EPA United States Environmental Protection Agency

Advancing Application of NAMs and Evidence Integration in Risk Assessment: Dosimetry is Critical to Exposure Alignment

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Using In Silico and In Vitro Approaches for Next Generation Risk Assessment of Potential Respiratory Toxicants

Inhalation Webinar Series organized by EPA OCSPP, PSCI, Syngenta and Unilever

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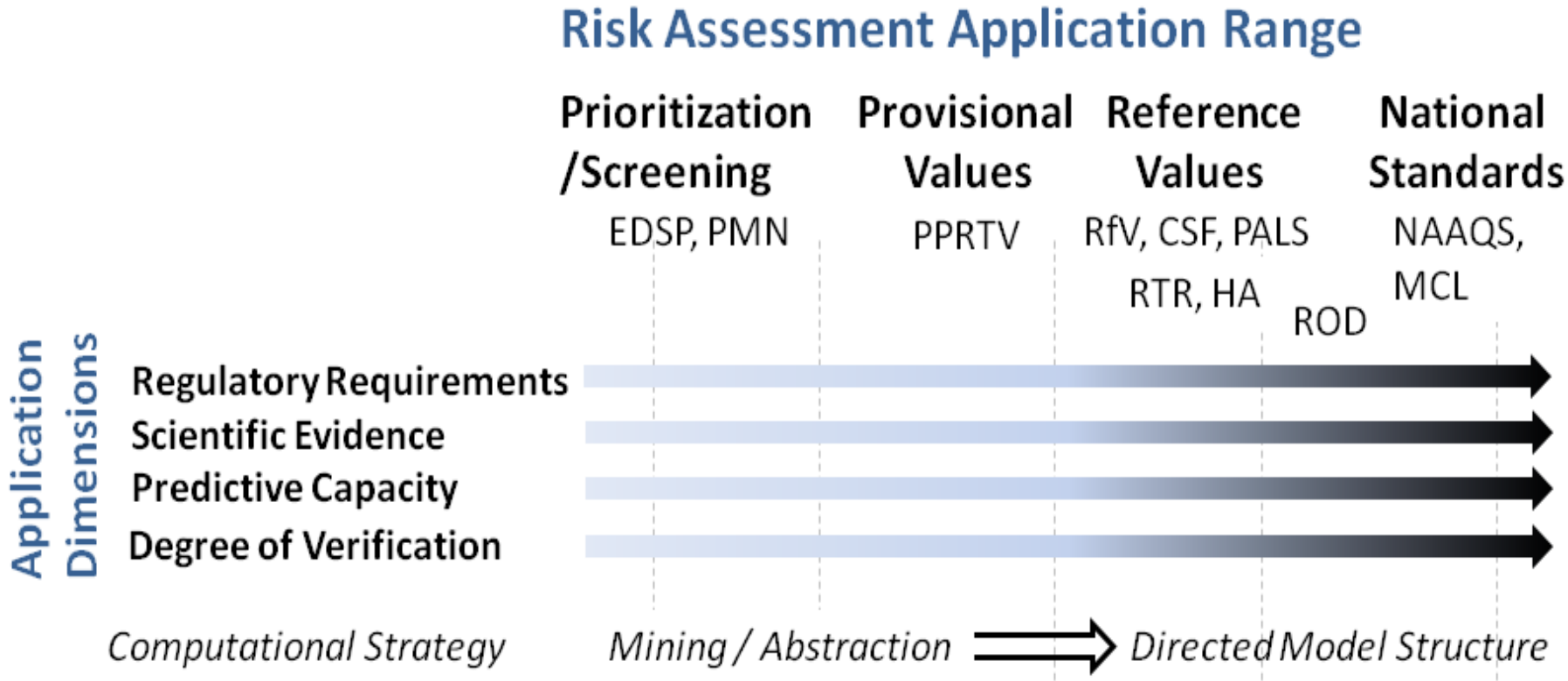
Office of Research and Development
Center for Public Health and Environmental Assessment (CPHEA)

Topics

- **Challenges:** Coherent evidence integration across large landscape of risk assessment applications
- **Transitions:** Conceptual and computational
  - "Big data" descriptions
  - New approach methods (NAMs)
  - AEP and AOP frameworks
- **Translations:** Mechanistic modeling and reporting standards
  - Exposure alignment
  - Quantitative AOP and IATA
- **Summary**

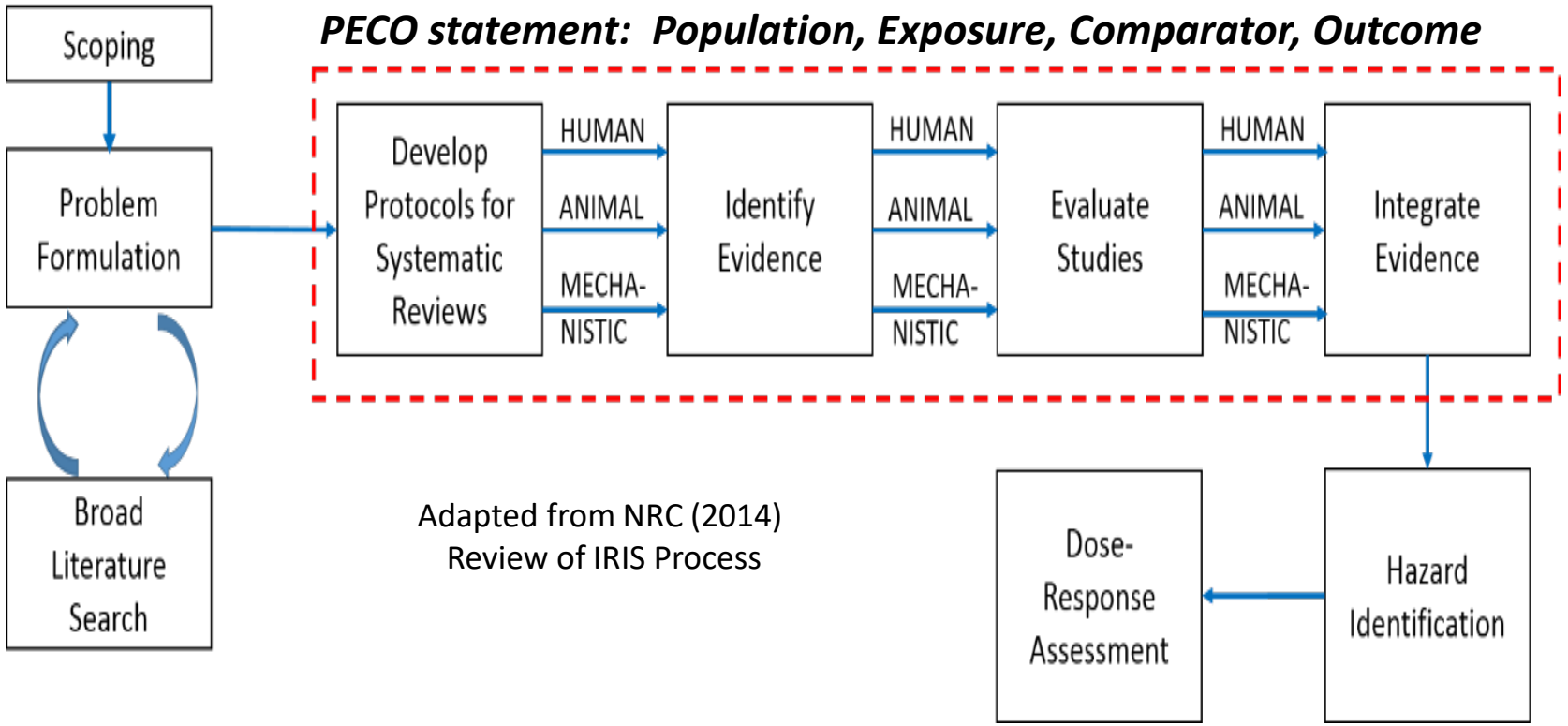
Disclaimer: These views are those of the author and do not represent US EPA policy.

Risk Assessment Landscape



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

Challenge: Evidence Integration



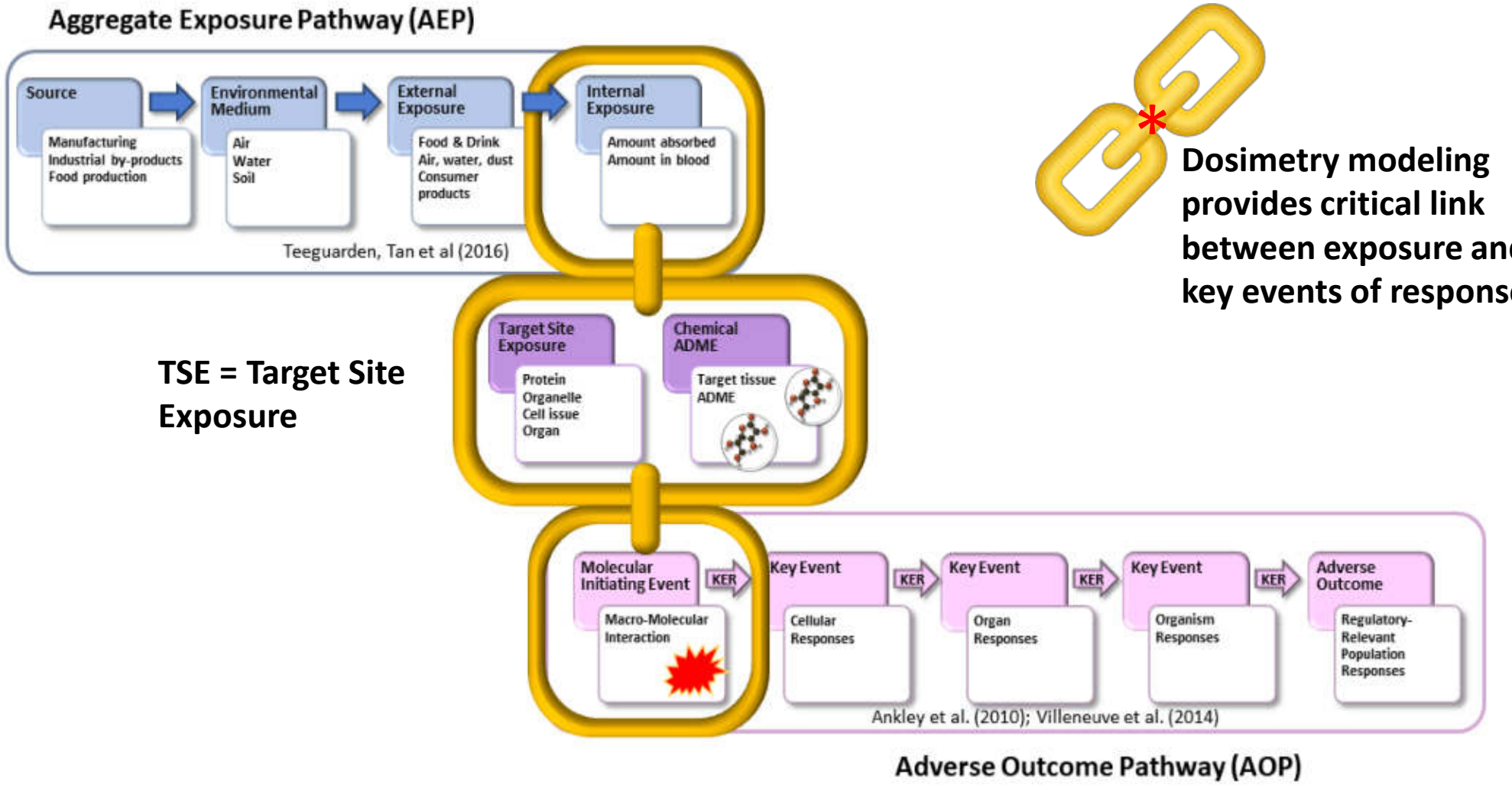
Adapted from NRC (2014)
Review of IRIS Process

