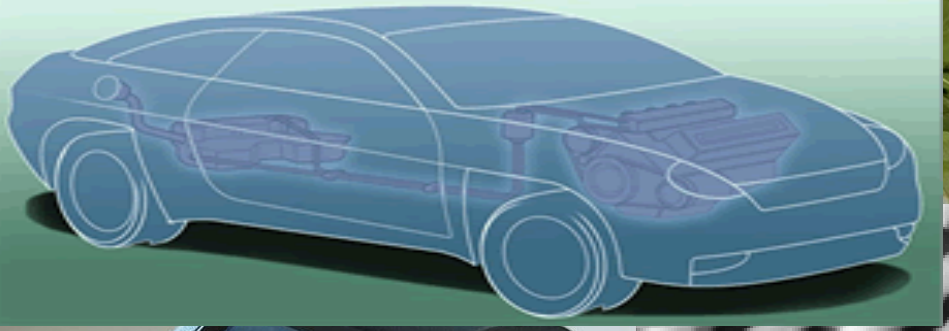

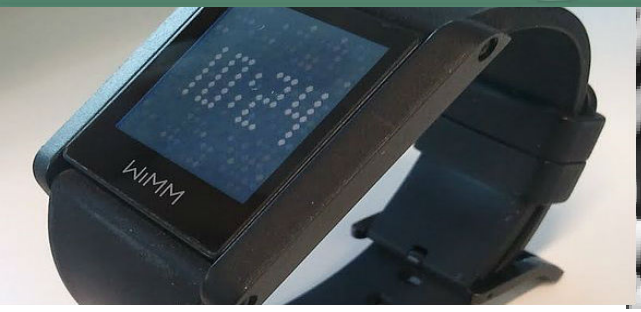

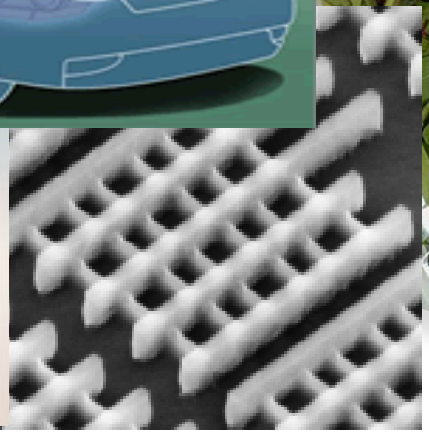
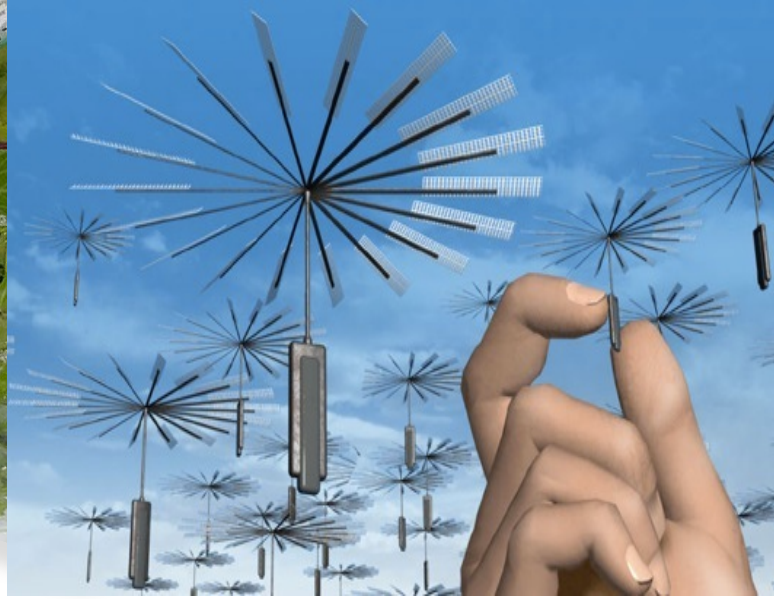

Environmentally Realistic Exposures in Consumer Products

JO ANNE SHATKIN, PH.D.

QEEN NNCO Workshop July 7, 2015

Consumer Exposure Studies I: General Products

Vireo Advisors, LLC

Elements of Environmentally-relevant Exposure Assessment

ELEMENTS

- Realism
- "Reasonable worst case"
- Matrix effects
- Time
  - Aging
  - Frequency
- Dynamism

FRAMEWORKS

- Use category
- Complete exposure pathway
- Tiered approaches
- Life Cycle Stage

Key dimensions of exposure

- Material characteristics – relevant metrics, predictive release properties
- Timing
- Receptor characteristics
- Magnitude

Approaches for Environmentally Relevant Exposure Assessment

- Nano LCRA
- Coating/textile standard methods (EPA nanosilver guidance)
- DF4nanoGrouping (ECETOC)
- NanoGRID/Collier et al 2015
- Sharma et al. 2015

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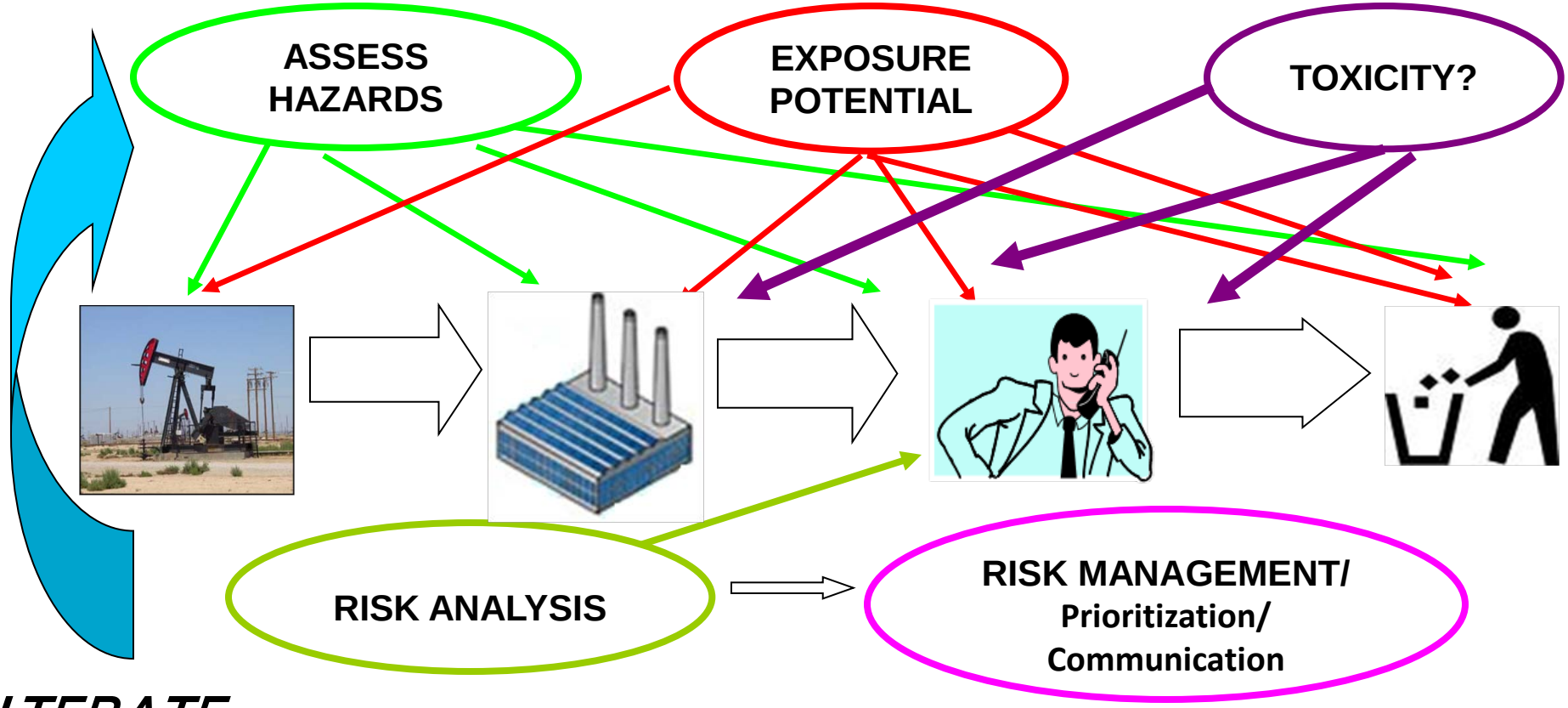
NANO LCRA: Streamlined Life Cycle/ Risk Assessment Framework for Nanomaterials



Shatkin 2012

Vireo Advisors, LLC

Key Attributes

- Screening level – Life cycle “thinking” – not a lengthy quantitative LCA study
- Consider range of relevant applications and use categories
- Consumer exposure can occur at any LC stage
- Also considers unintended uses
- Comparative - not necessarily quantitative data
- Flexible focus – highlighting differences from conventional substance

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Exposure Scenario Ranking

	Hazard	Magnitude	Likelihood	Frequency
Low	covalently bound particles in substrate	Exposure is to article where one component is > 1% NM	Direct contact mitigated.	Infrequent - Exposure possible < 10 times per year
Med	particles potentially releaseable from substrate	Exposure to material > 1% to <10%	Unintentional - exposure possible based on activity.	Incidental - use 10-50 times per year
High	dried particles in powder form	Exposure to material is greater than 10% of mixture	Intentional - repeat exposure during normal use	Regular - greater than 50 times per year

