OPP-ORD Collaboration to Develop a Nano Determination Framework

November 4, 2021

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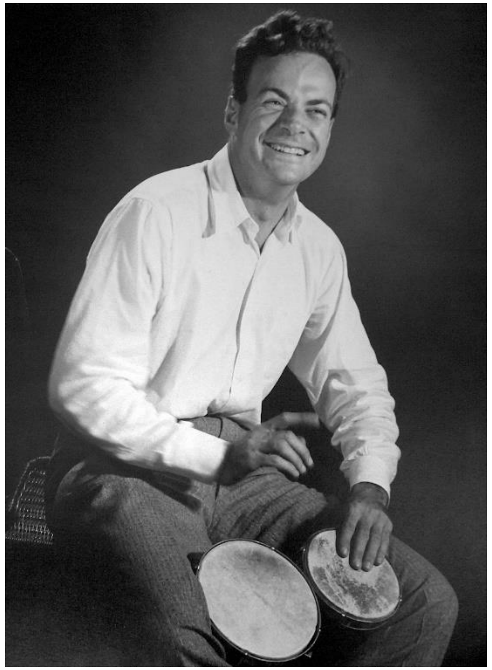
What is nanotechnology and why do we care?



- Obligatory photo of Feynman Playing Bongos
- Plenty of Room at the Bottom

- Quantum and surface properties dominate material properties.
- All the same material (CdSe)

- Different size
- Slight differences have profound effects on properties

http://www.bu.edu/research/files/2017/05/h_research_800px_quantum-dot-rainbow.jpg

Silver reclassification completed 6/20/19

# FINISHED products	**121**
TOTAL PRODUCTS	123
# still under consideration	2
% finished	98.37%
# reclassified from original	61
# reclassified as AgNPs	10

- Every registered silver/silver ion/silver salt/silver glass
- Individually examined by three experts
- Multiple rounds of data requests, struggles with obtaining usable data
- Took ~ 2 ½ years
- DCI issued August 2019

Industry's Response to Reclassification

- How may we demonstrate the selected stabilizer is not present to create nanosilver?
- If this stabilizer were removed or replaced would the Agency re-classify the product as silver?
- What does the particle size need to be to be considered non-nano?
- What is the specific definition of Nanosilver that companies can rely on for making regulatory decisions?
- What scientific evidence must the industry provide to disprove the notion that these particles are more hazardous than other silver forms?
- How could this industry share data across multiple Nanosilver products? For example, what would be criteria necessary for selection of representative test substances?

What does this tell us about the current method of nano classification?

- Too slow
  - ~550 antimicrobial copper products require ~11 years to sort.
- Resource intensive for the Agency
  - Requires experts; “I know it when I see it.”
  - Not standardized; bespoke determination
  - No bridging
- Process is opaque and not clear to stakeholders (creates confusion)

The Solution: A Nano Determination Framework

- Low Hanging Fruit
  - Narrow focus to materials encountered NOW
  - Metals, Metal Oxides, Silicon dioxide/silica
- Scientifically robust
- What data we need, why we need it, form we need
- Must allow industry to come to us with arguments why/why not
- 80/20 Method: Good enough most of the time, experts required rarely; can still make judgement calls

The Development of the Framework

- Collaborative effort
- Scientific and regulatory expertise
- Frequent meetings
- Time dedicated to debate before working on deliverable
- Use internally at first, then develop workplan to release to industry

A Framework for Evaluating Engineered Nanomaterials within EPA's Pesticide Program

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CSS BOSC Meeting
November 4, 2021

