Hazards, Exposures, and Risks Associated with Engineered Nanomaterials

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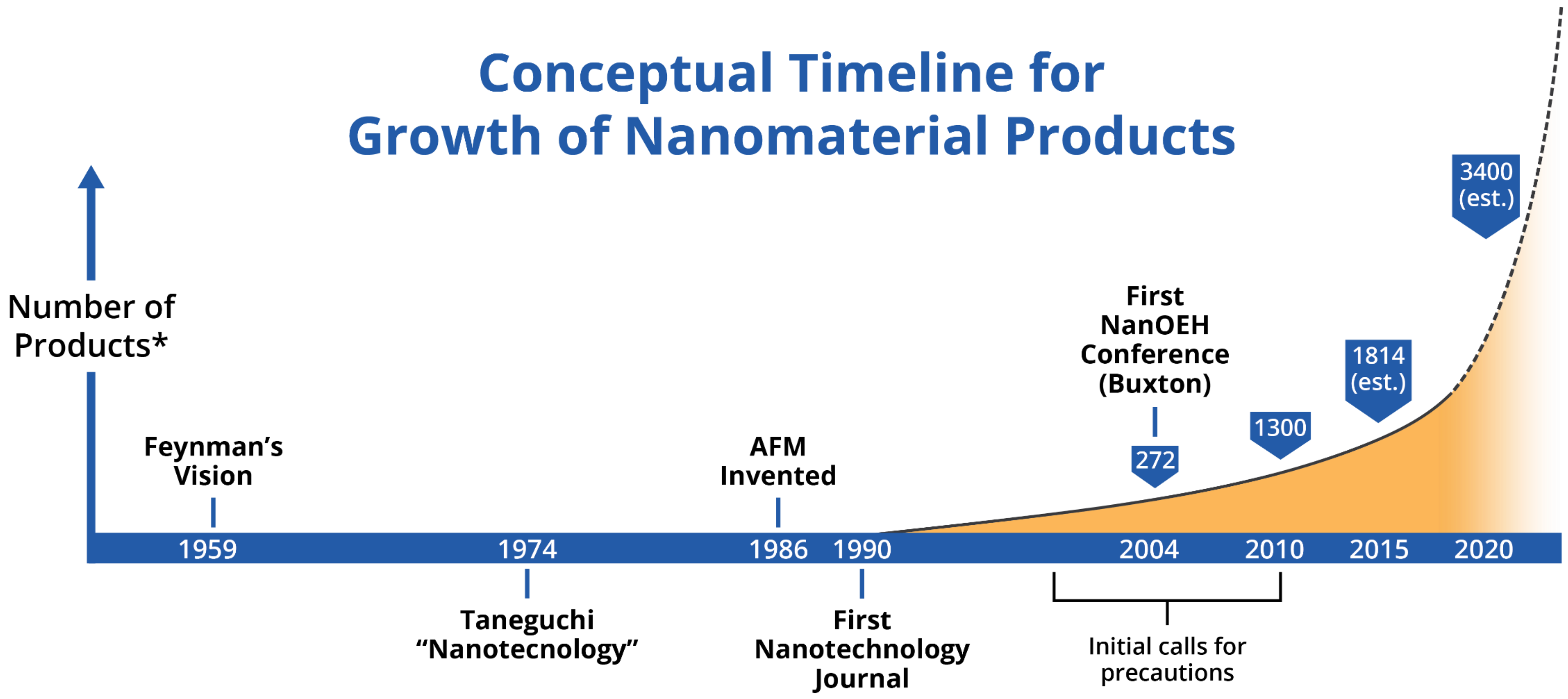
Conceptual Timeline for Growth of Nanomaterial Products



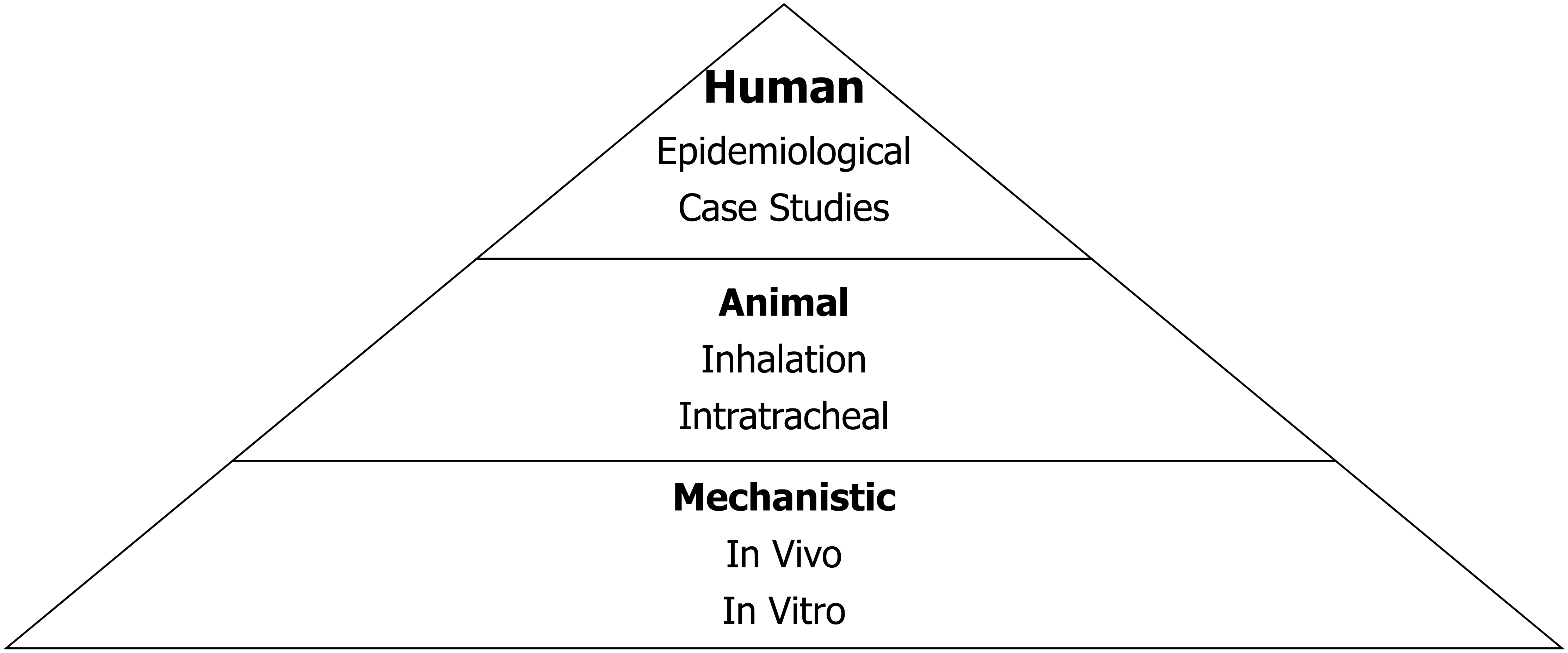
*Number of Products on the Wilson Center Project Emerging Nanotechnologies Inventory

Hazards

Identification of adverse effects engineered nanomaterials (ENM) is a function of

- Whether these effects exist
- Whether they have been studied

Hierarchy of information related to human health effects from nanomaterial exposures



Summary of Epidemiological and Animal Data for ENMs by Commercial Volume

Nanomaterial	Commercial Tonnage (Tons)[1]	Epidemiologic findings pathologic effects in workers	Potential biomarkers of adverse effects in epidemiological studies of workers	Adverse effects in animals[2]
Carbon black	9,600,000			
Synthetic amorphous silica	1,500,000			
Aluminum oxide	200,000			
Barium titanate	15,000			
Titanium dioxide	10,000			
Cerium dioxide	10,000			
Zinc oxide	8,000			
Carbon nanotubes/nanofibers	100-3000			
Silver nanoparticles	20			

