Center of Excellence for 21st Century Toxicology
A Division of ToxStrategies

Introduction to IVIVE-PBPK Modeling for In Vitro-based Inhalation Toxicity Testing

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Abbreviations

- ADME – absorption, distribution, metabolism, excretion
- AOP – adverse outcome pathway
- CFD – computational fluid dynamic model
- IVIVE – in vitro to in vivo extrapolation
- MOA – mode of action
- MPPD – multiple-path particle dosimetry model
- PBPK – physiologically based pharmacokinetic model
- PK – pharmacokinetics
- PD - pharmacodynamics

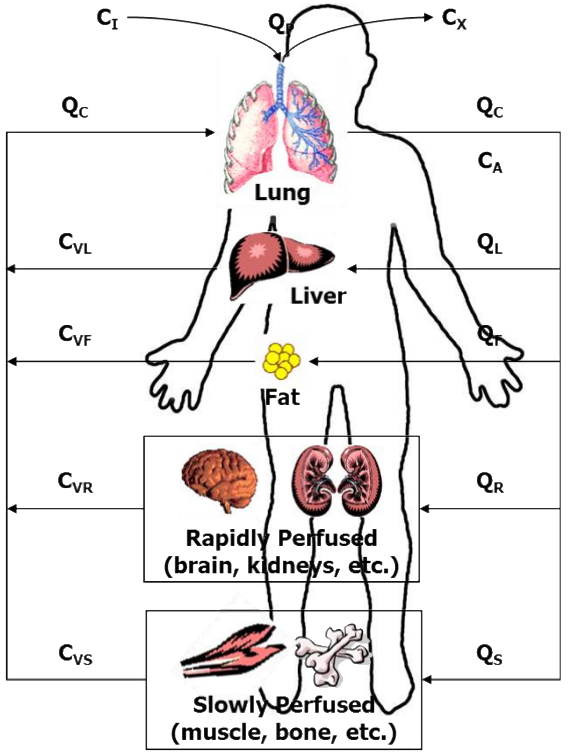
Pharmacokinetics vs. pharmacodynamics

- Pharmacokinetics - study of time-course of chemicals in blood or tissues
  - What the body does to the chemical
  - Absorption, Distribution, Metabolism, Excretion (ADME)
  - Also called biokinetics, kinetics, toxicokinetics