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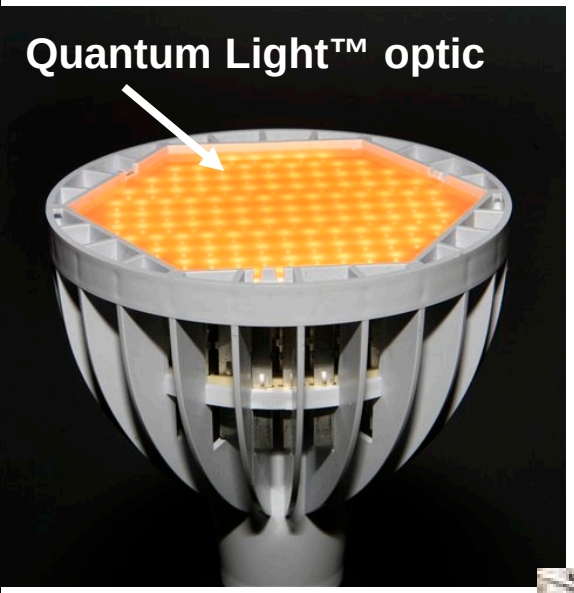
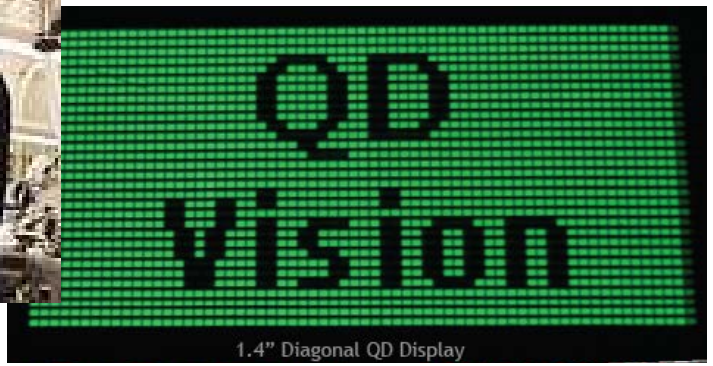
Example: Quantum Dots in a Coating Matrix

QD Vision – where color, power, and cost matter

- Founded 2004 out of MIT - 50+ employees (2009)
- Focus on displays & lighting markets
- First to market with quantum dot product for solid state lighting
- Thought leader in QD EH&S and technology



Nexxus PAR 30 LED Array

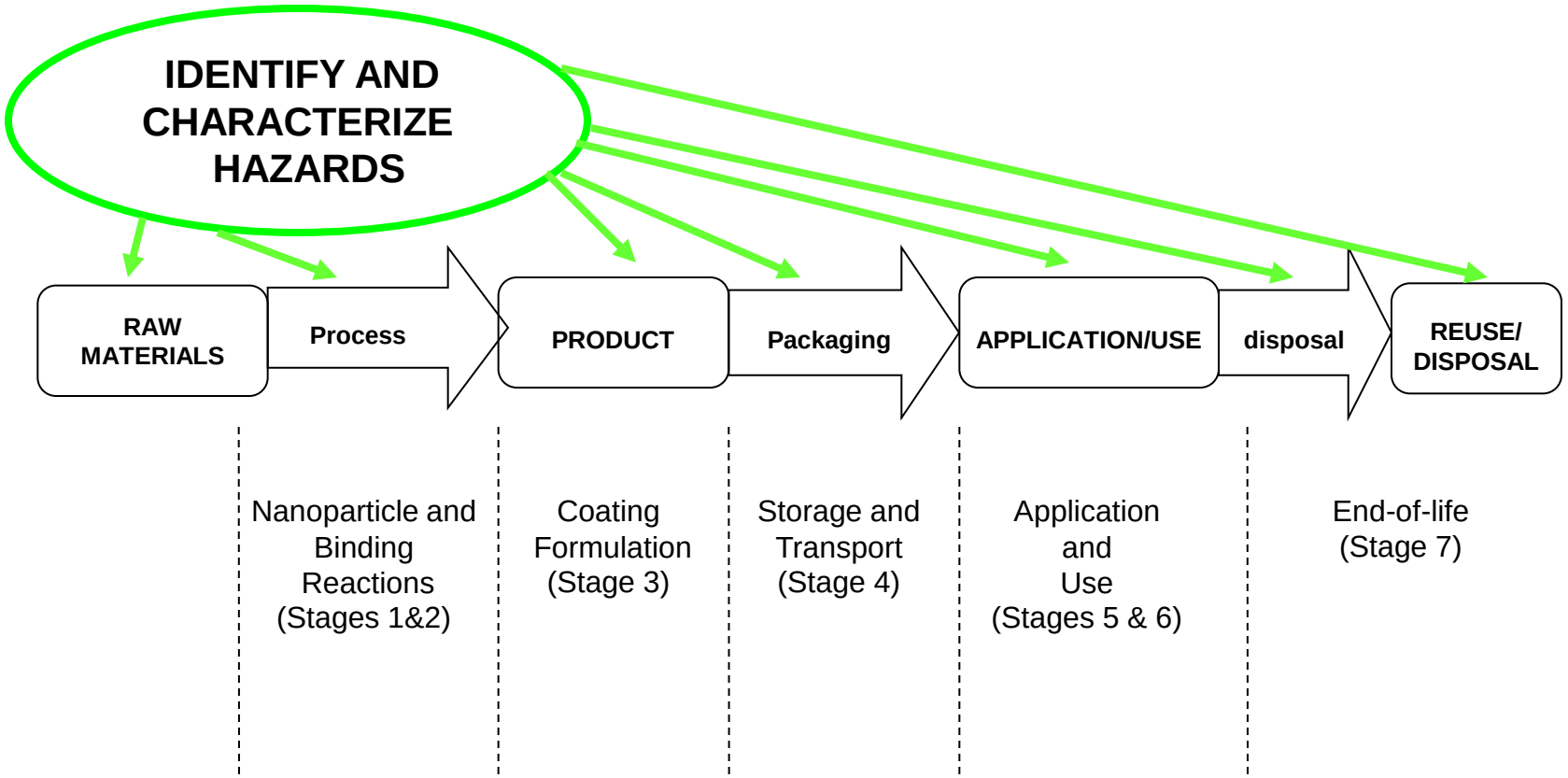


Physical-Chemical Properties change during the product life cycle

Life Cycle Stage	Stage of Product	Description	Material weight (grams)	Agglomeration State/ Aggregation	Composition	Crystal Structure	Particle Size/Size Distribution	Porosity	Purity	Shape	Solubility	Stability	Surface Area per particle (m^2)	Surface Area total per batch (m^2)*	Surface Chemistry	Surface Charge
1	Nano-material Reaction	Nanoparticles														
2	Binding reaction	Micron size aggregate														
3	Product formulation	Liquid Coating (in lab) with aggregate														
4	Storage and Transport	Liquid Coating (out of lab)														
5	Application	Spray aerosol														
6	Use	Dry Coated surface														
7	Post Use (end of life)	Unknown														

NANO LCRA Ex. 1

Hazard Identification for a nanoparticle in coating



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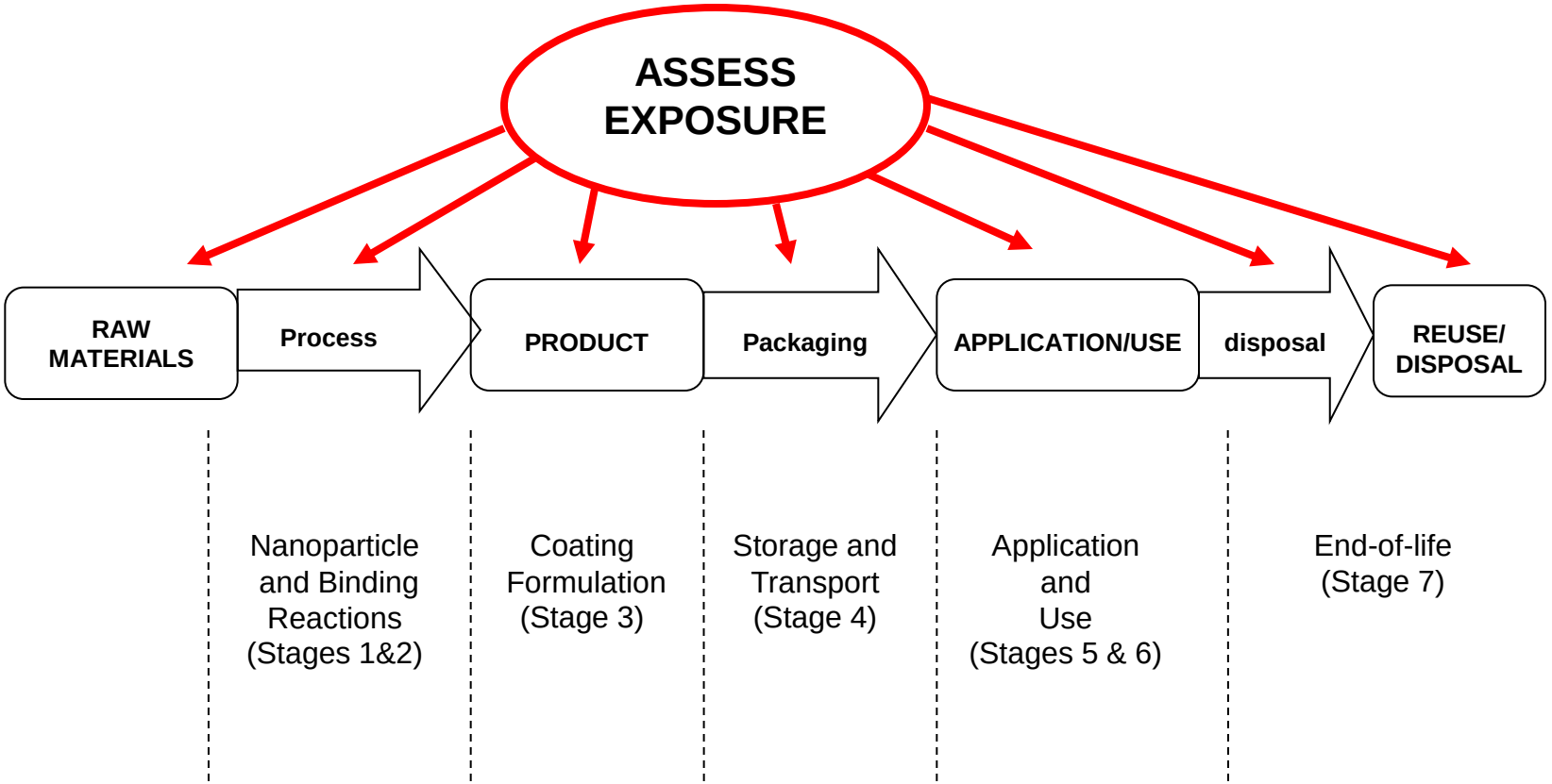
NANO LCRA