1. Based on WHO report (2017)

Figure 2. Flow chart for inclusion of epidemiologic/human case studies

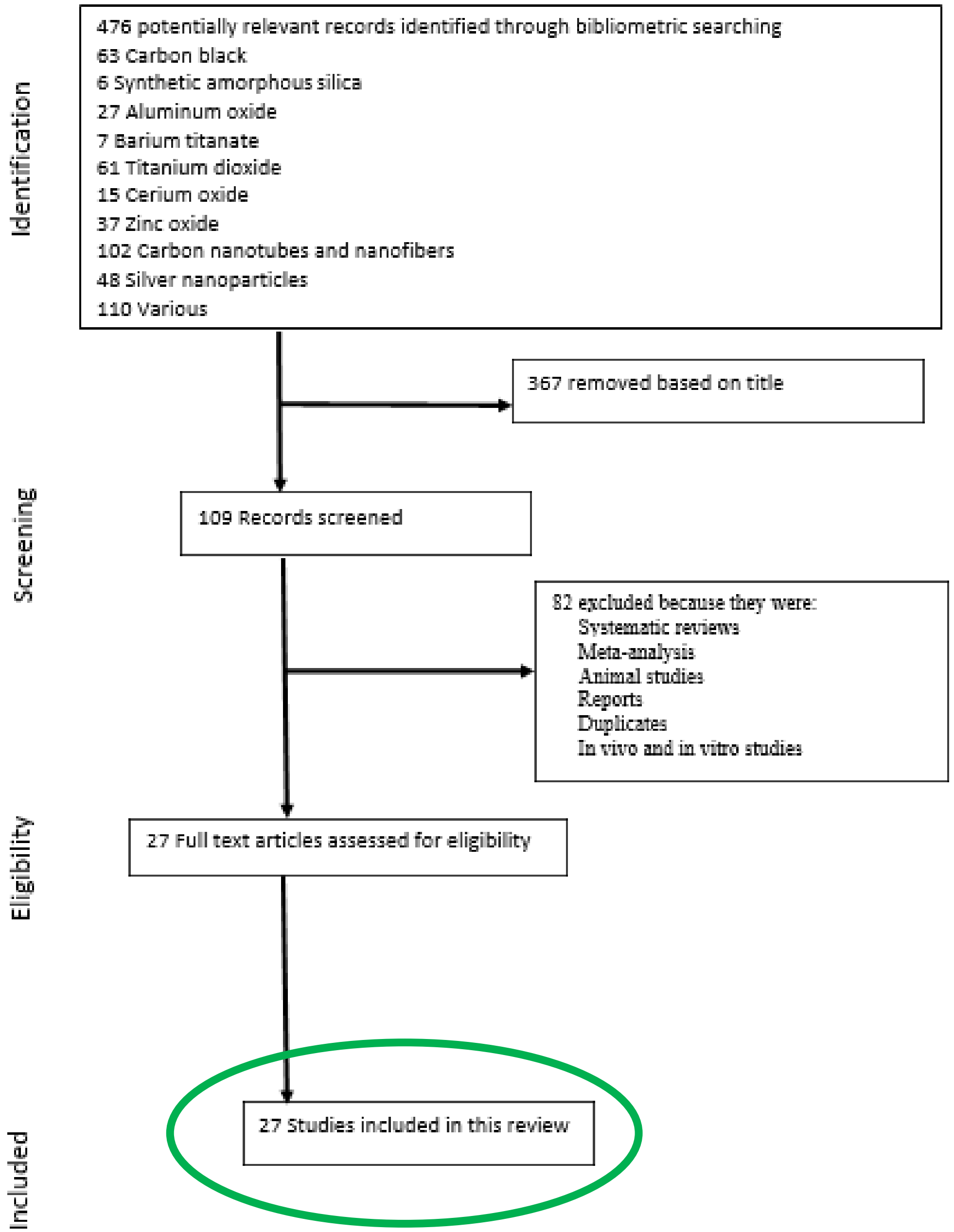
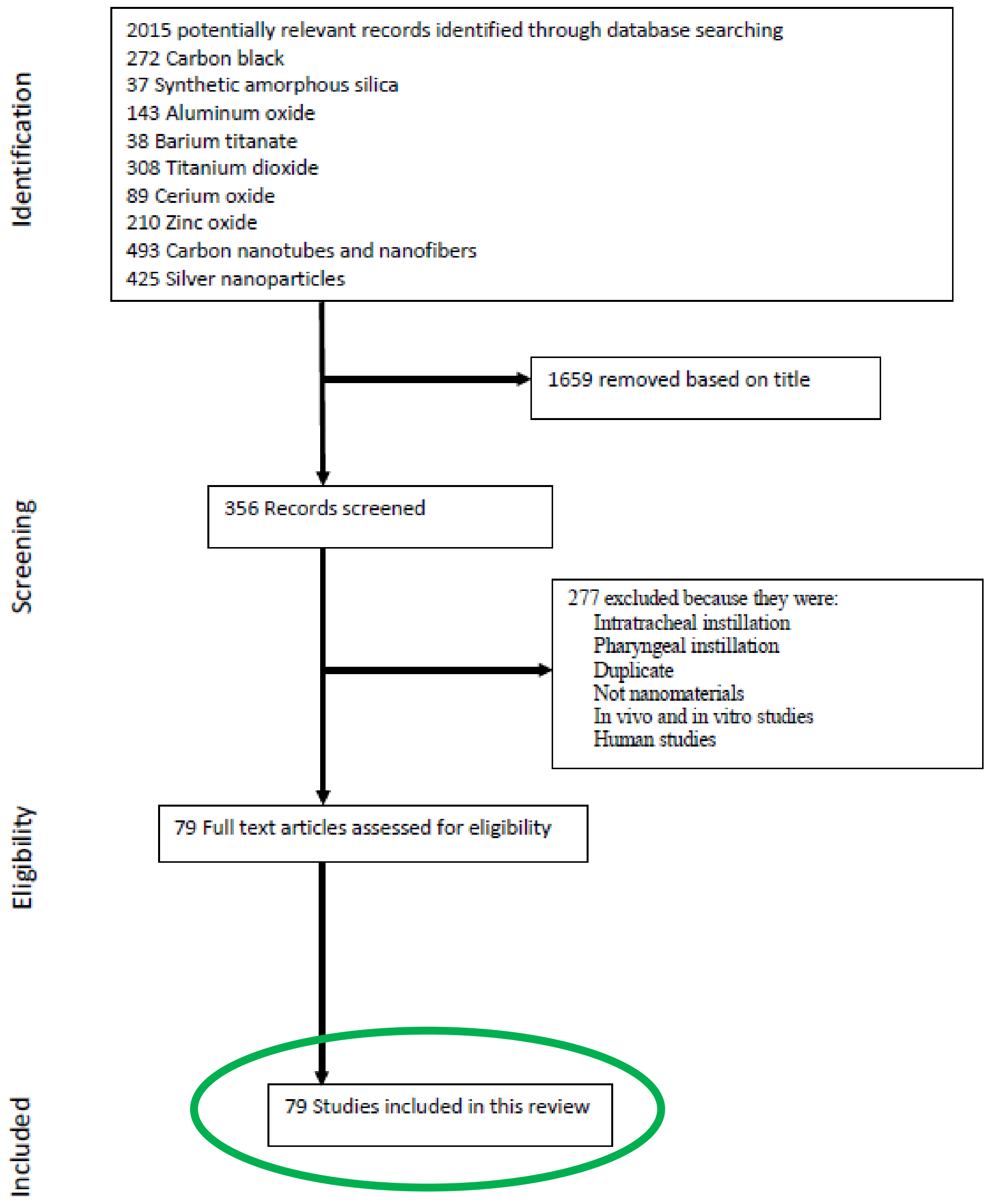


