the nanometer (1 to 100+ nm) length scale and the exploitation of novel properties and phenomena developed at that scale." http://www.lanl.gov/mst/nano/definition.html

NIH defines nanotechnology as:

> [R]esearch and technology development at the atomic, molecular, or macromolecular levels in the dimension range of approximately 1-100 nanometers to provide fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size. The novel and differentiating properties and functions are developed at a critical length scale of matter typically under l00 nm. Nanotechnology research and development includes control at the nanoscale and integration of nanoscale structures into larger material components, systems, and architectures. Within these larger scale assemblies, the control and construction of their structures and components remains at the nanometer scale.

http://www.becon.nih.gov/nstc_def_nano.htm

The Royal Society defines nanotechnologies as: "the design, characterization, production and application of structures, devices and systems by controlling shape and size at nanometer scale." Available at: http://www.nanotec.org.uk/report/chapter2.pdf.

Finally, the Woodrow Wilson Center Program on Emerging Nanotechnologies and the U.S. National Nanotechnology Initiative (NNI) present a definition of nanotechnology as: "the understanding and control of matter at dimensions of roughly 1 to 100 nanometers ... nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale." Available at: http://www.nanotechproject.org/file_download/30.

The Woodrow Wilson Center also references the definition provided by the Royal Society as described above.

[3] Available at: http://www.nano.gov/html/facts/.

sunscreen products, which have been evaluated thoroughly for safety, as described below. Liposomes, which are used commonly as moisturizers, which dissolve on the surface of the skin and do not penetrate the skin, may also be included[4]

Given the broad spectrum of materials and applications that the term "nanotechnology" may encompass, a single, one-size-fits-all approach to the regulation of nanotechnology would be ill–advised and unworkable. Subjecting any and all technologies that fall under existing definitions of nanotechnology to more rigorous review or banning them from the marketplace would limit consumer access to products with established safety and efficacy records, unnecessarily denying consumers of products that have a clear public health benefit. As described below, the current regulatory regime is sufficient to address any potential implications of nanotechnology in personal care products.

III. FDA Has Ample Authority to Regulate the Safety of "Nanotechnology" in Personal Care Products

A. Current Authorities Ensure that Personal Care Products are Safe and Properly Labeled

Under the FFDCA, all OTC drugs and cosmetic products and ingredients must be safe and properly labeled. The regulatory system established by the FFDCA and FDA regulations has proven effective in assuring consumers of the high standards of safety they have come to expect from the personal care products they use every day. The FFDCA does not recognize a separate definition for nanotechnology, nor does it provide different safety standards for products based on the technology they utilize. As FDA has stated, "FDA regulates products based on their statutory classification rather than the technology they employ."[5] Products are classified as drugs and/or cosmetics based upon their intended use.

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[4] The National Library of Medicine defines liposomes as "[a]rtificial, single or multilaminar vesicles (made from lecithins or other lipids) that are used for the delivery of a variety of biological molecules or molecular complexes to cells, for example, drug delivery and gene transfer. They are also used to study membranes and membrane proteins." Available at: http://ghr.nlm.nih.gov/ghr/glossary/liposome. Liposome technology, in the context of cosmetic products, is a formulation technique that [is similar to that used in drug delivery] and can deliver a desired ingredient to the surface of the skin. Liposomes are a refinement of micelle technology. Micelles are defined as "colloid particles formed by an aggregation of small molecules. "Dorland's Illustrated Medical Dictionary, 26th edition, W.B. Saunders Company, Philadelphia, 1981. In aqueous solution micelles form a roughly spherical or globular aggregate with the hydrophilic "head" regions in contact with surrounding solvent, sequestering the hydrophobic tail regions in the micelle center. Micelles are often globular and roughly spherical in shape, but ellipsoids, cylinders, and bilayers are also possible.

[5] FDA and Nanotechnology Products, Frequently Asked Questions. Available at http;//www.fda.gov/nanotechnology/faqs.html.

1. Over-the-Counter Drugs

Over-the-counter (OTC) drugs must undergo a rigorous safety review process by FDA. Drugs are defined under the FFDCA as articles "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals..."[6] "New drugs" are those that are "not recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof...."[7] Conversely, those drugs that meet the conditions contained in an OTC monograph and other applicable regulations are generally recognized as safe and effective and may be marketed over the counter without prior approval by FDA.[8]

FDA's procedure for regulating OTC drugs entails a multi-step, public process that results in the establishment of OTC drug monographs.[9] An OTC drug monograph is a regulation that establishes conditions under which an OTC drug is generally recognized as safe, effective and not misbranded.[10] Ingredients in OTC drug monographs are classified in three categories: category I ingredients are generally recognized as safe and effective and not misbranded, category II ingredients are not generally recognized as safe and effective and are misbranded, and category III ingredients are those for which available data are insufficient to permit a final classification.[11]

In the development of a monograph, the initial step is an advisory panel review of the safety and efficacy of ingredients for a product category. An advisory panel, comprised of experts in the field, reviews data and information on each active ingredient and determines if it meets the following safety standard:

> Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon

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6 21 U.S.C. § 321(g).

7 21 U.S.C. § 321(p).

8 21 C.F.R. § 330.10.

9 Id.

10 21 C.F.R. § 330.10(a)(6).

11 Id.

published studies which may be corroborated by unpublished studies and other data.[12]

After the panel makes its recommendation, FDA issues a proposed rule, available for public comment. This public process ensures that FDA has all available data to make a proper safety assessment. The FDA then considers all relevant comments and issues a final monograph. A product that does not meet the specifications of the final monograph would not be generally recognized as safe and effective and not misbranded, and, unless marketed under an NDA, would be an unapproved new drug.

2. Cosmetics

Like OTC drugs, cosmetics in interstate commerce must be safe and not misbranded. Under the FFDCA, cosmetics are defined as articles "intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance...."[13]

The general authority that allows FDA to take action on an unsafe cosmetic product is contained in 21 U.S.C. § 361(a), which prohibits the introduction into interstate commerce of a cosmetic that "bears or contains any poisonous or deleterious substance which may render it injurious to users" under labeled or customary conditions of use. In addition, a cosmetic is considered adulterated if it contains a filthy, putrid, or decomposed substance; if its container is composed of a harmful substance; if it is manufactured or held under unsanitary conditions whereby it may have become contaminated with filth, or may have become harmful to consumers; or if it is not a hair dye that contains a non-permitted color additive.[14] Manufacturers of cosmetics products are responsible for substantiating the safety of their products and ingredients prior to introduction into interstate commerce, or else the product must bear the warning label statement: "Warning—the safety of this product has not been determined."[15]

Cosmetics must also be properly labeled. FDA regulates the labeling of cosmetics under 21 U.S.C. § 362(a), which states that a cosmetic is misbranded if the labeling is false or misleading in any particular. Further, under 21 U.S.C. § 321(n), a product is misbranded if the labeling fails to reveal a material fact.

FDA may issue regulations to ban or restrict the use of unsafe cosmetic ingredients and has done so in the past for several problematic ingredients,

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12 21 C.F.R. § 330.10(a)(4)(i).

13 21 U.S.C. § 321(i).

14 21 U.S.C. § 361(b)-(e).

15 21 C.F.R. § 740.10.

including bithionol, mercury compounds, vinyl chloride, halogenated salicylanilides, zirconium complexes in aerosol cosmetics, chloroform, methylene chloride, chlorofluorocarbon propellants, and hexachlorophene.[16] FDA has also required certain warning statements on various cosmetic products in order to prevent them from being misbranded.[17] As with any product under its jurisdiction, FDA may conduct an investigation on products of concern and issue public health warnings if a safety issue exists.[18]

3. Color Additives

Color additives, whether used in cosmetics, foods, medical devices, or drugs, must undergo a pre-market safety review by FDA. A color additive is defined in FDA's regulations as:

> [A]ny material...that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal or mineral, or other source and that, when added or applied to a food, drug, or cosmetic or to the human body or any part thereof, is capable...of imparting a color thereto."[19]

A party may request review of an unapproved color additive through a petition process delineated in the regulations.[20] In order to be considered safe, Petitioners must demonstrate that "there is convincing evidence that establishes with reasonable certainty that no harm will result for the intended use of the color additive."[21] Color additives are approved by regulation and listed in the Code of Federal Regulations. Color additives are approved for use in a particular product category and cannot be used in the area of the eye, in injections, or in surgical sutures unless specifically provided for in the listing regulation. Color additive review is quite stringent, and the United States has fewer approved colors than most other nations for this reason.[22]

In addition to the requirement for being listed in a regulation, batches of color additives must also be certified for conformance with the requirements in the

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16 21 C.F.R. §§ 700.11 - 700.23 and § 250.250.

17 See 21 C.F.R. § 740.

18 *See, e.g., FDA Alerts Consumers About Adverse Events Associated With "Permanent Makeup."* Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01295.html.

19 21 C.F.R. § 70.3(f).

20 21 C.F.R. § 71.1.

21 21 C.F.R. § 70.3(i).

22 See Rosholt, A. ed., CTFA International Color Handbook, 3rd Ed. 2003.

listing regulation unless the FDA finds that certification is not necessary in the interest of the protection of public health and the listing regulation so states.[23]

4. Conclusion

The FFDCA requires that all cosmetic and OTC drug products on the market are safe and properly labeled, without regard to the technology involved. Furthermore, the FFDCA does not recognize a separate regulatory scheme for products that utilize nanotechnology. Products are regulated as cosmetics or drugs based on their intended use, not according to the technology they incorporate. FDA has ample authority to take action on cosmetics that are unsafe and OTC drugs and color additives must undergo a thorough pre-market review process. Thus, consumers can be assured of the safety of the personal care products they use.

B. FDA Regulation of New and Emerging Technologies—the Case of Bioengineered Foods

The issue of nanotechnology is not the first and will likely not be the last time that FDA is faced with the challenge of determining how to regulate a new or emerging technology. The product areas that FDA regulates—food, drug, cosmetics, and medical devices—are products inherently on the cutting edge of modern technology. Yet the statutory standards that have existed since the passage of the FFDCA in 1938, and some since the Pure Food and Drugs Act of 1906, have stood the test of time, assuring consumers high standards of safety they have come to expect for the products they use on a daily basis. An important and applicable case in point is the regulation of bioengineered foods. There, as with nanotechnology products, FDA's existing authorities have ensured the public of safe and properly labeled products. Importantly, FDA has always held the position, supported by the courts, that the regulation of bioengineered foods depends not merely on the fact that they are derived from a particular technology, but on the actual properties of a particular product.

1. FDA Regulation of the Safety of Bioengineered Foods

Genetic engineering technology that developed in the 1970's allowed the transfer of genes between species in a manner that was not previously possible. The advent of bioengineering techniques brought the promise of foods that contained traits that would make them resistant to pests, grow more productively, and have better taste and nutritional properties than their non-bioengineered counterparts. With the promise of biotechnology also came concerns about their potential risks. FDA has consistently held that as a safety matter, the mere fact that a bioengineering technique is used in the development of the food is not relevant; rather, safety issues must be assessed on a case-by-case basis depending on

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[23] 21 U.S.C. § 721(c).

the properties of the food itself. If a legitimate safety concern exists resulting from the use of bioengineering, *i.e.* the introduction of allergens or toxins, FDA would act accordingly with respect to the particular food.

FDA issued the first regulation for the use of recombinant DNA-produced food ingredient in 1990, affirming that it was generally recognized as safe.[24] FDA based its decision on the facts that the introduced gene encoded a protein that was the same structure and function as the naturally derived gene and that the production microorganisms and any antibiotic resistant marker genes were destroyed or removed during processing.[25]

FDA issued its Statement of Policy: Food Derived from New Plant Varieties on May 29, 1992 (1992 Policy), which set forth how FDA would treat genetically modified organisms in food under the existing regulatory regime.[26] Importantly, FDA's position, which may be extended to the nanotechnology situation, is that "the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used."[27] The agency went on to say that "In most cases, the substances expected to become components of food as a result of genetic modification of a plant will be the same as or substantially similar to substances commonly found in food, such as proteins, fats and oils, and carbohydrates," and therefore the agency did not have large safety concerns about bioengineered foods.

The authority for regulation of food safety is derived from 21 U.S.C. § 342(a)(1) & 348. 21 U.S.C. § 342(a)(1) states that a food is adulterated, in part, if it "bears or contains any poisonous or deleterious substance which may render it injurious to health...." In addition, the food additive provisions in 21 U.S.C. §348 require premarket clearance of substances intended to become components of food that are not generally recognized as safe. Introduction into interstate commerce of a food with an unapproved food additive causes the food to be adulterated.[28] Penalties for introduction of an adulterated food into interstate commerce include seizure, injunction, and criminal sanctions.[29] In its 1992 Policy, FDA stated that it "considers the existing statutory authority under sections 402(a)(1) and 409 of the Act [21 U.S.C. §§ 342(a)(1) and 348], and the practical regulatory regime that flows from it, to be fully adequate to ensure the safety of new food ingredients and foods derived from new varieties of plants, regardless of the processes by

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24 21 C.F.R. § 184.1685.

25 See FDA'S Policy for Foods Developed by Biotechnology. Available at http://www.cfsan.fda.gov/~lrd/biopolcy.html.

26 57 Fed. Reg. 22984 (May 29, 1992) [hereinafter 1992 Policy].

27 Id. at 22985.

28 21 U.S.C. § 342(a)(2)(c)(i).

29 Id. § 332, 333, 334.

which such foods and ingredients are produced."[30] In addition, FDA stated that generally it would not expect that transferred genetic material would be subject to food additive regulations. However, if "the intended expression product in a food [were] a protein, carbohydrate, fat, or oil, or other substance that differs significantly in structure, function, or composition from substances found currently in food," the substance may not be GRAS and may be subject to the food additive approval process.[31]

In the 1992 Policy, FDA recommended a voluntary consultation process for producers of genetically modified foods that may pose safety concerns. FDA issued a guidance document in 1996 on the consultation process.[32] In 1999, FDA issued a proposed rule on premarket notification of bioengineered foods.[33] In the preamble, FDA reiterated its position that transferred genetic materials are presumed to be GRAS, and that there is unlikely to be a safety question sufficient to question the presumed GRAS status of proteins or other substances produced from genetically transferred material when the proteins or substances do not differ significantly from other substances commonly found in food.[34] It stated:

> FDA recognizes that whether there is a change in the legal status of a food resulting from a particular recombinant DNA (rDNA) modification depends almost entirely on the nature of the modification, and that not every modification accomplished with rDNA techniques will alter the legal status of the food. In other words, many modifications will result in food that does not contain an unapproved food additive, does not contain an unexpected allergen, and does not differ significantly in its composition compared with its traditional counterpart or otherwise require special labeling. For this reason, FDA is neither proposing to require premarket approval for all foods developed using rDNA technology nor is the agency proposing an across-the-board requirement that all such foods bear special labeling.[35]

At the time of publication of the 1999 proposed rule, FDA believed that all marketers of bioengineered foods had consulted with FDA prior to marketing.[36] In its proposed rule, FDA tentatively concluded that FDA must be notified of the intent to market bioengineered foods 120 days prior to the initiation of

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30 1992 Policy at 22989.

31 Id. at 22990.

32 FDA, Guidance on Consultation Procedures: Foods Derived From New Plant Varieties. Available at http://www.cfsan.fda.gov/~lrd/consulpr.html.

33 Premarket Notice Concerning Bioengineered Foods, Proposed Rule, 66 Fed. Reg. 4706 (Jan. 18, 2001).

34 Id. at 4709.

35 Id. at 4711.

36 Id. at 4708.

commercial distribution. The proposed rule also recommends that a prospective notifier consult with the agency prior to notification. The 1999 proposed rule, however, was never finalized.

In the meantime, FDA issued a separate guidance, finalized in June 2006, which recommends early food safety evaluations of new proteins produced by new plant varieties intended for food use.[37] The purpose of the guidance is to encourage the food developer to provide food safety information to FDA in the early development of new proteins prior to the stage of development where the protein may inadvertently enter the food supply. In the guidance, FDA reiterated its belief that:

> In most cases, the proteins expected to become components of food, whether as a result of the use of traditional or modern biotechnology methods, will be the same or quite similar to proteins commonly found in food. FDA believes that any food safety concern related to such material entering the food supply would be limited to the potential that a new protein in food from the plant variety could cause an allergenic reaction in susceptible people or could be a toxin in people or animals.[38]

In sum, FDA's regulation of the safety of bioengineered foods focuses not on the type of technology involved in producing the foods, but on the actual property of a particular bioengineered food. FDA recognizes that as a safety issue, the mere fact that bioengineering techniques are utilized is not relevant. If legitimate safety concerns exist, *e.g.* the introduction of allergens or toxins, the agency would address them on a case-by-case basis.

2. FDA Regulation of the Labeling of Foods Derived from Biotechnology

FDA regulation of the labeling of bioengineered foods is again premised on the notion that the sole fact that a certain technology is used to develop the food is not material unless the technology leads to actual differences in the food. FDA regulates the labeling of foods under 21 U.S.C. § 343(a), which states that a food is misbranded if its labeling is false or misleading in any particular. In addition, under 21 U.S.C. §321(n), a product is misbranded if the labeling fails to reveal a material fact. In its 1992 Policy, FDA stated that consumers should be informed by appropriate labeling "if a food derived from a new plant variety differs from its traditional counterpart such that the common or usual name no longer applies to the new food, or if a safety or usage issue exists to which consumers must be alerted." As an example, FDA stated that if an allergenic protein was introduced

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[37] FDA, Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use. Available at http://www.cfsan.fda.gov/~dms/bioprgu2.html.

