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EPA United States Environmental Protection Agency

Application of Mechanistic Data in Risk Assessment: Exposure Alignment and Evidence Integration

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Advancing New Approach Methods for Tobacco Harm Reduction
Virtual Symposium
CORESTA **Smoke Science and Product Technology Conference**
October 19, 2021

EPA at 50 Progress for a Stronger Future

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

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Topics

- **Challenge:** Coherent evidence integration across large landscape of risk assessment applications
- **Building confidence:** Create context for translation based on mechanistic modeling to advance novel approach methods (NAMs)
  - AEP and AOP frameworks
  - Exposure alignment
  - Quantitative AOP and IATA
- **Case study:** Evaluation of new chemical substances under TSCA
- **Specific considerations:** Communication and characterization
  - Reporting standards
  - Uncertainty / variability and new translation factors
- **Summary**

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

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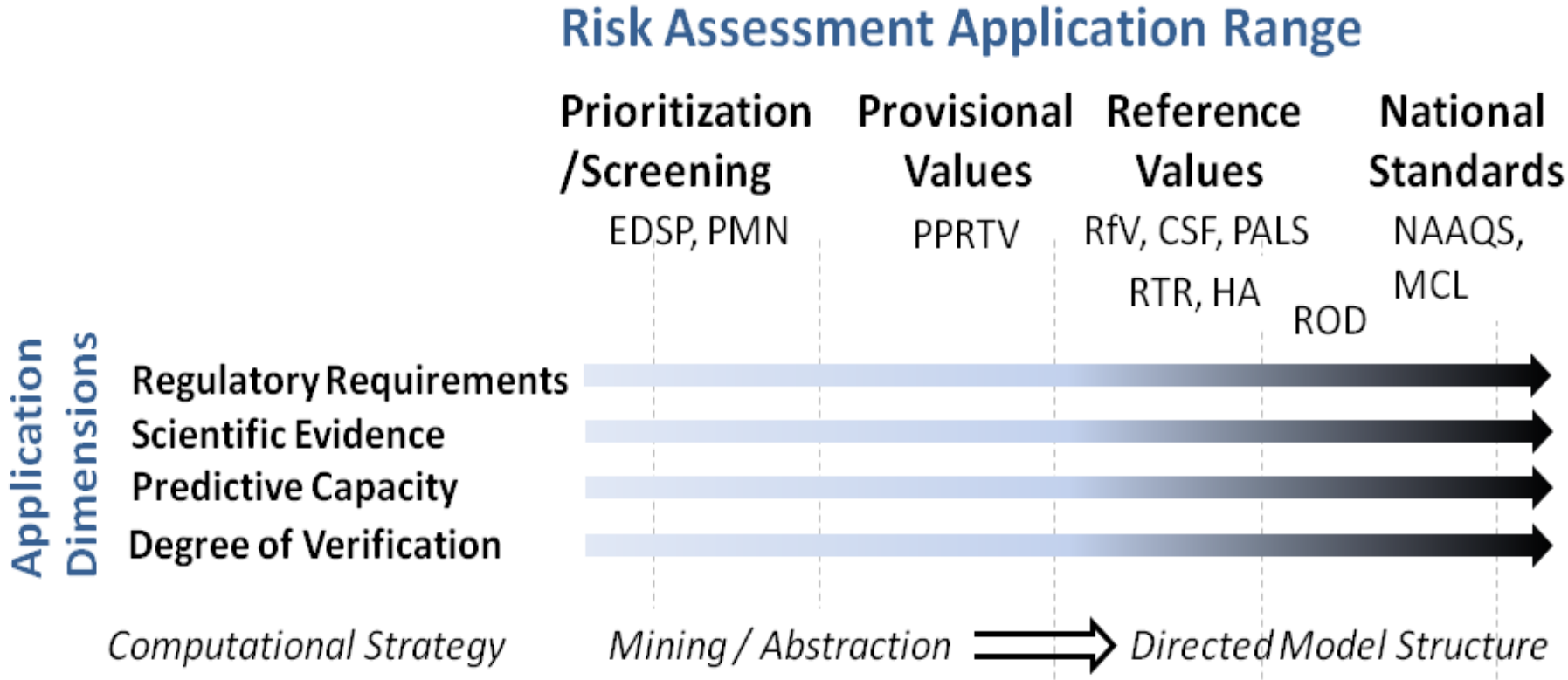
Risk Assessment Landscape



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

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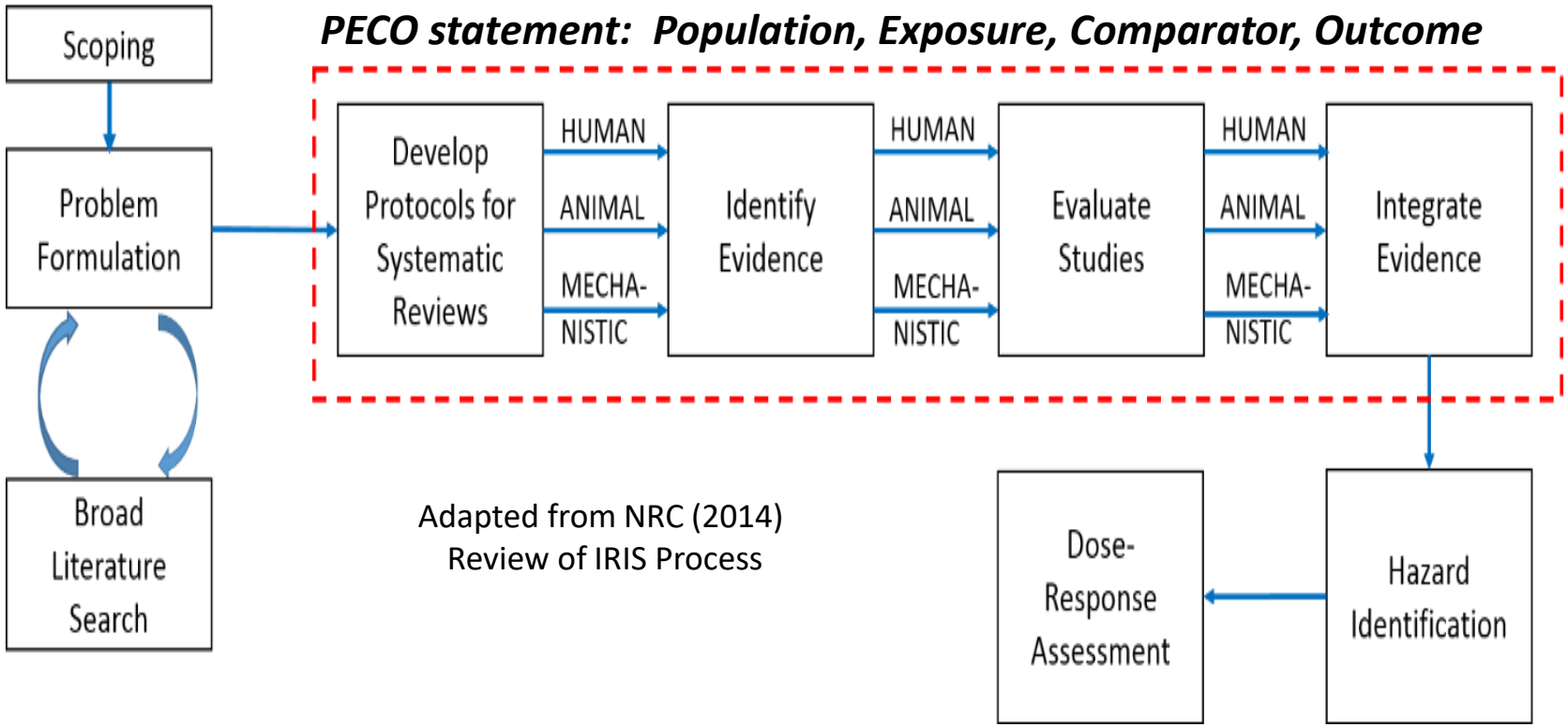
Challenge: Evidence Integration



