ADVANCING NEW APPROACH METHODS (NAMs) TO SUPPORT REGULATORY TOXICOLOGY EVALUATIONS OF TOBACCO PRODUCTS

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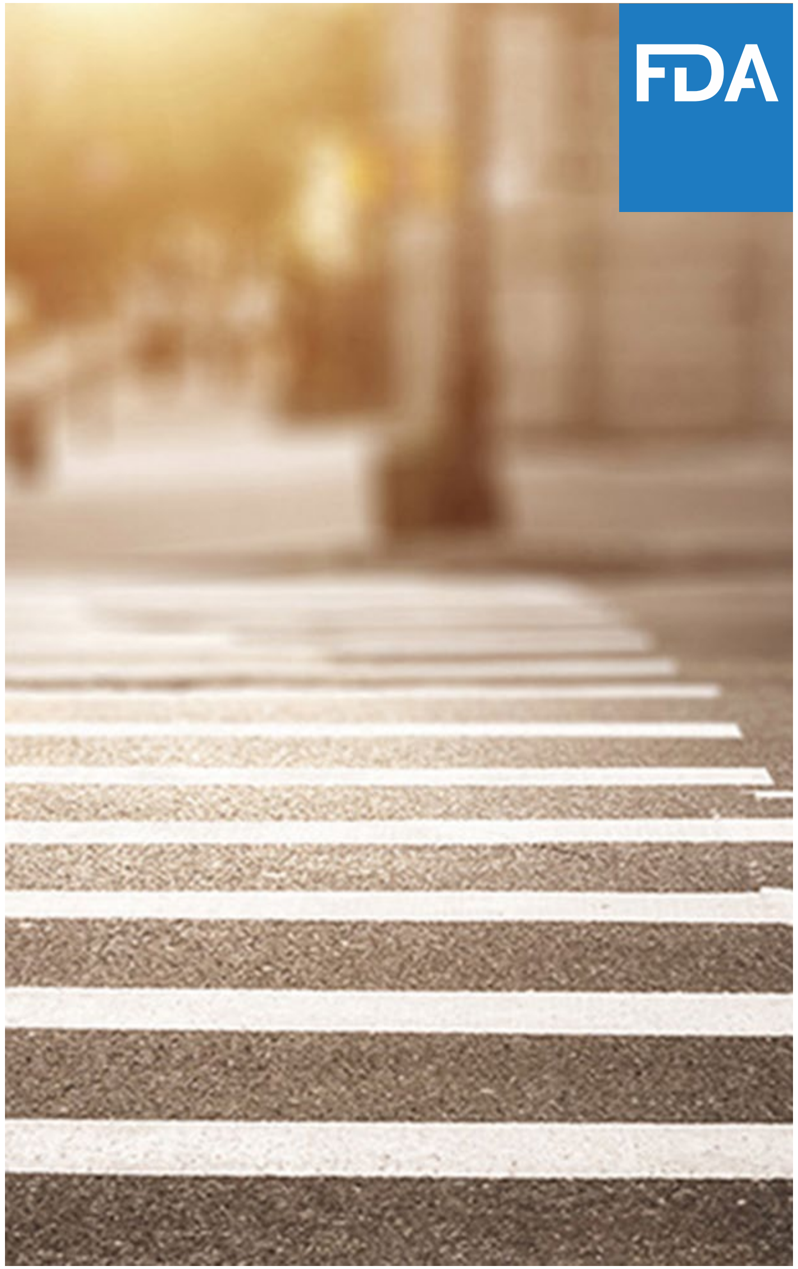
TOPICS

- Tobacco Products
  - Regulatory authority over tobacco products
  - Diversity of products
- CTP interest and commitment to new approach methods
- Programmatic approach to NAMs for regulatory toxicology evaluations of tobacco products
  - Inhalation toxicology research
  - Computational toxicology model predictions to support application review



MISSION

To protect Americans from tobacco-related death and disease by regulating the manufacture, distribution, and marketing of tobacco products and by educating the public, especially young people, about tobacco products and the dangers their use poses to themselves and others.

CENTER FOR TOBACCO PRODUCTS

- **Family Smoking Prevention and Tobacco Control Act (2009)** gives FDA broad authority to regulate tobacco products (e.g., cigarettes, cigarette tobacco, smokeless tobacco, and roll-your-own tobacco).

- **In 2016, FDA issued final deeming regulation** to bring all tobacco products under its authority, including cigars, pipe tobacco, hookah, dissolvable tobacco products, electronic nicotine delivery systems (ENDS, e-cigarettes), and any other product containing tobacco, or nicotine derived from tobacco.

