# Nano Testing Consortium

May 10, 2007

Via E-Mail

Scott A. Masten, Ph.D.
Director
Office of Chemical Nomination and Selection
NIEHS/NTP
111 T.W. Alexander Drive
P.O. Box 12233
Research Triangle Park, NC 27709

Re: National Toxicology Program (NTP); Office of Chemical Nomination and Selection; Announcement of and Request for Public Comment on Toxicological Study Nominations to the NTP; 72 Fed. Reg. 14816 (Mar. 29, 2007)

Dear Dr. Masten:

The Nano Testing Consortium (Consortium) is pleased to submit these comments in response to the National Institute of Environmental Health Sciences' (NIEHS) notice and request for comment and additional information, which was published in the *Federal Register* on March 29, 2007, regarding the nomination of nanoscale gold and nanoscale silver to the National Toxicology Program (NTP) for toxicological studies.[1] The Consortium is composed of companies that produce nanotechnology-enabled products regulated by the U.S. Food and Drug Administration (FDA) and other federal agencies. The Consortium was formed to assist and interact with NTP scientists who are involved in the Nanotechnology Safety Initiative (Initiative), as well as with scientists in other government agencies, such as the FDA, engaged in the testing, review, and risk characterization of engineered nanoscale materials, and the government's public dissemination of information pertinent to these materials.

**Brief Summary**

NIEHS is proposing to accept the nomination of FDA to test nanoscale gold and silver based on FDA's belief that there is a general lack of toxicology and pharmacokinetic data on these materials. FDA states in the nomination that the testing is needed to make certain that the assays and tests presently being required of manufacturers are adequate for regulatory

[1] 72 Fed. Reg. 14816 (Mar. 29, 2007), available at http://ntp.niehs.nih.gov/files/NTPICCEC032907p.pdf.



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purposes. NIEHS outlines in general terms the tests it proposes to conduct to address FDA's concerns, but provides no details of the manner of chemical selection or the study process. NTP has acknowledged that nanoscale material testing is in the initial stages of development and that there is no agreement on test methodology that will elicit meaningful data. To fulfill NTP's legal obligations and its commitment to transparency, NTP should publish its full plans for implementation of nanoscale gold and silver testing and permit public comment by knowledgeable third-parties. Presently, the implementation process is carried out in-house at NTP, by a project leader and a design team that choose the materials to be used in the study, and decide on the parameters of the study. No outside input is required. The process should be changed, and implementation of the study program opened for public comment. This is particularly important where it is stated that the study results may be the basis of early regulatory decisions concerning products already properly on the market.

**Basis for Nominating Nanoscale Gold and Silver**

NIEHS explains in the notice that FDA nominated nanoscale gold and silver for NTP testing. The stated rationale for FDA's nomination, as set forth in an FDA document entitled *Nanoscale Materials [no specified CAS]: Nomination and Review of Toxicological Literature* (Background Document),[2] is that nanoscale gold and silver are being used in a variety of regulated products, and that there is a general lack of toxicology and pharmacokinetics data on these materials, as well as data on absorption, distribution, metabolism, and elimination (ADME). FDA also reported that it requires these biological and toxicological data to "assure[] that the current assays and tests that the agency requires sponsors to conduct in support of product safety are adequate to detect adverse biological and toxicological events."[3] FDA requested that NTP undertake the following studies:

> Nanoscale gold -- Conduct (1) absorption, distribution, metabolism and elimination studies in rodents using oral and intravenous routes of administration (including blood-brain transfer), (2) acute (single and repeat dose) toxicity studies (28 days) in rodents, and

[2] FDA, Chemical Selection Working Group, *Nanoscale Materials [no specified CAS]: Nomination and Review of Toxicological Literature* (Dec. 8, 2006), *available at* http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Nanoscale_materials.pdf.

[3] *Id.* at Section 7.0 Research and Testing Needs.