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

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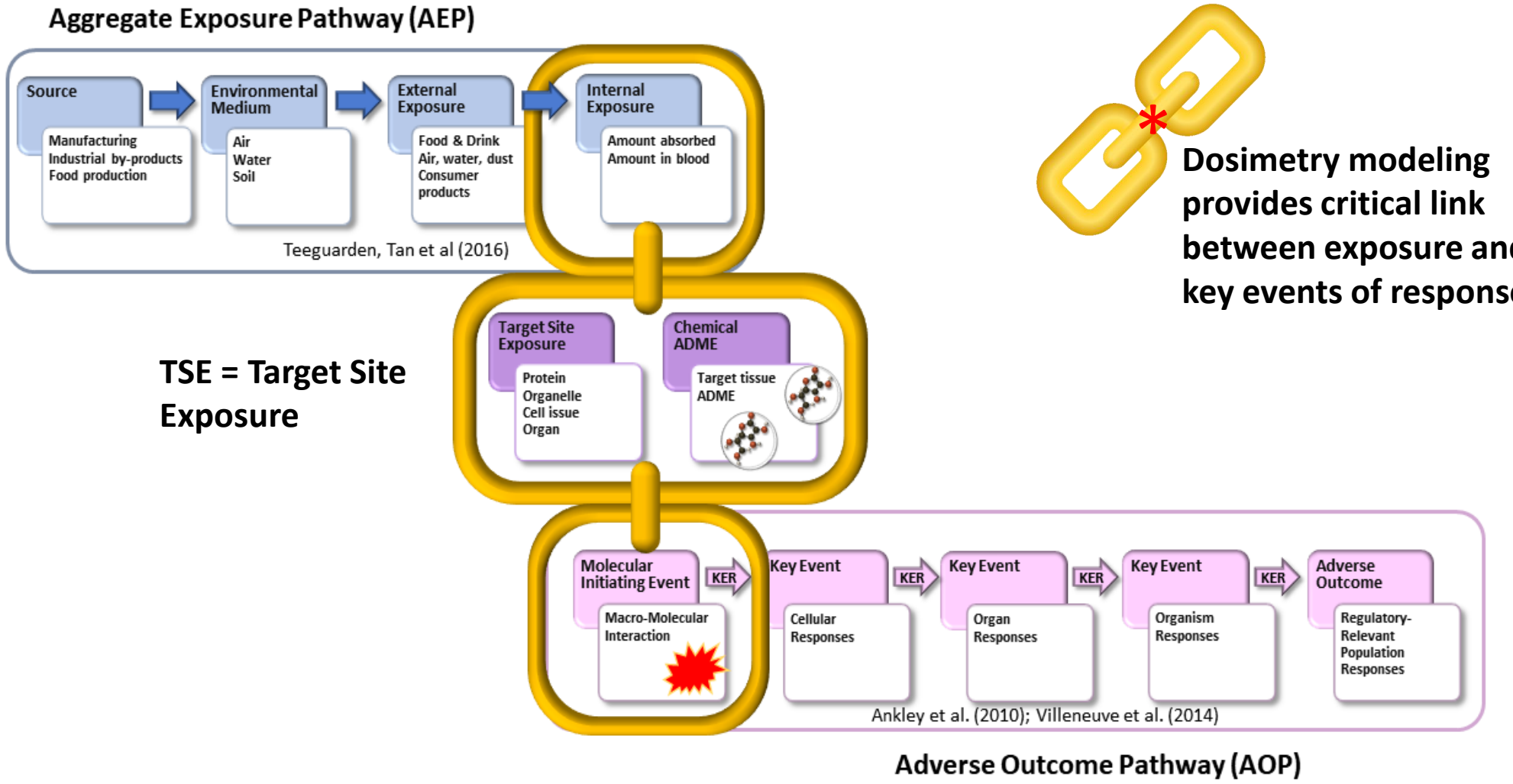
Transitions: Comprehensive Characterization



TSE = Target Site Exposure

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

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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)

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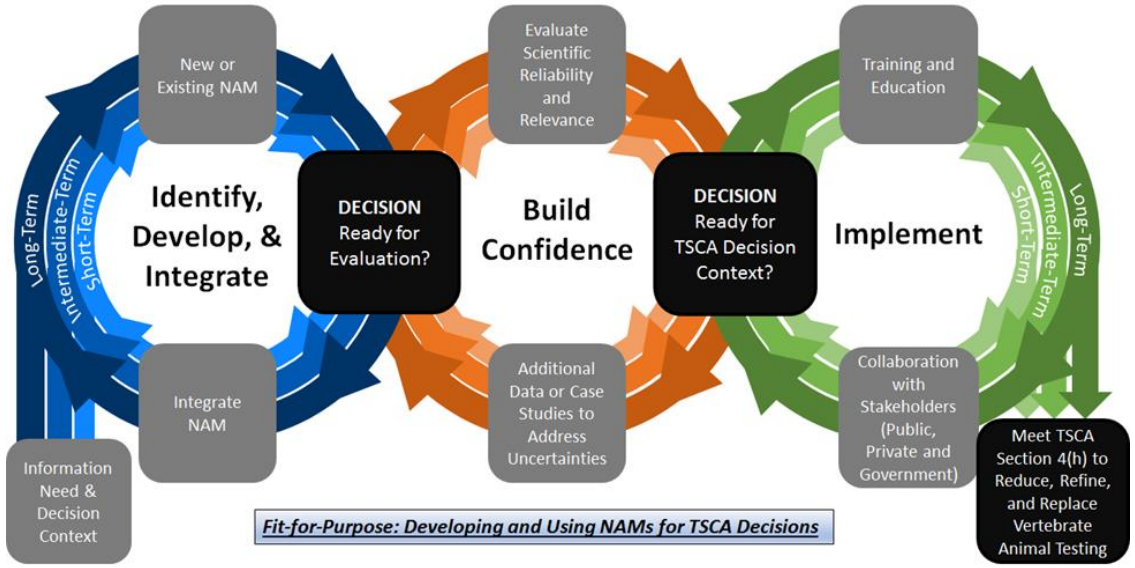
NAMs: Strategy for Success

- **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** in various AOP
  - **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]

