Implementing alternative approaches for inhalation toxicity testing: Recent success and remaining hurdles

Amy Clippinger[1], David Allen[2]
[1]PETA International Science Consortium Ltd.
[2]ILS, Contractor supporting NICEATM
AmyJC@PISCLtd.org.uk

Acknowledgements

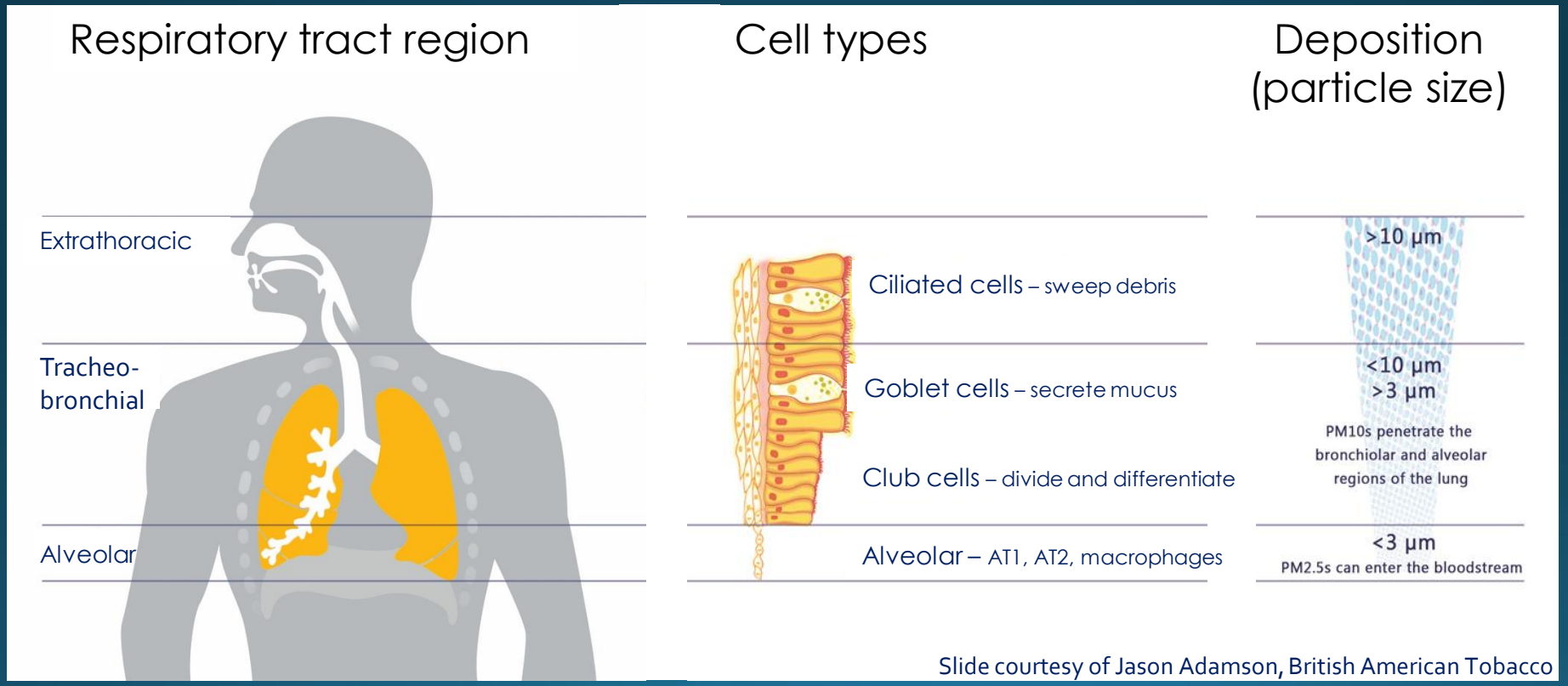
The Dow Chemical Company
Dow AgroSciences
Syngenta
British American Tobacco
Simulations Plus
ToxMetrics
ScitoVation
Netherlands Organisation for Applied Scientific Research (TNO)
Free University of Brussels, Belgium
Cardiff University
University of Pennsylvania
US Environmental Protection Agency
Health and Safety Executive, UK
NICEATM
PETA International Science Consortium

