

## **Comments on the Regulatory Considerations for Nanopesticides and Veterinary Nanomedicines: A Draft APVMA Report**

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November 2014

### **Summary**

The National Toxics Network (NTN) participated in the APVMA's *Nanotechnology Regulation Symposium* on the 28<sup>th</sup> October 2014. After consideration of the presentations and a review of the draft APVMA report, NTN provides the following comments for consideration in the final report to be prepared by the APVMA.

Overall, the draft report provides a thorough and useful summary of the available scientific literature concerning the health and environmental risks of nanomaterials, potential benefits, manufacturing challenges, physicochemical properties and nanometrology.

Our concerns about the draft report relate to fundamental definitional issues for nanoparticles. We note that definitions are evolving internationally, which the APVMA does recognize in the draft report. We suggest that the APVMA follow the European Medicines Agency and the US Food and Drug Administration Office of Pharmaceutical Science and define nanotechnology as “... *the use of tiny structures - less than 1,000 nanometres across - that are designed to have specific properties*”<sup>[1],[2]</sup>.

The other area of fundamental concern relates to the Legislative and Policy Considerations in the Australian Regulatory Framework (Chapter 2 in the draft report).

A number of speakers made the point that nanoparticle properties change depending on their environment and they also have the potential to alter the environment they are in. This raises complex challenges for risk characterization and management in the diverse range of Australian environments. Given the novel properties and the novel ways that nanomaterials interact with living organisms and the environment, it is clear that all nanomaterials must be considered new chemicals.

The APVMA draft report notes, “The potential risks to human health and the environment outlined in the report and during the symposium are significant and varied”.

As yet, Australia doesn't have a nanomaterial register, making it impossible for regulators to determine which nanomaterials are already be in the marketplace. There are no mandatory requirements that compel manufacturers to disclose this information. No are there mandatory labelling requirements. We urgently need both!

While the APVMA maintains they only have one veterinary nanomedicine application, it's unclear whether formulation changes may have already occurred with existing approved products on the market such as microemulsions that may include nanoparticles.

## Definitions, properties and size

A critical question when assessing the regulation of nanomaterials is their precise characterisation and definition. The APVMA says – “However, the APVMA acknowledges that biological and health, safety and environmental (HSE) issues may require a different size range above 100 nm. “

But limiting the definition nanomaterials to a nanoscale of between 1 nm and 100 nm is inappropriate, especially for nano veterinary applications (and such applications are planned for companion animals as well as), as size is only a crude index of novel properties. Indeed the biological behaviour of materials between 100 nm and 1000 nm (in one, two or three dimensions) can pose novel risks, as at this scale they may share many of the characteristic behaviours of nanomaterials below 100 nm in size. These shared properties may include very high reactivity, bioavailability, increased influence of particle surface effects, strong particle surface adhesion, strong ability to bind proteins and very high bioavailability<sup>[3],[4],[5],[6],[7]</sup>.

Many nanoveterinary (and pesticide) products do not fall neatly into the conventional size definition for nanomaterials of 1-100 nm. For instance, nanomedicines for humans that aim to passively target sites are typically between 100 nm to 200 nm in size, but particles up to 400 nm have also been used successfully<sup>[1]</sup>. Nanomaterials being developed for a variety of human clinical applications include liposomes measuring 100-200 nm, nanoshells measuring 60-400 nm<sup>[8]</sup> and drug delivery systems measuring 100-200 nm<sup>[9]</sup>. A recent survey of human nanomedicine products noted that most were sized up to 300 nm, but that some were larger still <sup>[1]</sup>. Perhaps this is the reason why both the European Medicines Agency and the US Food and Drug Administration Office of Pharmaceutical Science define nanotechnology as “... *the use of tiny structures - less than 1,000 nanometres across - that are designed to have specific properties*”<sup>[1],[2]</sup>.

The common assessment paradigm for toxicological assessment is that there is a correlation between mass and toxicity, but a number of studies have shown that this may not be the case for nanomaterials. Other properties such as surface area, surface chemistry, etc., may give a better indication of toxicological endpoints<sup>[10]</sup>. Furthermore, given that bioavailability may be enhanced in some nanomaterials, particularly those devised for medical or pesticidal purposes, this will result in a change of biological effects and it may be difficult to predict or to include in existing environmental risk assessment schemes <sup>[10]</sup>.

