EPA
United States
Environmental Protection
Agency

Towards an Inhalation IATA for Poorly Soluble, Low Toxicity (PSLT) Polymer Particles

Annie M. Jarabek
Senior Science Advisor

Human Health Risk Assessment Frameworks for Micro- and Nanoplastic
EU CUSP Virtual Workshop
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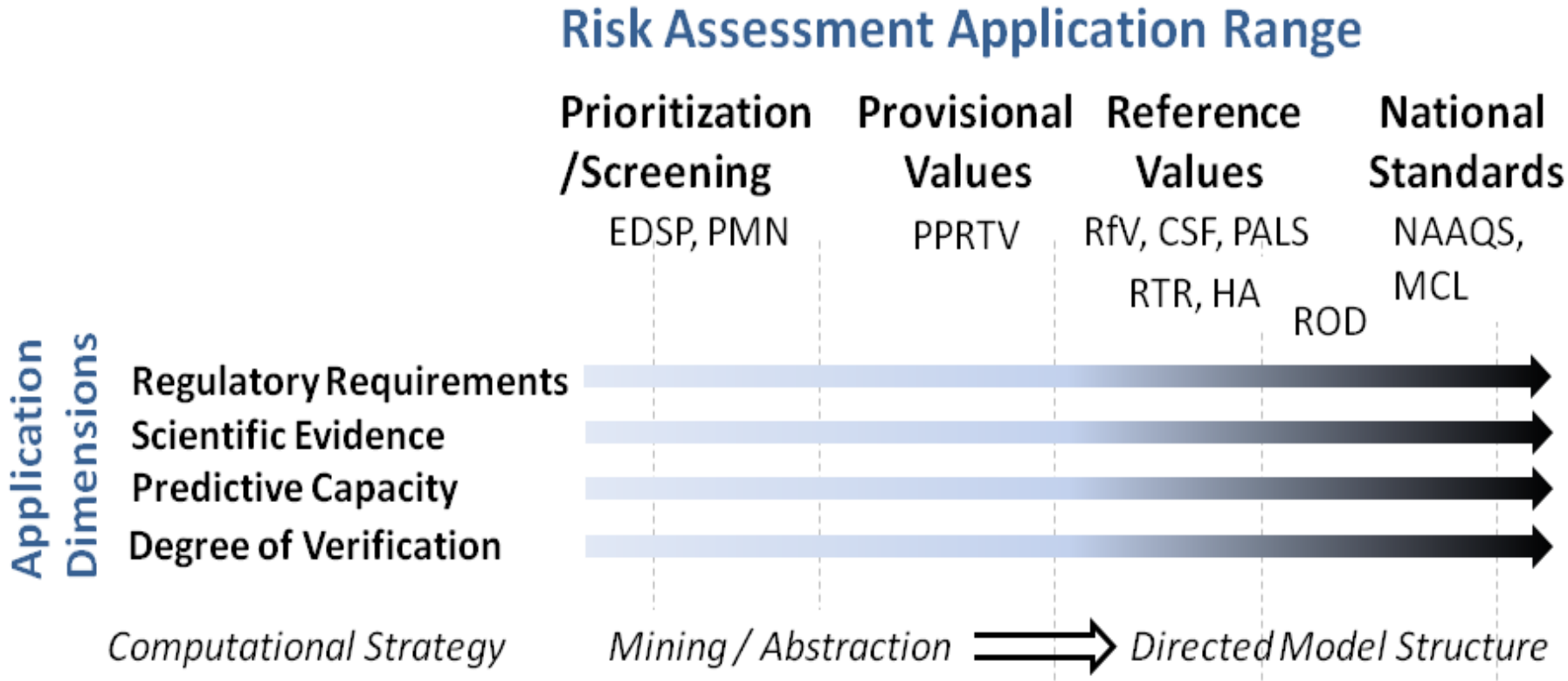
Office of Research and Development
Center for Public Health and Environmental Assessment (CPHEA)

Topics

- **Challenges:** Coherent evidence integration across large landscape of risk assessment applications
- **Modernized workflows:** Conceptual and computational
- **Translations:** Mechanistic modeling and role of dosimetry
- **Building a better battery:** *inhalation* Approach to Testing and Assessment (iIATA) based on dosimetry and NAMs
- **Specific challenges:** Characterizing PSLT particles and emerging evidence on ENM/Ultrafine particles
- **Summary**

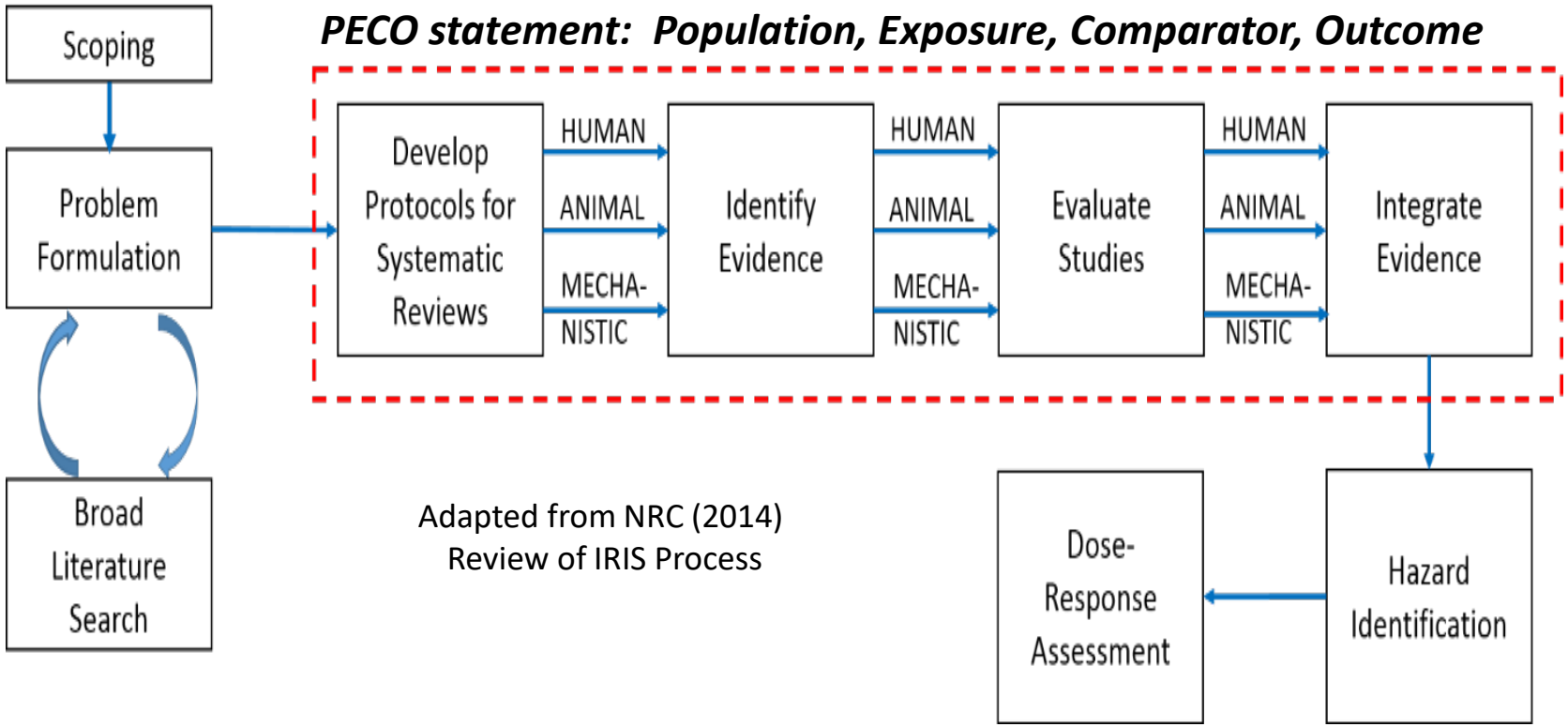
Disclaimer: These views are those of the author and do not represent US EPA policy.

Risk Assessment Landscape



- Problem formulation: Fit for purpose
- Different data sources and strategies across landscape
- ***Mechanistic approach can create coherent context***

