Registration of nanopesticides in the US

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The first nanopesticide to be registered in the US received its registration from the authorities last year and work continues on assessing the potential risks and data needs. But, says Erik Janus and Anna Gergely, gaps in the availability of test guidelines and guidance on issues such as methods to generate data on particle-size distribution means it is still early days in the development of the country's policy towards such products.

The powerful advantages that the use of nanotechnologies and nano-enabled products offer to agricultural production is expected to lead to greater use of these technologies in the near future. Brazil, China, India, South Africa and some European countries have already put significant strategic investment into nanotechnology applications for agriculture.

Doing more with less

One of the biggest advances afforded by deployment of nanotechnologies in the production and storage of food crops is the principle of "doing more with less". Overall, the use of nano tools such as encapsulation, entrapment, nanoporous materials and specialised particle coatings, allows controlled delivery (also over time, if necessary) to specific targets with greater specificity, and this in turn allows the use of less chemicals at the point of application and results in lower environmental burdens. A nano-encapsulated form of an insecticide is efficacious at lower doses than the conventional formulation.

Nanopesticide formulations have been shown to prevent loss of material at the site of application from ultra violet degradation, hydrolysis, etc. Research in this area has also been applied to remediation, where the use of nanoparticles has been observed to enhance the breakdown of crop protection chemicals in the environment. As with nanopesticides, nanofertilisers may also allow for slow and sustained uptake and are considered more efficient, cheaper and less polluting. Food storage, particularly of grains, in situations where insects have become resistant to some existing pesticides, is another important area where nano-enabled fungicides and insecticides have been successfully used.

How will these applications be regulated, and how acceptable will they be to the public?

Nano-enabled biosensing applications can achieve the real-time detection of humidity, nutrient status, temperature, pH or the presence of chemicals in air, water, soil or plant tissues. These applications, which can help detect contamination in raw agricultural commodities as well as diseases in crops, seem to be the biggest priority area for agricultural uses. Towards this end, nano-enabled sensor technologies for plants have been developed using nanoparticle-modified electrodes. In addition to new biosensing applications, advances in nanofabrication have helped provide novel strategies for researching and treating plant diseases.

We can expect similar advances in increased production capacity for livestock, where nanotechnologies and nano-enabled products can increase yields in meat production, while ensuring a healthier animal population as measured by greater fecundity, fewer reproductive problems and lower disease burdens among production animals. Use of nanotechnologies and nano-enabled products in livestock production may include monitoring the health of the population by using "nanodetectors", not only to detect pathogenic bacteria, but also to bind and remove these disease-causing agents. For instance, the use of surfaces functionalised with nanostructured material that binds to the foot-and-mouth disease virus in chickens, may help to visually recognise the presence of the virus. Nanocapsules can be used to increase absorption of important biomolecules (proteins, peptides, vitamins) to improve the nutritional status of animals.

Perhaps more importantly, the use of plants as living production systems in which to "organically" produce nanoparticles shows enormous promise in achieving sustainable use in agriculture. This practice, known as "particle farming", can be a promising technique to synthesise nanoparticles in a number of different plant species.

The question is: how will these revolutionary applications be regulated, and how acceptable will they be to the public?

In the US, nanopesticides would be

regulated under two federal laws: the Federal Insecticide, Fungicide and Rodenticide Act (Fifra) and the Federal Food, Drug and Cosmetic Act (FFDCA). Under Fifra, the Environmental Protection Agency (EPA) registers pesticides for use, and prescribes labelling and other regulatory requirements to meet the statutory mandate to prevent unreasonable adverse effects on human health or the environment. Under the FFDCA, the EPA establishes tolerances (maximum legally permissible levels) for pesticide residues in food for those pesticide applications that could come into contact with food, such as those used on residential surfaces, food-processing facilities, institutional kitchens, etc. Within the EPA, decision-making for pesticide registrations resides with the office of pesticide programmes (OPP), which is split into three divisions: registration, which is responsible for conventional pesticides; biopesticides and pollution prevention, which covers biochemical and microbial pesticides, as well as plant-incorporated protectants; and antimicrobials, which has responsibility for the registration of antimicrobial pesticides or biocides.