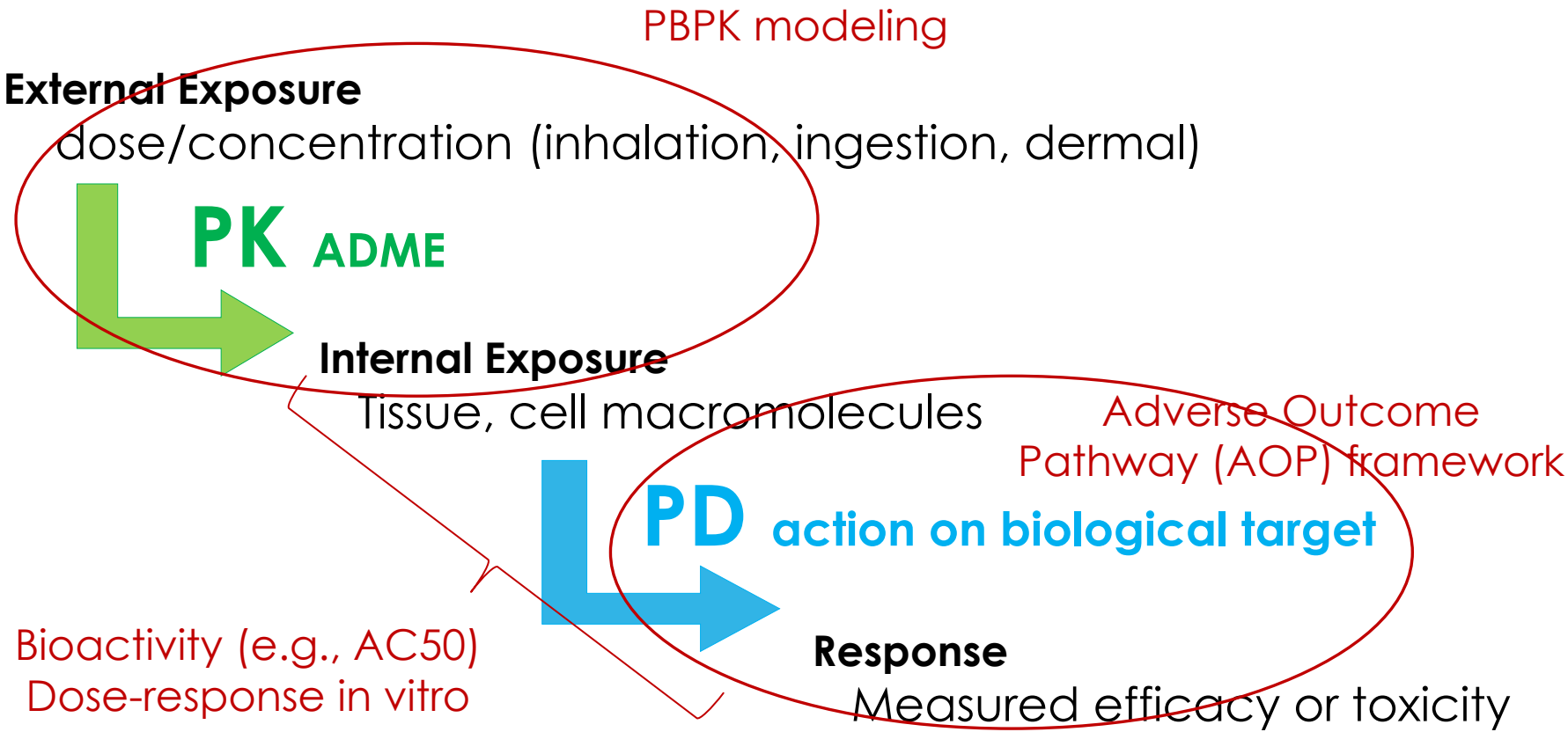
- Pharmacodynamics - study of biological effects of chemicals
  - What the chemical does to the body
  - Also called toxicodynamics, mode of action

What is PBPK model?

- Describes physiology of the organism as a set of tissue compartments interconnected by blood flow
- Mechanistic PK model based on biological processes (e.g., metabolism, transport, partitioning)
- Mathematical representation of biology and hypothesis systems of differential equations based on mass balance
- Greater predictive power because of the mechanistic basis of the description (route, dose, species, system extrapolations)