- **Non-Tobacco Nicotine Products**: Congress passed a federal law that went into effect on **April 14, 2022,** clarifying the FDA's authority to regulate tobacco products containing nicotine from any source.
  - Does not include nicotine products that are intended for a therapeutic purpose or food products

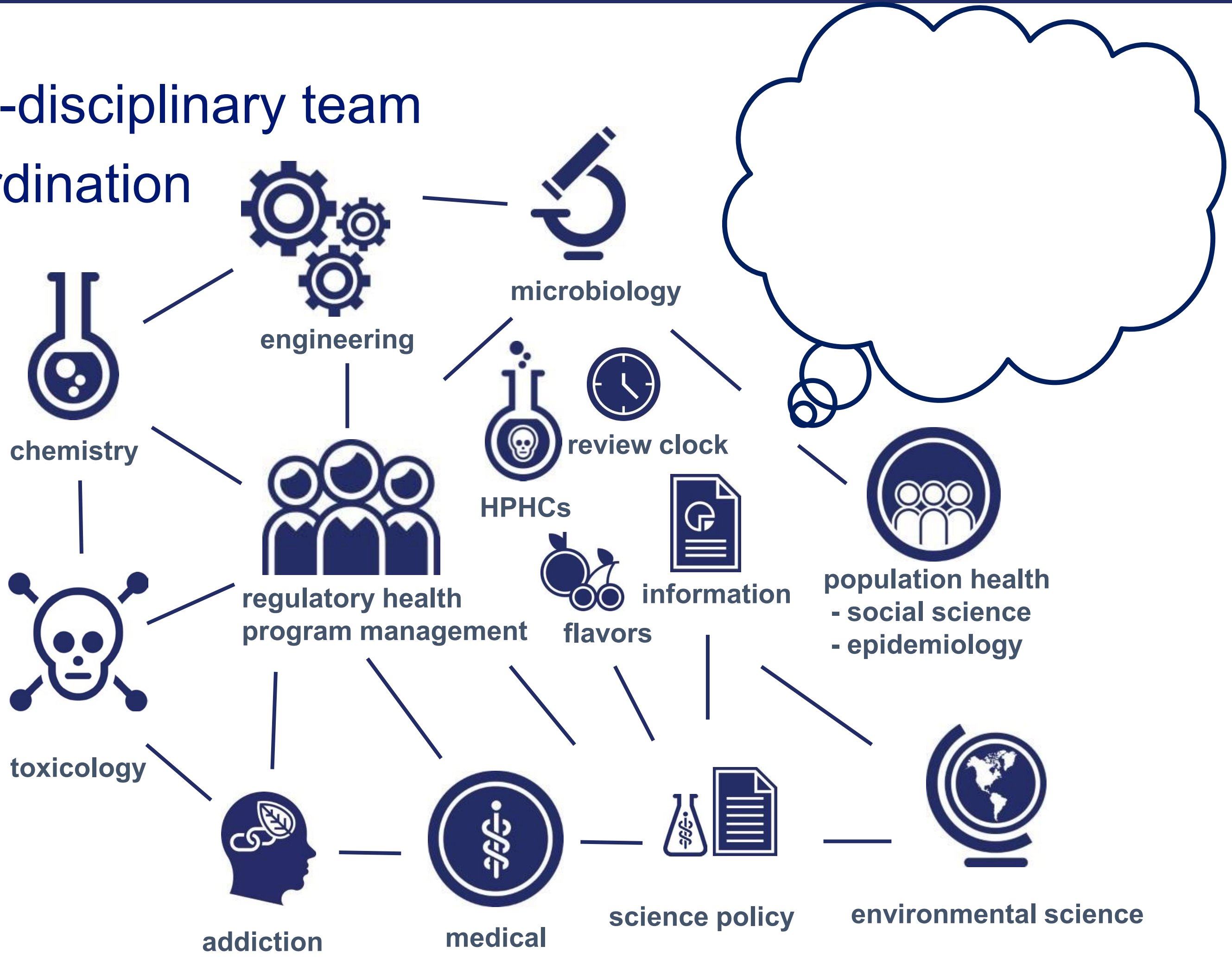
PATHWAYS TO MARKET FOR TOBACCO PRODUCTS

Per the tobacco control act, tobacco products entering the market after February 2007 must obtain premarket authorization from FDA. This is through one of three pathways:

- Substantial Equivalence (SE)
- Exemption from Substantial Equivalence (EX)
- Premarket Tobacco Product Application (PMTA)
  - The applicant must demonstrate that marketing of the new product is “ .” Entails consideration of risks and benefits of the new product to the whole population by assessing the impact on cessation (i.e., effect of adult users), impact on initiation (i.e., impact on youth and other non-users), **toxicological effects**, and many other human health, scientific, manufacturing, labeling, and other considerations.
- Action is either: Marketing authorization or no marketing authorization (denial)

PRODUCT APPLICATION REVIEW – TEAMWORK

- Multi-disciplinary team
- Coordination



CENTER FOR TOBACCO PRODUCTS

Cigarettes

Roll-your-own

Loose Leaf

Plug

Twist

Nicotine gels

Hookah pens

Hookah (Waterpipe) Tobacco

Dry snuff

Pipe Tobacco

SNUS (Portioned)

SNUS (Portioned)

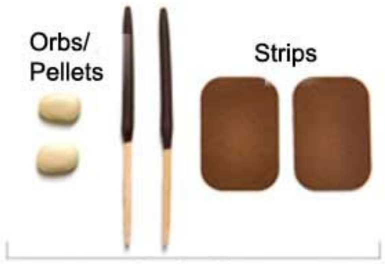
SNUS (Loose)