Exposure Assessment Ex. 1

Event → Substrate → Pathway → Receptor Type



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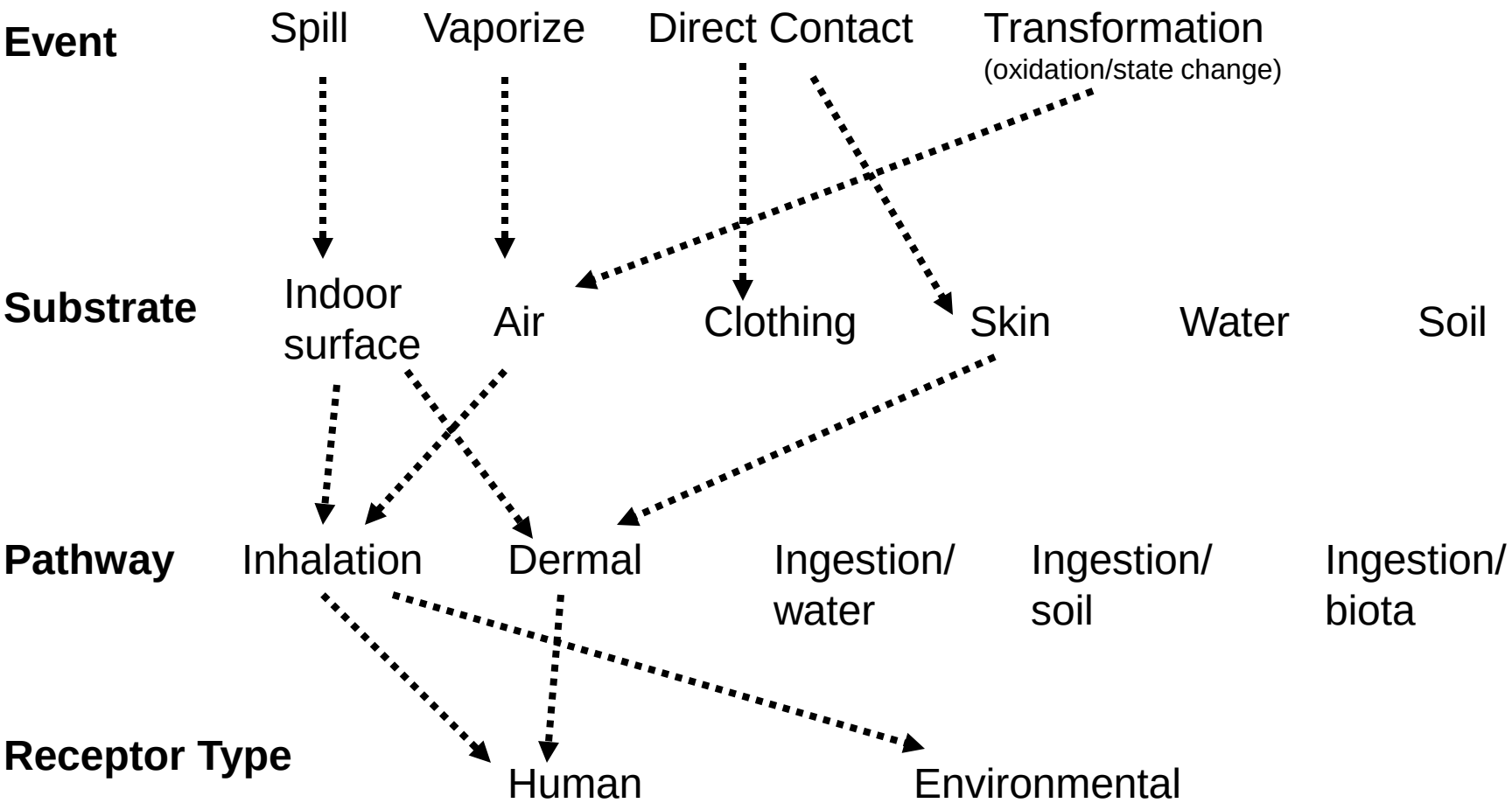
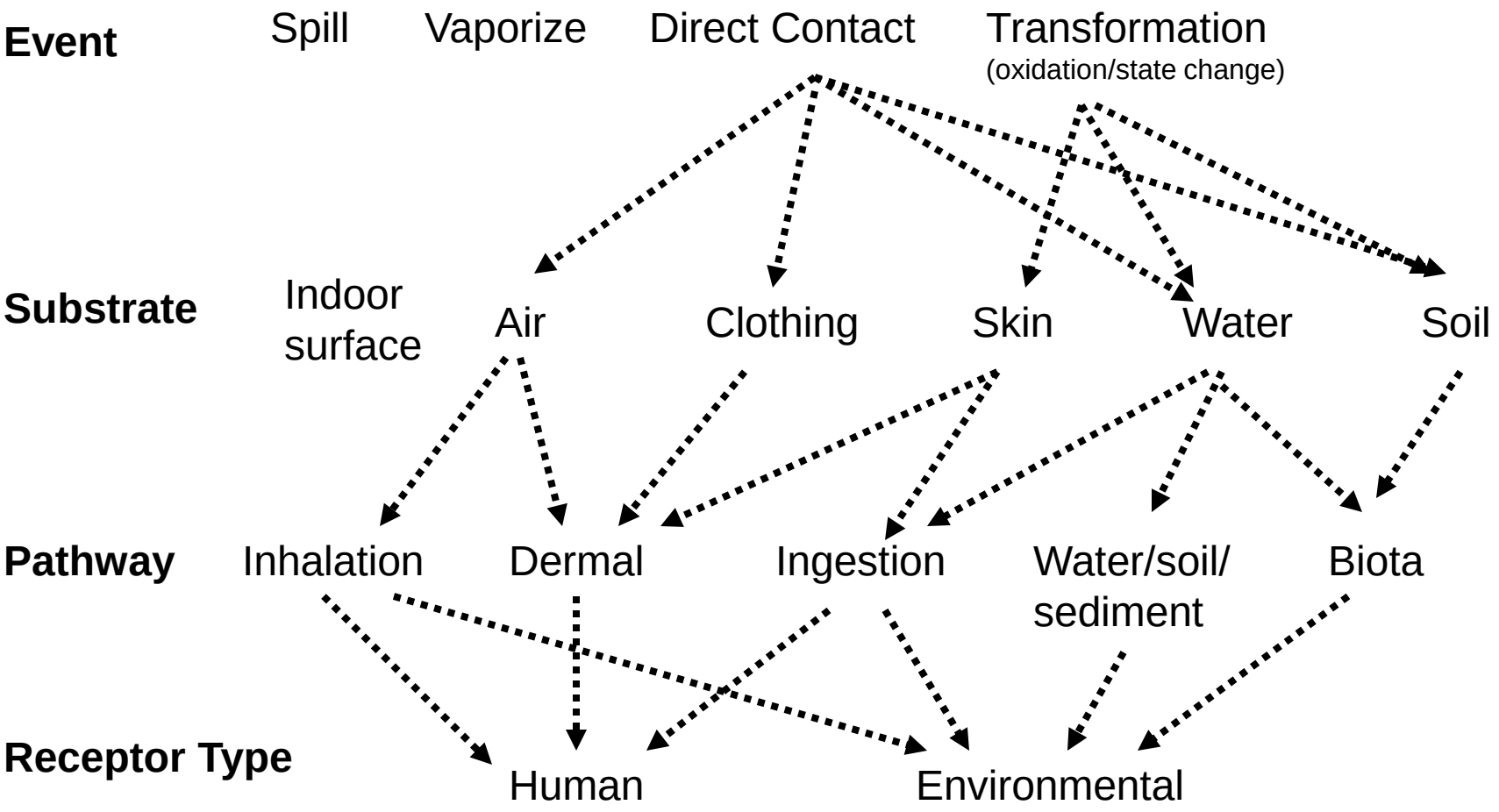
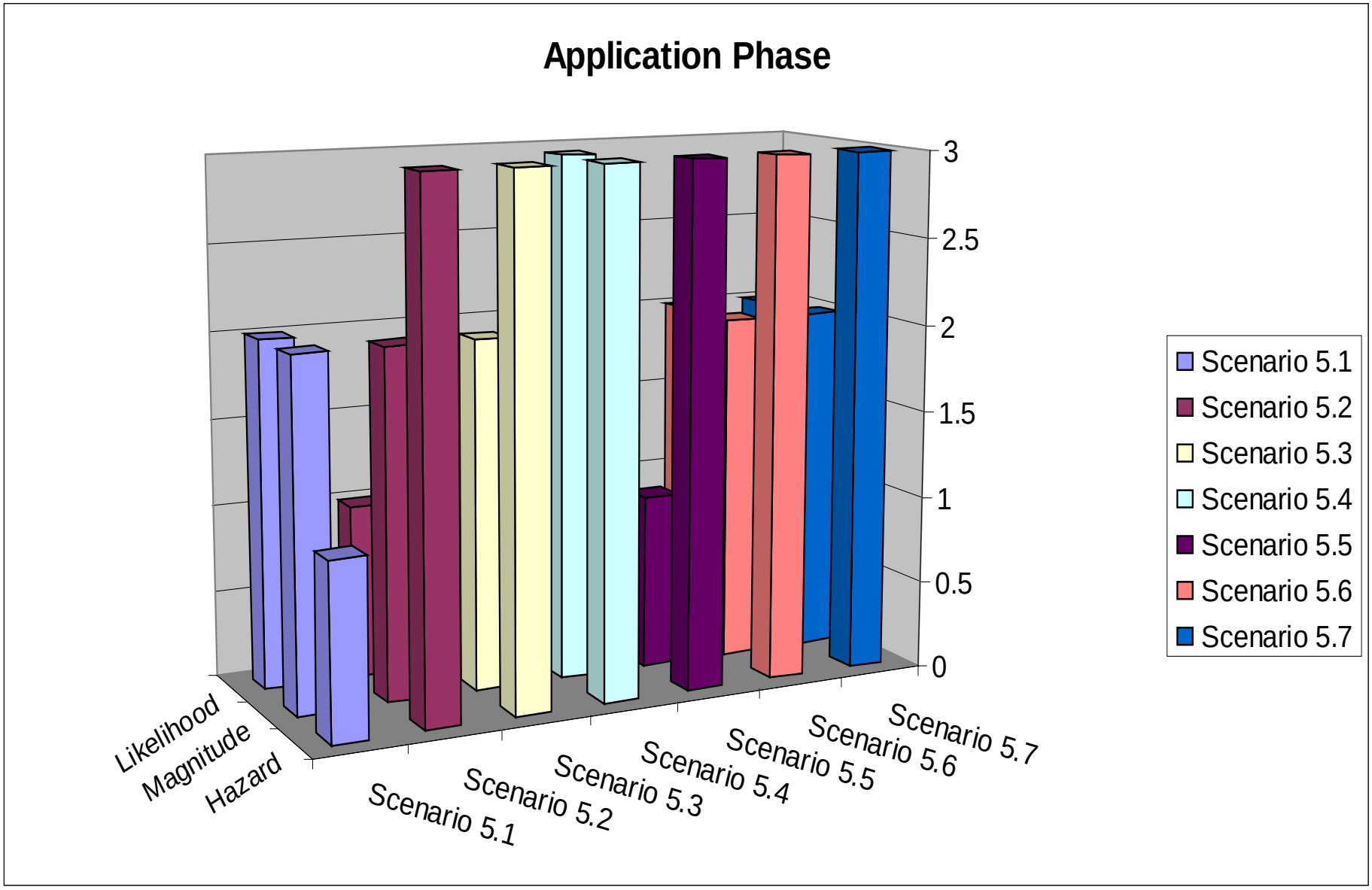
Potential Exposure – Stage 1
(In-lab example)