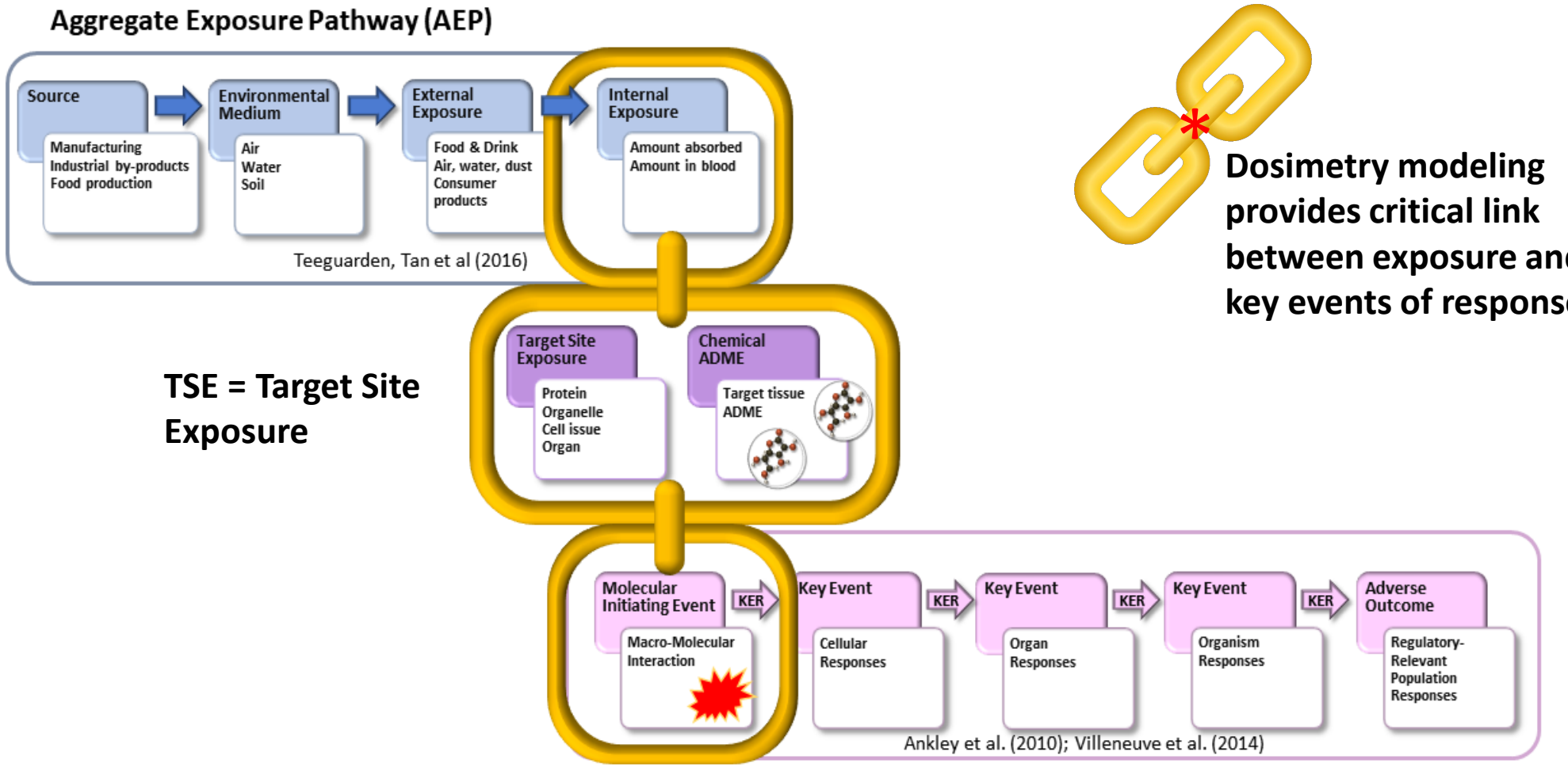
Challenge: Evidence Integration



Adapted from NRC (2014)
Review of IRIS Process

- Diverse exposure systems
- Dose at different levels of biological organization
- Various types of outcomes and modeling approaches
- ***Mechanistic data not considered in an integrated structure***

Transitions: Comprehensive Characterization



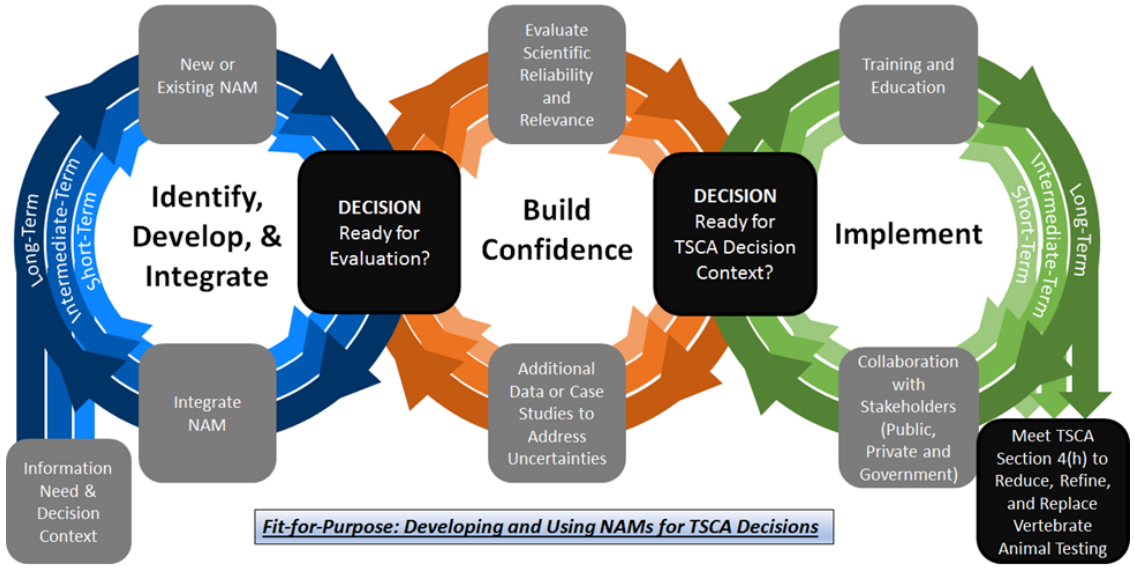
TSE = Target Site Exposure

Dosimetry modeling provides critical link between exposure and key events of response

NAMs: Strategy for Success

- **Strategic plan** components
  - ID, Develop, Integrate
  - Build confidence
  - Implement
- Demonstrated approach for skin sensitization adapted to inhalation
- **Create context** to advance understanding
  - **Target** *in vitro* assays to **evaluate key events**
  - **Bridge acute to chronic** pathogenesis

Fig. 1 Core Components of EPA Strategic Plan to Develop and Implement New Approach Methodologies (NAMs) in TSCA



Toxicology in Vitro 52 (2018) 131–145

Contents lists available at ScienceDirect

Toxicology in Vitro

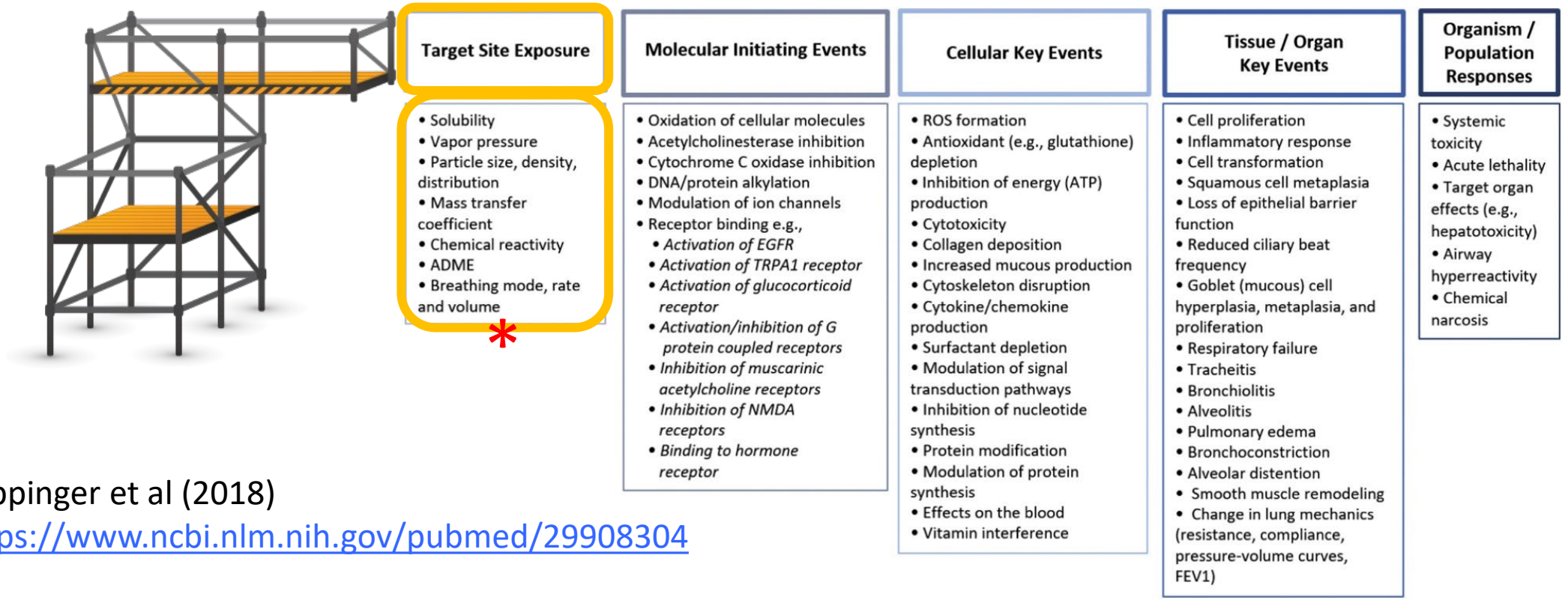
journal homepage: www.elsevier.com/locate/toxinvit

Review

Pathway-based predictive approaches for non-animal assessment of acute inhalation toxicity

Amy J. Clippinger[a,*], David Allen[b], Holger Behrsing[c], Kelly A. BéruBé[d], Michael B. Bolger[e], Warren Casey[f], Michael DeLorme[g], Marianna Gaça[h], Sean C. Gehen[i], Kyle Glover[j], Patrick Hayden[k], Paul Hinderliter[l], Jon A. Hotchkiss[m], Anita Iskandar[n], Brian Keyser[o], Karsta Luettich[n], Lan Ma-Hock[p], Anna G. Maione[k], Patrudu Makena[o], Jodie Melbourne[a], Lawrence Milchak[g], Sheung P. Ng[q], Alicia Paini[r], Kathryn Page[s], Grace Patlewicz[t], Pilar Prieto[r], Hans Raabe[c], Emily N. Reinke[u], Clive Roper[v], Jane Rose[w], Monita Sharma[a], Wayne Spoo[o], Peter S. Thorne[x], Daniel M. Wilson[m], Annie M. Jarabek[y]