> (3) subchronic, dose-response toxicity studies in rodents (only if warranted). The studies should be conducted on nanoscale gold of one or two sizes (*e.g.*, 10 nm-60 nm) with and without surface coatings (*e.g.* polyethylene glycol or protein coated). The nanoscale material should be thoroughly characterized before use, and after recovery from tissues.
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> Nanoscale silver -- Conduct (1) absorption, distribution, metabolism and elimination studies in rodents using oral and intravenous routes of administration (including blood-brain transfer), (2) acute (single and repeat dose) toxicity studies (28 days) in rodents, and (3) subchronic, dose-response toxicity studies in rodents (only if warranted). The studies should be conducted on nanoscale silver of one or two sizes (*e.g.* 10-60 nm). The nanoscale material should be thoroughly characterized before use, and after recovery from tissues.[4]

FDA included in the Background Document its analysis of the available technical literature. FDA did not, however, describe in any detail the "current assays and tests" that had been required of sponsors in the immediate past and why FDA is concerned that those assays and tests might not be sufficient to demonstrate product safety. FDA also did not explain its reasons for believing that the requested studies would supply the missing information or how exactly they would do so if conducted.

**The NIEHS Nomination**

NIEHS cited FDA's rationale for the nomination of nanoscale gold and silver for additional study, reflecting, presumably, NIEHS' concurrence with the rationale FDA offered in making the nomination. NIEHS recited in general terms the tests it would complete, but offered no specific information on what tests exactly it would seek to undertake, and no indication that it would undertake the same studies, modified studies, or entirely different studies than those FDA requested. The absence of any specific information in this regard makes it difficult to provide informed, meaningful comment on the proposal and points to a basic but easily correctable flaw in the NTP process for nominating, selecting, and testing nanomaterials. It is a fundamental and long-established principle of federal administrative law that the public must have an opportunity

[4] *Id.* at Section 9.0 Recommended Studies.

"to comment meaningfully," and that such an opportunity is not possible when an agency -- in this case NIEHS -- neglects to provide sufficient factual detail and rationale.[5]

NTP's processes have been the subject of criticism in recent years for a lack of transparency, particularly with respect to the nomination and testing of chemical substances.[6] In response to such criticism, NTP has reaffirmed its commitment to transparency.[7] The Consortium is gratified that NTP is so committed, and supports NTP's efforts to engage in open and transparent processes, particularly as they may relate to the inclusion of nanoscale chemicals in the Initiative.[8] Inasmuch as Consortium members are manufacturers of nanotechnology-enabled products regulated by the FDA, the Consortium is deeply concerned that the March 29, 2007, *Federal Register* notice falls far short of NTP's stated goal of providing opportunities for interested stakeholders to engage in meaningful discourse on topics of shared concern. Indeed, as described below, there is virtually no information on which to comment arising out of the notice, and the processes that lead to the nomination of nanoscale gold and silver are anything but interactive and transparent.

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5 *See Florida Power & Light Co. v. U.S.*, 846 F.2d 765, 771 (D.C. Cir. 1988), *cert. denied*, 490 U.S. 1045 (1989); *see also Connecticut Light & Power Co. v. NRC*, 673 F.2d 525, 528-531 (D.C. Cir. 1982), *cert. denied*, 459 U.S. 835 (1982).

6 *See, e.g.*, Letter from Dr. John D. Graham, Ph.D., Administrator, Office of Information and Regulatory Affairs, Office of Management and Budget, to Dr. Elias A. Zerhouni, Director, National Institutes of Health (Nov. 16, 2004), *available at* http://reginfo.gov/public/prompt/nih_ntp111604.pdf. The letter describes a variety of instances of lack of transparency in the preparation of the NTP *Report on Carcinogens*.

7 *See, e.g.*, NTP's Response to Public Comments and Discussion on the Preparation and Review of the Report on Carcinogens Received at the January 27, 2004 Public Meeting, at 3 ("The NTP is committed to maintaining an open and transparent process for preparation of the RoC that is unencumbered by special interest, that is a high-quality, open scientific review . . . that allows stakeholder input at multiple levels, and that uses the best, publicly available, peer-reviewed science."), *available at* http://ntp.niehs.nih.gov/ntp/meetings/2004/NTPresponseFINAL092104.pdf.

8 A multistep review process for nominations is detailed on the NTP website. *See* Study Nomination Review & Selection Process, *available at* http://ntp.niehs.nih.gov/index.cfm?objectid=25BE6793-BDB7-CEBA-F46CCDD066D7008.

