Practical Application to Regulatory Toxicology: Issues Faced in Consideration of Developing Health Guideline Values (HGVs)

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Conflict of Interest Statement

- This presentation has been reviewed by US Consumer Product Safety Commission (CPSC) staff, but the opinions expressed are my own. The presentation has not been reviewed or approved by the Commission and may not represent the views of the Commission or CPSC staff.

Objectives

- Address real-world challenges associated with nano assessments from both exposure and hazard perspective
- Highlight key questions
- Present a bold proposal for thinking differently about (nano) research

A Confession

I’m not conflicted…

But I do have a specific perspective

I value basic science, but I really want to see the studies that address the fundamental questions that I need to answer as a risk assessor.

Health-Based Guidance Values (HBGVs) for Nanomaterials (NMs)–There Appears to Be a Need

- Regulatory awareness
  - Regulatory programs (e.g., TSCA, REACH, FIFRA, ANSES, FHSA) regulate NMs in commerce, may require labels for nanomaterial use, and may ban "NM" in foods.
- Research funding
  - International and national programs have been requiring or funding the development of dossiers for NM safety evaluation for more than 15 years.

- **TSCA** US EPA Toxic Substances Control Act; **REACH** EU Registration, Evaluation, Authorisation and Restriction of Chemicals; **FIFRA** US EPA Federal Insecticide, Fungicide, and Rodenticide Act; **ANSES** French Agency for Food, Environmental and Occupational Health & Safety; **FHSA** Federal Hazardous Substances Act

Availability of HBGVs for NMs–Why Are There so Few?

Searches for regulatory HBGVs show very few overall and none for oral exposure

Is this because there is no need?

Is it too difficult?

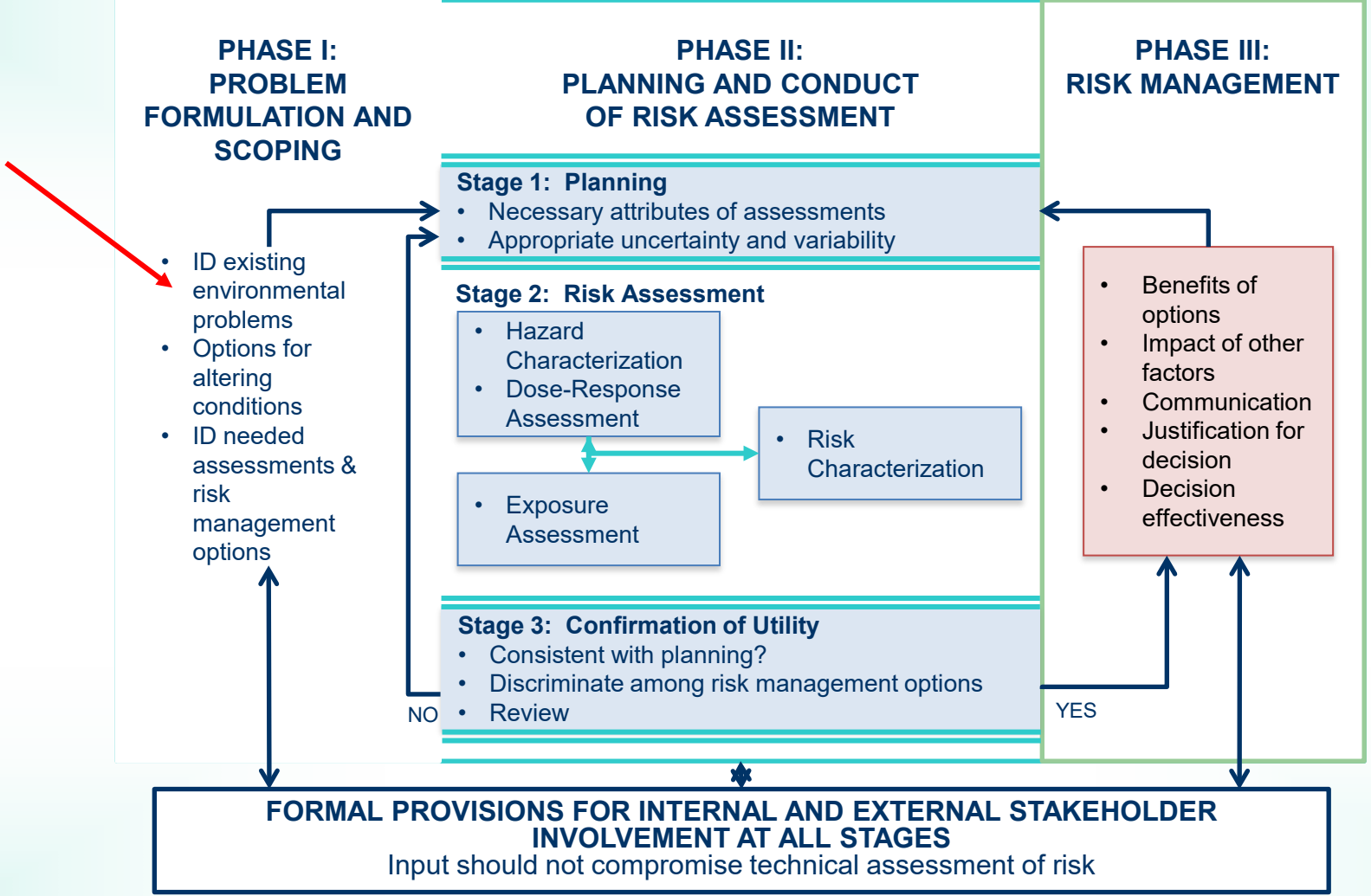
Or have we failed in developing the right data?