Role of PBPK in 21st century safety assessment

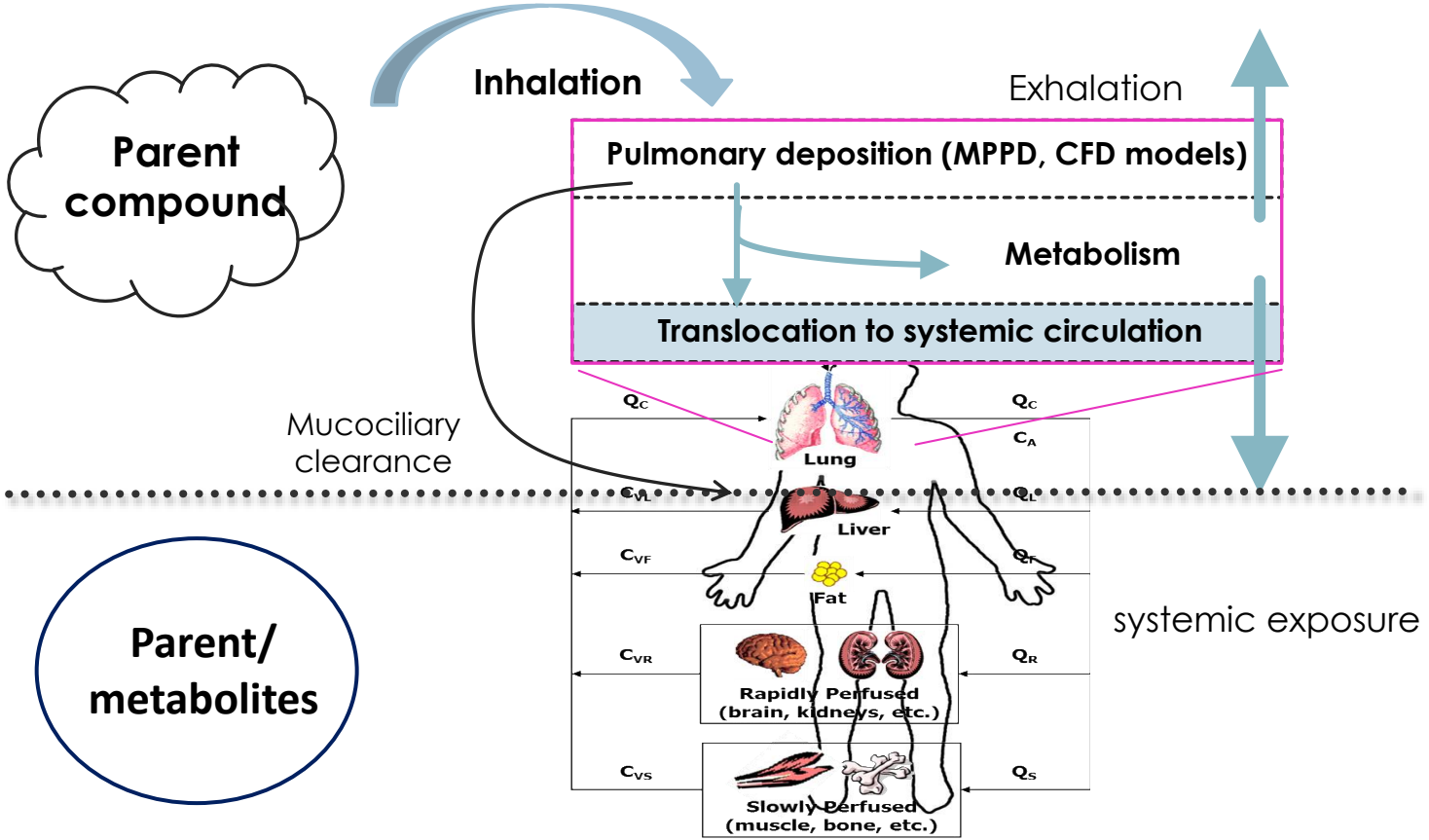


PBPK model components

- Model purpose/goal – a tiered approach
- Model structure
  - Exposure conditions (e.g., inhalation scenarios)
  - Physiology
  - Biological hypothesis (e.g., metabolism /transport/target tissue)
- Model parameters – IVIVE-based parameterization
  - Physiological data (organ weights, blood flows)
  - Biochemical data (partition coefficients, metabolic constants)
- Model equations
  - System of mass-balance differential equations
  - One equation for each tissue
  - Connected by equation for blood

$$dA_L / dt = Q_L \times (C_A - C_L / P_L) - V_{\max} \times C_L / P_L / (K_M + C_L / P_L)$$

PBPK for inhalation assessment



Understanding exposure at the portal of entry and systemic target(s)

- Respiratory tract effects
  - Specific regions in the respiratory tract
  - Deposition and metabolic activation
  - Parent and/or metabolites
- Systemic target effects
  - Diffusion/transport to systemic circulation (bioavailability)
  - Blood air partition, pulmonary metabolism, diffusion/transport to blood
  - Parent and/or metabolites