[38] Id.

into a different food variety, a label declaration would be required to alert consumers who are allergic to the food the protein was derived from.[39] FDA went on to state that it had not to date "considered the methods used in the development of a new plant variety...to be material information within the meaning of [21 U.S.C. § 321(n)]." Further, it stated:

> FDA believes that the new techniques are extensions at the molecular level of traditional methods and will be used to achieve the same goals as pursued with traditional plant breeding. The agency is not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by new techniques present any different or greater safety concern than foods developed by traditional plant breeding."[40]

In January of 2001, FDA issued draft guidance on voluntary labeling indicating whether foods have or have not been developed using bioengineering.[41] In the draft guidance, FDA reiterated that it was not aware of any evidence to conclude that the fact that a product was produced using bioengineering was a material fact that must be disclosed under the FFDCA. FDA recognized that some manufacturers may want to provide information for consumers about their bioengineered foods, and provided examples of how manufacturers may do this in a non-misleading manner. FDA also set forth its policy of the labeling of foods that are not bioengineered or are free of bioengineering, cautioning that it may be misleading to state that a product was "free" of bioengineered material since definitional threshold levels for "free" had not been established.[42]

FDA's determinations on the labeling of biotechnology-derived foods have been upheld in court. In *Stauber v. Shalala*,[43] a consumer rights organization sued FDA for not requiring mandatory labeling of products derived from cows treated with recombinant bovine growth hormone (rbST). FDA had determined in its new drug approval of the synthetic bovine growth hormone drug that because there was no material difference between milk from treated cows versus untreated cows, the information was not required by law. The court agreed, stating that "plaintiffs have been able to point to no evidence in the administrative record indicating that milk derived from rbST-treated cows has performance characteristics or organoleptic properties different from milk from untreated cows." The court stated that even though consumers may wish to know that the milk was derived from rbST treated cows:

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39 Note that for the major food allergens, this policy may have been superseded by the Food Allergen Labeling and Consumer Protection Act of 2004.

40 1992 Policy at 22991.

41 FDA, Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering. Available at http://www.cfsan.fda.gov/~dms/biolabgu.html.

42 Id.

43 895 F.Supp. 1178 (W.D. Wis 1995).

> [P]laintiffs are incorrect in their assertion that by itself consumer opinion could suffice to require labeling. The FDA does consider consumer opinion relevant when determining whether a label is required to disclose a material fact, but a factual predicate to the requirement of labeling is a determination that a product differs materially from the type of product it purports to be. If there is a difference, and consumers would likely want to know about the difference, then labeling is appropriate. If, however, the product does not differ in any significant way from what it purports to be, then it would be misbranding to label the product as different, even if consumers misperceived the product as different. In the absence of evidence of a material difference between rbST-derived milk and ordinary milk, the use of consumer demand as the rationale for labeling would violate the Food, Drug, and Cosmetic Act.[44]

Thus the court found that consumer demand, without any material difference in the product, could not justify differential labeling and that such labeling would misbrand the product.

In another case concerning labeling of rBST products, *International Dairy Foods Association v. Amestoy*,[45] the Second Circuit struck down a state requirement mandating the labeling of products derived from cows given recombinant bovine growth hormone. Since it was undisputed that neither consumers nor scientists could distinguish between milk from treated or untreated cows, the court concluded that there was no basis to compel labeling that would distinguish such products. The court stated:

> Absent...some indication that this information bears on a reasonable concern for human health or safety or some other sufficiently substantial governmental concern, the manufacturers cannot be compelled to disclose it.... Accordingly, we hold that consumer curiosity alone is not a strong enough state interest to sustain the compulsion of even an accurate, factual statement.

Under First Amendment principles, the court concluded that the state had not established a substantial government interest in compelling the speech, and therefore the court struck down the state requirement.[46]

3. Conclusion

FDA's regulation of bioengineered foods since the advent of bioengineering technology has been premised on existing regulations as well as voluntary

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44 Id. at 1193.

45 93 F.3d 67 (2d Cir. 1996).

46 Id. at 74.

information exchanges with the agency. This regime has stood the test of time. FDA has stated, "FDA regulates foods and food ingredients developed by genetic engineering by the same provisions and regulations under the [FFDCA] that it regulates other food products. This means that a food or food ingredient developed by genetic engineering must meet the same rigorous safety standards under the Act as other food products, and FDA has broad authority to take legal action against a substance that poses a hazard to the public."[47] Similarly, the existing authorities in the FFDCA and in current regulations ensure that personal care products, including cosmetics and OTC drugs, are safe.

IV. Scientific Evidence Supports the Current Assessment Methods for Ensuring the Safety of Personal Care Products Containing Nanotechnology

The position of the Citizen Petition is that FDA-regulated products which contain nanoparticles are uniformly unsafe. This position is incorrect. In fact, a fair and balanced evaluation of the scientific data demonstrates that reduction in particle size does not necessarily correlate with increased safety risk. Rather, the data indicate that particle size is but one factor that may affect safety. Other considerations, include chemical structure, dosage form, level of use, route of administration, and intended use. Differences associated with particle size can vary depending on surface chemistry, route of administration, and other factors. In addition, it is possible that reduced particle size may affect absorption, distribution, metabolism or excretion, which could in turn cause either increased or decreased toxicity. Recent opinions of expert panels indicate that current toxicological paradigms are sufficiently robust to address the safety of nanoparticles in personal care products.[48]

Each of these points is discussed in more detail below.

A. Particle Size Does Not Necessarily Correlate with Toxicity Profile

The Petitioners claim that because of their physiochemical properties, nanoparticles are inherently different from other larger sized particles and present *new* risks to human health and the environment. The available scientific studies on nanoparticles and nanomaterials do not support the hypotheses that these materials are uniquely toxic or that they possess *novel* toxicological

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[47] FDA'S Policy for Foods Developed by Biotechnology. Available at http://www.cfsan.fda.gov/~lrd/biopolcy.html.

[48] Sayes C.M., Wahi R., Kurian P.A., Liu Y., West J.L., Ausman K.D., Warheit D.B., and Colvin V.L., 2006. Correlating Nanoscale Titania Structure with Toxicity: A Cytotoxicity and Inflammatory Response Study with Human Dermal Fibroblasts and Human Lung Epithelial Cells. Toxicol Sci 92(1), 174-185; Warheit D.B., Webb T.R., Sayes C.M., Colvin VL, and K.L. Reed KL. 2006. Pulmonary instillation studies with nanoscale TiO_2 rods and dots in rats: Toxicity is not dependant upon particle size and surface area. *Toxicol. Sci.* 91(1):227-236.

properties. Particle size may have an impact on toxicity in some cases because as particle size decreases, there is an increase in surface area per unit mass, resulting in an increased potential for a larger concentration of charged molecules on the surface of the particles. However, literature shows that particle size is not directly correlated with increased toxicity; therefore, generalizations such as those stated by the Petitioners are not supported by data for many nanoparticles or nanomaterials. In addition, it is possible that smaller size may affect the pharmacokinetic properties of a chemical (absorption, distribution, metabolism, or elimination), potentially resulting in either increased or decreased toxicity. Again, this hypothesis has not been scientifically confirmed for nanomaterials and remains speculative.[49]

Petitioners claim that:

> "the human species has evolved mechanisms of protection against environmental agents; size is an important factor in the efficacy of these mechanisms. The exposure to engineered nanoparticles, having characteristics not previously encountered, presents new challenges to the normal defense mechanisms of, *inter alia*, the body's immune and inflammatory response systems."

However, as the report from the Royal Society and the Royal Academy of Engineering[50] states:

> "It is important to set these concerns in context by noting that humans have always been exposed to some types of nanoparticles arising from natural sources such as atmospheric photochemistry and forest fires, and exposures to millions of pollutant nanoparticles per breath have been commonplace since the first use of fire."

Thus, while the specific chemical forms of the same material at the nanoparticle size may be novel in their use in cosmetics, humans have been exposed to nanoparticles throughout their evolution and have developed defense mechanisms to them, as they have to larger particles. As discussed below in section IV.A and Table 1, studies consistently show that zinc oxide and titanium dioxide nanoparticles in sunscreens do not penetrate the skin. For most chemicals, the stratum corneum is the rate-limiting barrier to percutaneous penetration and serves to prevent chemical substances, such as micronized titanium dioxide or zinc oxide or other nanoparticles, from reaching the dermis layer. Thus, the data on these materials indicate that it is incorrect to assert that nanoparticles will result in an increased safety risk.

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[49] Id.

[50] Royal Society and the Royal Academy of Engineering. 2004. Nanoscience and nanotechnologies: opportunities and uncertainties. Available at http://www.nanotec.org.uk/finalReport.htm.

In inhalation studies, there are conflicting results regarding systemic absorption of nanoparticles. In rat inhalation studies, titanium dioxide nanoparticles have been shown to cross cellular membranes and reach the systemic circulation (Geiser et al. 2005)[51] and Elder et al. (2006)[52] demonstrated translocation of inhaled 30 nm manganese oxide particles to the central nervous system via the olfactory neuronal pathway. In addition, Oberdörster et al. (1992)[53] reported that nanoparticles (<100 nm) of titanium dioxide can be deposited in the alveolar region of the respiratory tract and potentially can be transported into the bloodstream more readily than larger particles. Nemmar et al. (2002)[54] reported that inhalation of ^{99m}Tc-labeled ultrafine carbon particles (<100 nm) resulted in the rapid appearance of the label in the blood and liver in human subjects. More recently, using the same Technegas methodology (Carbon NPs labelled with 99mTc), studies showed that there was no significant translocation of 100 nM particles (99% of the radioactivity remained in the lungs over the study period, i.e. 70 h ; Wiebert et al., 2006a)[55], 4-20 nM particles (96% of radioactivity retained in the lungs, Mills *et al.*, 2006)[56] or 35 nM particles (no significant translocation, Wiebert et al. 2006b).[57] Moreover, these studies suggest that residual activity may originate from leached activity due to unstable labelling, rather than genuine translocation of labelled insoluble particles. In addition, Brown et al. (2002)[58] did not observe any uptake of ^{99m}Tc-labeled ultrafine carbon aerosol (33 nm) nanoparticles into the liver following inhalation in human subjects. Furthermore, it has been shown that the clearance kinetics and translocation of nanoparticles of Iridium (Ir) was similar to those previously

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51 Geiser M. et al. 2005. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environ. Hlth. Perspect. 113(11):1555-1560.

52 Elder A. et al. 2006. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ. Hlth. Perspec. 114:1172-1178.

53 Oberdorster G, Ferin J, Gelein R, Soderholm SC, Finkelstein J. 1992. Role of the alveolar macrophage in lung injury: studies with ultrafine particles. Environ Health Perspect. 97:193-199.

54 Nemmar, A., P.H. Hoet, B. Vanquickenborne, D. Dinsdale, M. Thomeer, M.F. Hoylaerts, H. Vanbilloen, L. Mortelmans, and B. Nemery. 2002. Passage of inhaled particles into the blood circulation in humans. Circulation 105(4):411-414.

55 Wiebert P, Sanchez-Crespo A, Seitz J, Falk R, Philipson K, Kreyling WG, Moller W, Sommerer K, Larsson S, Svartengren M. 2006a. Eur Respir J. 28(2) :286-290. Negligible clearance of ultrafine particles retained in healthy and affected human lungs.

56 Mills NL, Amin N, Robinson SD, Anand A, Davies J, Patel D, et al. 2006. Do inhaled carbon nanoparticles translocate directly into the circulation in humans? Am J Respir Crit Care Med 173(4):426-431

57 Wiebert P, Sanchez-Crespo A, Falk R, Philipson K, Lundin A, Larsson S, Moller W, Kreyling WG, Svartengren M. 2006b. Inhal Toxicol. 18(10):741-747. No significant translocation of inhaled 35-nm carbon particles to the circulation in humans.

58 Brown, J.S., K.L. Zeman, and W.D. Bennett. 2002. Ultrafine particle deposition and clearance in the healthy and obstructed lung. Am. J. Respir. Crit. Care Med. 166(9):1240-1247.

reported for their micrometer-size counterparts (Semmler et al., 2004).[59] Larger surface area of smaller particles may influence toxicity following inhalation, either in a positive or negative direction (increasing lung retention for poorly soluble particles, or allowing more rapid elimination of soluble particles). However, broad generalizations regarding decreased size being associated with increased toxicological potential is clearly not a universal behavior of nanoparticles. In fact, there is little scientific justification for this generalization, particularly in the case of zinc oxide or titanium dioxide nanoparticles. Finally, and most importantly, the relevance of inhalation studies to dermal exposure to cosmetics and sunscreens is not established.

Indeed, although there are scientific studies that support the influence of size on toxicity (Oberdörster et al. 2005)[60], most of the information regarding a difference in toxicity as a result of size comes from studies that have evaluated pulmonary toxicity of ultrafine versus "fine" or larger particles. Whether these findings can be extrapolated to dermal toxicity remains unclear and available dermal studies do not support reporting differences in toxicity as a result of particle size. In addition, results from toxicological studies on chemically different nanoparticles show that toxicity may be more dependent on the structure or chemical nature of the substance rather than particle size. However, very few toxicology studies have been conducted to systematically examine the role of particle size and surface area in producing pulmonary toxicity (e.g., immunological or respiratory effects) (Warheit et al. 2006)[61] and no studies were identified that report a difference in toxicity following dermal administration.

Although we question whether studies of pulmonary toxicity are relevant to personal care products, the following provides a summary of the available data, which consist mainly of studies that have been conducted to evaluate potential differences in toxicity between ultrafine and fine particles in the ambient air. Because titanium dioxide is used in both ultrafine (<100 nm) and fine or pigmentary forms (>100 nm) for a variety of consumer products, studies have also been conducted to compare the toxicities of the different size ranges.

An inhalation toxicity study with silicon dioxide particles suggested that micro-sized (1-5 μm) particles were more toxic than the equivalent dose of

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[59] Semmler M, Seitz J, Erbe F, Mayer P, Heyder J, Oberdorster G, Kreyling WG. 2004. Long-term clearance kinetics of inhaled ultrafine insoluble iridium particles from the rat lung, including transient translocation into secondary organs. Inhal Toxicol. 16(6-7):453-9.

[60] Orberdörster, G., Oberdörster E., and J. Oberdörster. 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Hlth. Persp. 113:823-839.

[61] Warheit D.B., Webb T.R., Sayes C.M., Colvin VL, and K.L. Reed KL. 2006. Pulmonary instillation studies with nanoscale TiO_2 rods and dots in rats: Toxicity is not dependant upon particle size and surface area. *Toxicol. Sci.* 91(1):227-236.

nanoparticles (10 nm) (Chen et al. 2004).[62] Similarly, a study in human volunteers found no differences in adverse effects (e.g., changes in blood pressure, heart rate, ECG, sputum production, or hematological and immunological parameters), following inhalation of ultrafine (<100 nm) or micro-fine (0.1 to 1 µm) zinc oxide (Beckett et al. 2005).[63] Chen et al. (2004)[64] reported milder fibrogenesis of nanosized silicon dioxide than microsized silicon dioxide, "potentially resulting from nanoparticles tending to be diffused and easily translocated due to their ultrafine particle size compared to microsized particles." A recent pulmonary instillation study reported that there were not any differences between the toxicity of nano and micro-sized titanium dioxide at equivalent mass dose concentrations (Warheit et al. 2006). The authors concluded, "The results described herein provide the first example of nanoscale particle types which are not more cytotoxic or inflammogenic to the lung compared to larger sized particles of similar composition" (Warheit et al. 2006). In addition, research on titanium dioxide, and zinc oxide indicates that nanoscale materials may not always be more toxic on a mass basis than their larger versions (Sayes et al. 2006).[65]

While studies have reported size-dependent effects of nanoscale titanium dioxide, those may be intrinsically confounded by differences in sample structure (shape) and photoactivity potential (Sayes et al. 2006). An *in vitro* study was conducted to evaluate the effects of anatase versus rutile nanoscale titanium dioxide on dermal fibroblasts and human lung epithelial cells (Sayes et al. 2006). When two forms of titanium dioxide were administered at a dose of particles with similar surface areas, anatase nanoparticles produced greater toxicity than the rutile nanoparticles. Anatase, rutile, and anatase/rutile nanoparticles differ substantially in their surface chemistry, particularly as it relates to generating reactive oxygen species (Sayes et al. 2006). The authors concluded that the phase composition (shape) of nanoparticles is the more important parameter for determining toxicity than surface area, though they noted that their study does not rule out nanoparticle size as a parameter that can influence toxicity. Size, however, is far less important than shape in the case of titanium dioxide

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[62] Chen Y, Chen J, Dong J, and Y.X. Jin. 2004. Comparing study of the effect on nanosized silicon dioxide and microsized silicon dioxide on fibrogenesis in rats. *Toxicol. Ind. Health* 20, 21-27.

[63] Beckett WS, Chalupa DF, Pauly-Brown A, Speers DM, Stewart JC, Frampton MW, Utell MJ, Huang LS, Cox C and W. Zareba. 2005. Comparing inhaled ultrafine versus fine zinc oxisde particles in healthy adults: a human inhalation study. *Amer. J Resp.Crit. Care Med.* 171(10):1129-1135.

[64] Chen, Y, Chen, J., Dong, J., and Y. Jin. 2004. Comparing study of the the effect of nanosized silicon dioxide and microsized silicon dioxide on fibrogenesis in rats. Toxicol. Ind. Health 20(1-5):21-7.

[65] Sayes C.M., Wahi R., Kurian P.A., Liu Y., West J.L., Ausman K.D., Warheit D.B., and Colvin V.L., 2006. Correlating Nanoscale Titania Structure with Toxicity: A Cytotoxicity and Inflammatory Response Study with Human Dermal Fibroblasts and Human Lung Epithelial Cells. Toxicol Sci 92(1), 174-185.

nanoparticles. An in-depth evaluation of the role of particle size and shape in the cytotoxicity of micro- and nano-sized insoluble ceramic particles, including titanium dioxide, aluminum oxide, zirconium dioxide, silicone nitride or silicone carbide particles in mouse skin fibroblasts and lung macrophages was conducted (Yamamoto et al. 2004).[66] The study reported that larger particles of titanium dioxide (1600 nm), zirconium dioxide (530 nm), aluminum oxide (590 nm) or silicone nitride (700 nm) were more cytotoxic to fibroblasts and macrophages than smaller titanium dioxide (90 or 130 nm) or silicone carbide (180 nm) particles.

