

The Application of New Approach Methodologies (NAMs) for Next-Generation Tobacco and Nicotine Product Assessment: CORESTA Symposia

K Monica Lee¹, Liam Simms², Kei Yoshino³ and Marianna Gaca⁴
¹Altria Client Services LLC, 601 E Jackson St. Richmond, VA 23219 USA
²Imperial Brands 121 Winterstoke Road, Bristol, UK BS3 2LL
³Japan Tobacco Inc., R&D Group, Yokohama, Japan
⁴British American Tobacco, R&D, Southampton, Hampshire SO15 8TL, UK

12th annual ASCCT meeting, Silver Spring, MD, USA
 October 23-25, 2023

Abstract

The field of in vitro toxicology has accelerated in recent years with the advances in computational tools and human in vitro tissue systems. These New Approach Methodologies (NAMs) tools in cellular and molecular biology facilitate a paradigm shift in toxicology testing, harnessing mammalian cell lines of better human relevance. NAMs have already been implemented for chemical testing and candidate drug development, driven by the need for faster and clinically relevant toxicological risk assessment. In tobacco fields, alternative, next-generation tobacco and nicotine products (NGPs), such as heated tobacco products (HTPs), electronic nicotine delivery systems (ENDS), smokeless tobacco products (snus) and tobacco-free oral nicotine pouches (NPs) are introduced with the potential to reduce risk of smoking-related diseases compared to cigarettes. Here also, NAMs offer effective toxicity screening tools as part of a testing framework for these potentially less toxic NGPs. Indeed, the in vitro-based toxicity tools are actively applied in various industry sectors and have started to demonstrate potential utility for NGP development and testing. In this poster, we introduce the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), an international organization that is leading collaboration and promoting research into tobacco and nicotine products, with >800 experts from 162 organizations including industry, contract laboratories, academic, governmental and non-governmental organizations. In the last few years, the CORESTA members (via Next Generation Tox Task Force and In Vitro Subgroup) are actively exploring the application of NAMs in tobacco regulatory sciences, through literature reviews, scientific studies, and recently at two CORESTA symposia. We present the goals and outcomes of these symposia, the utilities and strengths of NAMs as well as gaps and opportunities and related CORESTA activities. The importance and opportunity for the fit-for-purpose testing and method standardization will also be discussed to support the regulatory acceptance and implementation of NAMs for NGP assessment.

Tobacco Harm Reduction & Next-Gen Tobacco & Nicotine Products



Next-Generation Tobacco & Nicotine Products (NGPs):
Inhalables: e.g.,
 • ENDS – electronic nicotine delivery systems
 • HTPs – heated tobacco products
Oral: e.g.,
 • ST - Smokeless tobacco (snus)
 • NPs - Tobacco-free nicotine pouches

CORESTA

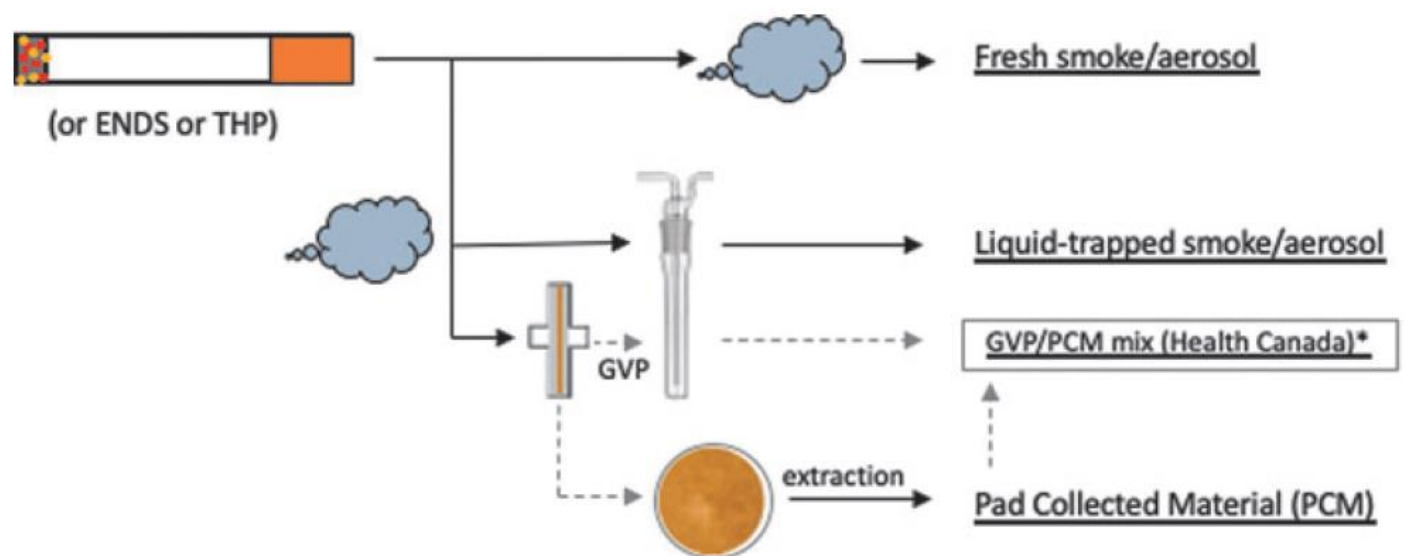
Cooperation Centre for Scientific Research Relative to Tobacco:
 • A non-profit organization created in 1956 governed by French law
 • Purpose: To promote and facilitate cooperation in scientific research relative to tobacco and its derived products
 • Vision: To be recognized by our members and relevant external bodies as an authoritative source of publicly available credible science and best practices related to tobacco and its derived products