- 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: Pathways to Predictions

- *More than manuscripts:* ***Reproducibility and Rigor in Big Data Era*** (Waller and Miller, 2016) https://www.ncbi.nlm.nih.gov/pubmed/26811418
- **Era of the "3V": Volume** (big) | **Velocity** (fast measurement and computing) | **Variety** (multiple sources)
- Define and realize the **establishment of a data ecosystem** or "commons" whereby **data are shared** for use by all in a **common infrastructure** (Boyles et al., (2019). **Ontology-based data integration** for advancing toxicological knowledge *Current Opinion Tox* 16, 67 – 74)
  - **Common semantics** and data repositories
  - Investment in making data **"born interoperable"**
  - ***Publication alone is insufficient***

Transitions: Comprehensive Characterization

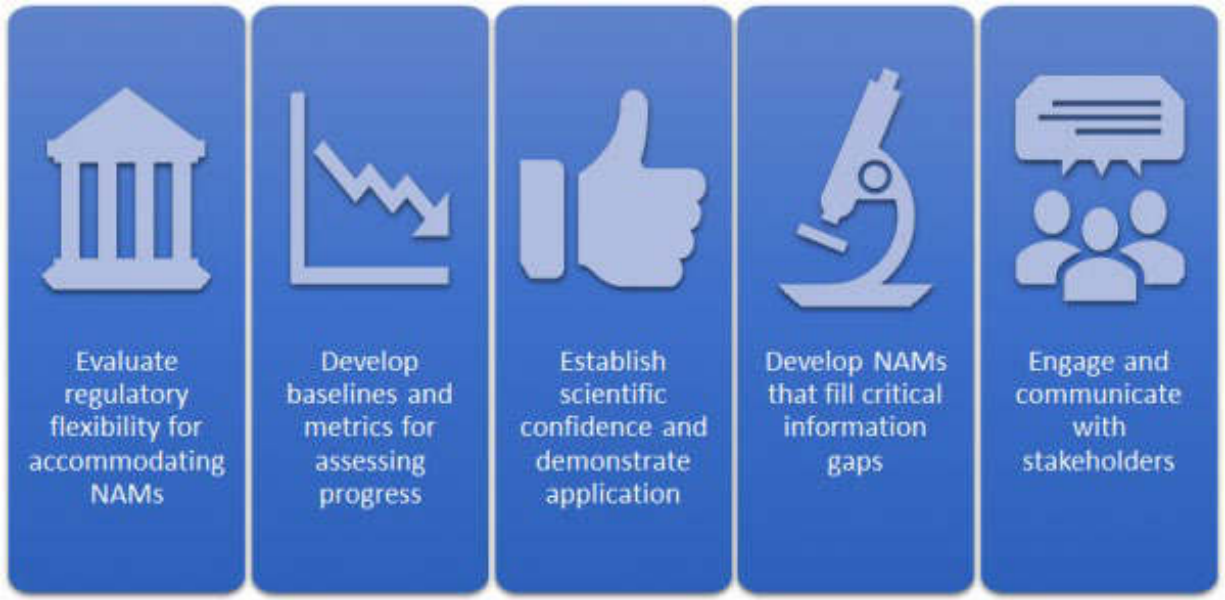


TSE = Target Site Exposure

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

Transitions: Novel Approach Methods (NAMs)

- EPA Strategic Plan published June 22, 2018 (https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical)
- EPA views the term New Approach Methodologies (NAMs) as equivalent to alternative test methods and strategies (the language in the statute)

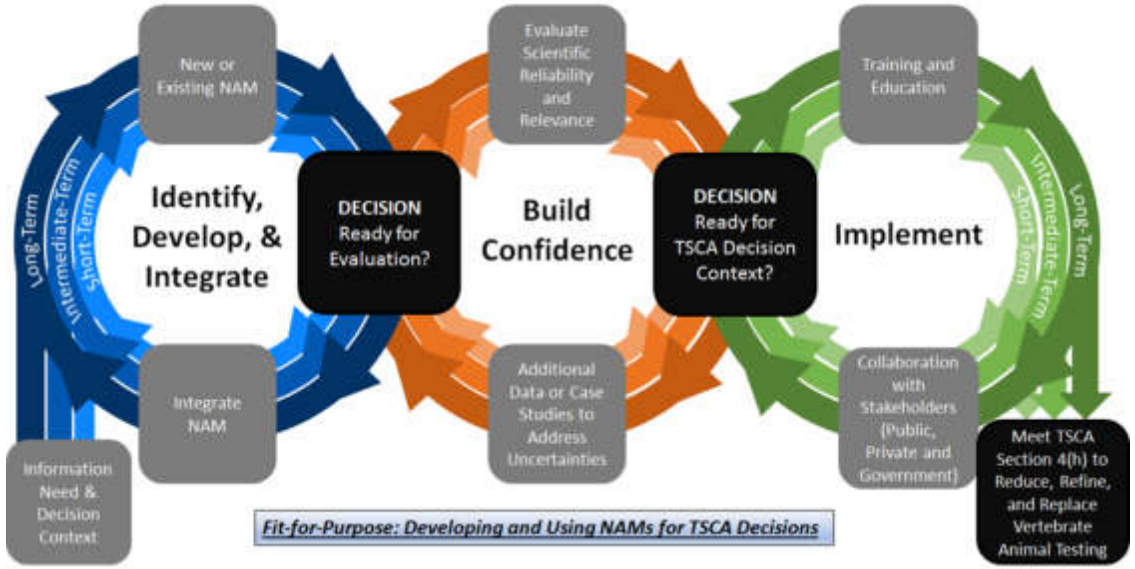


- EPA Work Plan for Reducing Use of Animals in Chemical Testing published June 2021 (https://www.epa.gov/chemical-research/epa-new-approach-methods-work-plan-reducing-use-animals-chemical-testing)

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

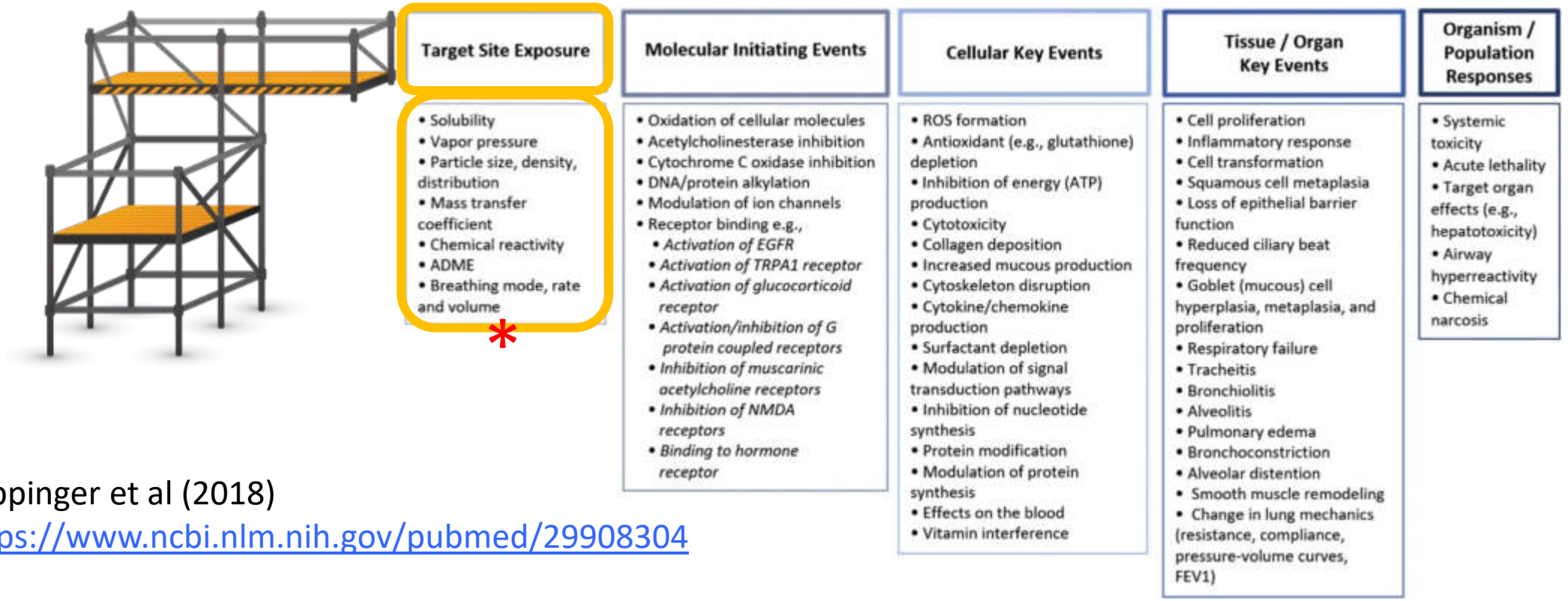
journal homepage: www.elsevier.com/locate/toxinvit

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[p], Lan Ma-Hock[q], 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[n], Peter S. Thorne[x], Daniel M. Wilson[m], Annie M. Jarabek[y]

