

Human Health Risk Consideration on Nano-enabled Pesticides for Industry and Regulators

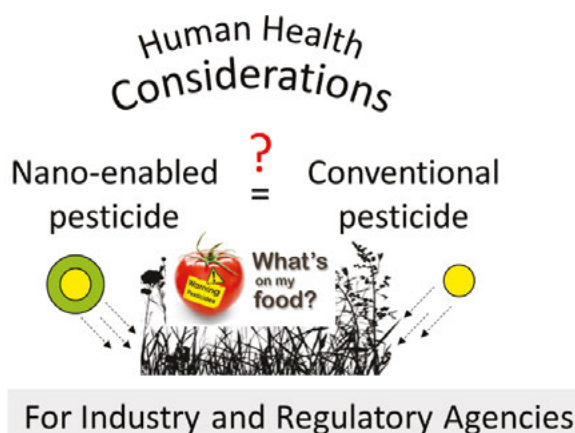
Nanotechnology is emerging as a highly attractive tool for the formulation and delivery of pesticide active ingredients (AIs) as well as enhancing and offering new AIs. There is a great deal of potential to decrease the amount of AI required as well as to produce alternative AI (Bioclay), but there are also concerns related to possible additional or alternate toxicity mechanisms for both the environment and human health. Several nano-enabled pesticides are in the pipeline and will need to be evaluated in the near future. Currently there is a lack of understanding among industry and regulators on:

1. The human health effects data that regulators will require to determine the risk profile of nano-enabled pesticides,
2. What methods/approaches are appropriate and acceptable to give industry confidence in obtaining and submitting the data required to satisfy the regulatory requirements?

To address the above, a IUPAC project was jointly developed by IUPAC Divisions VI and VII with COCI on Human Health Risk Consideration on Nano-enabled Pesticides to provide guidance to industry and regulators. The key objective of the project is to assist industry, contract research organizations and regulators in determining an acceptable and practical approach for identifying and generating the data relevant to human health risk assessment required for the registration of nano-enabled pesticides.

The project got an excellent start in June 2018 with a workshop in Boston that coincided with the Gordon Research Conference on Nanoscale Science and Engineering for Agriculture and Food Systems. The objective of the workshop was to identify questions that are specific to nano-enabled pesticides that must be addressed in addition to the questions normally asked for conventional pesticides.

The workshop brought together a range of expertise from regulators, industry, researchers, and academia. Regulatory agencies included the US Environment Protection Agency (EPA), US Food and Drug Administration (FDA), Health Canada, Australian Pesticides and Veterinary Medicines Authority (APVMA), each provided an overview of their approach for regulating nano-enabled pesticides/nanomaterials. Vive Crop Protection provided an overview of products likely to enter the market as well as an industry perspective on how these products are likely to be different than



For Industry and Regulatory Agencies

After Walker et al. 2017

conventional AIs. In breakout sessions, the group then discussed different routes of exposure (e.g. dermal, inhalation, ingestion) as well as stages of exposure (e.g. during mixing-loading, during application, workers, bystanders, residents). These were considered in relation to two case studies where (i) a nanocarrier system is used for a slow release of a pesticide AI (e.g. an insecticide molecule) and (ii) a pure AI nanoparticle is used for modifying the inherent chemical properties of the AI (e.g. to increase the "apparent solubility," retention on leaves or uptake in target organisms).

The workshop raised more questions than answers and identified several issues that need to be addressed while considering nano-enabled pesticides implications for human health, for example:

- Different jurisdictions have slightly different criteria for defining nano-enabled pesticides at the moment, similar to the current situation with defining nanomaterials by regulatory agencies. The boundaries are not yet clearly defined.
- The vast majority of nano-enabled pesticides are based on existing and already authorised AIs. The AI is the bioactive component, which is primarily tested for efficacy and potential undesirable effects, similarly to pharmaceuticals. In many cases, the other components of the formulations (inerts/excipients) also have to be considered.
- Pesticide AIs are always formulated, e.g. with surfactants, solvents, and/or inerts. Many formulations currently contain relatively large amounts of inerts, including non-nano forms of TiO_2 or silica. Can data related to existing excipients be used or should these inerts/excipients be treated differently in nanoformulations?
- The persistence of a nanocarrier may be assessed as part of the inert assessment on individual

components. However, the persistence of the fully formulated nanocarrier (with all ingredients, including the AI) may not be known. Does this raise issues?

- Considering the variability in excipients and formulations, what is the correct reference material? AI alone is currently used for toxicity studies, not the formulations.
- Nano AI may be stabilised with e.g. surfactants: Does the fact that they are, or are associated with, a nanoparticle, make them different from a toxicological perspective?
- For a nanocarrier composed of ingredients that are already considered safe: are there ways to design bridging studies and potentially use existing toxicity data? How should the dose be compared? What data is needed for bridging? How does one determine dose? What tests/end points are needed?

Considering the above and many more questions that were raised at the Boston workshop, a follow up workshop was organised to coincide with the IUPAC Centenary Celebrations and General Assembly in July 2019. Ultimately, as an outcome of this project, we hope to develop well-considered views on some of the above challenges.

Reference

1. Walker, G; R.S. Kookana; N.E. Smith; M. Kah et al. *Journal of Agricultural and Food Chemistry*, 66(26): 6480-6486, 2017. DOI: 10.1021/acs.jafc.7b02373.

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Trace elements analysis of environmental samples with X-rays

An increasing number of scientists from around the world are using X-ray based methods for the analysis of trace elements in environmental samples. X-ray analyses can be successfully performed both at synchrotron facilities and in modern laboratories with dedicated instrumentation.

Synchrotron X-ray methods can provide information on both the concentration and the speciation of trace constituents and is being utilized to unravel many chemical processes and transformations. Synchrotron generated X-rays can also help scientists to elucidate reactions occurring over different lengths and time scales, usually not possible with conventional



Roberto Terzano (IUPAC Division VI secretary and Project Task Group) and other Task Group Members (from left: David Paterson, Gerald Falkenberg and Ryan Tappero) presenting awards to the winners of the "IUPAC Division VI Best Poster Prize."

laboratory instruments. In recent years, new beamlines dedicated to environmental analyses have been commissioned at synchrotron facilities around the world and new methodologies have been developed for fast and sensitive trace elements analyses in environmental matrices. However, the number of requests for beamtime at synchrotrons has also increased exponentially making it increasingly difficult to obtain access to these large facilities.

Nevertheless, recent technological improvements in X-ray optics and detectors (many of which were pioneered at synchrotron facilities) have been incorporated into modern analytical instruments. These