In 2011, the antimicrobial division registered its first nanopesticide: a nanosilver preservative that can be used on textiles to suppress bacteria that generate odours and stains. This first-ever approval of a nanoscale pesticide took several years and involved consultation with the Science Advisory Panel (SAP), a group of experts who provide scientific advice to the EPA on a wide range of health and safety issues related to pesticides. The original pesticide registration application was submitted by the Swiss company HeiQ in 2008 for its material preservative product, AGS-20. This sinters silver nanoparticles (1-50nm in size, with an average of 10nm) onto micron-sized amorphous silicon dioxide, which is then incorporated into textiles for topical surface treatment at ppm level.

In 2009, EPA convened a SAP to discuss the evidence that nanosilver and some metal oxides in the size range of 1 to about 100nm have unique behaviour under relevant conditions of human exposure, and to provide recommendations on: the types of data that may be required per the Fifra mandate; the priority of collecting these different types of data; and how the OPP should conduct risk assessments of nanosilver antimicrobial products. Based on the outcome of these recommendations, in August 2010, EPA proposed that AGS-20 be granted a four-year conditional registration pending the generation of additional product chemistry, toxicology, exposure, and environmental data.

Following the collection and consideration of public comment on the proposed registration decision, the EPA officially granted HeiQ a registration for AGS-20 in December 2011, but specified further data requirements from HeiQ and certain worker protection measures. In July this year, the EPA opened nanosilver's "registration review docket" – a document which explains what information the EPA has on the pesticide and the anticipated risk assessment and data needs. The opening of a registration review docket usually happens about 15 years after the original registration, but can be issued earlier at the EPA's discretion. The nanosilver docket imposes the same data requirements as those which were issued for AGS-20 on a handful of additional nanosilver registrants, all of whom have not yet been fully determined by the EPA.

The data requirements are tiered, consisting of a core set of data requirements (Tier I), and "higher tier" (Tier II) data which can be triggered according to the nature of the stability of the nanosilver/silicon dioxide composite materials that are incorporated into textiles. The core data include requirements for physical characteristics, such as particle-size distribution and surface area; ecotoxicity requirements, such as acute avian oral, acute aquatic invertebrate and acute fish toxicity; and human health effect tests, such as 90-day inhalation, 90-day dermal, modified reproductive/developmental toxicity screening and an *in vitro* micronucleus test.

Release characteristics data

Data fields to help describe release characteristics of the composite nanosilver/silicon dioxide material (and thus determine whether Tier II data are required) include dissolution kinetics, leaching, attrition and applicator inhalation and dermal exposure studies.

If the release characteristics data indicate that nanosilver particles are released, Tier II requirements would be required. These include data requirements for physical characteristics (including those previously listed, plus data on zeta potential and UV spectra), ecotoxicity (modified aquatic food chain transfer, terrestrial and aquatic plant toxicity, algal toxicity and chronic sediment organism toxicity), human health effects and environmental fate (including requirements for the rate of deposition, activated sludge isotherm, adsorption/desorption, soil column characterisation and activated sludge, and respiration inhibition).

Fulfillment of the data requirements is complicated by the fact that "official" harmonised test guidelines – standardised protocols available for the majority of the standard pesticide data requirements – do not exist for several studies being asked of nanosilver registrants. Some of these are critical data needs, such as particle-size distribution and leaching.

While there are many techniques (such as dynamic light scattering and electron microscopy) available to measure the size distribution of nanoparticles, each technique has its own distinct advantages and limits and EPA approval of a particular approach is currently decided on a case-by-case basis. No guidance on preferred technologies to develop size distribution data has been offered by EPA at this stage.

Regarding leaching (a key determinant of whether Tier II is required) there is, again, no test guideline, which means companies must seek private consultation with the agency to obtain protocol approval. Another question looming in the mind of registrants facing nanosilver data requirements is the selection of test material for Tier II testing: should it be the composite material, or nanosilver itself?

The answers to these questions, and the manner in which the EPA will consider and decide upon the nanosilver data requirements, will be determined in the coming months and years.

Protocols for several of these tests are still pending and the registrant of AGS-20, as well as the products captured in the July 2012 registration review activity, will need to submit required data over the next few years as these protocols are further refined and approved. This will also help to shape the future policies of other jurisdictions.

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Nanowatch is a series of articles by Steptoe and Johnson LLP's transatlantic nanotechnologies practice group (**www.steptoe.com** *). Anna Gergely (right) is head of Steptoe's nanotechnologies group, Erik Janus (left) is a regulatory scientist in the firm's Washington DC office.*