Moving beyond nanogeneralities - Providing focus to nanopolicy progress

ORACBA Risk Forum

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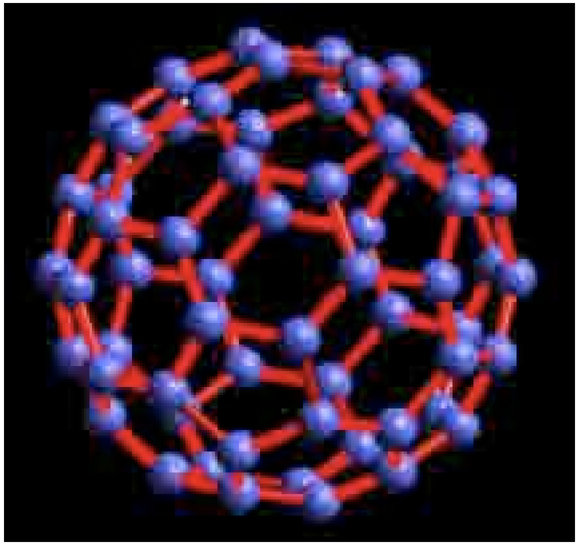
Main theme of the presentations

- We propose that the issues confronting assurance of sustainable use of nanomaterials are so varied, general, and at times controversial that they impede the development of beneficial uses of the technology even where the risks are negligible.
- We will lay out many of the issues in risk assessment and risk management and try to frame the overall discussion in this risk forum in terms of the need for problem selection and problem formulation early in any discussion and in any risk assessment of nanomaterial uses.
- However, we feel that once you select and formulate well, you can make progress in risk assessment policy and risk management of specific uses of the materials, and we should seek opportunities to do that for clearly beneficial uses of the technology.

Brief History of Nanotechnology



- Richard Feynman (1959) “There’s plenty of room at the bottom”.
- Norio Taniguchi (1974) nanotechnology 1st defined.
- Eric Drexler (1986) “Engines of Creation: The coming era of nanotechnology”.
- U.S. National Nanotechnology Initiative (2000) coordinates Federal research and development.

What's Nano-science?

Louis Pasteur's work with spoilage bacteria (1866): ~1000nm

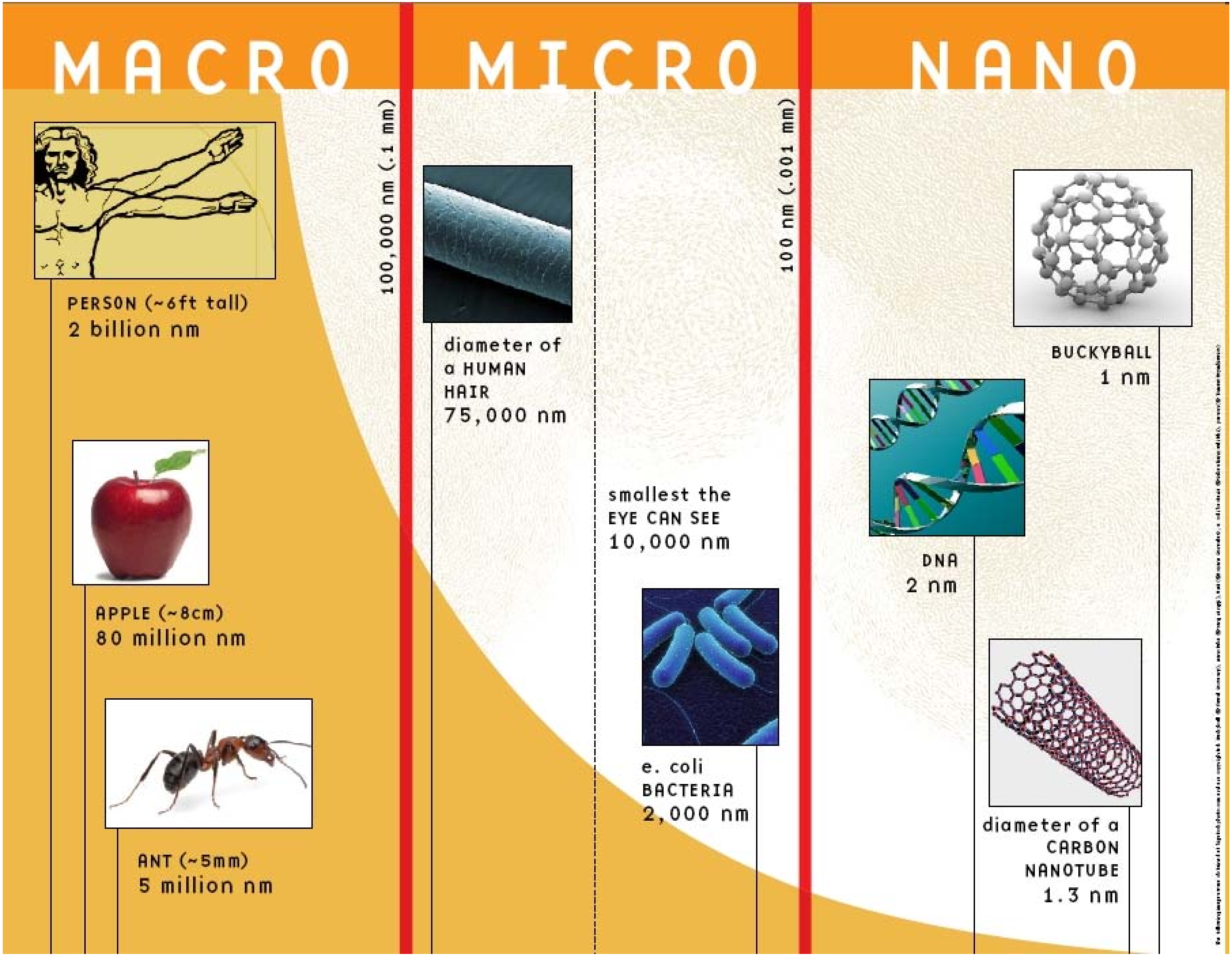
- Lead to a revolution in food processing; developing safer, better quality foods

Watson and Crick's crystallography of DNA (1953): ~2.5nm

- Lead to a biotechnology revolution and the development of better biomedical treatments and agricultural production.

Richard Smalley's research of 'Buckyballs' (1996): ~1nm

Marks the beginning of the current era of nano-scale science and technology.


MACRO
MICRO
NANO
100,000 nm (.1 mm)
100 nm (.001 mm)
PERSON (~6ft tall)
2 billion nm
APPLE (~8cm)
80 million nm
ANT (~5mm)
5 million nm
diameter of a HUMAN HAIR
75,000 nm
smallest the EYE CAN SEE
10,000 nm
e. coli BACTERIA
2,000 nm
BUCKYBALL
1 nm
DNA
2 nm
diameter of a CARBON NANOTUBE
1.3 nm

Definitions

ISO; NNI; OECD; Health Canada; BSI; EU; FDA

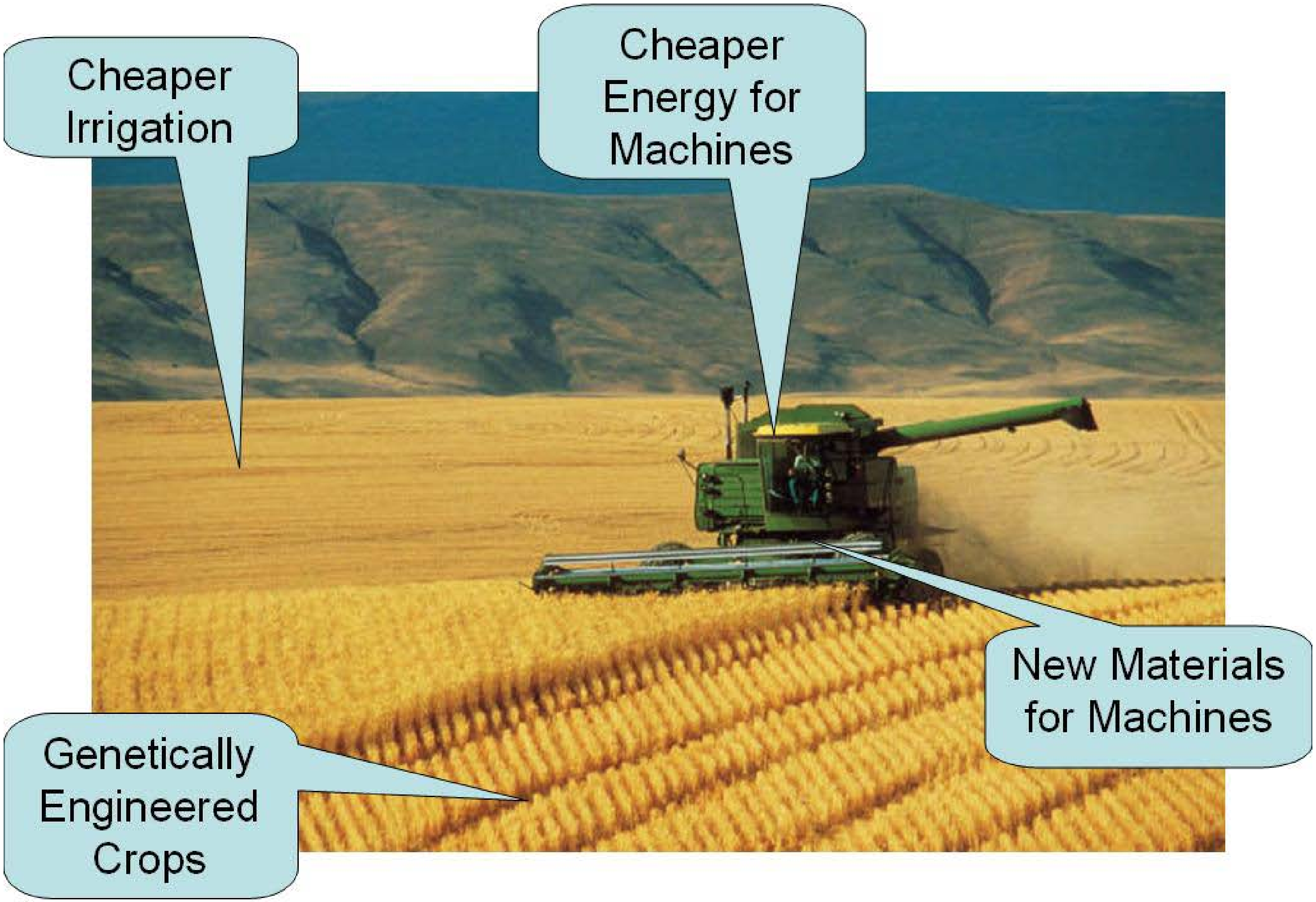
Common themes:

- Use specific
- Roughly nano-scale in 1 or more dimensions
- Intentional, engineered or manufactured
- Exhibits ‘nanoscale properties’
- Not natural
- Not accidental

Uncommon themes:

- Solubility
- Internal structure / aggregation
- Tiered treatment of boundaries
- Whether & how boundaries are “softened”
- Others…

Industrial Scale Applications of Nanotechnologies



Where is “nano” - farm to fork

Farm: Pesticides, fertilizers, soil stabilizers, remote sensors, animal biologics and vaccines

Commodity chain: Enhanced coatings on harvest machinery, grain elevators, storage containers, ship holds

Food processing: Additives, flow agents, supplements, coloring, enhance ‘mouth feel’, increase or decrease bio-availability

target nutrient delivery; “functional foods”

Preservation and packaging: Fresh fruit and vegetable preservation, less permeable packaging and improved pathogen detection

Nanotechnology in the Food Industry

Agriculture	Food Processing	Food Packaging	Supplements
Sensors to monitor soil conditions & crop growth	Selective binding & removal of chemicals or pathogens from food	Biodegradable nanosensors for temperature, moisture & time	Vitamin sprays that disperse nanodroplets
Efficient delivery of pesticides & fertilizers	Improved bioavilability of neutraceuticals in cooking oils	Nanoclays & nano-films to prevent spoilage, or oxygen absorption	Nanochleates to improve nutrient delivery in foods
Controlled delivery of growth hormones	Nanotubes & nanoparticles as viscosifying agents	Electrochemical nanosensors for detecting ethylene	Nano-scale powders to increase nutrient absorption
Targeted plant & animal transgenics	Encapsulated flavor enhancers	Antimicrobial and antifungal surface coatings	Nanocrystal composites as drug carriers

- Nanotechnology in Food Products Workshop, Institute of Medicine, 2009

Potential Applications for Developing and Emerging Markets

Nanotechnology application area	Water purification	Pathogen Sensor	Food safety and nutrition, packaging	Agriculture
Developed economy application	Reduced cost hazardous waste cleanup	Food inspection and outbreak investigation through specific typing of pathogen species and strain with field durable sensors	Shelf- life enhancement and security	Soil stabilization. More efficient pesticides, herbicide fertilizer, and feed additives Improved water retention
Example of possible specific and cost-effective applications in emerging economies	Pathogen removal. Desalinization. Removal or detoxification of harmful pollutants.	Monitoring systems to improve food security through optimization of safe food transport and storage	Long shelf-life, In-package detection of pathogens or spoilage organisms Detection of pesticides, heavy metals or other chemical contaminants	Soil stabilization. More efficient pesticides, herbicide fertilizer, and feed additives Improved water retention

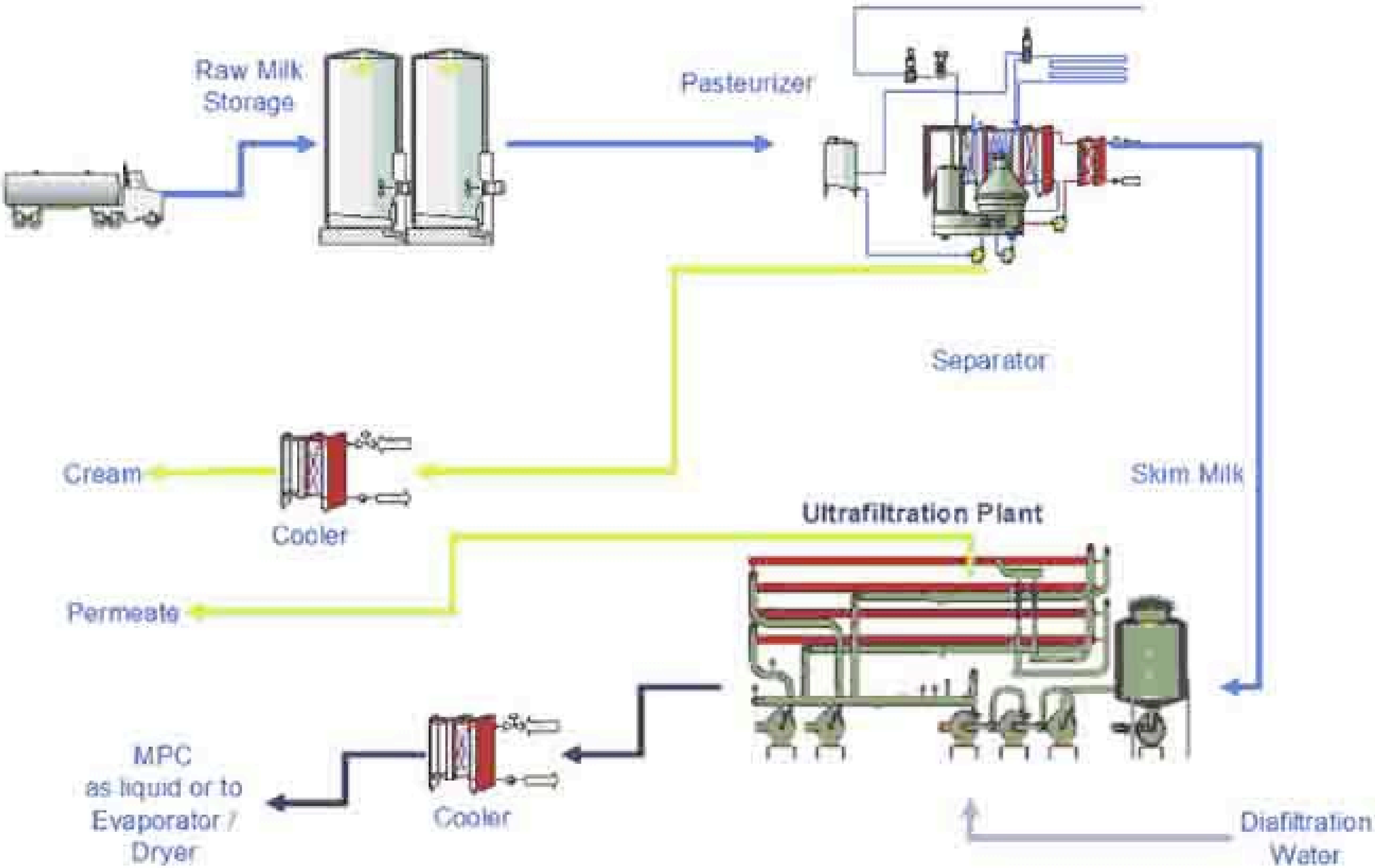
DRAFT EU Novel Foods Regulation

“any intentionally produced material

that has one or more dimensions of the order of 100 nm or less

or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic to the nanoscale”