Disclaimer: This presentation does not necessarily reflect EPA's policy

Nanopesticides Toward Sustainable Agriculture

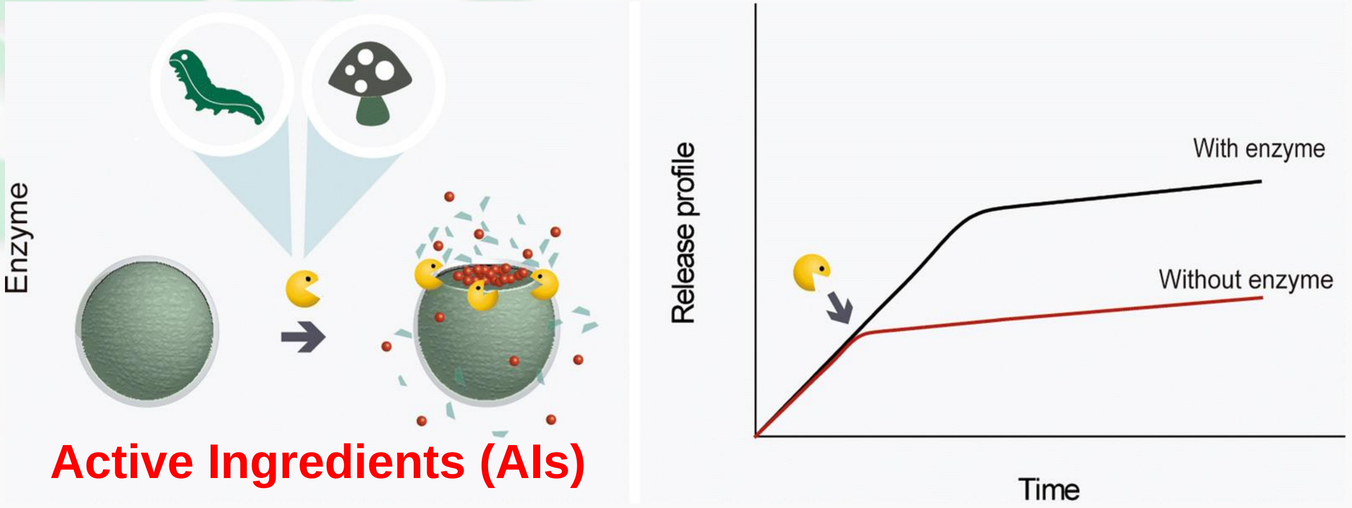
Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA): EPA OPP

Problems of Conventional Pesticides:

- ~4 million tons of pesticides are used annually with <0.1% reaching the target organisms, leaving 99.9% to the environment
- Ineffective use of pesticides results in economic loss of ~$220 B annually due to inefficient control of agricultural pests

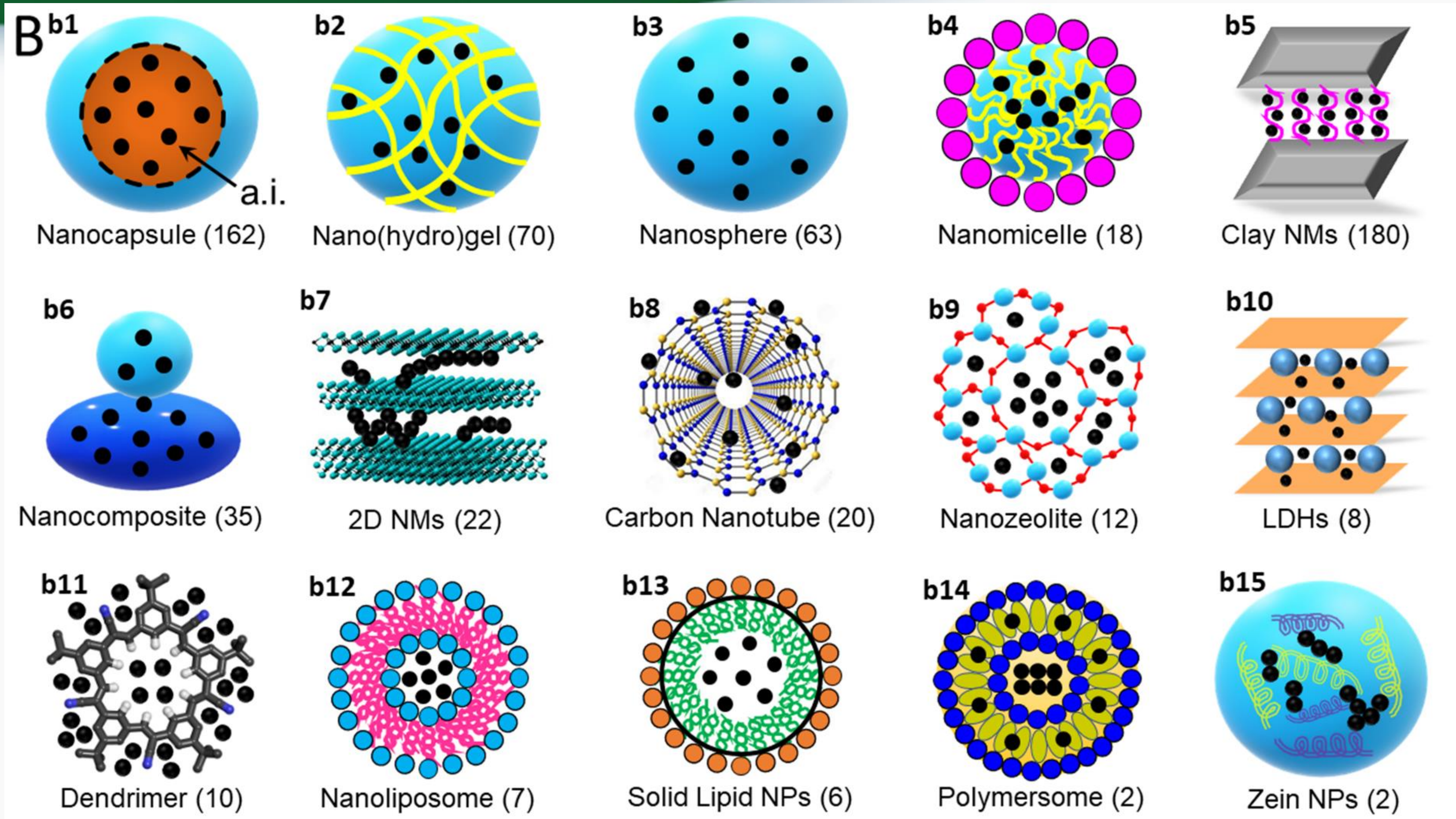
The Advantages of Nanopesticides:

- Controlled & targeted release of AIs
- Environ. & biological stimuli-responsive
- Enhanced bioavailability and less loss



(Camara et al., 2019, *J. Nanobiotechnology*, 17, 100)

Two Types of Nanopesticides



- Google Patents Search (Nano* & Pesticides*): 12,441
- Nanopesticides: 893
- Type 1: Ag-, Ti-, Cu-based NMs as AIs
- Type 2: Nanocarriers like nano-polymer and nano-clay to house AIs

(Wang et al., 2021, *Nature Nano*, accepted)

Nano-Enabled Pesticides: A Path Toward Sustainable Agriculture and Global Food Security

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White Paper on Nanopesticides

- At this time, OPP has no strict scientific definition for what is considered a nanomaterial
- Until now, Agency scientists reviewed each product and alerted every registrant of the data necessary to submit for each product on a case-by-case basis
- There is a need to establish a framework for identifying what kinds of data are required and examples of acceptable versions of these data
- We are developing a framework to guide the user through a decision tree to determine whether or not a material would be considered a NM by OPP and OPPT.
- The framework is currently limited to determination of most metals, metal oxides, silica, and combinations of these
- This white paper is broken into two parts: the flowchart and the explanation

CSS3.1.3 Update Risk Assessment Framework for Nanomaterials

White Paper: A Nano Determination Framework for Evaluation of Nanopesticides

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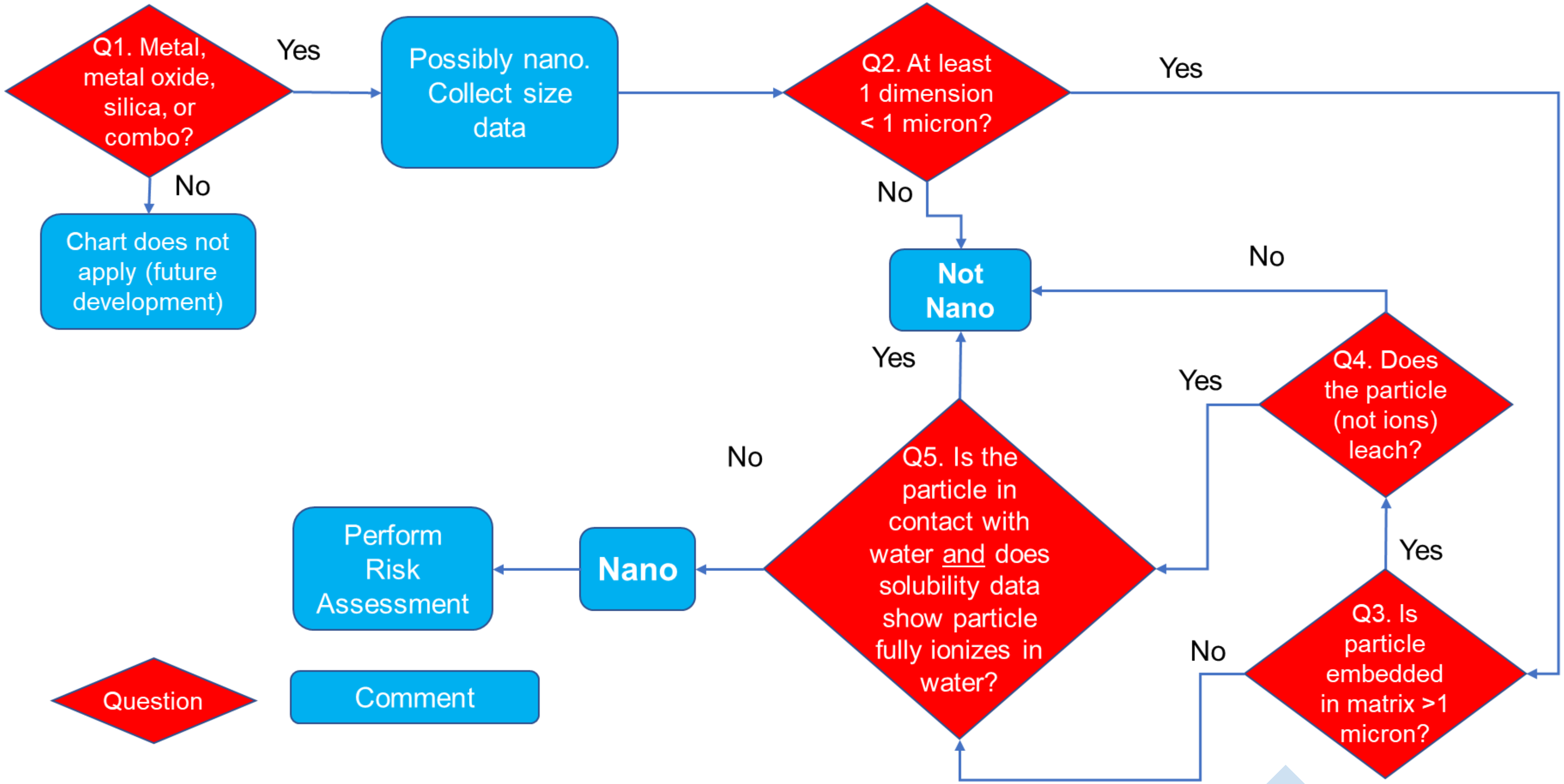
Nano Determination Framework