In some cases, studies of pulmonary administration of ultrafine titanium dioxide have shown more lung injury and pathology than equivalent deposited mass concentrations of pigmentary titanium dioxide (Ferin et al. 1992[67]; Janssen et al. 1994[68]). Comparisons between these two particle sizes on a *mass* basis do not correlate well with the observed tissue responses; however, comparisons using the *surface area per unit mass* have yielded an improved correlation of the rat data for some end points (Oberdorster 1996).[69] These studies have been conducted to evaluate **pulmonary** toxicity of relatively high doses of titanium dioxide and/or other types of particles and both *in vitro* and *in vivo* studies have reported that nanoparticles have the potential for greater toxicity than fine or micro-sized particles. Ultrafine particles (diameter of <100 nm), have been shown to have a greater capacity to induce inflammatory responses than larger "fine" particles of the same material (e.g., polystyrene, titanium dioxide, carbon black) in some studies (Gurr et al. 2005[70]; Brown et al. 2001;[71] Donaldson et al. 2002[72]; Bermudez et al. 2004[73]; Bermudez et al. 2002;[74] Renwick et al. 2004[75]).

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66 Yamamoto A, Honma R, Sumita M, and K. Hanawa. 2004 Cytotoxicity evaluation of ceramic particles of different sizes and shapes. *Journal of Biomedical Materials Research* 68A, 244-256.

67 Ferin, J., Oberdorster, G., and Penney, D. P. 1992. Pulmonary retention of ultrafine and fine particles in rats. *Am. J. Respir. Cell Mol. Biol.* 6, 535–542.

68 Janssen, Y. M., Marsh, J. P., Driscoll, K. E., Borm, P. J., Oberdorster, G., and Mossman, B. T. 1994. Increased expression of manganese-containing superoxide dismutase in rat lungs after inhalation of inflammatory and fibrogenic minerals. *Free Radic. Biol. Med.* 16, 315–322.

69 Oberdorster, G. 1996. Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. *Inhal. Toxicol.* 8, 73–89.

70 Gurr J.R., A.S. Wang, C.H. Chen, and K.Y. Jan. 2005. Ultrafine titanium dioxide particles in the absence of photoactivation can induce oxidative damage to bronchial epithelial cells. *Toxicology* 213(1-2):66-73.

71 Brown, D.M., M.R. Wilson, W. MacNee, V. Stone, and K. Donaldson. 2001. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. Toxicol. Appl. Pharmacol. 175(3):191-199.

72 Donaldson, K., D. Brown, A. Clouter, R. Duffin, W. MacNee, L. Renwick, L. Tran, and V. Stone. 2002. The pulmonary toxicology of ultrafine particles. J. Aerosol. Med. 15(2):213-220.

73 Bermudez, E., J.B. Mangum, B.A. Wong, B. Asgharian, P.M. Hext, D.B. Warheit, J.I. Everitt, and O.R. Moss. 2004. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. Toxicol. Sci. 77(2):347-357.

It is important to note that the studies evaluating the response to ultrafine and fine titanium dioxide were separate experiments conducted at different times by the same investigator and that no qualitative new toxicities were observed with ultrafine material. Similarly, Renwick et al. (2004) demonstrated that carbon black nanoparticles (14.3 nm) and titanium dioxide nanoparticles (29 nm) were more toxic than their larger counterparts (260 and 250 nm, respectively).

Furthermore, Gurr et al. (2005) reported that 10-20 nm titanium dioxide particles induced oxidative DNA damage, lipid peroxidation, micronuclei formation, and increased hydrogen peroxide and nitric oxide production in a human bronchial epithelial cell line, whereas 200-250 nm particles did not. Hohr et al. (2002)[76] concluded particle surface area, rather than hydrophobic surface determines the acute pulmonary inflammation induced by both fine (180 nm) and ultrafine (20-30 nm) titanium dioxide following intratracheal instillation in rats. Brown et al. (2001) evaluated the pro-inflammatory effects following pulmonary instillation of 3 different sizes of polystyrene microspheres (64, 202, 535 nm in diameter) in rats and reported that there was a significantly greater influx of inflammatory cells (neutrophils) into the lungs of the rats treated with 64 nm particles than the other two sizes. Donaldson et al. (2002) reported that nanoparticles of low-solubility, low-toxicity materials (e.g., titanium dioxide, carbon black, latex) caused more inflammation in the rat lung than fine, respirable particles made from the same material, and that they can impair the ability of macrophages to engulf and clear other particles, thereby increasing the inflammatory process. A 90-day inhalation study by Bermudez et al. (2004) with rats, mice, and hamsters reported that ultrafine titanium dioxide (21 nm) was more toxic than fine titanium dioxide on a per-mass basis but produced similar toxicity on a per-surface-area basis.

Clearly, the toxicological results from these studies are equivocal and it appears that in some instances smaller size was reported to be associated with enhanced toxicity, while in other studies, larger sized particles induced greater toxicity than smaller particles. This suggests that no general conclusions regarding particle size and correlation with inhalation toxicity can be reached based on the available information.

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[74] Bermudez, E. , Mangum, J.B., Asgharian A., Wong, B.A. Reverdy E.E., Janszen, D.B., Hext P.M., Warheit , D.B. and Everitt, J.I. 2002. Long-Term Pulmonary Responses of Three Laboratory Rodent Species to Subchronic Inhalation of Pigmentary Titanium Dioxide Particles. Toxicological Sciences 70, 86-97.

[75] Renwick, L.C., D. Brown, A. Clouter, and K. Donaldson. 2004. Increased inflammation and altered macrophage chemotactic responses caused by two ultrafine particle types. Occup. Environ. Med. 61(5):442-447.

[76] Hohr, D., Y. Steinfartz, R.P. Schins, A.M. Knaapen, G. Martra, B. Fubini, and P.J. Borm. 2002. The surface area rather than the surface coating determines the acute inflammatory response after instillation of fine and ultrafine TiO_2 in the rat. Int. J. Hyg. Environ. Health 205(3):239-244.

A recent publication, in which toxicity studies on a variety of engineered quantum dots were reviewed, also supports the conclusion that toxicological potential may be affected by several physiochemical variables other than size (Hardman 2006).[77] Quantum dots are semiconductor nanocrystals (~2–100 nm) with unique optical and electrical properties that have led to their development for uses, including advanced flat-panel displays, fluorophores for biomedical imaging, and possibly as tools for site-specific gene and drug delivery. They are composed of a core consisting of a variety of metal complexes, such as indium phosphate, zinc sulfide, or cadmium selenide, with shell or cap that can render them more bioavailable, surrounded by a hydrophilic (e.g., polyethylene glycol) coating, often with additional bioactive functional groups. Hardman (2006) concluded that the absorption, distribution, metabolism, excretion, and toxicity of quantum dots depend on multiple factors related both to inherent physicochemical properties and to environmental conditions. In addition, in an *in vitro* study with porcine skin, Ryman-Rasmussen et al. (2006)[78] demonstrated that quantum dots of different sizes, shapes, and surface coatings can penetrate the stratum corneum and localize within the epidermal and dermal layers. Thus, there is no evidence of a toxicity profile common to nanomaterials such as quantum dots, titanium dioxide, or zinc oxide. A recent FDA work showed no evidence of skin penetration of quantum dots on intact mouse skin or tape-stripped mouse skin. Dermabrasion (removal of the entire stratum corneum) was needed to produce penetration of quantum dots into mouse skin.[79] These observations indicate that there is no basis for concluding that nanoparticles are inherently unsafe. Rather, a safety evaluation of products that use forms of nanotechnology should take into account all of the traditional causal factors that may affect safety, one of which may be particle size.

B. Existing Paradigms for Evaluating the Safety of Micronized Material are Suitable for Ensuring the Safety of Personal Care Products

Petitioners selectively cite documents to support their contention that existing testing paradigms are not adequate to assess the safety of nanotechnology. They quote one sentence from a report by an insurance conglomerate[80] as

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[77] Hardman R. (2006) A toxicologic review of quantum dots: toxicity depends on physicochemical and environmental factor. *Environ. Health Perspect.* 114(2): 165-172.

[78] Ryman-Rasmussen JP, Riviere JE, Monteiro-Riviere NA. Penetration of intact skin by quantum dots with diverse physicochemical properties. *Toxicological Sciences* 91 (1), 159-165, 2006. These results are preliminary.

[79] Gopee NV, Roberts DW, Webb P, Cozart C, Siitonen P, Warbritton AR, Walker NJ, Yu WW, Colvin VL, Howard PC. Penetration of nanoscale quantum dots in dermabraded mouse skin. 2006 FDA Science Forum, Poster Abstract B-38, 27 March, 2006. Available at: http://www.cfsan.fda.gov.

[80] Allianz Group. 2005. Small sizes that matter: Opportunities and risks of nanotechnologies. Available at:

saying, "Experts are *overwhelmingly* of the opinion that the adverse effects of nanoparticles cannot be reliably predicted or derived from the known toxicity of the bulk material" (emphasis added by Petitioners). The only reference cited to support this statement, however is to an editorial written by a single scientist to accompany the publication of the results of two studies, performed using routine testing methods, evaluating the toxicity of carbon nanotubes in the lungs of rodents.[81] While Dr. Dreher comments that the toxicity of these particles is greater than particles of graphite, another form of carbon, there is no indication that a new testing paradigm is needed to detect this toxicity. Furthermore, the opinion of a single scientist does not equate to *overwhelming* expert opinion.

Similarly, Petitioners mischaracterize other documents they cite to support their position, such as a report from the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).[82] That document includes the following statement:

> "Experts are of the *unanimous* opinion that the adverse effects of nanoparticles cannot be predicted (or derived) from the known toxicity of material of macroscopic size, which obey the laws of classical physics." (Emphasis added by Petitioners).

However, contrary to Petitioners' statement, this is *not* the conclusion of the SCENIHR report, but a poorly supported statement in the "Background" section of the report. The conclusion of the report includes the statement:

> "Conventional toxicity and ecotoxicity tests have already been shown to be useful in evaluating the hazards of nanoparticles. However, some methods *may* require modification and some new testing methods *may* also be needed." (Emphasis added).

This hardly constitutes an overwhelming rejection of the value of the current toxicity testing paradigm for ensuring the safety of nanoparticles or other nanomaterials.

In two recent reports conspicuously *not* cited by Petitioners, expert panels of scientists in relevant fields concluded that although the assessment of nanomaterials (e.g., micronized particles, nanoparticles) is not without unique

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http://www.allianz.com/Az_Cnt/az/_any/cma/contents/796000/saObj_796424_allianz_study_Nanotechnology_engl.pdf.

[81] K.L. Dreher, 2004. Health and Environmental Impact of Nanotechnology: Toxicological Assessment of Manufactured Nanoparticles. *Toxicol. Sci* 77:3-5. Available at: http://toxsci.oxfordjournals.org/cgi/reprint/77/1/3.

[82] Scientific Committee on Emerging And Newly Identified Health Risks (SCENIHR). 2005. Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies. Available at: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003.pdf

challenges, existing toxicity testing protocols and risk assessment paradigms are suitable. The first report summarizes the conclusions from a workshop conducted to evaluate experimental approaches for assessing the safety of nanomaterials organized by the University of Florida and the National Institute of Environmental Health Sciences in Gainesville, Florida, November 3 and 4, 2004[83]. This workshop included 75 invited participants representing expertise in biology, medicine, toxicology, risk assessment, physics, chemistry, and materials science, drawn from government, industry, academia and public interest sectors and was sponsored by the US Department of Health and Human Services National Toxicology Program (NTP), National Science Foundation (NSF), US Environmental Protection Agency (EPA), US Air Forces Office of Sponsored Research, and the University of Florida. Following the two days of workshops, several central themes emerged. First, it is essential that the physiochemical properties of nanomaterials be thoroughly and completely characterized in toxicological studies and the scientific literature. Participants urged the need for multi-disciplinary studies and meetings to bring together the expertise of toxicologists, chemists, and material scientists. Second, the experts concluded that nanotoxicology need not be a new scientific discipline, stating, "Based on our current understanding, the traditional approaches and study protocols now used for routine toxicological characterization of chemicals or larger particles are sufficiently robust to provide meaningful toxicological characterizations of nanoscale materials." In addition, workshop participants agreed that even considering the unique chemical and physical properties, the "manifestation of biological interactions of nanoscale materials will likely be the same as for any other potentially hazardous agent."[84]

The second consensus report summarizes the conclusions of the International Life Sciences Institute (ILSI) Research Foundation/Risk Science Institute Nanomaterial Toxicity Screening Working group, convened in February 2005 to develop a screening strategy for conducting hazard identification of engineered nanomaterials for subsequent risk assessments and safety evaluations.[85] Again, the authors point out the importance of physiochemical characterization of not only the pure test material, but characterization of the test material as formulated for administration (e.g., once in solution or vehicle) and the material following administration (e.g., cellular or tissue analysis to evaluate material once administered or absorbed) in all *in vitro* and *in vivo* studies. However, the underlying elements for the evaluation of the safety of nanomaterials are those of a "typical" risk assessment paradigm, including the physiochemical characterization of the test material, the selection of appropriate *in vitro* and

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83 Final Report, "Developing Experimental Approaches for the Evaluation of Toxicology Interactions of Nanoscale Materials", Gainesville, FL, November 3-4, 2004. Available at http://ntp.niehs.nih.gov/files/NanoToxWorkshop.pdf.

84 Id.at 9.

85 "Principles for Characterizing the potential human heath effects from exposure to nanomaterials: elements of a screening strategy." Particle and Fibre Toxicology, 2:8, 2005.

tiered *in vivo* methods for hazard identification and dose-response evaluations, determination of human exposure potential, and risk characterization.

Other reviews have raised the possibility that new techniques may be needed to deal with nanotechnology. For example, the European Commission asked the independent experts of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) for a scientific opinion on the "appropriateness of existing methodologies to assess the potential risks of nanotechnologies." In their report issued in March of 2006, the SCENIHR concludes that "current risk assessment methodologies require some modification in order to deal with the hazards associated with nanotechnology and in particular that existing toxicological and ecotoxicological methods may not be sufficient to address all of the issues arising with nanoparticles." (SCENIHR, 2006).[86]

In 2004, a European Commission report[87] concluded that nanomaterials may have different toxicological and ecotoxicological properties than the substances in bulk form and therefore their risks need to be assessed on a case-by-case basis. They stated, "Although the existing toxicological and ecotoxicological methods are appropriate to assess many of the hazards associated with the products and processes involving nanoparticles, they may not be sufficient to address all the hazards. Specifically, particular attention needs to be given to the mode of delivery of the nanoparticle to the test system to ensure that it reflects the relevant exposure scenarios."

Considering all of the expert opinions that have been offered, we believe it is reasonable to conclude at this time that existing paradigms for evaluating nanotechnology are suitable for ensuring the safety of personal care products. At the same time, if further study indicates a need for revisions to existing test methods, we are confident that these can be made within the current knowledge of practical toxicology. We do not believe that expert opinion supports the Petitioner's contention that current methods are wholly unreliable for evaluating the safety of nanotechnology.

C. Conclusion

The Petitioners raise several concerns about the increased potential for enhanced toxicity of nanomaterials versus larger-sized particles of the same chemical materials (e.g., titanium dioxide). The scientific community is

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86 Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Modified Opinion (after public consultation) on "The appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies." Health and Consumer Protection Directorate General of the European Commission, March 2006 (SCENIHR/002/05).

87 European Commission, 2004 "Nanotechnologies: A Preliminary Risk Analysis," Health and Consumer Protection Directorate General of the European Commission.

evaluating the toxicity of several types of nanomaterials and nanoparticles, and the evidence does not support a general assumption of increased toxicity. In addition, the Petitioners raise the issue of the potential for nanoparticles to "be absorbed by organs and tissues and penetrate into cells" and "[O]nce inside cells, they can interfere with cell signaling, cause structural damage, and cause harmful damage to DNA" (p.18). However, many of the hypotheses regarding the potential for differences in the toxicokinetics of nanomaterials are not supported in scientific studies. More importantly, as discussed below in section IV.A and Table 1, studies consistently show that zinc oxide and titanium dioxide nanoparticles in sunscreens do not penetrate the skin. In addition, the purported enhanced toxicity of nanomaterials, as described by Nel et al. (2006)[88] has not been verified in standardized well-designed toxicological studies for most nanomaterials, and is not seen for micronized titanium dioxide and zinc oxide.

IV. Titanium Dioxide and Zinc Oxide Have Established Safety Records

Petitioners specifically attack the use of microfine titanium dioxide and zinc oxide in sunscreens. However, these particles have been used for decades and have been extensively studied by scientists. Furthermore, the FDA has concluded time and time again that these microfine particles are safe and are not new substances.

A. Studies consistently show that zinc oxide and titanium dioxide nanoparticles in sunscreens do not penetrate the skin

The ability of micronized titanium dioxide and zinc oxide to be absorbed through the skin has been investigated in several *in vitro* and *in vivo* dermal penetration studies (Dussert et al. 1997; Bennat and Müller-Goyman 2000; Pflücker et al. 1999; Menzel et al. 2004; Gamer et al. 2006; Lademann et al., 1999; Pflücker et al. 2001; Schulz et al, 2002; Tan et al. 1996).[89 90 91 92 93 94 95 96 97] These studies

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[88] Nel, A., Xia, T., Madler, L., Ning, L. (2006). Toxic potential of materials at the nanolevel. *Science*, 311;622-627.

[89] Dussert, A.-S., E. Gooris, and J. Hemmerle. 1997. Characterization of the mineral content of a physical sunscreen emulsion and its distribution onto human stratum corneum. *Intl. J. Cosmet. Sci.* 19:119-129.

[90] Bennat, C., and C.C. Müller-Goymann. 2000. Skin penetration and stabilization of formulations containing microfine titanium dioxide as physical UV filter. *Intl. J. Cosmetic Sci.* 22:271–283.

