Establishing Evidence-Based OELs for Nanomaterials

Tee L. Guidotti, MD, MPH, DABT, QEP
FRCPC, FFOM, FCBOM

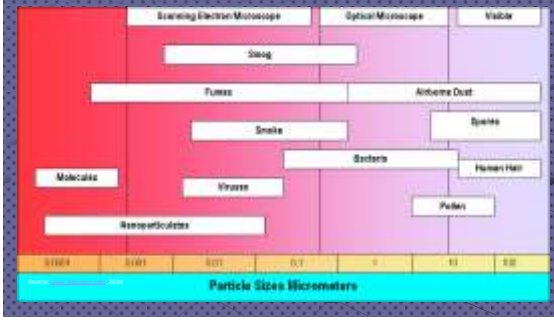
National Medical Advisory Services
Rockville MD

Presentation to Ontario Ministry of Labour, 15 January 2010.

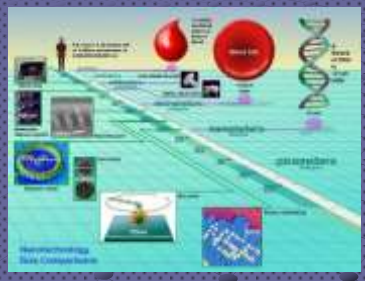
Executive Summary

- Nanomaterials are a form of matter, not just small solid particles.
- Effects distinct on quantum scale: cannot extrapolate from conventional toxicology.
- Air quality guideline for fine particulate air pollution provides a "peg" for regulation.
- Specific OELs based on this peg would depend on material properties.
- Integrated regulatory approach needed.

Size Range



Engineered Nanomaterials

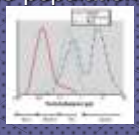


Behaviour in Workplace

- Diffuse rapidly, sediment slowly
  - Expect to become ubiquitous at relatively homogenous concentrations for long periods where airborne.
  - Aggregate into larger particles.
- Resuspension, entrainment dynamics are complicated.
  - Depends on aggregation, humidity, charge, etc.
  - Containment will likely be required.

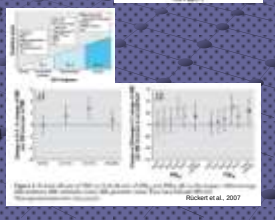
Lessons from Air Pollution

- Small mass may be associated with disproportionate effect.
- Exposure-response still holds within like exposures but no threshold apparent.
- Mortality and health outcomes observed in non-susceptible population groups.
- Allergy
- Irritation



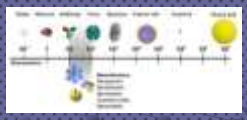
Theories of Pathophysiology Dictate What to Measure

- Decompensated lung function (Hoek)
- Interaction with other air pollutants (Moolgavkar)
- Macrophage overload (Mauderly)
- "Irritation signal" (Oberdorster)
- Acid effect - acid-forming particles
- Transition metals, Fenton-like catalysis (various)
- Oxidative stress - reactive O_2 species (Donaldson)
- Conduction instability (Peters)
- Vagal interruption (Godleski)
- Inflammation, blood viscosity, and coagulation balance (Seaton, Peters)



Metrics for Nanoscale Particulates

- Particle mass
- Particle count (number)
- Structure, dimension
  - Particle surface area
  - Particle volume
  - Fibre shape or other structure
  - Aggregation
  - Adsorption, "corona"
- Chemistry (examples)
  - Composition, if soluble
  - Surface activity (e.g. ζ)
  - Metal content (catalysis)



Same problem for synthesized nanoparticles. (b5media)

Proposed nanoparticle developed by Univ. of Texas for oil saturation monitoring..