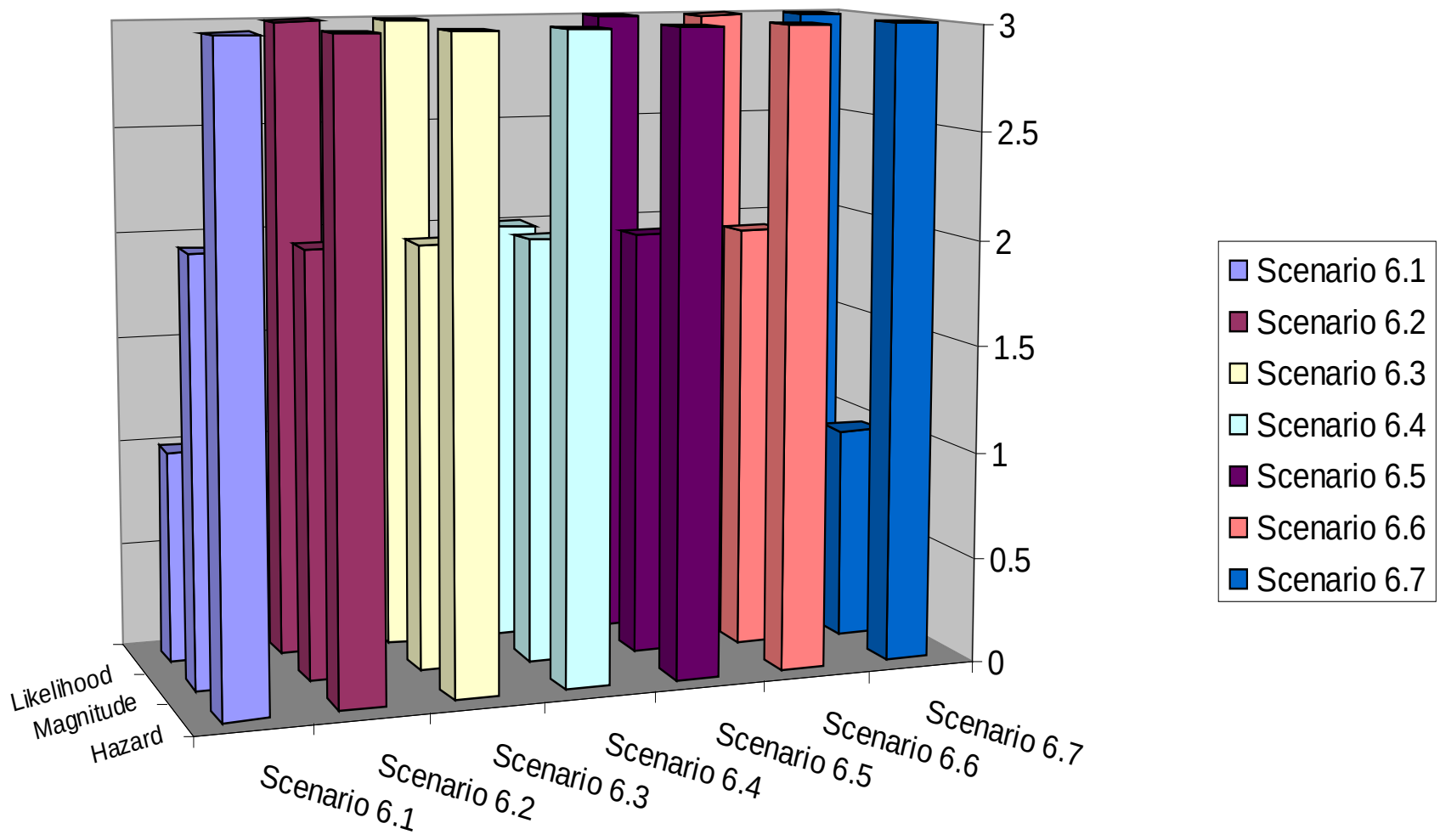


Potential Exposure – Stage 6
(Out-of-lab example)




Application Phase
3
2.5
2
1.5
1
0.5
0
Likelihood
Magnitude
Hazard
Scenario 5.1
Scenario 5.2
Scenario 5.3
Scenario 5.4
Scenario 5.5
Scenario 5.6
Scenario 5.7
Scenario 5.1
Scenario 5.2
Scenario 5.3
Scenario 5.4
Scenario 5.5
Scenario 5.6
Scenario 5.7

Use Phase


3
2.5
2
1.5
1
0.5
0
Likelihood
Magnitude
Hazard
Scenario 6.1
Scenario 6.2
Scenario 6.3
Scenario 6.4
Scenario 6.5
Scenario 6.6
Scenario 6.7
Scenario 6.1
Scenario 6.2
Scenario 6.3
Scenario 6.4
Scenario 6.5
Scenario 6.6
Scenario 6.7

First Iteration Risk Characterization

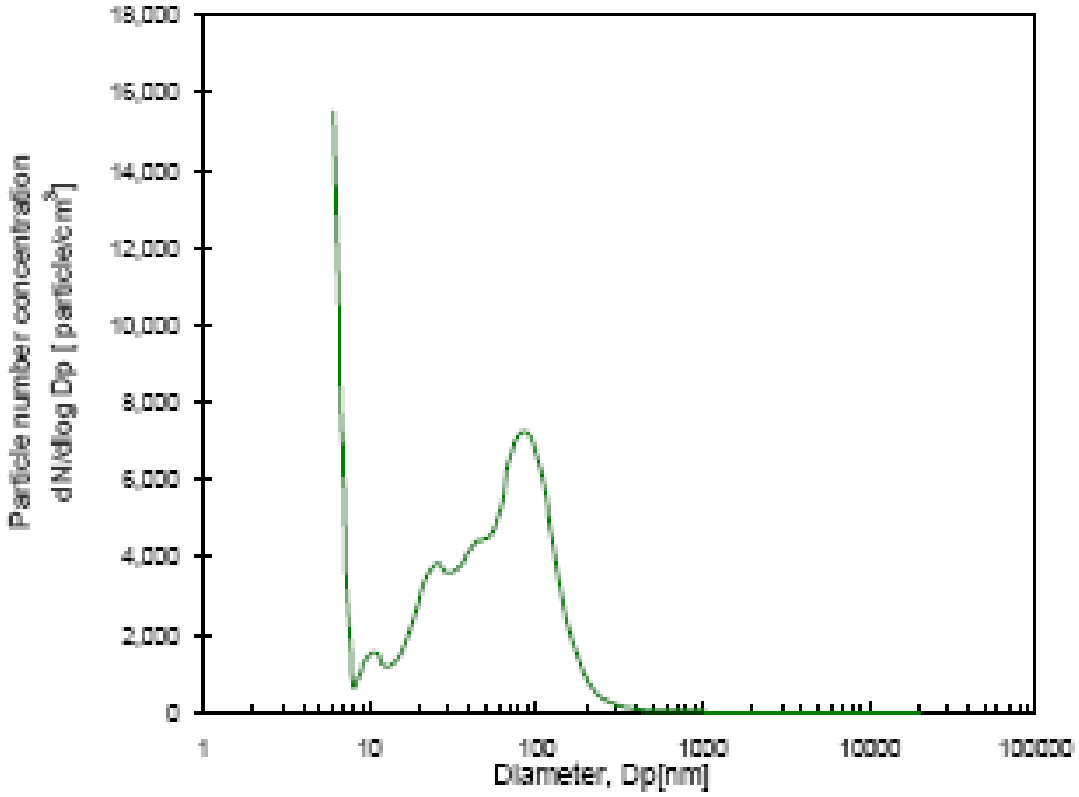
- Exposure Assessment suggested only a few high concern scenarios
  - Lab/production stages are well controlled
  - Designed and conducted product testing, to inform second iteration Exposure Assessment and Risk Characterization