In Vitro Toxicity Testing Sub-Group
Technical Report
Rationale and Strategy for In Vitro Toxicity Testing of Combustible Tobacco Products
 September 2019

In Vitro Toxicity Testing Sub-Group
Technical Report
In vitro Micronucleus Assay Inter-Laboratory Proficiency Study
 April 2023

In Vitro Tox SG since 2002
NextG Tox TF since 2019



NGTX - 21st Century Toxicology for Next Generation Tobacco and Nicotine Products (NGPs)
 Spring Meeting April 2023
 Antibes Juan-les-Pins, France

A survey of aerosol exposure systems relative to the analysis of cytotoxicity: A Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) perspective

CORESTA NAM Symposium-I (2021)

Table 1. Symposium agenda *

Speaker	Title
NAM-00: K Monica Lee, Altria; S Bell, ILS	Advancing New Alternative Methods for Tobacco Harm Reduction: Introduction
NAM-01: Nicole Kleinreuter, U.S. NIEHS	U.S. Federal Efforts to Develop and Implement Alternatives to Animal Testing
NAM-02: Alicia Paini and Andrew Worth, EC JRC ¹	Application of Biokinetic Modeling for IVIVE in Chemical Risk Assessment
NAM-03: Richard Corley, CCTC LLC	Inhalation Exposure Modeling for Assessing Health Risks of Toxic Aerosols and Vapors
NAM-04: Andreas O. Stucki, PETA Science Consortium International	Assessing Respiratory Toxicity of Chemicals in Two Human Bronchial In Vitro Systems
NAM-05: Luis Valerio Jr., U.S. FDA/CTP	In Silico Toxicology as a New Approach Methodology in Tobacco Regulatory Science
NAM-06: Annie Jarabek, U.S. EPA	Application of Mechanistic Data in Risk Assessment: Exposure Alignment and Evidence Integration