Aggregation of ultrafine particulate air pollution. (UCLA)

Nanoparticle Configurations

Shapes

- Spherical
- Arboreal, dendrimers
- Fullerenes
- Graphenes, sheets, plates
- Nanotubes, nanowires, fibres
- Nanocrystals
- "Cages" containing atoms or small molecules

Structures

- Solid, "simple"
- Fluorophores
- "Caged" metal ions
- Semiconductors ("quantum dots")
- Nanomachines (mechanical devices dependent on an energy source)
- Nanobots (currently science fiction!)
- Nanopharmaceuticals

Integrated Regulatory Framework

- An OEL-reference "peg" consistent with environmental exposure objectives
- Application of safety or uncertainty factors reflecting special characteristics
- Environmental monitoring requirement will drive technology but for now keep simple and depend on protective standard.
- Medical monitoring over surveillance, because outcomes not known.

Regulating by Analogy

- Compare to $PM_{2.5}$. (2.5 μm = 2500 nm)
- CCME Canada-Wide Standard (CWS):
  - 30 μg/m³, 24-h average, 98th %ile over 3 years, after 2010.
- Converted to an OEL: 30 μg/m³ 8-h TWA
  - Assume objective is to avoid adding to community exposure effect.
  - Reasonable given log-N distribution to treat 98 %ile as upper limit, ≅ MAK
  - Not based on threshold effect, susceptibility

Applying Regulatory Framework

- Set benchmark or "peg" at 30 μg/m³ 8-h TWA:
  - This is very low level of exposure.
  - Apply without modification to biomaterials thought to be relatively inert (e.g. TiO_2)
- Use as benchmark (≅ RfD) for setting product-specific OELs:
  - Characteristics of specific products
  - Apply additional uncertainty factor(s)

Product-Specific OELs

- Start with benchmark or "peg".
- Apply additional UF for toxicologically significant properties:
  - Metal or semimetal content
  - Fibrous shape
  - Biological activity
  - Resemblance to known hazards
- Provisional standard until data become available to support definitive standard

Regulating by Analogy

Pros of this approach

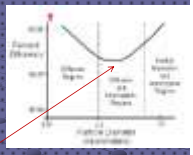
- Likely to be protective
- Regulatory consistency
- Few assumptions required
- Biological activity despite small mass.
- Can adjust down from the "peg"
- Industry confidence
- Drive technology

Cons of this approach

- Low airborne exposure levels impose reg burden
- Complicated
- Scale comparability is not assured.
- Peak levels v. prolonged exposure
- Adjustment of OEL not easy, data-intensive.
- Strictly provisional

Protection

- Engineering controls, containment will be key
- Ventilation as for a gas
- N95 respirators perform >APF although not at peak efficiency 200 – 2000 nm.
- Stringent RPP (fit testing, etc.) absolutely required



Hierarchy of Controls

- Isolation, containment
- Engineering
- Ventilation
- (Housekeeping)
- Personal Protection
- Administrative

Environmental Monitoring

- Nanoparticles and ultrafine particulate matter are hard to monitor, measure in air.
- TEOM (Tapered Element Oscillating Microbalance) is only currently practical method – used in air quality monitoring.
- Mass may not be the essential metric, but only practical metric at moment.
- Passive diffusion monitoring: new technology will emerge.

Health Outcomes

- Suffient evidence:
  - Respiratory
  - Cardiovascular
  - Neurodegenerative
  - Carcinogenesis
  - Irritant potential
- Unknown but of theoretical concern:
  - Allergy and immunomodulation

There is insufficient evidence to predict health outcomes in people.

Medical Monitoring

- Periodic health surveillance not possible :
  - Do not know what to look for.
  - Cancer risk, neurodegenerative disorders have latency issues.
  - No validated biomonitoring test for oxidant stress, other important effects
  - Immune effects probable
- Better approach for present is population health monitoring.
  - Wide range of health outcomes

Continuous Review of Regulation

- Benchmark against:
  - EU, including European Agency for H & S at Work, REACH
  - NIOSH
  - Environment Canada and current regulation of air quality
  - HSE
  - Industry leaders
- Track emerging research and experience.

Executive Summary

- Nanomaterials are a form of matter, not just small solid particles.
- Effects distinct on quantum scale: cannot extrapolate from conventional toxicology.
- Air quality guideline for fine particulate air pollution provides a “peg” for regulation.
- Specific OELs based on this peg would depend on material properties.
- Integrated regulatory approach needed.