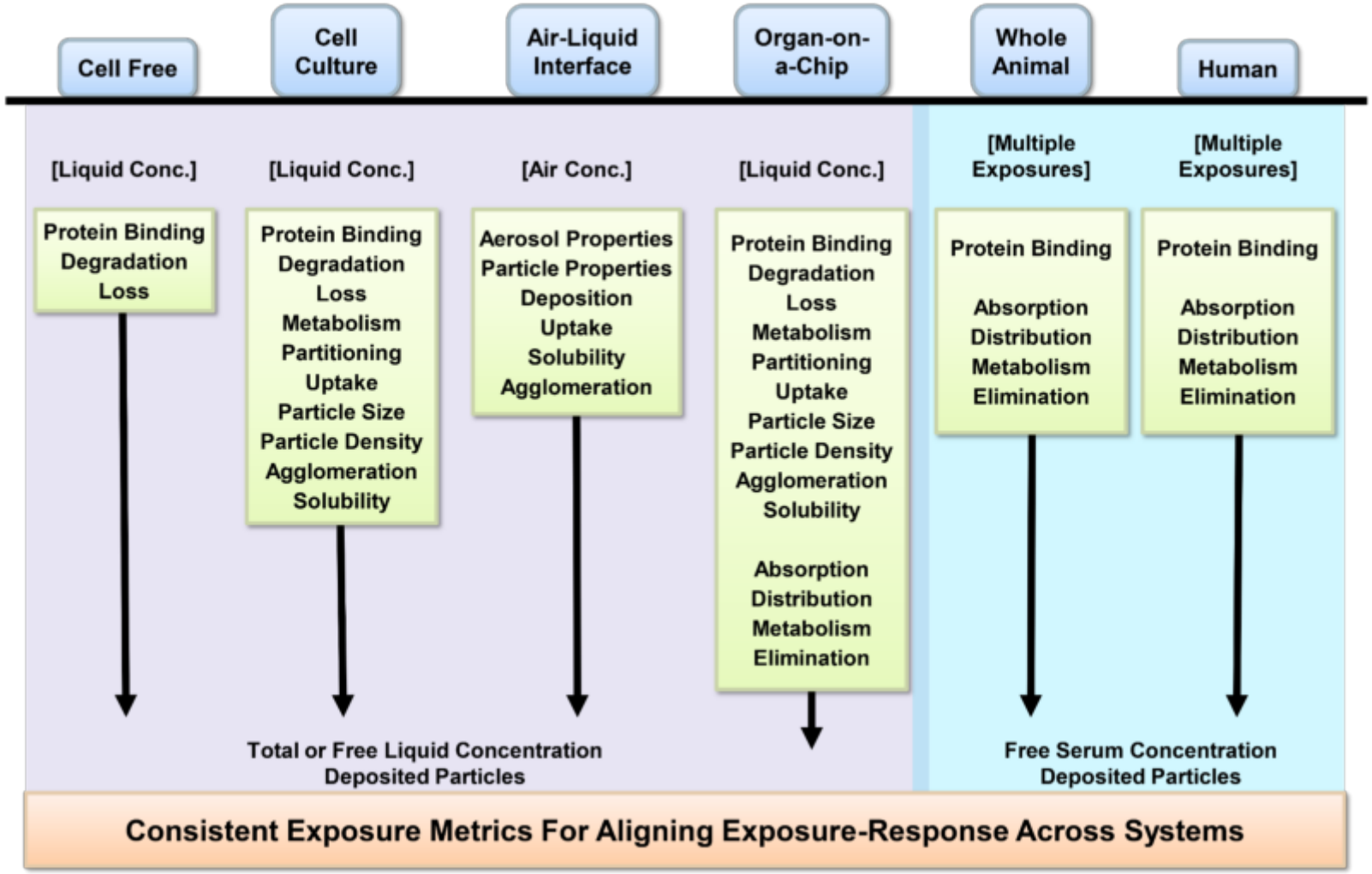
Transitions: AOP as Mechanistic Scaffold



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



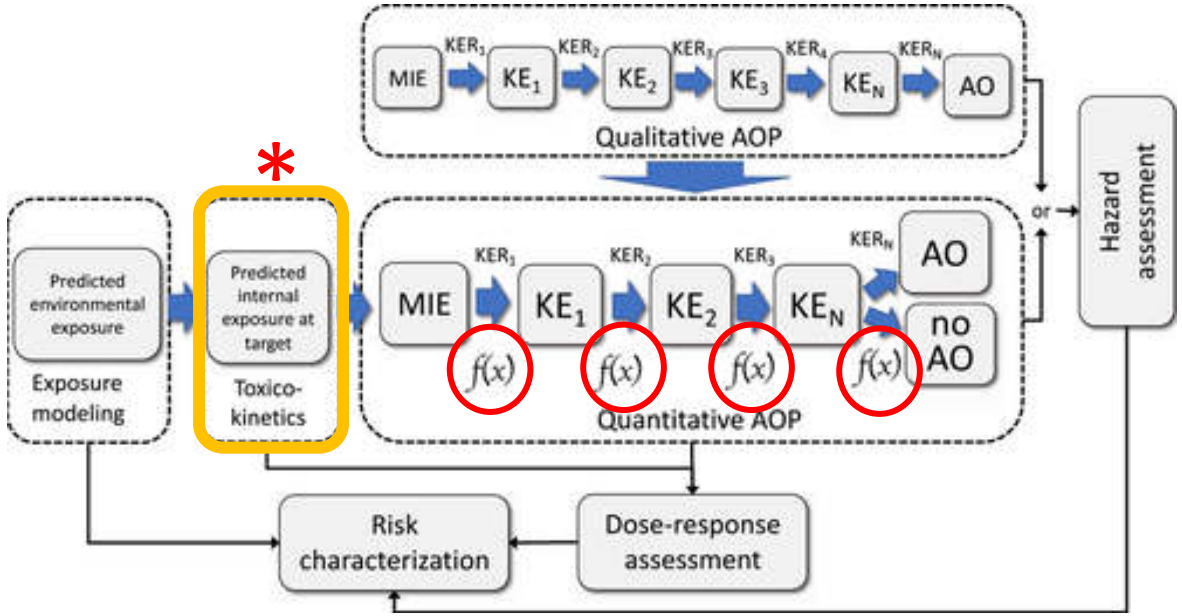
NAS (2017). Using 21st Century Science to Improve Risk-Related Evaluations
http://www.nap.edu/24635

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**



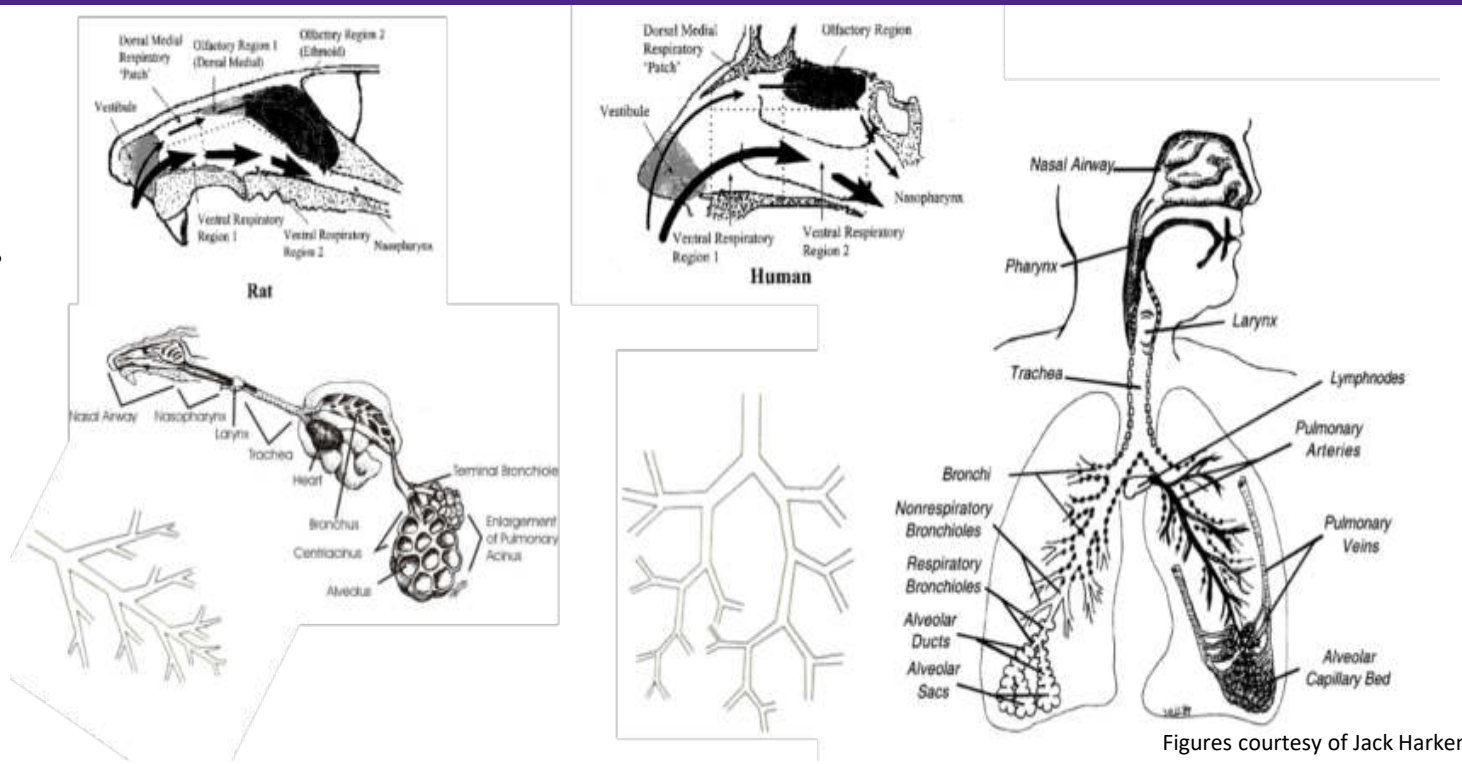
Perkins et al (2019)
https://www.ncbi.nlm.nih.gov/pubmed/31127958

Dosimetry Models in Risk Assessment

- **"Dose"**
  - Exposure versus internal amount (deposited or retained)
  - *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 (#)
  - Scale of metric should be same as observation or response endpoint (e.g., lung region versus local, specific cell type)
- **"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 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)

Historical Precedent

- Early appreciation: Coal dust
- Data rich: Radionuclide effort in 1940's
- Size-selective sampling strategies and standards
  - "Respirable"
  - Total suspended particulate (TSP) → PM_{10} / $PM_{2.5}$
  - National Ambient Air Quality Standard (NAAQS) for particulate matter (PM)
- Basis of dosimetric adjustment factor (DAF) used for interspecies extrapolation for risk assessment
- Evaluation criteria for refractory ceramic fibers (RCF) and man-made vitreous fibers (MMVF)
- Used to target pharmaceutical drug delivery