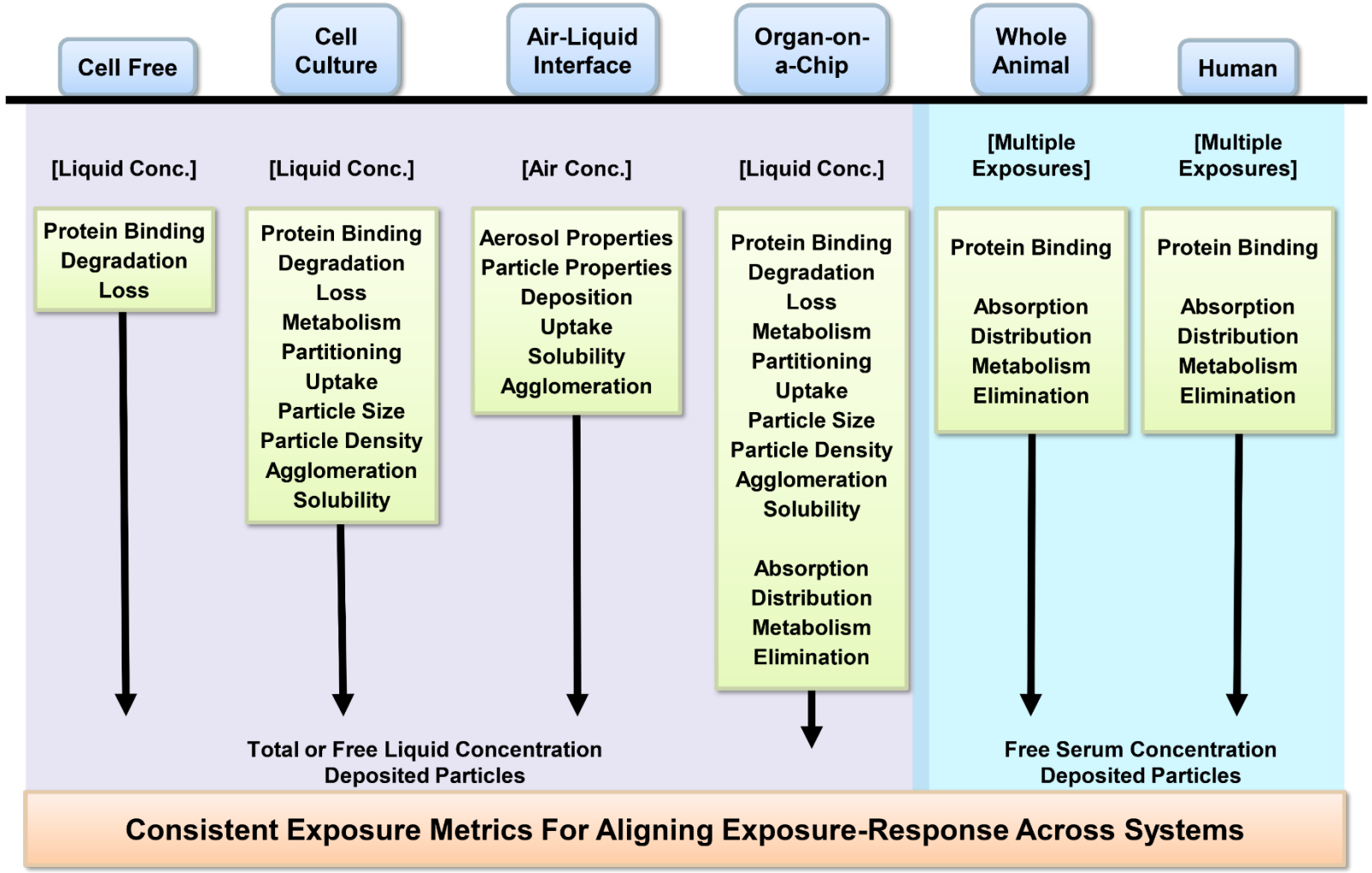
Transition: AOP as Mechanistic Scaffold



Clippinger et al (2018)
https://www.ncbi.nlm.nih.gov/pubmed/29908304

- **Mechanistic data** to characterize **key events (KE)**
- ***Transition* assays** from prioritization / hazard ID to **quantitative AOP (qAOP)** for ***in vitro* to *in vivo* extrapolation (IVIVE)**

Translation: Exposure Alignment



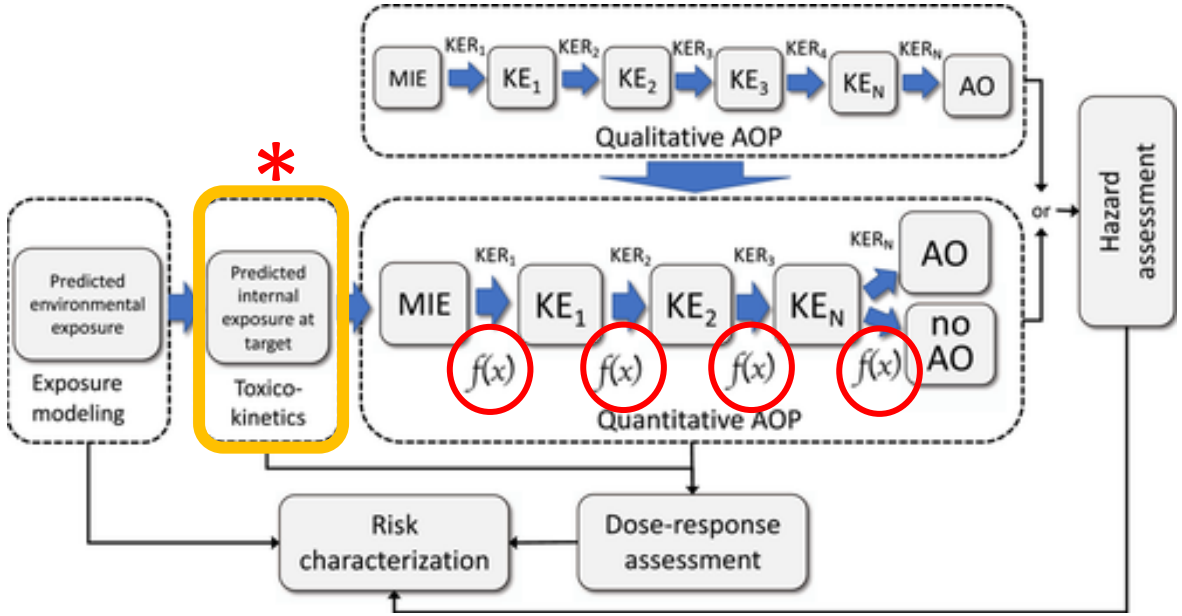
NAS (2017). Using 21st Century Science to Improve Risk-Related Evaluations
http://www.nap.edu/24635

Translation: Mechanistic Modeling

- **Evolves empirical modeling** (observations of **WHAT**) → to ***HOW*** **and** ***WHY*** they occur
  - **Qualitative agreement** with current **biological understanding** of ADME and pathogenesis processes
  - **Quantitative agreement** with **test measures of key events**
- Provides insights on **important physicochemical properties**
- **Translates** dose across various **experimental designs** to improve **data integration**
- **Addresses differences** between test systems, species and humans to **refine inferences**
- **Quantifies** and explores properties **systematically and consistently**

Translation: TSE Alignment and Quantitative AOP

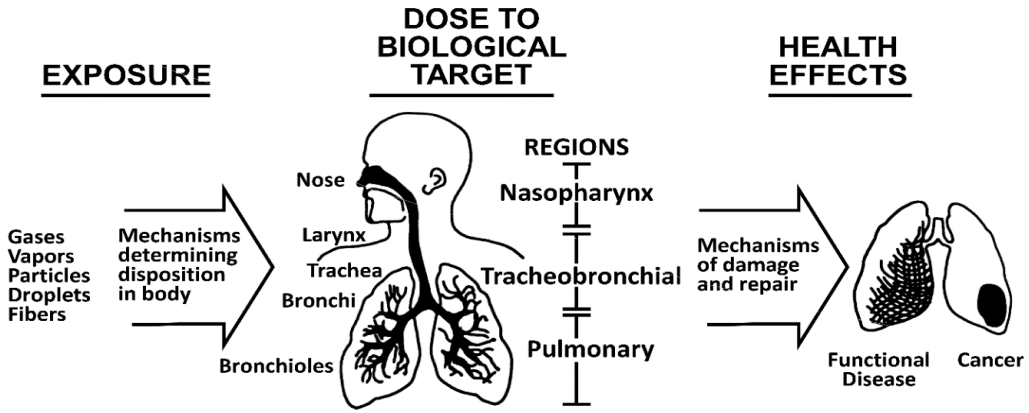
- Account for **key characteristics of exposure**
- Incorporate **physicochemical properties**
- **Characterize** anatomical or physiological parameters and processes determining **dosimetry / ADME**
- **Describe *quantitative* relationships among key events (KE) in an AOP**