Question 1 (Q1): Is the Material a Metal, Metal Oxide, Silica, or a Combination of Two or More of These?

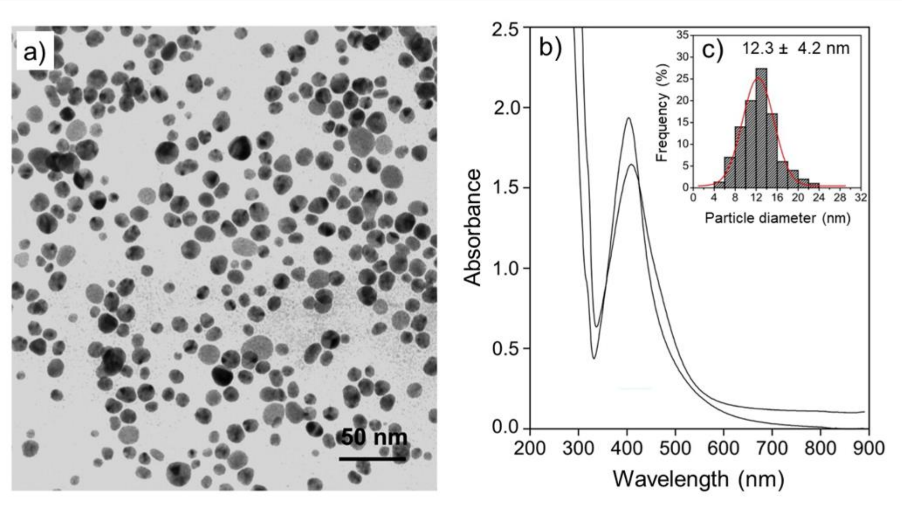
- Data about chemical elemental composition should be provided. This variable identifies the elements and substances making up the particle. For pure particles (i.e., particles composed of a single element), composition is generally simple to determine. However, distinguishing the composition of particles involving many elements or substances, especially at the nanoscale level, is challenging.

Particle Property	Technique	Information Provided	Comments	Recommended Methods
Elemental Composition	Energy dispersive X-ray spectroscopy (EDX)	Elements present in particle	Can determine elemental composition (i.e., chemical elements and estimates of abundance)	(ASTM, 2019b; Liu, 2005)
	X-ray photoelectron spectroscopy (XPS)	Elements present on particle surface	Can characterize particle surface (i.e., oxidation state can be determined)	(Baer et al., 2019; 2021; van der Heide, 2011)

