Product Stewardship Maximizes the Harm Reduction Potential of Potentially Reduced Risk Products (RRPs)

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Center for Research and Technology

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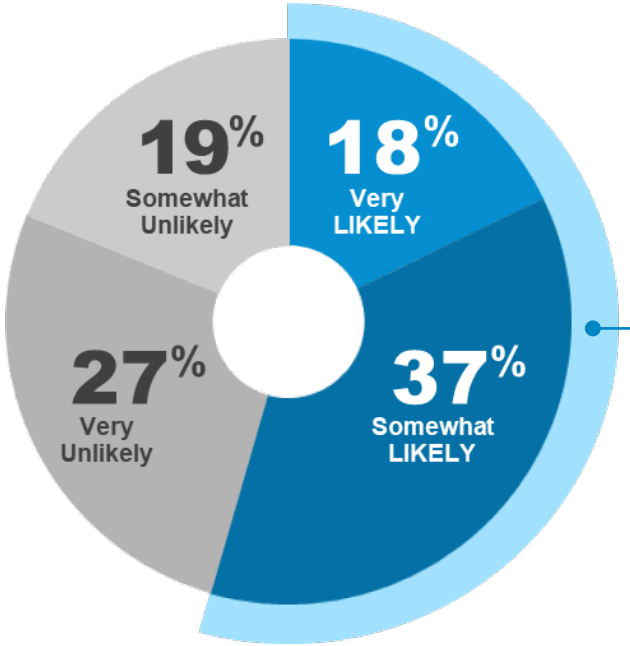
The Case for Product Standards for RRPs



55%
Adult Smokers INTERESTED in Reduced-Risk Tobacco Products[1]

Adult Smokers, who cannot or will not quit, should have access to acceptable RRP alternatives that are substantiated through science and evidence[2]

- FDA should implement product standards under 907(a)(3) that facilitate the innovation of potentially RRPs and allow such products to enter the market more rapidly.
- Compliance with product standards may
  - Alleviate the amount of product-specific information required in a product application
  - Provide the basis for an abbreviated marketing authorization pathway for RRPs
  - Create industry-wide baselines for safety and quality

[1]Based on ALCS analysis of PATH Wave 1 data Sept 12, 2013 – Dec 14, 2014. Response to question – "If a tobacco product made a claim that it was less harmful to health than other products, how likely would you be to use that product?" Numbers may not foot due to rounding.

[2]Press Release, FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (July 27, 2017), available at https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death ("Envision[] a world . . . where adults who still need or want nicotine could get it from alternative and less harmful sources. . .").

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EVALI – Absence of Product Stewardship

https://www.nytimes.com/2019/08/31/health/vaping-marijuana-ecigarettes-sickness.html

Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report

https://doi.org/10.1056/NEJMoa1911614 Preliminary Report, Sep 6, 2019, Final Report Mar 5, 2020

https://www.cnbc.com/2019/09/25/tenth-patient-dies-from-vaping-related-illness.html

Centers for Disease Control and Prevention

- Vitamin E acetate is strongly linked to the EVALI outbreak. Vitamin E acetate has been found in product samples tested by FDA and state laboratories and in patient lung fluid samples tested by CDC from geographically diverse states. Vitamin E acetate has not been found in the lung fluid of people that do not have EVALI.
- Evidence is not sufficient to rule out the contribution of other chemicals of concern, including chemicals in either THC or non-THC products, in some of the reported EVALI cases.

