Flow of the talk

• Benefits of the new technology
• Is it here yet? Hype wars vs 10’s of billions invested
• Confusion of where nano starts and ends
• Where are the risks?
• Can we agree to methods to clarify and focus on the risks?
Research investment is promising fantastic, highly beneficial new products

Reduced Farm Inputs & Reduced Environmental Stress

- Targeted pesticides
- Sustained release fertilizers
- Soil stabilizers
- Water filtration for crops & food safety
Food Security:
Reduce Post-Harvest Loss, Improve Safety

- Commodity storage
- “Shelf-life” for fresh produce
- Pathogen/contaminant detection
- Traceability
Promise of Improved Food Additives and Supplements

Better
- Flavors
- Colors
- Processing aids
- Nutrient delivery
Is nano in foods yet?
When will hype meet the reality of the spread of a new technology?

• There is concern that nanomaterials of concern are in food and that we are not addressing the risk
  — Petitions to US FDA and EPA, actions in European Parliament

• Multi-billion dollar competitive national annual research investment means that more and more nanotechnology uses are possible
Regulators dilemma:
 a) we don’t want to miss anything
 b) we don’t want to add new regulation to innocuous materials

Are we ready to re-regulate all the materials that will be roped in?
European Union’s Definition

"Nanomaterial" means a *natural, incidental or manufactured material containing particles*, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, *one or more external dimensions is in the size range 1 nm – 100 nm.*

(And other conditions regarding aggregates agglomerates and specific included materials)

Emphasis added
The FDA “not a definition”

“At this time, when considering whether an FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, FDA will ask:

– Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm);

or

– Whether an engineered material or end product exhibits 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.

These considerations apply not only to new products, but also may apply when manufacturing changes alter the dimensions, properties, or effects of an FDA-regulated product or any of its components. Additionally, they are subject to change in the future as new information becomes available, and to refinement in future product-specific guidance documents.”
Frame of reference: what is the nanoscale?

Microns to Nanometers – Biological/Chemical/Atomic

Plant, Animal Cell

100 µm

10 µm

1 µm

100 nm

DNA “turn”

DNA base

0.1 nm

Protein

10 nm

Virus

Simple Molecules

Atoms

Bacteria

Source: Purdue University
The problem for food is that gut absorption works at nanoscale

- Food constituents are mechanically and chemically broken down to particles, solute, and suspensions
- Nanoscale and below is the entry size to the body by various mechanisms
And many food components fit the nanoscale definition

<table>
<thead>
<tr>
<th>Material</th>
<th>Food Product</th>
<th>Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All polysaccharides</td>
<td>Edible plant and muscle tissues, milk, eggs, processed foods</td>
<td>~50–1500</td>
</tr>
<tr>
<td>Glycogen</td>
<td>Edible muscle tissue and liver</td>
<td>8–43</td>
</tr>
<tr>
<td>Starch granules' internal concentric rings</td>
<td>Edible plant tissues</td>
<td>100–400^b</td>
</tr>
<tr>
<td>Starch granules' amylopectin clusters</td>
<td>Edible plant tissues</td>
<td>5–10</td>
</tr>
<tr>
<td>Unsaturated triglyceride</td>
<td>Vegetable oils</td>
<td>~3</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Animal lipids</td>
<td>~1.5</td>
</tr>
<tr>
<td>Myosin</td>
<td>Edible muscle tissue</td>
<td>1.5–2 diameter, 100 in length</td>
</tr>
<tr>
<td>Collagen</td>
<td>Edible muscle tissue</td>
<td>1.4- to 1.5-wide units</td>
</tr>
<tr>
<td>Whey</td>
<td>Milk</td>
<td>4–6</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Naturally existing or added</td>
<td>1–10</td>
</tr>
<tr>
<td>A, D, E, K, C, thiamin, riboflavin, niacin, B6, B12, biotin</td>
<td>Naturally existing or added</td>
<td>&lt;1–2</td>
</tr>
<tr>
<td>Lycopene</td>
<td>Tomatoes</td>
<td>~3</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>Carrots, oranges, peaches, peppers</td>
<td>~3</td>
</tr>
<tr>
<td>Capsaicin, gingerol, tumerone</td>
<td>Capsicum peppers, ginger, turmeric</td>
<td>~1–2</td>
</tr>
<tr>
<td>Casein micelle</td>
<td>Raw milk</td>
<td>30–300</td>
</tr>
</tbody>
</table>
• Standard wet chemistry is not excluded by these definition/specifications.