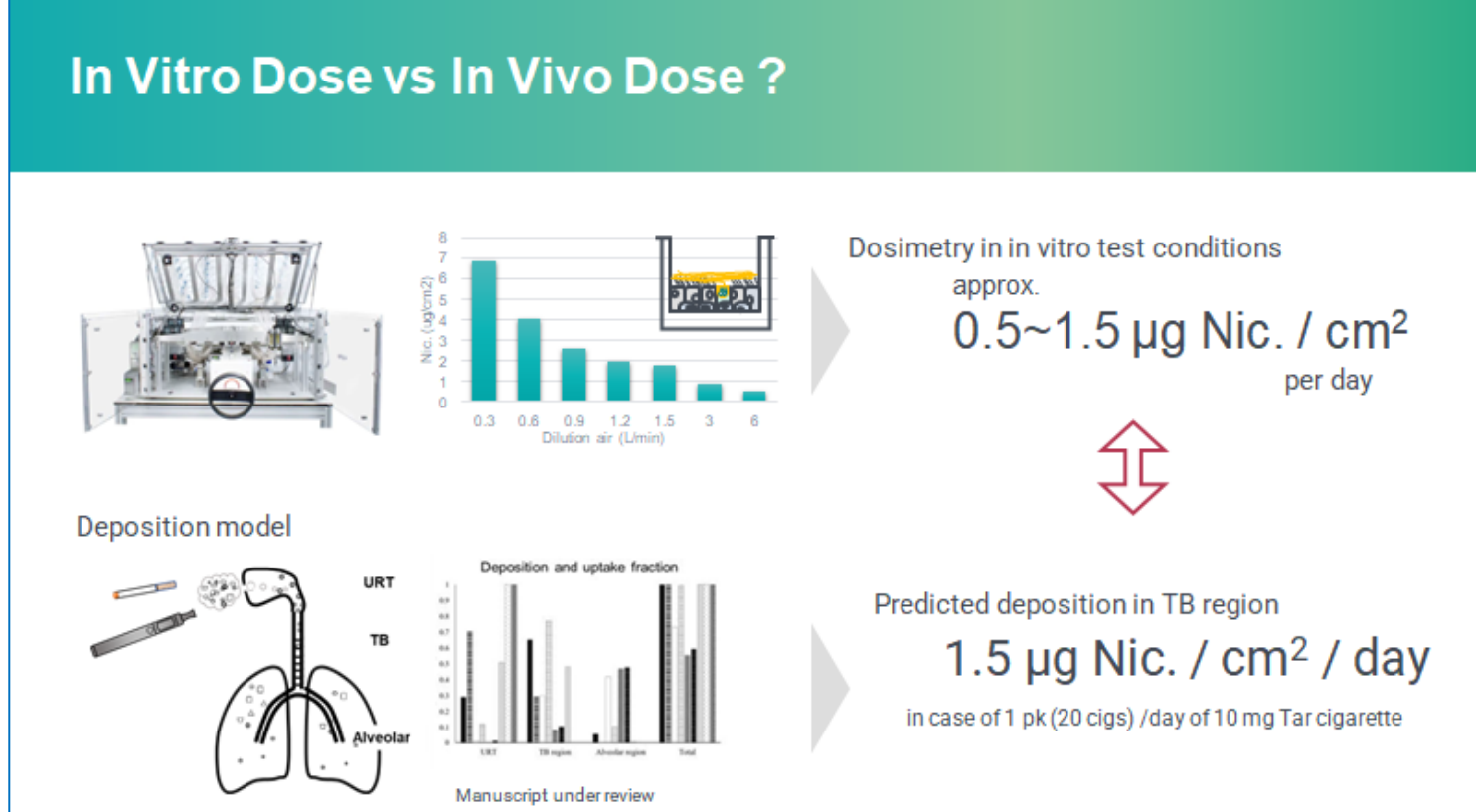
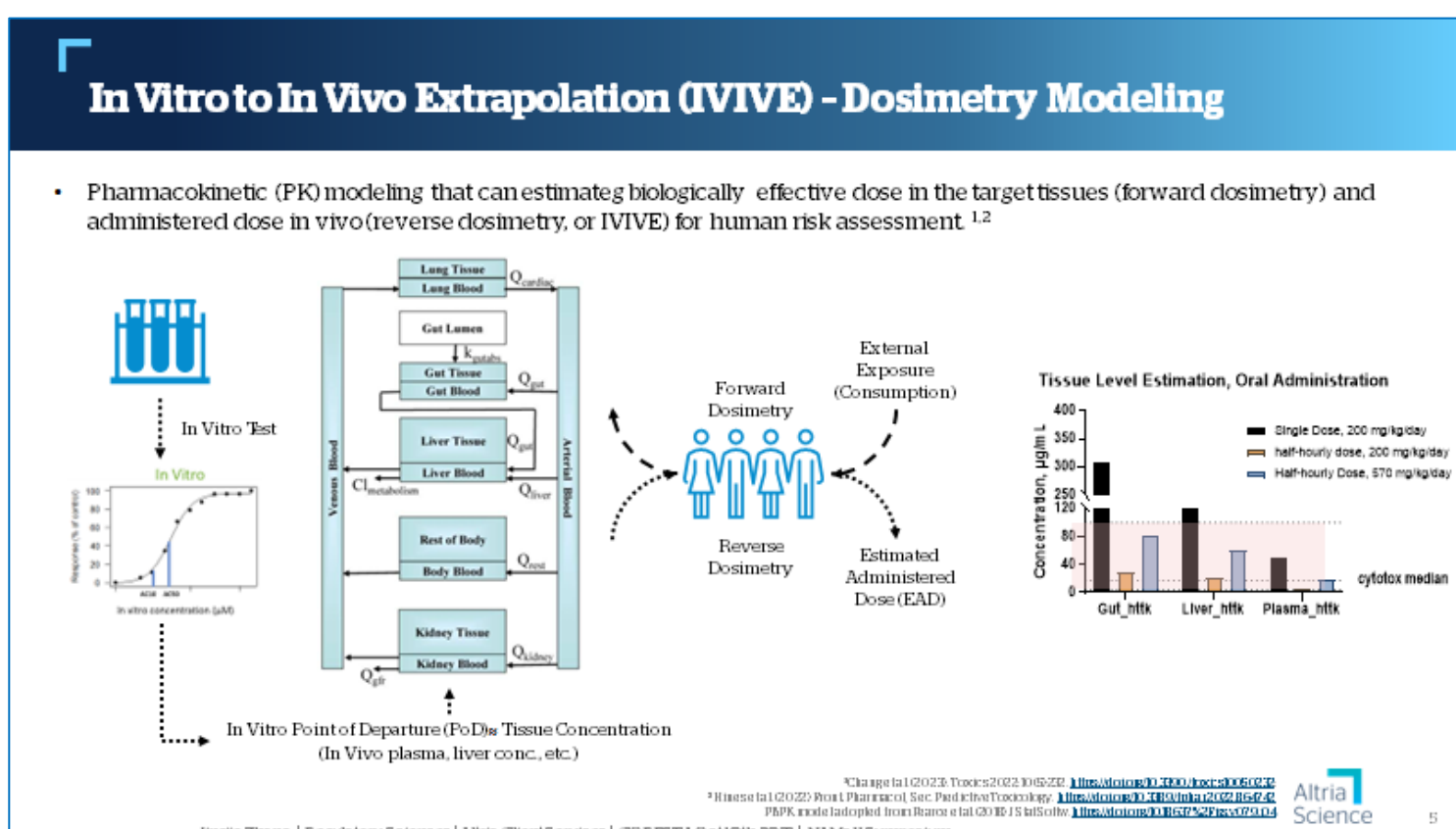
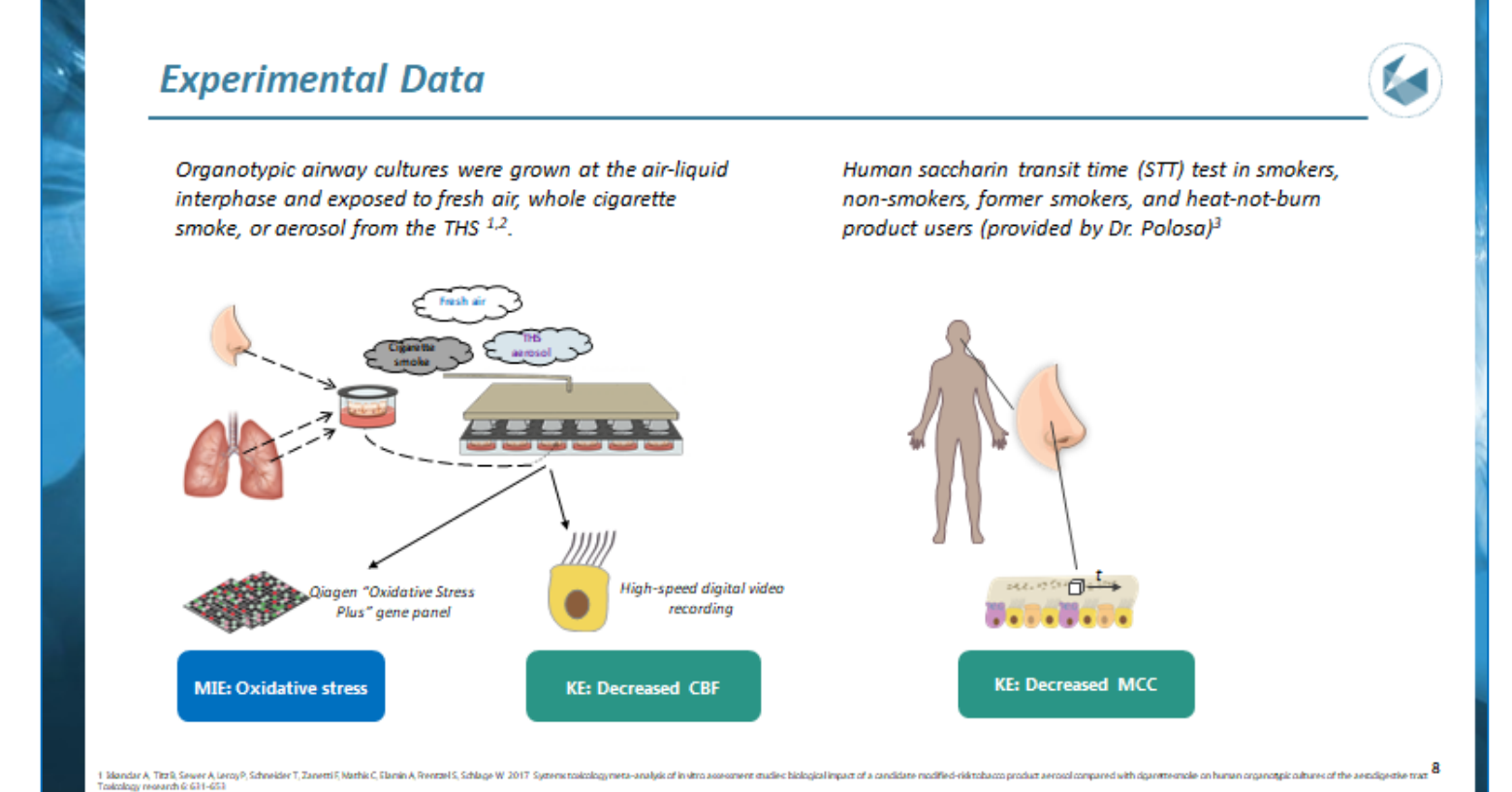