Little cigars, cigars, and premium cigars

Sticks

Orbs/
Pellets

Strips



Dissolvables

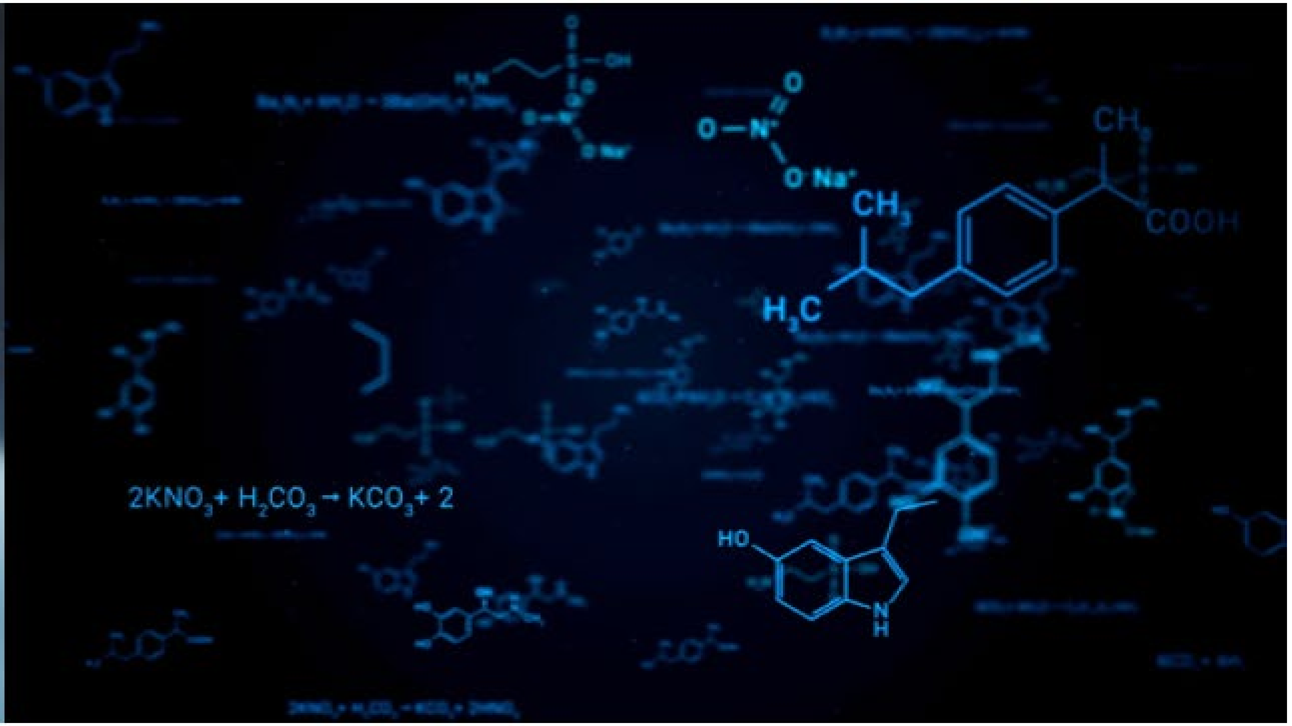
E-cigarettes, Vapes, and other Electronic Nicotine Delivery Systems

CHEMICAL LANDSCAPE OF E-CIGARETTE LIQUIDS AND AEROSOLS

Report: nearly 2,000 unknown chemicals found in some e-liquids and e-cigarette aerosols[1]

Myriad of chemicals

Modified Photo from Johns Hopkins University HUB. https://hub.jhu.edu/2019/09/30/vaping-related-illness-public-health-expert-qa/