• Large food complexes with nano-substructure are not excluded.

• Biomolecules are not excluded.

• Spray dried ingredients are not excluded.

• *Is that creamer in your coffee a nanomaterial?*

• It is difficult to say what is not excluded, so agencies will have to make case by case decisions.
US FDA: “At least one dimension in the nanoscale range”
EU: “one or more external dimensions is in the size range 1 nm - 100 nm.”

is it “engineered” nano to modify starch structure to reduce its glycemic index?

AFM topography image of a pea starch granule showing the blocklet structure within the granule.

http://www.ifr.ac.uk/spm/Starch.htm
When is intentional processing of complex food molecules not an exception to nano definitions?

- Polysaccharides: amylopectin (5-10 nm)
- Lipids: triglycerides (~3nm)
- Proteins: myosin, whey (1-20 nm)
- Vitamins: A, E C, B₂ (<2nm)
- Pigments: lycopene, β-carotene (~3nm)
Are there simple ways of reducing the infinite class of “between 1 and 100 nm” to the risks we are concerned about for oral exposure (through foods)?

**Proposal:** A good start to getting our arms around risks is to see if we can identify the nanomaterials that are likely to be absorbed as particles into the body.
Practical guidance for the safety assessment of ENM in food

Step 3. Decision Tree

Starting from Alessandro Chiodini’s presentation of the ILSI Europe guideline
What if we were to agree to methods to measure uptake in a trusted dialogue between stakeholder experts?

Could we start reducing the uncertainty and mistrust about which nanomaterials in food warrant closer attention?

Seems an obvious point, but it’s not in the definitions.
Hypothetical decision sequence for nanoparticle uptake assessment to prioritize data needs or aid product development

- Is it soluble in gastric conditions in adult? In infant? Disease states?
- If insoluble, does it aggregate/bind irreversibly to particles greater than 10 micron?
- Are particles found in tract lining cells in adult? Age/disease variation?
- Do particles pass to systemic circulation in adult? Age/disease variation?

Decreasing relative proportion of materials in commerce?

Increasing need to apply nanoparticle specific toxicity tests

Design products preferably in this range
Widely agreed to, robust methods allow sustainable product development and transparent evaluations

As a product developer
  – Can I make it dissolve to non-toxic materials
  – If no, then can I make it agglomerate or bind irreversibly to particles that pass without absorption?
  – If no, then can I use a material that results in cell uptake below detection?

As a concerned stakeholder
  – Using a standard test, does the material dissolve?
  – Is uptake undetectable using standard tests?
NanoRelease Food Additive Project

ISSUE AT HAND
• No widely accepted methods for assessing the oral uptake of nanomaterials
• Reliable methods → would clarify hazard debates → thus safer, faster sustainable development of nanomaterials (food, water, medical products)

GOALS
• Identify and develop measurement methods for ingested nanoparticles to determine whether they are likely to be taken up by the body

THE PROJECT
• Public-private partnership
• Multi-stakeholder, multi-national Steering Committee
NanoRelease Food Additive

Objectives

• Gather published information and unpublished knowledge
• Identify measurement needs and methods
• Identify gaps
• Design methods development workplan(s)
• Allow continuous technical dialogue internationally across key stakeholder experts about what is “nano” in foods and the measurement methods relevant to oral exposure of nanomaterials
Participant Experts From All Over

- Univ. of Florida, US
- Univ. of Michigan, US
- Univ of Guelph, Canada
- Heriot Watt Univ., UK
- Saarland Univ., Netherlands
- Univ. of Massachusetts, US
- Medical Research Council, Human Nutrition Research, UK
- Univ. of California Davis, US
- Univ. of East Anglia, UK
- Univ. of Toronto, Canada
- Ohio State Univ., US
- Univ. of Maryland, US
- Louisiana State Univ., US
- Rutgers Univ., US
- Purdue Univ., US
- Illinois Institute of Technology, Institute for Food Safety & Health, US
- Italian Research Council
- Leitat Tech. Center, Spain
- TNO, Netherlands
- RIKILT – Institute of Food Safety, Netherlands
- Pew Charitable Trusts, US
- Consumers Union, US
- European Commission, Joint Research Centre
- US Food and Drug Administration
- Health Canada
- US Dept Agriculture
- Food and Environment Research Agency, UK
- US National Institute of Standards and Technology
- ILSI Europe
- ILSI North America
- US Pharmacopeia
- ColorCon, Inc.
- Taiyo Kagaku
- Nanotechnology Industries Association
- Evonik Degussa
- DSM
- Cargill
- Southwest Research Institute, US