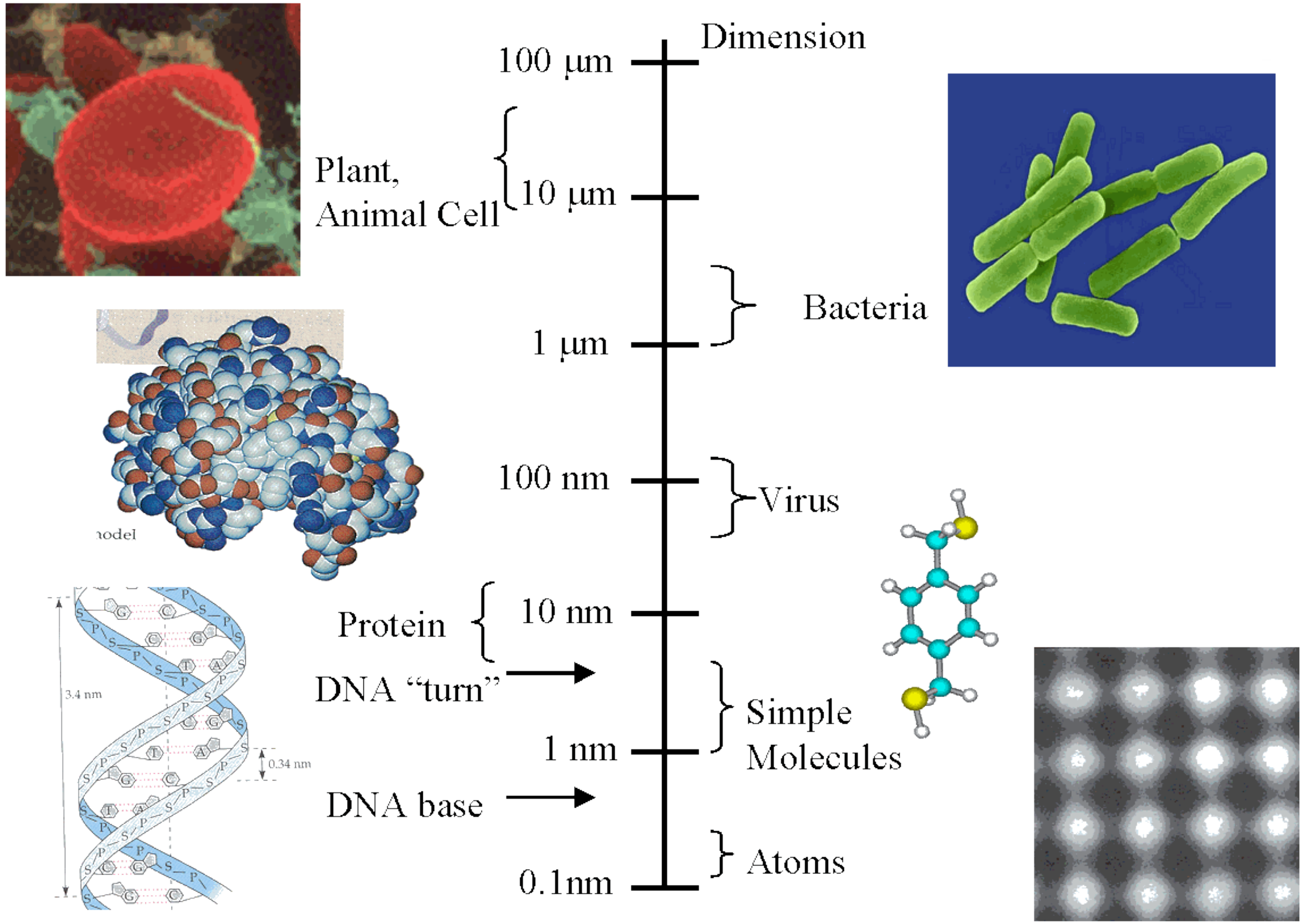
Milk Processing: Top-down Nanotechnology?



Source: GEA Filtration; info@geafiltration.com

How do we avoid regulatory "collateral damage" of general definitions for nanomaterials on benign materials and highly beneficial uses?

Microns to Nanometers -- Biological/Chemical/Atomic



Source: Purdue University

Food components: “traditional” nanotechnology

Material	Food Product	Size (nm)
All polysaccharides	Edible plant and muscle tissues, milk, eggs, processed foods	~50–1500
Glycogen	Edible muscle tissue and liver	8–43
Starch granules’ internal concentric rings	Edible plant tissues	100–400[b]
Starch granules’ amylopectin clusters	Edible plant tissues	5–10
Unsaturated triglyceride	Vegetable oils	~3
Cholesterol	Animal lipids	~1.5
Myosin	Edible muscle tissue	1.5–2 diameter, 100 in length
Collagen	Edible muscle tissue	1.4- to 1.5-wide units
Whey	Milk	4–6
Enzymes	Naturally existing or added	1–10
A, D, E, K, C, thiamin, riboflavin, niacin, B6, B12, biotin	Naturally existing or added	<1–2
Lycopene	Tomatoes	~3
Beta-carotene	Carrots, oranges, peaches, peppers	~3
Capsaicin, gingerol, tumerone	Capsicum peppers, ginger, turmeric	~1–2
Casein micelle	Raw milk	30–300

Casein micelles in raw milk

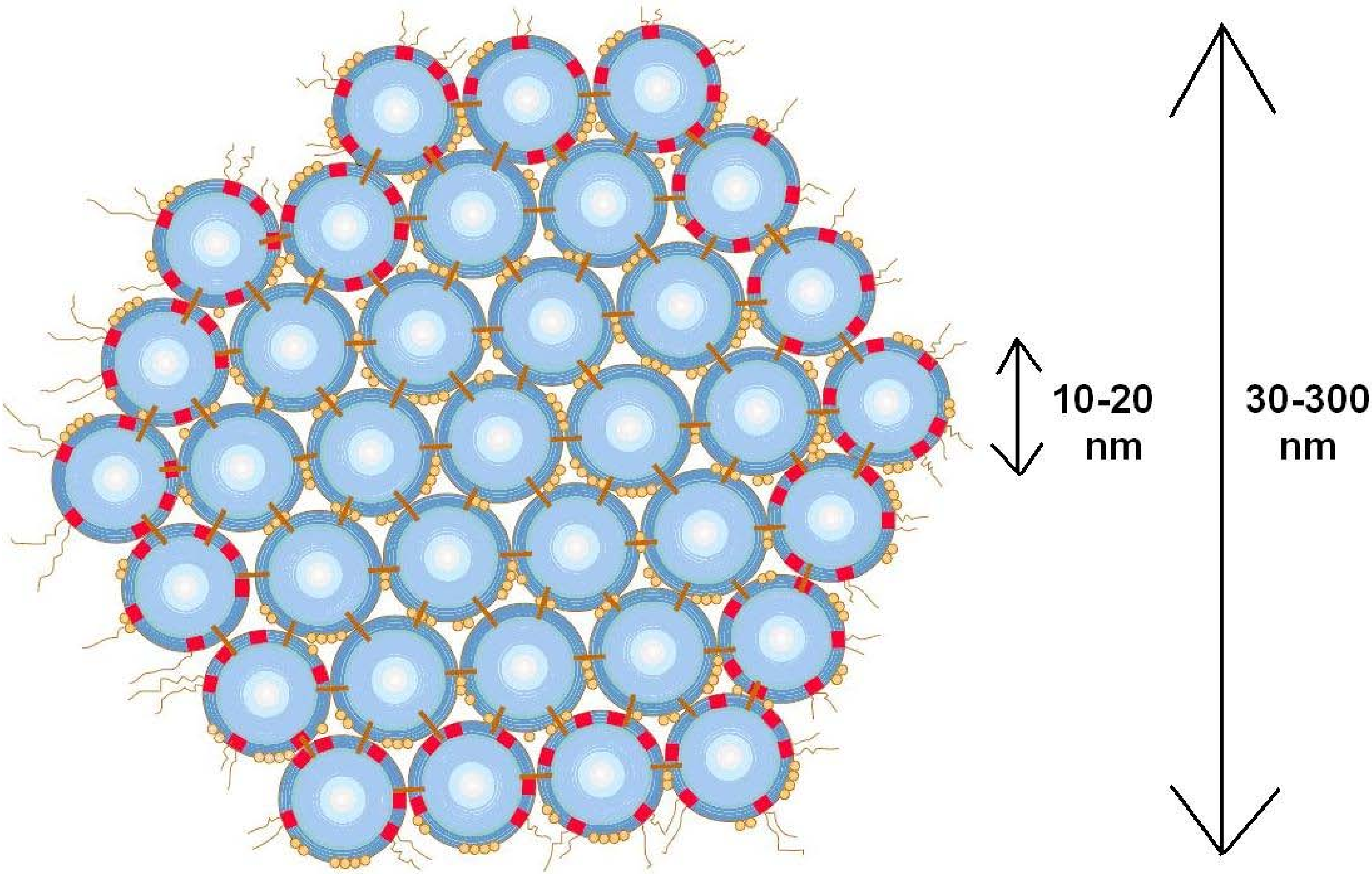
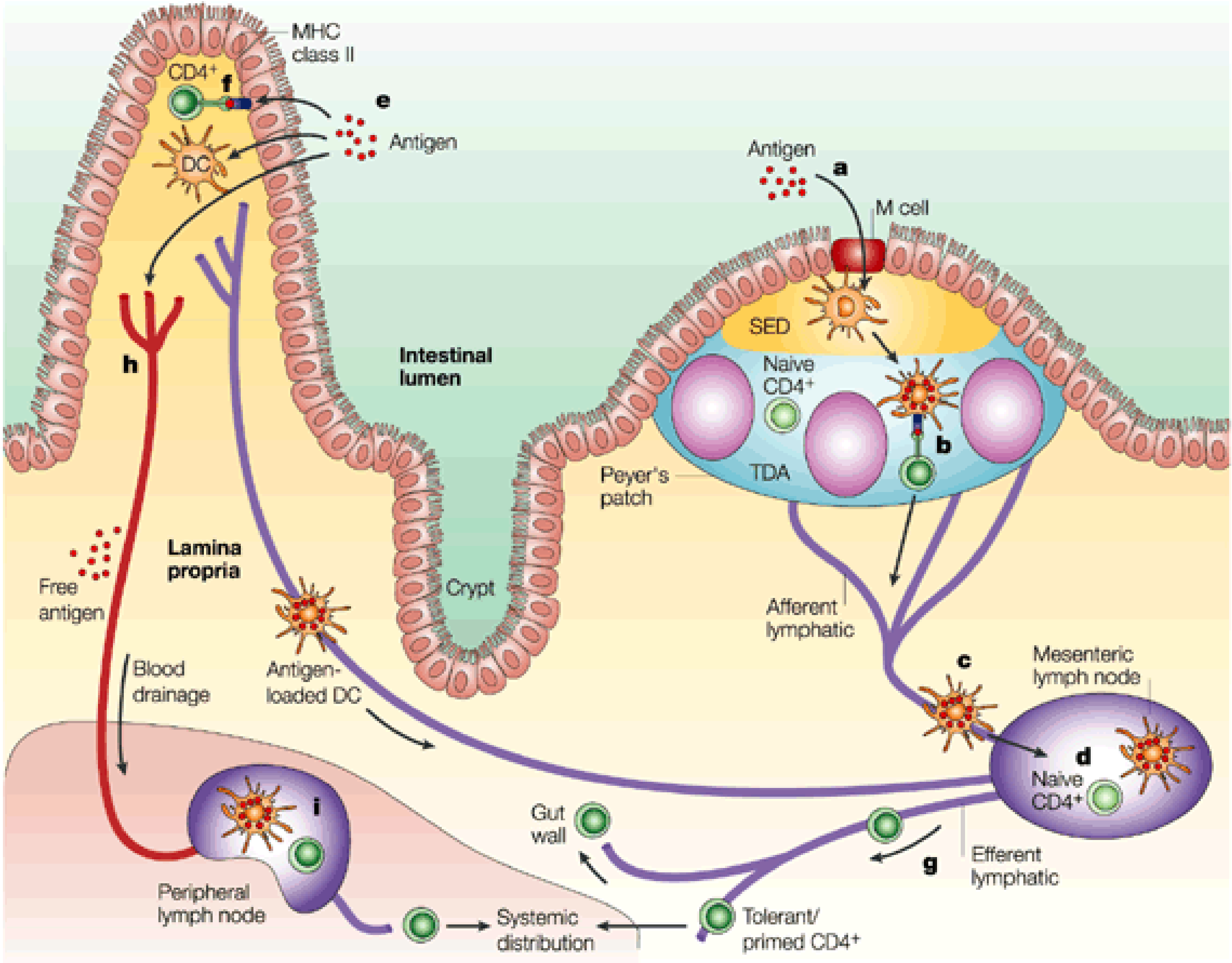