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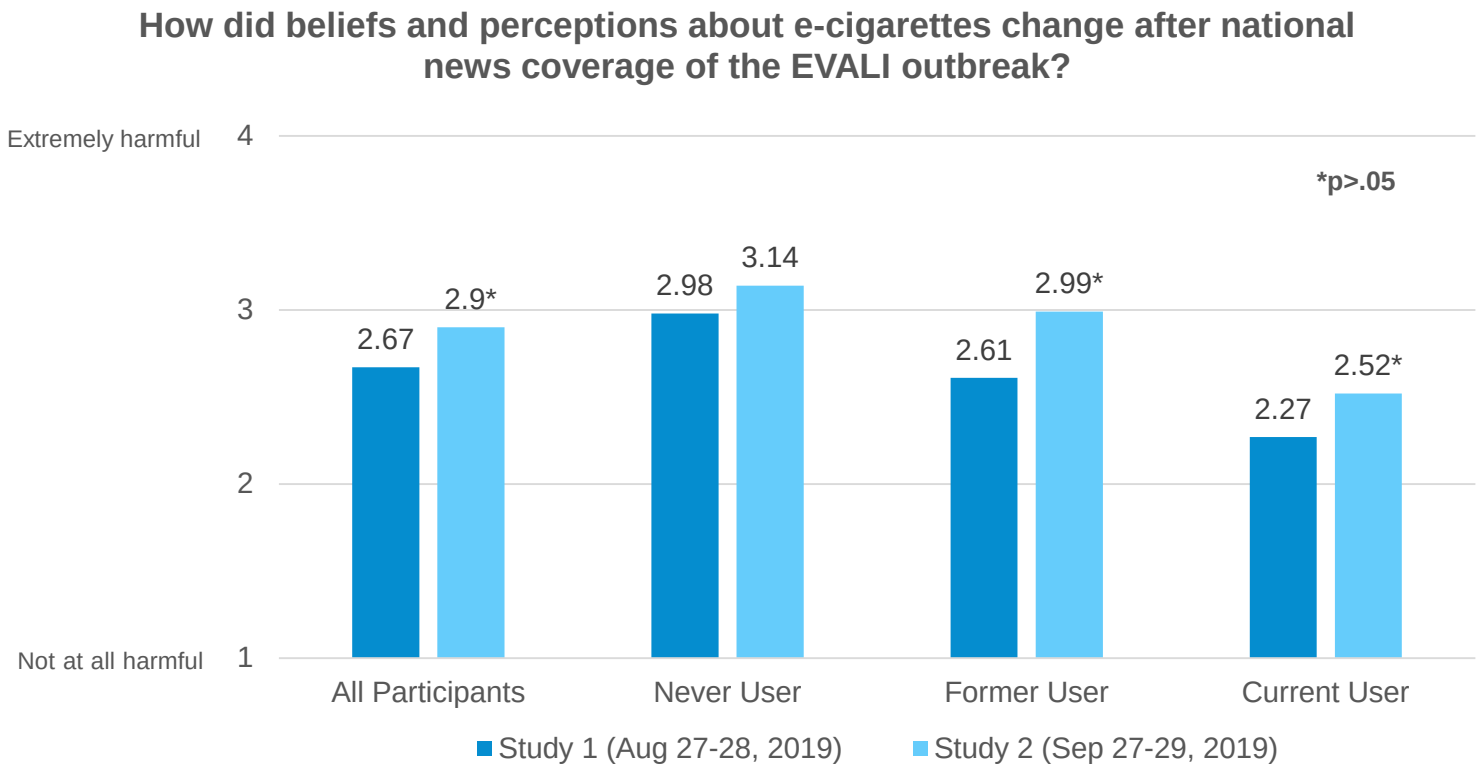
Impact to Risk Perceptions



Perceived harm of e-cigarettes increased during a month of intense news coverage of EVALI

Adapted from Morgan JC, Silver N, Cappella JN (2021) How did beliefs and perceptions about e-cigarettes change after national news coverage of the EVALI outbreak? PLoS ONE 16(4): e0250908. https://doi.org/10.1371/journal.pone.0250908

What is Product Stewardship?

"the act of minimizing the health, safety, environmental, and social impacts of a product and its packaging throughout all lifecycle stages, while also maximizing economic benefits."

PRODUCT STEWARDSHIP INSTITUTE

https://www.productstewardship.us/page/Definitions

- Our product stewardship program focuses on the potential health impact – health and safety – to adult consumers independent of regulatory framework.
- We rely on core product stewardship principles that are practiced across the chemical, pharmaceutical, food and consumer packaged goods industries.