Outline

- Respiratory tract
- Why conduct inhalation toxicity testing?
- Current test guidelines
- *In vitro* and *in silico* approaches
- Ongoing efforts

Respiratory tract

- The respiratory tract serves as a portal of entry from the external environment to the systemic circulation



Slide courtesy of Jason Adamson, British American Tobacco

- International regulatory agencies require inhalation toxicity testing for hazard labeling and risk management of chemicals when exposure to the respiratory tract is possible

- Acute inhalation toxicity tests are designed to identify chemicals that could cause illness or death after a short-term inhalation exposure

OECD/OCDE

436

Adopted:
7 September 2009

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Acute Inhalation Toxicity - Acute Toxic Class Method

INTRODUCTION

1. OECD Guidelines for the Testing of Chemicals are periodically reviewed in the light of

OECD/OCDE

403

Adopted:
7 September 2009

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Acute Inhalation Toxicity

INTRODUCTION

1. OECD Guidelines are periodically reviewed in the light of scientific progress, changing

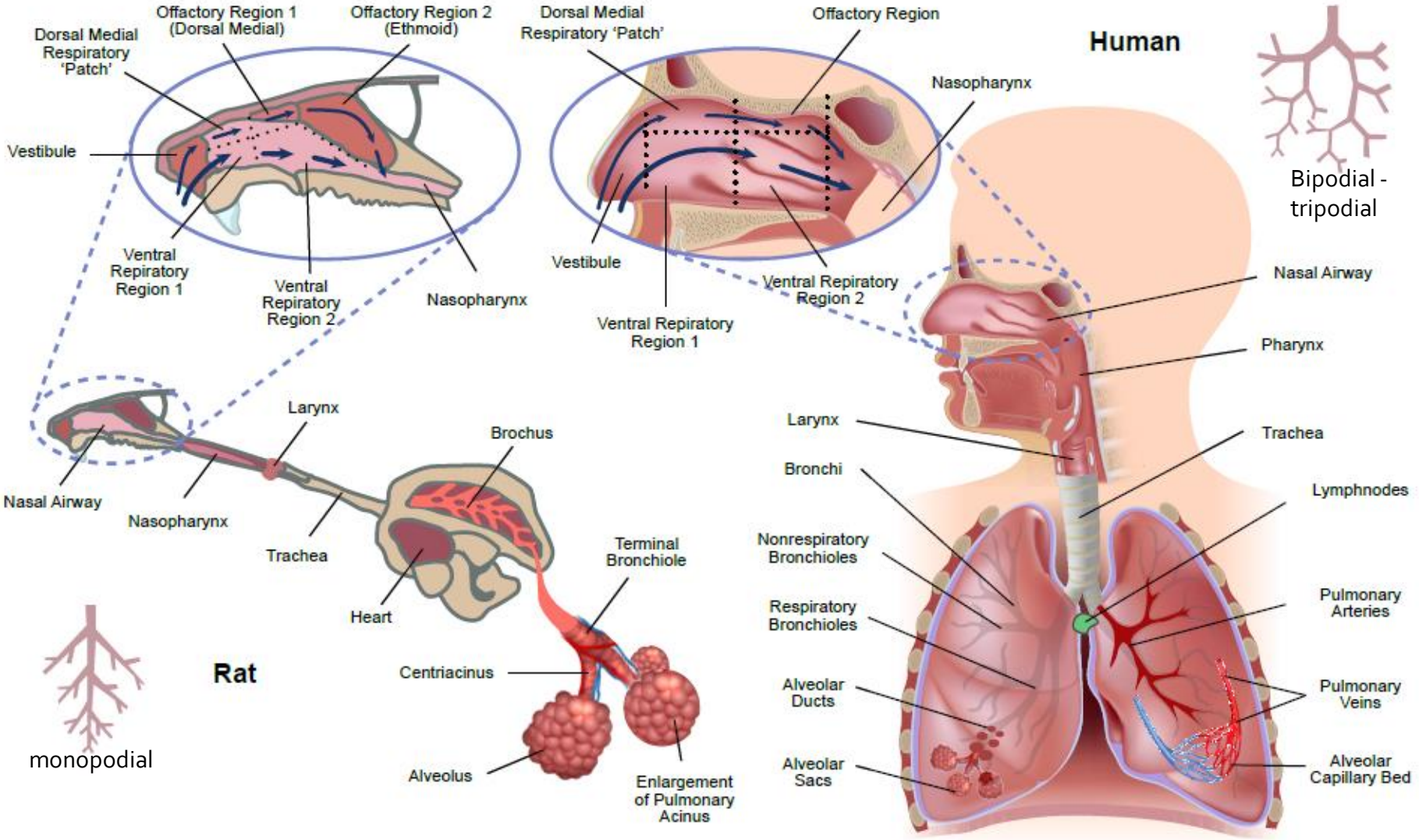
18th December, 2015

DRAFT PROPOSAL FOR A NEW GUIDELINE: 433

Acute Inhalation Toxicity - Fixed Concentration Procedure

INTRODUCTION

1. OECD Guidelines for the Testing of Chemicals are periodically reviewed in the light of scie



- Ventilation rates and breathing mode