Perkins et al (2019)
https://www.ncbi.nlm.nih.gov/pubmed/31127958

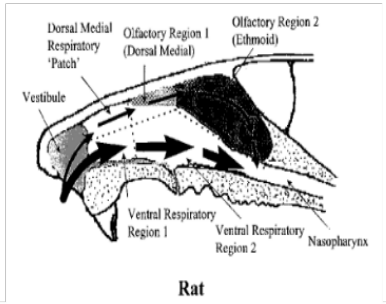
Dosimetry Models in Risk Assessment

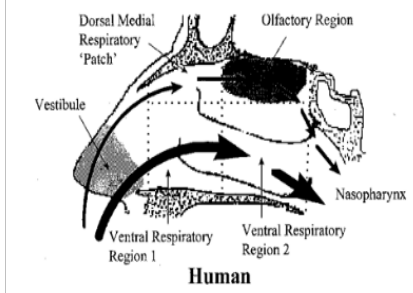
- **"Dose"**
  - Exposure versus internal amount at target site of exposure (e.g., deposited or retained; tissue / cell / molecular)
  - *Defined best as causal or at least a metric best associated (correlated) with toxicity or key event / endpoint used to evaluate "dose-response" relationship*
- **"Metric"**
  - Measurement: mass, surface area (SA), number (#); peak concentration, AUC
  - Scale of metric should be same as observation or the key event used as response endpoint (e.g., lung region versus local, specific cell type)
  - Motivate based on understanding of mode of action
- **"Model"**
  - Conceptual or quantitative description of important processes
  - Simulate different exposure scenarios and experimental designs

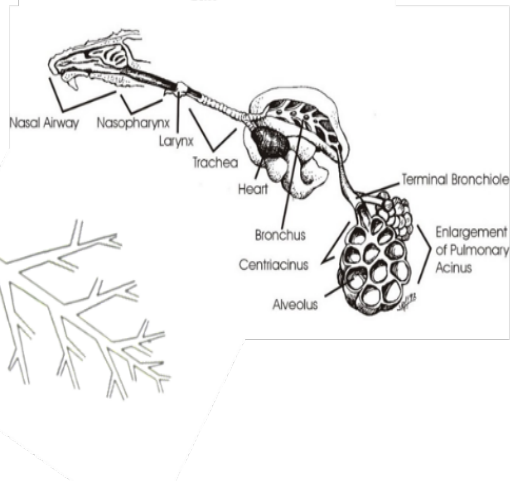


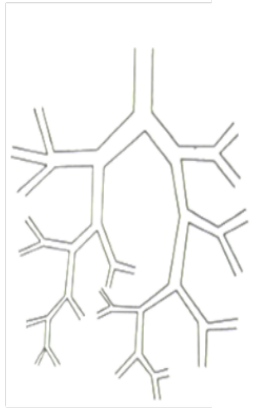
Conceptual Basis of Extrapolation

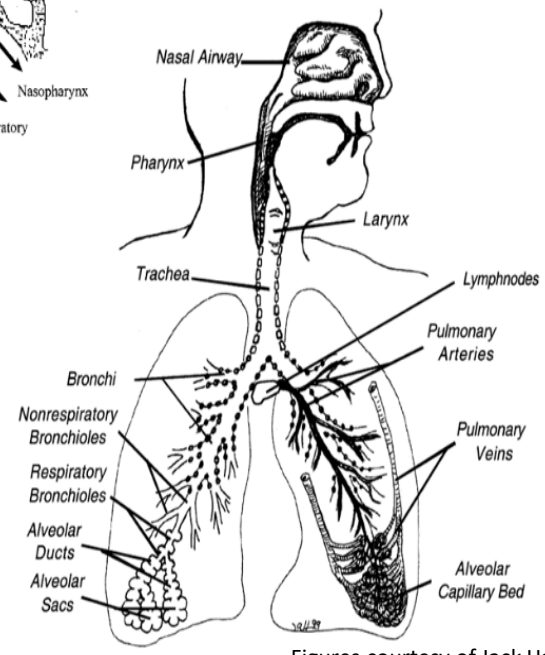
Not to scale

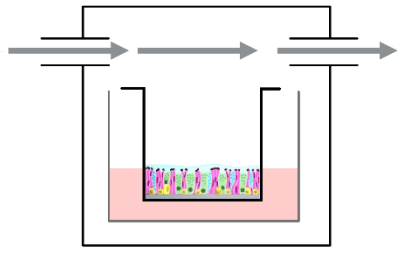


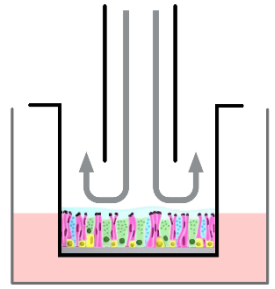


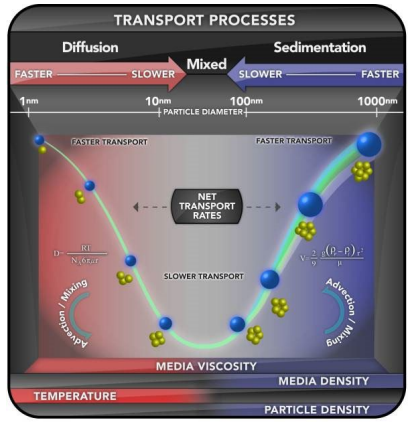












Figures courtesy of Jack Harkema, MSU

- To **integrate** human / laboratory animal and *in vitro* data need to **systematically** account for how **physicochemical properties** interact with differences in
  - **Exposure systems and regimen** (e.g., occupational vs laboratory vs *in vitro*)
  - **Anatomy** (e.g., species and age-specific architecture)
  - **Physiology** (e.g., breathing mode and ventilation activity pattern)

Physicochemical Properties

Particle / Fibers / Manufactured Nanomaterials

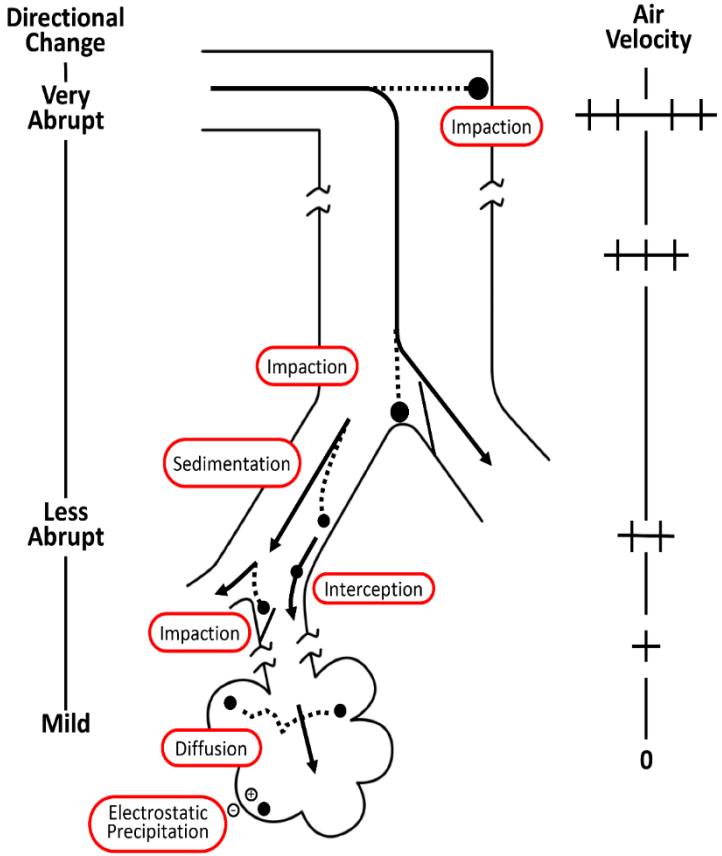
- Density / Dimensions and Distribution
- Hygroscopicity
- Shape and surface area
- Agglomeration state

Determine aerodynamics and deposition

MMAD and GSD

- Solubility and dissolution rate
- Crystal structure
- Chemical composition (spatially averaged (bulk) and heterogenous)
  - Physiosorption or chemisorption of biomolecules (e.g., proteins)
  - Biochemically-induced changes in surface chemistry
- Surface chemistry
- Surface charge (Zeta potential)
- Porosity

Exposure ≠ internal dose



Retained burden = (Inhalability + Deposition) - Clearance

Note: Relative contribution of each mechanism is different in each region of respiratory tract

Multiple-path Particle Dosimetry (MPPD) Model

- **New customized EPA version of the MPPD model** software developed with Applied Research Associates, Inc. (ARA)
  - Revised graphical user's interface (GUI) and refined and updated algorithms
- Aimed at audience with a broad range of expertise and experience
- Multi-purpose: Technical support documentation *and* user's guide
  - Introduction to inhalation dosimetry
  - Step-by-step explanation of input fields
  - Guidance on input parameters and procedures
  - Specific use case illustrations
- Recently completed external peer review
  - ICRP scientists, particle dosimetry modelers, inhalation toxicologists, risk assessors
  - Endorsed for deployment in Agency quantitative applications
    - *"Implementing the MPPD model would represent a major step forward and is viewed as a major improvement over currently used models."* – Chantal Darquenne, UCSD