Scientific Framework

CONSTITUENT REDUCTION

Product Design and Control

Chemical and Physical Characterization

INDIVIDUAL RISK REDUCTION

Toxicology and Risk Assessment

Studies in Adult Human Subjects

POPULATION HARM REDUCTION

Perception and Behavior Assessment

Risks and Benefits to Health of the Population

THE PRODUCT

- Chemistry Manufacturing and Controls
- Product Stability
- Chemical characterization

EXPOSURE and HEALTH RISK

- Toxicology & Risk Assessment
- Health risk assessment (absolute and relative)
- Human Studies
- Human Factors Assessment

IMPACT on the POPULATION

- Risk perceptions (absolute and relative)
- Impact of product on users
- Impact on non-users
- Overall impact on the population
- Environmental Assessment

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Product Stewardship Framework

- Robust processes to select and qualify product ingredients and materials
- Toxicological risk assessments of ingredients and constituents to minimize human health risks
- Pragmatic use of toxicological assays to assess the health impact of potentially reduced risk products

Data Requirements for all RRP categories

- Use only raw materials that are USP or food grade, if available
- Finished product recipe – full ingredient disclosure
  - On a chemical specific level
- Exposure estimate - daily use patterns of the finished product
- Physical and Mechanical Hazards Analysis
  - e.g., UL 8139
- Data on the stability of the product (as needed)

Toxicological Risk Assessment – Oral Products

- Select and qualify suppliers of USP/food grade materials that can provide sufficient documentation of purity/grade etc.
  - Ensures that each material contains the lowest levels of impurities/contaminants that are technically feasible and are in parallel with ingredients used in the food supply
  - Each ingredient should be generally recognized as safe (GRAS) for use in food
- Obtain FULL ingredient disclosure of the product.
  - This disclosure should be at the chemical level and, for almost all cases, each chemical should be identified with a CAS RN and a FEMA number (if applicable)
- Estimate daily consumption of the product
  - This data may be from actual use studies, in-market data or estimated from other sources

Toxicology and Risk Assessment

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Toxicological Risk Assessment – Oral Products

- Conduct an exposure assessment on each chemical entity and compare to acceptable daily exposure levels
  - Exposure levels should be are supported by the available data on which authoritative bodies (e.g., FDA, JECFA) made their GRAS determination, if available
  - Other comparisons may include the FEMA PADI, the threshold of toxicological concern (TTC), or derived values from toxicology studies
- Conduct risk assessments on any available constituent and stability data on compounds of interest
  - Guidance from EPA, OEHHA, TCEQ, ECHA, PQRI, etc.

EPA – US Environmental Protection Agency, OEHHA – The Office of Environmental Health Hazard Assessment (California Proposition 65), TCEQ – Texas Commission on Environmental Quality, ECHA – European Chemicals Agency, PQRI – Product Quality Research Institute

Toxicological Risk Assessment – Inhalable Products

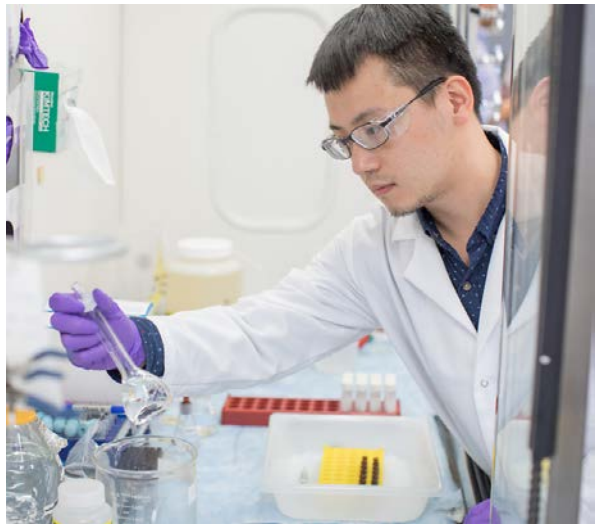
Toxicology and Risk Assessment

- Selection of suppliers should have the same rigor as for oral products
  - All ingredients should be GRAS (if applicable) and food or USP grade
- Obtain FULL ingredient disclosure just as with oral products
- Estimate daily consumption of the product
- Conduct an exposure assessment on each chemical entity added to the e-liquid

Costigan S and Meredith C (2015) An approach to ingredient screening and toxicological risk assessment of flavors in e-liquids. Regulatory Toxicology and Pharmacology 72 https://doi.org/10.1016/j.yrtph.2015.05.018