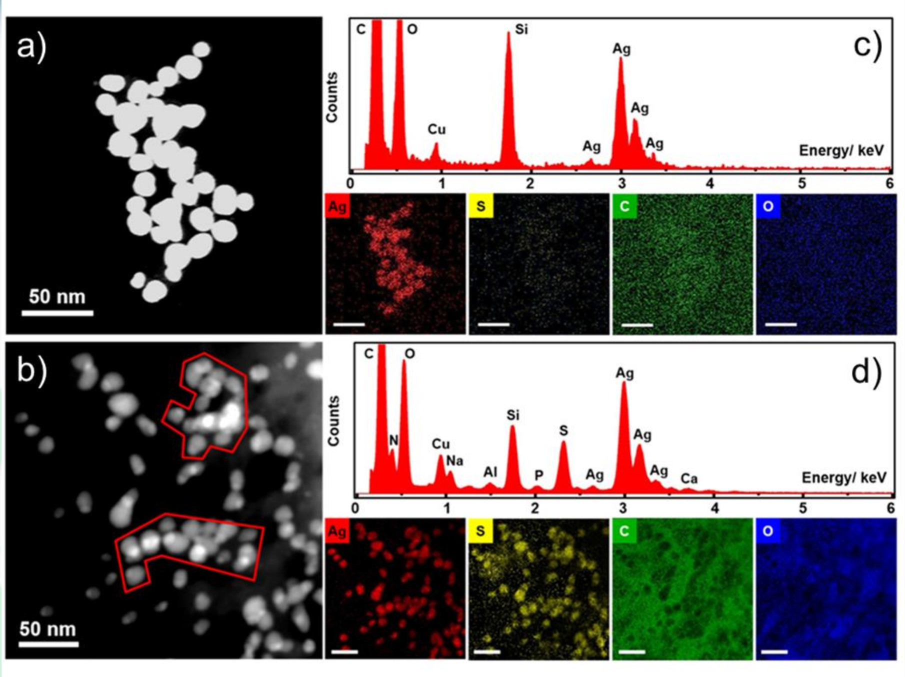
Question 2 (Q2): Is at Least One Dimension of the Primary Particle (Metal/Metal Oxide/Silica) Below One Micron?

- A size cutoff for consideration as a NM is by having a minimum of 1% of the total number of particles (metal/metal oxide/silica) having one dimension measuring less than one micron (1 µm; or 1,000 nm). The dimension value of 1,000 nm is consistent with current literature, and 1% was chosen as a reasonable yet conservative cutoff.
- Particle size can be determined by a variety of techniques as: transmission electron microscopy (TEM), scanning electron microscopy (SEM), Scanning TEM (STEM), atomic force microscopy (AFM), dynamic light scattering (DLS), photon correlation spectroscopy (PCS), and analytical ultra-centrifugation (AUC).

Examples of Acceptable TEM and STEM Images

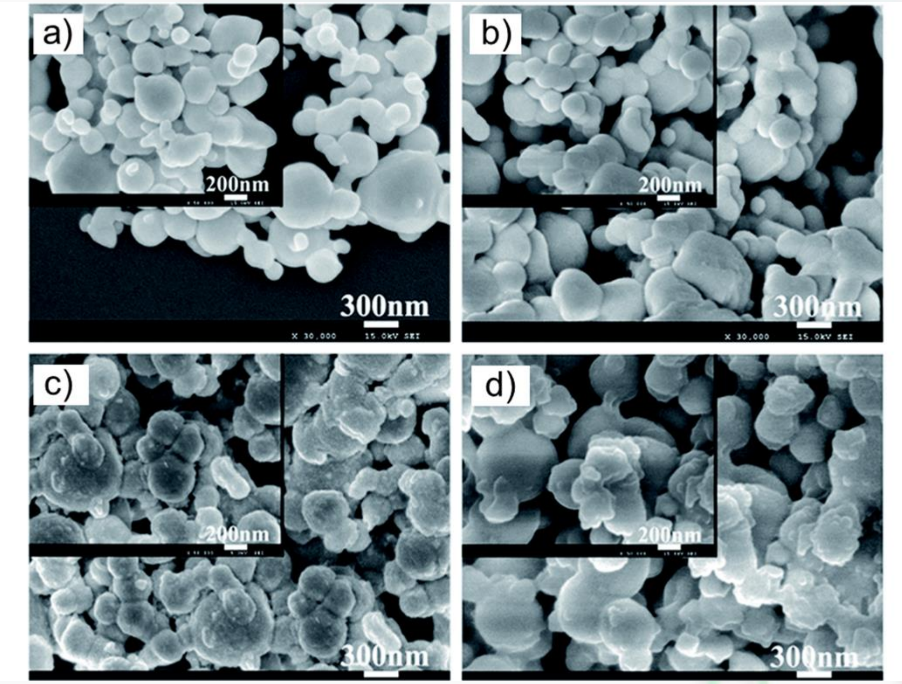


Example of acceptable TEM image, including the scale (e.g., 50 nm; a) and particle size distribution b) is from the scanning absorption spectra; c) is the mean particle diameter ± standard deviation (12.3 ± 4.2 nm) of silver nanoparticles. Source: (Sondi and Salopek-Sondi, 2004). Copyright: 2004 Elsevier.