Exposure Assessment
Initial Product Testing

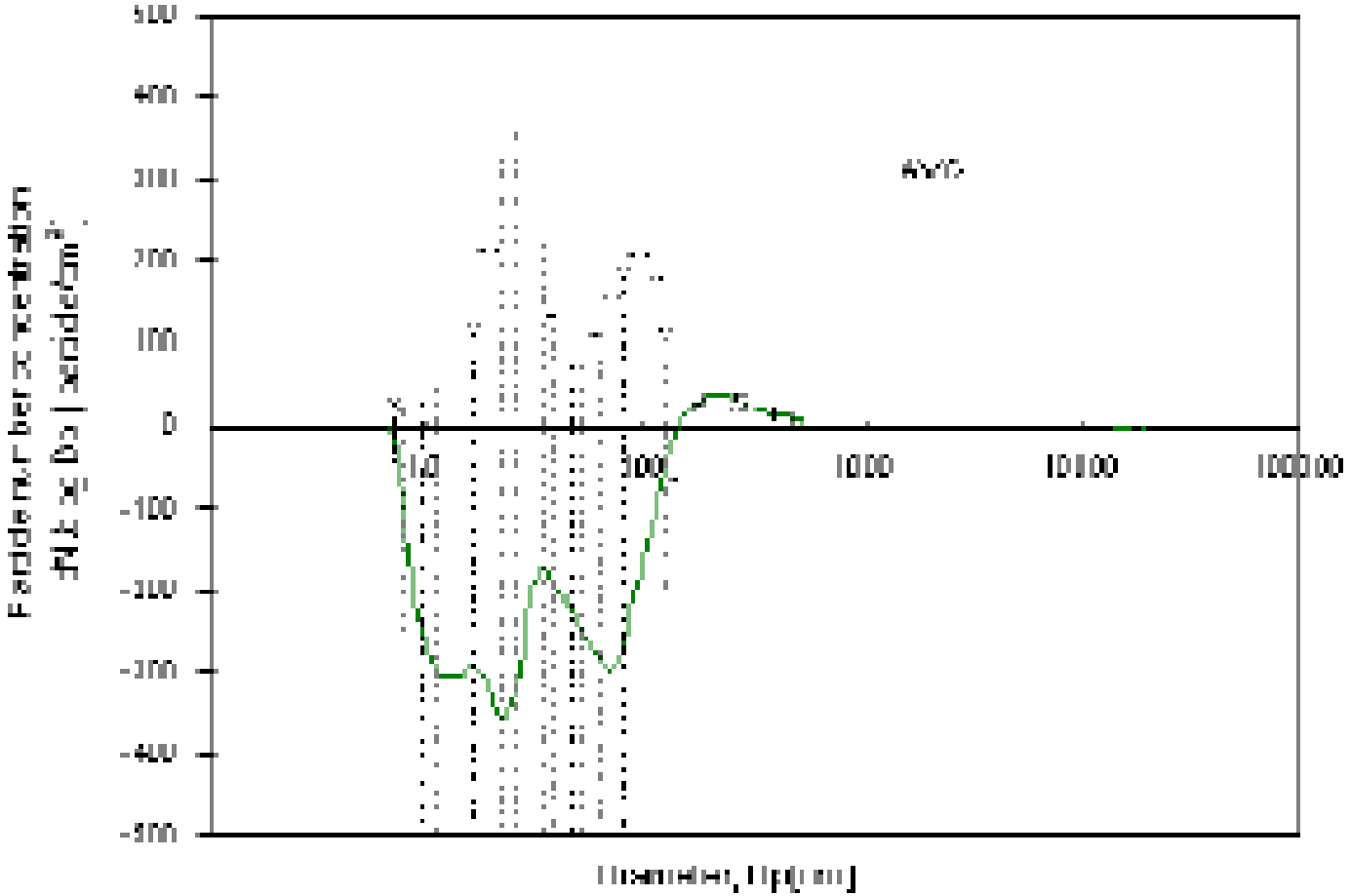
- Tested highest concern exposure scenarios
  - Inhalation during coated product application
  - Wear testing of applied/dried coating product

- Prepared coated plaques
- 1 year accelerated aging simulation
- Specially designed test lab
- Real time and electron microscopy

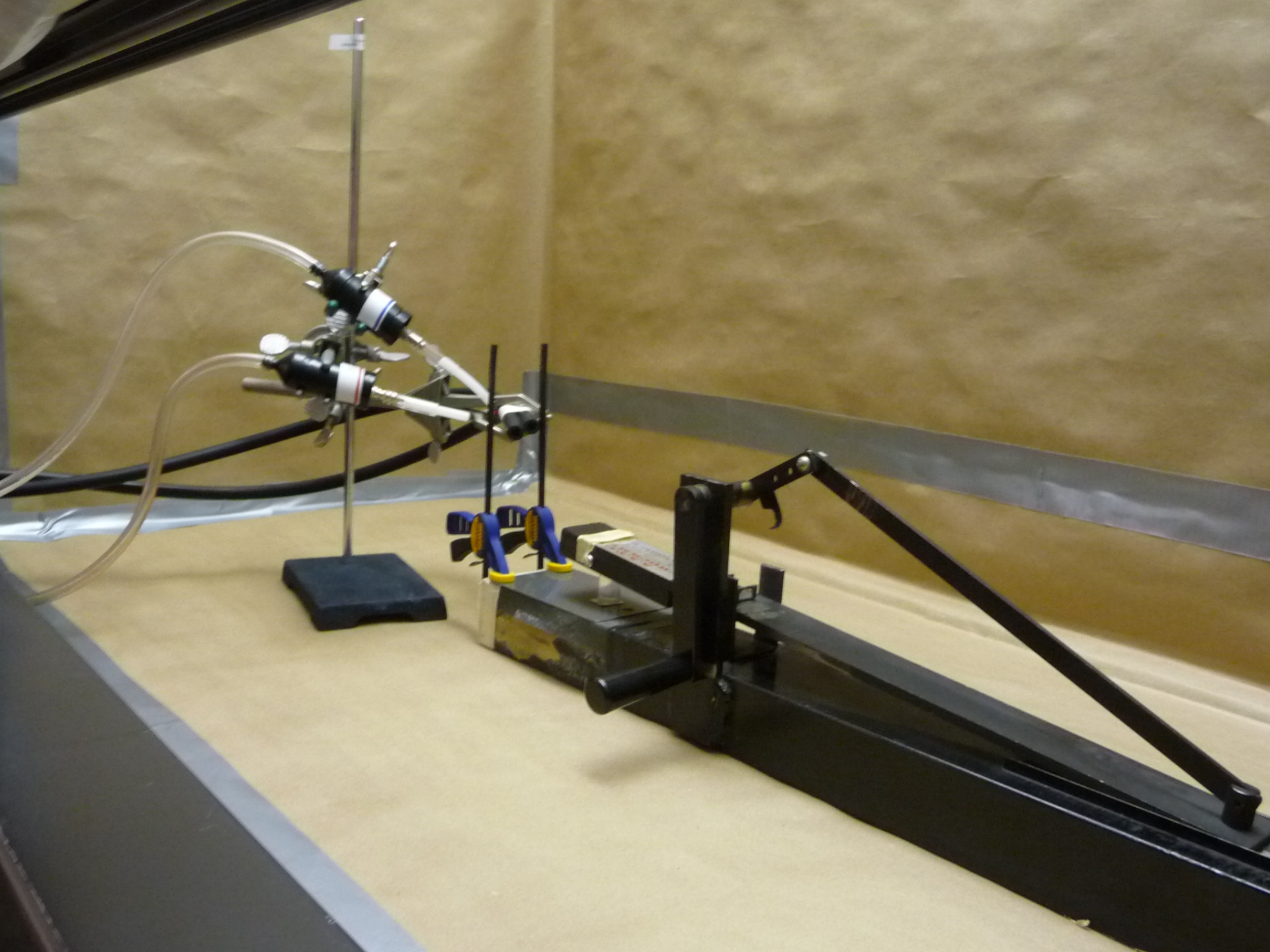
Measured Background Levels of Nanoparticles