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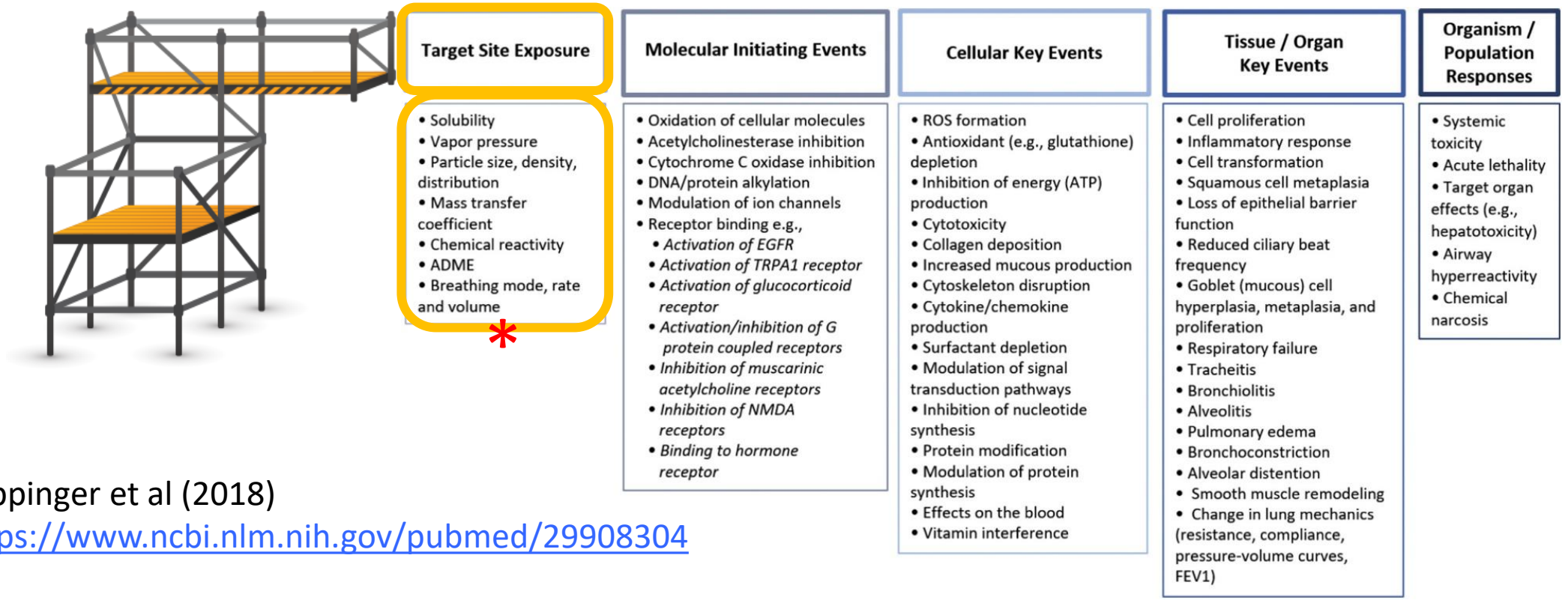
Translation: AOP as Mechanistic Scaffold



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

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

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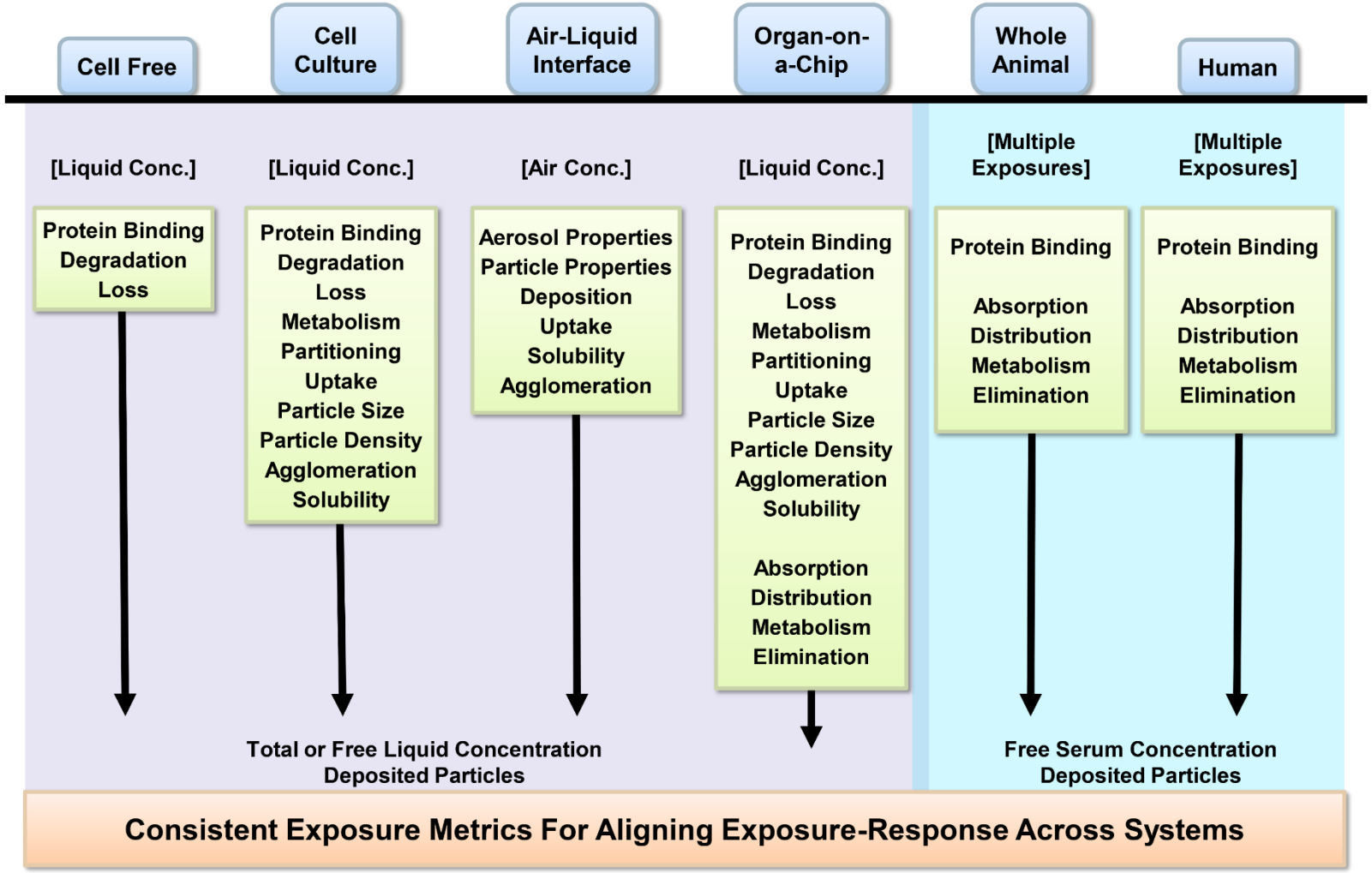
Translation: Exposure Alignment



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

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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

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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**
- Incorporates 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**