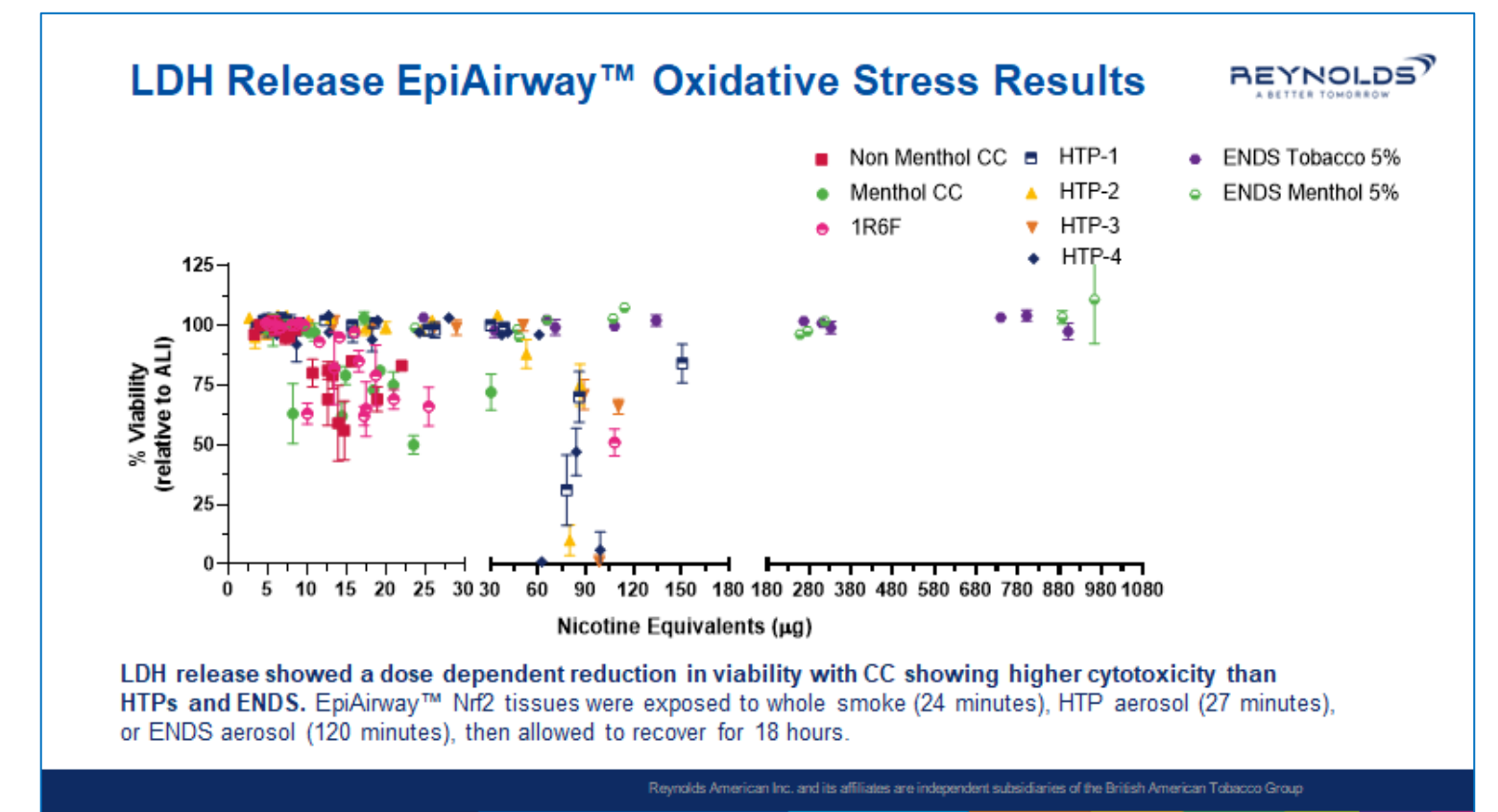
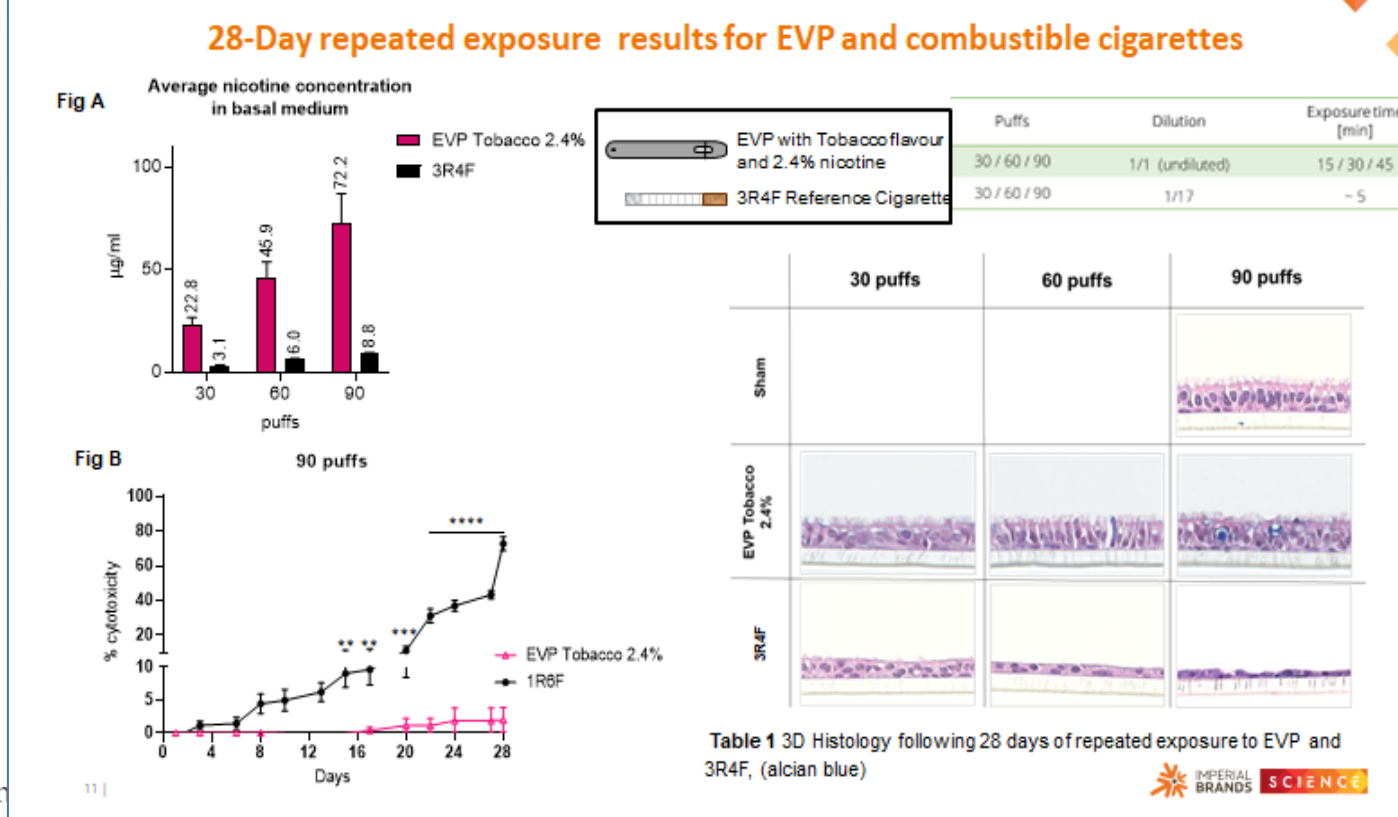
