Comments of Consumers Union on
Food and Drug Administration (FDA)
Proposed rule on Substances Generally Recognized as Safe; Reopening Comment Period
Docket No. FDA—1997—N—0020
Prepared by Michael Hansen, Ph.D.
Senior Scientist
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Consumers Union[1] (CU) welcomes the opportunity to comment on FDA's proposal to replace the voluntary petition process to affirm the generally recognized as safe (GRAS) status for substances used in human and animal feed with a voluntary notification policy. CU opposes this change because we think that this policy is weaker in terms of protecting food safety than the voluntary GRAS affirmation petition that it is replacing. However, if FDA continues forward with this change, we believe that they should finalize their 1997 proposed rule that lays out their framework and criteria for the voluntary notification policy for GRAS substances. In addition, **FDA should seek authority from Congress to require companies to inform FDA of all GRAS determinations made by the company**. **FDA should also consider engineered nanomaterials to be new materials with unfamiliar properties or a significant new use of a material**. **Existing GRAS determinations for macroscale materials should not be considered valid for versions made with engineered nanomaterials**.

In general, we believe that the FDA should ensure the safety of all substances added to food. In the case of GRAS substances, companies, at a minimum, should be required to notify FDA of any GRAS determinations they make. At present, the FDA does not have statutory authority to require that companies even inform them of any GRAS determinations that they make. Consequently, companies can make their own determination that a substance is GRAS, not tell the FDA of that decision, and then start adding that substance into food and selling it to consumers. We believe that this system allows for potentially dangerous substances to enter the food supply, without FDA's knowledge or supervision.

Large changes have taken place in the US food system since 1958, when the food additives amendment which exempted "substances that are generally recognized as safe under the conditions of their intended use, as shown through scientific procedures or based on common usage in food" prior to 1958 was passed. Our food production and distribution system has become much more centralized and foods travel much greater distances to market. A major change since 1958 has been the astronomical rise in the amount of imported foods. As of 2007, roughly 15% of the overall volume of U.S. food

[1] *Consumers Union, publisher of Consumer Reports, is an expert, independent nonprofit organization whose mission is to work for a fair, just, and safe marketplace for all consumers and to empower consumers to protect themselves. To achieve this mission, we test, inform, and protect. To maintain our independence and impartiality, Consumers Union accepts no outside advertising, no free test samples, and has no agenda other than the interests of consumers. Consumers Union supports itself through the sale of our information products and services, individual contributions, and a few noncommercial grants. Roughly 8 million people subscribe to Consumer Report or Consumer Reports online.*

supply consists of imports; for fresh fruit and vegetables the figure is 60%, and for seafood 80%[2]. Now, China is the third largest food exporter to the US[3]. At present, a Chinese company could decide that a certain substance is GRAS, add it to food and send it to the US, all without notifying FDA that it determined that the substance is GRAS. A Chinese company could decide that a given substance is GRAS—say a substance that helps maintain the color or texture of seafood—because it has a "common usage in food prior to 1958" in China, or because Chinese scientists regard it as safe, even if that substance has never been a part of the US food supply.

Further, companies can inform the FDA of some GRAS determinations they make, but not others. We have no information to help us determine the percentage of all GRAS determinations made by a company that are subsequently reported to the FDA. Thus, we do not know how many GRAS determinations have gone unreported so far. Consequently, **FDA should seek authority from Congress to require companies to inform FDA of all GRAS determinations made by the company**.

Consumers Union also believes that all "engineered nanoscale materials" (ENM) (defined as a material purposefully manipulated at nanoscale that exhibits novel properties and/or behaviors as a result) have the potential for structure-dependent health effects that are uniquely different than their larger counterparts and raise toxicity questions. Therefore, they should never be allowed GRAS status.

We agree with the conclusions of the July 2004 report of UK Royal Society and Royal Academy of Engineering, which concluded, "We believe that chemicals in the form of nanoparticles and nanotubes should be treated separately to those produced in a larger form. Given the evidence that increased surface area can lead to greater toxicity per unit mass, regulation of exposure on a mass basis to nanoparticles and nanotubes may not be appropriate."[4] As a particle gets smaller and smaller, the ratio of surface area to volume/mass increases exponentially. Thus, the surface area of 100 grams of lead in a sphere 2.6 centimeters in diameter is 0.0002 m^2. If that particle size is reduced from 2.6 cm to 50 nm (nanometers), the total surface area is over 1,000 m^2 or 500,000-fold (or almost 6 orders of magnitude) greater. The drastically greater surface area means potentially greater reactivity with biological or chemical materials around them—such as increased reactivity with the immune system.