Furthermore, one of their greatest potential dangers may be the propensity of some nanomaterials to cross biological barriers in a manner not predicted from studies of larger particles of the same chemical composition <sup>[11]</sup>.

A further complication is that nanomaterials may also acquire new “biological identities” (and thus new properties) via the adsorption of biomolecules onto their surface, giving what is termed a “bio-corona”. Toxicological studies need to assess the interaction between the bio-corona and the nanomaterials and how they might interact with each other, as well as assessing the physiological response of the organism to the bio-corona<sup>[11]</sup>.

## **Environmental impacts are uncertain**

A recent review of toxicological research on nano metal oxides (silver, copper and zinc oxide) reported that they are extremely toxic (as defined by EU Directive 93/67/EEC) to freshwater aquatic organisms including fish and algae, with crustaceans being most affected<sup>[12]</sup>. Freshwater may stabilise nano metal oxides and make them more persistent and hence increase availability for fish and algae filter feeders, while sea water appears to facilitate aggregation and settling and hence reduce toxicity<sup>[13]</sup>. This report confirms the need for strict assessment and regulation of the use and disposal of nanomaterials in general and nanomedicines in particular.

Nano metal oxides have also been shown to contaminate soils and enter the food chain via plant uptake. Recent studies reported that different plant communities experience reduced growth or biomass after taking up nanosilver from soil<sup>[14],[15]</sup>. Soya beans, a major human and animal food source, have been shown to absorb and be adversely affected by nano zinc oxide and nano cerium oxide from contaminated soils<sup>[16]</sup>. Cerium oxide nanoparticles (despite conflicting *in vitro* and *in vivo* toxicity data), are viewed as having great potential as a cancer treatment and treatment for other diseases such as macular degeneration and hepatitis<sup>[17]</sup>. Yet, at the same time its interaction with important food crops raises serious issues about how and when it should be used and, very importantly, its disposal<sup>[13]</sup>.

A recent review concluded that risk assessment of nanoparticles in soil will be difficult because of the varying soil conditions<sup>[18]</sup>. However, nanosilver, nano copper oxide and zinc oxide nanoparticles have been shown to damage beneficial soil microbes to varying extent depending on the soil type<sup>[19]</sup>. Exposure to carbon nanoparticles may harm earthworms by slowing population growth, increasing mortality and damaging tissue<sup>[20]</sup>. Data for many other nanoparticles used in nanomedicine is still lacking or sketchy.

## **Possible synergistic effects**

An often-overlooked aspect of environmental contaminants is that they usually exist as part of a complex mixture of chemicals in the environment. The composition of this mixture may increase or decrease the bioavailability of individual components and hence toxicity to organisms. For instance the presence of nano titanium dioxide may increase the accumulation of cadmium in carp (*Cyprinus carpio*)<sup>[21]</sup>. To date, little research has been done in the area of ecotoxicological effects of engineered nanoparticles in chemical mixtures and more research is urgently needed<sup>[21]</sup>.

## **Lack of knowledge is hampering assessment of ecotoxicity**

Ascertaining the ecotoxicity of nanomaterials and how they are distributed in the environment and the effect they may have on organisms is currently not only challenging, but also beset with limitations due to a lack of suitable monitoring equipment and extensive knowledge gaps<sup>[22]</sup>. Currently no actual environmental monitoring of nanomaterials in the field has been reported, but this may change in the near future. In the interim, environmental models of the effect of nanomaterial release into the environment are being calculated and reported<sup>[23]</sup>.

An extensive review of the potential health impact and environmental safety of engineered nanoparticles was conducted in 2010, as part as the EU's 7<sup>th</sup> Framework ENRHES project<sup>[22]</sup>. This review recognised that understanding of the environmental exposure risk of engineered nanomaterials was hampered by the general lack of data relevant to their soil and sediment behaviour, especially in relation to metal oxides and carbon nanotubes<sup>[24][24][23]</sup>. A further key issue identified was the lack of comparability of research due to different functionalisation of nanomaterials, different

experimental approaches and different levels of attention given to the characterisation of the nanomaterials used<sup>[24]</sup>.

Given the novel properties and the novel ways that nanomaterials interact with living organisms and the environment, it is clear that all nanomaterials must be considered new chemicals.