The Challenge

- Thousands of publications on nanomaterials
- Large sums of money spent
- Yet often fundamental questions remain

- For example: Is x nanomaterial a reproductive toxin?
- Good quality guideline compliant studies of 70 nm sized commercial NM are negative.
- Several studies with 5-10 nm particles of the same NM found adverse reproductive effects after evaluating selected endpoints.

How should I integrate the data?



(Adapted from NRC, 2009)

Key Questions

- What is the appropriate dose metric?
- Can I group related types of nanomaterials? Or does each one need to be evaluated separately?
- What are the key determinants of toxicity?
  - Impacts of surface coatings, functionalization
- How do we correlate toxicity and exposure?

Importance of Nanomaterial Characterization

- Primary particle size
- Hydrodynamic size and polydispersity index when in liquid form, aerodynamic diameter (MMAD, GSD) for aerosols
- Purity
- Zeta potential

- Commercial vs. laboratory-synthesized
  - Challenge of interpreting relevance to human exposure of non-commercial NM preparations

Weight of Evidence Challenges

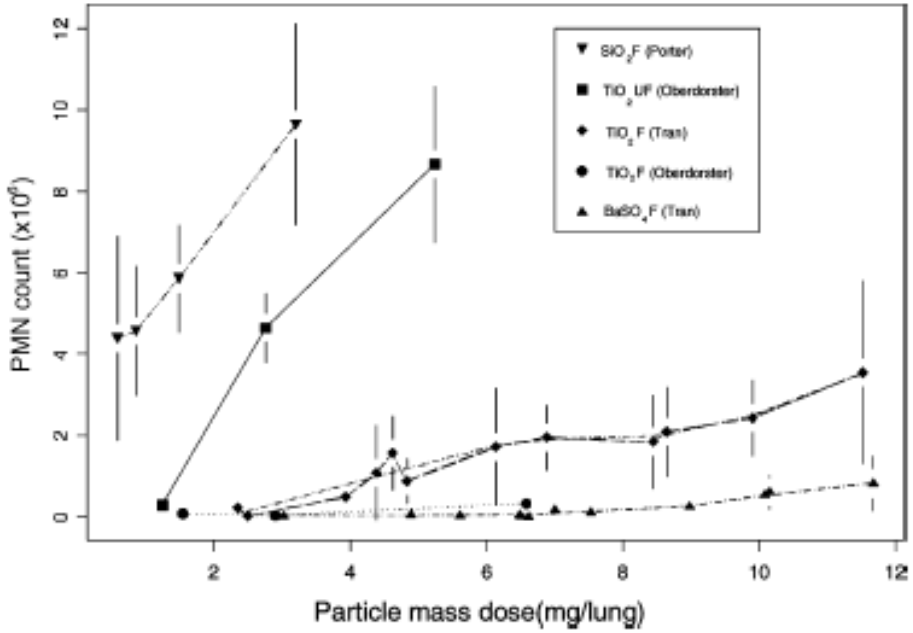
Of 14 subchronic-chronic oral studies evaluated for one NM:

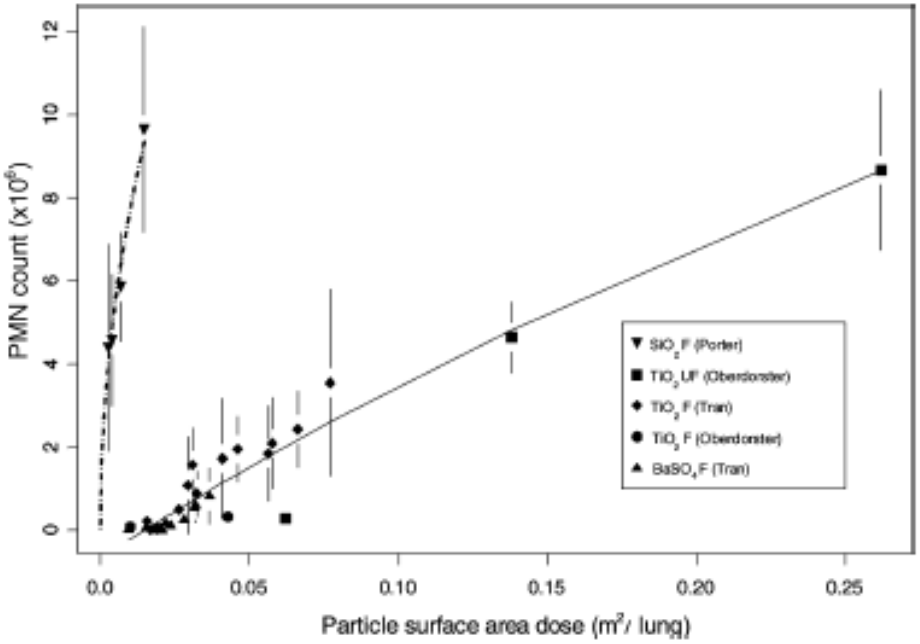
- 9 had inadequate NM characterization
- 13 evaluated some subset of a standard toxicity study design
  - Some evaluated standard endpoints (body weight, organ weight, histopathology) as part of mechanistic evaluation, but often lacked standard array for weight of evidence)
  - Many focused on mechanistic endpoints
- 5 different manufacturers, 8 tested non-commercial material
- 5-80 nm primary particle size
- 5-40/sex/dose; top dose 0.1-1200 mg/kg-day
- 3 tested a single dose (plus control)

Options for a Health-Based Guidance Value

- Use the most sensitive/conservative (worst case scenario)
  - How do we ensure that the result is meaningful?
- Throw out the poor-quality studies and use the most conservative
  - Criteria for inclusion/exclusion of studies?
- Use a weight of evidence approach on studies meeting minimum criteria
  - May need to define the NM characteristics to which the calculated guidance value applies