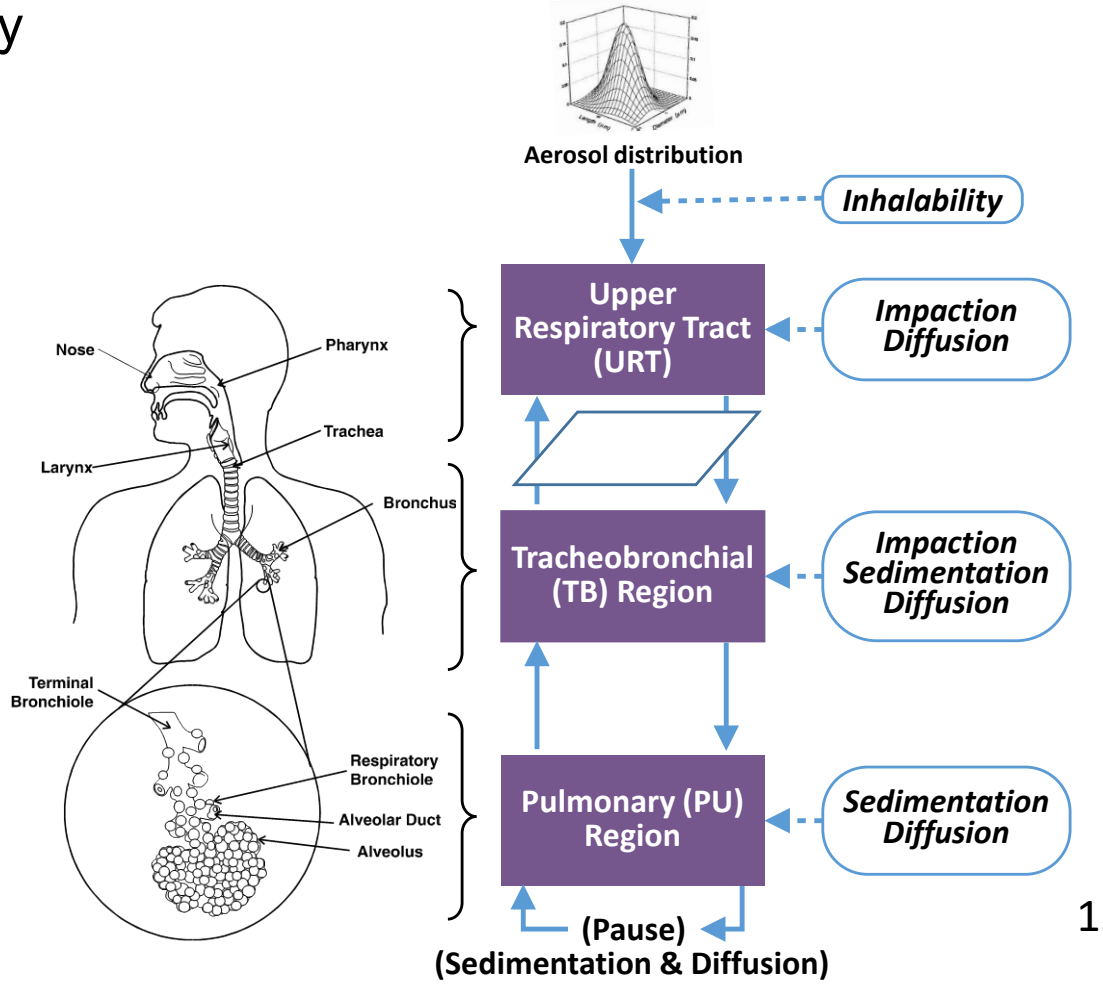
Release of US EPA MPPD v.2.0 (2023) is expected this Summer

Mechanistic Particle Dosimetry Modeling: Deposition

- **Major elements** of particle deposition modeling include:
  - Specification of an **architecture or geometry** for the given airways (e.g., humans versus laboratory animal species)
  - Development of a model that describes **airflow transport** (i.e., air flow via ventilation shown by solid blue arrows) in and out of the respiratory tract
  - Implementation of a **transport model for particles** in a specified geometry that uses ventilation to determine the fate of particles
  - Description of **deposition efficiency** in each airway because of **various mechanisms** (i.e., impaction, sedimentation, diffusion) shown as ovals
  - A **computational procedure** must be developed that accounts for the transport and deposition of the particles in the airways.

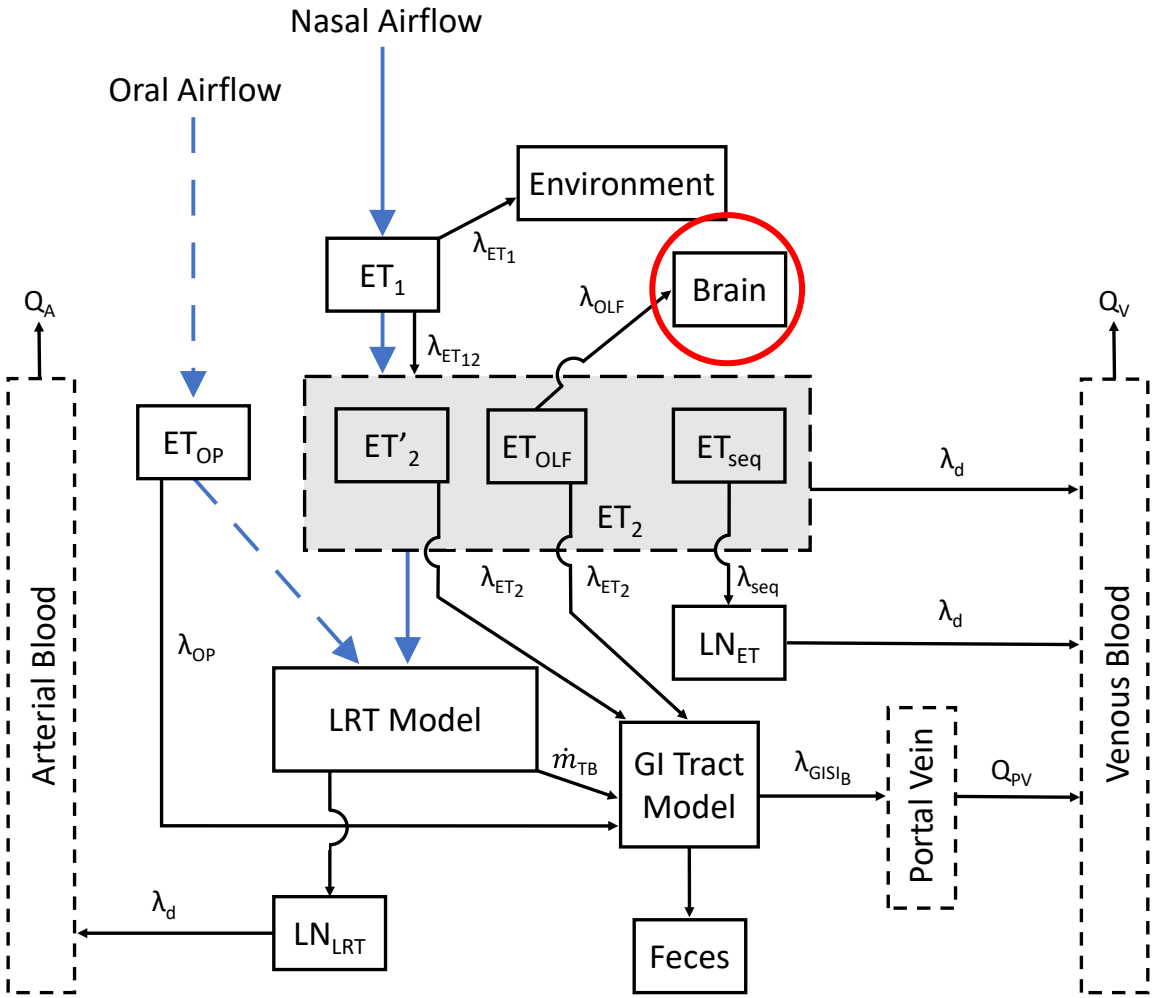
Retained burden = (Inhalability + Deposition) - Clearance

Note: Relative contribution of each mechanism is different in each region of respiratory tract



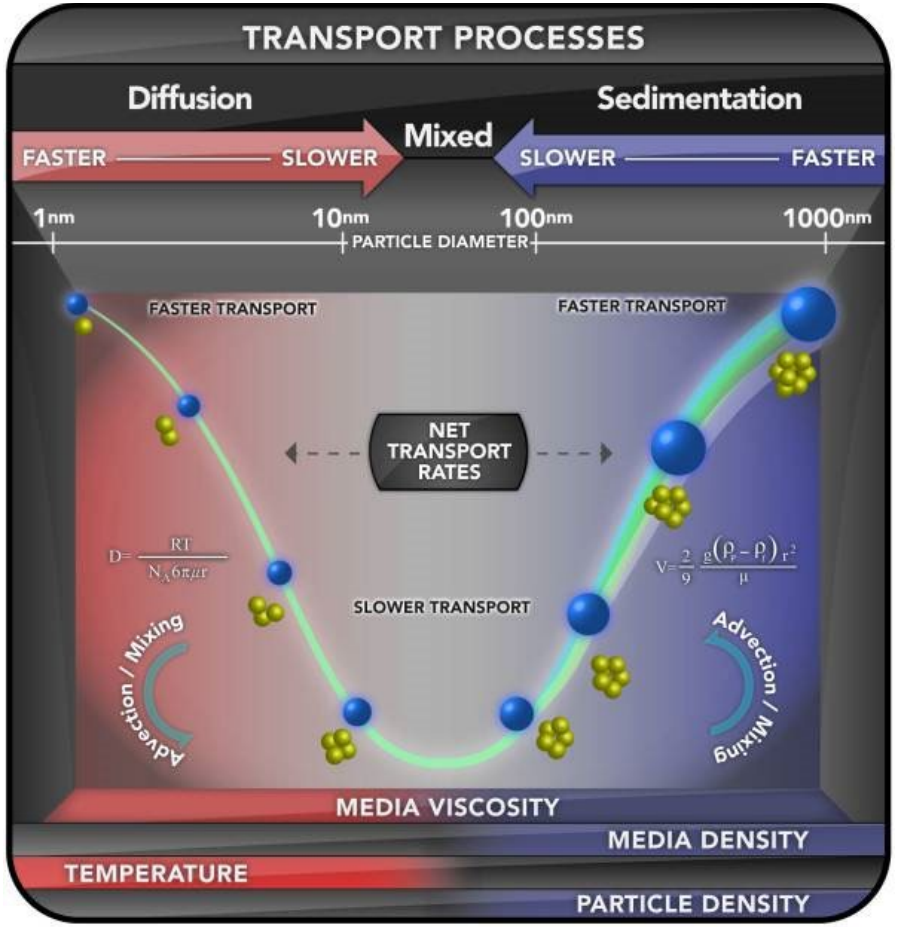
EPA MPPD Dosimetry Modeling: Clearance

- Clearance in the ET region for humans is based on modification of the ICRP HRTM (2015) compartmental model
- **Translocation to brain from ET regions** is based on computational fluid dynamics (CFD) models rendered from high-resolution imaging
- Clearance in the LRT is based on ICRP HRTM (2015) model with modification to predict absorption to blood