Figure 3. Flow chart for inclusion of animal studies



Summary of Epidemiological and Animal Data for ENMs by Commercial Volume

Nanomaterial[a]	Commercial Tonnage (Tons)	Epidemiologic findings pathologic effects in workers	Potential biomarkers of adverse effects in epidemiological studies of workers	Adverse effects in animals
Carbon black	9,600,000	++++ Nonmalignant respiratory disease	+ + Pulmonary function; +++Pulmonary inflammation	+ + +Lung cancer; + + ++ Pulmonary inflammation
Synthetic amorphous silica	1,500,000	n.a.	+++ Oxidative stress ++ DNA methylation	++ NMRD +++ Fumed silica
Aluminum oxide	200,000	n.a.	n.a	+++ Pulmonary inflammation
Barium titanate	15,000	n.a.	n.a.	n.a
Titanium dioxide	10,000	+ Lung cancer + NMRD	+++ Inflammatory and oxidative stress ++ Pulmonary disease +++ Cardiovascular disease	+ + + + ROS and pulmonary inflammation ++ Genotoxicity +++ Lung cancer
Cerium dioxide	10,000	n.a.	n.a.	+++ Pulmonary inflammation; fibrosis
Zinc oxide	8,000	+++ Metal fume fever	n.a.-	+ + + Acute inflammatory change
Carbon nanotubes/nanofibers	100-3000	n.a.	+ + + Pulmonary Immunological, Cardiovascular ++ Gene-specific DNA methylation	+ + + + Pulmonary inflammation + + + + Fibrosis + + + Cardiovascular +++/++++ Cancer (MW-CNTs7)
Silver	20	n.a.	n.a.	+ + + Pulmonary inflammation + + + Liver effects including bile duct hyperplasia

n.a. = not available
a: list in table by tonnage

Major types of adverse effects found in epidemiologic studies

- Decrement of pulmonary function
- Pulmonary Inflammation
- Oxidative stress
- Cardiovascular changes

What do these epidemiologic findings mean?

- Limited evidence of adverse health effects
- However biomarker identification may be indicative of preclinical or subclinical changes that could be linked to future disease or dysfunction
- Need for robust longitudinal epidemiological studies
  - Clear exposure assessment
  - Use of same core group of biomarker

Exposures

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REVIEW

A Systematic Review of Reported Exposure to Engineered Nanomaterials

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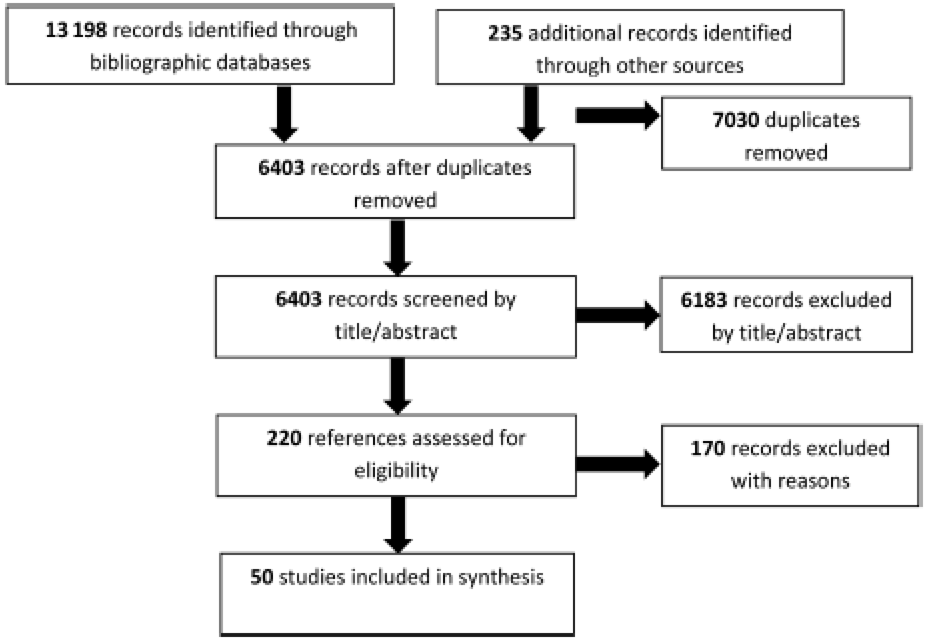
Literature Strategy for Systematic Review of Exposure to ENM



(Debia et al 2016)

- High quality evidence
  - Single-walled CNTs
  - CNFs
  - Aluminum oxide
  - Titanium dioxide
  - Silver NPs
- Moderate quality evidence
  - Silicon dioxide NPs
  - Non-classified CNTs
  - Nanoclays
  - Iron
- Low quality evidence
  - Fullerence C60
  - Double-walled CNTs
  - Zinc oxide NPs
- No evidence
  - Cerium oxide NP

(Debia et al 2016)

- High quality evidence
  - Potential exposure is most frequently due to handling tasks
  - Workers mostly exposed to micro-sized agglomerated NP.
  - Engineering control, considerably reduce workers' exposure
  - Multiwalled carbon nanotubes (CNTs)
- Moderate quality evidence
  - That workers are exposed in secondary manufacturing industrial scale plants
- Low quality evidence
  - That workers are exposed to airborne particles with a size <100 nm

(Debia et al 2016)

Risks

Risk assessment

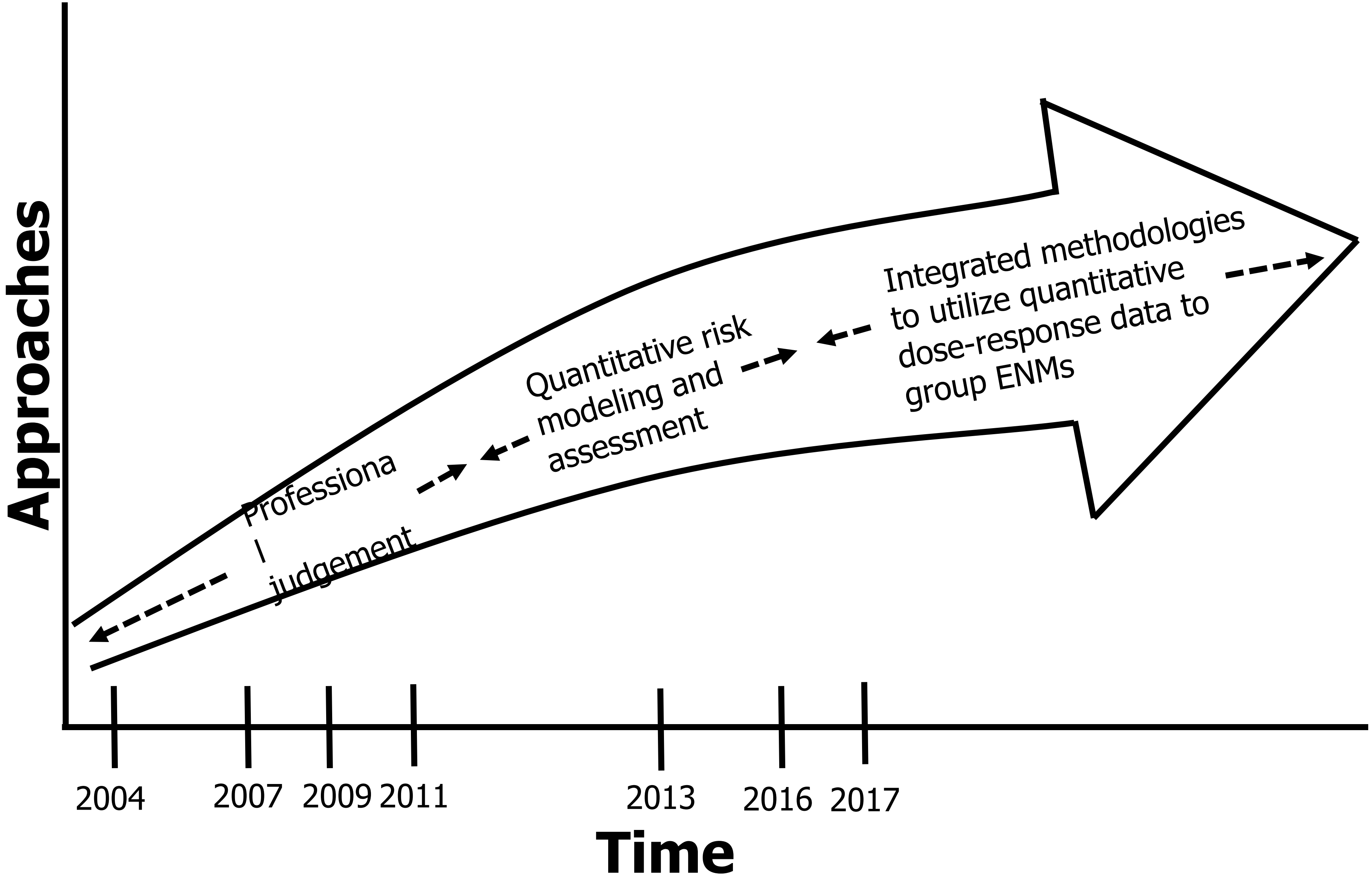
- Tool for society and decision-makers when **complete** information on risk is **not known**
  - When social policy decisions are in dispute
  - When consequences of options are not subject to direct measurement
  - When scientific analysis of a hazard is incomplete