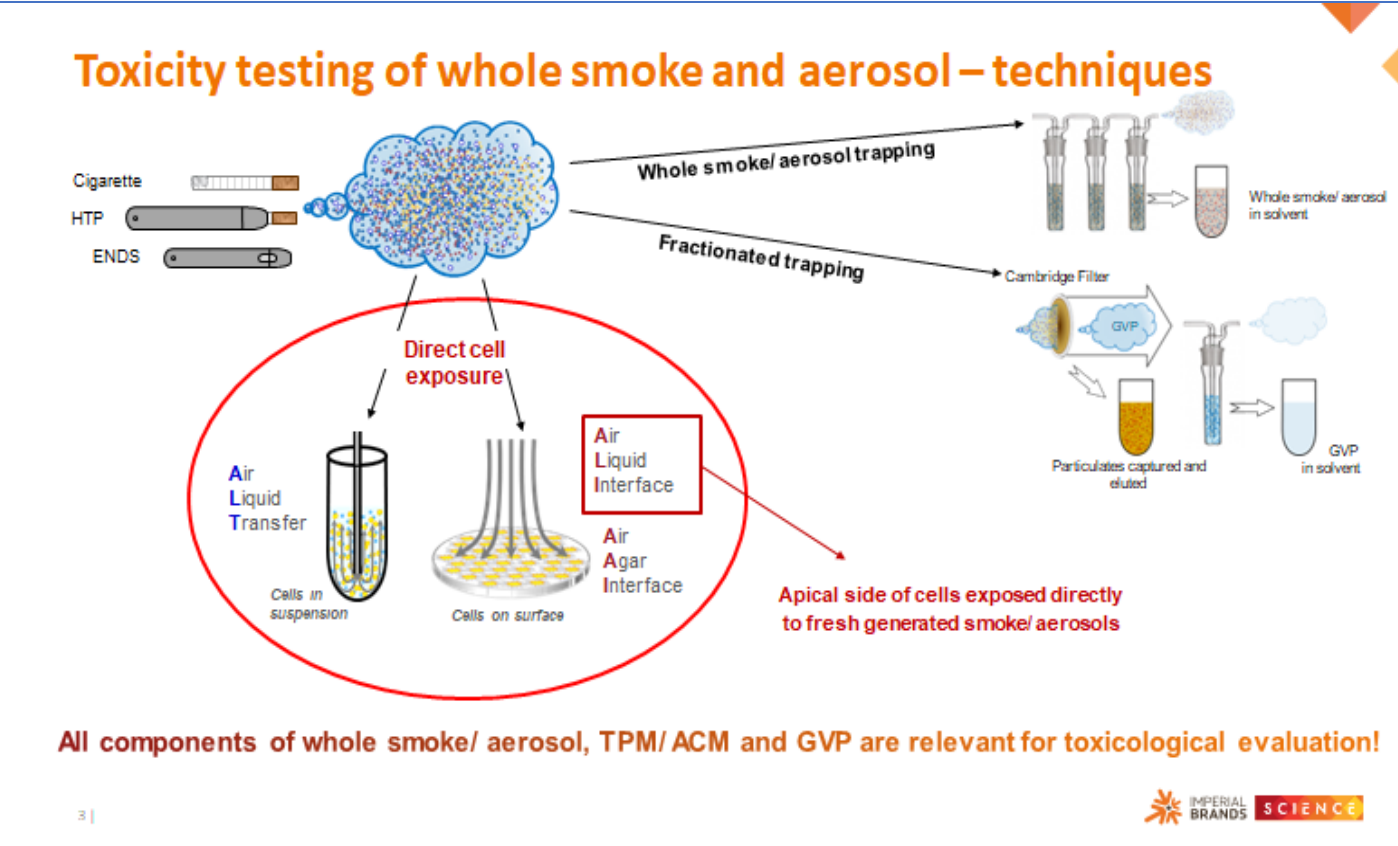
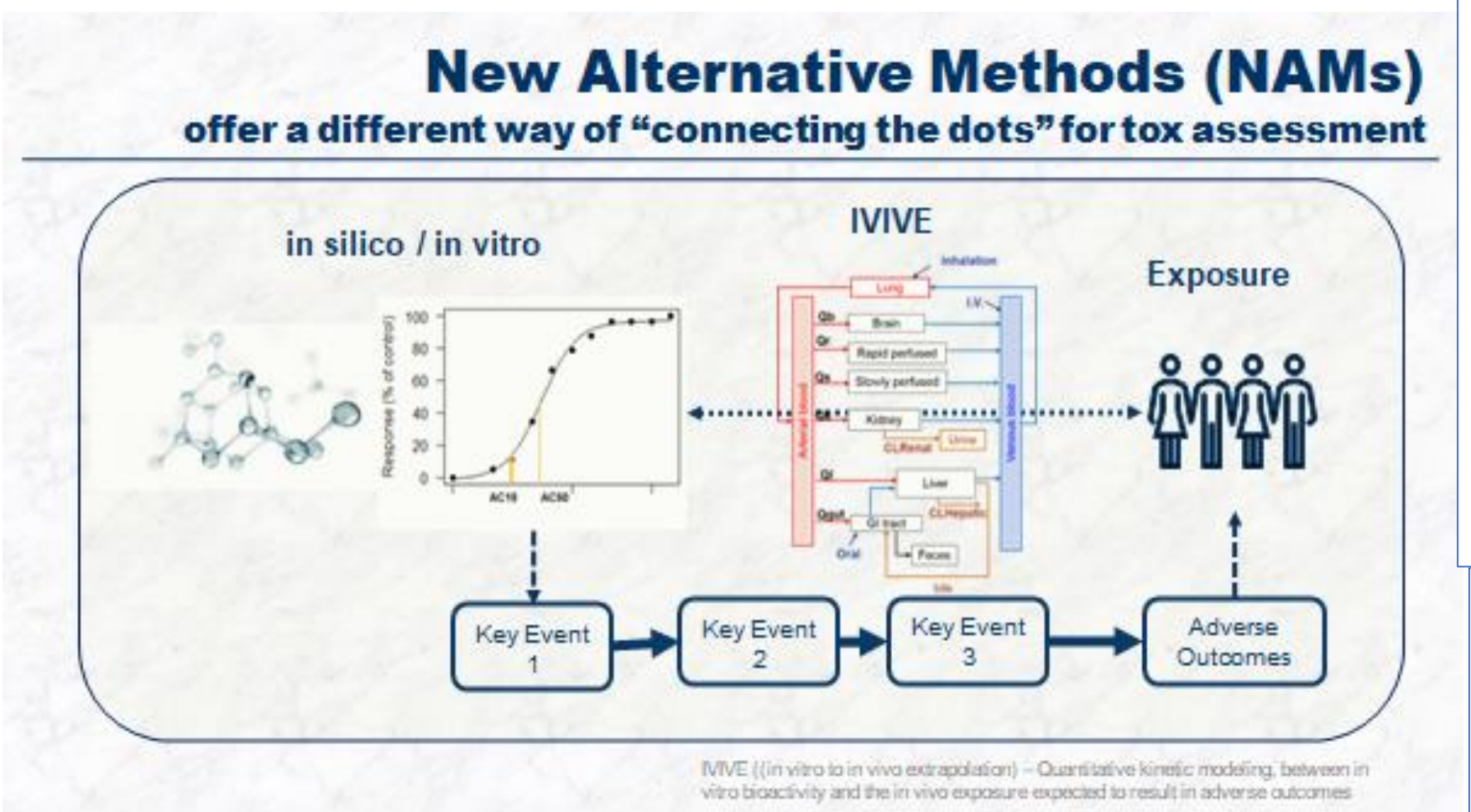
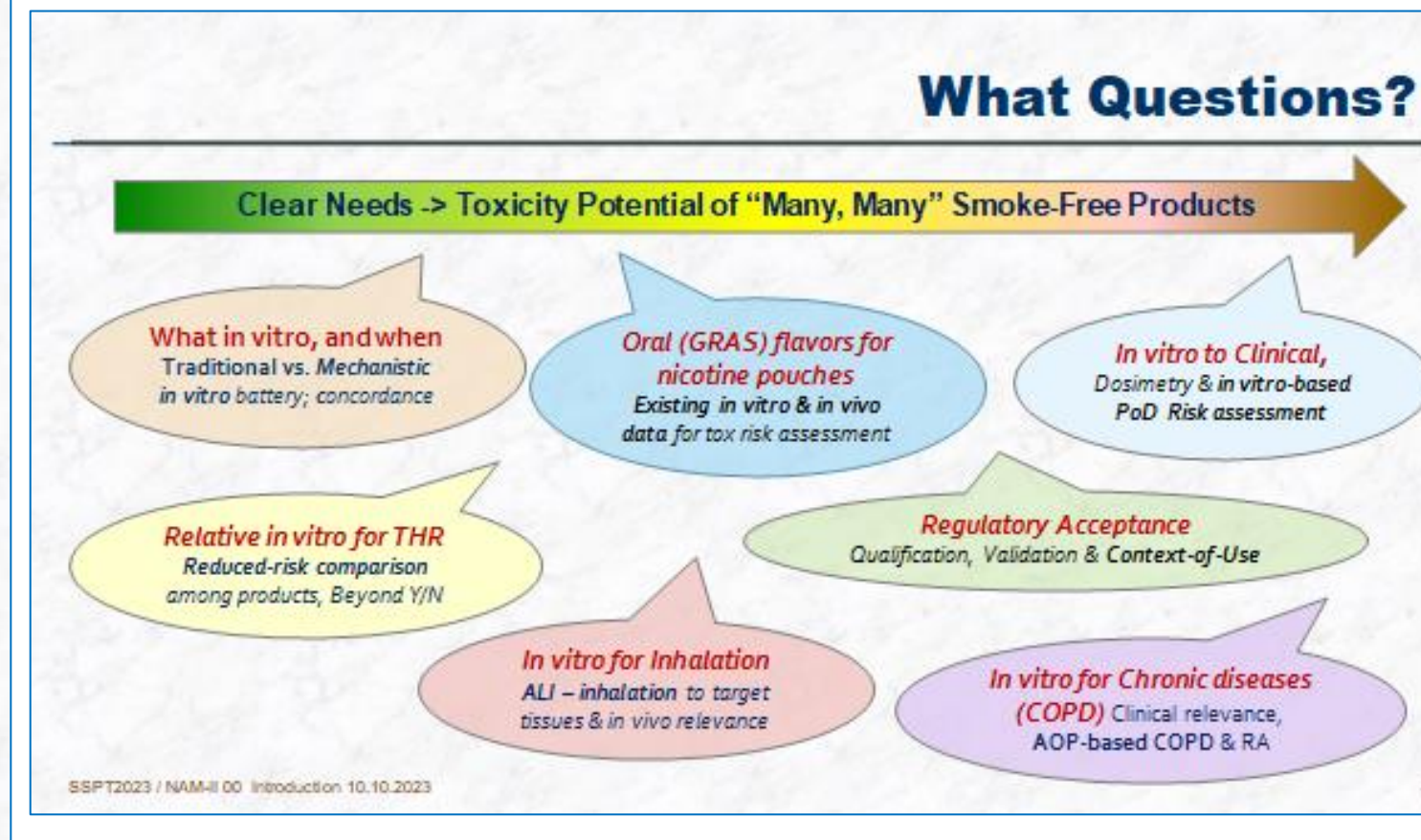
¹Affiliation: Alicia Paini changed to esqLABS GmbH, Saterland, Germany. * A copy of the presentations (including NAM Symposium program and the bibliographies) is provided in the Supplementary Files.