Note: ILSI Research Foundation is serving as the secretariat on this project.
Multi-stakeholder Steering Committee defines scope and objectives for project

Expert task groups develop white papers on key issues in understanding methods needs

Steering Committee develops workplan for methods improvements needs

Methods improvements are developed through inter-laboratory studies
Task Group 1: MATERIAL CHARACTERISTICS
What do we need to know about the nanomaterials and the food matrices to predict absorption as particles into the body?

Task Group 2: ALIMENTARY CANAL ENVIRONMENT
What do we need to know about alimentary tract conditions to understand whether and where a nanomaterial will be absorbed into the body?

Task Group 3: ALIMENTARY CANAL MODELS
What kinds of models are useful in creating the conditions to measure and understand nanomaterial uptake by the body?

Task Group 4: MEASUREMENT METHODS
What methods can be used to measure characteristics of materials to understand and predict nanomaterial uptake by the body?

Task Group 5: RISK MANAGEMENT CONTEXT
Where in the decision process do we most need agreement to such measurement methods?
<table>
<thead>
<tr>
<th>CASE STUDY</th>
<th>Example materials</th>
<th>Differential aspects?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOFT/WET DELIVERY SYSTEMS</strong></td>
<td>Lipid-based encapsulates</td>
<td>Mostly dissolve in mouth</td>
</tr>
<tr>
<td><strong>SOLID DELIVERY SYSTEMS</strong></td>
<td>Protein/polysaccharide-based encapsulates</td>
<td>Dissolve at different rates depending on material</td>
</tr>
<tr>
<td></td>
<td>Encapsulated antimicrobials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polymer delivery systems</td>
<td></td>
</tr>
<tr>
<td><strong>SOLID PARTICLES</strong></td>
<td>Silver</td>
<td>Surface chemistry affects agglomeration and persistence/uptake</td>
</tr>
<tr>
<td></td>
<td>Titanium dioxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zinc oxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aluminosilicates, nano-clays, aluminum oxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Silica (synthetic amorphous silica, fumed silica, silicon dioxide, porous silica)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iron/iron oxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Copper/copper oxide</td>
<td></td>
</tr>
</tbody>
</table>
Outcomes

• Trusted dialogue of what is needed to inform safety decisions

• Trusted, robust methods that all can use to develop comparable data

• Framework for applying methods that
  – Clarifies risk management and data development decisions
  – Enables safe product development
Will build on existing work

- ILSI Europe Novel Foods TF guidance on nanomaterial risk assessment for foods
- ILSI Europe Packaging Materials TF review of migration studies for nanomaterials from food packaging
- Europe’s FP7 “NanoLyse” and “InLiveTox” projects
- The “NanoCharacter” project to implement consistent reporting of nanocharacteristics in studies related to risk assessment.
- OECD Working Party on Manufactured NanoMaterials sponsorship programs (on nanomaterials also used in food additives and packaging)
NanoRelease Food Additive Sponsors

- The Pew Charitable Trusts
- US Food and Drug Administration
- ILSI North America, Food and Chemical Safety Committee
- Illinois Institute of Technology’s Institute for Food Safety and Health
- The Coca Cola Company
- Substantial in-kind support is provided by the Nanotechnology Industries Association
- Other sponsors are in process of being confirmed
Closing Thoughts

- The NanoRelease Food Additive project is a start; however, formal cooperation at international levels is needed.

- Organization for Economic Cooperation and Development (OECD) working parties have been addressing nano-risk methods in the chemicals domain.

- Efforts in food safety domain have *not* begun in similar detail.

- Please press for multilateral cooperation on methods development relevant to food safety.
Thank you

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