NTP clarified that the purpose of testing under the Initiative is to develop model systems that can be used to investigate fundamental questions concerning if and how nanoscale materials interact with biological systems.[9] The Initiative testing program is very much a work in progress, however. NTP seeks to develop a verified methodology that can be used to examine questions regarding nanoscale materials. In these circumstances, the Consortium believes that multi-level input on the manner in which a nomination to test will be implemented is of paramount importance, particularly, as NTP admits, there is no verifiable basis for selecting a particular methodology based on available science. As NTP notes, "[t]here is very little research focus on the potential toxicity of manufactured nanoscale materials."[10] Despite the embryonic state of the implementation process, however, NTP does not seek or involve any third-party input, insure that the best available science will be utilized in implementing the nomination, or otherwise engage in any meaningful way stakeholders whose unique expertise in the manufacture of and/or research into nanoscale materials may be best utilized by NTP. A summary review of the NTP process, as described on its web page, confirms these flaws.

1. A nomination is assigned to an NTP staff scientist who assesses the available data;

2. That staff scientist, as project leader, develops research concepts through informal in-house discussions, and discussions with others as he or she, in his/her sole judgment, chooses;

3. The research concepts are then used to outline the general elements of NTP testing; and

4. The leader meets with a design team to develop a study plan. The sole review of the study plan is by an in-house project review committee.[11]

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9 NTP Fact Sheet, NTP Nanotechnology Safety Initiative (Year 2006), *available at* http://ntp.niehs.nih.gov/files/NanoColor 06SRCH.pdf.

10 *Id.*

11 Study Nomination Review & Selection Process, *available at* http://ntp.niehs.nih.gov/index.cfm?objectid=25BE6793-BDB7-CEBA-F46CCDD066D70D08#5.

This process confirms that no outside input by knowledgeable third-parties is sought or provided, and no external review of in-house FDA recommendations is conducted. The Consortium believes that this process would benefit considerably from greater transparency. Given the universal acknowledgement regarding the limitations on data pertinent to nanoscale materials and the degree to which more traditional testing methodologies may or may not be relevant to such materials, the contributions from knowledgeable third-parties would appear to be all the more essential.

The Consortium believes that transparency is even more important in the case of studies that may be conducted on nanoscale gold and silver. NTP's public statements would lead to the false conclusion that the testing methodology contemplated by NTP is fully developed. As many critically important questions remain unresolved in this regard, the Consortium is all the more alarmed that the notice suggests that the results obtained from the testing that FDA recommends may have direct and immediate regulatory and product approval consequences for FDA-regulated companies. The methodology NTP intends to employ should, therefore, be fully disclosed, and comment upon the methodology and related important details should be explicitly solicited. NTP should describe in detail how the tests will be conducted, on what test material they will be conducted, how the data will be collected, verified, and analyzed, and how the test results will be communicated and used by the federal government. FDA and NIEHS should also provide an explanation of how the proposed studies are expected to fill any data gaps that FDA believes now exist. In failing to disclose these critically important categories of information, stakeholders cannot be expected to provide meaningful comment, and any defensible reliance on study results for future regulatory actions will be compromised.

An illustration explains the Consortium's concern. In the recent past, NTP has used surrogates for testing without in all cases justifying how the results might scientifically be extrapolated to products subject to FDA or other government agency approval. NTP has, for example, used materials believed to be sufficiently similar to the materials representative of a class of products, but only similar (not chemically identical), and only to some products in the class, and then not even from the actual suppliers of the materials to the manufacturers of the regulated products.[12]

[12] *See, e.g.*, Final Report -- Developing Experimental Approaches for the Evaluation of Toxicological Interactions of Nanoscale Materials (Nov. 3-4, 2004) at 26 (stating that "the surrogate should have the same external properties as the [nanoscale] material of interest"), *available at* http://ntp.niehs.nih.gov/ntpweb/index.cfm?objectid=303109D5-F1F6-975E-769B905AC23723FF; NTP Board of Scientific Counselors Nanotechnology Working Group, Minutes for the March 15, 2006 Meeting of the NTP Board of Scientific