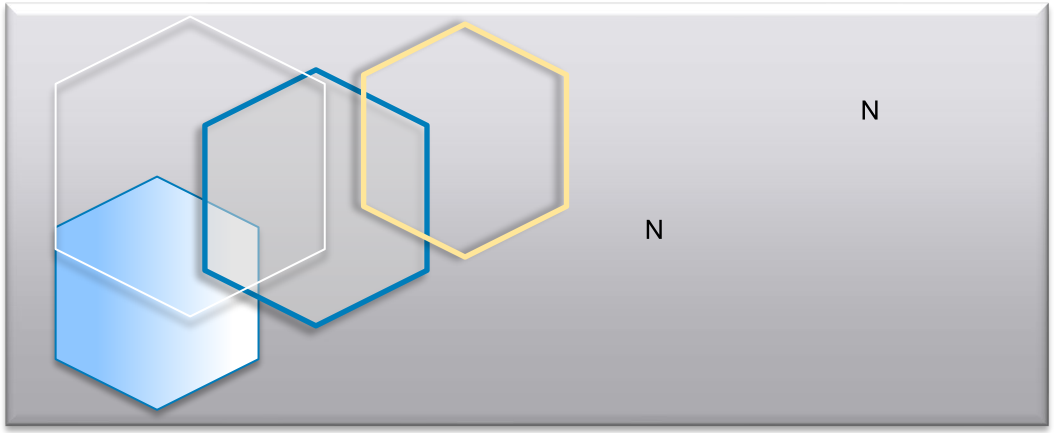


[1] Chem. Res. Toxicol. 2021, 34(10), 2216-2226

CTP'S STEADFAST COMMITMENT TO ADVANCE NAMs

FDA

Making Evidence-Informed Decisions



- CTP is committed to scientific stewardship of NAMs by investigating and optimizing approaches so that these approaches may generate evidence that can be used to inform programmatic, operational, and tobacco regulatory science
- Tobacco regulatory science research is critical to understanding impact of the product on manufacturing, marketing, and distribution of tobacco products on public health
- NAMs research helps support the toxicology review of tobacco product applications

PROGRAMMATIC APPROACH TO NAMs

Applied Research

CTP performed and contracted research on NAMs

Regulatory science

Impact of these projects

Knowledge, publications, partnership with NCTR and engagement with stakeholders

Application Review

Enhancing quality of information

Real-world public health impact

Supports making better decisions

APPLIED RESEARCH

- Multi-faceted science-based approach crucial to CTP’s regulatory programs and mission
- Tobacco regulatory science research critical to understanding impact of manufacturing, marketing, and distribution of tobacco products on public health
- Research informs policy development, product standards, and review of tobacco product applications