## **Legislative and Policy Considerations in the Australian Regulatory Framework**

Despite repeated attempts by civil society organisations to engage early on with government, regulators and industry on the emergence of nanotechnology in the marketplace and the need for a precautionary approach and further research, it appears industry has charged ahead regardless and regulators are playing catch-up.

The APVMA draft report says, “In reality, nanoparticle application in the various industries has outpaced the research that is needed to determine which of their characteristics might pose unique hazards.”

The premise put forward at the symposium and outlined in the draft report says, “The general consensus is that, for the foreseeable future, the existing regulatory framework developed for non-nanoscale chemicals, in conjunction with a case-by-case approach, will be used to regulate nanomaterials. Over time, however, the framework will evolve as new information highlighting limitations in the current risk assessment paradigm becomes available”.

The first point is whose ‘general consensus’ is this? It’s certainly not the general consensus of civil society organizations such as NTN and others that the current regulatory regime would be up to this task.

We have significant concerns about the capacity and track record of the APVMA to effectively regulate non-nanoscale chemicals, let alone nanopesticides and veterinary nanomedicines.

We do not support the notion of an evolving risk assessment framework as risks become evident either. This approach is business as usual and locks the community into endless years of ‘proving’ that nanopesticides might have caused harm, much like the drawn out tobacco debate and our experience with the way current regulation works in terms of removing dangerous pesticides from the market.

Industry must prove their products are safe and can be managed before they are permitted on the market. If they don’t have the data they should not have a market. The APVMA needs to adopt a precautionary approach to ensure that people and the environment are protected and not made guinea pigs in an uncontrolled experiment with nanopesticides and veterinary nanomedicines.

Why do we have concerns about the capacity of the APVMA and Australia’s AgVet chemical regulatory regime?

Australia currently has a considerable number of pesticide products on the market that have never been assessed to today’s regulatory and scientific standards and there is no system in place to make sure this will happen within a reasonable timeframe.

Essentially, the APVMA are allowing poorly assessed products to stay on the market when there has not been an adequate risk assessment and appropriate controls put in place.

Hundreds of active ingredients and their associated products were grandfathered onto the national scheme in 1996 and could represent between 60-80% of products on the market today.

Comparable jurisdictions like Canada, USA and the EU all have what's termed 're-registration' programs to ensure that older chemistries and products are re-assessed to ensure they are not causing unacceptable risks to people and the environment today.

In the absence of a legislated and systematic re-registration scheme to address the backlog of older chemistries still on the market, Australia's AgVet regulatory system could hardly be called 'world's best practice'. For instance, Australia has at least twelve highly hazardous pesticides permitted for use that are banned in Canada, USA and the EU.

The APVMA also has a very poor track record with its chemical review program. It has allowed some reviews to continue for between 10-17 years while people and the environment were exposed to unacceptable residues as a result of APVMA approved pesticide use.

For instance, Australia was one of the last countries to ban endosulfan, despite an international scientific consensus that it is a persistent, bioaccumulative and toxic pesticide that was finding its way into women's breast milk and the environment.

Instead of acting to protect people and the environment, the APVMA did all it could to keep the pesticide on the market. Endosulfan was subsequently listed on the *Stockholm Convention for Persistent Organic Pollutants* to which Australia is a signatory which required its use to cease.

Very little environmental monitoring or biomonitoring for pesticide residues is undertaken in Australia. What environmental monitoring is done often finds a problem.

A 2014 paper titled *Australia's pesticide environmental risk assessment failure: The case of diuron and sugarcane*<sup>1</sup> illustrates just how precarious environmental risk assessment can be for one herbicide. This is just one example of one pesticide in a complex ecosystem, so imagine introducing the complexities and unknowns of nanomaterials into this assessment.

"In November 2012, the Australian Pesticide and Veterinary Medicines Authority (APVMA) concluded a 12 year review of the PSII herbicide diuron. One of the primary concerns raised during the review was the potential impact on aquatic ecosystems, particularly in the catchments draining to the Great Barrier Reef. The environmental risk assessment process used by the APVMA utilised a runoff risk model developed and validated under European farming conditions. However, the farming conditions in the sugar-cane regions of the Great Barrier Reef catchments have environmental parameters beyond the currently validated bounds of the model. The use of the model to assess environmental risk in these regions is therefore highly inappropriate, demonstrating the pitfalls of a one size fits all approach".