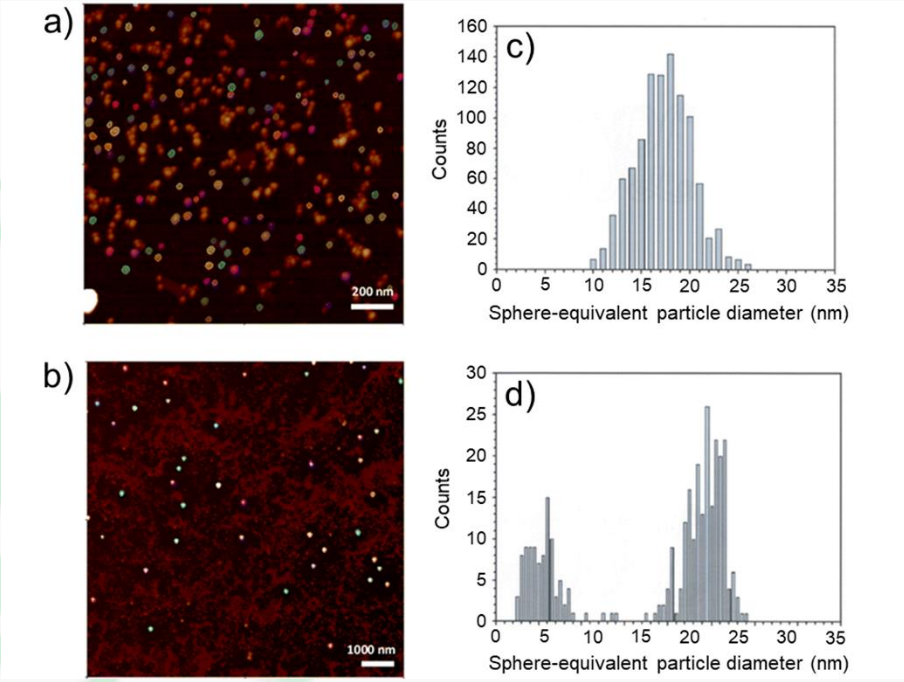


Example of STEM images and elemental mappings of pristine (a) and wastewater borne silver nanoparticles (b). The normalized EDX spectra (c, d) correspond to the highlighted areas (in red). The spectral image intensities represent the atomic fraction, and the scale bars (c, d) are identical to those in the STEM images (a, b). Source: (Steinhoff et al., 2020). Copyright: 2020 American Chemical Society.

Examples of Acceptable SEM and AFM Images



Example of SEM images of silver nanoparticles, showing different structures of Ag@polydopamine (PDA) NPs. NPs fabricated at different reaction times of 0 h (a), 2 h (b), 6 h (c), and Ag@PDA@hydroxyapatite (HAP) NPs (d). Source: (Chen et al., 2017). Copyright: 2017 The Royal Society of Chemistry.



Example of AFM images of silica NPs deposited on a silicon substrate. Non-touching particles of size class a (top left) and size class b (bottom left) were automatically detected (colored) and their height measured. Graphical representations of the corresponding number-weighted particle size distributions were shown on the right (c, d). Source: (Kestens et al., 2016). Copyright: 2016 Springer.

Question (Q3): Is the Particle Embedded in a Matrix Which Is Larger Than 1 Micron?