We already know that for air pollution, the smaller-size particles with their greater surface area are typically more toxic than larger particles and can penetrate further into the lungs to cause damage. In addition, the small size of nanoparticles (ENMs) means that they may be able to pass through membranes—evade the immune system[5] or pass

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[2] US Food and Drug Administration. 2007. Food Protection Plan: An Integrated Strategy for Protecting the Nation's Food Supply. At: http://www.fda.gov/downloads/aboutfda/centeroffices/oc/officeofoperations/ucm121761.pdf

[3] Becker, GS. 2008. Food and Agricultural Imports from China. *CRC Report for Congress*. At: http://www.fas.org/sgp/crs/row/RL34080.pdf

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

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

through the blood-brain barrier or directly enter cells and their nuclei[6], and travel to places that conventional scale materials cannot. Finally, ENMs can be of an intermediate size—larger than individual atoms and molecules, but smaller than other larger blocks of material—that causes them to have properties that can't be easily extrapolated from their component chemicals or the bulk substance. For all these reasons, **FDA should consider ENMs to be new materials with unfamiliar properties or a significant new use of a material**. **Existing GRAS determinations for macroscale materials should not be considered valid for versions made with ENMs**. At this point, given the new and unique risks posed by ENMs due to their small size and scientific unknowns associated with assessing their potential toxicology (e.g. increased toxicity per unit mass), **ENMs should not be granted GRAS status**. Rather, ENMs should be required to go through full safety assessments.

In terms of a definition of ENMs, we believe that FDA should incorporate the definition used by the Office of Pharmaceutical Science in their June 2010 Reporting Format for Nanotechnology-Related Information in CMC Review: "Nanomaterial/Nanoscale Material**:** Any materials with at least one dimension smaller than 1,000 nm."[7]

Detailed comments on various Issues

Issue 1. Description of Common Knowledge Element and Related Definition of "Scientific Procedures"

We agree with FDA that they should change their description of common knowledge. In 1997, FDA proposed describing common knowledge as "* * * based upon generally available and accepted scientific data, information, methods, or principles, which ordinarily are published and may be corroborated by unpublished scientific data, information, methods" (second sentence of §170.30(b)). However, scientific principles are known within the scientific community and will always be published. Thus, scientific principles cannot be "unpublished." Consequently, FDA should change the second sentence of §170.30(b) to "* * * based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods."

In 1997, FDA also proposed a definition of scientific procedures (§170.30(h)) of "Scientific procedures include scientific data (such as human, animal, analytical, or other scientific studies), information, methods, and principles, whether published or

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[6] De Jong WH and PJ Borm. 2008. Drug delivery and nanoparticles: applications and hazards. *International Journal of Nanomedicine*, 3(2): 133-149. At: http://www.dovepress.com/articles.php?article_id=1836

[7] Pg. 3 in FDA Office of Pharmaceutical Science. 2010. Reporting Format for Nanotechnology-Related Information in CMC Review. MAPP 5015.9, at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM214304.pdf

unpublished, appropriate to establish the safety of a 'substance.' " Again, scientific principles cannot be "unpublished." Consequently, FDA should change the definition of scientific procedures to "Scientific procedures include application of scientific data (including, as appropriate, data from human, animal, analytical, and other scientific studies), information, methods, whether published or unpublished, as well as the application of scientific principles, appropriate to establish the safety of a 'substance.' "

Issue 6. Notifier's Responsibility for a GRAS Conclusion

We agree that FDA should require that a GRAS notice explicitly state the name and position or title of the person who signs it, given that some GRAS Notices submitted to FDA only had illegible signatures.

In addition, the GRAS affirmation petition process had explicit language that the petition "is a representative and balanced submission that includes unfavorable information, as well as favorable information, known to him and pertinent to the evaluation of the safety of the substance," and the notifier was required to certify this statement. We believe that this same explicit language should be required for the GRAS notification procedure and that the notifier should be required to certify to such a statement.

Issue 9. Including Confidential Information in a GRAS Notice

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9b We agree with FDA that they should require the notifier in the GRAS notice to explain why specific information is trade secret information and how qualified experts could conclude that the intended use of the notified substance is GRAS without access to the trade secret(s).

9c We agree that FDA should require a notifier who identifies confidential commercial or financial information in the GRAS notice to explain why it is confidential commercial or financial information and how qualified experts could conclude that the intended use of the notified substance is GRAS without access to such information.

Issue 13. Substances Intended for Use in Products Subject to Regulation by the US Department of Agriculture

We agree that a coordinated review process between FDA and FSIS should be made explicit in final rule, since > 25% of GRAS notices during interim period involved products also regulated under FSIS. In addition, we agree that the notifier should be required to include additional paper or electronic copy of the GRAS notification so FDA can send it to FSIS.

Issue 15. Conflict of Interest

We agree with Government Accountability Office (GAO)[8] that FDA should require GRAS notices to include information regarding expert panelists' independence. We also agree that FDA should develop guidance for companies on conflict of interest

Issue 16. Additional Guidance on Documenting GRAS Conclusions

We agree with GAO that FDA should take steps to ensure that companies maintain proper documentation to support their GRAS determinations. FDA has responded that such guidance exists in the preamble to the GRAS proposal and the FAQ (Frequently Asked Questions) on GRAS on the FDA's website. We believe that FDA should explicitly state that such guidance also applies to all GRAS determinations made by a company, whether or not they are submitted to FDA under the proposed notification procedure. We also believe that FDA should conduct random audits of data and information maintained by these companies vis-à-vis their GRAS determinations. Although FDA announced in the 1997 proposal that they would conduct such audits, FDA officials told GAO they have not conducted such audits.[9]

[8] GAO. 2010. Food Safety: FDA Should Strengthen its Oversight of Food Ingredients Determined to be Generally Recognized as Safe (GRAS). GAO-10-246. At: http://www.gao.gov/new.items/d10246.pdf
[9] IBID