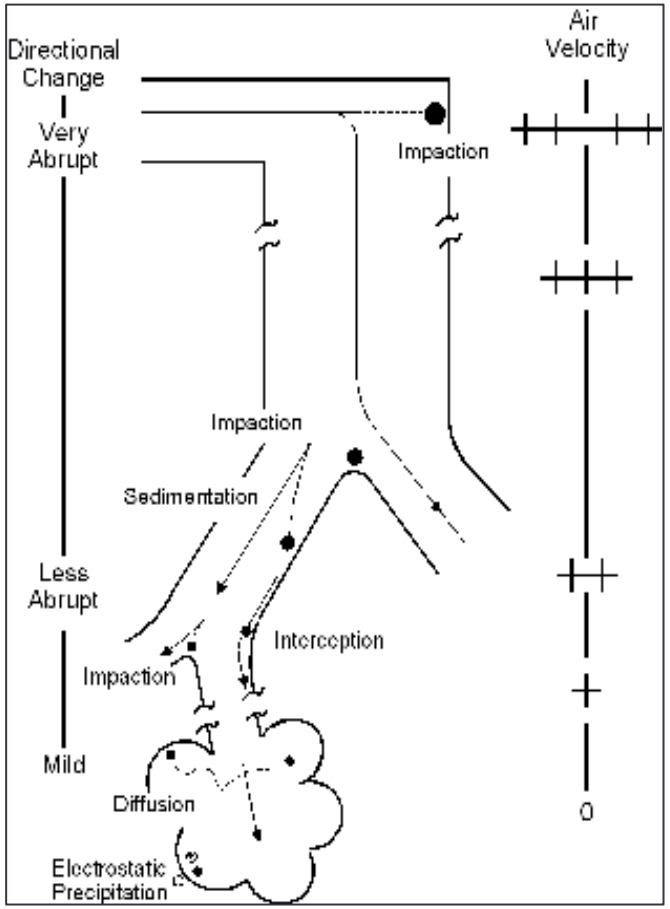
Physicochemical Properties

Particle / Fibers / Manufactured Nanomaterials

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

Determine aerodynamics and deposition

- 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

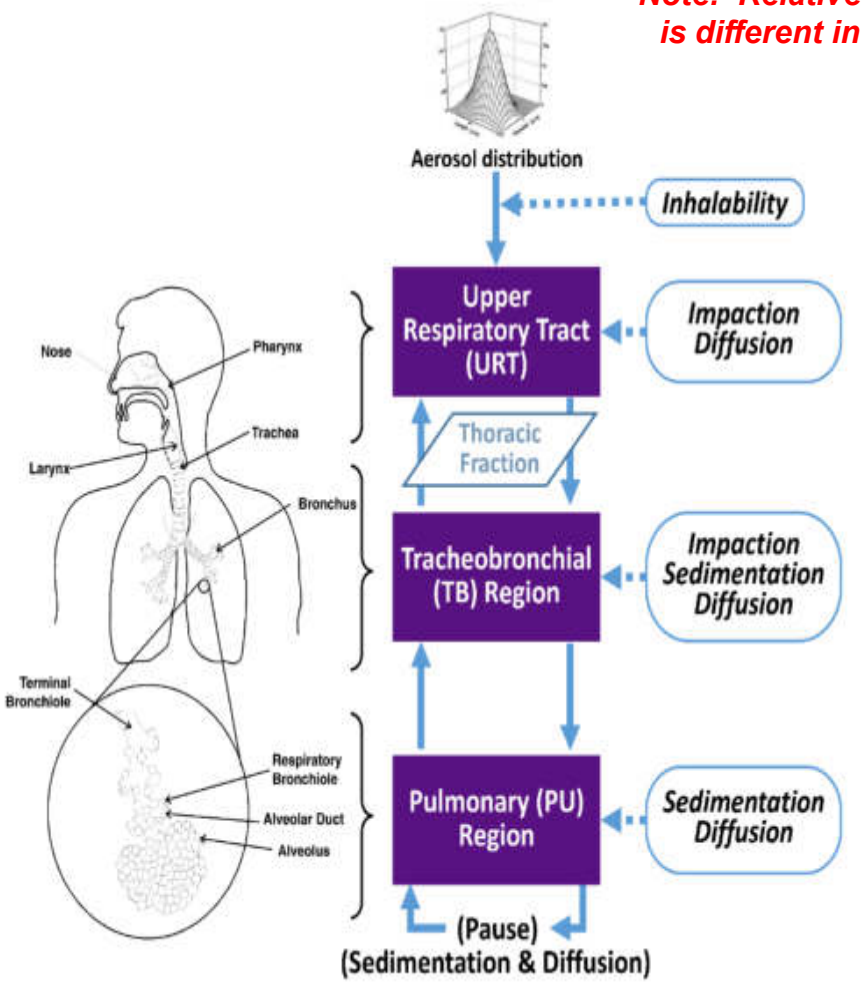


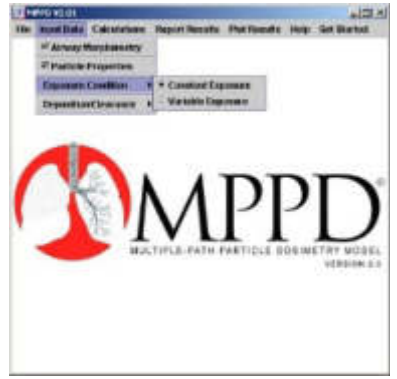
Particle Dosimetry Modeling

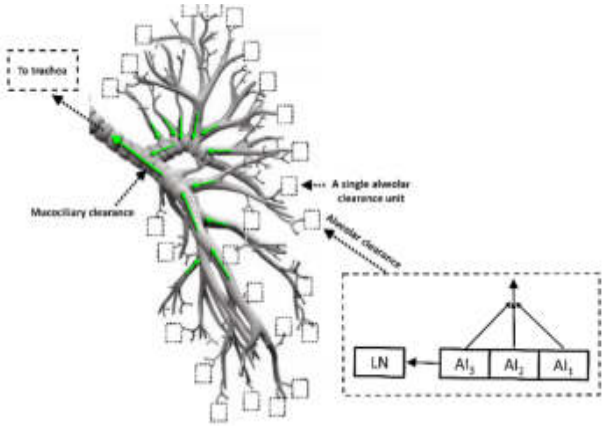
- **Modeling has matured into mechanistic structures:** based on fit to data and theory
- **Species-specific architecture** and **airflows,** breathing **modes** and activity patterns
- **Fundamental first principles** of physics
  - **Laws of conservation** of mass and momentum for airflow and particle transport
  - **Equivalent aerodynamic diameters** derived based on dimensions and density for each deposition mechanism

Retained burden = (Inhalability + Deposition) - Clearance

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





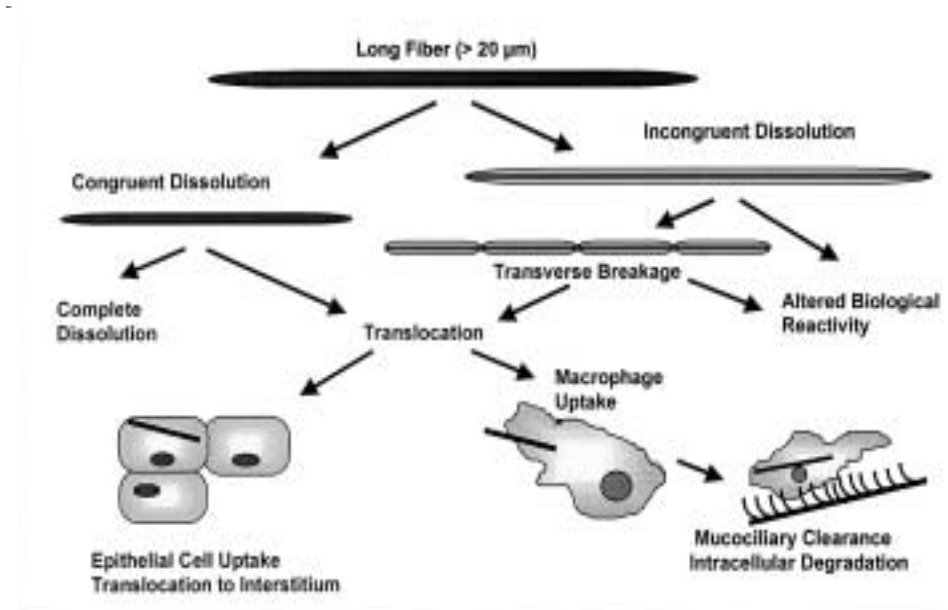


Clearance Mechanisms

- **Requires time course data**
  - Target tissues
- **Clearance mechanisms**
  - ***Dissolution = opportunity for in vitro data***
  - Physical translocation (mucociliary)
  - Phagocytosis by macrophages
  - Lymphatic drainage
- **Additional determinants of tissue response**
  - Composition
  - Shape
  - Surface reactivity