- Airway architecture and branching pattern
- Cell type distribution and mucous composition
- Metabolic activity

Illustration modified from Dr. Jack R. Harkema, Professor of Comparative Pathology, Michigan State University

National Toxicology Program
U.S. Department of Health and Human Services

PETA INTERNATIONAL SCIENCE CONSORTIUM LTD.

Alternative Approaches for Acute Inhalation Toxicity to Address Global Regulatory and Non-regulatory Data Requirements

Working groups

WORKING GROUP 1
Establish a database of existing acute inhalation toxicity data

WORKING GROUP 2
Prepare a review on mechanisms of acute inhalation toxicity, dosimetry considerations, & available non-animal methods

WORKING GROUP 3
Optimize (Q)SAR models

WORKING GROUP 4
Design a non-animal testing approach and conduct a proof-of-concept study

- Reference chemicals based on *in vivo* data availability
- Develop a decision tree to guide the need for *in vitro* testing
- Select relevant *in vitro* test systems

Integrated approach to testing and assessment

Weight-of-evidence

Existing information
(human, animal, *in silico*, *in vitro* data)

Exposure information

Properties of the test substance
- Physicochemical: physical form, viscosity, volatility, particle size and distribution; irritation/corrosivity
- Chemical: reactivity

Computational biology models
- Multiple Path Particle Dosimetry model
- Computational Fluid Dynamics modeling