Key parameters in addition to those for the systemic PBPK model

- Physiological parameters – lung physiology (blood flow, respiratory rate)
- Chemical specific parameters – blood to air partition coefficient
- Biochemical parameters – metabolic constants in a specific pulmonary regions and/or pulmonary cells (e.g., club cells)

Rapid estimation of systemic exposure

General equation

$$Css = Cair/[(1/PB)+(QL/QP)*Clint/(QL+Clint)]$$

for poorly soluble & poorly metabolized (e.g., perchloroethylene),

$$Css = Cair*PB$$

for soluble & extremely well metabolized (e.g., isopropanol),

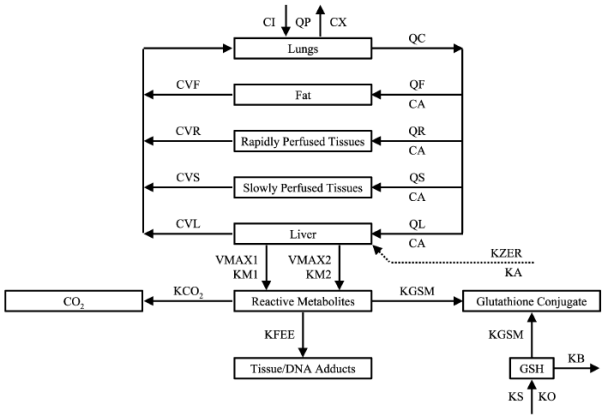
$$Css = QP*Cair/QL$$

Blood:air partition coefficient (PB); Liver metabolic clearance (Clint); Ventilation rate (QP); Liver blood flow (QL)

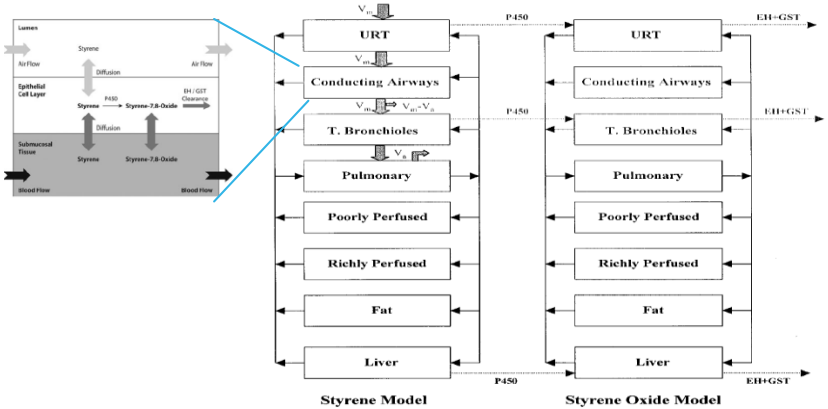
(Andersen, 1981; Clewell et al., 2004; Yoon et al., 2014)

Respiratory tract descriptions with different complexity in inhalation PBPK models

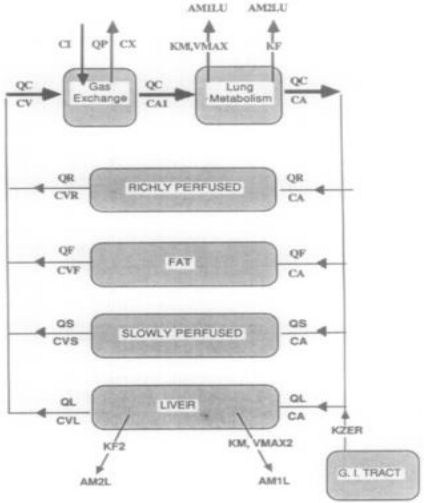
- A single homogeneous 'lung' in equilibrium with arterial blood
  - e.g., vinyl chloride in Clewell et al., 2001
- Addition of metabolism to simple lung compartment
  - e.g., dichloromethane in Andersen et al., 1987
- Multi-compartment respiratory tract
  - e.g., styrene in Sarangapani et al., 2002; 1,3-butadiene models in Campbell et al., 2015
- Multi-compartment lung coupled with lung dosimetry models such as MPPD, CFD models
  - e.g., hybrid CFD-PBPK model for naphthalene in Campbell et al., 2014