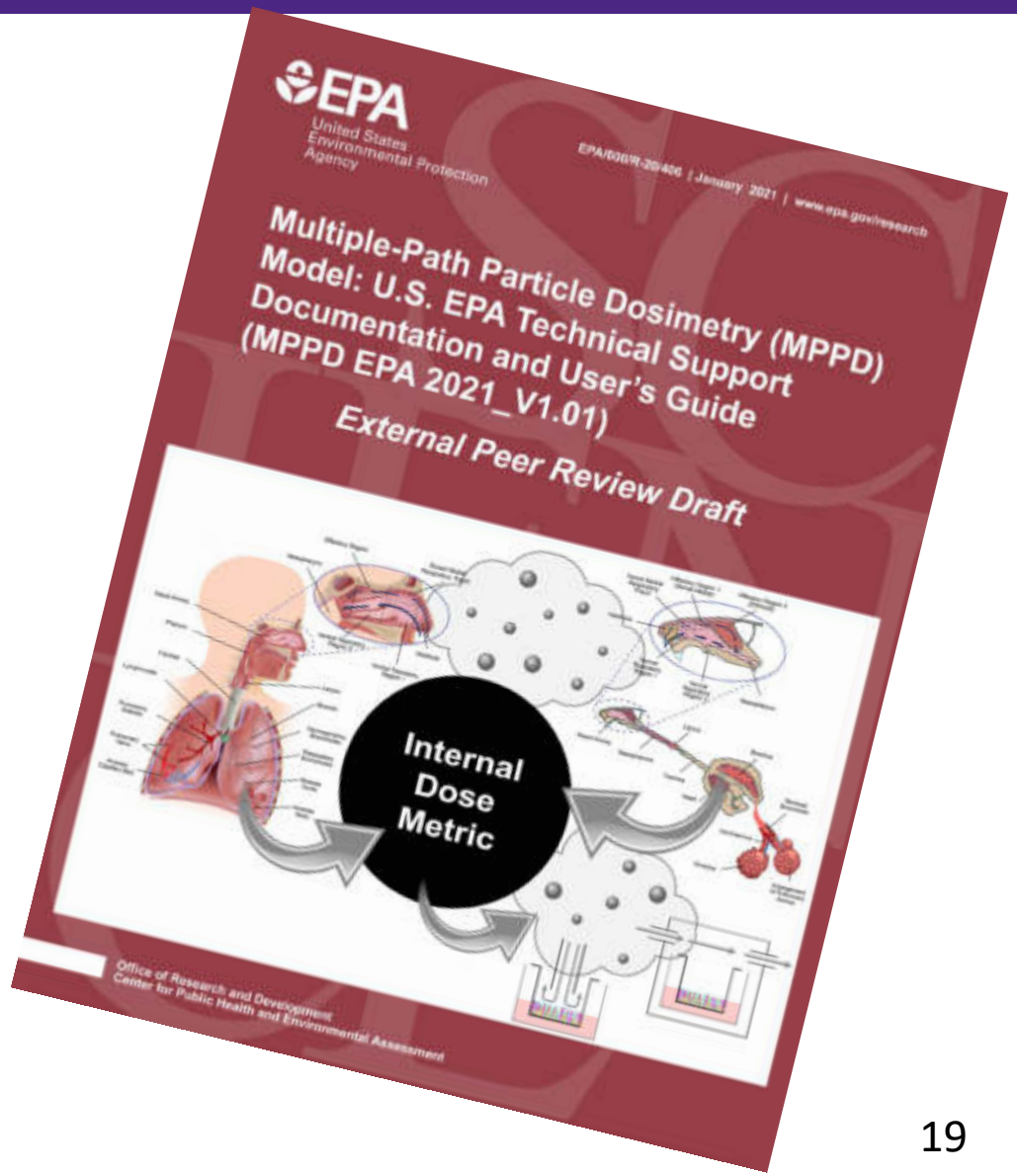
Exposure ≠ internal dose

Retained burden = (Inhalability + Deposition) - Clearance



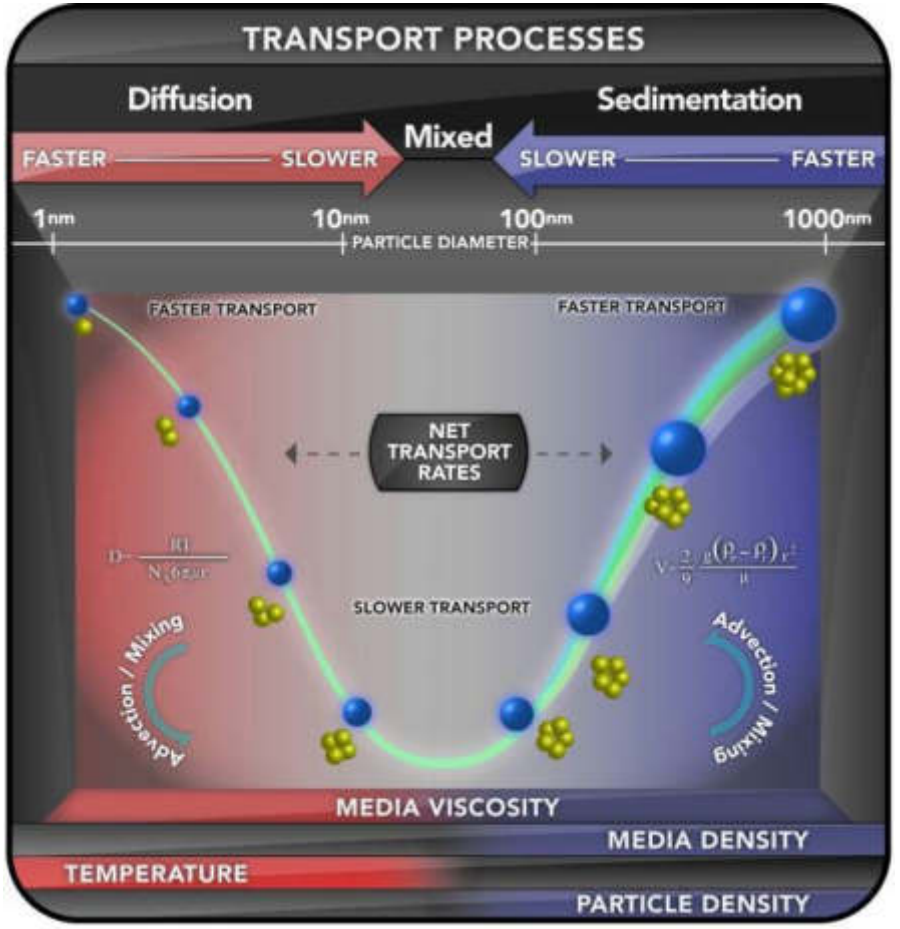
Multiple-path Particle Dosimetry (MPPD) Model

- New EPA version of the MPPD model software developed by Applied Research Associates, Inc. (ARA)
  - Revised graphical user's interface (GUI)
  - Some updated algorithms
- Multi-purpose: Technical support documentation *and* user's guide for broad audience
  - Introduction to inhalation dosimetry
  - Step-by-step explanation of input fields
  - Guidance on input parameters and procedures
  - Specific use case illustrations
- Base model: Coupling with computational fluid dynamics (CFD) underway and interface with other models in the future
- Recently completed external peer review



Dosimetry in the Dish

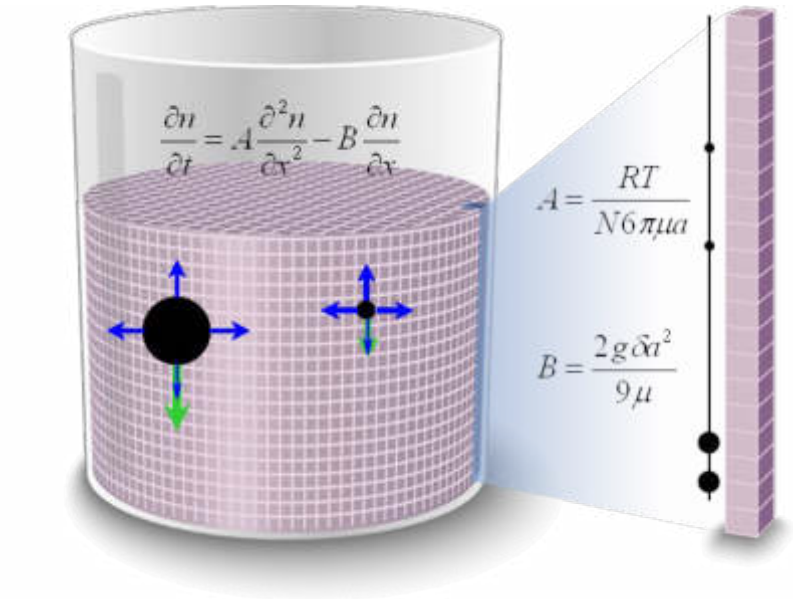
- Dosimetry is inherent issue for ***ALL* experimental designs!**
- Considerations of **transport mechanisms** for particles in an *in vitro* system shown to be a **major factor in delivered dose** to cells in culture.
- These considerations should be interfaced with **predicted doses to respiratory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

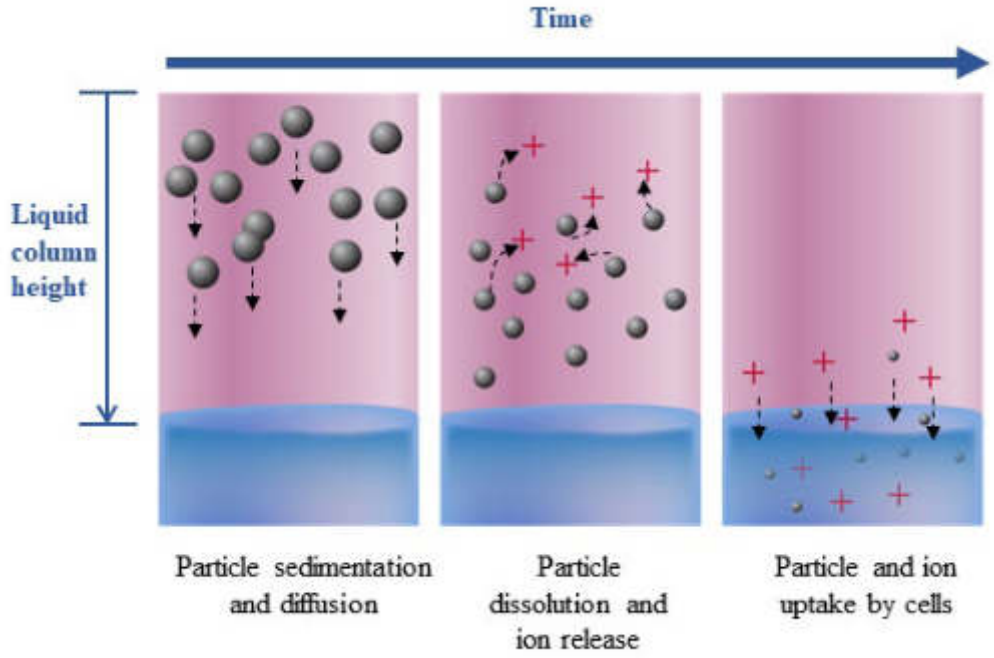
Dosimetry Models for *in vitro* Submerged Systems

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

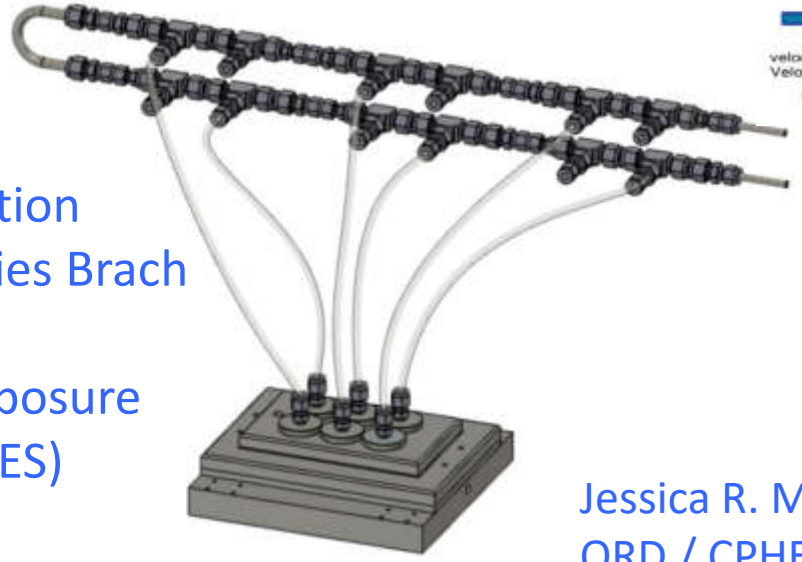


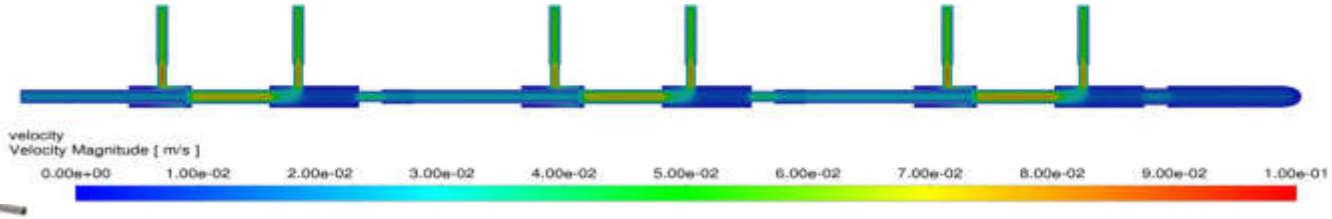
https://nanodose.pnnl.gov/default.aspx?topic=ISD3

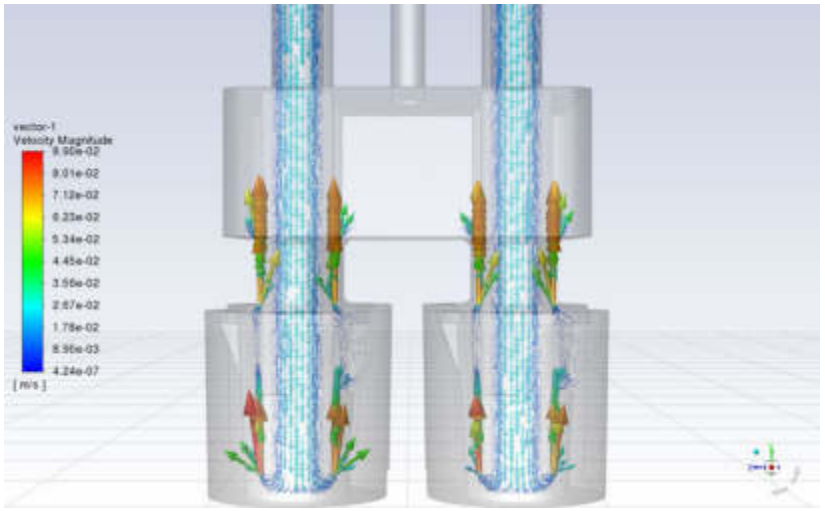
Thomas *et al.* 2018. *Part Fibre Toxicol.* 15(1) 6

Design of Air-liquid Interface (ALI) Exposure Systems

EPA's Inhalation Toxicology Facilities Brach (ITFB)
Cell Culture Exposure System (CCES)





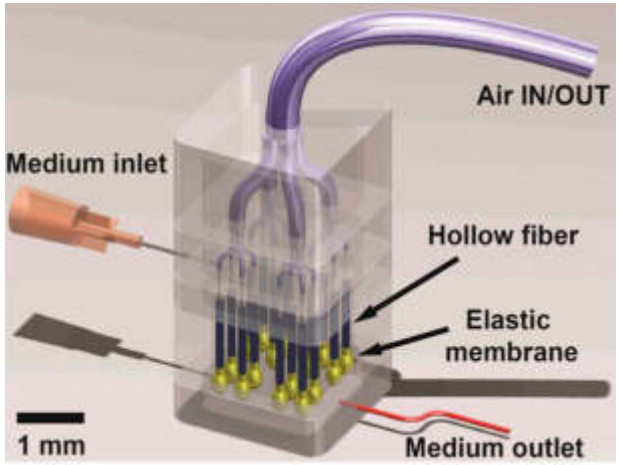


Jessica R. Murray
ORD / CPHEA / ITFB

- Computer Aided Design (CAD) + Computational Fluid Dynamics (CFD) models allow virtual testing of air-liquid interface exposure technology:
  - Predicts VOC and aerosol delivery to allow CCES re-design for aerosol transport
  - Time- and cost-effective method to target appropriate dose and optimize operational parameters