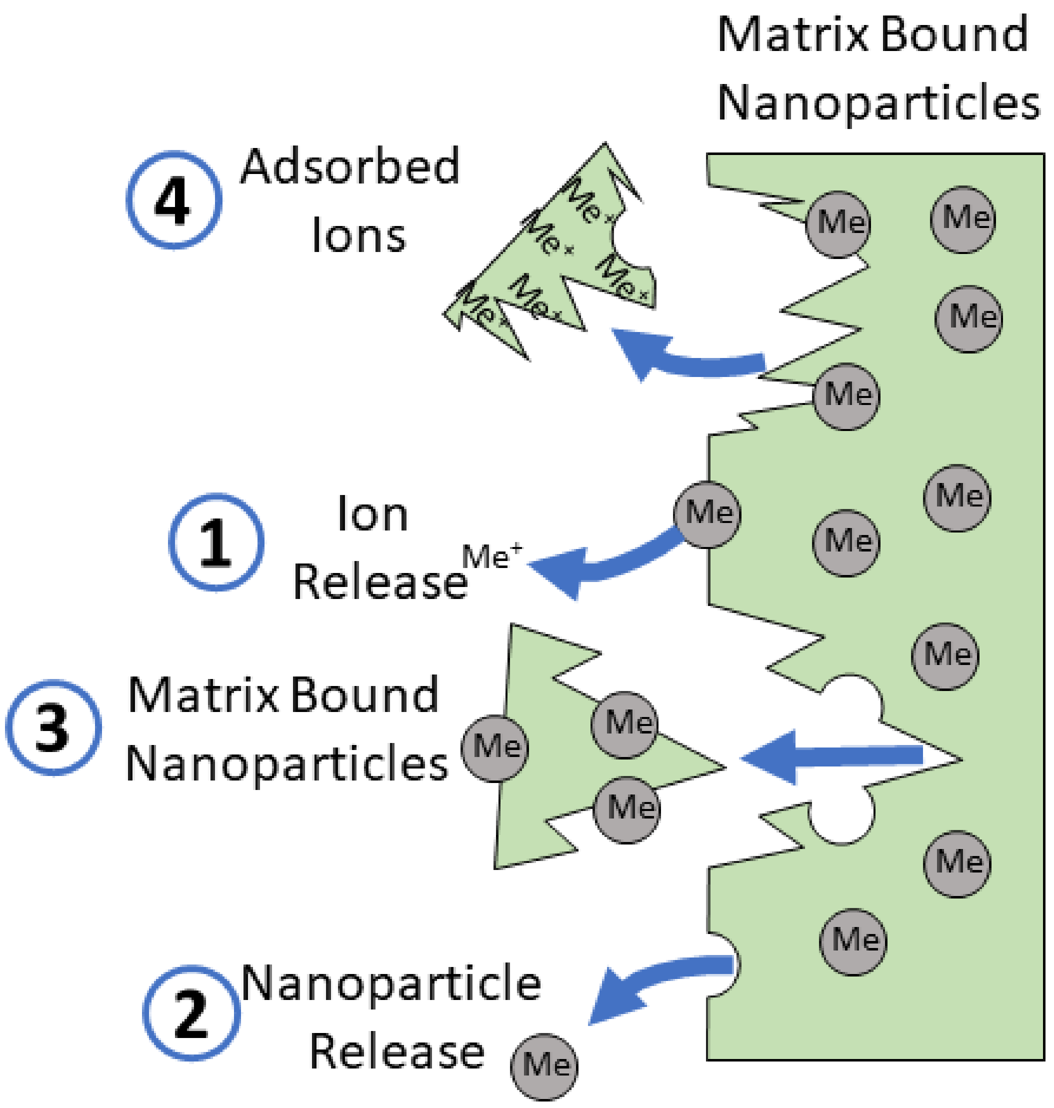
- Matrix here refers to a type of material such as polymer or resin that separates a pesticidal active ingredient (a.i.) from the surrounding environment. Other terms such as carrier, encapsulation material, and inert ingredient are used, instead of matrix in pesticide terminology.
- XPS is useful for the characterization of surface chemistry, including detection of surface coatings and determination of the oxidation state of elements. Scanning TEM (STEM) may also be able to distinguish surface coatings and coronas surrounding NPs. Note that surface coatings should be included in the characterization, as they are expected to affect the stabilization of the nanoparticle, but would not be considered as part of an embedded matrix. Scanning TEM (STEM) may also be able to distinguish surface coatings and coronas surrounding NPs. Micro x-ray fluorescence (µXRF) image of a cross section of a product can also provide information about matrix.

Question (Q4): Does the Particle (Not the Ion) Leach?

- Engineered NMs can be released/leached from the matrix. In general, there are four primary processes or mechanisms by which NMs or their constituents such as dissolved ions are released from nanoformulated matrix surfaces:

    1. Ion release
    2. Individual nanoparticle release
    3. Release of a matrix fragment with nanoparticles bound to the surface
    4. Release of a matrix fragment with ions adsorbed to the surface