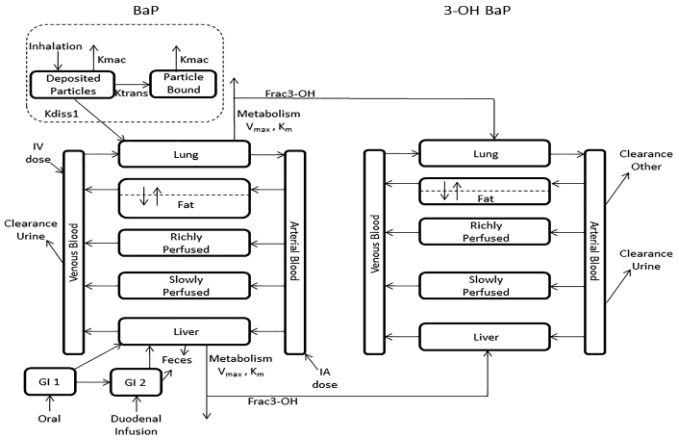
Vinyl chloride, Clewell et al., 2001



Styrene, Sarangapani et al., 2002

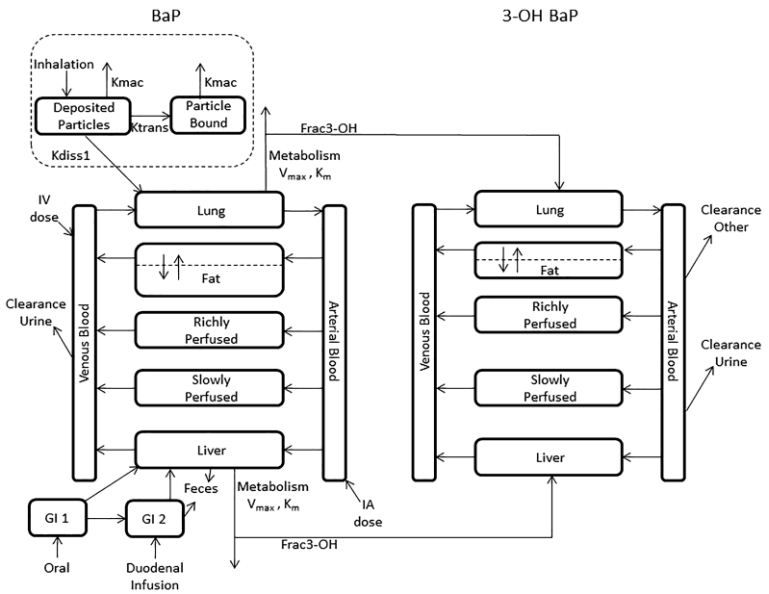


Methylene chloride, Andersen et al., 1987

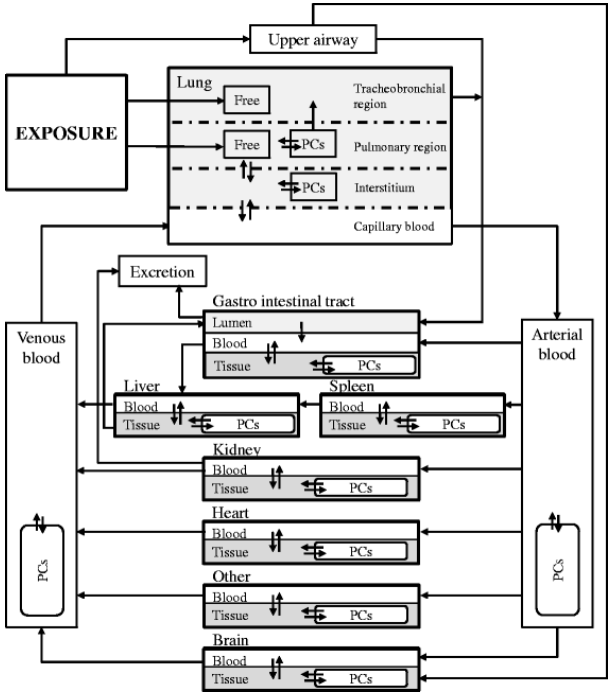


Benzo[a]pyrene, Campbell et al., 2016