Dosimetry Informs "Lung on a Chip"

- The **Reynolds number** is used to study fluids as they flow.
- The **Reynolds number** determines whether a fluid flow is laminar or turbulent. If a flow is laminar, fluids will move along smooth streamlines.
- Also used in the **scaling** of similar but **different-sized flow** situations.



$$Re = \frac{\rho \upsilon L}{\mu}$$

ρ = density of fluid
υ = flow speed
L = characteristic linear dimension
μ = dynamic velocity

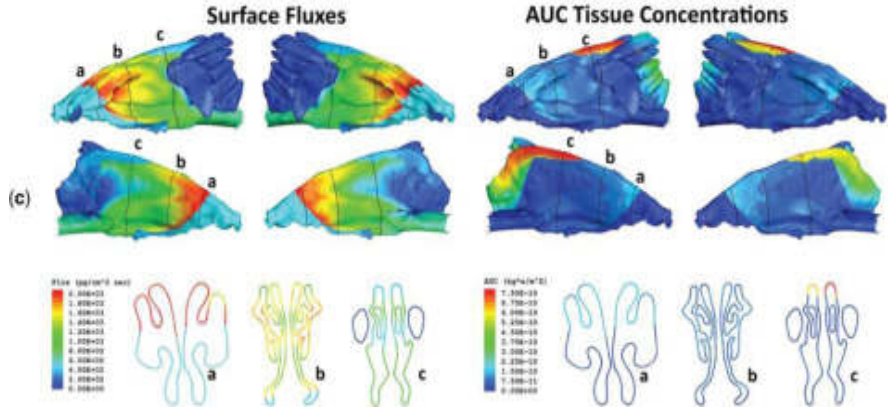
length (mm)	width (mm)	height (μm)	compartment volume (μL)	% of total blood (culture medium) volume	*U* (mm/s)	*Re*
			milli-device			
10000	7	597.21	41804.65	836.09	134.51	133.359
1000	70	188.85	13219.79	264.40	42.53	14.435
100	700	59.72	4180.46	83.61	13.45	1.447
10	7000	18.89	1321.98	26.44	4.25	0.145
1	70000	5.97	418.05	8.36	1.35	0.014
			micro-device			
1000	0.07	447.70	31.34	626.78	100.83	10.998
100	0.7	141.57	9.91	198.20	31.89	6.766
10	7	44.77	3.13	62.68	10.08	0.808
1	70	14.16	0.99	19.82	3.19	0.081
0.1	700	4.48	0.31	6.27	1.01	0.008

scale factor	body mass (g) (b = 1)	blood volume (mL) (b = 1)	area of the lung (mm^2) (b =1)	cardiac output (mL/s) (b = 3/4)
$1 \times 10^0 = 1$	100000	5000	70000000	100
$1 \times 10^{-3} =$ 1/1000 (milli)	100	5	70000	0.5623
$1 \times 10^{-6} =$ 1/100000 (micro)	0.1	0.005	70	0.00316

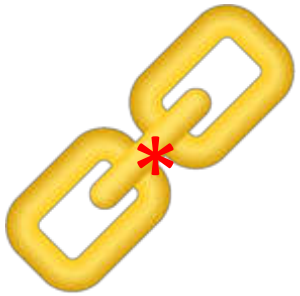
Bajaj, P et al (2021). doi: 10.1021/acsbiomaterials.5b00480
Journal of Aerosol Science special issue: Inhaled aerosol dosimetry: Models, applications and impact. https://www.sciencedirect.com/journal/journal-of-aerosol-science/special-issue/10XFX3JRGMF

Dosimetry Deployed to Compute the TSE

- **Range** from default to sophisticated forms
- Differ by **physicochemical property**
  - Particle: MPPD and CFD
  - Gas: CFD, PBPK, hybrid PBPK-CFD
- Account for **key characteristics of exposure:**
  - Concentration, duration, and frequency
  - Regimen: Acute, episodic, ambient (constant), workplace
- Characterize **anatomical and physiological determinants** of ADME
  - Breathing rate, mode (oral, nasal), ADME and metric
- **Determine dose** in exposure test system
  - Submerged vs. air-liquid interface
  - Cell sample type



Corley et al. *Toxicol. Sci.* 2015;146:65-88

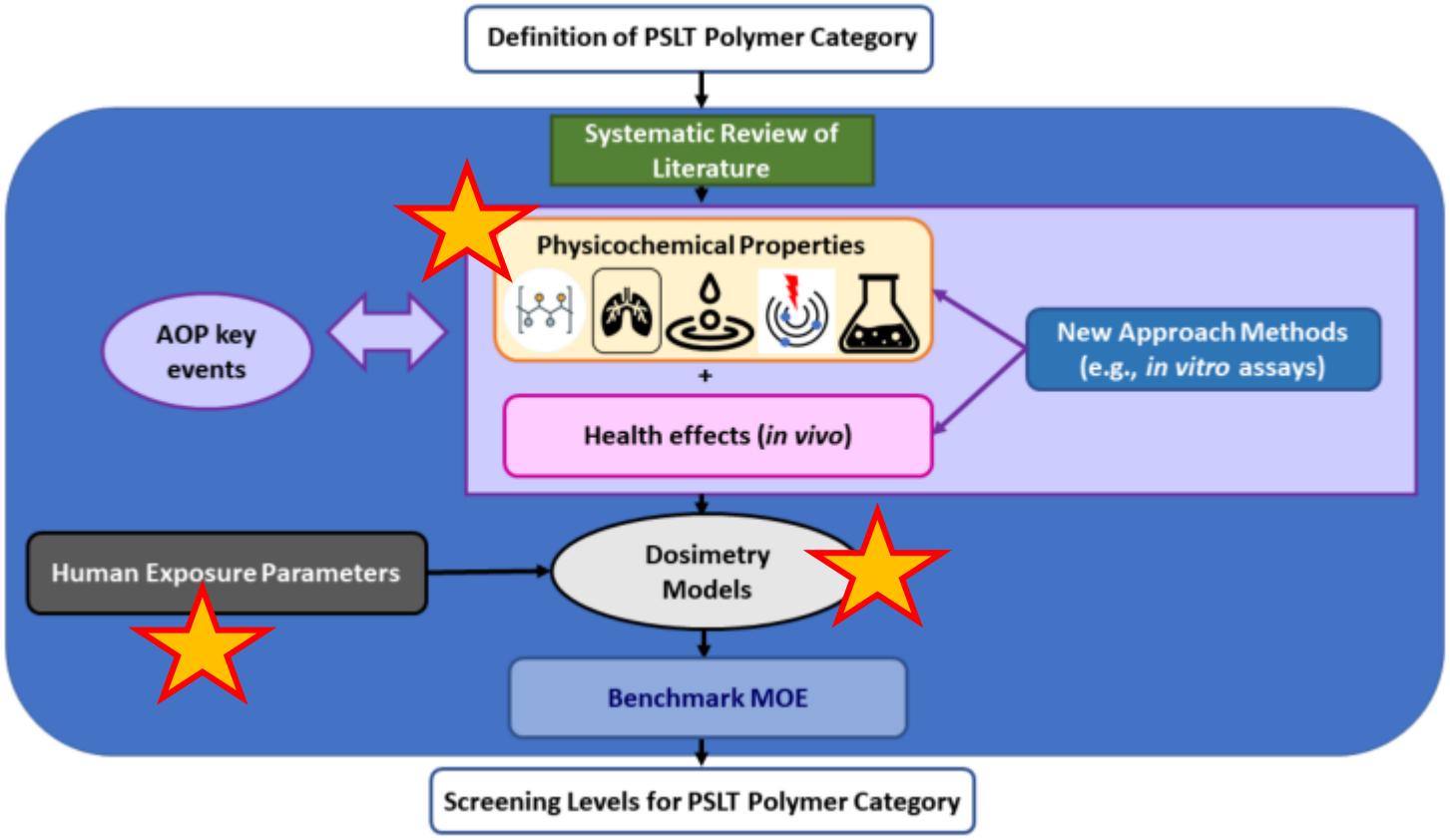


TSCA Application: New Chemical Substances (NCS)

- 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)

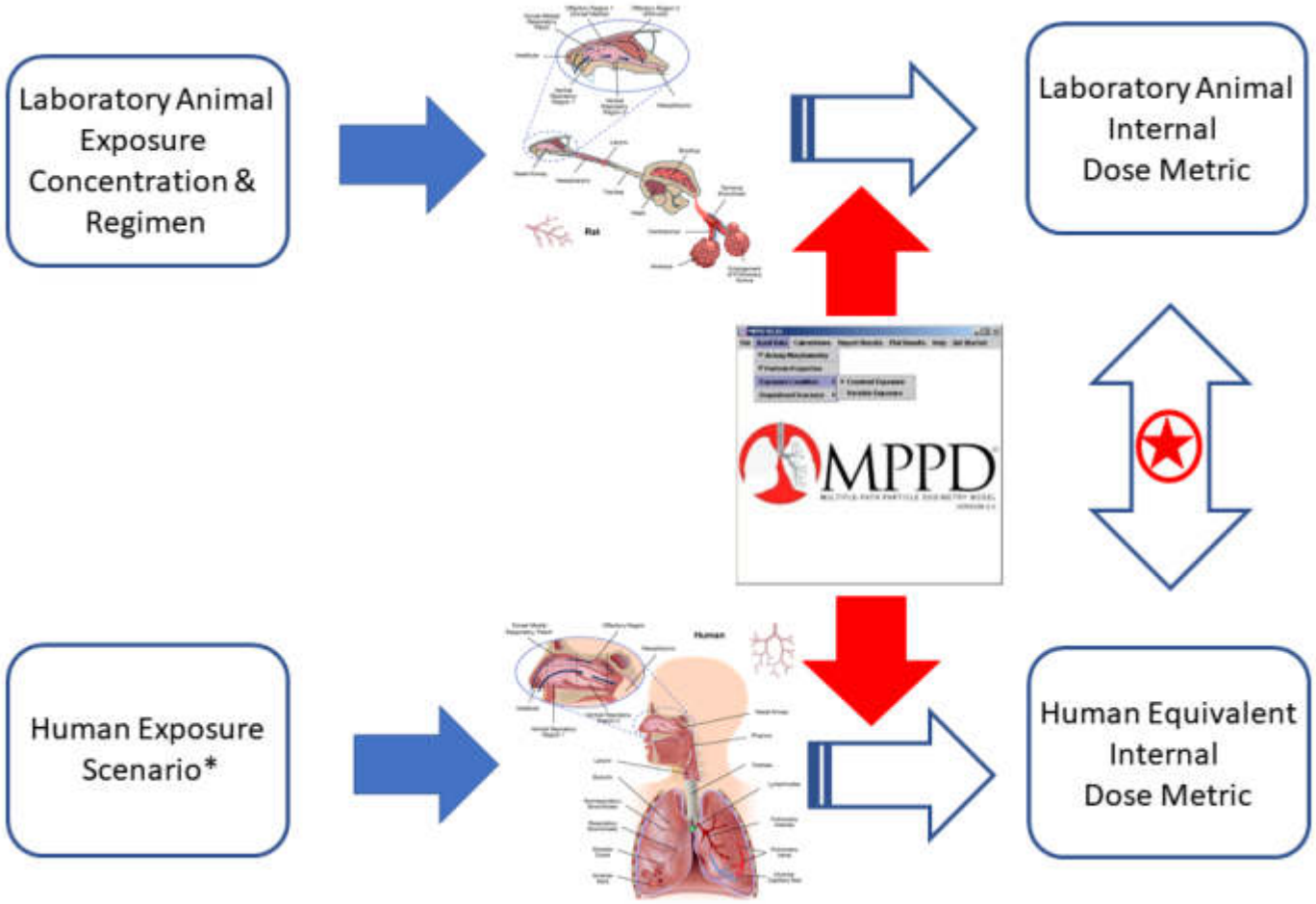
- Dosimetry plays critical role in strategy for evidence integration and evaluation to aid assessments
  - Inclusion criterion
  - Translation of dose across experimental platforms
  - Target specific exposures
- NAMs can provide data to
  - Inform physicochemical properties and health effects
  - Refine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