Comparing Mass and Surface Area as Metrics

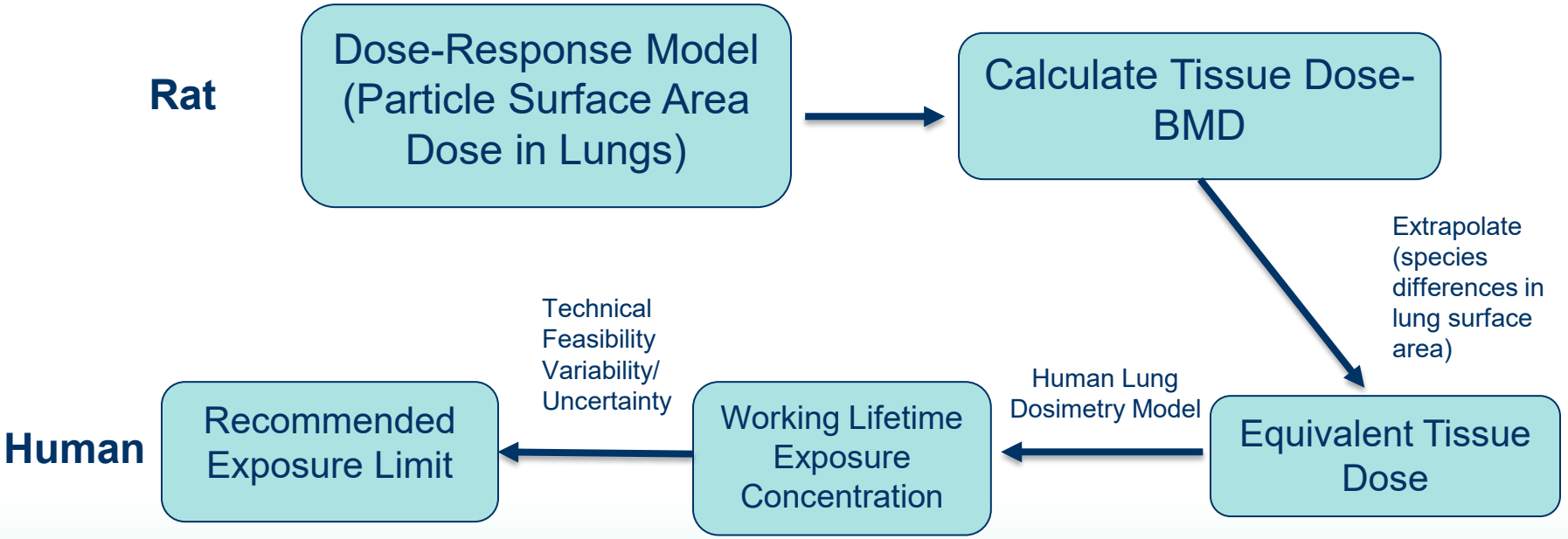




From Dankovic et al., 2007

Case Study–TiO_2–NIOSH 2011

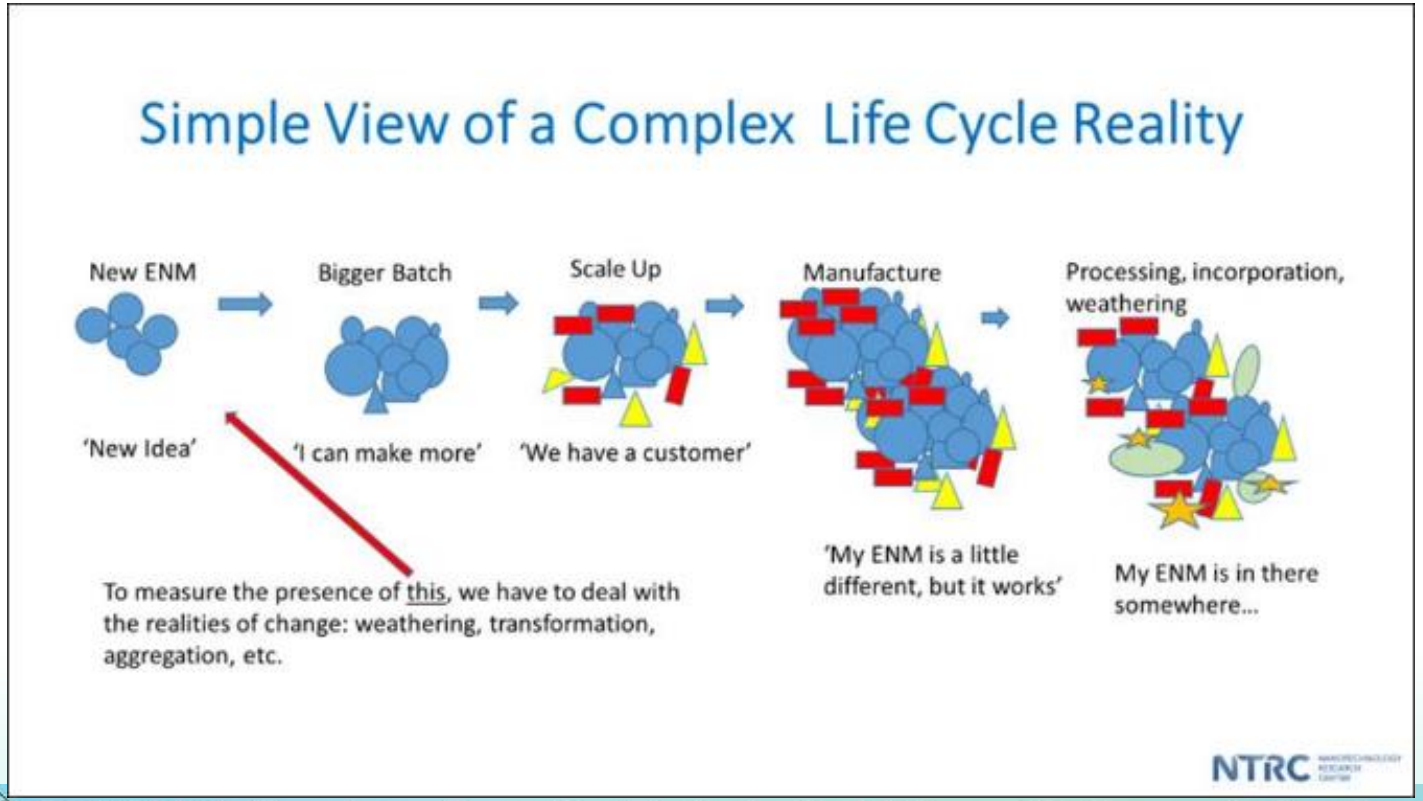
Adapted from Fig. 4-1



In an Ideal World… (according to Lynne)

- Coordinated consortia designing “fit for purpose” testing
  - Well-characterized test material
  - Standard and standardized test protocols
  - Systematically vary one parameter at a time (recognizing that is hard)
- But it’s been done (OECD, Japan METI, NanoReg, US NTP)–what else is needed?
  - Publications with negative results are as valuable as those with adverse effects–if tested according to guideline up to limit dose.
  - Funding organizations need to recognize necessity of dose-response evaluation.

Exposure is Not Only to the Primary Nanoparticle



ENM = engineered nanomaterial

Provided by Charles Geraci, NIOSH

What is the Actual Nature of the Exposure?

- If in an enclosed compartment in the product material, release may be contained and there may be no exposure.

- Need to consider what is actually released from the product
- Example: matrix with embedded NM
  - Relative resilience of matrix and NM important in determining what is released
  - No exposure until abraded or weathered and released
  - For carbon nanotubes (CNT) in a less resilient matrix, released material is a mixture of matrix w/o CNT, CNT embedded in polymer but protruding, polymer with CNT fully embedded, and agglomerated CNT.
- CNTs embedded in matrix may be too large to inhale.

You've Developed a HGV–Now What?

- How broadly can it be applied?
- How should exposure be measured?
