



CENTER FOR FOOD SAFETY

TO: Food and Drug Administration: Center for Veterinary Medicine

FROM: Jaydee Hanson, Senior Policy Analyst

RE: Draft Guidance for Industry on Use of Nanomaterials in Food for Animals
(Docket No. FDA-2013-D-1009)

Comments submitted electronically via Regulations.gov September 10, 2014

The Center for Food Safety (CFS), a 501 (c)(3) non-profit, non-governmental organization, is pleased to have the opportunity to comment on the Guidance. CFS submitted a comment to FDA on its Draft Guidance on the use of nanomaterials in food substances (Docket No.: FDA-2011-D-0490).ⁱ

General comment

We are particularly concerned about reports that animal feed may be altered using nano forms of vitamins and pharmaceutical drugs as an additive in the feed.ⁱⁱ Nanotechnology is being tested by food manufacturers, and pharmaceutical manufacturers to changing the ways medicated animal feeds work. We are concerned about the health and safety of humans that eat the nano-medicated livestock and for the animals themselves as these new “drugs” become a part of animal feed. We expect the agency to carefully assess the ways that nanotechnology can change the chemical, physical and biological properties of animal feed and the livestock drugs it contains.

The FDA should look especially carefully at products which claim to manipulate feeds to achieve particular results such as altering an animal’s ability to absorb calories or chemicals/drugs in the feed.

CFS believes that while agricultural and animal feed uses of nanotechnologies are in the early stages, we note that the European Food Safety Agency (EFSA) recently produced a report on nanomaterials available on the market that reviews developments in nano enabled feed additives.ⁱⁱⁱ EFSA found that

“nanomaterials are being developed and tested for efficacy to replace antibiotics, to absorb bacteria and toxins, and to improve digestibility of feed. Antibacterial nanosilver is believed to have a similar effect as the usual antibiotics and is being added to drinking water for chickens and pigs. ... nanosilver has also been tested to reduce the toxicity of aflatoxin in chickens. In another potential application polystyrene-based particles are added to chicken feed to bind bacteria. These particles with the bound bacteria clump together when passing through the gastrointestinal tract of the chicken along with other fecal matter. Another development is the potential use of nanoclay as a feed additive. The contamination of animal feed with mycotoxins represents a worldwide problem for farmers and can cause serious diseases in farm

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animals. Researchers have developed a montmorillonite based nanoclay specifically to absorb mycotoxins in the gastrointestinal tract of animals to protect them from mycotoxosis. As a specific example, Shi et al. tested the efficacy of a modified montmorillonite nanocomposite to reduce the toxicity of aflatoxin in chickens. Finally, the effect of high dose of nano-selenium on feed digestibility was tested with sheep. The results indicated that supplemental selenium in the form of nano-selenium significantly improved the feed digestion in sheep.”^{iv}

We will now comment on the Guidance section by section.

A. Definition of nanomaterials

CFS believes that the primary definition being used by the FDA for nanotechnology in general, limiting it to 1-100nm is too limiting, but we find it wise that the FDA included in its definition a second point that has great merit, namely “ (2) whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).” By considering nano-like changes up to 1000nm, we believe that most nanoscale changes will be detected. However, we would note that for a margin of safety related to worker and animal inhalation of particles, the FDA should consider inhalation studies of ultrafine materials up to 2500nm.

B. Physicochemical properties of Nanomaterials in Food for Animals

We agree that “materials manipulated on the nanoscale level through the use of nanotechnology may affect the bio-distribution, biocompatibility, or toxicity of the material.” We would also urge the FDA to carefully assess the following:

- effects that manipulation on the nanoscale has on the chemical composition of the other chemicals in the feed; the effects of the purity, coatings, encapsulating materials, dispersing agents and other aspects of the engineered nanomaterial;
- the effects of the range of particle size of the nanomaterial (does batch to batch variation affect the properties of the nanomaterial?);
- information on concentration in terms of particle number and mass per volume when in dispersion and per mass when as dry powder;
- information on the particle’s surface, including surface charge and any chemical/ biochemical modifications that could modify the surface reactivity, or add new functions.

Other concerns include: redox potential, water solubility, pH, density, dustiness, and photo reactivity. In short, the nanomaterial(s) to be added to the feed should be extremely well characterized as new materials and the FDA should not rely on characterizations of the bulk scale of the substance.

Toxicity tests should pay special attention to the likelihood that tissues of the animal could concentrate nanomaterials in a way that will pay through to humans eating the tissues. Likewise, special attention

should be paid to any increase in gastric inflammation and changes in immune system reactions as they may differ at the nanoscale.

C. Nanotechnology and GRAS Substances in Food for Animals

CFS has sued the FDA on the issue of GRAS approvals, so we believe that you have adequate advice from us on why GRAS is an inappropriate way of approving food additives. Nonetheless, we appreciate your recognition in this draft guidance that nanochemicals should not be considered GRAS. We are concerned that this advice should also go the Association of American Feed Control Officials (AAFCO)^v as the FDA accepts the AAFCO feed approvals, including the AAFCO determinations of GRAS status. We urge FDA to not recognize AAFCO GRAS determinations, including those for nano feed ingredients.

V. Recommendations for Nanomaterial Animal Food Ingredient FAPs

A. Identity

In addition to the listed requirements, CFS urges FDA to require a company to identify the range of the sizes of nanoparticles in a food additive from 1nm to 1000nm so that it is clear what portion of the chemical is in which size ranges. This characterization should include sizes of individual particles in agglomerations of the feed additive.