Jarabek Stedeford et al. (*accepted*)

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



Refining ChemSTEER "Exposure" Estimates

- **Chemical Screening Tool for Exposures and Environmental Releases** (ChemSTEER)
- Estimates exposure as either
  - **Daily acute potential dose rate** (PDR) which represents average exposure over an 8-hr workday, or
  - **Lifetime average daily dose** (LADD) which estimates long-term exposures to the chemical substance and is averaged over a lifetime exposure of **80 years**
- The PDR or LADD is used to evaluate the **margin of exposure (MOE)** by comparison with the HEC
- *Parameters used to calculate PDR or LADD are redundant with MPPD simulations to calculate the HEC based on internal dose and **do not target specific exposures***

Refining ChemSTEER "Exposure" Estimates

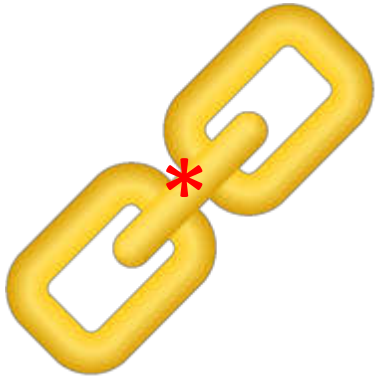
Table 2. Default values used for calculating the PDR and LADD.

Description	Equation	Parameter	Defaults	Units
PDR (mg/day)	Cm × b × h	Mass concentration of chemical in air (Cm)	5	mg/m³
		Volumetric inhalation rate (b) (0 < b ≤ 7.9)	1.25	m³/hr
		Exposure duration (h) (0 ≤ h ≤ 24)	8	hrs/day
LADD[a] (mg/kg-bw/day)	(I × ED × EY) (BW × ATc × 365 days/yr)	Inhalation PDR (I)	50	mg/day
		Days exposed per year (ED) (0 ≤ ED (integer) ≤ 365)	250	days/site-yr
		Years of occupational exposure (EY) (0 ≤ EY)	40	years
		Body weight (BW) (0 ≤ ATc)	80	kg
		Averaging time over a lifetime (chronic) (0 ≤ ATc)	75	years

- **Mass concentration** based on National Institute for Occupational Safety and Health (NIOSH) value for Particulates Not Otherwise Regulated (PNOR) and **not specific to aerosol under evaluation**
- **Parameters in red** already accounted for in MPPD simulations **to predict HEC**
- MPPD could be deployed again to predict **targeted exposure** estimate using **specific data**
  - Size distribution, density, solubility
  - Activity pattern and duration
- Incentivize **quality data submissions**

Cultivating Best Practices: Reporting Standards Roadmap

- **Data sharing: Standards**
  - MIAME: Minimum Information About a Microarray Experiment
  - SEND: Standard for Exchange of Non-clinical Data
- **FAIR Principles: Findable / Accessible / Interoperable / Reuseable**
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4792175/pdf/sdata201618.pdf
  - **Translate TSE across exposure systems to aid evidence integration**
    - Exposure system operating parameters and conditions
    - Rationale for choice of cells and assays
    - Support interoperability with modular, multi-scale dosimetry
  - **Develop data pipelines and analytical work flows: Meta data**
    - Experimental annotation: ***WHAT / HOW / WHY***
    - Curation and consistency: Domain expertise and detail
    - Interdisciplinary dialogue
    - ***Repurposing: Applicability***



Reporting Standards: Exposure Systems

- **Generation system and specifications**
  - Dimensions and volume
  - Air flow rate
  - Delivery mechanism(s)
  - Plate size and number, inserts
- **Concentration** (delivered relative to nominal should be consistent)
- **Analytical methods**
- **Temperature**
- **Humidity**
- **Relevance to target scenario**
  - Regimen and duration
  - Physicochemical characteristics
    - Gas: Mass transfer properties
    - Particle: Deposition mechanisms

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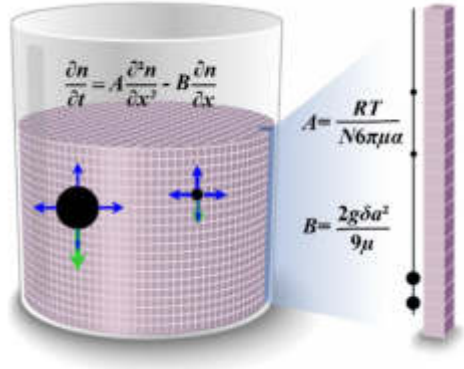
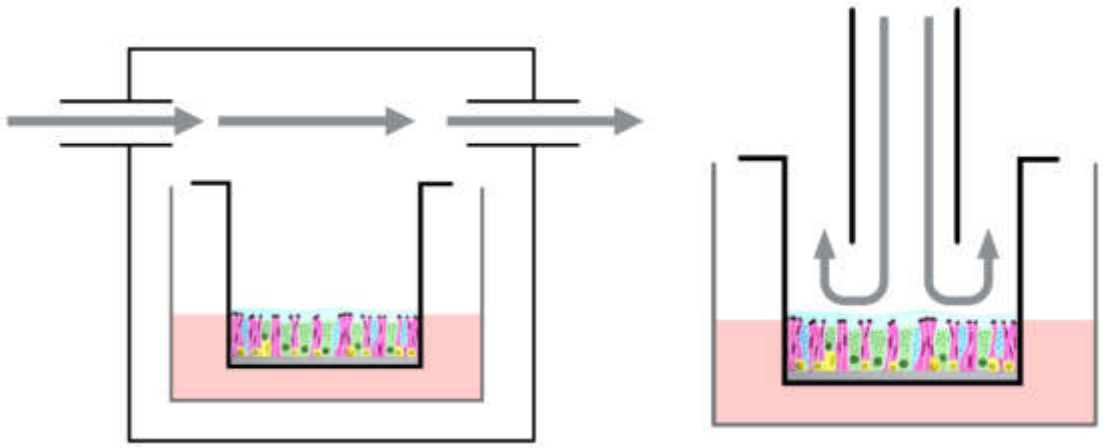


Hinderliter *et al.* 2010. *Part Fibre Toxicol.* 7(1) 36
https://nanodose.pnnl.gov/default.aspx?topic=ISDD



Reporting Standards: Cell Systems

- **Culture system**
  - Demonstrated reliability
- **Cell type(s)**
  - Source(s)
  - Metabolic competency
  - Rationale for choice (e.g., relevance to target scenario)
- **Media**
  - Type (components / lot #)
  - Location (epithelial or endothelial)
  - Volume
- **Viability**
  - Evaluation
  - Duration

Jarabek et al (*in preparation*)

- **Assays**
  - Relevance to key events and respiratory tract
  - Established performance and variability
  - Response levels and rationale

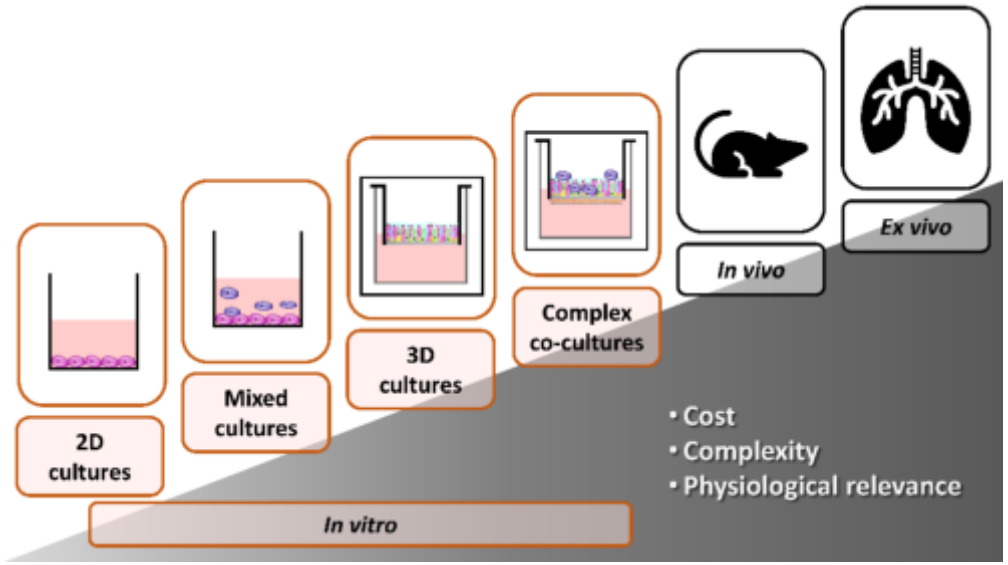


Figure adapted from Lacroix et al (2018). *Appl in vitro Tox*, 4(2), 91 – 106. https://www.liebertpub.com/doi/full/10.1089/aivt.2017.0034

Scale up to Human Equivalent Concentration (HEC)

- **Ratio of internal doses used as adjustment factor across experimental designs**
- Illustrated for **regional deposited dose (RDD)** of particles in animals (A) ***or in vitro (*)*** and humans (H) but can be calculated for any other **particle dose metric** (SA, #) or **normalizing factor** (# epithelial cells, # alveolar macrophages)
- **Minute volume** can be age-specific and incorporate a ventilatory activity pattern reflecting breathing mode (nasal, mouth, oronasal)

$$(RDDR)_r = \frac{(RDD)_{A*}}{(RDD)_H} = \frac{(C_1)_{A*}}{(C_1)_H} \Big/ \frac{(\text{Normalizing Factor})_{A*}}{(\text{Normalizing Factor})^{\ddagger}_H} \times \frac{(\dot{V}E)_{A*}}{(\dot{V}E)_H} \times \frac{(F_r)_{A*}}{(F_r)_H}$$

$(\dot{V}E)$ = Minute volume (ventilation rate)
F_r = fraction of mass deposited in region predicted with model
r = Region of observed toxicity for extrapolation
‡ = Surface area (SA) for respiratory effects and body weight (BW) for remote effects