(Hattis and Silver 1993)

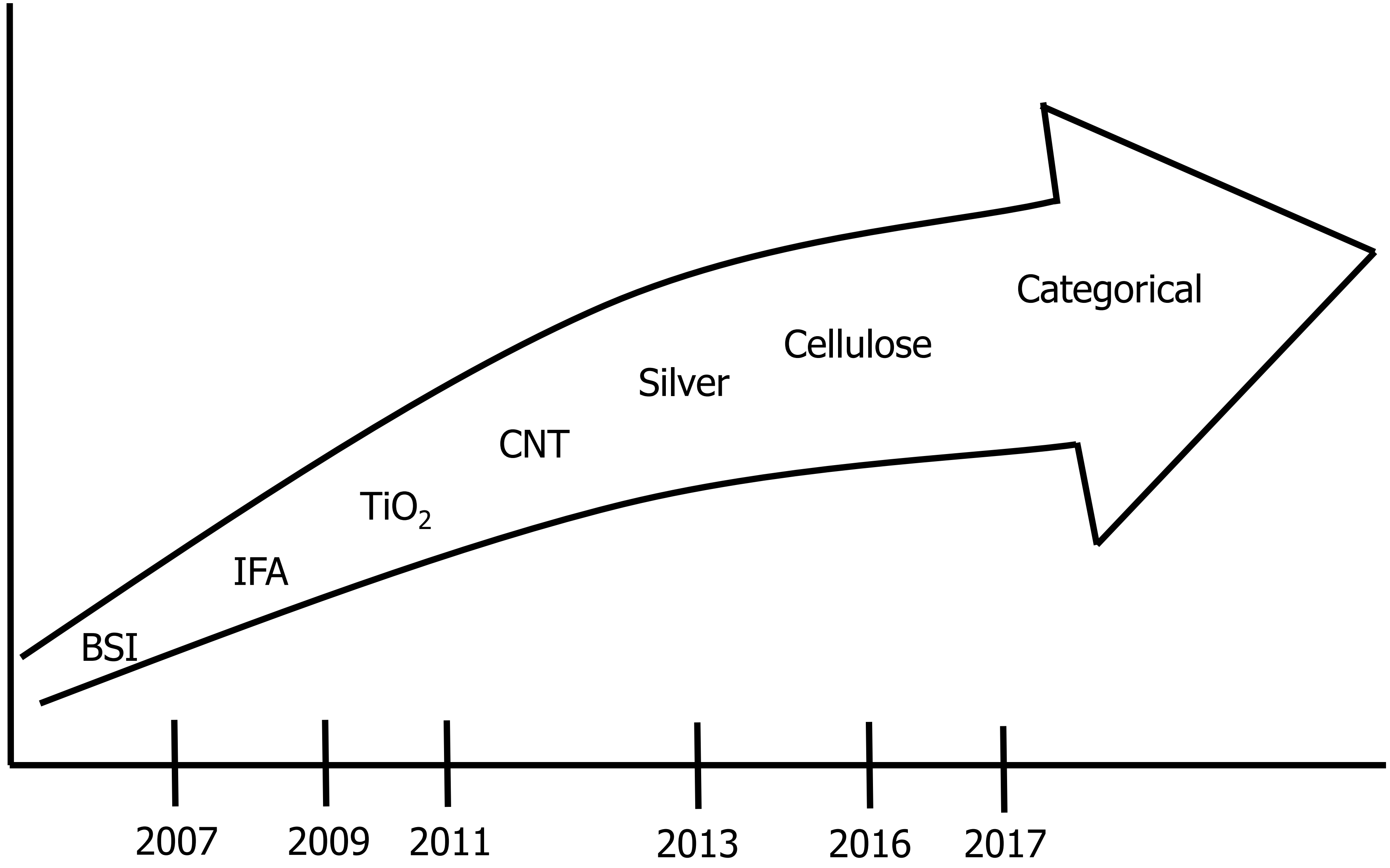
Protection of Workers

- Responsible development of a technology, such as nanotechnology requires that workers be protected from harm.
- There is a need to assess the risks of harm to workers.
- There is a need to use that risk assessment to be the basis for occupational exposure limits (OELs) and other risk management efforts to protect workers.