NAMs TOXICOLOGY RESEARCH

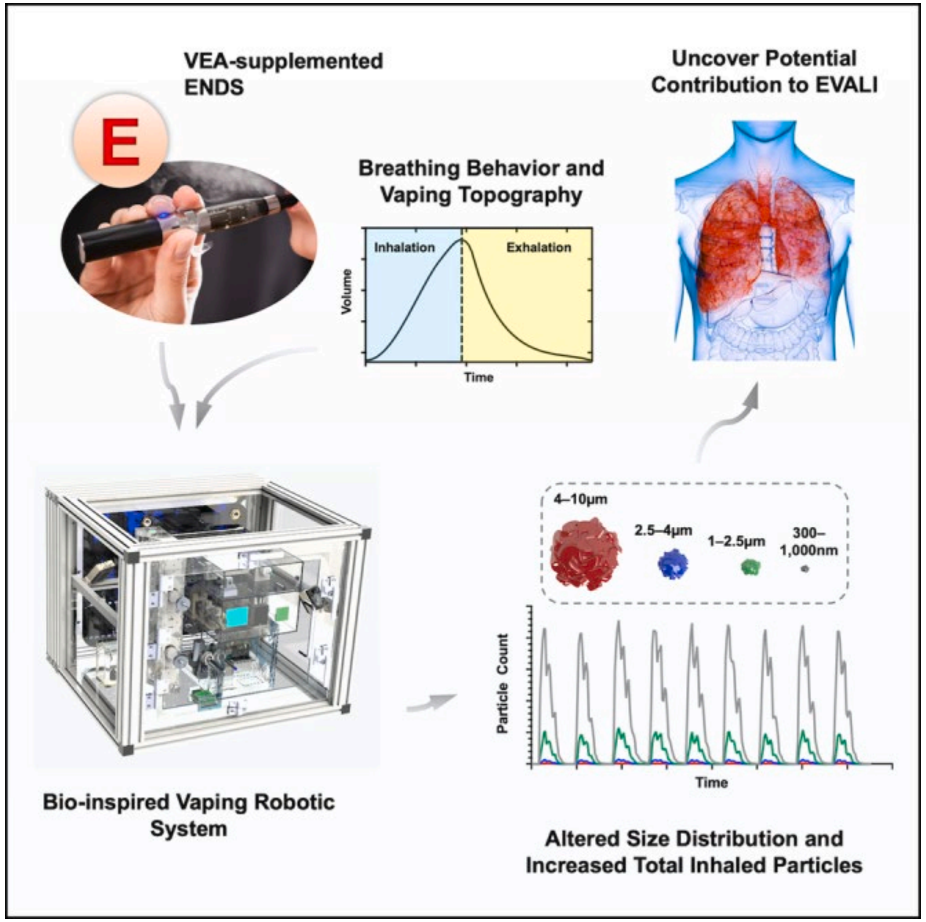
FDA

Inhalation

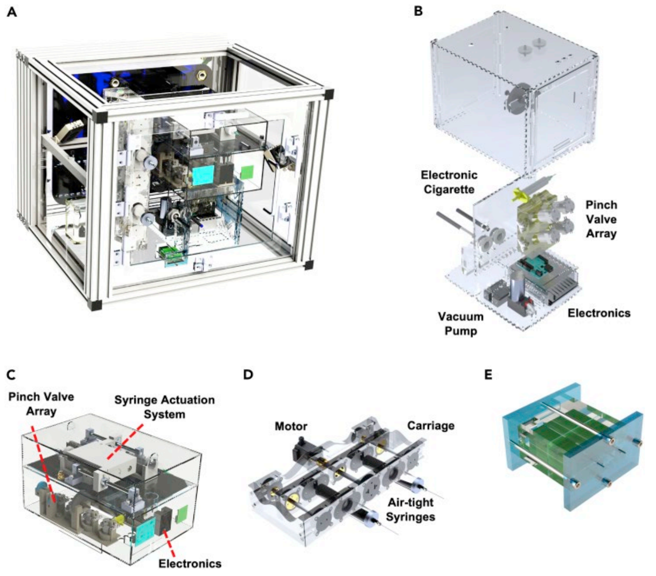
- **Broad Agency Announcement**: Toxicity and Carcinogenicity Profiling of Tobacco Products via Organ Microengineering and Systems Biology (Contract 75F40121C00039)
  - ❑ Develop a new platform that enables organ- and system-level analysis of exposure to emissions of different electronic nicotine delivery systems (ENDS) and hookah products
  - ❑ Microfluidically integrated system that generates and delivers smoke/vapors with exposures similar to those a human user experiences
  - ❑ System exposes co-cultured human lung airway epithelial cells embedded in a vascularized three-dimensional microstructure containing naturally occurring extracellular matrix proteins, fibroblasts, and immune cells
  - ❑ Completed system could allow for accurate and efficient prediction of product toxicity and carcinogenicity using human lung cells in vitro
- Project has the potential to serve as a tool to help modernize and enhance understanding of inhalation toxicology of tobacco products

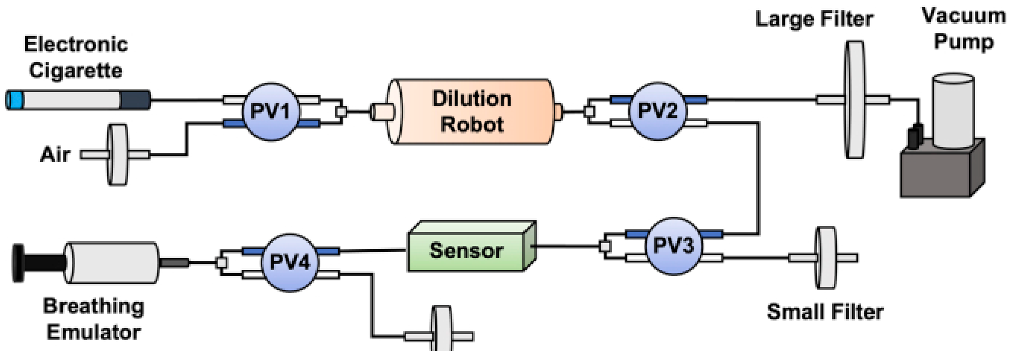
NAMs INHALATION TOXICOLOGY RESEARCH

Vaping Robot



Kaiser et al., iScience. 2021 Sep 29;24(10):103091





Bogdanoff et al., STAR Protoc. 2022 Dec 16;3(4):101885

NAMs INHALATION TOXICOLOGY RESEARCH

FDA

Publications

Electronic cigarette menthol flavoring is associated with increased inhaled micro and sub-micron particles and worse lung function in combustion cigarette smokers. Chandra D, Bogdanoff RF, Bowler RP, Benam KH. Respir Res. 2023 Apr 11;24(1):108.

- Using the robotic smoking system, they found that menthol vs. non-menthol (tobacco) flavored pods from commercially available ECs leads to generation of significantly higher quantities of 1–10 µm particles upon inhalation. And found an association between enhanced inhaled particles due to menthol addition to ECs and worse lung function indices.

Protocol for the operation of a breathing and vaping biomimetic robot to delineate real-time inhaled particle profile of electronic cigarettes. Bogdanoff RF, Kaiser AJ, Benam KH. STAR Protoc. 2022 Dec 16;3(4):101885. doi: 10.1016/j.xpro.2022.101885. Epub 2022 Nov 30.

- Method paper providing a detailed description of the smoking robot, i.e., the robotic human vaping mimetic real-time particle analyzer (HUMITIPAA), used to evaluate the impact of change in chemical constituents and breathing profiles of electronic cigarettes (ECs) on potential pulmonary toxicity.

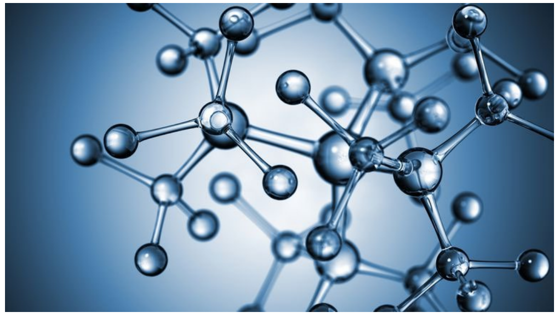
A robotic system for real-time analysis of inhaled submicron and microparticles. Kaiser AJ, Salem C, Alvarenga BJ, Pagliaro A, Smith KP, Valerio LG Jr, Benam KH. iScience. 2021 Sep 29;24(10):103091. doi: 10.1016/j.isci.2021.103091. eCollection 2021 Oct 22.