It is well known that engineered nanoscale materials are highly variable. For example, a single-walled carbon nanotube (SWCN) engineered by one company is not necessarily the same as a SWCN engineered by another company, and the test results of one type of SWCN cannot be said to be representative of the test results of any other kind of SWCN.[13] In fact, differences between engineered nanoscale materials often are intentional. With respect to nanoscale gold particles, dispersions of 5 nanometer-sized particles take on different colors than do dispersions of 7 nanometer-sized particles. The highly variable nature of nanoscale materials makes it extremely difficult to extrapolate the test results on a particular nanoscale material to another nanoscale material, notwithstanding that the two materials may have the same or similar names. This is not to say that this type of extrapolation can never occur. Rather, more than merely saying so (*i.e.*, simply announcing that extrapolation from one material to another is appropriate) is needed to make it so. The U.S. Environmental Protection Agency has identified as a risk assessment-related research need the question of whether "properties and effects [can] be extrapolated within a class of nanomaterials,"[14] and the general area of nanoscale material characterization is and will be for at least the next several years the focus of much international research. The Consortium strongly concurs with these observations and believes that the unique properties of chemical substances, particles, and structures quintessentially "nano" must be fundamentally factored into the NTP chemical selection and study process. NTP also must keep

Counselors Nanotechnology Working Group (NWG), *available at* http://ntp.niehs.nih.gov/files/NWGMinutesMarch2006VF050706.pdf.

13 *See, e.g.*, Maynard, *et al*. (2006). Safe Handling of Nanotechnology, *Nature* 444:267-269, at 268 ("The enormous diversity of engineered nanomaterials with different sizes, shapes, compositions and coatings matches, and possibly exceeds, that of conventional chemicals."), *available at* http://www.nature.com/nature/journal/v444/n7117/full/444267a.html; U.S. Environmental Protection Agency, Nanotechnology White Paper (Feb. 2007) at 31 ("The diversity and complexity of nanomaterials makes chemical identification and characterization not only more important but also more difficult."), 32 ("A given nanomaterial can be produced in many cases by several different processes yielding several derivatives of the same material. For example, single-walled carbon nanotubes can be produced by several different processes that can generate products with different physical-chemical properties (*e.g.*, size, shape, composition) and potentially different ecological and toxicological properties [citations omitted]."), *available at* http://www.epa.gov/ncer/nano/publications/whitepaper12022005.pdf.

14 *Id.* at 72.

in mind that differences between identically or similarly named substances often are intentional and do not represent a range in product quality.

For NTP to fulfill its stated commitment to engage stakeholders meaningfully in the chemical selection and study design process, the comment process for materials nominated for testing under the Initiative must be revisited and revised along the lines suggested above. The research concepts developed by the staff scientist assigned to a nanoscale material should be released publicly, along with all aspects of the study plan proposed to address the research needs, in the instant case the information sought by FDA in making the recommendation. The choice of the materials to be used should be fully disclosed. In the case of studies that could be relied upon by FDA for regulatory purposes in regulating drugs, foods, or devices, a justification for the specific study should be provided, describing how the study will address any stated concern about the adequacy of existing data. Any decisions regarding implementation of recommended nominations should be disclosed and public comment on them should be solicited. In the course of product development, a manufacturer may have conducted the very tests the FDA proposes to have NTP undertake, and the manufacturer may have valuable insight into how the tests should be performed. The public process NIEHS uses to compel such testing should elicit this type of information to avoid unnecessary testing and conserve limited resources, animal testing, and laboratory capacity. Under the current nomination process, there is no opportunity for seeking or obtaining this information. Any data generated during the course of the studies should be available for comment by the public while it is being considered by FDA.

Furthermore, the Consortium is aware that the federal government is actively participating in international collaborative efforts involving nanotechnology, including the Organisation for Economic Co-operation and Development's Working Party on Manufactured Nanomaterials. Just as the U.S. is collaborating with other countries, NTP should look to collaborate with its colleagues in other federal agencies and thereby benefit from their knowledge and understanding, particularly regarding appropriate methods for the physical characterization and evaluation of nanoscale materials.

If the steps described above are followed, a dialogue can ensue regarding the merits of the NIEHS proposal for nanoscale gold and silver. The Consortium is concerned that any less engagement with interested, knowledgeable stakeholders compromises the integrity of the scientific process and undermines the government's ability to rely upon test results for regulatory purposes. The Consortium looks forward to engaging with NIEHS in these matters.

The Consortium is pleased to provide these comments, and would be happy to respond to any questions about them.

Sincerely,

*Michael F. Cole*

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