Nano/particle respiratory tract dosimetry

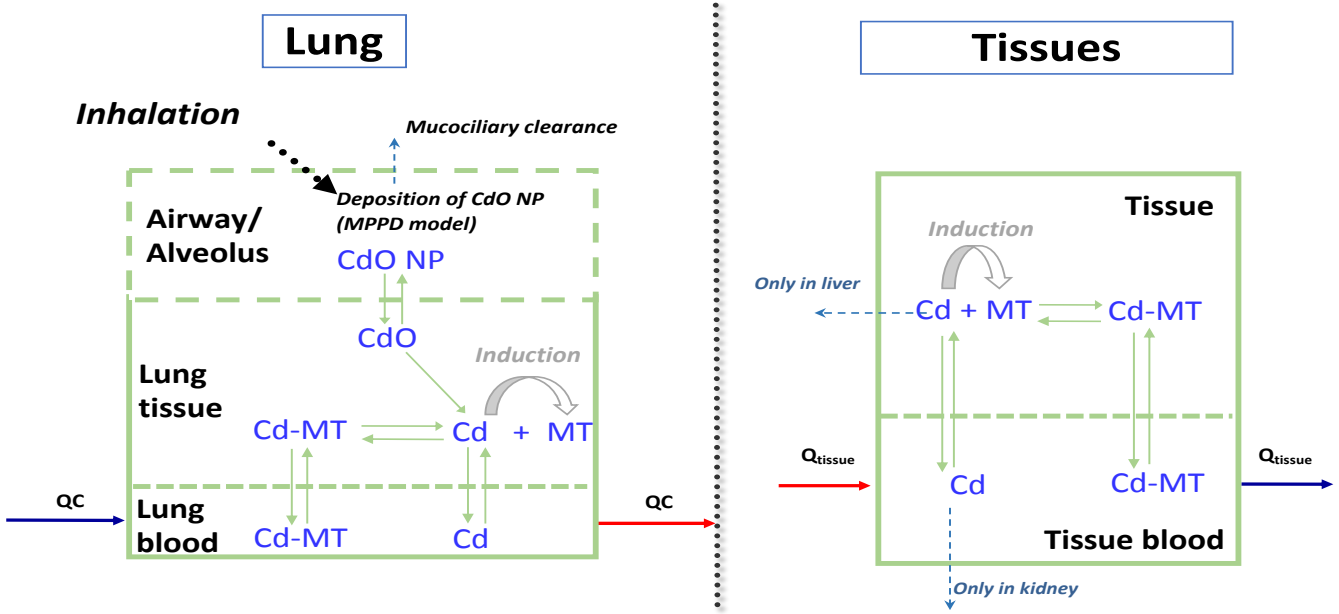


Benzo[a]pyrene, Campbell et al., 2016



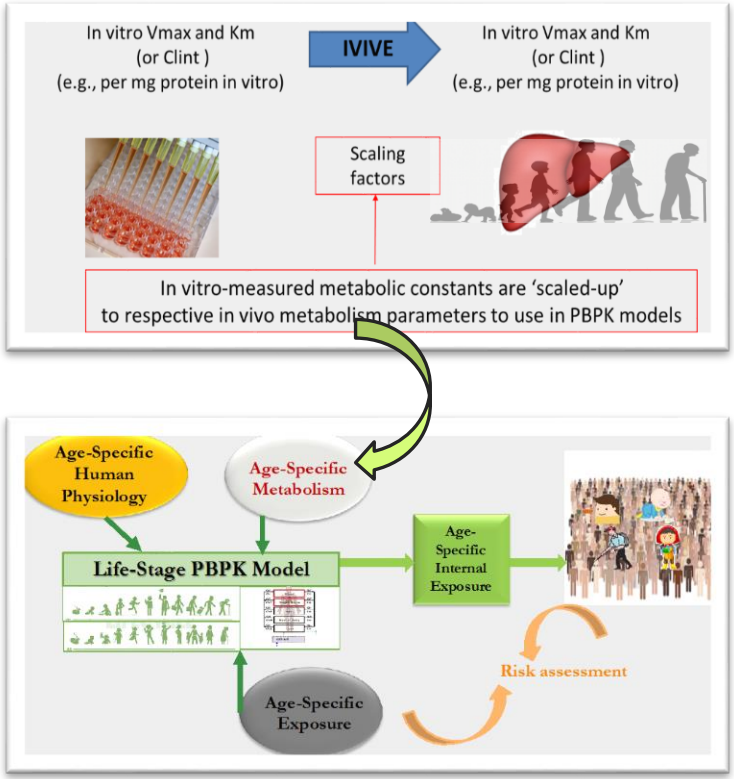
CeO_2 nanoparticles, Li et al., 2016

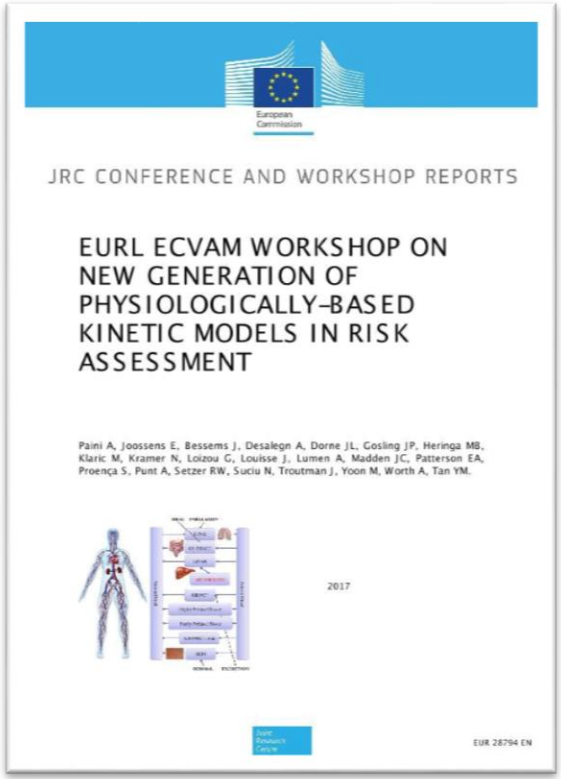
Importance of capturing cellular exposure and kinetics in respiratory tract



Zhao et al., 2014

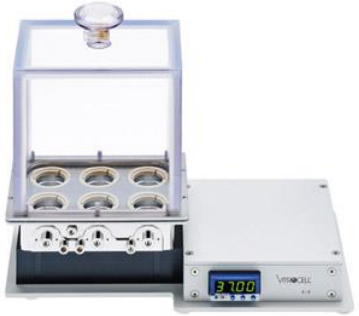
In vitro-based PBPK models for safety and risk assessment

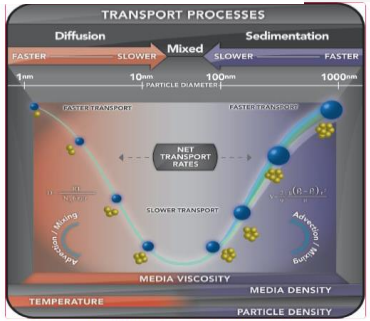




Opportunities with advanced in vitro lung models for inhalation IVIVE-PBPK models