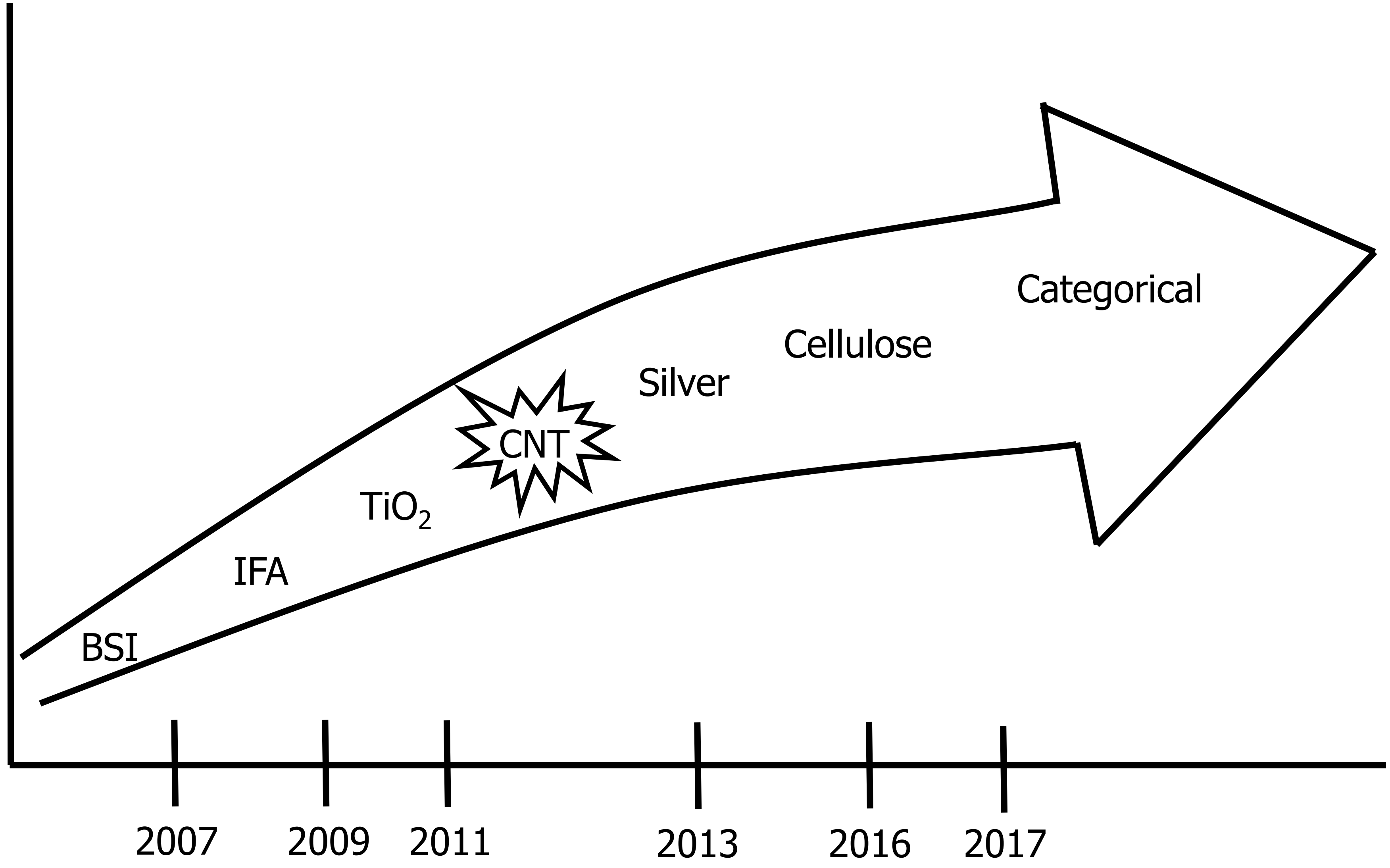
Eras of risk assessments and OEL development for nanomaterials

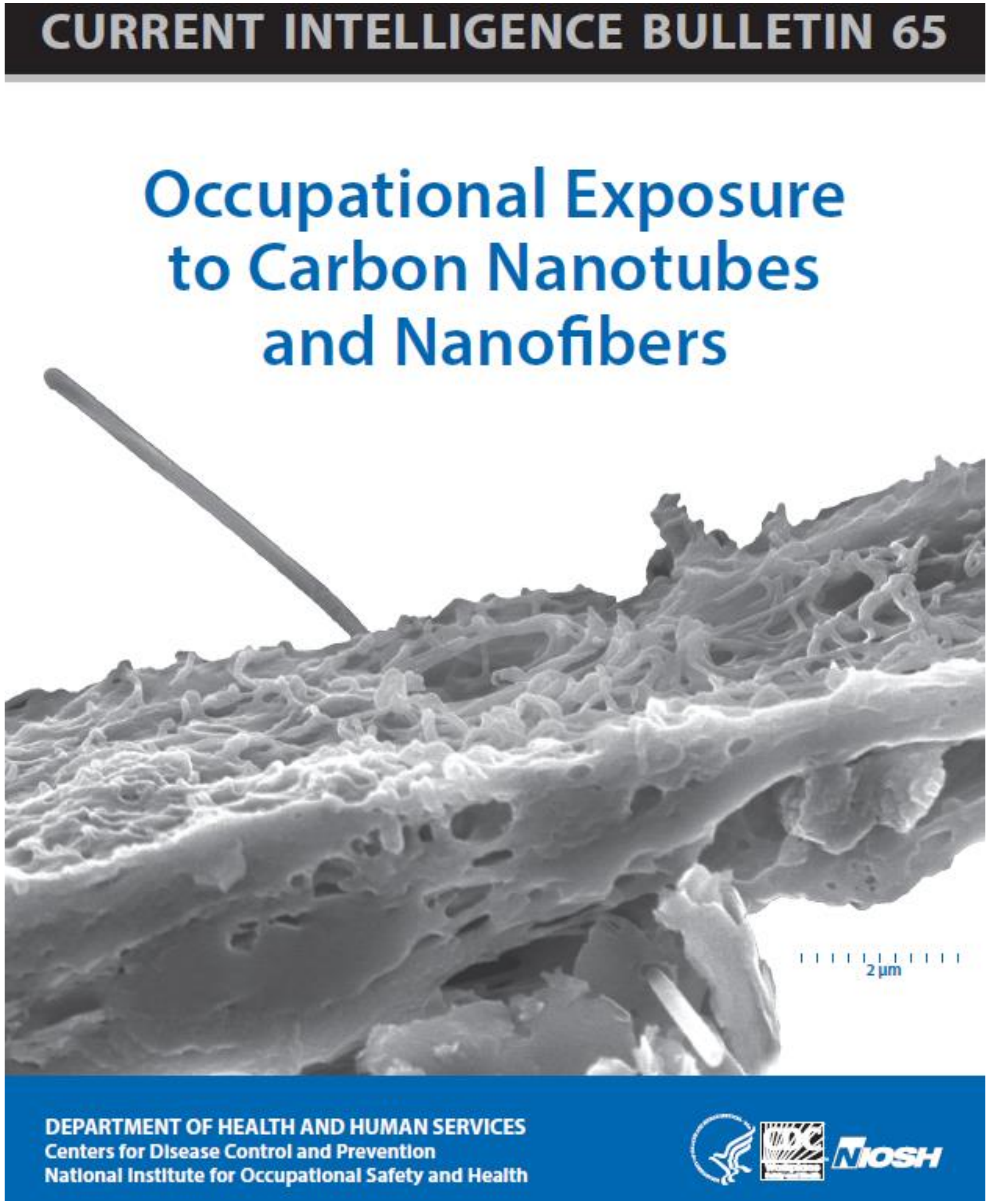


Trajectory of risk assessments and OEL development for nanomaterials



Trajectory of risk assessments and OEL development for nanomaterials





SWCNT
Public draft—2010
Published 2013

Rationale for Development of CIB

- Several animal studies showed pulmonary fibrosis (early onset, persistent) and granulomatous inflammation from carbon nanotube (CNT) exposure
- Associated with both unpurified and purified CNT (raw metal contaminated)
- Effects occurring at relatively low mass dose
- Some of CNT shown to persist and migrate to pleura
- Genotoxic effects include aneoploidy