B. Manufacturing Methods and Controls

In addition to requiring data on the differences between manufacturing the same product for dry feed and for wet feeds, the FDA should require manufacturing facilities to work with the Occupational Safety and Health Administration (OSHA) to limit the dermal and inhalation exposure of workers manufacturing the nanomaterials in the feeds to the lowest possible level. A hierarchy of controls to protect workers should be a requirement of approvals by the FDA.

Wastes from both the processing facility and the feeding operation need to be evaluated to determine whether the nanomaterial residues will result in hazardous environmental exposures. Wastes from animals fed these feeds should also be evaluated for their effects on water and soils to which they might be applied. The FDA should not approve requests for exclusions from environmental review for nano enabled feeds. Special attention should be paid to nano metals used as feed additives as studies at Duke University^{vi} have demonstrated uptake of nano silver in some plants grown in sludge containing nano silver. This may be true for other nano metals, too.

C. Intended Use, Use Level, and Labeling

CFS urges the FDA to require labeling of nano feed ingredients in any animal feed, both at the manufacturing level and in products sold to consumers.

D. Analytical Methods

The great range in the nanomaterials being used in or considered for feed applications means that one set of analytical methods may not fit all applications. The EFSA review found 55 types of nanomaterials for agri/feed/food.^{vii} The nanomaterials include metals, metal oxides, clay and full-carbon materials and organic nanomaterials consisting of nano-encapsulates and nano-composites. Still, at present, less than 20% of the different nanomaterials are involved in more than 80% of the applications and only a limited number of nanomaterials are involved in most of the applications.

It may be that the FDA should develop assessment tools first for the inorganic metals like nano-silver which make up much of the present applications and then develop ways of assessing the organic materials like chitosan, micelles, albumin that are and will be used for nano encapsulation. Then finally different assessment tools may be needed for products that are composites of two or more nanomaterials such as a metal oxide combined with or in a polymer.

E. Safety Evaluation and Proposed Tolerances for the Food Additive

FDA should not wait to require rigorous toxicological study of nanomaterials in feed.

Drs. Sass and Heine have demonstrated that it is possible to use standard toxicity tests to assess nanomaterials or at least determine where there are gaps in our assessment of particular chemicals.^{viii}

The European Food Safety Agency has also shown that traditional toxicology tests can be used with nano-toxicology . EFSA has developed a chart of the tests that should be used to assess nanomaterials in general, but this list also shows that nanomaterials should be able to be assessed through the standard range of toxicity tests.^{ix} See their chart reproduced below.

Table 2: ENM toxicity testing strategy

Type of test Information:

In vitro genotoxicity tests Necessary (see section 5.3.2.)

ADME Necessary (see section 5.4.1 and 5.4.2.)

Repeated-dose 90-day oral toxicity study in rodents Necessary (see section 5.4.3.)

In vitro digestion studies Might be necessary (see section 5.3.1.)

Other in vitro tests Might be necessary for screening and mechanistic information (see section 5.3.3.)

Reproduction study Might be necessary, or required by specific sector regulations or by EFSA guidance (see section 5.4.4)

Developmental toxicity study Might be necessary, or required by specific sector regulations or by EFSA guidance (see section 5.4.4)

In vivo genotoxicity tests Might be necessary, or required by specific sector

regulations or by EFSA guidance (see section 5.4.5.)

Chronic toxicity/carcinogenicity study Might be necessary, or required by specific sector regulations or by EFSA guidance (see section 5.4.4.)

Specific toxicity tests Might be necessary, or required by specific sector regulations or by EFSA guidance (see section 5.4.4.)

F. Proposed Regulation

CFS believes that proposed regulations should also assess the potential for the nano additive that is fed to livestock, poultry or fish to be present in the tissues of the animal that humans may eat. A complete assessment of the effects on human health should be required in the nano materials are found to be present in the food stuff. While an industry guidance is a good start, that CFS believes that FDA should address this issue through new proposed regulations.

G. Environmental Assessment

CFS believes that nano ingredients in animal feed should not be categorically excluded from environmental assessments. FDA should also complete a programmatic environmental assessment for nanomaterials used in animal feed.

Conclusion

CFS thanks FDA-CVM for requesting comments of the public. We look forward to following up with the FDA-CVM as companies request FDA approval for nano feed additive petitions. As noted above, we urge FDA to develop regulations that follow these guidances.

ⁱ <http://www.regulations.gov/#!documentDetail;D=FDA-2011-D-0490-0009>

ⁱⁱ Ibid at p. 8

ⁱⁱⁱ <http://www.efsa.europa.eu/en/supporting/doc/621e.pdf>

^{iv} Ibid at p.32

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<http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm115778.htm>

^{vi} Colman BP, Arnaout CL, Anciaux S, Gunsch CK, Hochella MF Jr, et al. (2013) Low Concentrations of Silver Nanoparticles in Biosolids Cause Adverse Ecosystem Responses under Realistic Field Scenario. PLoS ONE 8(2): e57189. doi:10.1371/journal.pone.0057189 available at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0057189>

^{vii} EFSA at p. 3.

^{viii} http://www.nano.gov/sites/default/files/jennifer_saas1.pdf

^{ix} European Food Safety Agency Scientific Committee, Guidance on risk assessment concerning potential risks arising from applications of nanoscience and nanotechnologies to food and feed, 2011, p. 18 available at: <http://www.efsa.europa.eu/en/consultations/call/scaf110114.pdf>