- Other size categories? How many size categories are needed?
- Does it apply to forms with surface functionalization or coatings?
- Other shapes?

➢ Key determinants of toxicity – what matters, what doesn't?

Recommendations/Wish List Going Forward

- Systematic evaluation of key determinants of toxicity
  - Nice work done on surface area, but not on other variables
  - Some systematic work has been done *in vitro*, but the *in vivo* relevance is not always clear–differences in kinetics, including biocorona formation
- Need testing with standardized set of assays
  - Difficulty in comparing across studies
- Need for coordinated testing strategy
  - Recognizing the challenge of varying only one characteristic

A Path Forward

- Several groups have developed grouping and read-across methods (reviewed by Lamon et al., 2019)
  - Grouping for hazard, based on phys-chem properties, limited information on standard methods
  - Occupational banding tools
  - Ranking–based on individual assays (e.g., cytotoxicity, comet assay)
- OECD has developed nano-specific test guidelines (Rasmussen et al., 2019)

- *In vivo* dose-response ultimate goal, but not there yet

Summary

- NM characterization is key in evaluating study quality and comparing studies.
- Development of HGVs needs to consider the appropriate dose metric – but work-arounds generally are needed, due to practical difficulties associated with best metrics.
- Consistent testing is needed to identify key determinants of toxicity.
- Read-across methods can aid in hazard characterization, but are less developed for dose-response.

References

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