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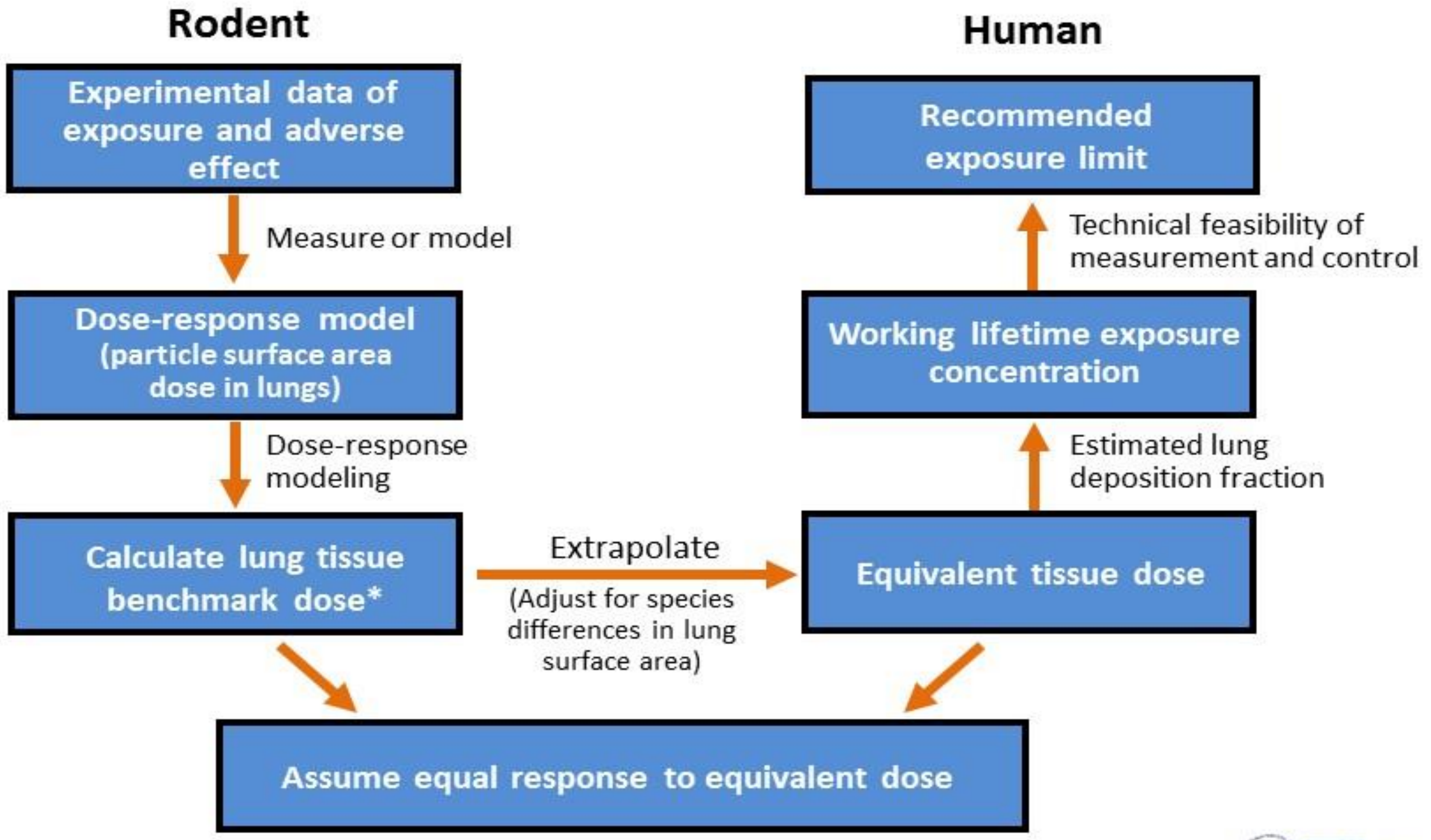
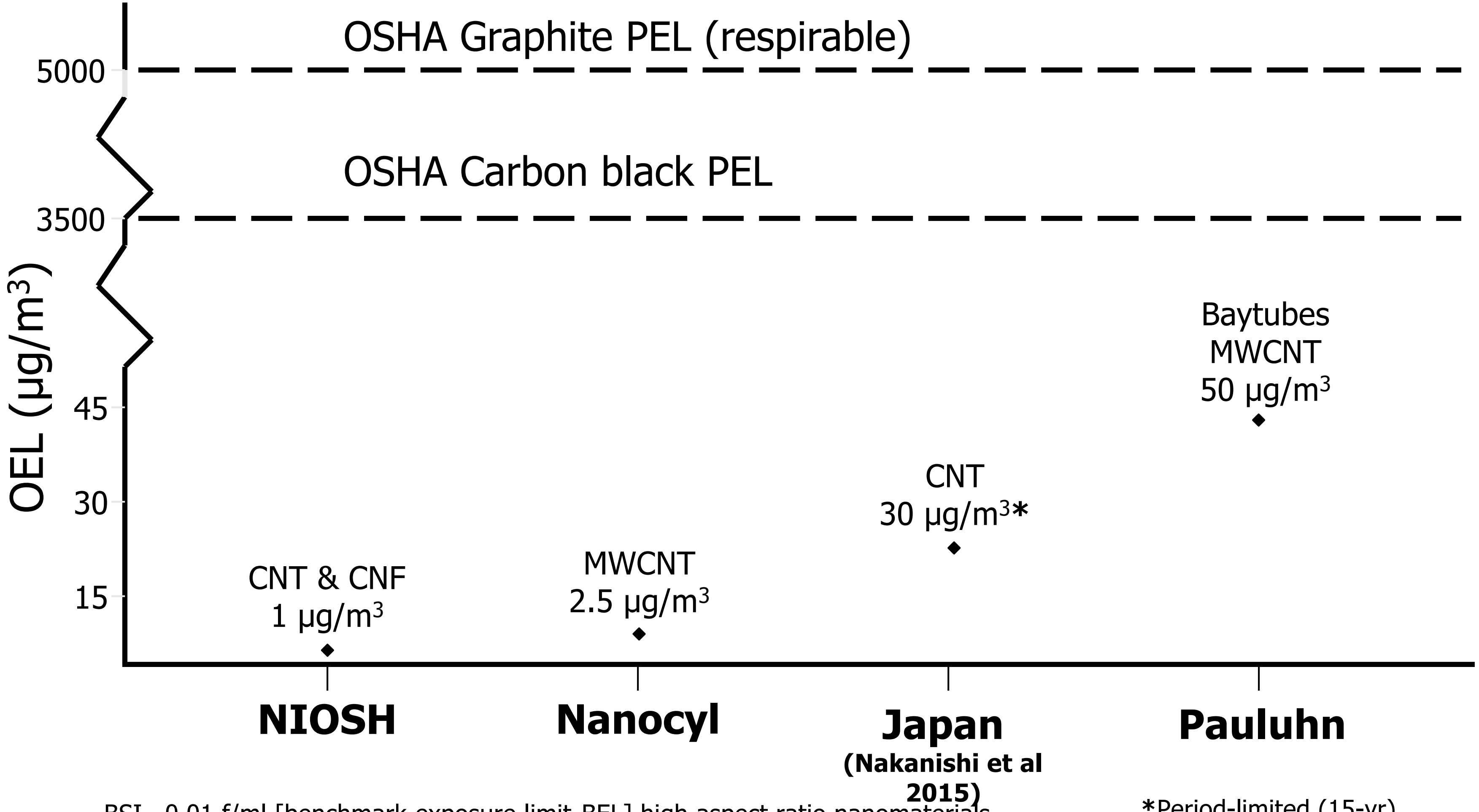
Quantitative Risk Assessment in Developing Recommended Exposure Limits for Inhaled Particles



*Dose associated with specified level of risk.

[Oberdörster 1989; Kuempel 2011; NIOSH 2011]