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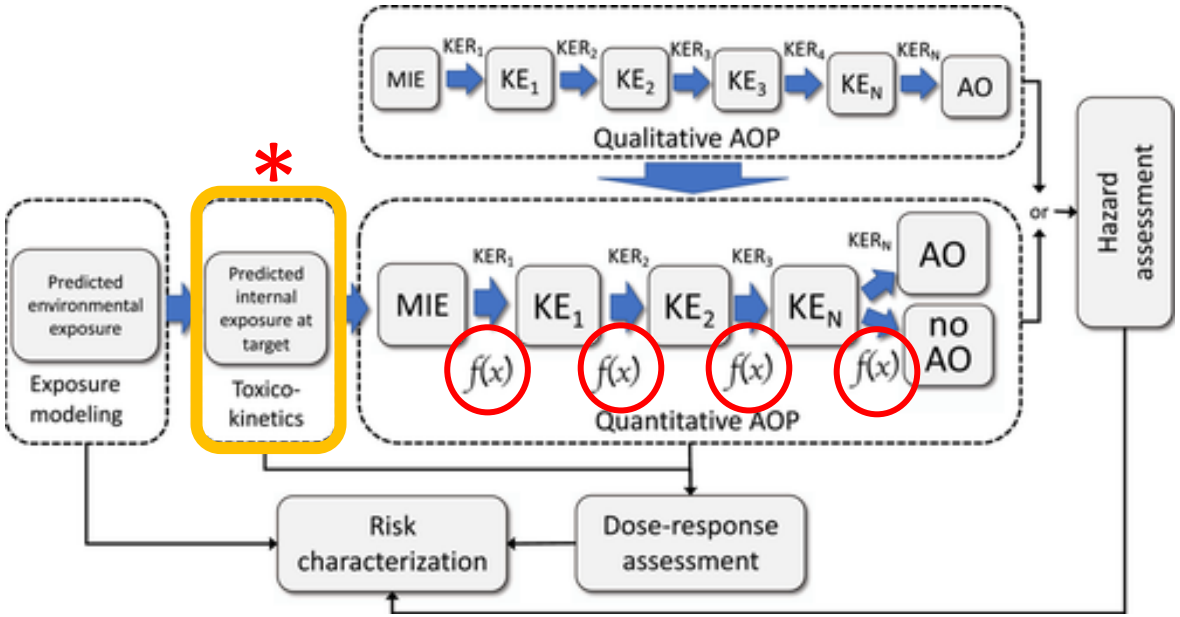
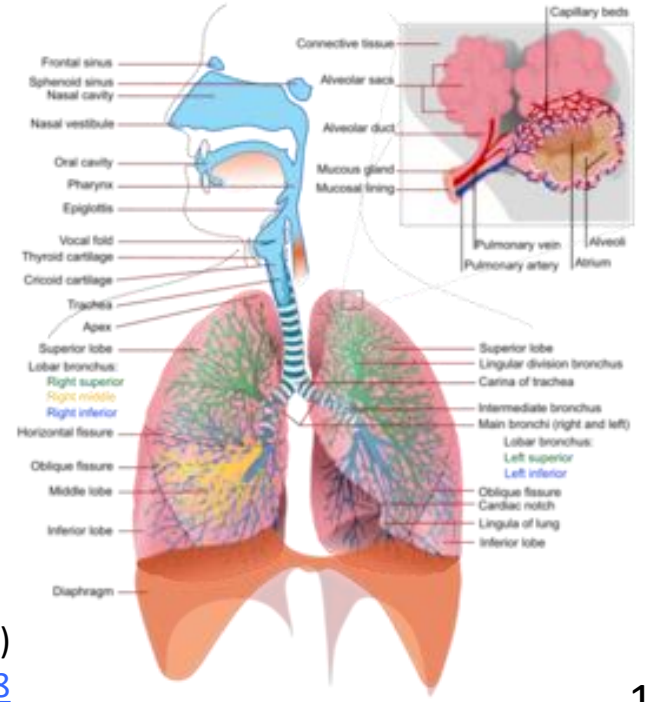
Translation: TSE Alignment and Quantitative AOP

- Account for **key characteristics of exposure**
- Address **physicochemical properties** as determinants of internal dose
- **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

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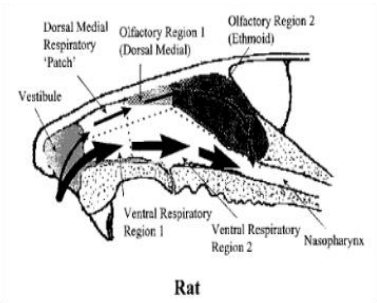
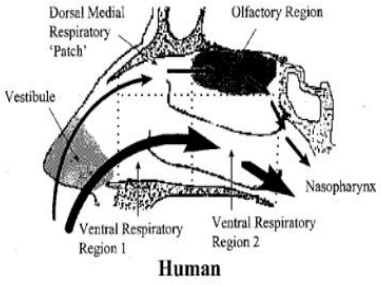
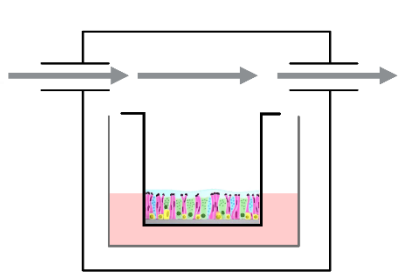
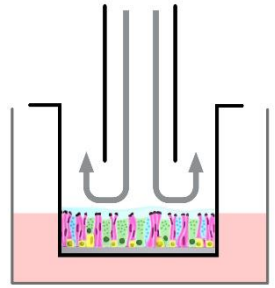
Conceptual Basis of Extrapolation

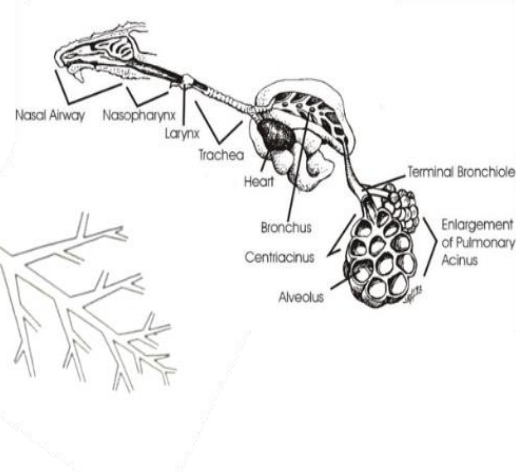
Not to scale

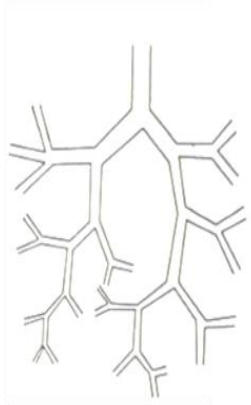


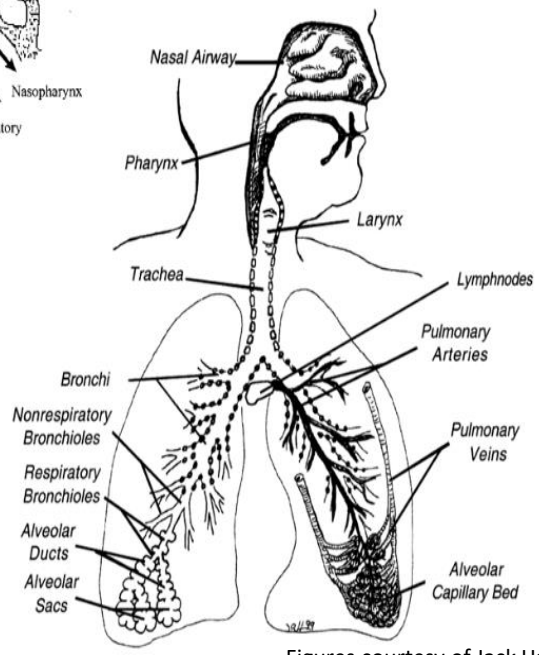


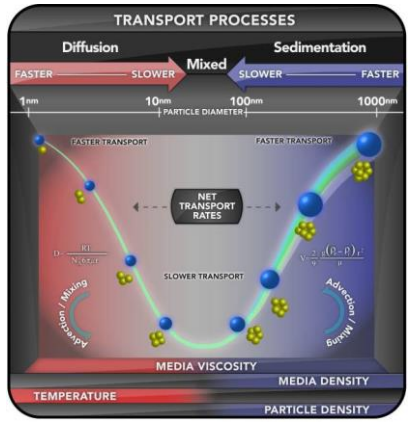












Figures courtesy of Jack Harkema, MSU

- 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)