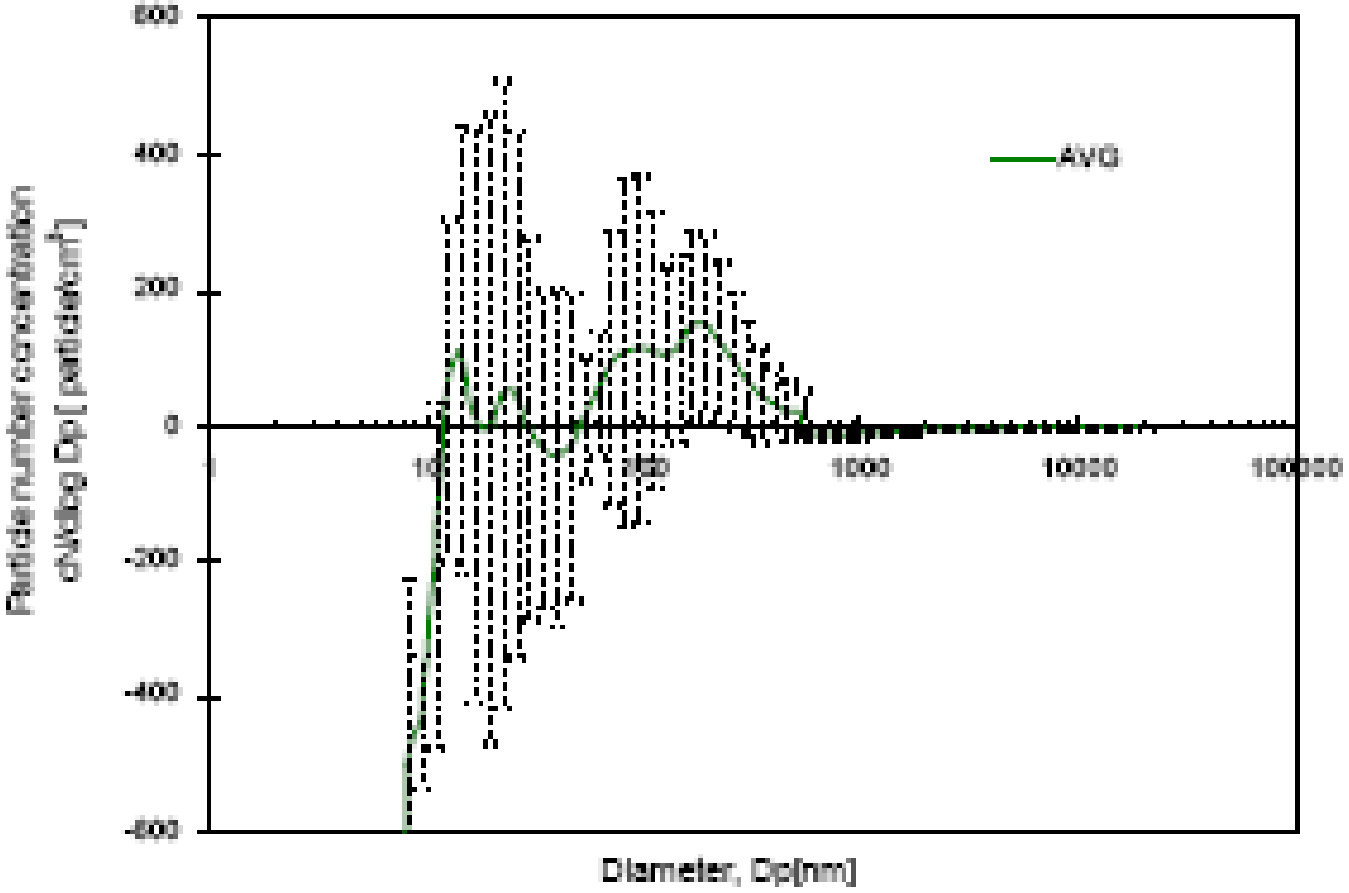
Nanoparticle counts - individual runs and average during spraying



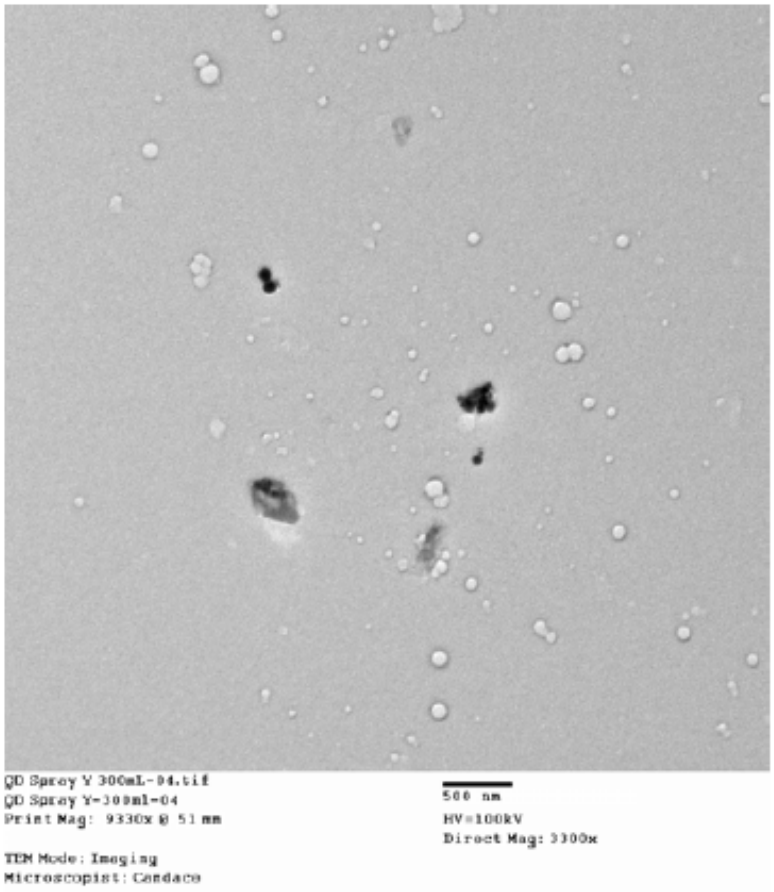
(b)



Nanoparticle counts – sanding tests



Transmission Electron Micrograph of Sprayed Paint Sample



(d)

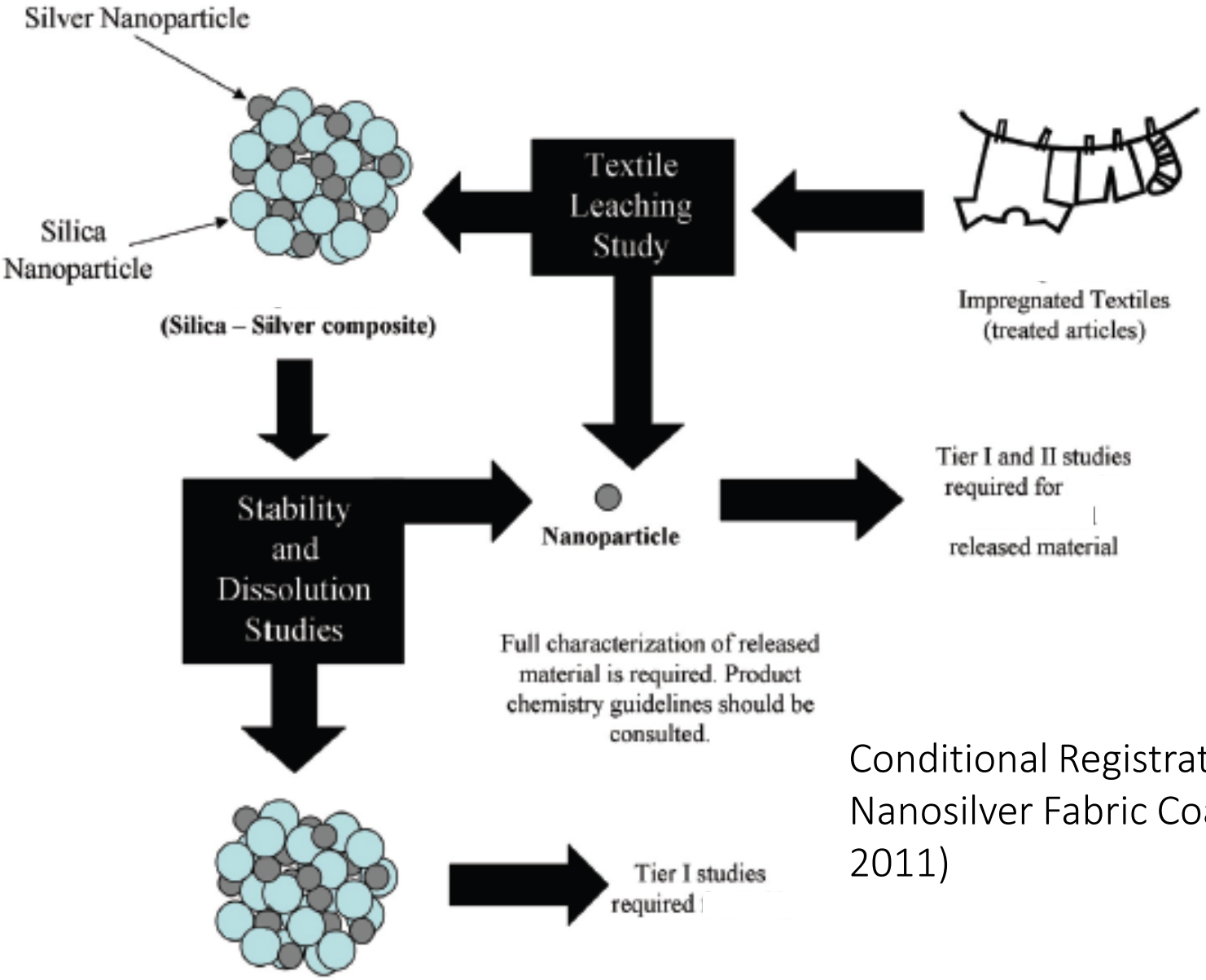
Second Iteration Risk Characterization

- Test results demonstrated very low exposure risk for application and use
- Risk Characterization updated – developed safe handling instructions
- Further review of recent literature lead to similar toxicity conclusions
- Overall product risk characterized as low