[91] Pflücker F et al. 1999. The outermost stratum corneum is an effective barrier against dermal uptake of topically applied micronized titanium dioxide. *Int. J. Cos. Sci.* 21:399-411.

[92] Menzel, F., T. Reinert, J. Vogt, and T. Butz. 2004. Investigations of percutaneous uptake of ultrafine Titanium dioxide particles at the high energy ion nanoprobe LIPSION. *Nuclear Instru. Meth. Phys. Res.* B 219-220:82-86.

consistently show that zinc oxide and titanium dioxide nanoparticles in sunscreens do not penetrate the skin.

Human skin is structured in three layers: epidermis, dermis, and subcutaneous layers. The epidermis, which consists of the outer keratinized horny layer including the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and the stratum basale, forms a very tight protective barrier layer for the underlying dermis. The stratum corneum consists of a relatively thick layer (10-15 µm) of keratinized dead cells. For most chemicals, the stratum corneum is the rate-limiting barrier to percutaneous penetration and serves to prevent chemical substances, such as micronized titanium dioxide or zinc oxide or other nanoparticles from penetrating the alternate hydrophobic/hydrophilic barrier layers and reaching the dermis layer, which consists of viable cells below. Factors affecting the ability to penetrate through the stratum corneum include molecular weight, lipophilicity, polarity, pH, solubility, valence, applied dose, vehicle, and skin parameters such as age, anatomical site, and skin condition (Hostynek 2003).[98]

Inorganic sunscreen agents such as titanium dioxide and zinc oxide reflect, scatter and absorb UV radiation and this ability is determined by a number of factors, including particle size, amount of sunscreen applied, refractive index, and dispersion in a base material (Moloney et al. 2002).[99] In the early 1990s, micronized forms of physical sunscreen became available, with particle sizes of 20 to 50 nanometers (Moloney et al. 2002). This smaller particle size renders the particle transparent on the skin and shifts the protection offered towards the UVB end of the spectrum. Microfine titanium dioxide attenuates UVB and UVA II (315 to 340nm) light, however, it is less effective than zinc oxide in the UVA I range

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[93] Lademann, J., H. Weigmann, C. Rickmeyer, H. Barthelmes, H. Schaefer, G. Mueller, and W. Sterry. 1999. Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. *Skin Pharmacol. Appl. Skin Physiol.* 12(5):247-256.

[94] Gamer A, Leibold E, and B. van Ravenzway. 2006. The *in vitro* absorption of microfine zinc oxide and titanium dioxide through porcine skin. *Toxicology In Vitro* 20, 301-307.

[95] Schulz, J., H. Hohenberg, F. Pflucker, E. Gartner, T. Will, S. Pfeiffer, R. Wepf, V. Wendel, H. Gers-Barlag, and K.P. Wittern. 2002. Distribution of sunscreens on skin. *Adv. Drug Deliv. Rev.* 54 Suppl 1:S157-163.

[96] Tan, M.H., Commens, C.A., Burnett, L., and P.J. Snitch. 1996. A pilot study on the percutaneous absorption of microfine titanium dioxide from sunscreens. *Australa. J. Dermatol.* 37(4):185-187.

[97] Pflücker, F., V. Wendel, H. Hohenberg, E. Gartner, T. Will, S. Pfeiffer, R. Wepf, and H. Gers-Barlag. 2001. The human stratum corneum layer: An effective barrier against dermal uptake of different forms of topically applied micronised titanium dioxide. *Skin Pharmacol. Appl. Skin Physiol.* 14(Suppl 1):92-97.

[98] Hostynek, J.J. 2003. Factors determining percutaneous metal absorption. *Food Chem. Toxicol.* 41(3):327-345.

[99] Moloney FJ, Collins S and GM Murphy. 2002. Sunscreens. Safety, efficacy, and appropriate use. *Am J Clin Derm.* 3(3):185-191.

(340 to 400nm) (Mitchnick et al. 1999).[100] Three points are particularly relevant to understanding the safety of small particle sizes of zinc oxide and titanium dioxide in sunscreens:

- Sunscreens are specifically formulated to maintain the reflective particles (e.g., titanium dioxide and zinc oxide) **on** the surface of the skin in order to be functional (i.e., to limit UV exposure of the skin).
- Microfine powders have always been present in zinc oxide or titanium dioxide-containing products but were optically overwhelmed by the larger particles; thus microfine particles do not represent an entirely new particle size, rather a refinement of the existing particle size distribution (Gasparro et al. 1998; FDA 1999).[101] [102]
- In addition, because of their high surface activity, the primary micronized particles tend to form agglomerates (Bennat and Müller-Goymann 2000).[103]

Both titanium dioxide and zinc oxide are semiconductors that can absorb light, and, under certain conditions (primarily *in vitro*), they may generate free oxygen radicals which may be capable of damaging DNA (Dunford et al. 1997; Nakagawa et al. 1997).[104, 105] The hypothesis that titanium dioxide may enhance UV radiation (UVR)-induced damage has been investigated in acute and chronic photocarcinogenicity studies in mice (Walter and DeQuoy 1980; Suzuki 1987; Bestak and Halliday 1996).[106] In acute studies investigating UVR-induced DNA damage, both titanium dioxide and zinc oxide applied to the skin of hairless mice prevented UVR-induced DNA damage and micronized titanium dioxide substantially reduced UVR-induced tumor formation in mice in two chronic

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[100] Mitchnick, M.A., D. Fairhurst, and S.R. Pinnell. 1999. Microfine zinc oxide (Z-cote) as a photostable UVA/UVB sunblock agent. *J. Am. Acad. Dermatol.* 40(1):85-90.

[101] Gasparro, F.P., M. Mitchnick, and J.F. Nash. 1998. A review of sunscreen safety and efficacy. Photochem. Photobiol. 68(3):243-256.

[102] FDA. 1999. Sunscreen drug products for over-the-counter human use: Final Monograph. 21 C.F.R. Parts 310, 352, 700, and 740, pp. 27666-27693, May 21, 1999.

[103] Bennat, C., and C.C. Muller-Goymann. 2000. Skin penetration and stabilization of formulations containing microfine titanium dioxide as physical UV filter. Intl. J. Cosmetic Sci. 22:271–283.

[104] Dunford R. et al. 1997. Chemical oxidation and DNA damage by inorganic sunscreen ingredients, FEBS Letters 418:87-90.

[105] Nakagawa Y., Wakuri, S., Sakamoto K., and Tanaka N. 1997. The photogenotoxicity of titatnium dioxide particles. Mutation Res. 394:125-132.

[106] Walter JF and DeQuoy. 1980. The hairless mouse as a model for evaluating sunscreens. Arch. Dermatol. 116: 419-420. Suzuki, M. 1987. Protective effect of fine-particle titanium dioxide on UVB-induced DNA damage in hairless mouse skin. Photodermatol. 4:209-211. Bestak, R. and Halliday G. 1996. Sunscreens protect from UV-promoted squamous cell carcinoma in mice chronically irradiated with doses of UV radiation insufficient to cause edema. Photochem. Photobiol. 64, 188-193.

bioassays (Gasparro et al. 1998; Nash 2006[107]). *In vivo* studies have shown that the topical application of metal oxides as sunscreens is beneficial; therefore, there is no evidence that repeated application of titanium dioxide or zinc oxide in the presence of UVR represents a potential human hazard (Gasparro et al. 1998; Nash 2006).

Zinc oxide or titanium dioxide particles used in sunscreen preparations are often coated with other materials such as silicones, fatty acids or oxides of aluminum, silicon or zirconium to aid in dispersion (Gasparro et al. 1998). Coating the anatase titanium dioxide particle with inert oxides of silica, alumina, or zirconium reduces or eliminates the generation of reactive oxygen species (ROS) following UV irradiation (Mills and Le Hunte, 1997).[108] Micronized titanium dioxide is formulated in the less photoactive rutile form and the particles are coated in aluminum oxide, zirconium, or silicon to make them less reactive (Moloney et al. 2002). As a result, the use of coated micronized titanium dioxide or zinc oxide in commercial products should eliminate the concern over the generation of ROS. In addition, microfine zinc oxide is shown to be photostable and non-photoreactive with other organic compounds when combined within a sunscreen (Moloney et al. 2002).

The micronized materials that have been evaluated for dermal penetration include both coated and uncoated particles of titanium dioxide and zinc oxide, and the methods include *in vitro* and *in vivo* studies (human or porcine skin, laboratory animals, human volunteers). Caution is necessary when evaluating results of dermal penetration studies conducted on laboratory animals because of differences in skin morphology, biochemistry, and metabolism between animals and humans. For example, animal skin is generally more permeable than human skin and therefore may overestimate human percutaneous absorption (OECD 2004).[109] The pig is a species of choice for dermal absorption studies because porcine skin structure is very similar to that of humans and the suitability of porcine skin preparations for *in vitro* absorption studies has been validated with *in vivo* penetration studies (Gamer et al. 2006). The principal difference between the *in vitro* and *in vivo* skin penetration methods is that *in vitro* methods reveal the *potential* of a substance to penetrate the skin, whereas *in vivo* methods indicate its *actual penetration*, metabolism, excretion, and body distribution under generally exaggerated use conditions. A limitation associated with *in vitro* studies is that the effects of the peripheral blood flow within the skin

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[107] Nash, J. 2006. Human safety and efficacy of ultraviolet filters and sunscreen products. Dermatol. Clin. 24, 35-51.

[108] Mills, A., and Le Hunte, S. 1997. An overview of semiconductor photocatalysis. J. Photochem. Photobiol. A 108, 1–35.

[109] Organization for Economic Co-operation and Development (OECD). March 2004. Joint meeting of the chemicals committee and the working party on chemicals, pesticides, and biotechnology. Guidance for the conduct of skin absorption studies OECD Series on Testing and Assessment Number 28, ENV/JM/MONO(2004)2.

may not be fully reproduced; however, skin absorption is primarily a passive process and studies undertaken using appropriate *in vitro* experimental conditions have produced validated data for a wide range of chemicals (OECD 2004). Some studies measure percutaneous absorption by the tape stripping method, a technique in which the stratum corneum is removed layer by layer with tape and various analytical methods used to quantify the test substance in the tape strips. Alternatively, absorption can be measured in a sample of treated skin obtained by punch biopsy. Skin penetration can also be determined in vitro, with test material applied to skin samples mounted in a diffusion cell chamber with receptor fluid underneath. The amount of test material in the skin and in the receptor fluid is then quantified over time using a variety of analytical methods. As shown in Table 1, the results from *in vitro* and *in vivo* dermal penetration studies have been almost uniformly consistent, showing that micronized titanium dioxide and zinc oxide do not penetrate into the viable layers of the skin, but rather remain on or within the stratum corneum, with some particles found within hair follicles, but still not in viable tissue.

Table 1
Summary of Dermal Penetration Studies with Micronized TiO_2 and ZnO

Study Type	Test Subject	Test Material	Method	Results	Reference
In Vitro	Human abdominal skin recovered from plastic surgery	Sunscreen containing micronized TiO_2 and ZnO (~100 nm)	TEM analysis of treated skin	No penetration beyond SC	Dussert et al. 1997
	Porcine skin samples	Sunscreen containing 4% ultrafine TiO_2 (20 nm)	Tape stripping and diffusion cells with cellulose; SEM and TEM analysis	No penetration beyond SC	Pflücker et al. 1999
	Human skin from healthy volunteers	Two sunscreen formulations containing 5% microfine TiO_2 (size not provided)	Tape-stripping and diffusion cells with receptor fluid; AAS analysis	No penetration beyond SC	Bennat & Müller-Goyman 2000
	Porcine skin punch biopsies	Four sunscreen formulations containing 4.5-40% micronized TiO_2 (45-150 nm long; 17-35 nm wide)	Frozen sections analyzed for TiO2 content by ion beam analysis	Reported some penetration into SG layer; no TiO_2 in hair follicles	Menzel et al. 2004
	Porcine skin	Sunscreen containing 10%	Diffusion cells with receptor fluid	No penetration beyond SC	Gamer et al. 2006

Table 1 Summary of Dermal Penetration Studies with Micronized TiO_2 and ZnO					
Study Type	**Test Subject**	**Test Material**	**Method**	**Results**	**Reference**
	samples	microfine uncoated ZnO (<160 nm) or coated TiO_2 (60 nm)	Tape-stripping and receptor fluid analysis; AS, AAS, ICP-AES, ICP-MS		
In vivo	Human volunteers	Two sunscreen formulations containing 5% microfine TiO_2 (size not provided)	Tape-stripping; AAS analysis	No penetration beyond SC Depth of penetration greater for skin with several hair follicles	Bennat & Müller-Goyman 2000
	Human volunteers	Three sunscreen formulations containing micronized TiO_2 (10-100 nm)	Punch biopsies after treatment; light and TEM microscopy	No penetration beyond SC	Pflücker et al. 2001; Schulz et al 2002
	Human volunteers	Sunscreen containing TiO_2 microparticles (size not provided)	Tape-stripping; UV/VIS spectroscopy, x-ray fluorescence	No penetration beyond SC; some penetration into hair follicles	Lademann et al. 1999
	Human subjects and cadaver skin	Sunscreen containing 8% microfine TiO_2 (size not provided)	Cyanoacrylate ester and elastic adhesive plaster stripping of epidermis followed by a punch biopsy and ICP-MS analysis	Reported higher concentration of titanium in the dermis of test subjects than untreated cadaver skin; (not stat. sig)	Tan et al. 1996

SC – stratum corneum; SG – stratum granulosum; TEM – transmission electron microscopy; SEM – scanning electron microscopy; AS – atomic spectrometry; AAS – flame atomic absorption spectroscopy; ICP-AES, ICP-MS – inductively coupled plasma-atomic emission spectrometry and mass spectrometry

Using transmission electron microscopy (TEM), Dussert et al. (1997)[110] found no evidence that microfine titanium dioxide or zinc oxide particles could traverse the stratum corneum of sunscreen-treated excised human skin samples. Pflücker et al. (1999) evaluated dermal penetration of titanium dioxide following treatment of excised porcine skin with sunscreen containing ultrafine titanium dioxide (20 nm). Using scanning electron microscopy (SEM) and TEM, the authors reported that titanium dioxide particles did not penetrate the stratum corneum or any underlying viable skin layers.

The formulation of the sunscreen may affect dermal penetration, as reported by Bennat and Müller-Goymann (2000). Microfine titanium dioxide was applied to excised skin samples and human volunteers in either an aqueous suspension or oily emulsion to evaluate skin penetration *in vitro* and *in vivo* using the tape stripping method and analysis by atomic absorption spectroscopy (AAS). Based on the number of tape strips necessary to reach the detection limit for titanium dioxide, the authors concluded that microfine particles of titanium dioxide penetrated deeper into the stratum corneum from an oily dispersion (12 tape strips) than an aqueous one (8 tape strips). In an *in vitro* experiment, skin samples with a large concentration of hair follicles were treated with an oily dispersion of microfine titanium dioxide (Bennat & Müller-Goyman 2000). Titanium penetration was greater when applied to hairy skin (limit of detection was reached after 14 strips), suggesting the potential for penetration into hair follicles or pores. However, no particles were reported to penetrate beyond the stratum corneum.

Menzel et al. (2004) evaluated the dermal penetration of sunscreen formulations containing various sizes and percentages of micronized titanium dioxide on excised porcine skin samples. After application of the sunscreens on porcine skin *in vivo*, titanium content in slices of sections of frozen skin biopsies was measured by ion beam analysis. Titanium was found in high concentrations at the skin surface and in the stratum corneum following treatment with all four formulations. There was some titanium detected in the stratum granulosum layer, however, there was no evidence of penetration of titanium into the stratum spinosum layer. In addition, there was no titanium detected in the hair follicles.

The recent study by Gamer et al. (2006) is the first *in vitro* Organization for Economic Co-Operation and Development (OECD) guideline-compliant study to be conducted to measure the dermal penetration of micronized titanium dioxide and zinc oxide from sunscreen formulations. Split thickness porcine skin samples from the abdominal region were obtained and mounted in dermal penetration cells and treated with two micronized titanium dioxide and one micronized zinc oxide sunscreen formulations. Virtually the total amount of the materials was removed by washing the skin. The amounts of titanium dioxide or

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[110] Dussert, A.-S., E. Gooris, and J. Hemmerle. 1997. Characterization of the mineral content of a physical sunscreen emulsion and its distribution onto human stratum corneum. *Intl. J. Cosmet. Sci.* 19:119-129.

zinc oxide found on the tape strips and the skin preparations were either just above or below the analytical determination limit. No micronized particles or free titanium or zinc ions were found in the receptor fluid and the micronized material did not penetrate into the deeper layers of the skin.

Using light microscopy and TEM, Pflücker et al. (2001) reported that three different sunscreen formulations containing micronized titanium dioxide particles did not penetrate the skin of human volunteers. The results of this study were also reported by Schulz et al. (2002). Using a variety of analytical techniques, Lademann et al. (1999) also reported that micronized titanium dioxide in a sunscreen formulation did not penetrate the stratum corneum of viable skin of human volunteers, although some titanium dioxide microparticles were reported to be observed in a few hair follicles. Importantly, Lademann et al. (1999) concluded, "However, this presence cannot be interpreted as penetration into living layers of the skin, since this part of the follicular channel (the acroinfundibulum) is covered with a horney layer barrier too." Lademann et al. (2001) reported that follicles and sweat glands account for approximately 1% of the skin surface area, so they are not considered to represent significant penetration routes and that titanium dioxide microparticles were found in only 1 out of 10 hair follicles in their 1999 study.

It is important to note that the Citizen Petition states on p. 61, "Several reports show penetration into the deeper parts of the stratum corneum and hair follicles, and a report of increased titanium in the epidermis and dermis following the application of sunscreens containing titanium dioxide" and the study by Lademann et al (1999) is cited for this incorrect and misleading statement. The results from the Lademann et al. (1999) study do not support Petitioners' conclusion regarding dermal penetration of titanium dioxide.