Image Source: . http://www.food-info.net/uk/protein/milk.htm (Accessed November 8, 2010)



Nature Reviews | Immunology

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
- Two-edged sword for safety in that our bodies are
  1. Accustomed to nanoscale in foods
  2. Probably good at extracting added nano from food matrices

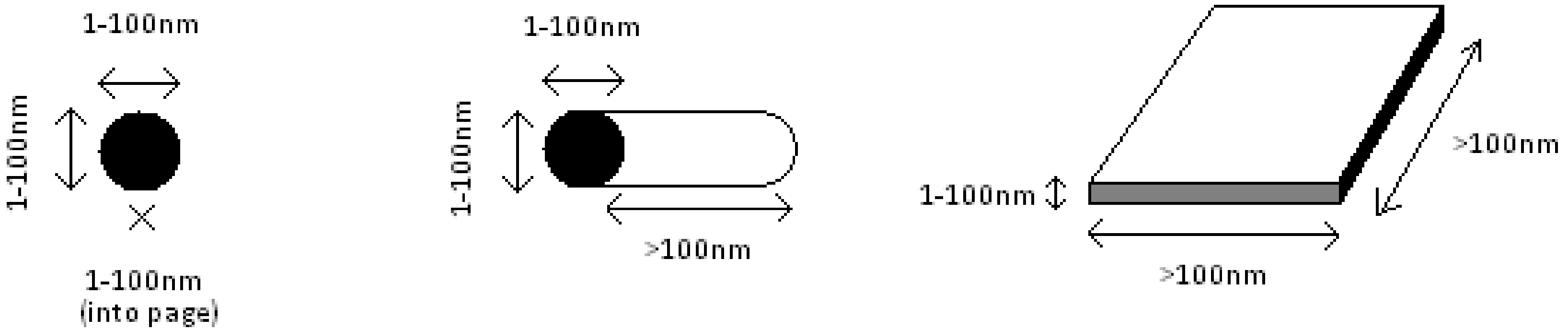
DRAFT Novel Foods Regulation Definition for Nanomaterial

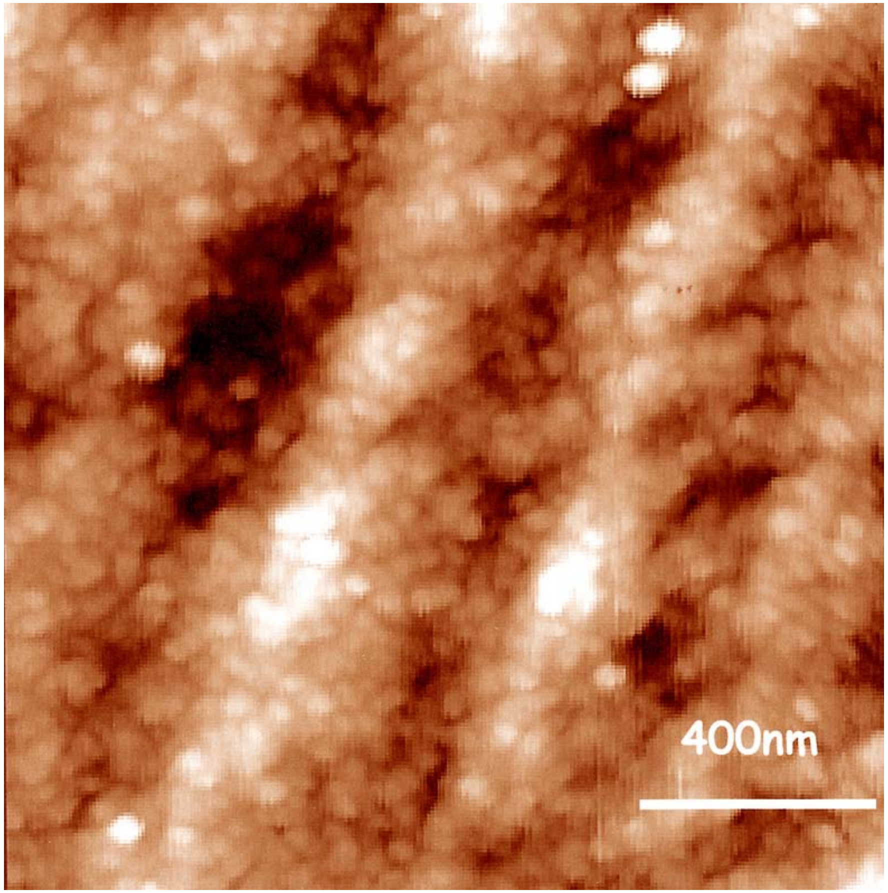
“any intentionally produced material

that has one or more dimensions of the order of 100 nm or less

or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic to the nanoscale”

One or more dimensions of the order of 100nm or less





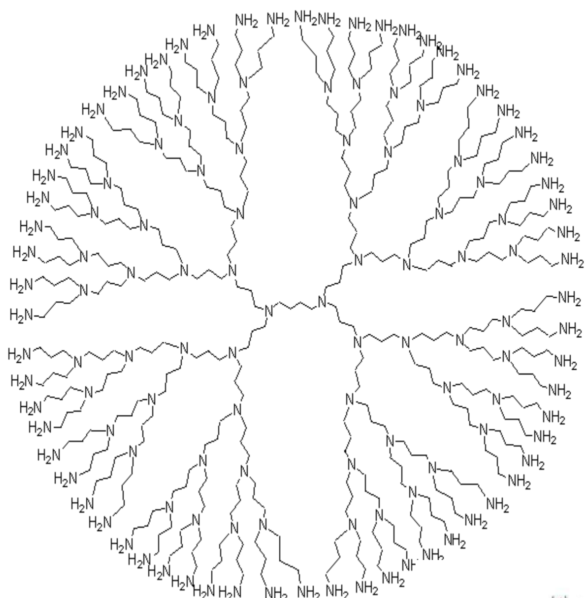
or is composed of discrete functional parts…of the order of 100 nm …

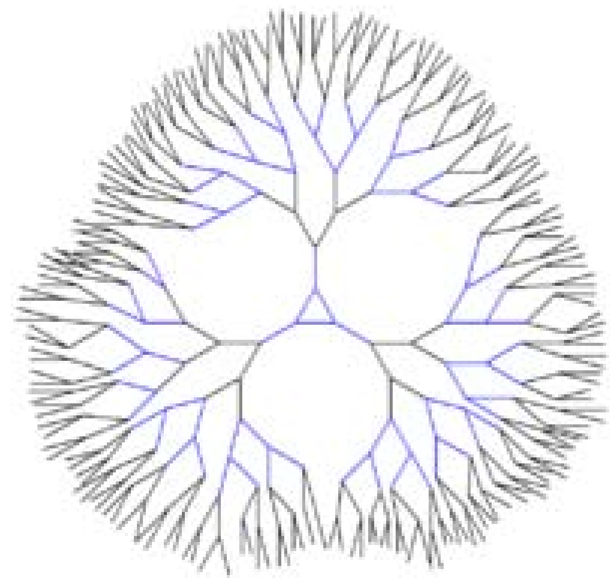
is it "intentional" nano to modify starch structure to reduce its glycemic index?