QDV LCRA Findings

- Life cycle exposure
  - Manufacturing and production phases well controlled
  - Exposure during application not distinguishable from background
  - Aggressive “wipe” testing produced no detectable exposure
  - End of life exposures uncontrolled
- Toxicity data extremely limited
  - recommendations for testing product as used
- Risk management focus on exposure prevention

Example: Tiered Research Needs for a Nano-Pesticide



Conditional Registration for Nanosilver Fabric Coating (EPA 2011)

DF4 nano Grouping (Arts et al 2015)

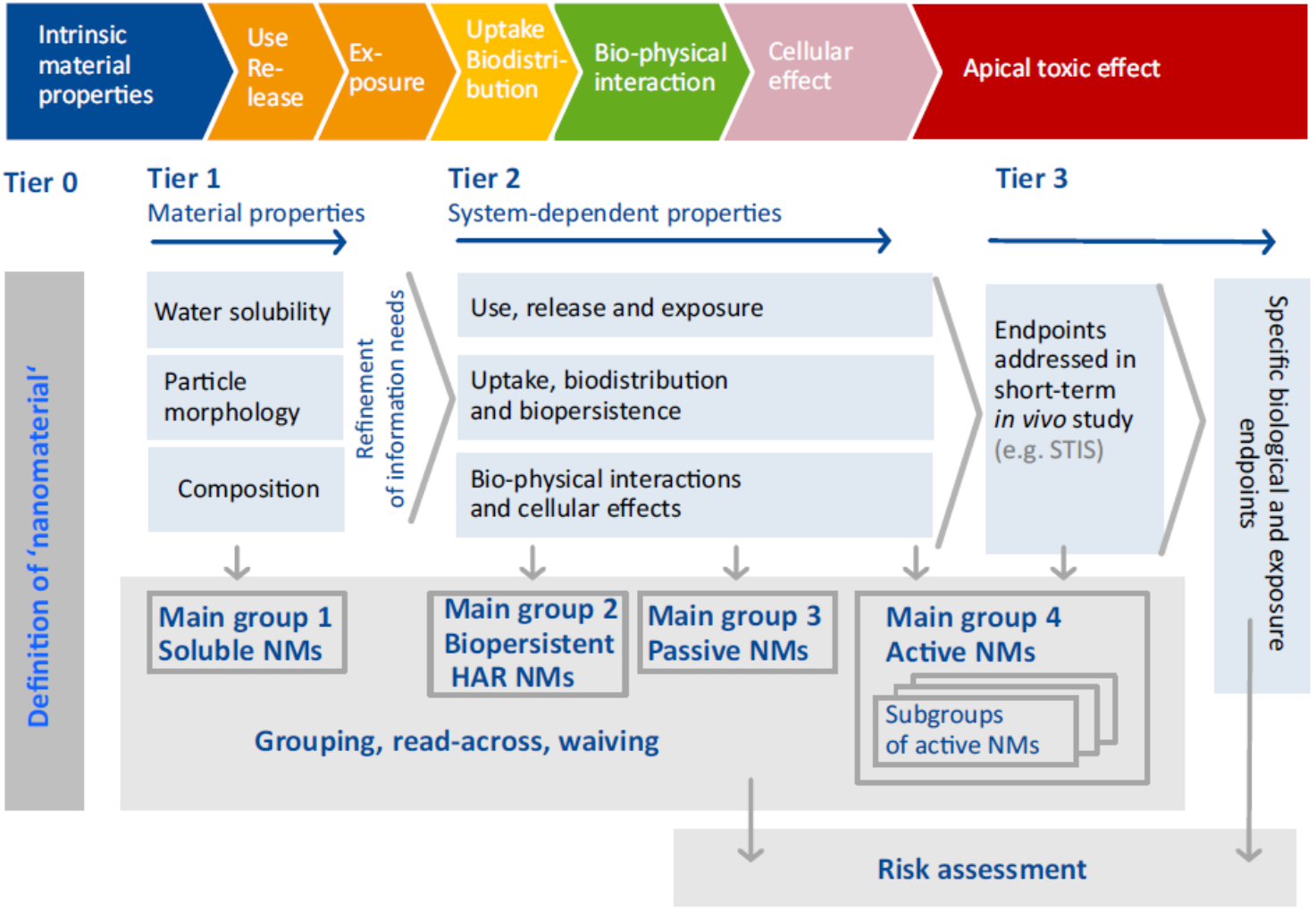
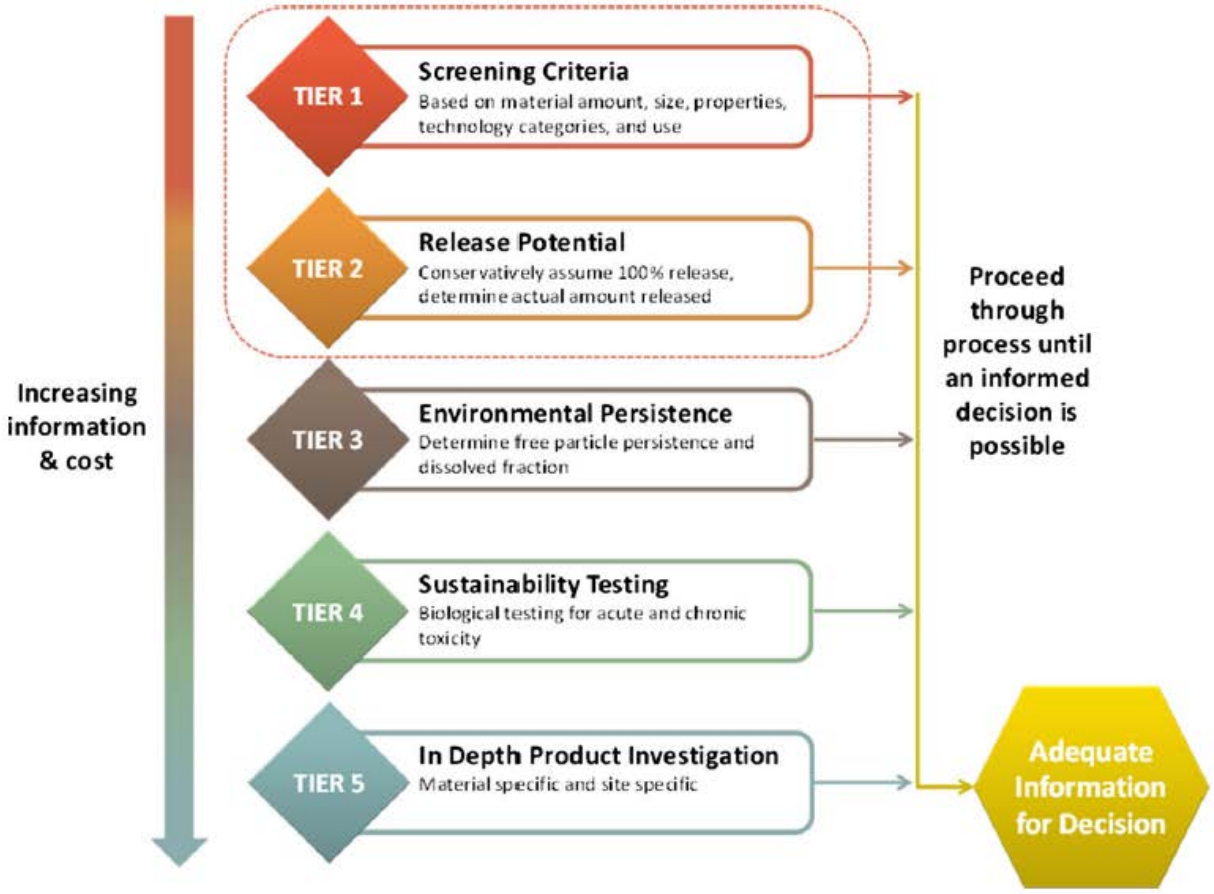


Fig. 2. The decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping).

NanoGRID Framework



Source Collier et al. 2015

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Sharma et al. “Framework to evaluate exposure relevance and data needs for risk assessment of nanomaterials using *in vitro* testing strategies.”

Risk Analysis [Under Review].