Most of the studies provide *indirect* evidence that micronized titanium dioxide particles do not penetrate the skin because these investigations only determined the penetration of these particles into the skin using tape stripping and electron microscopy or spectroscopy and no mass balance was measured (*i.e.*, the evidence of non-penetration was gained only indirectly) (Gamer et al. 2006). However, the recent study by Gamer et al. (2006) provides *direct* evidence that neither zinc or titanium ions nor micronized zinc oxide and titanium dioxide particles are able to penetrate porcine stratum corneum by quantifying the levels remaining on the skin and in various dermal layers.

In a study that Petitioners described as providing confirmatory evidence for dermal penetration of micronized titanium dioxide, the authors found no statistically-significant difference between subjects treated with titanium dioxide and controls. In this study,a sunscreen containing 8% microfine titanium dioxide was applied to the skin in human subjects (Tan et al. 1996). The subjects consisted of 13 individuals scheduled to have surgery for skin lesions, mean age 71. Subjects were treated with titanium dioxide-containing sunscreen (particle

size not reported) near the skin lesion being excised for "a period of 2-6 weeks" (it is not clear if they were all treated for the same amount of time). Nine cadaver skin samples were obtained from a body location "not likely to have been exposed to titanium dioxide-containing lotions" to serve as controls. After treatment, tissue concentration of titanium was measured by first removing the stratum corneum layer with cyanoacrylate ester and elastic adhesive plaster stripping followed by a punch biopsy of the remaining dermal layer and ICP-MS analysis of the digested skin tissue (Tan et al. 1996). The remaining skin tissue was not analyzed (e.g., light microscopy or TEM) to determine if the stratum corneum was entirely removed, so it is possible that the cyanoacrylate ester stripping method did not remove the entire stratum corneum layer. The authors reported that higher titanium levels were detected in the skin biopsy samples of treated subjects (16 samples) when compared to titanium levels in cadaver skin (9 samples), but this difference was not statistically significant. However, the authors reported that removal of one high value, with no *a priori* criteria for such action in the cadaver group resulted in a statistically significant increase in titanium in the dermis of treated subjects, leading them to conclude that this was evidence of skin penetration by microfine titanium dioxide. They concluded that there were higher levels of titanium in the dermis of the subjects that applied microfine titanium dioxide than in the cadaver controls. The authors also noted that a larger sample size would be necessary to confirm this finding.

This single study reporting greater potential of "microfine" titanium dioxide to be percutaneously absorbed has significant limitations, including: 1) the use of diseased skin from elderly patients; 2) the use of cadaver skin as unmatched controls; 3) failure to determine the distribution or localization of titanium dioxide in skin tissue; 4) use of an unconventional dermal penetration study method; 5) size of titanium dioxide particles in the test substance was not characterized or reported; and, 6) the reported differences in titanium levels between the treated and control groups were not statistically significant (Tan et al. 1996). Therefore, there are several significant problems with concluding that micronized particles from sunscreens or cosmetics will penetrate the skin based on the results of this preliminary pilot study. There are several well-designed studies that utilize standardized and sophisticated analytical methods for measuring the dermal distribution and quantity of absorbed titanium dioxide and/or zinc oxide, as shown in Table 1. The results from these studies and the weight-of-the-evidence definitely do not support Petitioners' conclusion that micronized titanium dioxide or zinc oxide penetrate the stratum corneum and get absorbed into viable skin layers.

Some absorption of zinc through damaged skin has been observed in burn patients treated with zinc oxide dressings (Barceloux 1999)[111]; however, skin absorption studies with intact and psoriatic skin reported a lack of zinc oxide

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[111] Barceloux, D.G. 1999. Zinc. J. Toxicol. Clin. Toxicol. 37(2):279-292.

absorption (Gasparro et al. 1998; Nash 2006).[112] A limited number of studies have reported that Zn^{2+} penetrated wounded rodent skin and human skin from a zinc oxide-containing dressing; however, Zn^{2+} was detected in the fluid of blisters, which is not representative of intact skin (Gasparro et al. 1998). According to Pinnell et al. (2000)[113], microfine zinc oxide particles are too large to enter the skin, and thus would not be expected to be dermally penetrable. Further, they state that, because zinc exists as a single ionization state at physiological pH, it would not be expected to demonstrate redox activity, and therefore, the safety of zinc oxide as a topical medication for human skin is unsurpassed. Microfine zinc oxide (<200 nm) became available for use in the 1990s (Mitchnick et al. 1999). It is the only sunscreen ingredient that appears in more than one FDA monograph (permitted for use in sunscreens and in diaper rash creams) and may be the most commonly used topical drug of all time (Mitchnick et al. 1999).

In conclusion, the extensive experience with the use of micronized titanium dioxide and zinc oxide in sunscreens, cosmetics, and/or diaper creams does not indicate any dermal toxicity or dermal penetration concerns.

B. Petitioners have failed to provide evidence that the use of nanoparticles of titanium dioxide and zinc oxide in sunscreens is unsafe

Petitioners put forth several arguments about the safety of micronized titanium dioxide and zinc oxide. They conclude that the physiochemical properties of micronized titanium dioxide and zinc oxide impart substantial differences in toxicity from larger-sized particles of the same materials (e.g. micrometer sized particles). Because of this potential difference in toxicity, Petitioners state that the safety of micronized titanium dioxide and zinc oxide cannot be inferred from testing on the larger-sized "bulk" material, and evaluation of their safe use in sunscreens and cosmetics will require a whole new testing paradigm. However, CTFA strongly disagrees with Petitioners' assertions and believes that the safety of titanium dioxide and zinc oxide for use in sunscreens and cosmetics has been thoroughly demonstrated. Further, as stated and in the opinion of independent experts, the current toxicological testing paradigms are sufficiently robust to address the safety of micronized materials and other nanoparticles that may be used in sunscreens and/or cosmetics.

Petitioners have failed to provide evidence that the use of nanoparticles of titanium dioxide and zinc oxide in sunscreens is unsafe because they have not

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[112] Gasparro, F.P., M. Mitchnick, and J.F. Nash. 1998. A review of sunscreen safety and efficacy. Photochem. Photobiol. 68(3):243-256.

[113] Pinnell, S.R., D. Fairhurst, R. Gillies, M.A. Mitchnick, and N. Kollias. 2000. Microfine zinc oxide is a superior sunscreen ingredient to microfine titanium dioxide. *Dermatol.Surg.* 26(4):309-314.

offered scientific evidence that these ingredients penetrate the skin and cause harm when used in sunscreens. Although they cite a study published by Lademann et al. as support for the proposition that there is increased titanium on certain parts of skin after sunscreen application, that study in fact found that penetration of microparticles into viable skin tissue could not be detected.[114] Reliance on the study conducted by Tinkle et al. (2003) for the proposition that titanium dioxide particles of up to one micron in diameter can get deep enough into the skin to be taken into the lymphatic system is similarly inappropriate. The Tinkle study simply examined dermal penetration of fluorospheres, and did not address, test or measure dermal penetration of titanium dioxide particles.[115]

Thus, Petitioners have conducted no tests and did not cite any studies reporting dermal penetration of titanium dioxide and zinc oxide nanoparticles from sunscreen or cosmetic products. In contrast to Petitioners' unsupported claims, CTFA can cite numerous studies showing that titanium dioxide and zinc oxide nanoparticles do not penetrate the skin or cause harm, as will be discussed in more detail below. Moreover, in Europe, the Scientific Committee on Emerging and Newly Identified Health Risks has found that there is no evidence that specific health problems are currently arising from dermal penetration of nanoparticles.[116] In light of evidence that titanium dioxide and zinc oxide nanoparticles in sunscreens do not penetrate the skin, Petitioners' argument that nanoparticles have "the unique ability to move from one area of the body to another, be absorbed by organs and tissues, and penetrate cells" has little relevance to sunscreens and fails to cast doubt upon the safety of the nanoparticles in sunscreens.[117] In contrast, the Scientific Committee on Cosmetic and Non-Food Products (SCCNFP), which advises the European Commission, has considered the safety of titanium dioxide nanoparticles, and declared them safe for use.[118]

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[114] Citizen Petition at 61; Lademann et al., Penetration of Titanium Dioxide Microparticles in a Sunscreen Formulation into the Horny Layer and the Folliculer Orifice, Skin Pharmacology and Applied Skin Physiology 1999;12:247-256.

[115] Citizen Petition at 61; Tinkle et al., Skin As a Route of Exposure and Sensitization in Chronic Berryllium Disease, Environmental Health Perspectives, Volume 111, Number 9, July 2003.

[116] Scientific Committee on Emerging and Newly Identified Health Risk, Modified Opinion (after public consultation) on the Appropriateness of Existing Methodologies to Assess the Potential Risks Associated with Engineered and Adventitious Products of Nanotechnologies at 40, March 10, 2006. Available at http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_003b.pdf.

[117] Citizen Petition at 18.

[118] The Royal Society and the Royal Academy of Engineering, Nanoscience and Nanotechnologies: Opportunities and Uncertainties at 43-44, July 2004, available at http://www.nanotec.org.uk/finalReport.htm.

C. FDA Already Comprehensively Regulates Titanium Dioxide and Zinc Oxide

For more than a quarter-century, FDA has regulated titanium dioxide and zinc oxide as ingredients in a wide range of products, including sunscreen drug products. Pursuant to the agency's public, multi-step OTC drug review, the agency has conducted a rigorous review of the safety and effectiveness of products containing these ingredients. In fact, in drafting the sunscreen monograph, the agency considered the scientific data regarding use of micronized and ultra-fine particles of titanium dioxide and zinc oxide and concluded that these ingredients may safely be used in OTC sunscreen drug products. Throughout this process, the agency has remained committed to a regulatory scheme that is firmly rooted in the most accurate and reliable scientific evidence available. The unsupported claims presented in Petitioners' Citizen Petition would disrupt this scientifically sound regulatory system. Regulatory history indicates that titanium dioxide and zinc oxide have established records of safe use in a variety of products.

FDA regulates titanium dioxide and zinc oxide in a variety of products. The agency has approved the use of titanium dioxide as a color additive in foods, drugs, cosmetics, and contact lenses, and as a preservative in polymeric coatings for polyolefin films intended for contact with food.[119] In addition, it has listed zinc oxide as an approved color additive in drugs and cosmetics.[120] These color additives are exempt from certification and may be used around the eye.[121] The agency has also endorsed the use of zinc oxide as a nutrient in food, a direct human food ingredient, a colorant for polymers, a protectant for injured and exposed skin, and an ingredient in anorectal drug products and treatments for diaper rash.[122] As recently as this year, FDA approved the use of mica-based pearlescent pigments coated with titanium dioxide as color additives in ingested drugs and food.[123] They may also be used in contact lenses.[124]

With respect to OTC sunscreen drug products, FDA has already conducted a comprehensive public examination of the scientific evidence regarding use of titanium dioxide and zinc oxide.[125] As a result of this review, the agency has concluded that sunscreens containing titanium dioxide and zinc oxide are generally recognized as safe and effective and not misbranded when these

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119 21 C.F.R. §§ 73.575, 73.1575, 73.2575, 73.3126, 175.320.

120 21 C.F.R. §§ 73.1991, 73.2991.

121 Id.

122 21 C.F.R. § 182.8991; 56 Fed. Reg. 60652; 21 C.F.R. § 178.3297; 68 Fed. Reg. 33362; 55 Fed. Reg. 31776; 55 Fed. Reg. 25204.

123 21 C.F.R. §§ 73.1128, 73.350.

124 21 C.F.R. § 73.3128.

125 37 Fed. Reg. 26456.

ingredients are present in concentrations up to 25%.[126]

1. Under FDA's regulation of over-the-counter sunscreen drug products, titanium dioxide and zinc oxide are generally recognized as safe and effective and not misbranded in concentrations of up to 25%

OTC sunscreen drug products have been part of FDA's OTC drug review since it was established in 1972.[127] That year, FDA invited the public to present data on sunscreen ingredients for review.[128] Subsequently, the agency published the Advisory Review Panel on OTC Topical, Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products' recommendations on the safety and effectiveness of sunscreen products and a proposed regulation containing the monograph recommended by the panel.[129] A public meeting was also announced to discuss the panel's recommendations regarding final product testing.[130] In 1993, the agency published the tentative final monograph (TFM).[131] After its publication, FDA announced a public meeting on procedures to demonstrate that OTC sunscreen drug products protect users from ultraviolet A (UVA) radiation.[132] The agency later amended the TFM to include only active ingredients for which United States Pharmacopeia (USP) monographs then existed or for which interest in developing USP monographs had been expressed.[133] It also announced a public meeting to obtain data on the photochemistry and photobiology of sunscreens and amended the TFM to classify zinc oxide as a category I ingredient.[134]

Finally, on May 21, 1999, FDA published the final monograph.[135] However, FDA stayed the effective date of the monograph so that the agency could address formulation, labeling, and testing requirements for both UVA and ultraviolet B (UVB) radiation protection.[136] Nevertheless, throughout its review, FDA has thoroughly examined the use of titanium dioxide and zinc oxide, utilizing this

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126 64 Fed. Reg. 27666, 27687.

127 37 Fed. Reg. 26456.

128 Id.

129 43 Fed. Reg. 28206.

130 52 Fed. Reg. 33598.

131 58 Fed. Reg. 28194.

132 59 Fed. Reg. 16042.

133 59 Fed. Reg. 29706. USP monographs include an ingredient's official name, chemical formula, and analytical chemical tests to confirm the quality and purity of the ingredient. 64 Fed. Reg. 27666, 27681.

134 61 Fed. Reg. 42398; 61 Fed. Reg. 48645; 62 Fed. Reg. 23350; 63 Fed. Reg. 56584.

135 64 Fed. Reg. 27666.

136 66 Fed. Reg. 67485.

multi-step, public process to take all available data into account.

a) FDA has repeatedly classified titanium dioxide as a safe and effective ingredient in sunscreens.

As early as 1978 when FDA published the proposed monograph, the advisory panel took the position that titanium dioxide was safe and effective for OTC use as a sunscreen in concentrations of up to 25%.[137] The panel's conclusion was grounded in preclinical data, clinical use data and market experience.[138] For example, acute oral toxicity studies revealed that a single dosage of titanium dioxide did not lead to fatalities or gross organ abnormalities in rats, and a pound of titanium dioxide had been ingested by humans without harm and distress, and was eliminated from the body in twenty-four hours.[139] Moreover, between 1949 and 1972, none of the complaints about sunscreen products could be attributed to titanium dioxide.[140] Also, studies showed that titanium dioxide effectively scattered UV rays.[141] Thus, the panel concluded that titanium dioxide was "'perhaps the most suitable and widely used' light-scattering ingredient in sunburn preventives," and classified it as a category I ingredient.[142]

After FDA published the proposed rule, it continued to regulate titanium dioxide as a category I ingredient.[143] In the TFM, FDA took the position that titanium dioxide was a category I ingredient that absorbed harmful UVA radiation.[144] It also concluded that sunscreen products containing titanium dioxide could bear UVA claims, and that titanium dioxide was the only category I sunscreen active ingredient that could be classified as a sunblock.[145] When FDA excluded active ingredients for which no USP monographs existed, titanium dioxide was one of fifteen ingredients that met this higher standard.[146]

After publication of the TFM, FDA continued to examine titanium dioxide's safety and effectiveness.[147] Although a study showed that the combination of titanium dioxide and UV radiation could be cytotoxic to certain cancer cells, FDA stated that the relevance of this study to sunscreen use in humans was not known

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137 43 Fed. Reg. 38206, 38250-51.

138 Id. at 38250.

139 Id.

140 Id. at 38251.

141 Id.

142 Id.

143 See, e.g., 58 Fed. Reg. 28194.

144 Id. at 28232, 28281.

145 Id. at 28233, 28240.

146 59 Fed. Reg. 29706.

147 See, e.g., 61 Fed. Reg., 42398, 42399; 62 Fed. Reg. 23350, 23354.

because the cells used in the study were not normal.[148] In 1997, FDA evaluated the combination of titanium dioxide and avobenzone.[149] After this extensive review of the safety and effectiveness of titanium dioxide in sunscreens, FDA classified titanium dioxide as a category I active ingredient in the final monograph.[150]

Significantly, while crafting a regulation for the use of titanium dioxide in sunscreens, FDA has made it clear that micronized titanium dioxide does not present a safety concern and that it is a specific grade of titanium dioxide originally reviewed by the panel.[151] In fact, FDA was aware of the existence of ultra-fine titanium dioxide before the final monograph was published, as evidenced by its 1996 comment that "ultra-fine forms of [titanium dioxide] have been developed that are more esthetically pleasing."[152] In the final monograph, the agency clearly stated that it "d[id] not consider micronized titanium dioxide to be a new ingredient but consider[ed] it a specific grade of the titanium dioxide originally reviewed by the Panel."[153] It recognized that "'fines' have been part of commercially used titanium dioxide powders for decades, and that a micronized product simply refers to a refinement of particle size distribution."[154] Moreover, FDA acknowledged that no evidence "demonstrate[ed] a safety concern from the use of micronized titanium dioxide in sunscreen products."[155] Rather, the data showed that micronized titanium dioxide did not cause deleterious effects in acute animal toxicity, irritation, sensitization, photoirritation, photosensitization, and human repeat insult patch and skin penetration studies.[156] FDA's final regulation of the use of titanium dioxide in sunscreens even took into account the use of micronized titanium dioxide by eliminating the use of the term "sunblock" because it was not consistent with how the micronized form of the ingredient functioned.[157]

In sum, FDA has regulated the use of titanium dioxide in sunscreens for more than a quarter-of-a-century and repeatedly concluded that it is safe, effective, and not misbranded.

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148 61 Fed. Reg. 42398.

149 62 Fed. Reg. 23350, 23354.

150 64 Fed. Reg. 27666, 27687.

151 Id. at 27671.

152 61 Fed. Reg. 42398, 42399.