- Vitamin E acetate (VEA) was strongly linked to an outbreak of electronic cigarette (EC) or vaping product use-associated lung injury (EVALI). The robotic system was used to quantitatively analyze submicron and microparticles generated from ECs mimicking clinically relevant breathing and vaping topography. Results found that the addition of even small quantities of VEA was sufficient to alter size distribution and significantly enhance total particles inhaled from ECs potentially impacting particle deposition in the lung.

NAMs USING COMPUTATIONAL MODELS

Artificial Intelligence

Transform data and chemical knowledge using existing data and machine learning into actionable insight.



Better decisions

By incorporating machine learning into programmatic and strategic plans, risks can be better understood and acted on using data-driven insights with speed and efficiency.

COMPUTATIONAL TOXICOLOGY AT CTP

Machine learning and chemoinformatics applied to chemical toxicology

ANN

$h = \sigma(W_1 x + b_1)$

$\hat{y} = W_2 h + b_2$

QM

$i\hbar \, \partial\psi/\partial t = H \psi$

Bayes Theorem

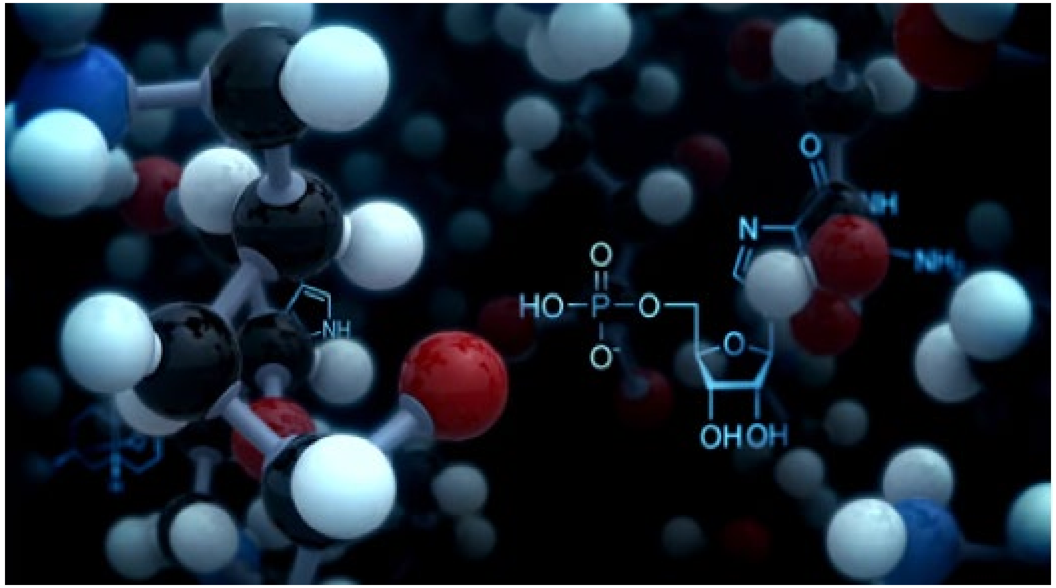
$P(A|B) = P(B|A) * P(A) / P(B)$

Naïve Bayes

$P(y \mid x_1, x_2, \ldots, x_n) = P(y) * P(x_1 \mid y) * P(x_2 \mid y) * \ldots * P(x_n \mid y) / P(x_1, x_2, \ldots, x_n)$