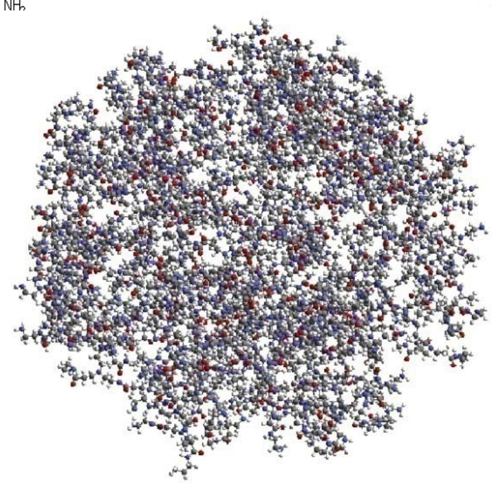
AFM topography image of a pea starch granule showing the blocklet structure within the granule.

http://www.ifr.ac.uk/spm/Starch.htm

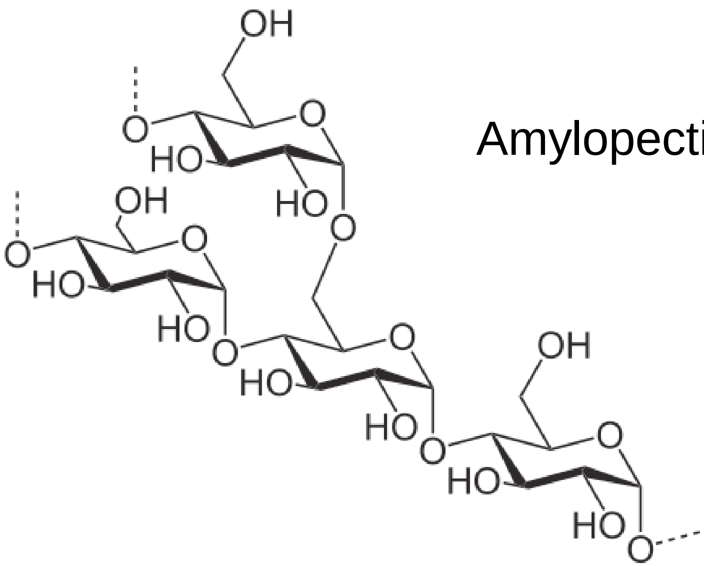
Dendrimers are a “classic” nanomaterial typically between 1 and 10 nm processed to add drugs, contrast agents, etc.



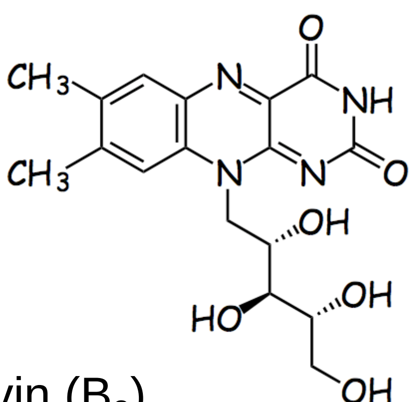




So, when is it "intentional nano" to process complex food molecules?