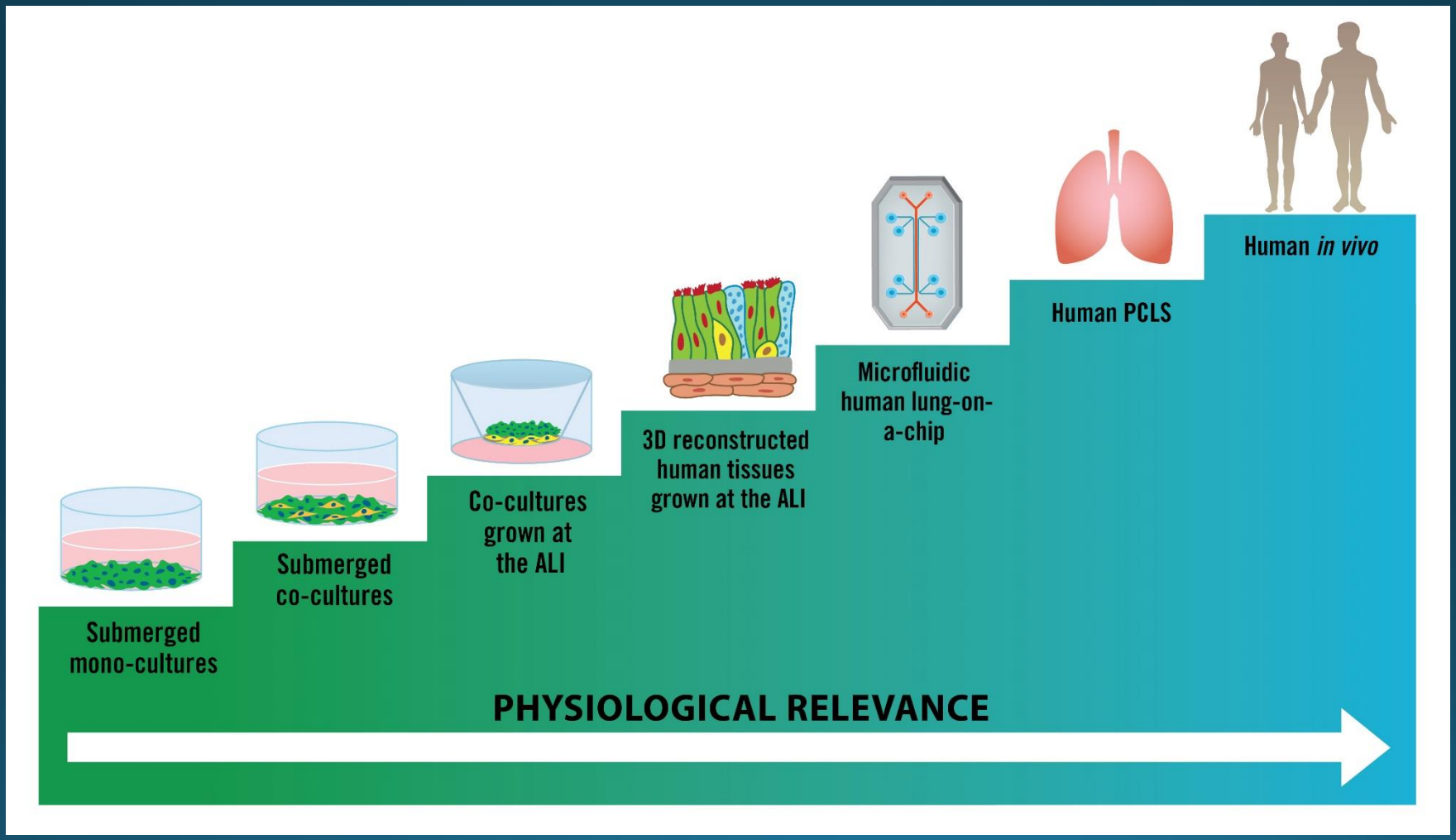
PBPK Modeling

Grouping, read-across, (Q)SARs, expert systems

Theory of additivity (for mixtures)

In vitro testing

In vitro model systems



Conclusions

- Multiple non-testing approaches and *in vitro* methods will be needed to assess the various mechanisms of acute systemic toxicity following inhalation exposure

- Multi-stakeholder collaborations on data sharing and validation efforts foster the development of *in vitro* and *in silico* approaches that can be used to protect human health without using animals

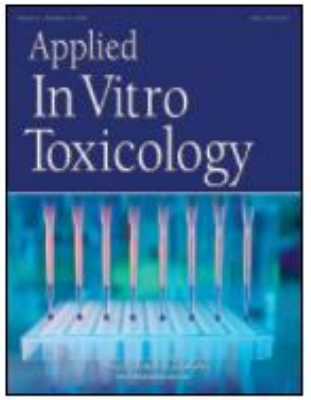
Applied In Vitro Toxicology Special Issue

SEND NOW

Mary Ann Liebert, Inc. publishers

CALL FOR PAPERS

Applied In Vitro Toxicology



Special Issue: Implementing Alternative Approaches for Inhalation Toxicity Testing

Deadline for manuscript submission: December 15, 2017

Guest Editor
Amy J. Clippinger, PhD
PETA International Science Consortium Ltd.

Inhalation toxicity testing provides the basis for hazard labeling and risk management of chemicals when there is potential for exposure of the respiratory tract. The tests commonly

Acknowledgements

The Dow Chemical Company
Dow AgroSciences
Syngenta
British American Tobacco
Simulations Plus
ToxMetrics
ScitoVation
Netherlands Organisation for Applied Scientific Research (TNO)
Free University of Brussels, Belgium
Cardiff University
University of Pennsylvania
US Environmental Protection Agency
Health and Safety Executive, UK
NICEATM
PETA International Science Consortium

Contact: AmyJC@piscltd.org.uk