Logistic Regression

$P(y = 1 \mid x) = 1 / (1 + \exp(-z))$



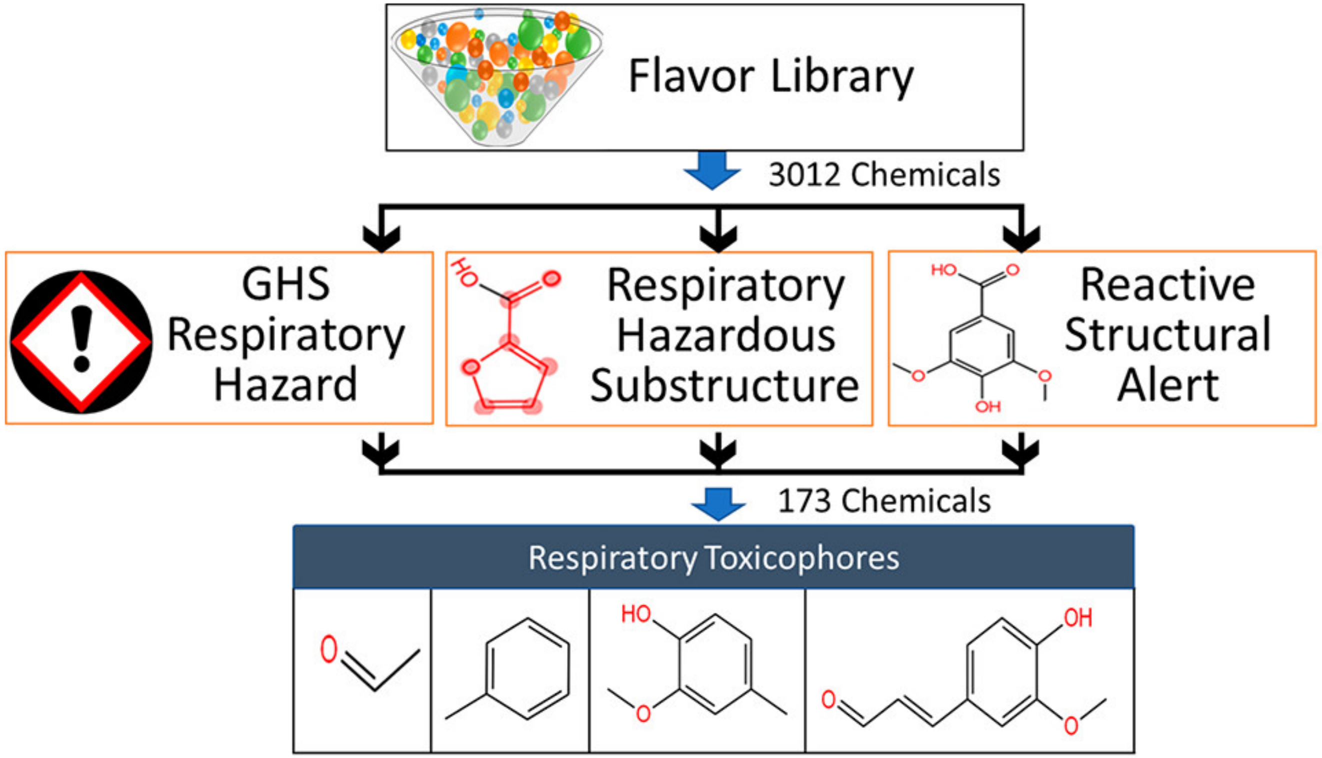
Leverage existing toxicology testing data as training sets for learning algorithms

A COMPUTATIONAL APPROACH FOR RESPIRATORY HAZARD IDENTIFICATION OF FLAVOR CHEMICALS IN TOBACCO PRODUCTS

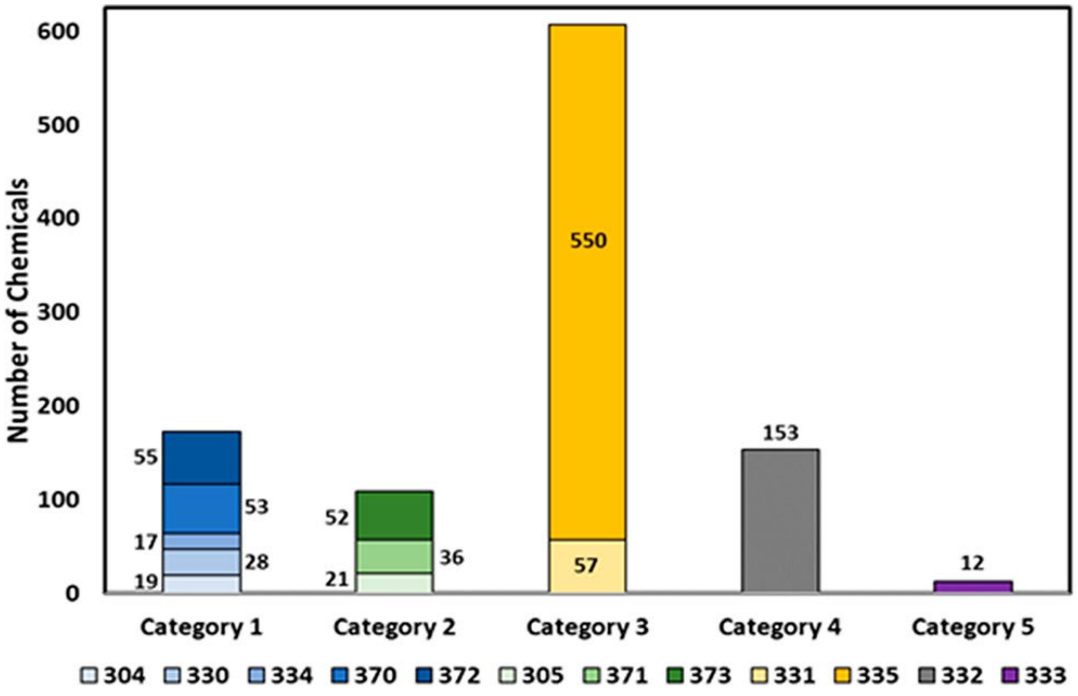
FDA

Chemical Research in Toxicology

Reema Goel, Samantha M Reilly, and Luis G Valerio Jr
Chem. Res. Toxicol. 2022, 35(3):450-450
https://doi.org/10.1021/acs.chemrestox.1c00361



STUDY RESULTS: RESPIRATORY HEALTH HAZARD CHARACTERIZATION BY GLOBALLY HARMONIZED SYSTEM (GHS)

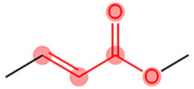
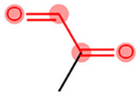
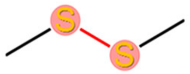
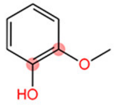
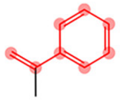
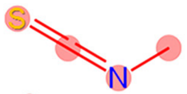
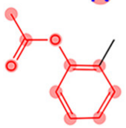


638 chemicals in the flavor library of 3012 chemicals that are potential respiratory health hazards by GHS classification grouped in hazard categories 1–5 (individual hazard codes in legend).