153 64 Fed. Reg. 27666, 27687.

154 64 Fed. Reg. 27666, 27671.

155 Id.

156 Id.

157 Id. at 27680.

b) FDA classifies zinc oxide as a safe and effective sunscreen ingredient.

FDA first identified zinc oxide as an ingredient in OTC sunscreen drug products in 1972 when it invited the public to submit data and other information pertinent to all active sunscreen ingredients.[158] After review, the panel classified zinc oxide as an inactive ingredient, but FDA classified it as a category III ingredient in the TFM.[159] When FDA published the TFM, data was insufficient to show zinc oxide's effectiveness because it only pertained to one subject.[160] Nevertheless, in the TFM, the agency recognized that the range of UV radiation absorbed by zinc oxide was similar to the UV radiation range reported for other sunscreen ingredients, and that zinc oxide had been used by consumers for many years as a sunblock.[161]

FDA continued to evaluate the safety and effectiveness of the use of zinc oxide in sunscreens after the TFM was published.[162] In 1996, FDA evaluated additional effectiveness data to support a category I safe and effective status for the ingredient.[163] It also issued a request for information on the absorption and long-term safety of topical applications of zinc oxide and on zinc oxide's ability to photocatalyze.[164]

In 1998, after extensive review of data on the use of zinc oxide, FDA classified it as a category I ingredient in concentrations of up to 25%.[165] FDA cited seven studies showing that zinc oxide was effective, one study showing it blocked radiation in the UVA II range, and spectral profiles of zinc oxide that demonstrated it provided both UVA and UVB protection.[166] Although FDA noted it was continuing to evaluate the photostability and photochemistry of zinc oxide and titanium dioxide, it continued to believe there were no safety concerns regarding the use of zinc oxide.[167] This belief was based on the panel's evaluation of zinc oxide as a safe and effective skin protectant and zinc oxide's long history of use in various drug and cosmetic products.[168]

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158 37 Fed. Reg. 26456.

159 43 Fed. Reg. 38206, 38208; 58 Fed. Reg. 28194, 28213.

160 Id.

161 Id.

162 See, e.g., 61 Fed. Reg. 42398, 42399.

163 61 Fed. Reg. 42398, 42399.

164 Id.

165 63 Fed. Reg. 56584.

166 Id. at 56584-86.

167 Id. at 56587.

168 Id. at 56587.

FDA confirmed the category I status of zinc oxide in the final monograph.[169] The monograph did not, however, authorize the combination of zinc oxide with avobenzone, and FDA stated its intention to further evaluate the issue of whether certain sunscreens containing zinc oxide could provide protection against photoaging.[170]

Significantly, FDA was aware of the existence of ultra-fine forms of zinc oxide in sunscreens before it crafted a regulation for the safe and effective use of the ingredient.[171] As early as 1996, the agency noted that "ultra-fine forms of [zinc oxide] [had] been developed that [were] more esthetically pleasing."[172] In fact, in the very notice FDA published to announce that it continued "to believe that there [were] no safety concerns regarding the use of zinc oxide as a sunscreen active ingredient," the agency recognized that manufacturers had "developed ultra fine forms of [zinc oxide] in the range of 0.02 to 0.10 microns that are transparent on the skin, may offer both UVA and UVB protection, and are esthetically pleasing."[173]

2. The current sunscreen monograph adequately regulates the use of titanium dioxide and zinc oxide nanoparticles in OTC sunscreen drug products

As FDA has repeatedly stated, it regulates products, not the technology used to produce them.[174] And in the case of products produced using nanotechnology, the agency's existing regulations are more than sufficient to ensure that products entering the market continue to be safe and effective.[175] Petitioners' arguments provide no basis to conclude otherwise. In fact, the Citizen Petition submitted by Petitioners provides no evidence that products containing nanoparticles -- including sunscreen products that use titanium dioxide and zinc oxide -- present a safety issue.

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169 64 Fed. Reg. 27666, 27680.

170 Id.

171 61 Fed. Reg. 42398, 42399.

172 Id.

173 63 Fed. Reg. 56584, 56586-87. Two inorganic or physical sunscreens, titanium dioxide and zinc oxide, tend to reflect or scatter energy rather than absorb it. They are based on inorganic salts and have been growing in popularity over the last 10 years due to their broad-spectrum properties and generally safer irritation potential than many organic or chemical sunscreens. There are smaller-size titanium and zinc oxide particles and better emulsifiers and formulations to assist in the creation of aesthetically acceptable finished products. *The Evolution of Sun Care*, Functional Foods & Nutraceuticals, September 2006. Available at: http://www.ffnmag.com/NH/ASP/strArticleID/1092/strSite/FFNSite/articleDisplay.asp.

174 See FDA and Nanotechnology Products, Frequently Asked Questions, available at http;//www.fda.gov/nanotechnology/faqs.html.

175 Id.

Petitioners' attack on FDA's position overlooks the fact that existing requirements and tests have already accurately assessed the safety of many of products that pass through the nano range.[176] Contrary to Petitioners' assertions, particle size does not present a new issue for FDA because most nanotechnology products the agency regulates are in the same size range as other products that FDA reviews.[177] For instance, degradable medical devices and injectable pharmaceuticals regulated by FDA generate particulates that pass through the nano size range during the process of absorption and elimination by the body.[178] To date, FDA has received no reports of adverse reactions related to the size of particles in these products.[179] The lack of complaints indicates existing regulations accurately assess safety.[180]

Even less substantiated by science, however, is Petitioners' claim that sunscreens containing titanium dioxide and zinc oxide nanoparticles are not properly regulated under the final monograph for OTC sunscreen drug products.[181] In order to find in favor of the aforementioned argument, FDA must conclude that products containing these particles are new substances that present a safety hazard to consumers. As Petitioners point out, however, FDA has already concluded that, smaller, micronized particles of titanium dioxide are not new substances and that there is no evidence demonstrating that these micronized particles are unsafe.[182] Additionally, Petitioners concede the effectiveness of zinc oxide and titanium dioxide nanoparticles by admitting that they have the ability to absorb and reflect UV light.[183] Thus, Petitioners have failed to offer any evidence that nanoparticles of titanium dioxide and zinc oxide are not safe and effective, or that they are new ingredients.

In sum, the current sunscreen monograph adequately regulates the use of all sizes of titanium dioxide and zinc oxide in sunscreen drug products. Petitioners' argument to the contrary must fail because it is not supported by science.

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176 Citizen Petition of the International Center for Technology Assessment ("Citizen Petition") at 14; FDA, FDA and Nanotechnology Products, Frequently Asked Questions, http://www.fda.gov/nanotechnology/faqs.html.

177 FDA, FDA and Nanotechnology Products, Frequently Asked Questions. Available at: http://www.fda.gov/nanotechnology/faqs.html.

178 Id.

179 Id.

180 Id.

181 Citizen Petition at 49-53.

182 64 Fed. Reg. 27666, 27671.

183 Citizen Petition at 16-17.

3. Conclusion

FDA comprehensively regulates the use of titanium dioxide and zinc oxide in a variety of different products. In particular, FDA has used a multi-step, public process to craft a regulation for OTC sunscreen drugs that recognizes these ingredients are safe and effective. Petitioners wrongly attempt to disrupt this carefully developed regulatory scheme by making claims about the safety of titanium dioxide and zinc oxide nanoparticles that are unsupported by science. In fact, products containing these ingredients continue to be adequately regulated under FDA's comprehensive regulatory system.

D. Determinations of Safety by Other Authoritative Bodies

1. Scientific Committee on Cosmetic Product and Non-Food Products Intended for Consumers (SCCNFP) Determination of Safety - Titanium Dioxide and Zinc Oxide

a) Titanium dioxide

The Scientific Committee on Cosmetic Product and Non-Food Products (SCCNFP)[184] , which is the scientific advisory body to the European Commission in matters of consumer protection for cosmetics and non-food products, undertook a comprehensive review of the data on titanium dioxide and published their finding in 2000.[185] SCCNFP was asked to: 1) consider if the safety profile for titanium dioxide was sufficient for listing the material in part 1 of Annex VII (i.e., list of UV absorbers permitted in cosmetics), 2) approve a concentration limit of 25% and, 3) comment on the need for additional requirements for the use of titanium dioxide in cosmetics. SCCNFP reviewed over 30 studies on various coated and uncoated preparations of micro-crystalline titanium dioxide (most studies evaluated materials containing 15-35 nm titanium dioxide particles; some studies were conducted with material containing 60-200 nm sized titanium dioxide particles).

SCCNFP performed a thorough review of over 100 published and unpublished studies with microfine and larger particle formulations of titanium dioxide (including "pigmentary" or "bulk"). SCCNFP reported that the acute oral toxicity of coated and uncoated titanium dioxide is very low and that subchronic oral toxicity of uncoated titanium dioxide is also low. Long term feeding studies in

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184 The SCCNFP is a scientific review panel operated by the European Commission for the purpose of assessing the safety of consumer products, including cosmetics. The committee was renamed the Scientific Committee for Consumer Products (SCCP) in 2004. Available at: http://ec.europa.eu/health/ph_risk/committees/sccp/sccp_en.htm and http://ec.europa.eu/health/ph_risk/committees/04_sccp/04_sccp_en.htm.

185 Opinion of the Scientific Committees on Cosmetic Product and Non-Food Products intended for Consumers concerning Titanium"; adopted by the SCCNFP during the 14th plenary meeting of 24 October 2000. (SCCNFP/0005/98).

rodents with uncoated pigmentary titanium dioxide showed no evidence of carcinogenesis. Inhalation studies in rodents and epidemiological studies suggest that titanium dioxide causes an increase in the incidence of lung tumors. This, however, probably reflects the actions of irritating dusts generally and pulmonary overload conditions. Irritation of the skin is low or absent in animals and humans treated with coated or uncoated titanium dioxide. Irritation of mucous membranes is low or absent, both with coated and uncoated material; however, in one ocular irritation experiment in rabbits, uncoated non-micronized titanium dioxide was judged to be a moderate irritant. Sensitization in animals and human subjects did not occur following treatment with either coated or uncoated material. Titanium dioxide was not phototoxic in *in vivo* or *in vitro* studies, and no photosensitization or photoirritation was observed. Titanium dioxide was reported to be photocatalytic in ultraviolet light, but the clinical relevance of this is unclear because of the lack of dermal penetration by micronized titanium dioxide, as well as the fact that the coated preparations show much less photo-catalytic activity than the uncoated material.

More than 10 different *in vitro* or *in vivo* studies on skin penetration of primarily micronized titanium dioxide are summarized in the SCCNFP opinion on titanium dioxide (SCCNFP 2000). SCCNFP concluded that the unpublished skin penetration studies suggest, "Extensive tests for percutaneous absorption, mostly *in vitro*, indicate that absorption does not occur, either with coated or uncoated material; one experiment found some evidence that a little of the material could be found in the openings of the follicles." The results of all studies consistently report that micronized titanium dioxide remains on the skin surface or within the outer layers of the stratum corneum and does not penetrate into or through the viable skin.

As part of their review, mutagenicity, photo-mutagenicity, and phototoxicity studies conducted on titanium dioxide were summarized as shown in Table 2. These studies were performed on more than 10 different forms of titanium dioxide used in sunscreens, including micrometer- and nanometer-size rutile and anatase crystalline forms, as well as coated and uncoated particles. The overall conclusion of the studies was that the hazard profile was similar for all test substances. No major difference in the safety profile was found between micro-sized and nanometer-sized particles, and no evidence was found suggesting that nano-sized particles pose any new health risks.

Table 2
Mutagenicity, Photomutagenicity, and Phototoxicity Studies with Titanium dioxide
SCCNFP 2000

Product Name	Crystalline Form [a]	Coating Material	Particle size (nm)	Test	Results

T805	RU/AN	SiO_2	21	Ames, photo-Ames, CA [b], photo-CA, NRU [c]	All negative
T817	RU/AN	SiO_2 / FeO	21	Ames, photo-Ames, CA, photo-CA, NRU	All negative
EUSOLEX 2000	RU	Al_2O_3	14	Photo-Ames, Photo-CA	All negative
M262, M212, M160, X161	RU	Al_2O_3 / stearic acid	15 – 20	Photo-Ames, Photo-CA	All negative
MT-100TV	RU	Al_2O_3 / stearic acid	15	Photo-Ames, Photo-CA, NRU	All negative
MT-100TV	RU	Uncoated	15	Photo-Ames, Photo-CA, NRU	All negative
X-200	RU	Uncoated	20	Photo-Ames, Photo-CA, NRU	All negative
SOLAVEIL	RU	Al_2O_3 / SiO_2	11-28	Photo-CA	Negative
MIRASUN TiW60	AN	Al_2O_3 / SiO_2	60	Photo-Ames, Photo-CA	All negative
AFDC	AN	Uncoated	200	Photo-Ames, Photo-CA, NRU	All negative
MIRASUN TiWGO	AN	Uncoated	60	Photo-Ames, Photo-CA	All negative

[a] AN = anatase; RU = rutile [b] CA = chromosome aberrations in mammalian cells
[c] NRU = Neutral red uptake phototoxicity test

In conclusion, SCCNFP stated, "The toxicological profile of this material does not give rise to concern in human use, since the substance is not absorbed through the skin. In view, also, of the lack of percutaneous absorption, a calculation of the margin of safety has not been carried out." Based on these data, titanium dioxide, irrespective of size (including micronized forms) was added to the list of allowed UV absorbers at a concentration of up to 25%.

b) Zinc Oxide

SCCNFP also reviewed the safety of micronized zinc oxide for use in sun-protection products.[186] The particle size of microfine or micronized zinc oxide is approximately 0.2 µm (200 nm) or less. SCCNFP reviewed approximately 25 published and unpublished studies with zinc oxide; however, it is not clear how

[186] http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out222_en.pdf.

many of the studies were conducted with micronized zinc oxide, as many of the studies did not provide information about the particle size of the tested material. They reviewed oral, inhalation, and dermal toxicity studies, and studies to evaluate irritation, sensitization, teratogenicity, percutaneous absorption, genotoxicity/mutagenicity, phototoxicity, and photoirritation potential of zinc oxide. In addition, studies conducted to evaluate the photostability and photoreactivity zinc oxide were also reviewed. Three percutaneous penetration studies on zinc oxide particles were reviewed and none of these studies suggested penetration into living human or porcine skin. As previously discussed, a recent, state-of-the-art percutaneous penetration study reported that zinc oxide nanoparticles did not penetrate into or through porcine skin (Gamer et al. 2006), thus providing the necessary data for SCCNFP to perform a safety assessment of zinc oxide.

SCCNFP reviewed a summary table of 8 genotoxicity studies and concluded: 1) zinc oxide and zinc salts have mutagenic and/or genotoxic *in vitro* activity (gene mutation, chromosome aberrations, and unscheduled DNA synthesis in mammalian cells) and 2) *in vivo* studies are not conclusive (some positive results have been reported, including bone marrow cytogenic assay in rodents and host-mediated assay in mice). These studies, which were probably all conducted with non-micronized zinc oxide, are summarized in Table 3. SCCNFP also reviewed 4 photomutagenicity studies with zinc oxide – 1 bacterial reverse mutation assay was negative for mutations in the presence or absence of UV irradiation and 2 mammalian chromosomal aberration assays and 1 photocomet assay were positive for DNA damage in the presence of UV irradiation. The results regarding the genotoxic or mutagenic potential of zinc oxide are inconclusive, primarily because the studies have been conducted with a variety of different types and sizes of zinc oxide in different assay systems, making it difficult to compare results. Further, in a toxicological review of zinc compounds, EPA concluded that tests of the genotoxic effects of zinc compounds, including zinc oxide have been equivocal (EPA 2005).[187]

SCCNFP released their report on zinc oxide in June, 2003 stating "Based on the conclusions (point 2.12), the SCCNFP is of the opinion that more information is needed to enable a proper safety evaluation of micronised zinc oxide for use as a UV filter in cosmetic products. Consequently, an appropriate safety dossier on micronised zinc oxide itself, including possible pathways of cutaneous penetration and systemic exposure, is required." This opinion was based on their conclusion from their review of 3 unpublished *in vitro* photomutagenicity tests and stated micronized zinc oxide was: 1) photoclastogenic (causes chromosome breaks by UV activation), 2) possibly photo-aneugenic (causes changes in chromosome number by UV activation), and, 3) is a photo-DNA-damaging agent

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[187] US Environmental Protection Agency. 2005. Toxicological review of zinc and compounds, EPA/635/R-05/002. Available at: http://www.epa.gov/iris/toxreviews/

in mammalian cells cultured *in vitro*. However, the relevance of these findings needs to be clarified by appropriate investigations *in vivo*. ZnO protects skin against UV-induced damage (see Van der Molen and Nohynek references quoted page 45), and therefore, such an in-vivo follow up study is highly unlikely to show a photo-carcinogenic potential of ZnO. SCCNFP also concluded that there is a lack of reliable data on the percutaneous absorption of micronized zinc oxide. In a 2005 statement, the SCCP concluded there is a lack of reliable data on the percutaneous absorption of microfine zinc oxide and the potential for absorption by inhalation and that more information is required to enable a proper safety assessment. [188]

The data that SCCNFP requested in their opinion on zinc oxide has been developed and provided to them. This data, as presented by Gamer et al. 2006, concludes that micronized zinc oxide is not absorbed and is safe for use in sun-protection products.[189] Importantly, SCCNFP also concluded that microfine zinc oxide is completely photostable, non-photoreactive, and is not phototoxic or photoallergenic (SCCNFP 2003). It has been recognized that photostability and lack of phototoxic or photoallergenic activity of a substance are strong indicators that it is unlikely to possess photogenotoxic properties.[190]

An alternative explanation for the observed clastogenic effects may be that UV irradiation produced a higher susceptibility of the CHO or V-79 cells to the intrinsic *in vitro* clastogenic activity of zinc oxide (Dufour et al. 2006).[191] Taking into account that *in vitro* tests for clastogenicity are known to have poor specificity, (*i.e.,* high percentage of false-positive results), it is important to investigate whether an increased clastogenic potency of a test compound such as micronized zinc oxide in the presence of UV irradiation represents a genuine photo-genotoxic potential or is an artifact, due to an increased sensitivity of the test system (Dufour et al. 2006). It has recently been shown that the clastogenic effects of micronized zinc oxide were not due to genuine photogenotoxicity, but were secondary to UV-induced experimental artifacts. In a recent study, zinc oxide was applied to CHO cells under three separate conditions: a) in the dark, b) under simultaneous irradiation with UV light, and c) to cells pre-irradiated with UV light followed by treatment with micronized zinc oxide in the dark (Dufour et al. 2006). Negative and positive control cell cultures were also treated with or without irradiation for comparison to the zinc oxide treated cultures. Interestingly,

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188 SCCP, Statement on Zinc Oxide Used in Sunscreens. Available at http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_00m.pdf.