Toxicological Risk Assessment – Inhalable Products

Toxicology and Risk Assessment



- Route of exposure considerations are paramount
  - GRAS may not be sufficient
  - Product aerosols may contain different chemicals than those that were intentionally added to the formulation
- Consider the potential of leachates from any metal or plastic components (or other sources) in the liquid or aerosol stream
- Analyze the aerosol to determine chemical composition (e.g., HPHCs, leachates, etc.) and then perform risk assessment on each identified chemical entity
- Review available stability data and conduct risk assessments on compounds of interest

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Risk Assessment Guides

- Threshold of Toxicological Concern (TTC) of 1.5µg/day – acceptable level for lifetime exposure to chemicals, including mutagens, via any route of exposure (ICH M7(R1))

U.S. FOOD & DRUG

Reviewer Guides and Scientific Policy Memoranda about FDA Review of Tobacco Product Applications

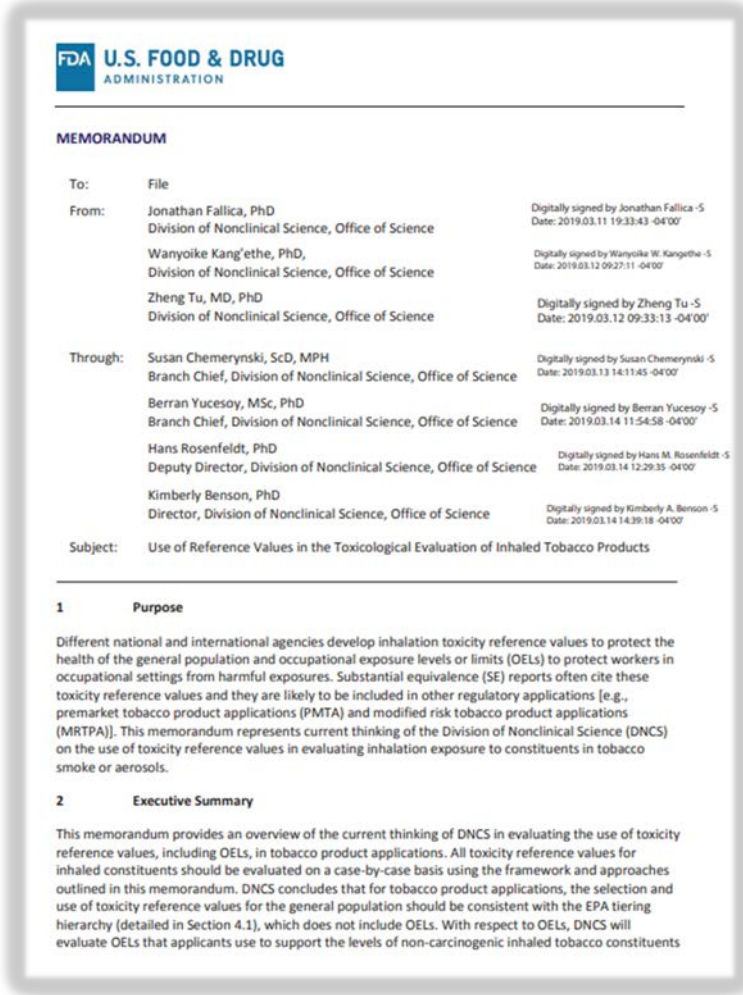
Documents to help reviewers evaluate tobacco product applications. This information adds detail about FDA review processes and regulatory science issues.

FDA's reviewer guides and science policy memoranda provide information about FDA review processes and several regulatory science issues. These documents were developed to assist FDA reviewers with the evaluation of new tobacco product applications. FDA has put these documents on this site in response to public interest, e.g. frequent Freedom of Information Act requests.

Information contained in these documents is subject to change based on advances in policy, the regulatory framework, and regulatory science, and is not binding on FDA or the public. These documents offer a snapshot of FDA's thinking on certain aspects of tobacco regulatory science at the time the documents were written but do not necessarily represent FDA's complete or current thinking. These documents should not be used as a comprehensive manual for preparing or anticipating review of tobacco product applications.