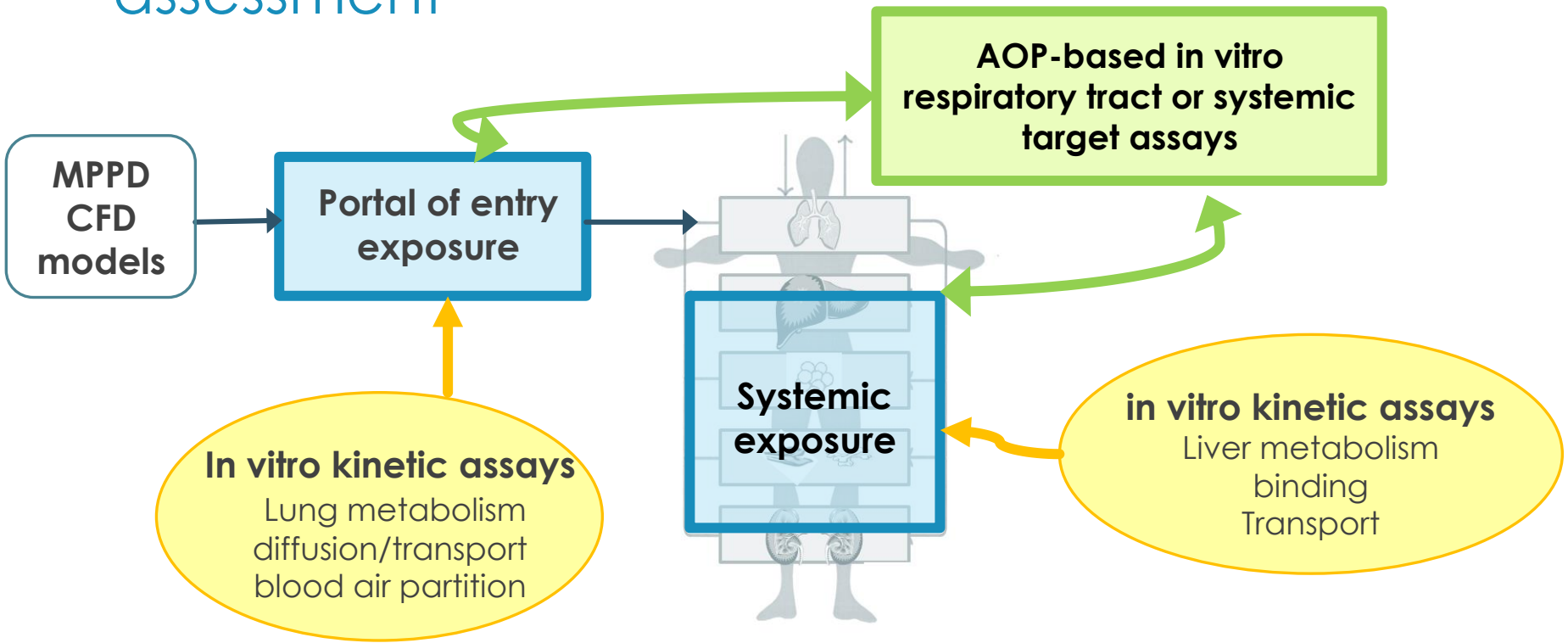
- Advanced in vitro respiratory tract models have promises to overcome current limitations
  - metabolic constants measured in whole lung homogenates
  - region and/or cell specific models in appropriate scale/size for metabolism/kinetics
  - recapitulating biological fidelity to describe cellular exposure in respiratory tract
- In vitro kinetic modeling is increasingly recognized and applied for IVIVE
  - in vitro air to cell exposure (e.g., simulation of air chamber concentration over time and cell partitioning)
  - in vitro specific kinetic behaviors (e.g., particokinetics in Hinderliter et al., 2010, Thomas et al., 2018)





ISDD: A computational model of particle sedimentation, diffusion and target cell dosimetry for *in vitro* toxicity studies

Integrated approaches for inhalation safety assessment



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