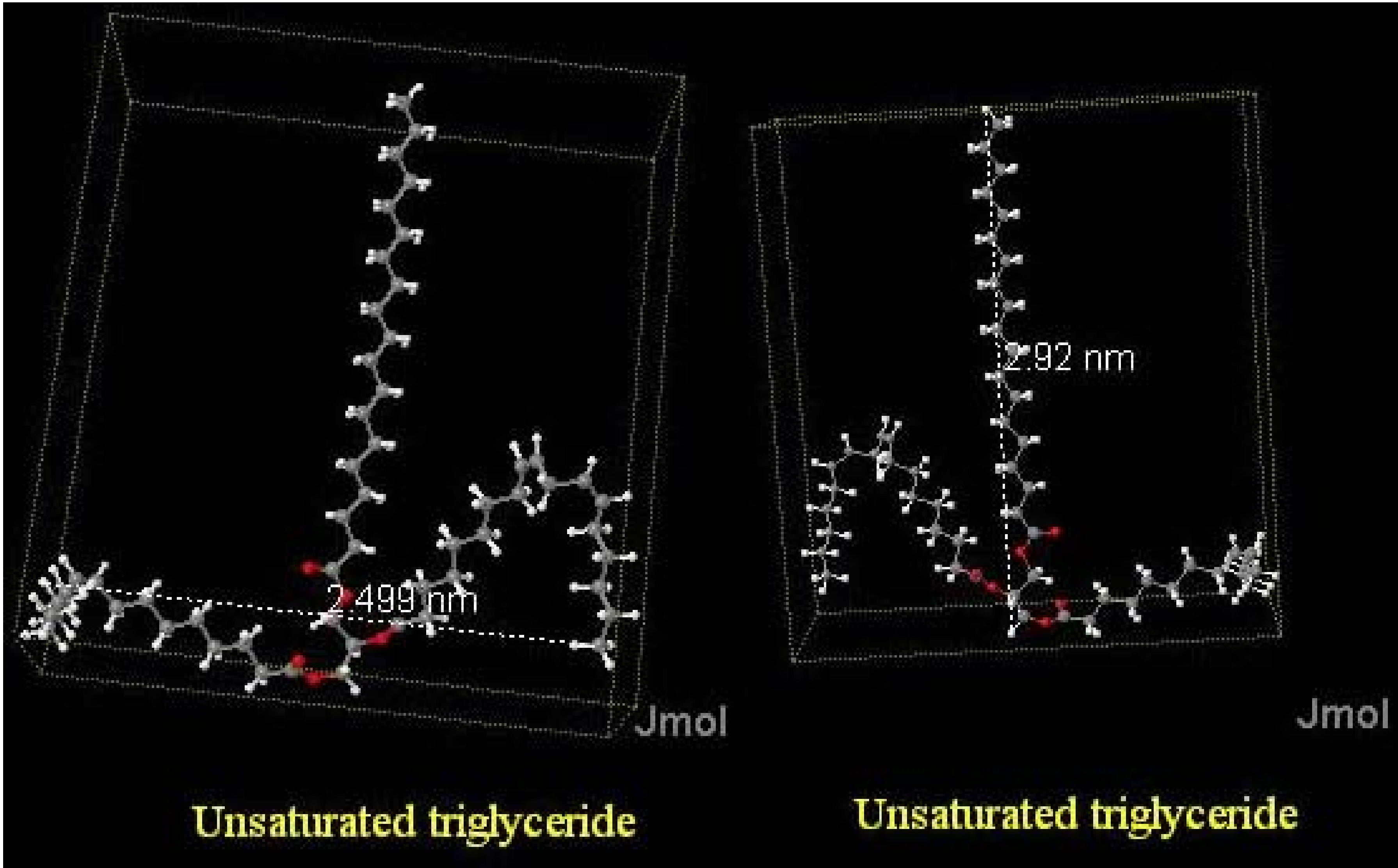


Amylopectin



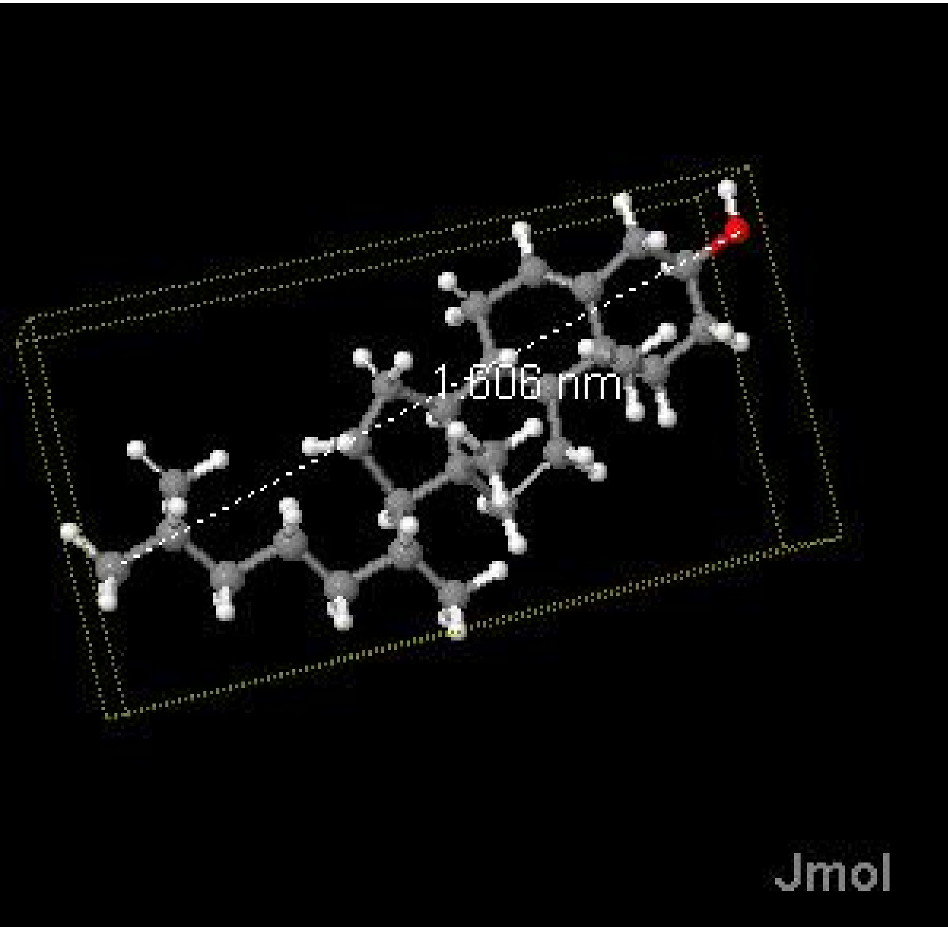
Riboflavin (B_2)

- Polysaccharides: amylopectin (5-10 nm)
- Lipids: triglycerides (~3nm)
- Proteins: myosin, whey (1-20 nm)
- Vitamins: A, E C, B_2 (<2nm)
- Pigments: lycopene, β-carotene (~3nm)

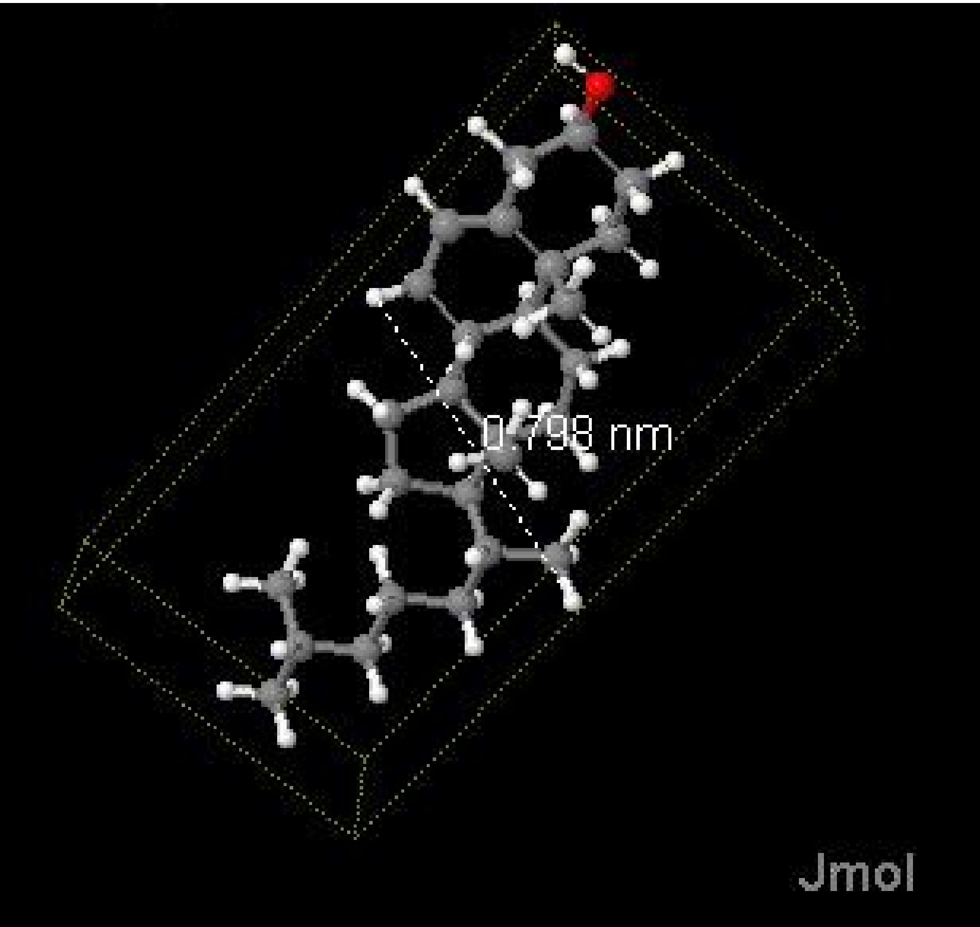


Unsaturated triglyceride

Unsaturated triglyceride

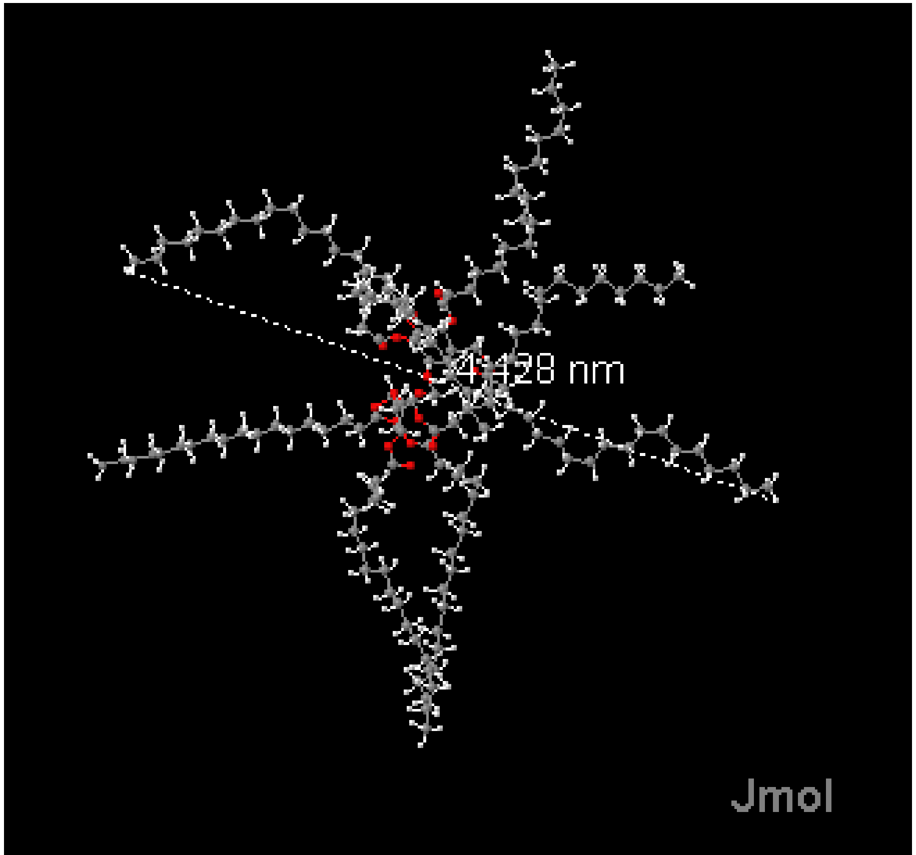


Cholesterol steroid



Cholesterol steroid

Intentional Nano Food Additives?