Dosimetry in the Dish

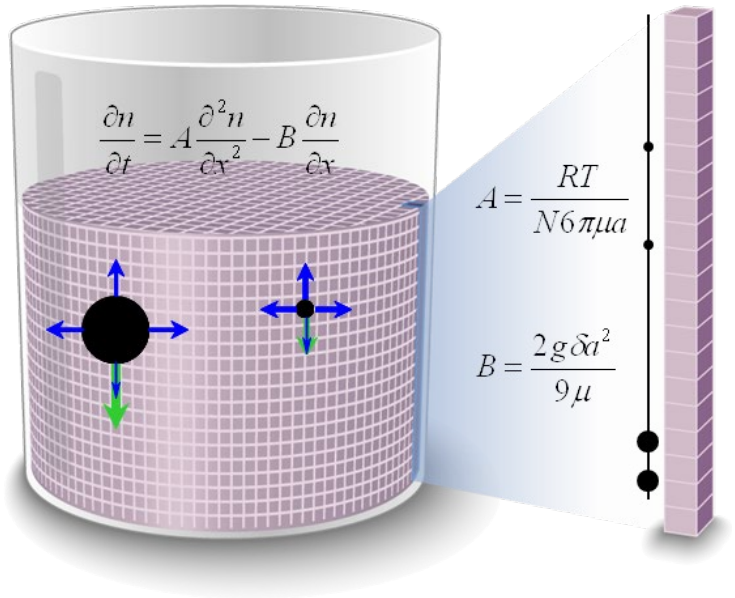
- Dosimetry is inherent issue for ***ALL* experimental designs!**
- Considerations of **transport mechanisms** for particles in an *in vitro* system shown to be a **major factor in delivered dose** to cells in culture.
- These considerations should be interfaced with **predicted doses to respiratory tract** of test species in question to best **estimate dose range for realistic testing**.



Hinderliter et al. (2010). ISDD: A computational model of particle sedimentation, diffusion, and target cell dosimetry for *in vitro* toxicity studies. Part Fibre Toxicol. Nov 30;7(1):36.

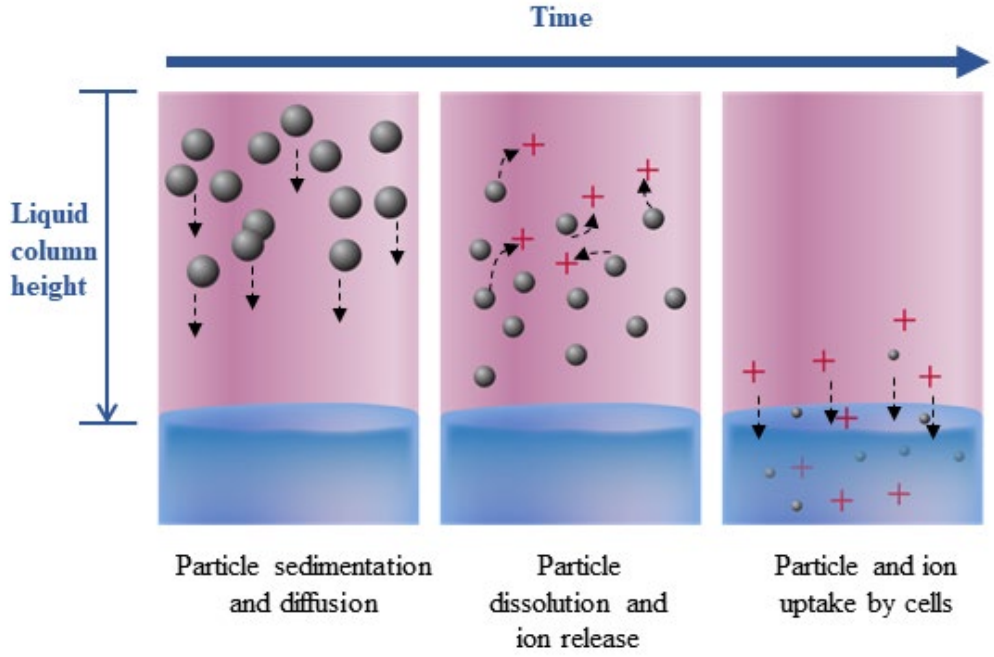
Dosimetry Models for *in vitro* Submerged Systems

Addressing in vitro sedimentation, diffusion (ISDD) and dissolution (ISD3)



https://nanodose.pnnl.gov/default.aspx?topic=ISDD

Hinderliter *et al.* 2010. *Part Fibre Toxicol.* 7(1) 36



https://nanodose.pnnl.gov/default.aspx?topic=ISD3

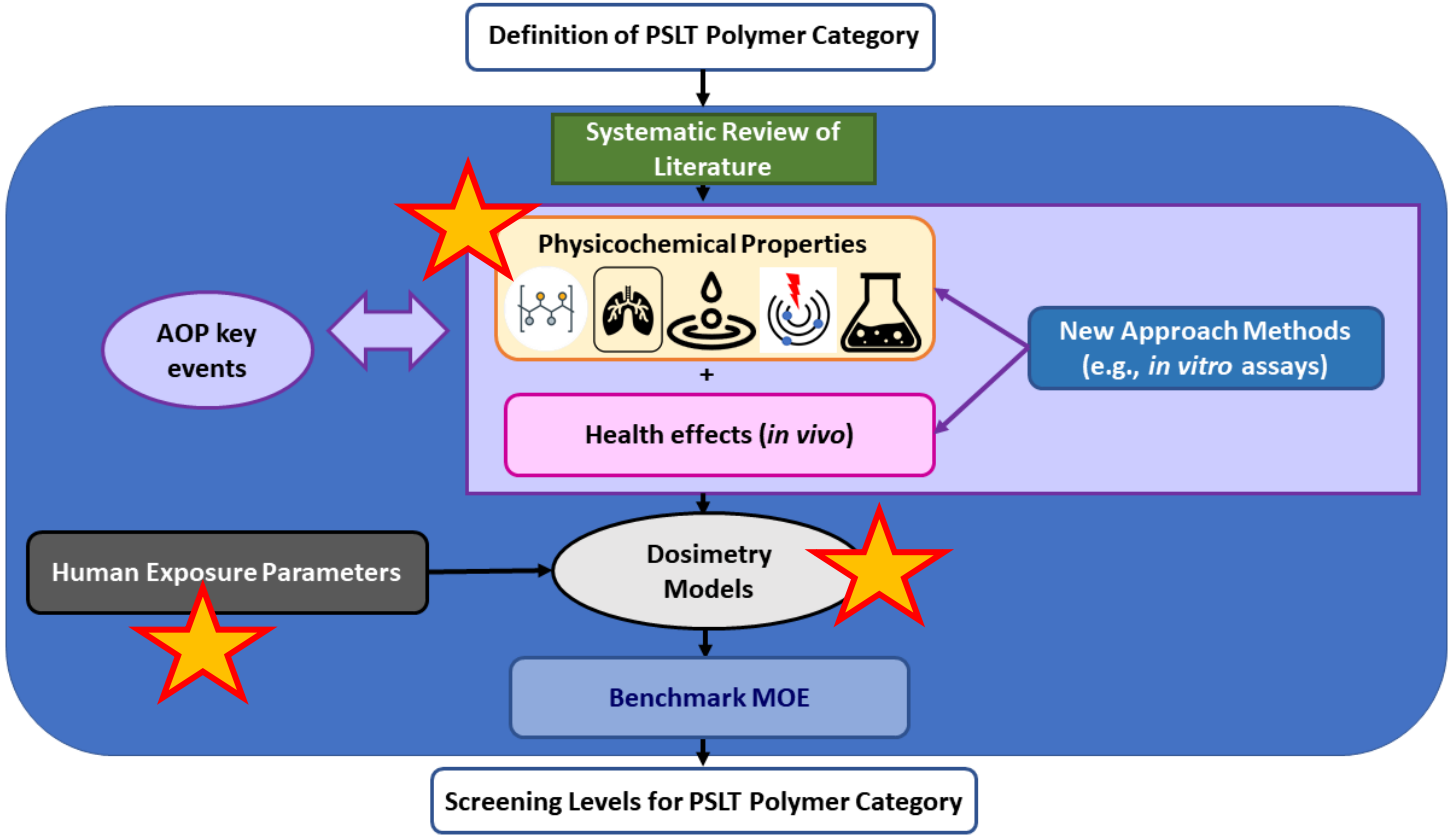
Thomas *et al.* 2018. *Part Fibre Toxicol.* 15(1) 6

TSCA Application: New Chemical Substances (NCS)

- Section 5 of TSCA does not require upfront testing for NCS; only extant data need be submitted
- Various methods to assess risks with limited data
  - Evaluation based on comparator chemicals. A **chemical category** is defined as a group of chemicals with structurally similar physicochemical properties and whose toxicity follows relevant pathogenesis due to an analogous mode of action.
  - "Read across" approaches using analogues
- Two Integrated Approaches to Testing and Assessment (IATA) to define categories deploy dosimetry modeling and NAMs (*accepted in Chem Res Tox*)
  - General Surfactants (Henry Salazar et al.)
  - Poorly Soluble Low Toxicity (PSLT) Polymers (Jarabek Stedeford et al.)