CORESTA NAM Symposium-II (2023)

2023 NAM Symposium-II: Agenda
Applications in Tobacco Regulatory Sciences

NAM - Today	NAM - Tomorrow
1. Robert Leverette - RAI	NAM In vitro-Genotox: Regulatory in vitro genotoxicity & Mechanistic Follow-ups
2. Jingjie Zhang - Altria	NAM in silico-IVIVE: Connecting exposure, dosimetry and toxicity responses in the evaluation of ingredients
3. Liam Simms - Imperial	NAM in vitro exposures to fresh whole smoke & aerosols: standard & novel (3D) in vitro models
Break	
4. Brian Keyser - RAI	NAM In vitro-Clinical: EpiAirway hRF2 - in vitro model of oxidative stress
5. Marja Talikka - PMI	NAM AOPs-COPD I: COPD & lung function
6. Shigeaki Ito - JT	NAMs AOPs-COPD II: In vitro model of mucous hypersecretion with quantitative AOP modeling
Panel Discussion (Q&A)	



Key Messages

- NAMs have the potential to not only replace but possibly outperform traditional animal testing: They are intended to be pragmatic in terms of cost, time, and resources and offer enhanced sensitivity in predicting human-relevant health impacts.
 - There are likely more than one set of NAM tools to answer toxicological questions typically addressed by in vivo testing. Case examples presented (whole aerosol in vitro toxicity of repeated exposures (Simms et al; Keyser et al, 2023) and COPD in vitro models of lung function and oxidative stress (Talikka et al; Ito et al, 2023) demonstrate the feasibility of the AOP-based toxicological knowledge framework to support chemical risk assessment based on mechanistic reasoning.
 - Understanding the dosimetry between in vitro and in vivo conditions is critical in ultimate use of the in vitro-based (NAM) results for quantitative toxicological risk assessment. We introduced publicly available computational kinetic models (Zhang et al, 2023) that allow extrapolation of dosimetry across in vitro, in vivo, and human exposures under different use scenarios using a case example of oral flavor ingredients.
- Expanded use of NAMs in toxicological assessment requires a shift in paradigm from the apical in vivo endpoints to mechanistic NAM-based outcomes. Change the question, for example, from seeking an "in vivo no effect level" to a "Point-of-departure (POD) for a cellular event" that leads to clinical adverse outcomes.
 - Opportunities exist in defining the context-of-use and standardization to gain confidence in wider applications. Clarity in the metrics for qualification and biological validation are needed before NAMs-based risk assessments achieve full legitimacy for regulatory decision making.
 - Continued communication and dedicated engagements among stakeholders (regulatory agencies, developers, and industry) are critical to sustain the momentum.

References

CORESTA : [Who we are](#) | [CORESTA / Smoke-Techno Conference \(SSPT2021\)](#) |
 IVTSG 2019: [Rationale and Strategy for In Vitro Toxicity Testing of Combustible Tobacco Products](#) |
 Moore et al 2020. <https://www.liebertpub.com/doi/10.1089/aivt.2020.0004>
 Lee et al. 2022 <https://www.mdpi.com/2305-6304/10/12/760>
 Thorne et al. 2011 <https://journals.sagepub.com/doi/10.1177/23978473211022267>
 OECD 2023. [OECD Series on Adverse Outcome Pathways | OECD iLibrary \(oecd-ilibrary.org\)](#)

Acknowledgement

Both NAM symposia (2021, 2023) were held during the CORESTA annual SSPT conferences; endorsed by the CORESTA Scientific Commission, Next-Generation Tox Task Force, Biomarker and In Vitro Tox Subgroups. We thank every speaker, a panelist (Dr. Todd Cecil, US FDA/CTP, NAM Symposium-II, 2023) and CORESTA coordinators for their preparation and active participation.