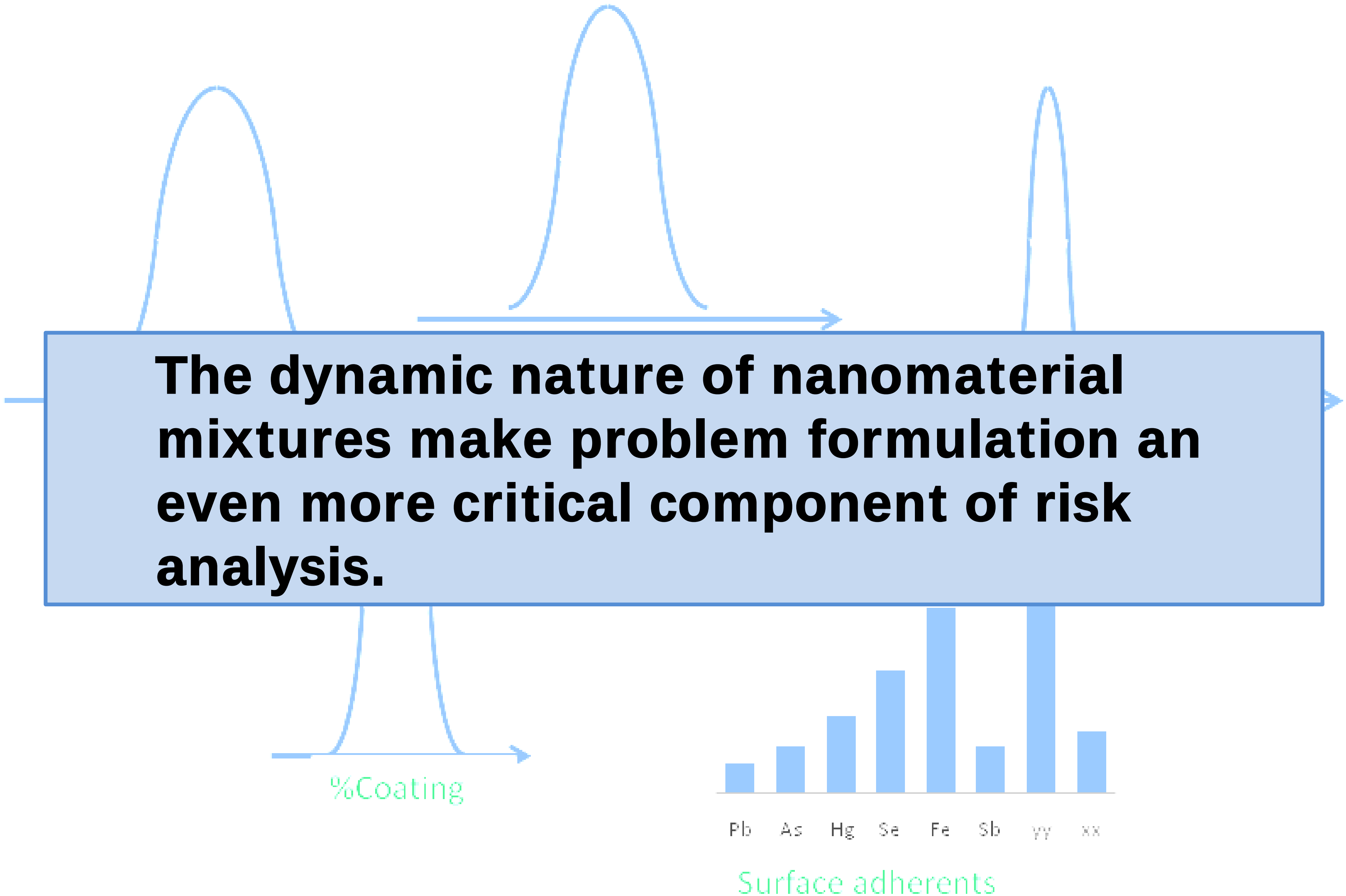


Olestra, typical structure

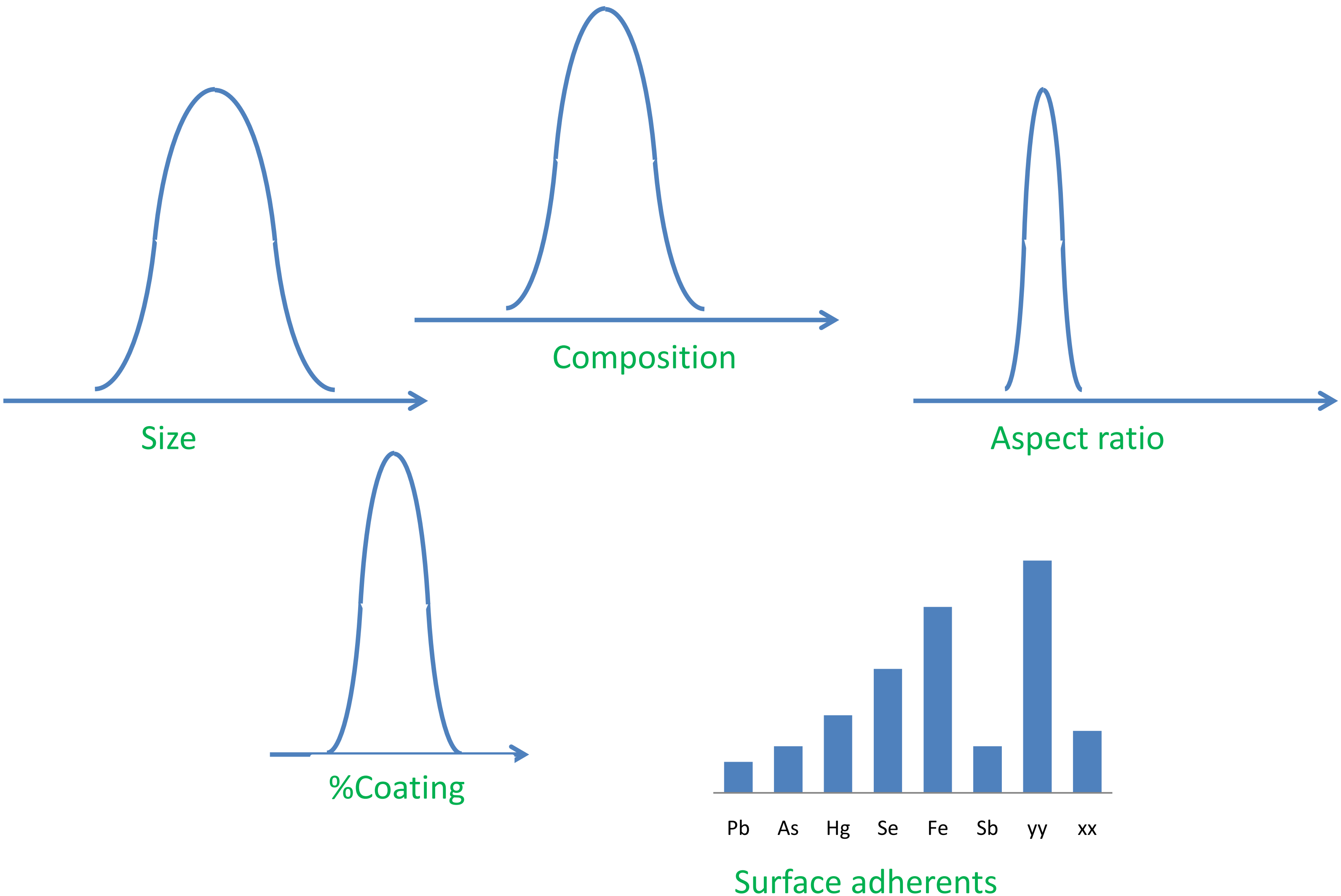
- Olestra (~4.5nm)
- Sucralose (~1nm)
- Neotame (~1nm)
- Micronized Lycopene (~3nm)
- Fumed silica (~10nm)

Where do you start and stop?

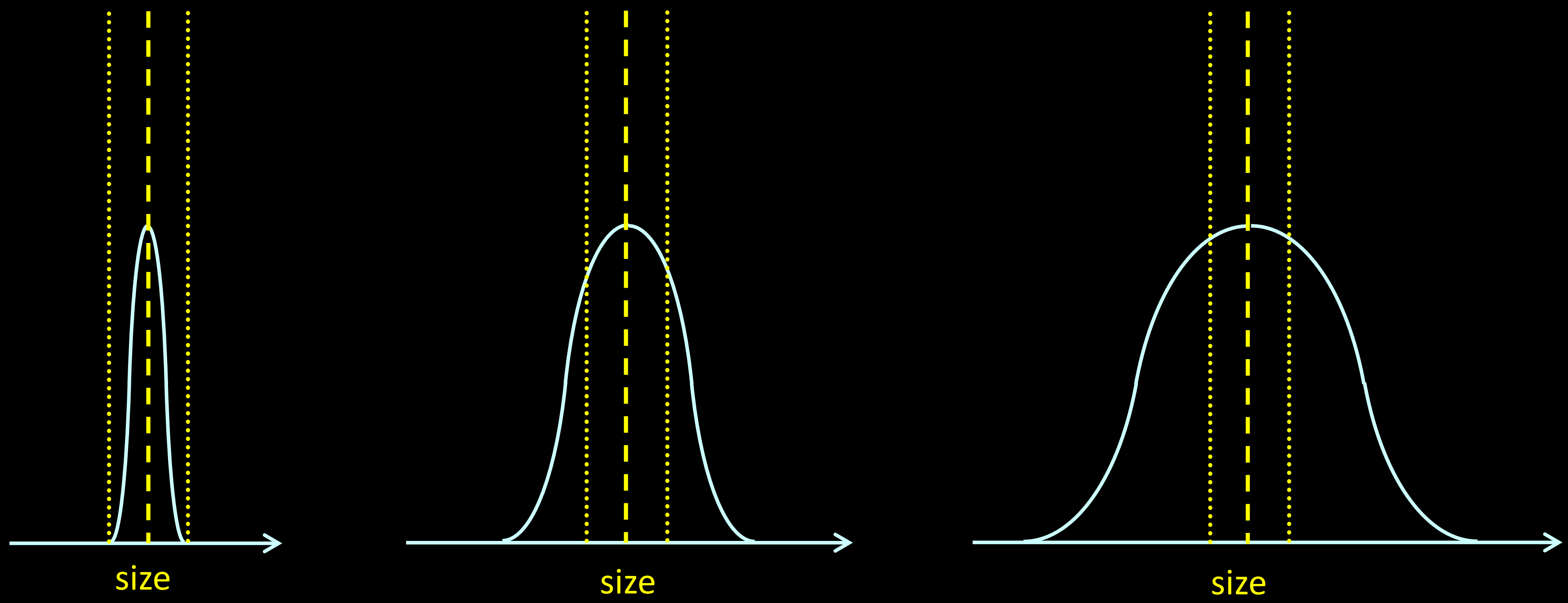
The dynamic nature of nanomaterial mixtures make problem formulation an even more critical component of risk analysis.