189 Verbal communication with Dr. Gerald Renner, Colipa.

190 S. Brendler-Schwaab, A. Czich, B. Epe, E. Gocke, B. Kaina, L. Müller, D. Pollet, and D. Utesch. 2004. Photochemical genotoxicity: principles and test methods. Report of a GUM task force, *Mutat. Res.* 566:65–91.

191 Dufour EK, Kumaravel T, Nohynek GJ, Kirkland D, Toutain H. 2006. Clastogenicity, photo-clastogenicity or pseudo-photo-clastogenicity? Genotoxic effects of zinc oxide in the dark, in pre-irradiated or simultaneously irradiated Chinese hamster ovary cells. *Mut. Res.*, in press.

the nature, incidence, and severity of chromosome aberrations in pre-irradiated and simultaneously irradiated cells treated with zinc oxide were identical (Dufour et al. 2006). These data suggest that zinc oxide is non-photoclastogenic and that the increase in the incidence of chromosome aberrations in the presence of UV light was due to a UV-mediated increased susceptibility of the mammalian cells to zinc oxide; in other words, UV irradiation made the cells more fragile.

Overall, there is little or no evidence that micronized titanium dioxide or zinc oxide pose a local (skin) or systemic (penetration) toxic, phototoxic, genotoxic, or photogenotoxic risk; on the contrary, there is robust evidence that these substances protect human skin against UV-induced damage, including immunosuppression, photoaging, DNA damage, and skin cancer (van der Molen et al. 1998; Nohynek and Schaefer 2001).[192] [193]

2. Australian Government; Department of Health and Aging, Therapeutic Goods Administration (TGA) - Determination of Safety of Nanoparticulate Titanium Dioxide and Zinc Oxide

The Therapeutic Goods Administration (TGA) of Australia's Department of Health and Aging undertook a comprehensive review of the literature on the use of micronized titanium dioxide and zinc oxide and presented their findings in report in January 2006[194]. According to TGA, around 70% of sunscreens with titanium dioxide and 30% of sunscreens with zinc oxide have these materials in nanoparticle form and titanium dioxide has been used in this way since at least 1990 and zinc oxide since 1999. According to TGA, there is no evidence that sunscreens containing these materials pose any risk to the people using them. To address the theoretical concern that zinc oxide or titanium dioxide in nanoparticle form could be absorbed into skin cells and possibly interact with sunlight to cause cellular damage, TGA conducted a review of the scientific literature on the use of nanoparticulate zinc oxide and titanium dioxide in sunscreens. A thorough literature search of Medline, Embase, Biosis, Cabi, and Dialog databases was conducted and 24 relevant references were identified and summarized in the report.

TGA concluded:

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192 Van der Molen, R.G., HMH Hurks, C. Out-Luiting, F. Spies, J.M. van't Noordende, H.K. Koerten, and AM Mommaas. 1998. Efficacy of micronized titanium dioxide-containing compounds in protection against UVB-induced immunosuppression in humans in vivo. *J. Photochem. Photobiol B:Biology* 143-150.

193 Nohynek GJ and H Schaefer. 2001. Benefit and risk of organic ultraviolet filters. Reg. Toxicol. Pharm. 33:285-299.

194 A Review of the scientific literature on the safety of nanoparticulate titanium dioxide or zinc oxide in sunscreens. Department of Health and Aging, Therapeutic Goods Administration (TGA), Australian Government; 16 January 2006. See http://www.tga.gov.au/npmeds/sunscreen-zotd.pdf.

> There is evidence from isolated cell experiments that zinc oxide and titanium dioxide can induce free radical formation in the presence of light and that this may damage these cells (photo-mutagenicity with zinc oxide). However, this would only be of concern in people using sunscreens if the zinc oxide and titanium dioxide penetrated into viable skin cells. The weight of current evidence is that they remain on the surface of the skin and in the outer dead layer (stratum corneum) of the skin.

The Medicines Evaluations Committee of the TGA also endorsed this conclusion at its meeting on February 2, 2006.

3. Germany BfR (Federal Agency for Risk Assessment) Titanium Dioxide and Zinc Oxide 2006

This conclusion is consistent with the consensus of the ECETOC Workshop that dermal exposure to NP is of minor concern (ECETOC 2006). The safety of nanoparticles in cosmetics was the subject of a recent review by the German Federal Institute for Risk Assessment (BfR). The review concluded that because studies have shown that nanoparticles of titanium dioxide or zinc oxide did not penetrate through the stratum corneum, and nanoparticles are too large for passive transport through the skin, that therefore, dermal absorption is improbable.[195] They also concluded that biological properties of nanoparticles are not necessarily different than those of larger particles and toxicological properties of nanoparticles are determined by their water solubility and their persistence. Taking into account the results of available studies with nano-sized zinc oxide and titanium dioxide in standard formulations, a health risk for the consumer is not expected (BfR 2006).

4. Conclusion

Petitioners raise a variety of issues regarding the potential for nanoparticles and other nanomaterials to penetrate the skin and to cause harm when they are added to cosmetic and sunscreen formulations. However, the ability of micronized titanium dioxide and zinc oxide, the most widely used nanoparticles, to be absorbed through the skin has been investigated in several *in vitro* and *in vivo* dermal penetration studies and the weight of the evidence clearly shows that there is little or no penetration beyond the stratum corneum. The skin provides a very formidable and effective barrier, and the potential for even nano-sized particles to penetrate this strict barrier is extremely low. In addition, the ability of micronized titanium dioxide or zinc oxide to interact with DNA or RNA, as Petitioners claim, has only been observed in a few *in vitro* assays, which are not predictive of how these materials behave *in vivo* when they are applied in

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[195] BfR. Bundesinstitut für Risikobewertung. Berlin, Germany. Nanotechnologie und Lichtschutz (nanotechnology and UV protection), 24 February, 2006. Available at http://www.bfr.bund.de/

cosmetic and/or sunscreen formulations. Because these materials cannot penetrate through the stratum corneum, they will not be available to damage viable cells. Thus, there is no basis for concluding that sunscreens containing titanium dioxide and/or zinc oxide nanoparticles are not generally recognized as safe.

V. Limiting Access to Products Utilizing Microfine Particles will have a Negative Impact on Consumer Health and Well-Being

The requested actions of Petitioners would have negative outcomes by restricting consumer access to products that promote and protect health and well-being. In particular, the benefits of sunscreens in avoiding sunburn and possibly skin cancer have been recognized by a host of authorities, including FDA.[196] Recently, the American Academy of Dermatology has reaffirmed their position that the regular use of sunscreens is an effective component in protecting consumers from skin cancer and damage to the skin.[197] According to the National Cancer Institute, the incidence of skin cancer has been rising in recent years.[198] Regular sunscreen use is a critical component of skin cancer prevention, and limiting consumer access to these safe and effective ingredients does not promote consumer health and safety.

Sunscreens prevent sunburn and may also prevent skin cancer by protecting against DNA damage caused by UV light.[199] A number of scientific studies show the effectiveness of sunscreens in preventing squamous cell skin cancer.[200] A growing body of evidence shows that sunscreens prevent the development of certain predictors of malignant melanoma.[201]

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[196] See, e.g., Sunscreen Drug Products for Over-the-Counter Human Use; Tentative Final Monograph; Proposed Rule, 58 Fed. Reg. 28194, 28205, 28222-23, 28227 (May 12, 1993).

[197] Available at: http://www.aad.org/aad/Newsroom/American+Academy+of+Dermatology+Reaffirms+Position+on+Sun+Protection+Benefit+of+Sunscreen.htm.

[198] NCI, Cancer Trends Progress Report, 2005 Update, available at http://progressreport.cancer.gov/trends-glance.asp, see also Mayo Clinic, Skin Cancers Growing in Young People - A Case for Prevention. Available at http://www.mayoclinic.org/news2005-rst/2989.html.

[199] Young, Anthony R., Sheehan, John M., Chadwick, Carline A., and Potten, Christopher S., Protection by Ultraviolet A and B Sunscreens Against In Situ Dipyrimidine Photolesions in Human Epidermis is Comparable to Protection Against Sunburn. J. Invest Dermatol 115:37-41, 2000.

[200] Glallagher, Richard P., Sunscrens in melanoma and skin cancer prevention. JAMC, 173(3): 244-245, 2005.

[201] Lee, Tim K., Rivers, Jason K., Gallager, Richard P., Site-specific protective effect of broad-spectrum sunscreen on nevus development among white schoolchildren in a randomized trial. J Am Adad Dermatol, 52(5), 786-792, 2005. Gallager, Richard P., Rivers, Jason K., Lee, Tim K., Bajdik, Chris D., McLean, David I., Coldman, Andrew J. Broad-Spectrum Sunscreen Use and the Develoment of New Nevi in White Children. JAMA 283(22):2955-2960, 2000. Al

Titanium dioxide and zinc oxide are established, efficacious sunscreen filters that have been marketed for decades. Nanosized titanium dioxide and zinc oxide, unlike the larger particle size ingredient, form a transparent coating, which leads to greater consumer acceptance and use of the products, and therefore greater protection from skin cancer and other damaging effects of the sun. The same improvement in formulation esthetics also applies to the use of these materials in cosmetics.

VI. Reponses to Specific Requests

Petitioners have requested the following specific actions with respect to nanomaterial products:

1) *Amend FDA regulations to include nanotechnology definitions*

The Petition calls for the establishment of a regulatory definition for materials that are considered to fall under the scope of nanotechnology. As with bioengineered foods, the same rigorous safety standards of the FFDCA apply to a product category regardless of the technology involved. Furthermore, the FFDCA does not recognize the term "nanotechnology"—the word is not defined and there are no separate standards set forth in the statute that are based upon a type of technology. Thus, regulations defining "nanotechnology" are not justified and are not necessary for the protection of public health.

CTFA is concerned that Petitioners' proposed definitions based on particle size is arbitrary, do not reflect true safety concerns, and will impede effective regulation. Therefore, CTFA believes that creating proposed definitions are unnecessary and may in fact hinder the assessment of safety by basing it on arbitrary criteria. Therefore, CTFA believes that this request should be denied.

2) *Issue a formal advisory opinion recognizing the inherent differences of engineered nanoparticles from bulk material counterparts in products regulated by FDA.*

An advisory opinion that sets forth different standards for nanoparticles is not supported by law or science. The same safety and efficacy standards of the FFDCA apply to a product category regardless of whether it uses nanotechnology or not. As with bioengineered foods, the fact that a certain technology is used is not material absent a true safety concern. As expressed above, safety and toxicity studies on microfine titanium dioxide and zinc oxide show the same safety profile for microfine particles as bulk particles. Microfine

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Mahroos, Mona, and Bhawan, Jag, Effect of Sunscreen Application on UV-Induced Thymine Dimers, Arch Dermatol. 2002; 138:1480-1485.

particles used in personal care products do not pose a safety concern, have been in marketed for decades, and provide a public health benefit. Thus, CTFA believes that this request should be denied.

3) *Enact new regulations directed at FDA oversight of nanomaterial products establishing and requiring that nanoparticles be treated as new substances, new nano-specific health and safety testing methodologies be adopted, and that nanomaterial products be labeled to delineate all nanoparticle ingredients.*

New regulations directed at products that utilize nanotechnology are not supported by law or science. As expressed above, the same safety standards apply to a product category regardless of its use of nanotechnology. Existing methods for assessing the safety of microfine materials are suitable for ensuring the safety of these materials. The FFDCA does not recognize nanotechnology as a separate product category, nor does it provide statutory authority to apply different standards to products that utilize nanotechnology than those without. The methodology used to determine the safety of a particular product or ingredient depends on the particular product or ingredient at hand. Furthermore, many substances that would meet Petitioners' definition of "nanotechnolology" are not "new"—they have been commercially marketed for many years without evidence of adverse effect based on particle size. In the case of micronized titanium oxide and zinc oxide, FDA has reviewed and approved the safety of these ingredients at these particle sizes. Regulations that would require specific methodologies that may not be applicable or necessary and that could interfere with FDA's safety assessment process do not promote public health.

Labeling of products to identify nanoparticle ingredients will be difficult or impractical without clear guidelines. Furthermore, labeling of nanomaterials may unnecessarily generate consumer confusion as to the safety and efficacy of products. Consumers may be unduly alarmed or confused by the word "nanomaterial" or "nanoparticle," which, if applying Petitioners' definition, could apply to products that have been safely on the marketplace for many years. Consumer confusion may lead to avoidance of health-promoting products, with detrimental public health outcomes. Courts have repeatedly held that the mere fact that a particular technology is used is not material unless the product is in fact different from its non-engineered counterpart. Courts have considered the mandatory labeling of bioengineered foods that are not materially different from the non-bioengineered food to constitute misbranding[202] or an unconstitutional requirement for compelled speech.[203] For these reasons, CTFA believes that the request should be denied.

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202 Stauber v. Shalala, 895 F.Supp. 1178 (W.D. Wis 1995).

203 International Diary Foods Association v. Amestoy, 93 F.3d 67 (2d Cir. 1996).

4) *Any currently existing or future regulatory FDA programs for nanomaterial products must comply with the requirements of NEPA*

A. The National Environmental Policy Act Does Not Require FDA to Undertake a Comprehensive Environmental Analysis of Nanotechnology.

Contrary to Petitioners' unfounded assertions, FDA is not required to undertake a major environmental analysis of nanotechnology under the National Environmental Policy Act of 1969 (NEPA). As argued elsewhere in this response, FDA has regulatory authority over products, not technologies. The provisions of NEPA requiring an Environmental Impact Statement (EIS) apply only if a federal agency has undertaken a "major federal action" that significantly affects the environment. But as Petitioners themselves have conceded, FDA has not yet undertaken a "major federal action" with respect to the field of nanotechnology, and, in fact, the Agency has no authority to do so. Because FDA has not and cannot take regulatory action that would trigger the EIS requirements of NEPA, Petitioner's claim that an EIS is required should be denied.

1. FDA's Current Regulatory System Complies with NEPA

NEPA requires all federal agencies to consider the environmental consequences of major regulatory actions and policies.[204] Consistent with this requirement, "FDA's policies and programs [are] planned, developed, and implemented to achieve the policies declared by NEPA" and to "ensure responsible stewardship of the environment for present and future generations."[205] FDA, therefore, is required to prepare an environmental assessment (EA) any time the agency initiates a major federal action. Moreover, any applicants/petitioners are also required prepare an EA whenever they ask the Agency to take a major federal action. Therefore, all "applications or petitions requesting agency action" require the submission of an EA or a claim that the application fits one of the categorical exclusions promulgated by FDA.[206] In fact, if an application does not contain an EA, this may be grounds for FDA to refuse to file or approve the application.[207]

Accordingly, whenever an application for a new product is submitted to FDA -- whether it be, *inter alia*, a new drug application (NDA), a biologics license

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[204] 42 U.S.C. § 4332(2). NEPA also established the Council on Environmental Quality (CEQ), which is charged with overseeing federal agencies' compliance with NEPA and has developed regulations under 40 C.F.R. §§ 1500-1518 to provide agencies with NEPA implementation guidance. FDA has promulgated 21 C.F.R. § 25 to implement NEPA requirements under the FDCA.

[205] 21 C.F.R. § 25.10.

[206] 21 C.F.R. § 25.15.

[207] Id.

application (BLA), an abbreviated new drug application (ANDA), an application for premarket approval (PMA) for a medical device, a food or color additive petition, a new animal drug application (NADA), or a GRAS petition -- that application must contain a section on the environmental impact of that product or a justification as to why the product meets one of the categorical exclusions established by the Agency.[208] Once FDA receives an application, its regulations require it to carefully evaluate the environmental assessment or the claimed exclusion.[209]

Pursuant to these regulations, any application submitted to FDA for a product containing ingredients engineered by nanotechnology must provide evidence describing the potential impact of the product on the environment. Based on its review of the EA, FDA decides whether the environmental impacts are "significant" enough to require a full-fledged EIS, or whether it can issue a "finding of no significant impact" (FONSI). Failure to provide an environmental assessment or a justification for categorical exclusion could result in the application being denied by FDA. This authority is precisely how FDA has regulated the environmental safety of products that contain ingredients manufactured by numerous technologies -- including, for example, genetically manufactured food products and biologics manufactured through novel biotechnology processes. Petitioners have supplied no reasonable basis to conclude that products engineered by nanotechnology should be treated differently.

2. The Regulation of Nanotechnology Does Not Require an EIS Because FDA has Not Proposed or Undertaken a "Major Federal Action" that "Significantly" Affects the Environment

Petitioners have argued that FDA is already required under NEPA to conduct an EIS with respect to nanotechnology.[210] However, NEPA only requires agencies to prepare an EIS for "major Federal actions significantly affecting the quality of the human environment."[211] Several prerequisites, therefore, must be present before an EIS requirement is triggered. First, if an agency has not engaged in a "major federal action" or is not proposing to undertake a major federal action, the

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208 21 C.F.R. § 24.20.

209 21 C.F.R. § 25.10.