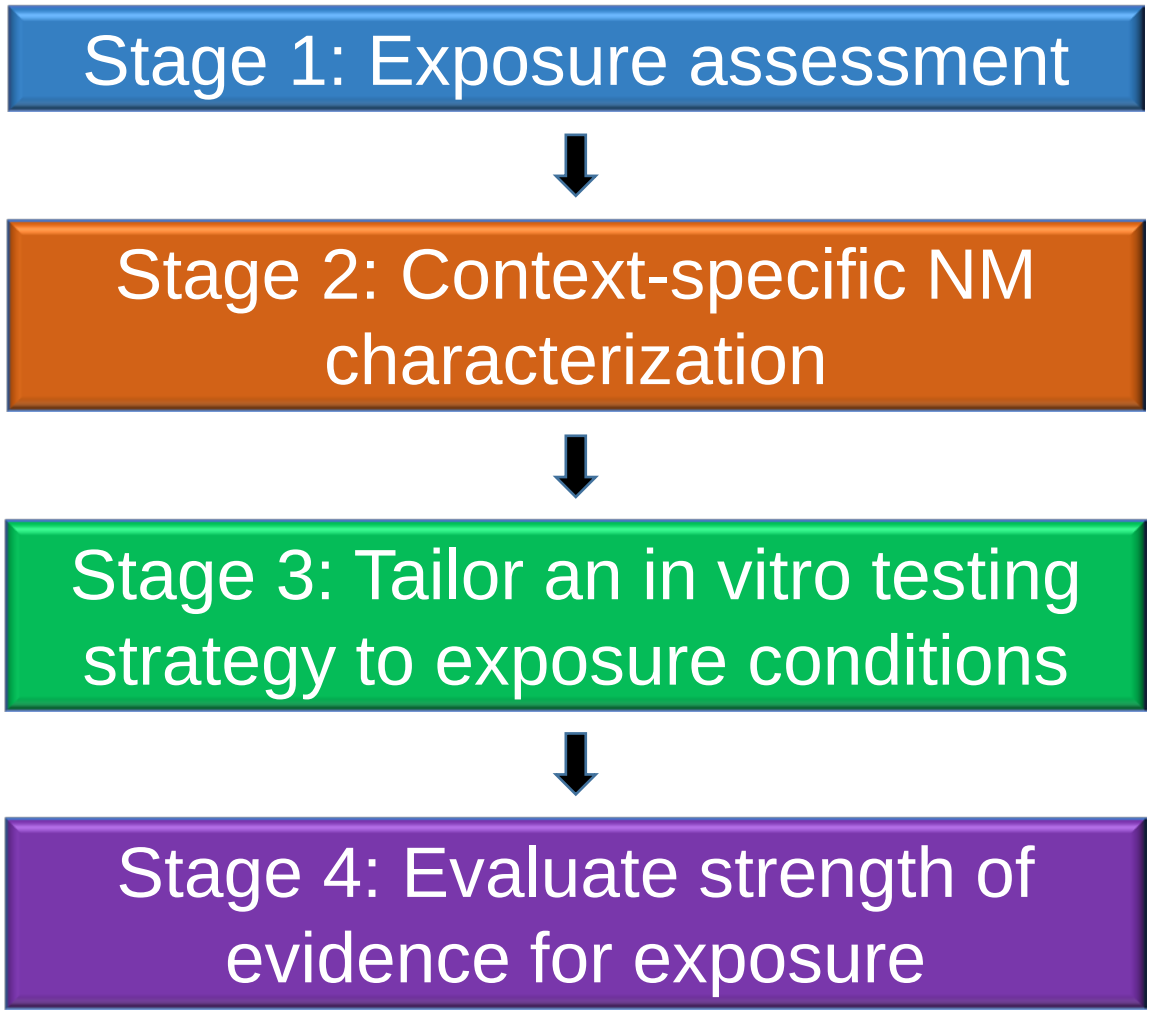
Slides from:
Monita Sharma, Jo Anne Shatkin, Richard Canady, Carolyn Cairns, Amy J. Clippinger

presented at the

Society for Risk Analysis
Workshop on Alternative Testing Strategies for Nanomaterials

September, 2014 Washington, DC

Framework for assessment



Sharma et al.

Stage 1: *Exposure assessment*

Determine likely route of exposure (inhalation, oral, dermal)	Determine likely exposure medium (e.g., water, air, dust, soil)	Exposure monitoring	Development of exposure scenarios

Stage 2: *Context-specific NM characterization*

Evaluation of analytical methods	Evaluation of phys-chem properties	Grouping & read-across

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Stage 3: *Tailor an in vitro testing strategy to exposure conditions*

Determine physiologically-relevant exposure conditions: - cell types - relevant matrix, such as stimulant or artificial fluids (e.g., lung surfactant, saliva, or gastric fluids)	Establish appropriate dose and dose metrics	Test using a realistic nanomaterial form e.g., appropriate life cycle stage when exposed (based on anticipated corona formation, dissolution, and aggregation)

Stage 4: *Evaluate strength of evidence for exposure*

Evaluate existing data for its relevance to expected human exposure scenario	Use existing data to determine what additional testing is necessary, if any	Use results to further develop and optimize *in vitro* testing strategies

Test	Exposure Source	Dose	Transformations	Biological Response
NM Characterization	Has NM been adequately characterized in source matrix?	Is the NM introduced to the system in a form representative of the human situation?	Can administered NM be effectively differentiated from transformation by-products, conventional scale substances and other NMs endogenous to the biological system?	How do the identified NM features relate to biological responses of interest? How is response being related to NM dose measurements?
	How is variability in NMs in source matrix evaluated and reported?	How completely are NMs characterized with biologically relevant criteria?	Are indirect indicators, radiolabeling or fluorescent tags needed to track NMs? Do they interfere with NM biological activity, detection or characterization?	What parameters of the biological system most influence NM activity and how are they being monitored?
		What, if any, impacts result from required sample prep processes?	What is the significance of possible bio-corona formation, dissolution, aggregation/agglomeration? How might such transformations affect NM measurements?	What is the significance of possible bio-corona formation, dissolution, aggregation/agglomeration? How might such transformations affect NM toxicity?
NM Detection	Is analytical equipment compatible with NMs and source matrices of interest?		Is analytical equipment compatible with NMs and biological matrices of interest?	How will NM measurements be correlated with dose-response measures?
		Can NM be detected in key biological matrices?		
		Are method detection limits in range of lowest anticipated dose levels and biologically important particle sizes and size distributions?		
Dose-Response Correlates	How can dose-response data be linked back to exposure source characterization and vice versa?	What, if any, impacts result from the required sample preparation processes?		How well are findings transferable to other cell types?
	What, if any, assumptions are inherent in the exposure and dose-response assessment?	How well does administered dose compare to delivered dose?	How well does delivered dose relate to cellular dose?	Are cells used in the test system the most vulnerable to or representative of NM exposure and its toxic effects?
				Does the test system simulate mechanical stresses important for physiological response?
				Does the test system contain microbial and other biological substances that are important mediators of NM toxicity?
				Does the test system simulate physiology in both diseased and healthy states? What is unique about NM behavior in these states?

Sharma et al.

Test	Exposure Source	Dose	Transformations	Biological Response
NM Character-ization	Has NM been adequately characterized in source matrix?	Is the NM introduced to the system in a form representative of the human situation?	Can administered NM be effectively differentiated from transformation by-products, conventional scale substances and other NMs endogenous to the biological system?	How might bio-corona formation, dissolution, aggregation/ agglomeration affect NM toxicity?

Sharma et al.

Key themes

- Tiered approaches are logical
- Address the 5 “W’s” (& How)
- Ensure testing is “environmentally relevant”
- Scenario ranking prioritizes key pathways for detailed evaluation.

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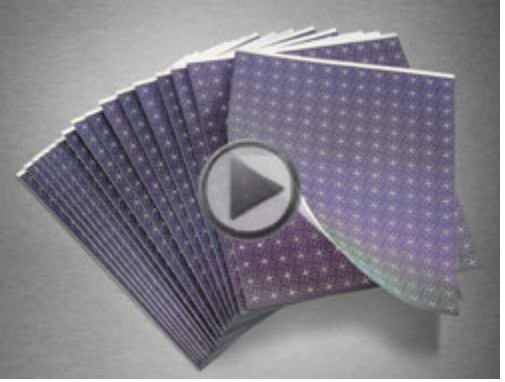

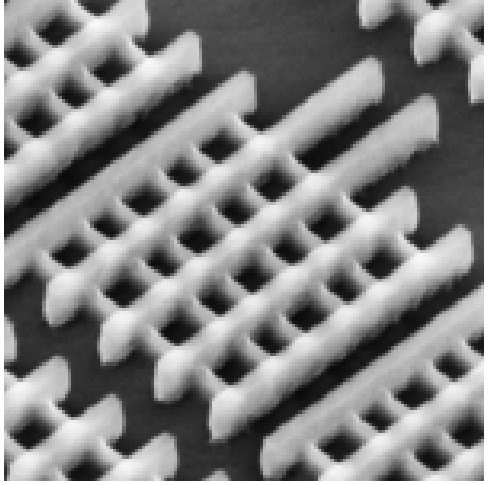

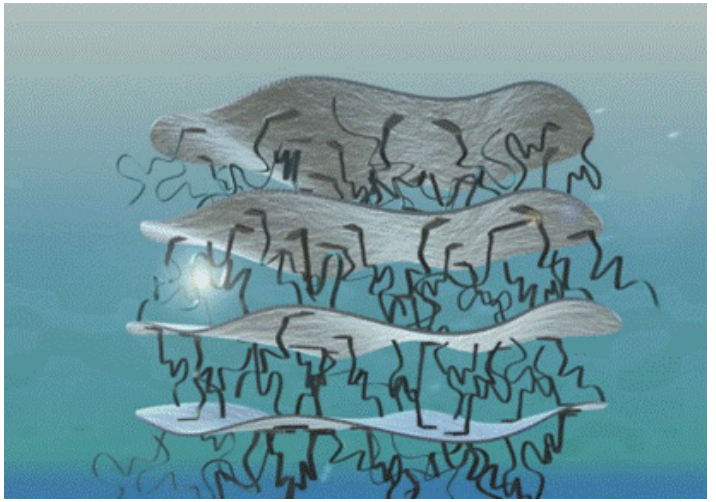

Thank you

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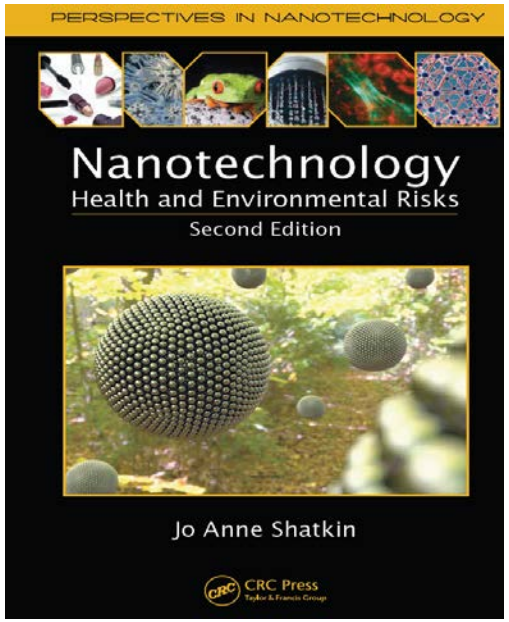

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