The typical nanomaterial is a mixture of distributions



What does "impurity" mean for a nanomaterial when size or shape or surface coating determines properties?



100% within range

50% within range
50% impurity?

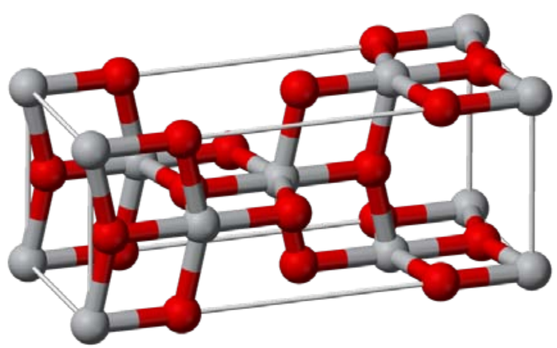
10% within range
90% impurity?

Tracking potency? – choose wisely

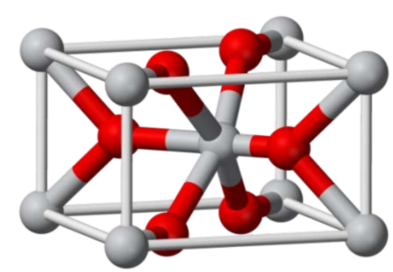
- What causes the external dose of a given nanomaterial to be toxic? How do you track it?
- For example, for benzene, it's the benzene you follow from release to receptor.
- For a metal oxide nano-object it could be a functional assay, or uncoated surface area, or coated area, or rutile vs anatase crystal fraction, or size for a certain morphology, or something else.

TiO_2

anatase



rutile



How do we address concordance of exposure and toxicity data for nano?

Issue 1: Is what was studied in toxicity tests a, b, c what was received by exposed population segments 1, 2, 3, etc?

Transformations will have changed the distributions that make up the nanomaterial.

“Aging” of PCBs is an analogous concept

Problem formulation consequence:

Define dose-metric within a context of protocols to match and track it across exposures and studies.

Issue 2: Inconsistent measurement and reporting methods preclude comparisons

- *Exposure misclassification* – exposure and tox data can’t be reliably linked
- *Wasted knowledge* – data can’t be combined to build knowledge
- *Development risk* – new data may not be useful to future assessments
- *Vulnerability to “killer studies”* – a hazard study can’t be compared to other nanomaterials

Problem formulation consequence:

Specify what you are measuring in context of clear data generation, reporting, and acceptance rules

Do nanoscale materials need new risk assessment methodologies, or special consideration of uncertainty in safety assessment?

Quantitative challenges

- New metrics – differentiating particles
  - Statistics for particle morphology/composition?
  - Fast scanning/counting?
  - *Rates of change in multiple dimensions*, not just the static state of aggregation, chemical corona, etc?
- Distributional analysis
  - Identifying and tracking critical features
  - Linking and building knowledge about features (WOE and theory/policy)
- New fate and transport modeling approaches?

Nano Uncertainty Factors in Safety Assessment

Case Study 1:

- A side by side comparison of a “nano” and non-nano formulation by experts shows they both have the same endpoints and species studied in a validated standard toxicity test battery.
- The nano formulation is more potent, but the endpoints showing toxicity are the same.
- Does the nano formulation need an extra uncertainty factor?

Nano UF Case Study 2

- A new manufacturing process decreases particle size distribution, with change from 1% to 10% of particles below 100 nm for a material.
- A single 2-year rat feeding study found no new toxicity or greater mass-related potency compared to the studies of the 1% below 100 nm material.
- ***Does the new material need an uncertainty factor?***
- What about another new material with 13% <100nm, would it need an additional factor?

Applying uncertainty factor analysis to nano

- Case by case, data set by data set
- Need to differentiate “knowledge base” UF from “nano” UF
- Need a rational (quantitative?) basis for where to draw lines and set numbers
- The rational basis should include a path for removing the uncertainty (can’t just always tack on 10 for nano)

The broader challenges of nano-food regulations

Problem formulation in risk analysis and risk assessment is motivated by socio-economic challenges

- **Economics of regulation**
  - Fixed and variable costs on the supply side
    - Can create barriers to innovation (opportunity costs of no nano)
    - Potentially deter competition,
    - But predictability matters more than costs
  - Mixed effects on the demand side
    - Safe products is critical
    - A stricter regulation can increase or decrease demand
    - Time horizon matters
- **Already complex but only one piece of the ELSI puzzle…**

Monitoring risk perception and the acceptance of nanotechnology

- Risk perceptions: critical for future of the technology
  - Low knowledge/ unstable/lower acceptance of food applications
  - Consumers in developed countries drive international frameworks
- Risk communication: getting it right
  - Right message and the right messenger for each public
- In search of transparency
  - Public agencies' openness
  - Companies' own policies
  - Product registration
  - Product labeling?

Labeling nanotech products?

- Many products are unlabeled, other are nano-labeled without nano, and not all nano claims are justified
- A number of groups are demanding mandatory labeling
- Two major issues precedes any labeling regulation:
  - Definition of targeted attribute
  - Relationship with a regulatory framework
- Existing labeling regulations
  - Only mandatory labeling regulation: the European Union EC Reg 1123/2009 in the case of Cosmetics;
    - Proposed EU Parliament regulation extending the Novel Food Regulation for cloned and nano food (July 2010) still has to be reconciled with the European Council.
  - *Nano Mark* voluntary guidelines in Taiwan
  - At the international level: no standard
    - ISO draft TS 13830:2011 guideline on "Labeling of Manufactured Nano-Objects and Products Containing Manufactured Nano-Objects"

- **Voluntary Labeling**
  - Discourage misleading claims, provide a standard for all, avoid risky mistakes (Magic Nano)
  - But it needs a good definition, or it will increase confusion, and it may not be used at all by companies (currently avoiding nano products)

- **The debate around blanket mandatory labeling**

For mandatory labeling	Against mandatory labeling
-Enables consumer's **freedom of choice** -Leads to greater **transparency** -Increase **consumer acceptance** -Helps build **trust** -Establish the **social legitimacy** of nanotech -Responds to **public demand**	-**Stigma effect** (consumer avoidance of nano products) and **decrease public acceptance** **> moving away from consumer products** decreased investment and possible large opportunity costs (health etc) -Presence of nano is **not useful information** -**Trade and spillover effects** on other countries: increase the **nano divide**

↑ or↓acceptance? The GMO experience- acknowledging its differences- suggests the dominance of the stigma effect, resulting in avoidance of new nano products
A lot more opposition to blanket labeling than specific labeling.

•**Implementation issues:** detection/measures/purity/consistency etc

•**Alternatives to labeling?** Product register/notice etc…

Trade considerations

- Regulations affecting market access:
  - Balancing safety needs with economic efficiency losses
  - Direct costs for consumers and foreign exporters
  - Possible new unsolvable trade wars…
- Spillover effects in third countries
  - Fear of export losses: influence on risk averse policy makers > limiting nano food investment
  - Possible segregation of markets creating new externalities
  - Regulatory imitations: race to the top or the bottom?

Some implications in the developing world

- Specific nano technologies present much higher benefits/risk ratios in developing countries than in developed countries
- But regulations are set up in developed countries:
  - Non active followers of the OECD debates
  - FAO roundtable on risk regulations in developing countries >Europe vs US
- The risk of under-regulation does matter, but what about the risk of over-regulation for these countries?

Closing soap-box

- Leave the nanohype and nanofear to the generalists with agendas
- Problem formulation as first step always
  - Spend as much time on unintended consequences as precaution
  - Segregate the discussion to tractable sets of materials, uses, scenarios, and data linkages
  - Select uses with high anticipated benefit/risk ratios to develop best practices agreed to by all
- Be inclusive, bridge silos and trenches, and build trust

Richard Feynman predicted that such a technology is “a development which…cannot be avoided” (1959).

There’s Plenty of Room at the Bottom

http://home.moravian.edu/students/d/stmnd04/images/richard-feynman.jpg
www.nanotech-now.com/Press_Kit/nanotechnology-history.htm)