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Physicochemical Properties

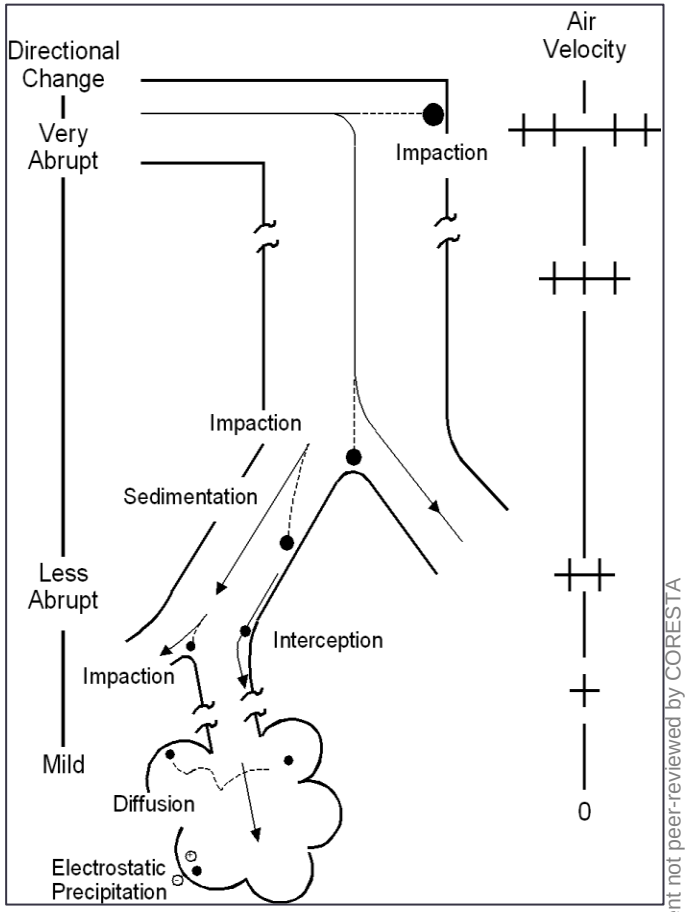
Particle / Fibers / Manufactured Nanomaterials

- 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

Exposure ≠ internal dose



Retained burden = (Inhalability + Deposition) - Clearance

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

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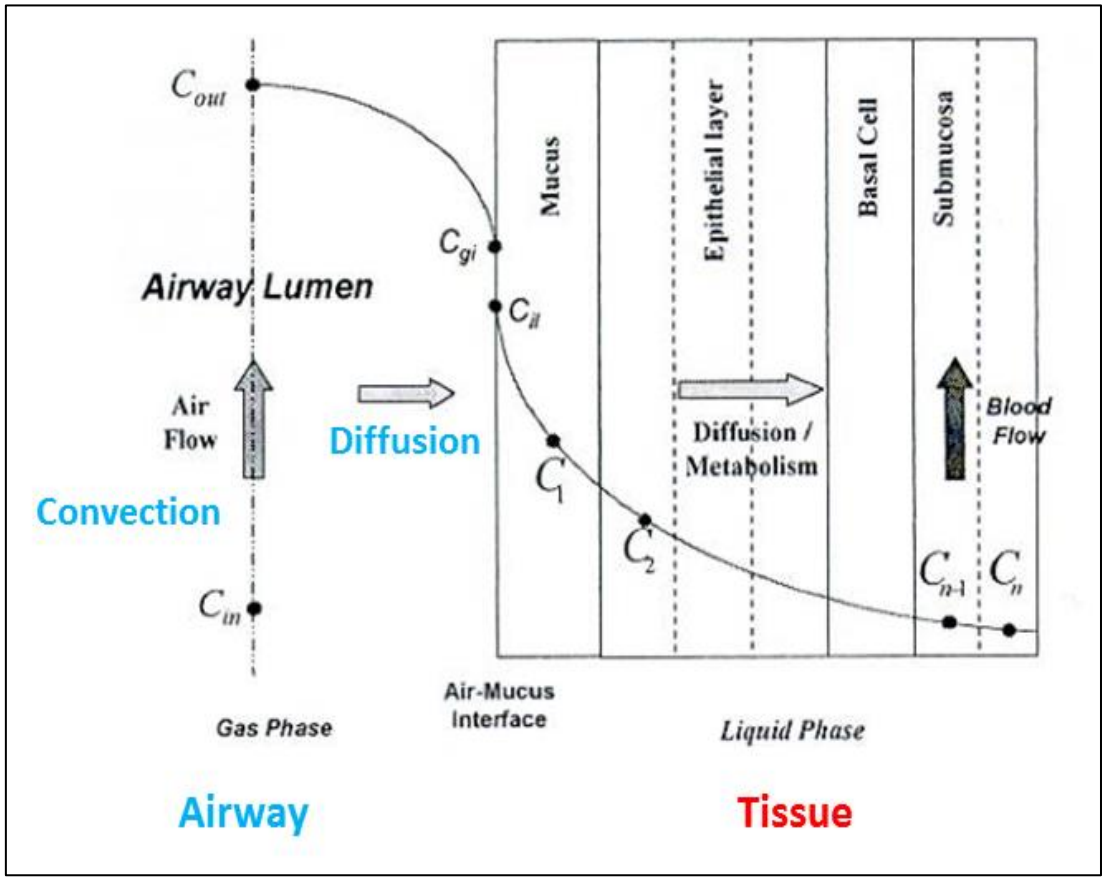
Physicochemical Properties

Gases

- Molecular diffusivity
- Reactivity
  - Hydrolysis
  - Protein binding
  - Metabolism / tissue reactions
- Solubility
  - Blood:air and blood:tissue partition coefficients



Bogdanffy and Jarabek (1995). *Toxicol Lett* 82-83:919-32.
https://www.ncbi.nlm.nih.gov/pubmed/8597163

Bogdanffy et al. (1999). *Toxicol Sci* Sep;51(1):19-35.
https://www.ncbi.nlm.nih.gov/pubmed/10496674

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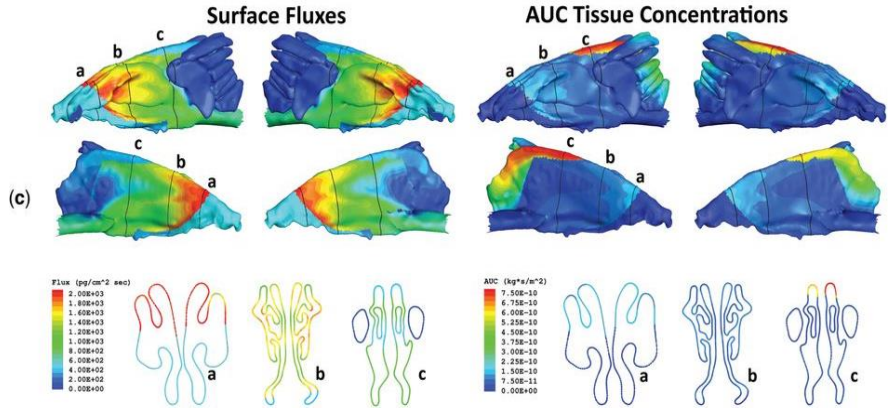
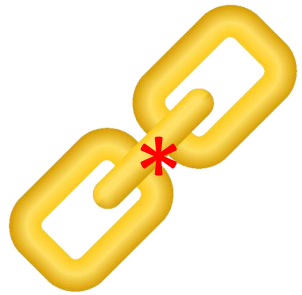
Dosimetry Deployed to Compute the TSE

- **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
  - Choice of cell type



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



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Translate TSE to Human Equivalent Concentration (HEC)

- **Account** for PC and ADME **determinants in test system**
  - Mass per volume of cell media and surface area differs across transwell sizes
  - $[Toxicant]_{reported} \neq [Toxicant]_{applied} \neq [Toxicant]_{aqueous}$ due to analytical issues and losses to media, plate, etc.
- **Adjust** relative to human target and conditions: ***Ratio to appropriately normalize***
- 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