Integrated Approach to Testing and Assessment (IATA)

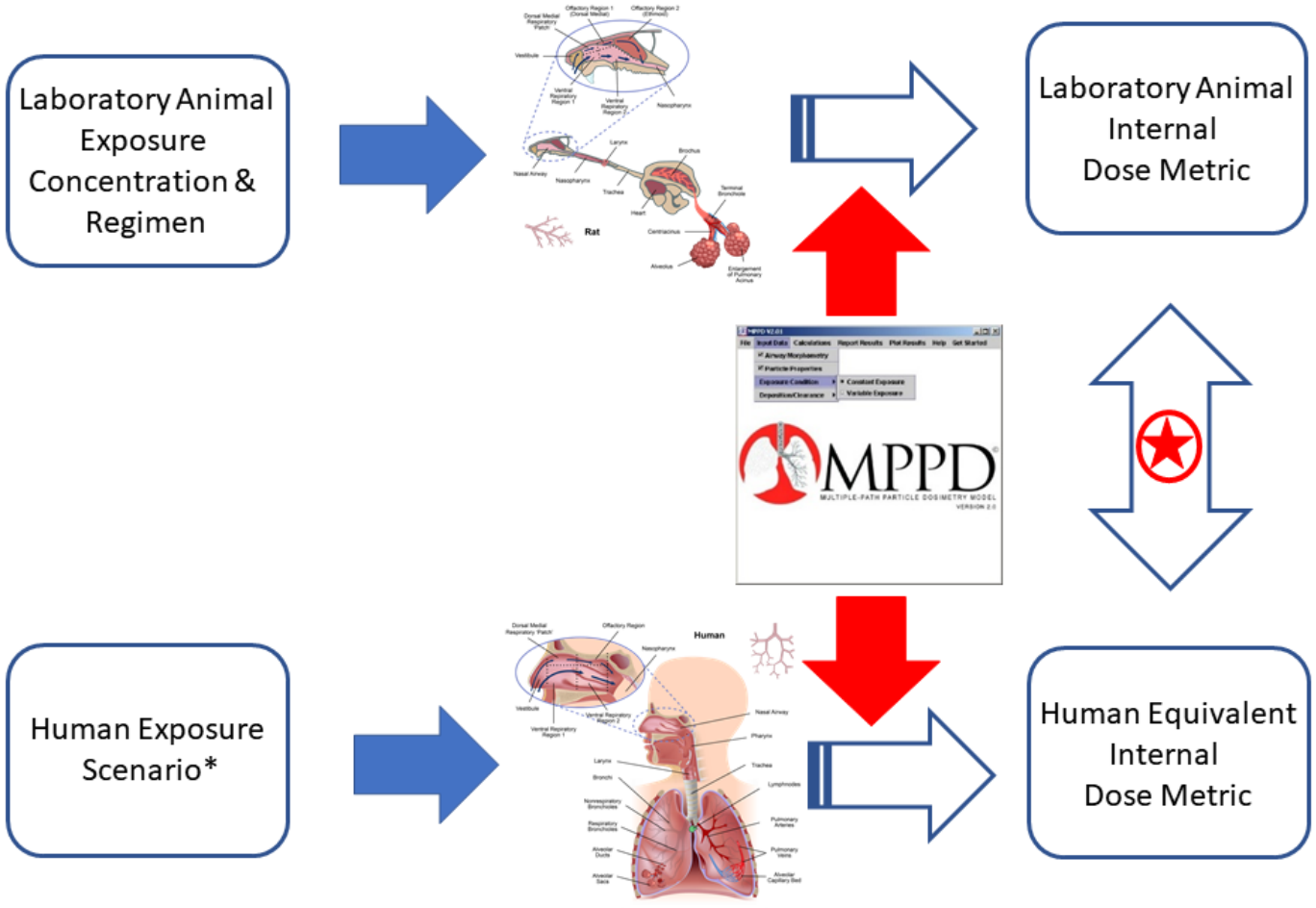
- **Dosimetry** plays critical role in strategy for evidence integration and evaluation to aid assessments
  - Inclusion criterion
  - Translation of dose across experimental platforms
  - Target specific exposures
- **NAMs** can provide data to
  - Inform physicochemical properties and health effects
  - Refine model parameters (e.g., solubility rates)



Jarabek Stedeford et al. (*in review*)

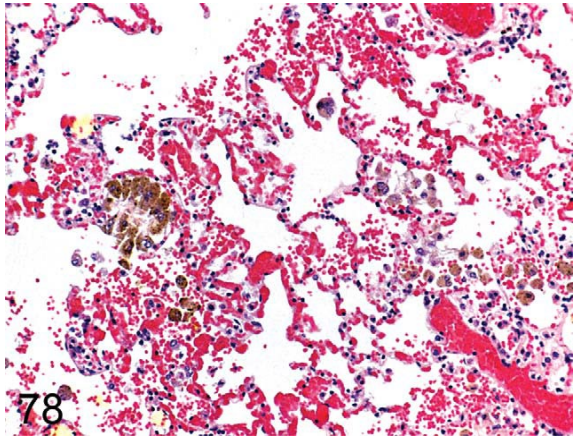
MPPD Model to Calculate HEC

- **Human equivalent concentration (HEC)** based on **extrapolation** of laboratory animal data
- **Multiple-path particle dosimetry (MPPD) model** deployed to **simulate** both the laboratory animal **exposure regimen** (e.g., 6 hr/day and 5 days/week for 28 days) and the human exposure scenario (e.g., occupational 8 hr/day and 5 days/week for 40 years)
- Human exposure scenario can be **default or targeted (*)** with specific data



PSLT Challenge: Definition and Lung Overload

- **"Lung overload"** is a special case for consideration when evaluating the toxicity of **inhaled PSLT particles**
  - Defined as the **overwhelming of clearance in the pulmonary (PU) region** leading to a reduction in the ability of the lung to remove particles, and a resultant accumulation or "overload" occurs which results in a retained mass burden in the lung greater than that which would occur with normal physiological clearance rates
  - Lung overload is a **kinetic phenomenon** and ***not a pathological finding per se***
- ***A key issue when considering whether overload occurred is that increased particle retention due to large lung burdens needs to be differentiated from that due to inherently high cytotoxicity (e.g., quartz)***
- Consideration of the hazard or **risk requires characterization of both possible particle overload and some knowledge of the inherent toxicity of the particle** under consideration, especially as many key events associated with "overload" are also embedded in pathways leading to various other adverse outcomes (Driscoll and Borm, 2020)
  - If overload is demonstrated to occur, especially when considering rat lung tumors, then these effects may be less relevant for human risk assessment (ILSI, 2000; Warheit et al., 2016)
  - However, as noted, several other "noncancer" events such as inflammation and hyperplasia are related to other adverse outcome pathways and should be evaluated as relevant (US EPA, 2022; 2019)