Perspective on OELs for Carbon Nanotubes

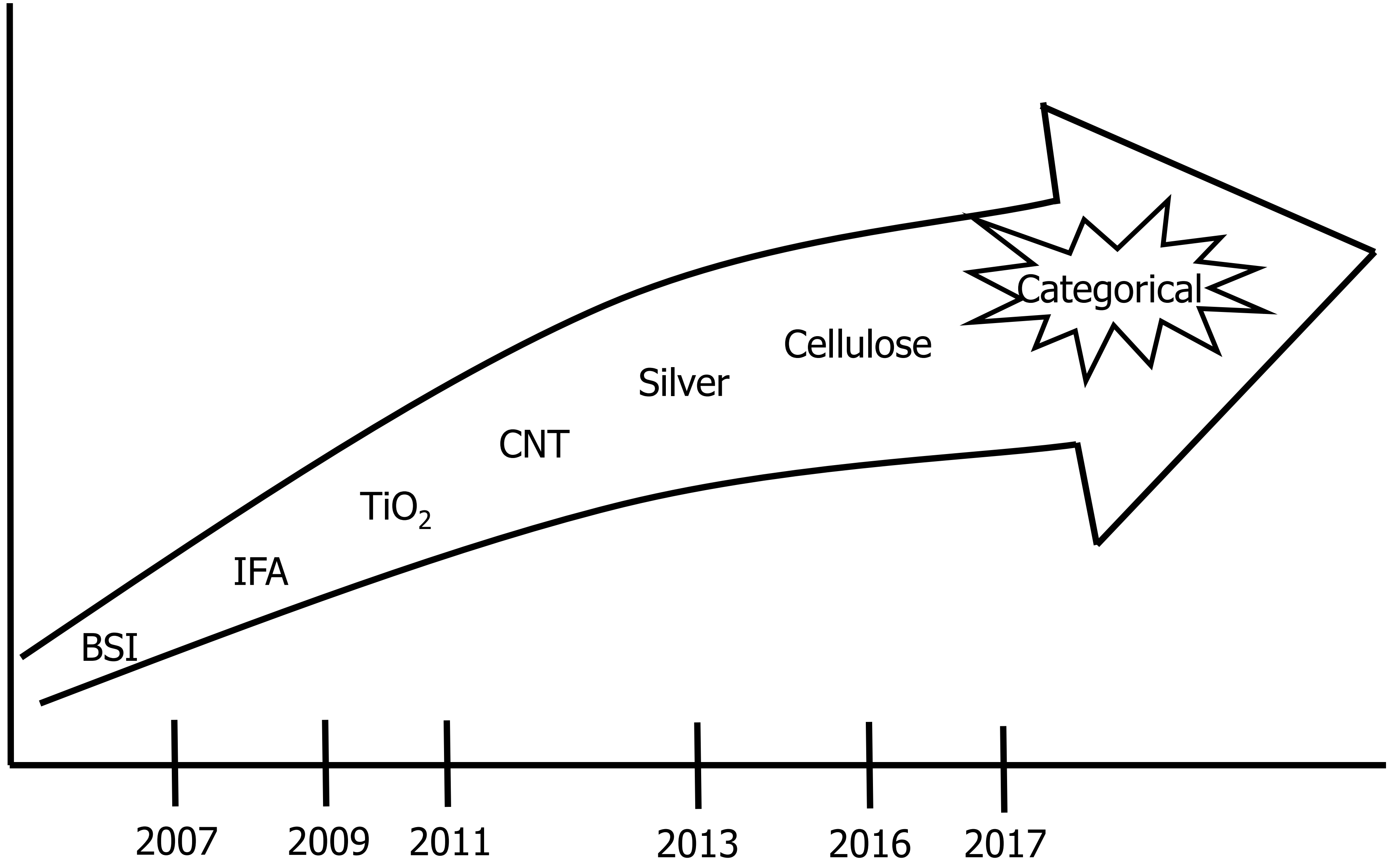


*Period-limited (15-yr).

BSI—0.01 f/ml [benchmark exposure limit-BEL] high aspect ratio nanomaterials –established at 1/10 asbestos OEL

Risk assessment use organic mass carbon practice continued

Trajectory of risk assessments and OEL development for nanomaterials



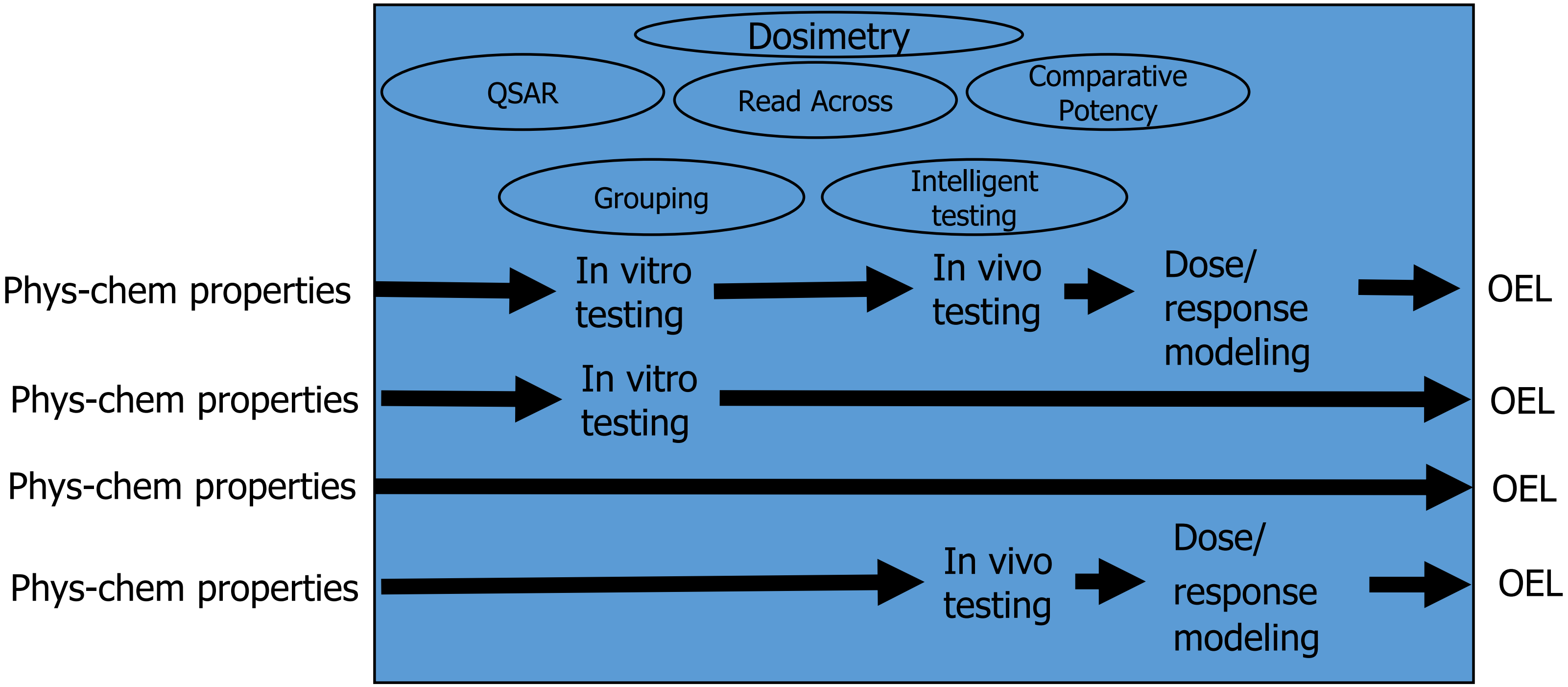
Frontier of Risk Assessment For ENM OEL Development