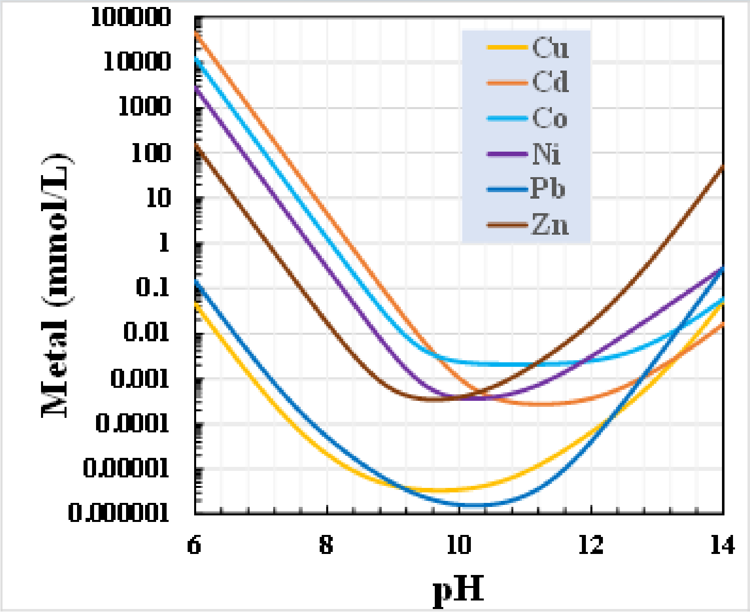
- As a general approach, a mass balance between the total concentration of a metal present in solution and the quantity passing through a 10 kDa filter should provide a reasonable estimate for the quantity of particulate released.



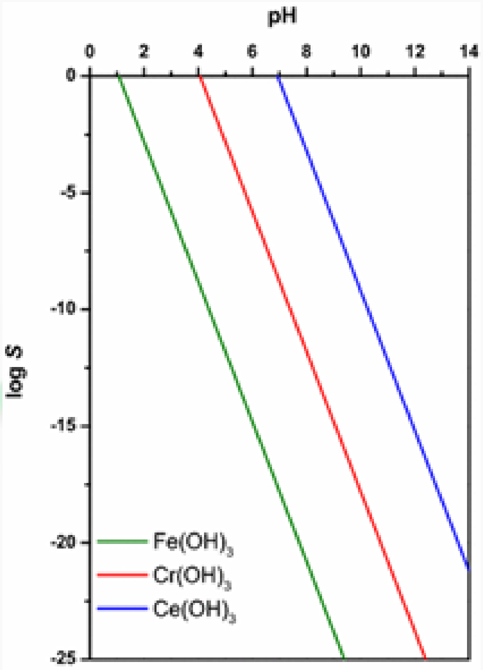
Question 5 (Q5): Is the Particle in Contact with Water; and Do Solubility Data Show the Particle Fully Ionizes in Water?

- This question applies to NMs in which the product is intended to be used in an aqueous solution, such as a water filter or antifoulant paint. It does not address products in which the a.i. is used in non-aqueous solutions such as hard non-porous surface coatings.
- The solubility equilibria of nanopesticides should be considered with discussion of the kinetics of precipitation and dissolution, as equilibria may not be instantaneously established.
- Other factors that likely affect nanopesticides’ solubility include temperature, ionic strength, and the presence of dissolved organic matter (DOM).
- Fully ionization: greater than 90% of total mass is in solution after 24 hours in contact with water.

Solubility of Metals At Equilibrium



The solubility (mmol/L) of metals (Cu, Cd, Co, Ni, Pb, and Zn) and their oxides and hydroxides (CuO, $Cu(OH)_2$, CdO, $Cd(OH)_2$, CoO, $Co(OH)_2$, NiO, $Ni(OH)_2$, PbO, Pb_2O, $Pb(OH)_2$, $Pb_2O(OH)_2$, ZnO, and $Zn(OH)_2$) in water as a function of pH (6 – 14). The data were calculated using MINEQL+ software. Calculation parameters include initial concentrations of 0.001 mol/L of Cu, 100 mol/L of Cd, 100 mol/L of Co, 100 mol/L of Ni, 100 mol/L of Pb, and 1 mol/L of Zn, respectively.



Plots of log solubility for three selected metal hydroxides as a function of equilibrium pH of the solutions. Source: (Scholz and Kahlert, 2015). Copyright: 2015 Springer.

Summary: Nano Determination Framework

- This nano determination framework has been developed to help determine if a pesticide product containing a.i. of metals, metal oxide, silica, and a combination of them should be considered nano or not.

- A pesticide product would be considered as a NM if

  (1) it has a minimum of 1% of the total number of particles of a. i. (metal/metal oxide/silica) having one dimension measuring less than one micron (1 μm; or 1,000 nm), and

  (2) the a.i. can leach from the matrix, and

  (3) the a.i. does not dissolve in water.

- While this framework has not explicitly discussed degradates of nanomaterials, degradates are expected to successfully have the framework applied to them in most cases.

- Additional work is needed to address other types of NMS such as those which are fully organic substances or are quantum dots.

Questions?

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