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<sup>1</sup> Glen Holmes (2014) *Australia's pesticide environmental risk assessment failure: The case of diuron and sugarcane*, Marine Pollution Bulletin.

## **Apply the precautionary principle**

The potential of nanotechnology to bring societal and environmental benefits remains largely unproven. Nanomaterials are essentially new and largely untested chemicals and little is known about their persistence, bioaccumulation and toxicity, although many would fall into the category of toxic materials as other hazardous chemicals. Therefore, in view of the potential risks of nanomaterials to human health and the environment and the lack of knowledge, preventive action should be taken and the precautionary principle must be applied. Without a clear knowledge of the risks involved for human health and the environment, products should not be allowed into the market.

Nanomaterials are new chemicals and should be classified as new substances in Australian legislation, placing the burden of proof for safety in the hands of nanotechnology producers and distributors.

It is important to:

- Improve the current nanomaterial definition by not restricting the size threshold to 100 nanometres in one or more dimensions.
- Specific data for the dossier information should be required to ensure that the manufacture, marketing and use of nanomaterials in nanoproducts or others have no harmful effects on human health or the environment during the entire life cycle.
- Review Australian waste management legislation to take into consideration specific properties and characteristics of nanowaste and to provide guidance on management of nanomaterials in waste, including in landfills, whilst avoiding health and environmental consequences.
- Address the failures in the current regulatory system for AgVet and industrial chemicals in Australia.

## **Identify and categorize nanomaterial characteristics to ensure appropriate testing methodologies**

Testing methods for nanomaterial toxicity are still very much under development, hence knowledge on toxicological and ecotoxicological properties is insufficient to conduct proper risk assessment<sup>[25]</sup>. The recommended testing requirements to ensure the safe use of nanomaterials can be grouped into:

- substance identification and characterisation based on physicochemical properties;
- toxicological properties; and
- environmental fate and behaviour based on ecotoxicological properties.

In order for appropriate testing to be carried out all nanomaterials need to be identified in terms of:

- crystal structure
- primary particle size distribution
- agglomeration/aggregation state
- specific surface area
- morphology/shape/aspect ratio
- information on surface modifications
- catalytic properties, free radical formation potential
- surface charge/zeta potential
- dustiness (i.e., the propensity of a material to generate airborne dust during its handling)

- the fate and properties of nanomaterials in water, and
- photo-degradation potential.

Also current test guidelines use conventional methodologies that are unlikely to be appropriate for the assessment of risks associated with nanomaterials. Therefore it is important to:

- Fill in the scientific knowledge gaps on safety, fate and persistence of nanomaterials in humans and the environment.
- Develop nanomaterial-specific standards, guidelines and tools to detect, monitor and measure nanomaterials in the environment and the effects of exposure of these materials on human health and the environment.

## **Mandatory Australian register and labelling**

A number of EU countries and NGOs have recently proposed the establishment of an EU register of nanomaterials used in products, and/or of products containing nanomaterials. We suggest that Australia follow the same pathway.

The purpose of such a register is to assure maximum transparency of the use of nanomaterials in all products, including in the agricultural and veterinary medicine area. A register fulfils a number of purposes: monitoring of the potential adverse health and environmental impacts of nanomaterials; improving companies' knowledge of the substances they are manufacturing and using; increasing information and traceability throughout the supply chain for all stakeholders; and increasing knowledge of toxicity and ecotoxicity and resources invested in risk assessments for nanomaterials. Overall, this would increase the sustainability of nanotechnology while providing confidence and transparency for the general public and workers. Additionally all products containing engineered nanomaterials should be labelled.

Australia could follow France which has already put in place a nano register (January 2013), while Belgium is proposing to start one in 2015 and Denmark is currently consulting interested stakeholders. The French nano register requires companies that manufacture, import and distribute nanomaterials in quantities of  $\geq 100$  g to submit to the authorities an annual declaration stating the quantity and information on use. The aim is to better understand how and where nanomaterials are being used; enable traceability; improve knowledge of the market and volume of nanomaterials involved; and collect available information on the toxicology and ecotoxicology of nanomaterials<sup>[26]</sup>.

Belgium is proposing a system in line with the French that would require all manufacturers, distributors or importers of substances at the nanoscale ( $>100$  g/year) to register their products via an online portal from 2015. Why the remit for such a system may lie with NICNAS, the APVMA could take the lead and together with NICNAS implement such a register and labeling requirements.

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