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Case Study: New Chemical Substances (NCS) under TSCA

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- Section 5 of TSCA does not require upfront testing for NCS; only extant data need be submitted
- Various methods used to assess risks with limited data
  - Chemical categories based on comparator chemicals
  - “Read across“ approaches using analogues
- Newly proposed integrated approach to testing and assessment (IATA) based on dosimetry modeling and AOP-inspired NAMs (SOT 2021)
  - General surfactants (Henry et al.; SOT Poster #2583)
  - Poorly soluble low toxicity (PSLT) polymers (Jarabek Stedeford et al.; SOT Poster #2593)
- Manuscripts undergoing re-submission to Chemical Research Toxicol

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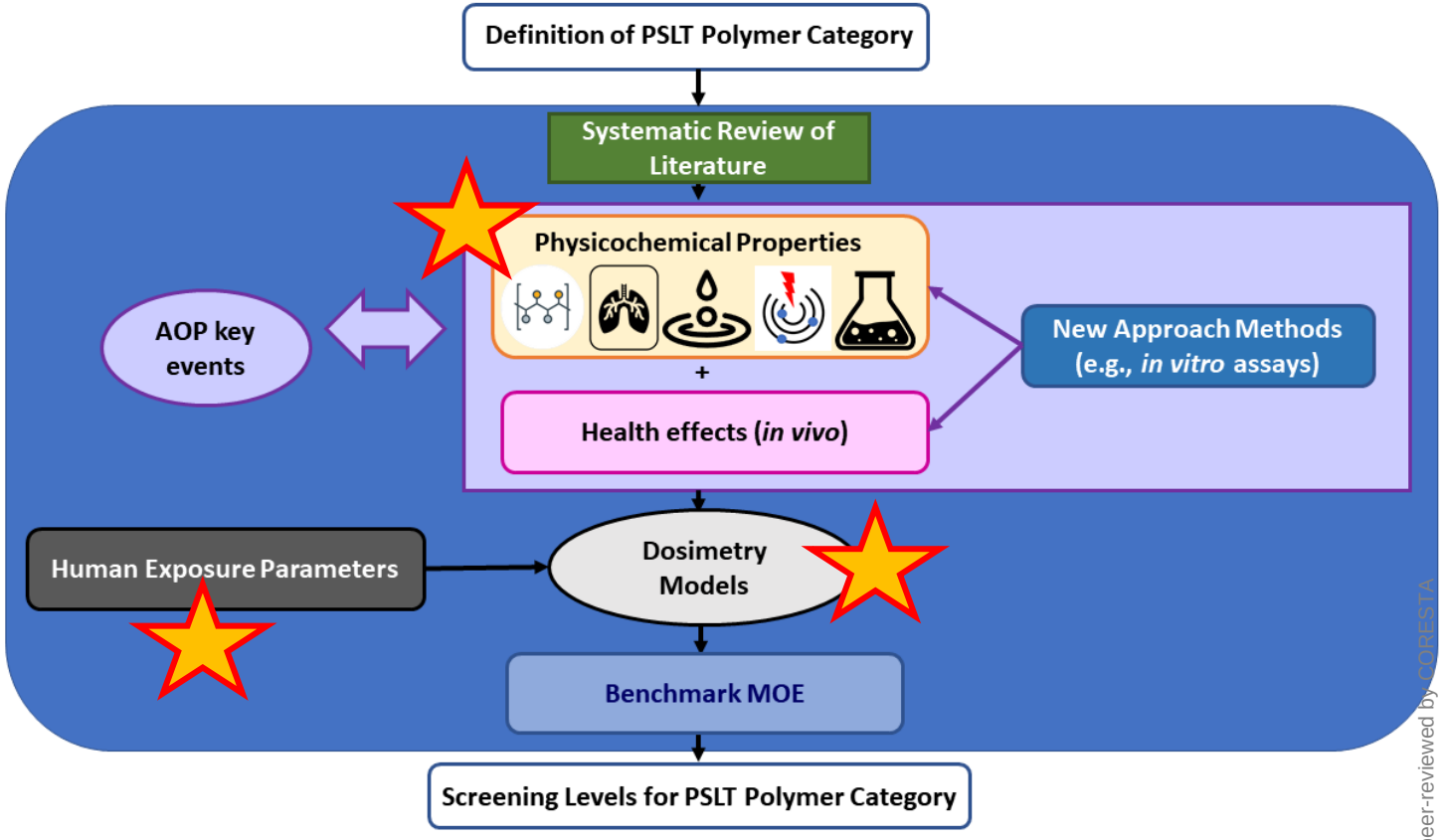
Integrated Approach to Testing and Assessment (IATA)

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



Jarabek Stedeford et al. (*accepted*)

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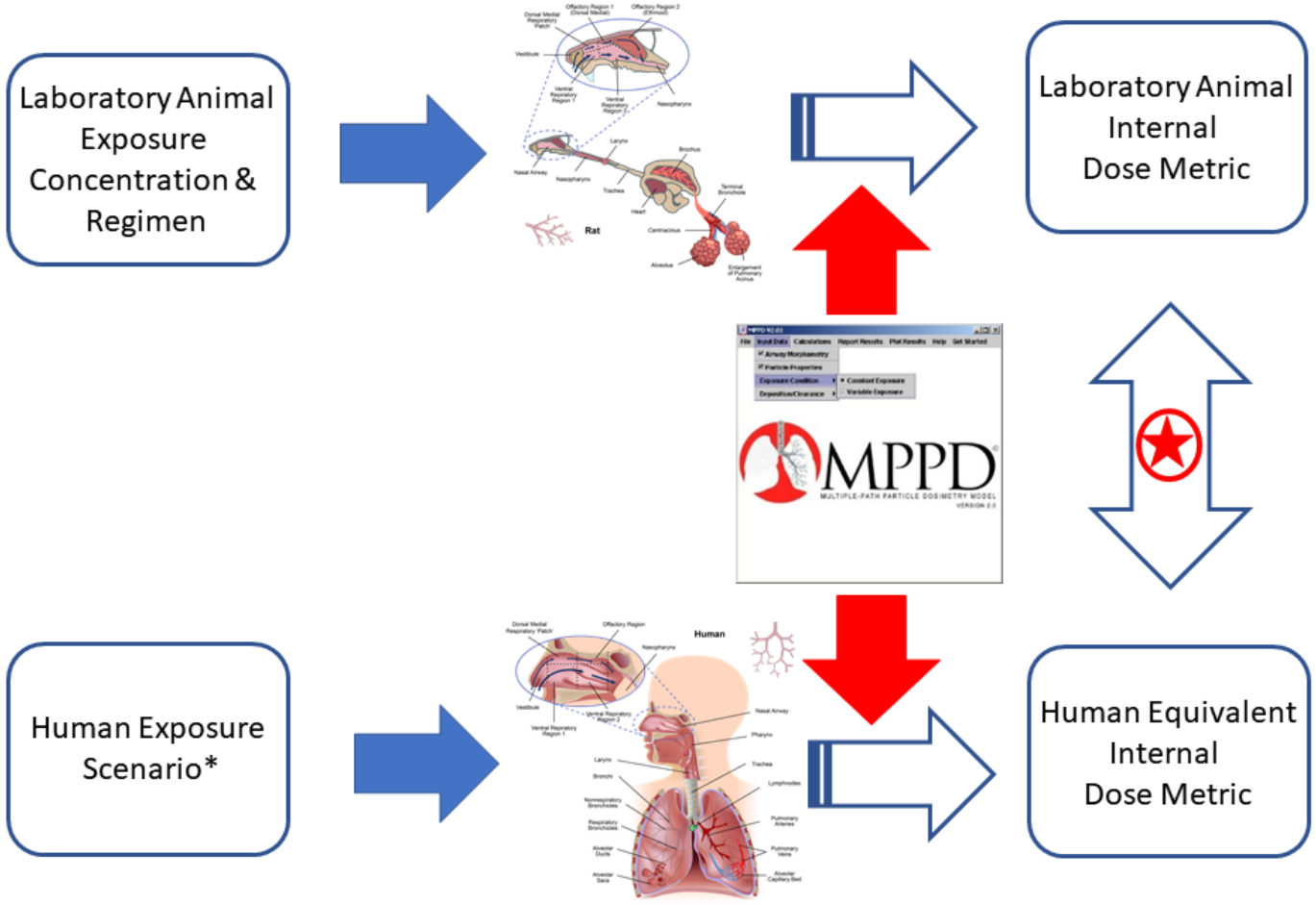
MPPD Model to Calculate HEC: PSLT Polymers