210 Petitioners also appear to suggest that the existence of possible environmental impacts means that FDA is required to take action and develop a special regulatory policy to address those environmental concerns. This argument attempts to flip the requirements of NEPA with respect to FDA on their head. FDA is not required to embark on "major federal actions" in order to address environmental concerns; rather, NEPA requires FDA to consider environmental concerns if – and only if – it decides to undertake a "major federal action."

211 42 U.S.C. § 4332(2)(C).

NEPA requirement to conduct an EIS does not apply.[212] Second, even if a proposed action is considered to be a "major federal action," the action must have a "significant[]" effect on the environment before the EIS requirement is triggered.[213]

In the case of nanotechnology, neither of these prongs is met.

a) FDA has Not Proposed or Undertaken a "Major Federal Action" with Respect to the Regulation of Nanotechnology.

NEPA requires a federal agency to undertake an EIS only if the proposed action represents a "major federal action." A major federal action describes significant regulatory undertakings, such as adoption of official policy, adoption of programs, and approval of specific projects.[214] In order to trigger an EIS, the courts have required that the agency must be prepared to undertake an "'irreversible and irretrievable commitment of resources' to an action that will affect the environment."[215]

In the instant case, Petitioners assert that FDA is required to undertake such an analysis for the entire field of nanotechnology. At the same time, however, Petitioners concede -- as they must -- that FDA has not imposed a comprehensive regulatory system for nanotechnology itself. Rather, FDA has regulated nanotechnology through its statutory authority and existing processes to review and regulate specific products that may be engineered through nanotechnology. Because FDA has not undertaken to specifically regulate the technology of engineering nanoparticles, it has not engaged in a "major federal action" with respect to nanotechnology as a field.

Under similar circumstances, federal courts have held that an EIS is not required. For example, in *Alliance for Bio-Integrity v. Shalala*, plaintiffs challenged an FDA policy that the Agency would presume that foods produced through the rDNA process were "generally recognized as safe" (GRAS) under the FDCA and

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212 Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166 (D.D.C. 2000); see also Macht v. Skinner, 286 U.S. App. D.C. 296 (D.C. Cir. 1990); 42 U.S.C. § 4332(2)(c).

213 Agencies may also develop a list of "categorical exclusions" for actions that "do not individually or cumulatively have a significant effect on the environment," and therefore do not require either an EA or an EIS. 40 C.F.R. § 1508.4; 21 C.F.R. § 25.30. Thus, certain actions can be carved-out and exempted from NEPA, provided the agency provides sound reasoning for the exclusion. However, actions that would otherwise be categorically excluded may nevertheless require completion of an EA under "extraordinary circumstances," such as when the "available data establish that, at the expected level of exposure, there is potential for serious harm to the environment." 21 C.F.R. § 25.21(a).

214 40 C.F.R. § 1508.18(b).

215 Wyoming Outdoor Council v. U.S. Forest Service, 165 F.3d 43, 49 (D.C.Cir. 1999) (quoting Mobil Oil Corp. v. FTC, 562 F.2d 170, 173 (2d Cir. 1977)).

therefore not subject to regulation as food additives.[216] The plaintiffs asserted that this policy statement violated NEPA because it was a major federal action that required an EA or an EIS.[217] The court held that FDA's regulation -- which in effect amounted to maintaining the status quo with respect to the regulation of genetically modified foods -- did not constitute a "major federal action" because "the FDA has neither made a final determination that any particular food will be allowed into the environment, nor taken any particular regulatory actions that could affect the environment." Rather, FDA would continue to evaluate the environmental impact of specific foods on a product-by-product basis. As the court stated in *Alliance for Bio-Integrity*, "[t]he core of Plaintiff's NEPA claim is that FDA has failed to regulate rDNA-modified foods, and that this failure to act engenders environmental consequences."[218] But, as the court held, "NEPA applies only to agency actions."

The court's holding in *Alliance for Bio-Integrity* applies with equal force to the current situation. FDA's decision to continue to regulate on a product-by-product basis rather than developing new policies does not constitute "action" with respect to the general field of nanotechnology. Furthermore, any necessary EIS's will be developed as needed based on FDA's environmental assessment of each individual product.

More recently, the key NEPA holdings from *Alliance for Bio-Integrity* were affirmed in *International Center for Technology Assessment v. Thompson*,[219] a case reviewing FDA's decision not to regulate GloFish, a genetically engineered ornamental fish. In that case, the plaintiffs disagreed with FDA's decision not to regulate GloFish and argued that FDA was in violation of NEPA.[220] Not only did the plaintiffs argue that FDA was required to complete an EA prior to allowing the proposed commercialization of GloFish, but also that it was required to complete an environmental assessment of genetically engineered animals generally.[221] The court held that FDA's decision not to impose a comprehensive system of regulation over genetically engineered animals generally did not constitute a major federal action.[222] NEPA was not triggered because FDA had not made an "irreversible and irretrievable commitment of resources" to the regulation of genetically engineered animals in general.[223]

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216 116 F. Supp. 2d 166, 171 (D.D.C. 2000).

217 Id. at 174 (citing 57 Fed. Reg. 23005).

218 Id.

219 421 F. Supp. 2d 1 (D.D.C. 2006).

220 Id. at 5.

221 Id.

222 Id. at 17.

223 Id. at 17-18.

These principles are directly applicable to Petitioners' claims with respect to nanotechnology. While on one hand arguing that FDA has not regulated nanotechnology, Petitioners nevertheless argue that an EIS is required because a "major federal action" has occurred. This contradictory argument should be rejected. In fact, FDA has not -- and we submit, cannot -- engage in the regulation of nanotechnology itself. And to the extent the FDA is acting pursuant to a "de facto" policy, as Petitioners suggest, it is analogous to the situation in *Alliance for Bio-Integrity* in that the "policy" merely presumes that products containing nanomaterials should be regulated in the same manner as all other products -- that is, on a case by case basis. As such, there is no basis to conclude that FDA should be required to conduct an EIS for nanotechnology as a whole.

b) Petitioners Have Provided No Evidence that Nanotechnology Significantly Affects the Environment.

Even if FDA's current stance on the regulation of nanotechnology could somehow be construed as constituting a major federal action, Petitioners have utterly failed to present evidence demonstrating that nanotechnology has a significant affect on the environment.

Federal regulations require the significance of federal action to be assessed according to a number of criteria. The impact of the regulatory action must be considered in the context of the "society as a whole (human, national), the affected region, the affected interests, and the locality."[224] Moreover, the intensity or severity of the environmental impact must be assessed by considering a variety of factors, including the beneficial and adverse impacts, and the affect on public health and safety.[225] Ultimately, agencies are afforded substantial discretion to make a final assessment as to whether its actions rise to the level of "significantly affecting the quality of the human environment."[226] If the proposed action is not deemed to be environmentally significant, the agency may prepare a "finding of no significant impact" or FONSI.[227] Both EAs and FONSIs are considered informal agency actions and are thus subject to the "arbitrary and capricious" standard of review.[228]

In the case of nanotechnology, Petitioners have essentially acknowledged that there is no concrete scientific basis to conclude that nanotechnology has a significant detrimental impact on the environment. The Citizen Petition nonetheless urges FDA to speculate about hypothetical risks in the absence of

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224 40 C.F.R. § 1508.27(a).

225 40 C.F.R. § 1508.27(b).

226 40 C.F.R. § 1501.4(c).

227 40 C.F.R. § 1501.4(e).

228 Stauber v. Shalala, 895 F. Supp. 1178, 1196 (W.D. Wis. 1995).

real scientific data or evidence, while simultaneously conceding that there are "few studies" on the environmental impact of nanotechnology.[229] In fact, the thrust of Petitioners' argument is that nanotechnology should be more thoroughly investigated precisely because there is not enough information about how it may or may not affect the environment. However, an absence of data or evidence cannot be relied on to demonstrate a "significant" environmental impact; this is simply insufficient to trigger the requirements of NEPA.

3. An EIS Addressing Nanotechnology Generally would be Virtually Impossible.

In addition to arguing that FDA is already obligated to conduct an EIS with respect to nanotechnology, Petitioners appear to also contend that any future regulation of nanotechnology would require an EIS. Their argument appears to be that if FDA embarks on an attempt to regulate nanotechnology itself (as opposed to individual products that use nanotechnology), an EIS covering all potential applications of nanotechnology would be required. This argument merely highlights the absurdity of Petitioners' position.

As Petitioners note, the potential applications for nanotechnology are nearly endless. Nanotechnology may apply to medical devices, OTC drugs, prescription drugs, biologics, cosmetics, and other classes of products. And as Petitioners have pointed out, the possible environmental impacts are not the same for each nanomaterial, nor are their potential impacts uniformly negative.[230] These disparate environmental effects make it obvious that developing a single EIS on the collective impact of all nanomaterials in all known or potential applications would not be a workable solution.[231]

In short, Petitioners' suggestion that FDA complete an EIS on the potential environmental effects of regulatory actions related to the general field of nanotechnology drastically oversimplifies the issue and risks entirely derailing the promising field of nanotechnology through overly burdensome, unrealistic, and unnecessary assessment requirements.

5) *Reopen the administrative record of the final sunscreen monograph*

Throughout the history of the sunscreen monograph, FDA has found time and time again that the available science supports the safety and efficacy of micronized titanium dioxide and zinc oxide. FDA has involved the public in a

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[229] Citizen Petition at 30.

[230] Citizen Petition at 16, 29-32. For example, petitioners cite a recent study suggesting that fullerenes can be toxic to largemouth bass, yet they also acknowledge the potential for engineered nanoparticles of iron to be useful in environmental remediation programs. Citizen Petition at 30-31.

[231] Equally implausible is Petitioners suggestion that, because NEPA would apply if FDA decides to regulate the field of nanotechnology, that therefore it must regulate nanotechnology.

process that has spanned over 25 years and multiple data requests, and each time FDA has concluded that titanium dioxide and zinc oxide are safe and effective. The scientific opinions and papers published recently by the SCCNFP, the Australian Therapeutic Goods Association, and numerous independent scientists support FDA's conclusions.[232] Based on the assessments of FDA and these other bodies, Petitioners' request is unsupported by the science.

At the same time, if FDA finds the issue of microfine particles in sunscreens to require further investigation, the sunscreen monograph is the proper process by which to address concerns about these ingredients. Since its inception in 1978, FDA has reopened the administrative record of the sunscreen monograph on several occasions in order to accept data and information on issues such as SPF testing,[233] UVA testing,[234] and the photochemistry and photobiology of sunscreens.[235] Were FDA to find that the issue of the safety of microfine titanium dioxide and zinc oxide in sunscreens warranted further investigation, a reopening of the sunscreen monograph on these issues would be appropriate. Reopening of the record on these issues should not affect the agency's proposal and finalization of other aspects of the monograph, such as testing.

6) *Amend the final sunscreen monograph to provide a clear definition of engineered nanoparticles, address the fundamental differences between engineered nanoparticles and larger particles, and instructing that sunscreen products containing engineered nanoparticles are not covered by the monograph and instead are "new drugs" for which manufacturers must complete a New Drug Application.*

As expressed above, the same safety standards apply to a product category regardless of whether it uses nanotechnology or not. There is no legal or scientific basis to apply different safety standards to products with nanotechnology than those without. After extensive review of the scientific evidence, the FDA has determined that titanium dioxide and zinc oxide are generally recognized as safe and effective as sunscreen filters at given concentrations.[236] In order to state that microfine particles of approved active ingredients are not covered by the monograph, FDA must conclude that they are not GRASE based on their size alone. Science does not support this conclusion. As previously stated, FDA has concluded that microfine titanium dioxide and zinc oxide are not "new" materials as they are not fundamentally different from their bulk counterparts. Scientific data supports the safety of microfine titanium dioxide and zinc oxide in sunscreens.

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[232] See section IV.
[233] 52 Fed. Reg. 33598 (Sep. 4, 1987).
[234] 59 Fed. Reg. 16042 (Apr. 5, 1994).
[235] 61 Fed. Reg. 42398 (Aug. 15, 1996).
[236] 64 Fed. Reg. 27687 (May 21, 1999).

Though Petitioners cite patent standards, they are not relevant for the determination of whether a drug is a new drug. The FFDCA defines new drugs as those drugs that are "not recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof...."[237] In the 1999 Final Monograph, FDA determined that the active ingredients listed for the labeled uses at the given concentrations are GRASE and therefore not new drugs. CTFA notes that a product claiming different effects than those listed in the monograph may be a new drug for which a NDA would be required.

7) *FDA should declare all currently available sunscreen drug products containing engineered nanoparticles of zinc oxide and titanium dioxide as an imminent hazard to public health.*

According to 21 C.F.R. § 2.5, the Commissioner may declare an imminent hazard when "the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held." In the case of titanium dioxide and zinc oxide in sunscreens, neither of these conditions is met.

As stated above, microfine particles of zinc oxide and titanium dioxide have been used in sunscreens for many years without any evidence of injury. These products have been used safely and effectively by consumers who rely upon them and provide a public health benefit. Current scientific data supports safety of microfine titanium dioxide and zinc oxide in sunscreens and there is no public health emergency that would warrant the declaration of an imminent hazard.

CTFA supports the use of the sunscreen monograph process as the proper venue to address any emerging safety issues concerning microfine titanium dioxide and zinc oxide, and believes that information pertaining to the safety of such ingredients should be supplied to FDA through the docket of this rulemaking so that a public dialogue may take place.

Petitioners have failed to satisfy their burden of proving that the use of nanoparticles of titanium dioxide and zinc oxide in sunscreens is unsafe because they have offered no sound scientific evidence to show that the use of these ingredients presents a genuine safety concern. This request, therefore, should be rejected.

8) *FDA should request a recall from manufacturers of all publicly available sunscreen products containing engineered nanoparticles of titanium*

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[237] 21 U.S.C. § 321(p).

dioxide and/or zinc oxide until the manufacturers of such products complete new drug applications.

FDA may request a manufacturer to recall a product when it determines that the product presents a risk of illness or injury or gross consumer deception and that agency action is necessary to protect the public health and welfare.[238] In the case of titanium dioxide and zinc oxide in sunscreens, this standard is clearly not met. Sunscreens have one of the best safety profiles of any drug on the market, with few adverse events given the high consumer use. Scientific data supports safety of microfine titanium dioxide and zinc oxide in sunscreens. Furthermore, eliminating these products from the marketplace will harm consumers, as these products provide a broad spectrum protection not found in other sunscreens. Therefore, CTFA believes that it would be unnecessary and unwise for FDA to limit access to these safe, health-promoting products.

Petitioners have failed to satisfy their burden of proving that the use of nanoparticles of titanium dioxide and zinc oxide in sunscreens is unsafe because they have offered no sound scientific evidence to show that the use of these ingredients presents a genuine safety concern. This request, therefore, should be rejected.

VII. Conclusion

CTFA supports FDA's efforts to study the science and technology of nanotechnology. FDA's upcoming public meeting on nanotechnology, as well as the agency's Nanotechnology Task Force, will allow the agency to investigate the scientific issues surrounding this technology. It is clear that although the science surrounding nanotechnology is still emerging, the agency's existing regulatory authorities provide it with sufficient tools to incorporate the evolving scientific understanding of nanotechnology into its regulation of specific products.

For this reason, the claims raised in Petitioners' citizen petition must be denied. In essence, Petitioners are requesting that FDA depart from its traditional regulatory principles and embark on a wholly new regulation of a technology. Petitioners have requested that FDA impose different standards for safety for products or product ingredients simply because they utilize nanotechnology. As has been thoroughly demonstrated by CTFA's comments, there is simply no scientific or legal basis to do this. There is no scientific consensus establishing that nanotechnology products raise new safety risks. In fact, most of the existing science suggests that the safety risks of nanomaterials are no greater than products using other technologies. Moreover, to the extent that any specific product -- whether engineered by nanotechnology or some other process -- raises a safety concern, FDA has ample authority to address that safety risk.

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[238] 21 C.F.R. § 7.45.

This is precisely how FDA has handled emerging technologies in the past. For FDA to impose a different standard on a technology would be contrary to the agency's longstanding policy and its statutory authority.

Furthermore, the specific products that the Petitioners attack are, in fact, among the safest products regulated by FDA. Sunscreens that utilize titanium dioxide and zinc oxide are used everyday by countless consumers to protect from the harmful effects of UVB and UVA radiation. Despite their widespread use, obvious benefits to consumers, and established pedigree of safety, Petitioners nonetheless request -- without scientific basis -- that these products be taken off the market. This request should unquestionably be denied. As illustrated by the extensive scientific literature on titanium dioxide and zinc oxide, microfine particles in personal care products do not necessarily pose a safety risk simply by virtue of their size. In fact, the scientific assessments and findings of a number of authoritative bodies have consistently concluded that titanium dioxide and zinc oxide in the nanoparticle range are not toxic and do not penetrate the skin. Petitioners' unfounded request to declare sunscreens that contain engineered nanoparticles of zinc oxide and titanium dioxide as an imminent hazard to public health has no scientific or legal basis. Similarly, Petitioners' request to amend the sunscreen monograph has no basis in law or science.

In conclusion, CTFA believes that all of Petitioners' requests should be denied. The scientific and regulatory issues presented by new technology are always complex and challenging. Nanotechnology is no exception. However, Petitioners' unfounded and reckless citizen petition provides no viable pathway for the agency to address these issues. Rather, FDA should continue to study the science of this new technology. As new data become available, the emerging science may be factored into FDA's regulation of specific products. In doing so, FDA will be able to continue to effectively safeguard the public health in a manner consistent with its statutory authority and the most accurate scientific data available.

Comments of the Cosmetic, Toiletry, and Fragrance Association (CTFA) Regarding the Scientific and Legal Issues Associated with Nanotechnology in Personal Care Products:

Literature References

Submitted in Regard to Docket Number 2006P-0210: Petition to FDA to Amend its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically

CTFA Comments on Petition to FDA to Amend its Regulations for Products Composed of Engineered Nanoparticles Generally and Sunscreen Drug Products Composed of Engineered Nanoparticles Specifically
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