Example: Dose Metric Parameters

Recommended Incubation Parameters

Transwell Insert Diameter	Insert Membrane Growth Area	Multiple Well Plate or Dish Type	Volume Added per Plate Well	Volume Added to the Inside of Transwell Insert
4.26 mm	0.143 cm^2	96-well	0.235 mL	0.075 mL
6.5 mm	0.33 cm^2	24-well	0.6 mL	0.1 mL
12 mm	1.12 cm^2	12-well	1.5 mL	0.5 mL
24 mm	4.67 cm^2	6-well	2.6 mL	1.5 mL
75 mm	44 cm^2	100 mm dish	13 mL	9.0 mL

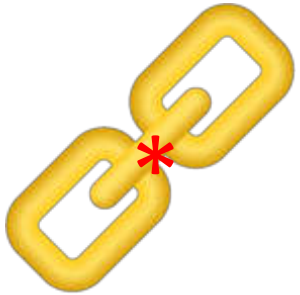
https://www.corning.com/worldwide/en/products/life-sciences/products/permeable-supports/transwell-guidelines.html

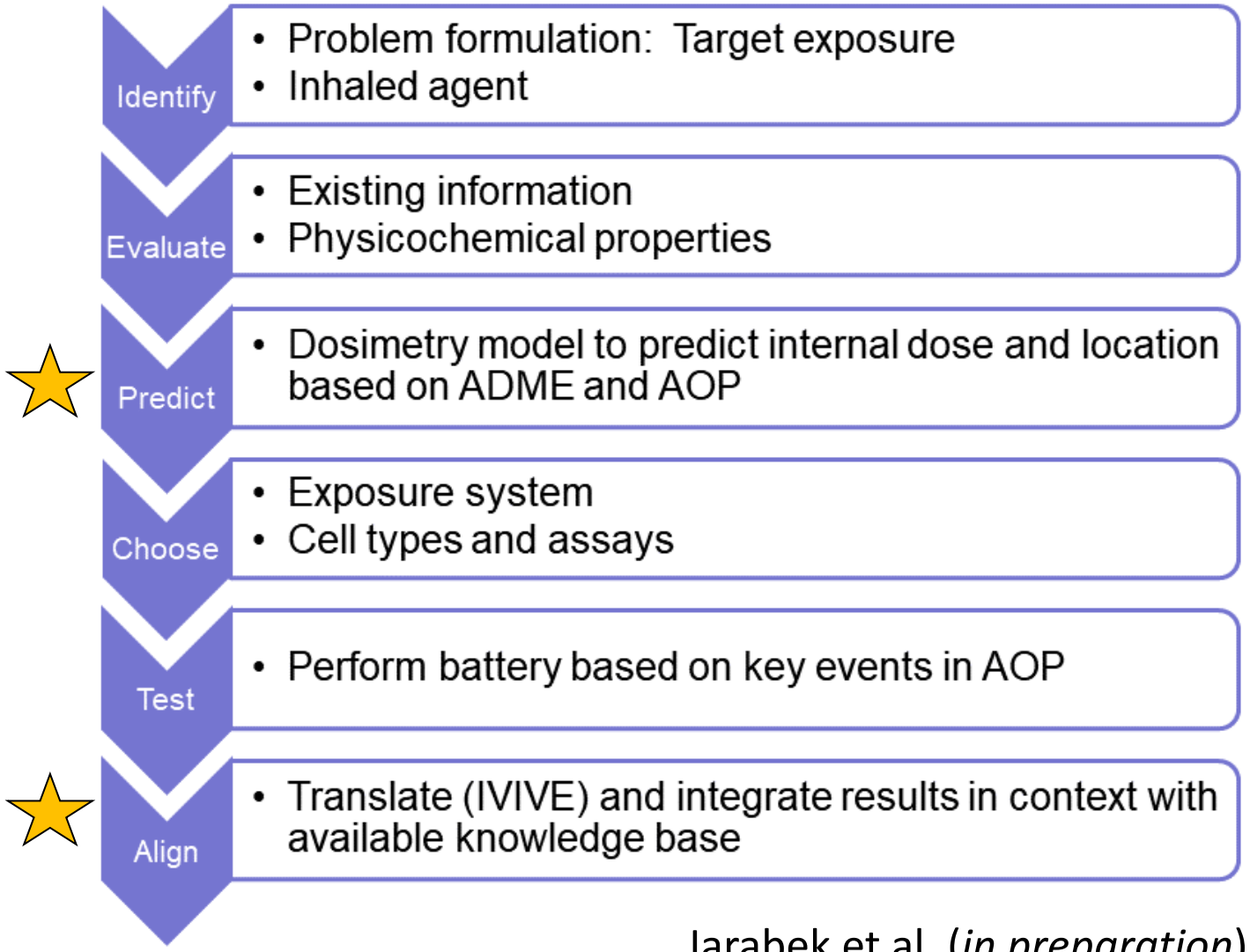
Volume/SA ml/cm^2	IV_{SA}/HU_{SA}
0.52	2.6×10^{-5}
0.30	$.06 \times 10^{-5}$
0.45	2.1×10^{-5}
0.32	8.7×10^{-5}
0.20	81×10^{-5}

Potential impacts:

- Confluence and polarity
- ***Delivery mechanisms and dose***
- Variability
- Inferences

AOP-*Inspired* Integrated Approach to Testing and Assessment





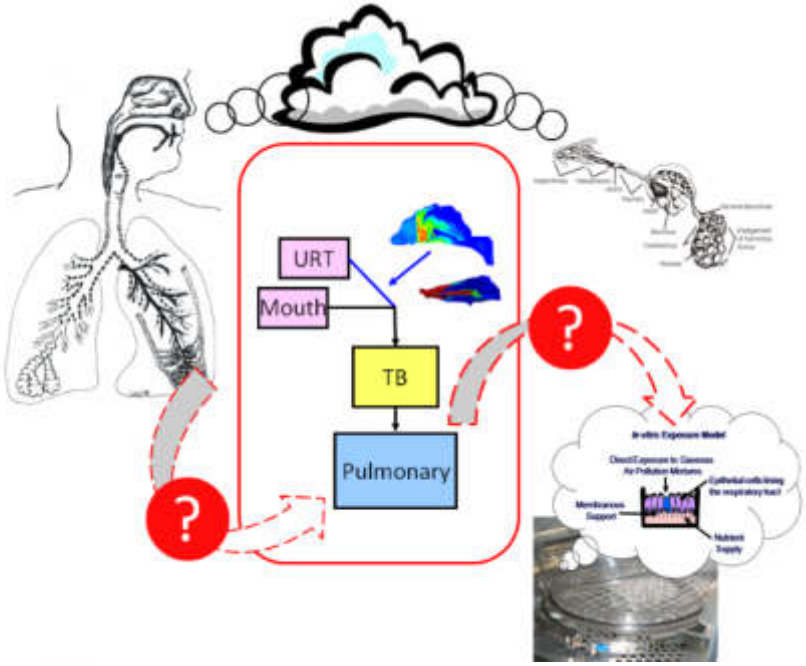
Jarabek et al. (*in preparation*)

Specific IVIVE Challenges

- **Define relevant dose metric: Detail commensurate with data**
  - Exposure versus internal dose
  - Generic, regional or mechanistic description
- **Scale up to human equivalent concentration (HEC)**
  - Exposure regimen, duration and relevance to target scenario
  - Default algorithm or quantitative PBPK-CFD model
- **Specify degree of demonstration / verification** for endpoint assays with prognostic value
- **Determine disease dimension(s) evaluated** (e.g., early or late key events)
- **Characterize uncertainty and variability**
  - UF for intra-human TK and TD are not necessarily obviated
  - Cell as target system surrogate
    - Target tissue specificity and viability
    - Spatial representation and variability
    - Metabolic competency and variability

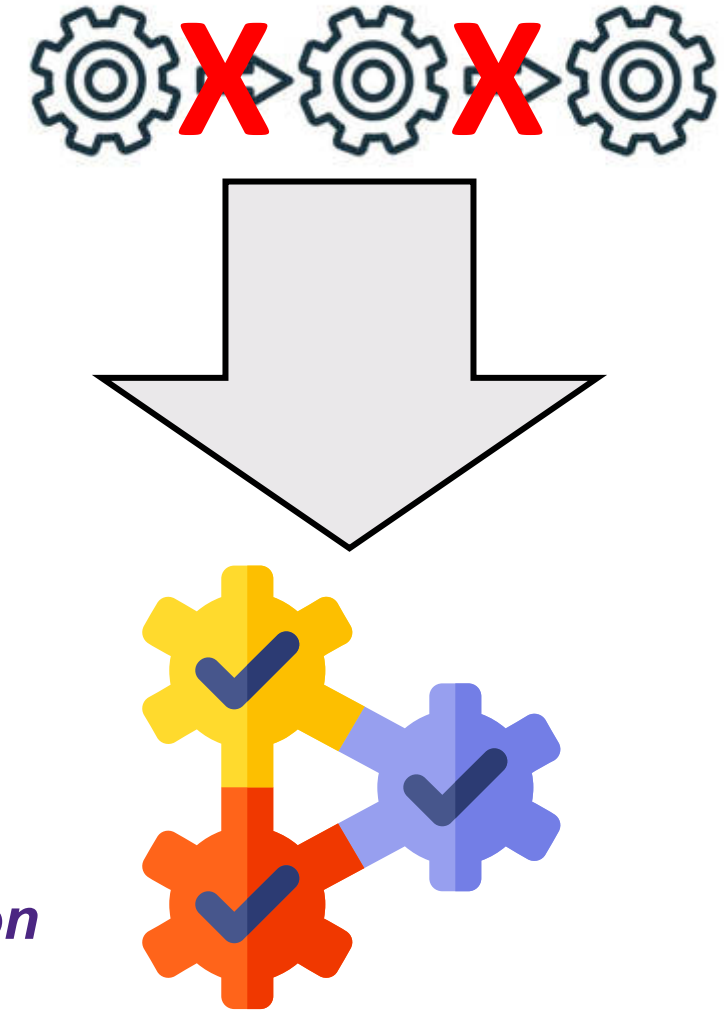
“Black Box” to Toolbox

- ***Modeling must be iterative with data development***
- **Create coherent context and hierarchical modeling strategy across**
  - *In vivo*
  - *In vitro*
- **Exposure generation and characterization** must consider the dynamics of physicochemical properties, transport and transformation in the **system**
- **Methods and models** used for interspecies extrapolation can be used to **create context** for characterizing *in vitro to in vivo* (IVIVE) **extrapolation**
- **Foster interdisciplinary dialogue**
- **Navigation guides for users (e.g., MPPD)**
  - Choice of models
  - Input parameter sources



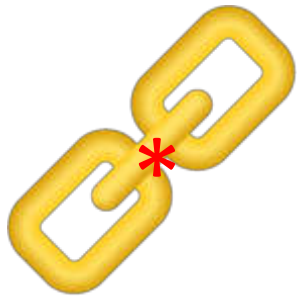
Impacts: Inferences and Integration

- **Restructure workflows** so silos not separated
  - Appreciate **assumptions and consequences**
  - **Integrate** both downstream AND upstream
- **Clarify** terminology and context
- **Elucidate study quality and utility**
- **Incorporate** computational outputs
  - Rectify units
  - Provide modular modeling capabilities
- Support **reusability and interoperability**
  - Develop reporting standards with sufficient meta data
  - Encourage targeted analyses
- ***TRANSFORM translation and improve evidence integration***



Summary: Advancing Assessments

- **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**



Thank you

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