- **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
  - Different particle distribution
  - Various ventilation parameters



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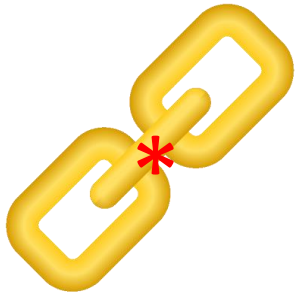
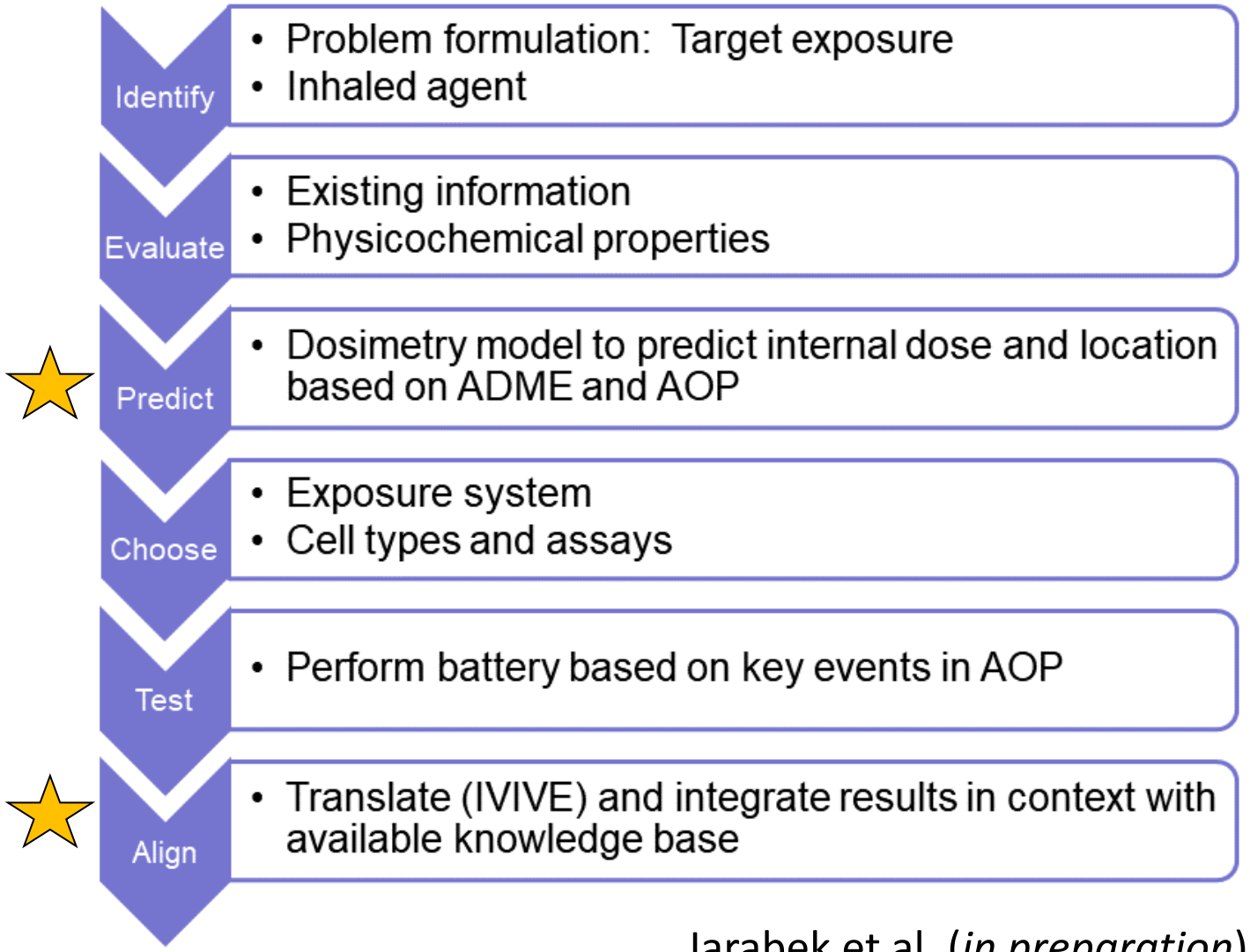
AOP-*Inspired* Integrated Approach to Testing and Assessment





Jarabek et al. (*in preparation*)

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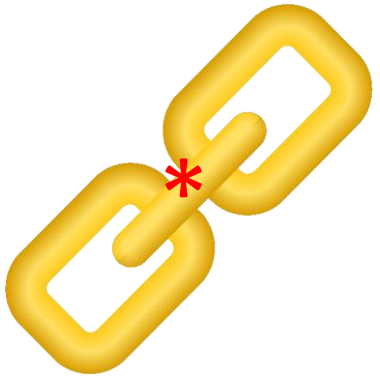
Communication Best Practices: Reporting Standards Roadmap

- **Data sharing: Standards**
  - MIAME: Minimum Information About a Microarray Experiment
  - SEND: Standard for Exchange of Non-clinical Data
- **FAIR Principles: Findable / Accessible / Interoperable / Reusable**
  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
    - Modular, multi-scale dosimetry to support interoperability
  - **Data pipelines and analytical work flows: Meta data**
    - Experimental annotation: ***WHAT / HOW / WHY***
    - Curation and consistency: Domain expertise and detail
    - Interdisciplinary dialogue
    - ***Repurposing: Applicability***



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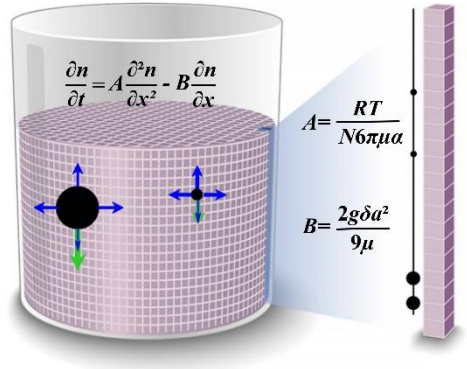
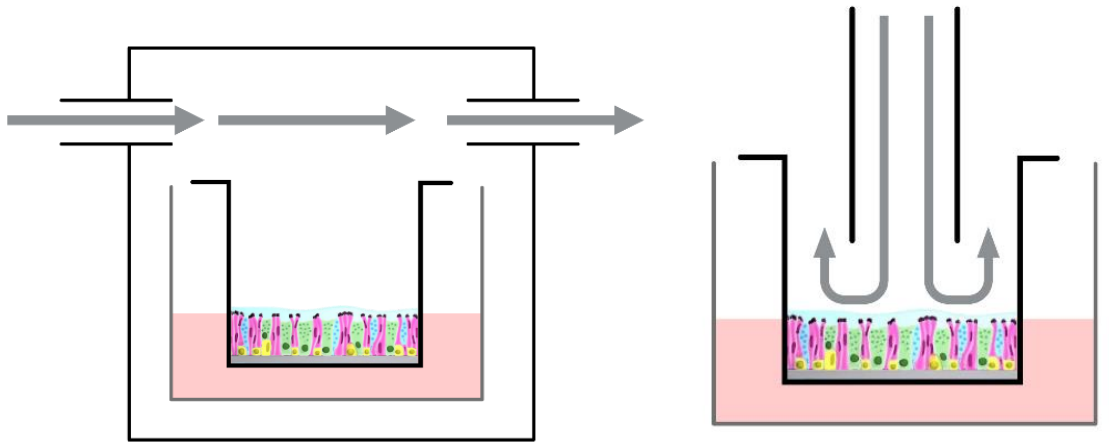
Reporting Standards: Exposure Systems