Standard Approach

Untested ENM → Hazard Info → Dose/response modeling → OEL

Innovative Approaches

Untested ENM - - - ? - - - → OEL



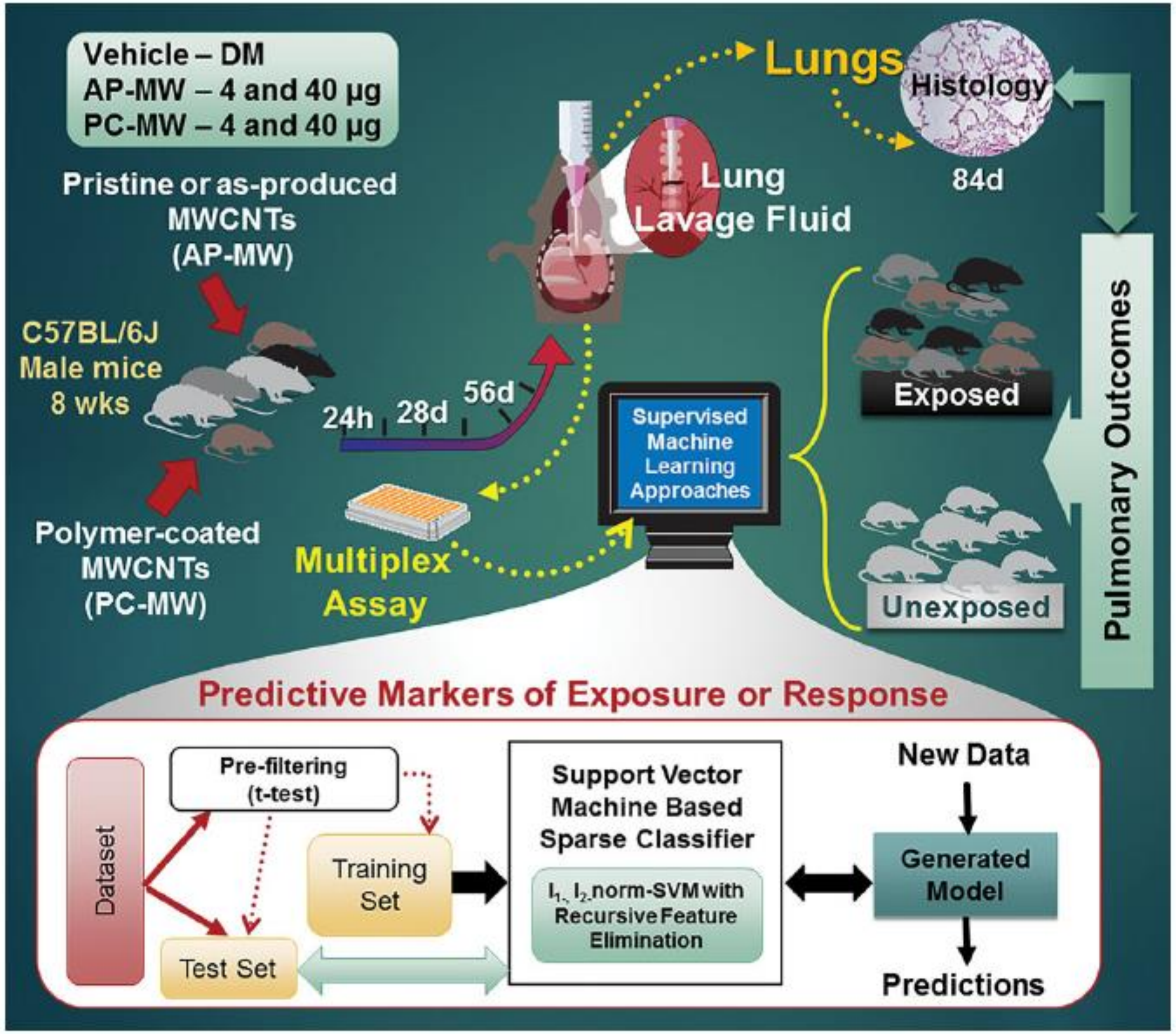


Figure 1. Schematic representation of the overall objective and study design.
Note. DM = dispersion medium; MWCNT = multiwalled carbon nanotube; AP-MW = as-produced MWCNT; PC-MW polymer-coated MWCNT.

(Yanamala et al 2018)

Submersion vs. Air-liquid Interface Culture Systems

Traditional

Submerged Cells

Uncertain Delivery Dose

Usually Non-confluent Cell Layer

Medium-Particle Interactions

Promotes Dissolution*

Air-Liquid Interface

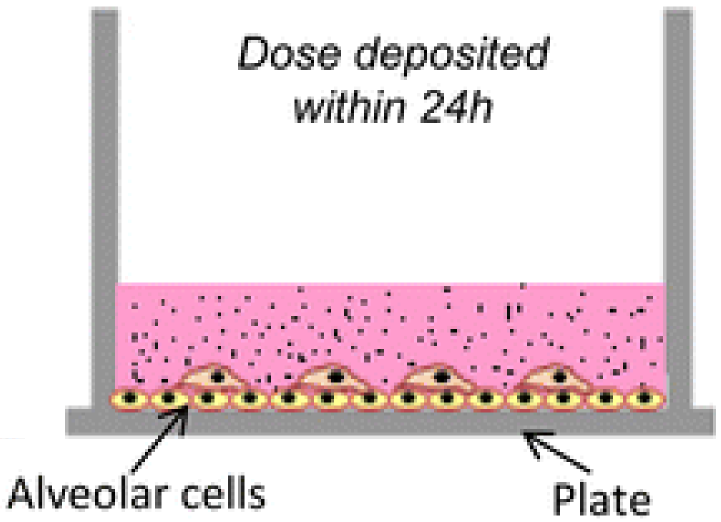
Physiological Interface

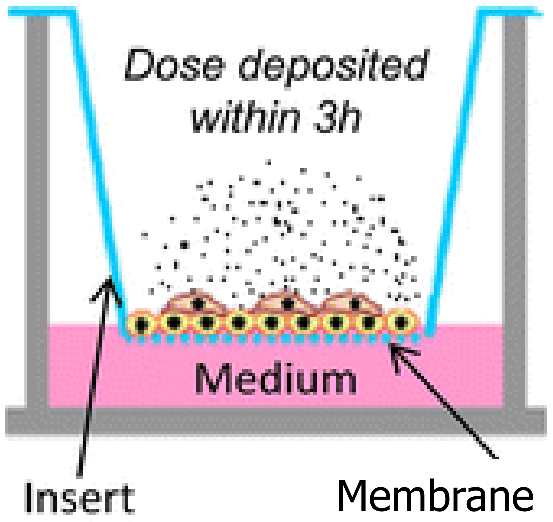
"Dry" Deposition

Dose Characterization

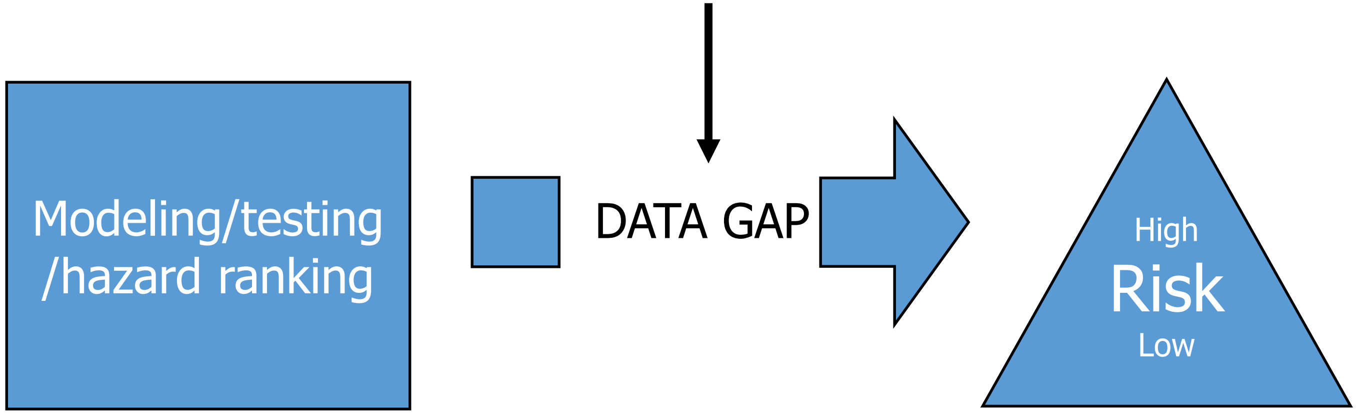
Usually Confluent Cell Layer

Minimal Dissolution Potential*





Gap between modeling/testing and risk level



Data Gap Issues

- ❑ Heterogeneity of the data
  - e.g. methodologic differences of tests and assays
- ❑ Uncertainty about relevance of early response endpoints to human health risk assessment
- ❑ Limited chronic exposure data
- ❑ Lack of minimum data reporting requirements
- ❑ In vitro to in vivo dose-response extrapolation

Thank You!

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