General

1. Unique Identification of Portioned Moist Snuff and Snus Products



U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

To: File

From: Jonathan Fallica, PhD
Division of Nonclinical Science, Office of Science
Digitally signed by Jonathan Fallica -S Date: 2019.03.11 19:33:43 -04'00'

Wanyoike Kang'ethe, PhD,
Division of Nonclinical Science, Office of Science
Digitally signed by Wanyoike W. Kangethe -S Date: 2019.03.12 09:27:11 -04'00'

Zheng Tu, MD, PhD
Division of Nonclinical Science, Office of Science
Digitally signed by Zheng Tu -S Date: 2019.03.12 09:33:13 -04'00'

Through: Susan Chemerynski, ScD, MPH
Branch Chief, Division of Nonclinical Science, Office of Science
Digitally signed by Susan Chemerynski -S Date: 2019.03.13 14:11:45 -04'00'

Berran Yucesoy, MSc, PhD
Branch Chief, Division of Nonclinical Science, Office of Science
Digitally signed by Berran Yucesoy -S Date: 2019.03.14 11:54:58 -04'00'

Hans Rosenfeldt, PhD
Deputy Director, Division of Nonclinical Science, Office of Science
Digitally signed by Hans M. Rosenfeldt -S Date: 2019.03.14 12:29:35 -04'00'

Kimberly Benson, PhD
Director, Division of Nonclinical Science, Office of Science
Digitally signed by Kimberly A. Benson -S Date: 2019.03.14 14:39:18 -04'00'

Subject: Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products

1 Purpose

Different national and international agencies develop inhalation toxicity reference values to protect the health of the general population and occupational exposure levels or limits (OELs) to protect workers in occupational settings from harmful exposures. Substantial equivalence (SE) reports often cite these toxicity reference values and they are likely to be included in other regulatory applications [e.g., premarket tobacco product applications (PMTA) and modified risk tobacco product applications (MRTPA)]. This memorandum represents current thinking of the Division of Nonclinical Science (DNCS) on the use of toxicity reference values in evaluating inhalation exposure to constituents in tobacco smoke or aerosols.

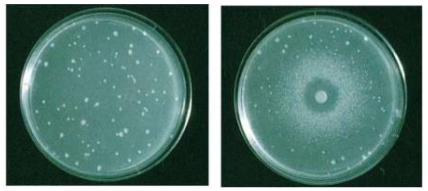
2 Executive Summary

This memorandum provides an overview of the current thinking of DNCS in evaluating the use of toxicity reference values, including OELs, in tobacco product applications. All toxicity reference values for inhaled constituents should be evaluated on a case-by-case basis using the framework and approaches outlined in this memorandum. DNCS concludes that for tobacco product applications, the selection and use of toxicity reference values for the general population should be consistent with the EPA tiering hierarchy (detailed in Section 4.1), which does not include OELs. With respect to OELs, DNCS will evaluate OELs that applicants use to support the levels of non-carcinogenic inhaled tobacco constituents

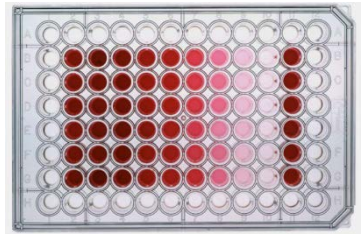
https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/reviewer-guides-and-scientific-policy-memoranda-about-fda-review-tobacco-product-applications

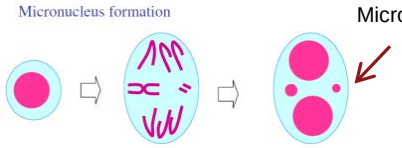
Toxicological Assays to Assess Potential Health Impact

- Ames reverse mutation assay (OECD 471)
- Neutral Red Uptake cytotoxicity assay (OECD 129/432)
- In vitro micronucleus assay (OECD 487)
- 90-day in vivo inhalation assay (OECD 413)

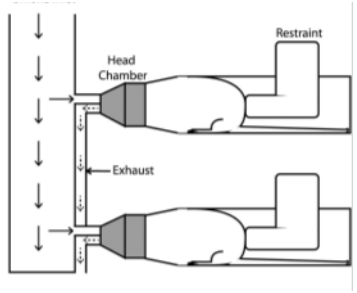


Negative Positive



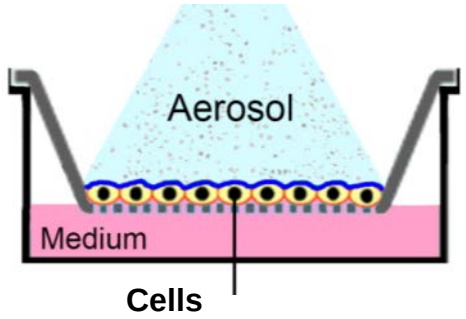


Adapted from Fenech et al, 2011 Mutagenesis, 26(1), 125.