- **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 determinants
    - Particle: Deposition mechanisms

Jarabek et al. (*in preparation*)



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



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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

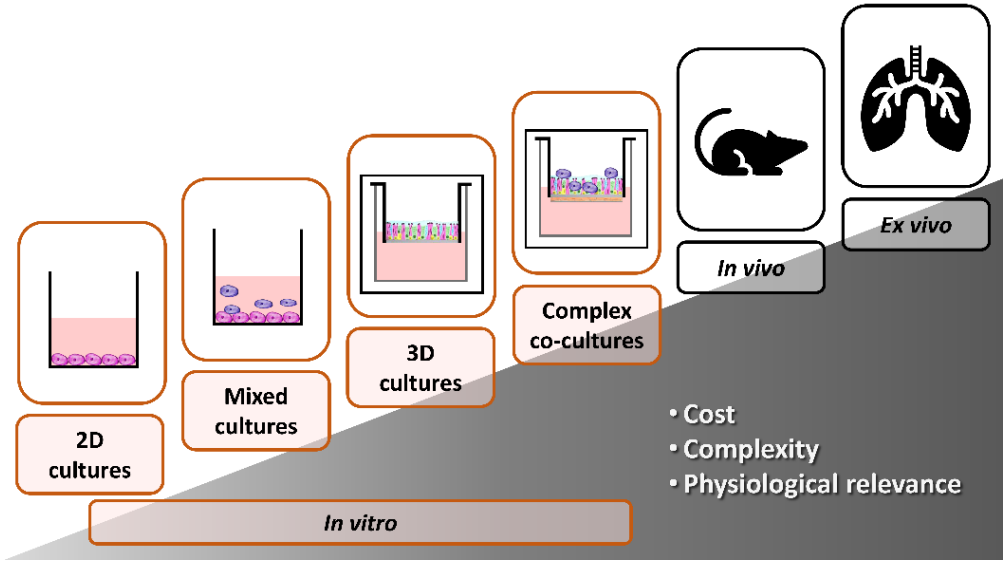

Figure adapted from Lacroix et al. (2018). *Appl in vitro Tox*, 4(2), 91 – 106. https://www.liebertpub.com/doi/full/10.1089/aivt.2017.0034

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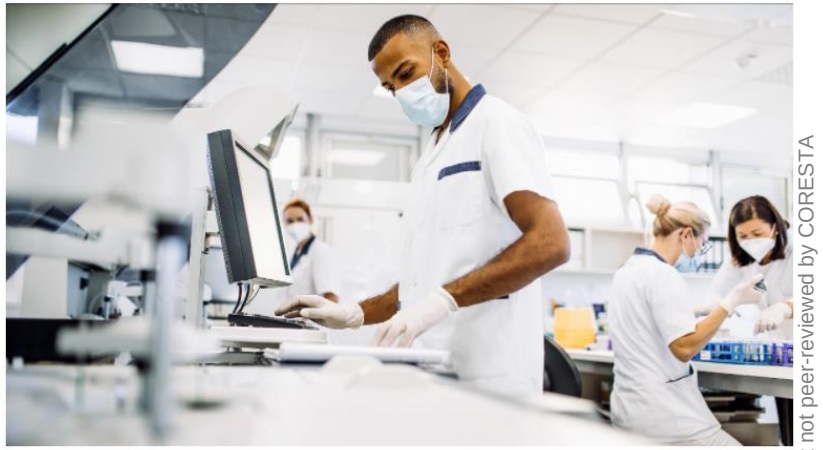
Characterization: Translation Factors

- **Traditional factors of uncertainty and variability**
  - **Intrahuman:** Variability within the human population, including susceptible subpopulations, due to differences in life stage, disease states, and other determinants of TK or TD
  - **Interspecies (across experimental systems):** Differences in TK and TD
  - **Duration:** Use of acute data to predict episodic or chronic exposure outcomes
  - **Severity:** Nature of effect and prognostic value
  - **Database:** Coverage to comprehensively address potential effects
- **Novel translations:** Cell system as target tissue / system surrogate
  - Target tissue specificity and viability
  - Spatial representation and variability of sample
  - Metabolic competency and variability

The National Academies of SCIENCES ENGINEERING MEDICINE — ENVIRONMENTAL STUDIES AND TOXICOLOGY

New Study Committee Announcement:
Variability and Relevance of Current Laboratory Mammalian Toxicity Tests and Expectations for New Approach Methods (NAMs) for use in Human Health Risk Assessment

DEADLINE: Sunday, August 29, 2021



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Impacts: Inferences and Integration

- Clarify terminology
  - "Model"
  - Effects, relationships and outcomes
- Evaluate new data resources
- Incorporate computational outputs
- Rectify units
- Elucidate study quality and utility
- Inform "causality" considerations
- Illuminate assumptions
- Support reusability and interoperability
- ***TRANSFORM translation and improve evidence integration***

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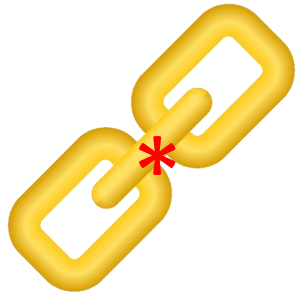
Summary: Advancing NAMs

- **Evolve empirical modeling** (observations of **WHAT**) → to **MECHANISTIC MULTISCALE MODELS** (***HOW*** and ***WHY)***
- Bridge to systems biology with **Integrated Approaches to Testing and Assessment (IATA)**: **key events** of pathogenesis and ***quantitative*** **AOP (qAOP)**
  - **Characterize** dose and effects at different **levels of observation**
  - **Understand** various **dimensions of disease** and relationships (e.g., early or late)
- **Translate targe site exposure** (**TSE) across exposure systems** to aid and transform **evidence integration: develop ANALYTIC WORKFLOWS**
  - **Align** human and animal **exposures**
  - **Refine** *in vitro* to *in vivo* extrapolation (**IVIVE**)
- Facilitate **interdisciplinary dialogue**
  - **Transparency** re: assumptions and foundational data
  - Appreciate **assumptions and impacts**
  - Support **modularity for interoperability** with other models



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SOT Poster #2583 | Surfactants Category: An Integrated Approach to Testing and Assessment (IATA) Including New Approach Methods (NAMs) for Assessing Inhalation Risks under the Toxic Substances Control Act (TSCA)

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SOT Poster #2593 | Poorly Soluble, Low Toxicity (PSLT) Polymer Category: An Integrated Approach to Testing and Assessment (IATA) Including New Approach Methods (NAMs) under the Toxic Substances Control Act (TSCA)

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