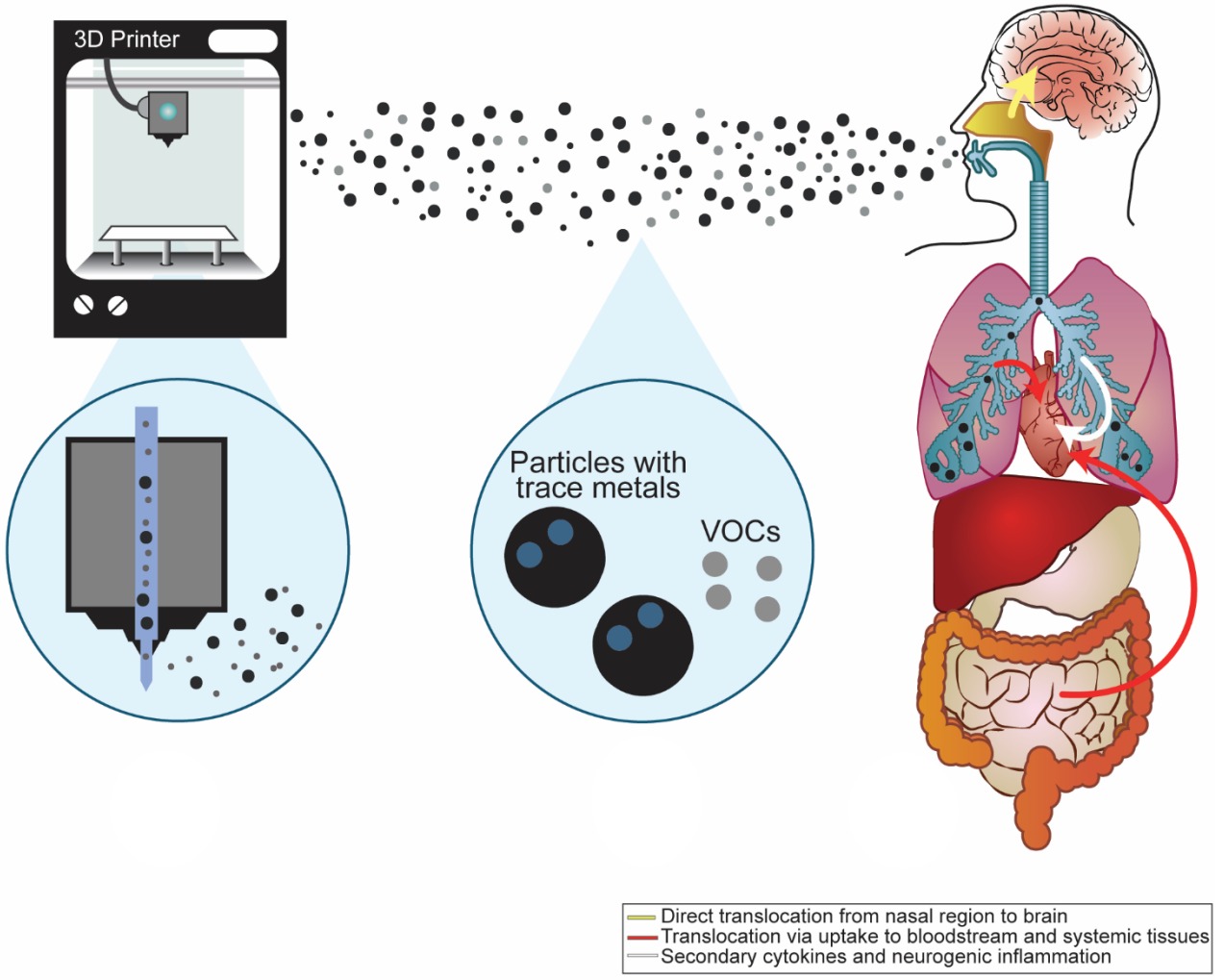


Renne et al. (2009)
doi:10.1177/0192623309353423

✓ ***The MPPD model can be used to demonstrate if overload occurred***

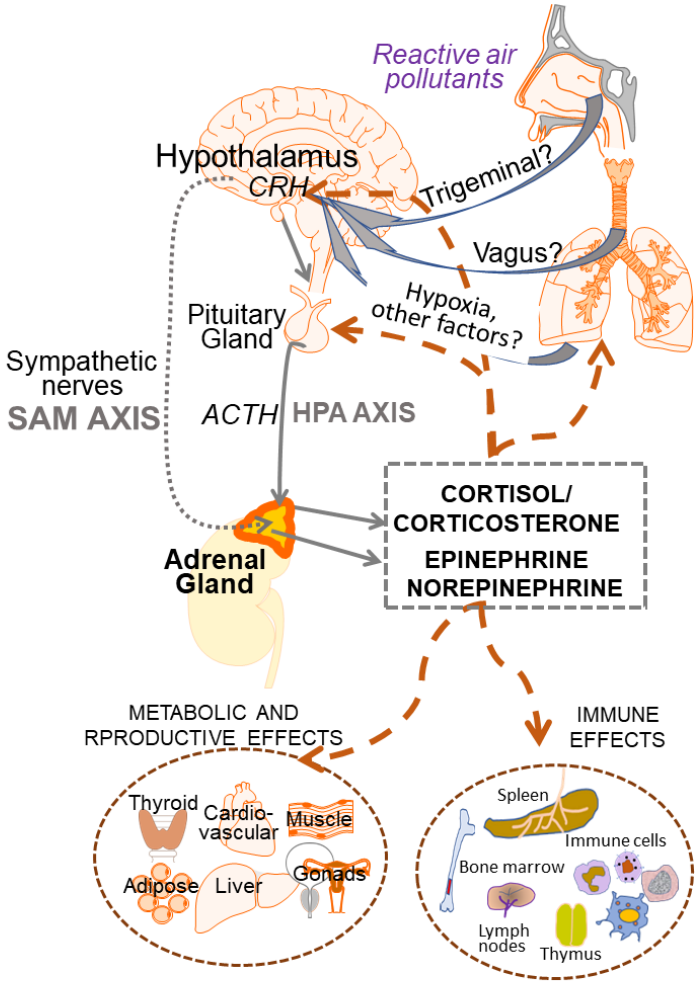
Ultrafine or Nanomaterial Inhalation Dosimetry

- **Consider the composition** of the emission
- **Ultrafine material may translocate to the brain**
  - Directly from ET region
  - From lower respiratory via systemic circulation
- Material physically cleared from the TB region and subsequently **swallowed to the gut may also be distributed systemically**
- **Secondary cytokines and inflammation** may also result in systemic effects from epithelial perturbation in the respiratory tract, including impacts on the neuroendocrine system



Tedla G, Jarabek AM, et al. Sci Total Environ. 2022 Mar 25;814:152622. doi: 10.1016/j.scitotenv.2021.152622

Lessons from Ultrafine Air Pollution: Systemic Toxicity



Air Pollutant impacts on the brain and neuroendocrine system with implications for peripheral organs: A perspective.
Kodavanti et al (2023). https://doi.org/10.1080/08958378.2023.2172486

Diseases, conditions and biomarkers affected by air pollution

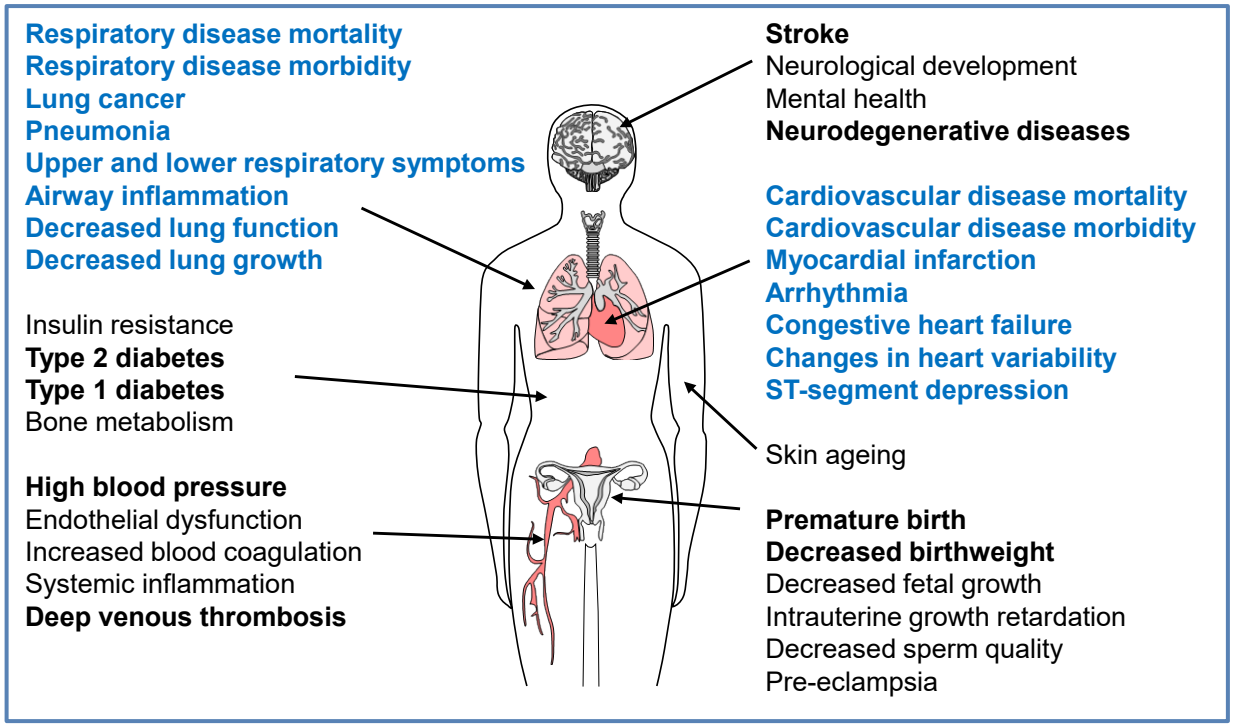
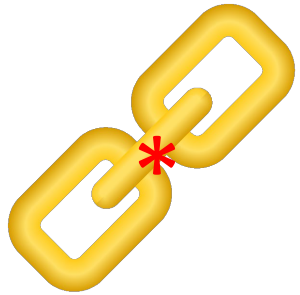


Figure adapted from: George D. Thurston et al. (2017). Eur Respir J; 49:1600419. https://erj.ersjournals.com/content/49/1/1600419

US EPA (2019; 2022). https://www.epa.gov/isa/integrated-science-assessment-isa-particulate-matter
US EPA (2020). https://www.epa.gov/isa/integrated-science-assessment-isa-ozone-and-related-photochemical-oxidants

Summary: Advancing iIATA

- **Evolve empirical modeling** (observations of **WHAT**) → to **MECHANISTIC MULTISCALE MODELS** (***HOW*** and ***WHY***)
- Bridge to systems biology: **key events** of pathogenesis and ***quantitative*** **AOP (qAOP)**
  - Different levels of observation
  - Various dimension of disease (e.g., early or late)
- **Translate TSE across exposure systems** to aid and transform **evidence integration: develop ANALYTIC WORKFLOWS**
  - Align human and animal exposures
  - Advance IVIVE and NAM applications
- Facilitate **interdisciplinary dialogue**
  - **Transparency** re: assumptions and foundational data
  - **Modular** to support **interoperability** with other models
  - Appreciate **assumptions and impacts**



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Annie M. Jarabek
Center for Public Health and Environmental Assessment
Office of Research and Development | US EPA
Jarabek.annie@epa.gov (919.637.6016)

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- **Applied Research Associates, Inc. (ARA)**
  - Owen T. Price
- **Dupont Nutrition and Biosciences**
  - Gregory S. Ladic
- **Proctor and Gamble Company**
  - Michael P. Hayes and Raphaël T. Tremblay
- **Syracuse Research Corp. (SRC)**
  - Marc Odin, Julie Melia, and Heather Carlson-Lynch
- **Peta Science Consortium International, e.V.**
  - Monita Sharma, Andreas O. Stucki, and Amy J. Clippinger
- **American Chemistry Council (ACC)**
  - Sahar Osman-Sypher
- **BASF Corporation**
  - Ann Tveit
- **Covestro LLC**
  - Stephanie A. Snyder