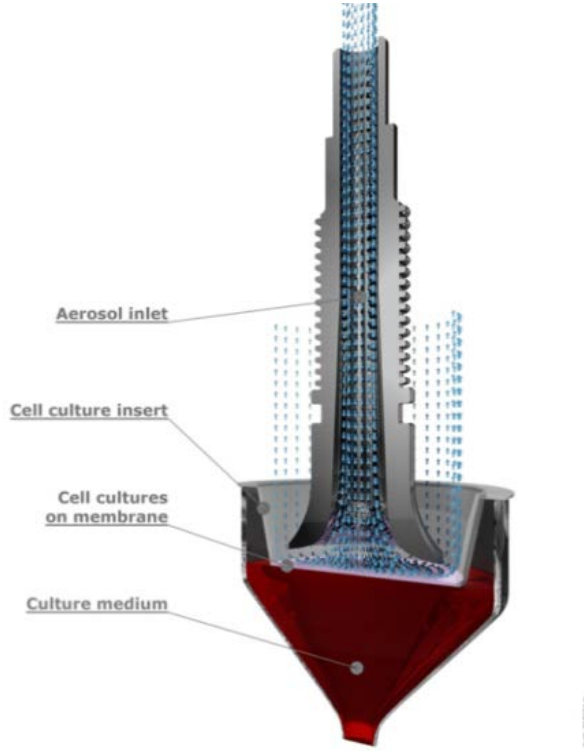
Advancing FDA's Tox 21 Roadmap for Tobacco Products

- Ultimate goal of reducing, refining and replacing animal usage as well as regulatory acceptance of the findings
- Clinically relevant cell-based assays
- Computational dosimetry - in vitro to in vivo extrapolation (IVIVE) to bolster the relevance to human health of in vitro findings



Utilizes lung cells grown in a more biologically relevant environment (Air-Liquid Interface)

Image Courtesy of N Castro, ALCS



CORESTA 2021 – Smoke-Science (NAM Symposium)

DAY 2

TUESDAY 19 OCTOBER

SYMPOSIUM

Advancing New Alternative Methods (NAMs) for Tobacco Harm Reduction

Chair: K. Monica LEE

Co-Chair: Shannon BELL

CET Time Zone		**PART 1**
13:30-13:35	Welcome	COLARD S. *CORESTA, 11 rue du Quatre Septembre, 75002 Paris, France*
13:35-13:45	NAM 00 Intro	**Advancing new alternative methods for tobacco harm reduction** LEE K.M.(1); BELL S.(2) *(1) Altria Client Services LLC, 601 East Jackson Street, Richmond, VA 23219, U.S.A.* *(2) Integrated Laboratory Systems, 601 Keystone Park Drive, Suite 200, Morrisville, NC 27560, U.S.A.*
13:45-14:10	NAM 01	**US federal efforts to develop and implement alternatives to animal testing** KLEINSTREUER N. *NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), U.S.A.*
14:10-14:35	NAM 02	**Application of biokinetic modelling for *in vitro* to *in vivo* extrapolation (IVIVE) in chemical risk assessment** PAINI A.; WORTH A. *European Commission Joint Research Centre (JRC), Ispra, Italy*
14:35-15:00	NAM 03	**Inhalation exposure modeling for assessing health risks of toxic aerosols and vapors** CORLEY R.A. *Greek Creek Toxicokinetics Consulting (GCTC), LLC, Boise, ID 83714, U.S.A.*

CORESTA 2021 Smoke-Techno Virtu@l

Register at www.CORESTA.org

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Summary

- Product stewardship is paramount to the success of tobacco harm reduction

- These principles should be institutionalized into product standards
  - Create industry-wide baselines for safety and quality
  - Help industry and public health focus on the ultimate goal – developing and authorizing products that move smokers to reduced risk products

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