Goel et al., *Chem. Res. Toxicol.* 2022, 35(3):450-450

STUDY RESULTS: SCREENING FLAVORS FOR TOXIC SUBSTRUCTURES

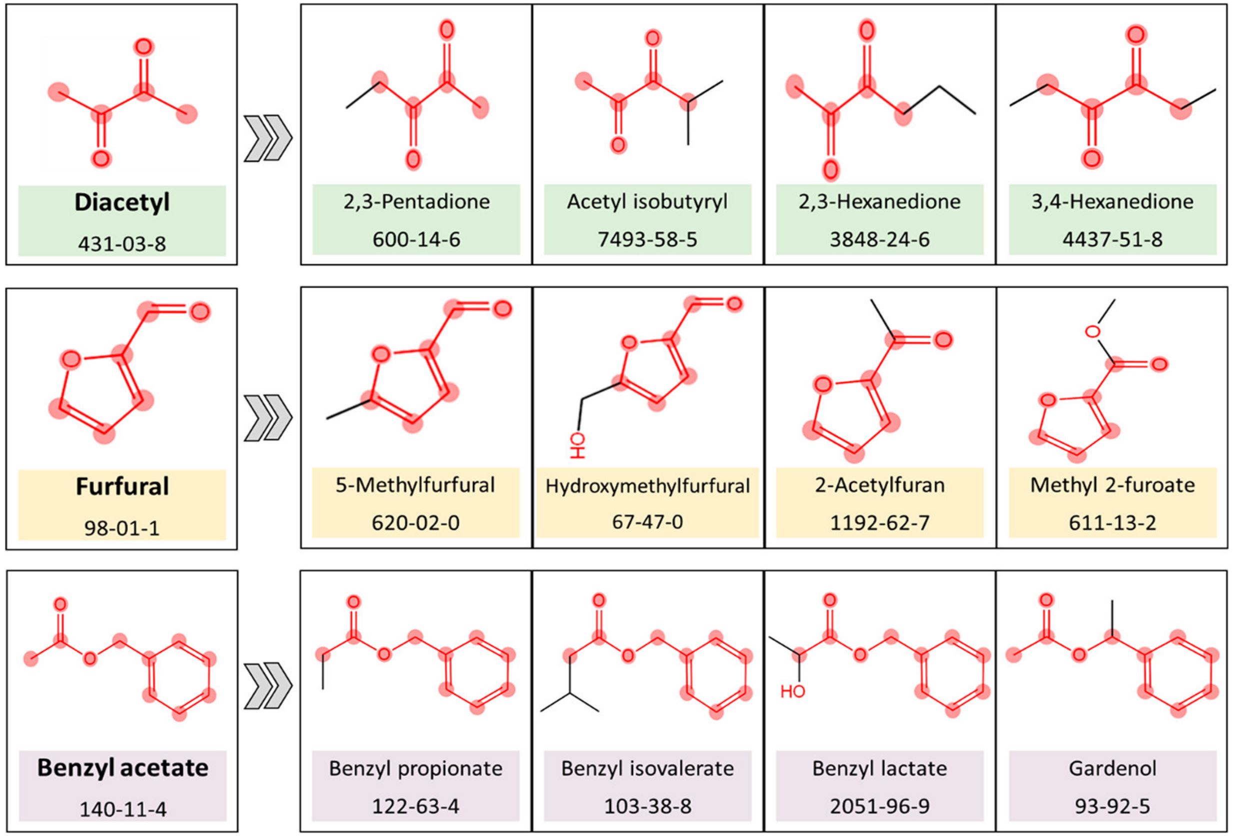
- Applied chemoinformatic software using molecular filtering against a set of 50 structural alerts known for reactive, unstable, and/or toxic functional groups
- A total of 1079 flagged out of 3012 flavors
- Some flavor chemicals identified with the corresponding structural alert for respiratory toxicity highlighted in the chemical structure

Structure	Registry Number	Name	Structural Alert
	554-14-3	2-Methylthiophene	Thiophene
	623-43-8	Methyl Crotonate	Acrylate
	78-98-8	Pyruvaldehyde	Dicarbonyl
	624-92-0	Dimethyl Disulfide	Disulfide
	90-05-1	Guaiacol	Hydroquinone
	98-83-9	Alpha-Methylstyrene	Vinyl benzene
	556-61-6	Methyl Isothiocynate	Isothiocyanate
	533-18-6	o-Tolyl Acetate	Phenol ester

Goel et al., *Chem. Res. Toxicol.* 2022, 35(3):450-450

STUDY RESULTS: USING RESPIRATORY TOXICANTS AS AN ANCHOR TO IDENTIFY OTHER POTENTIAL RESPIRATORY TOXICANTS

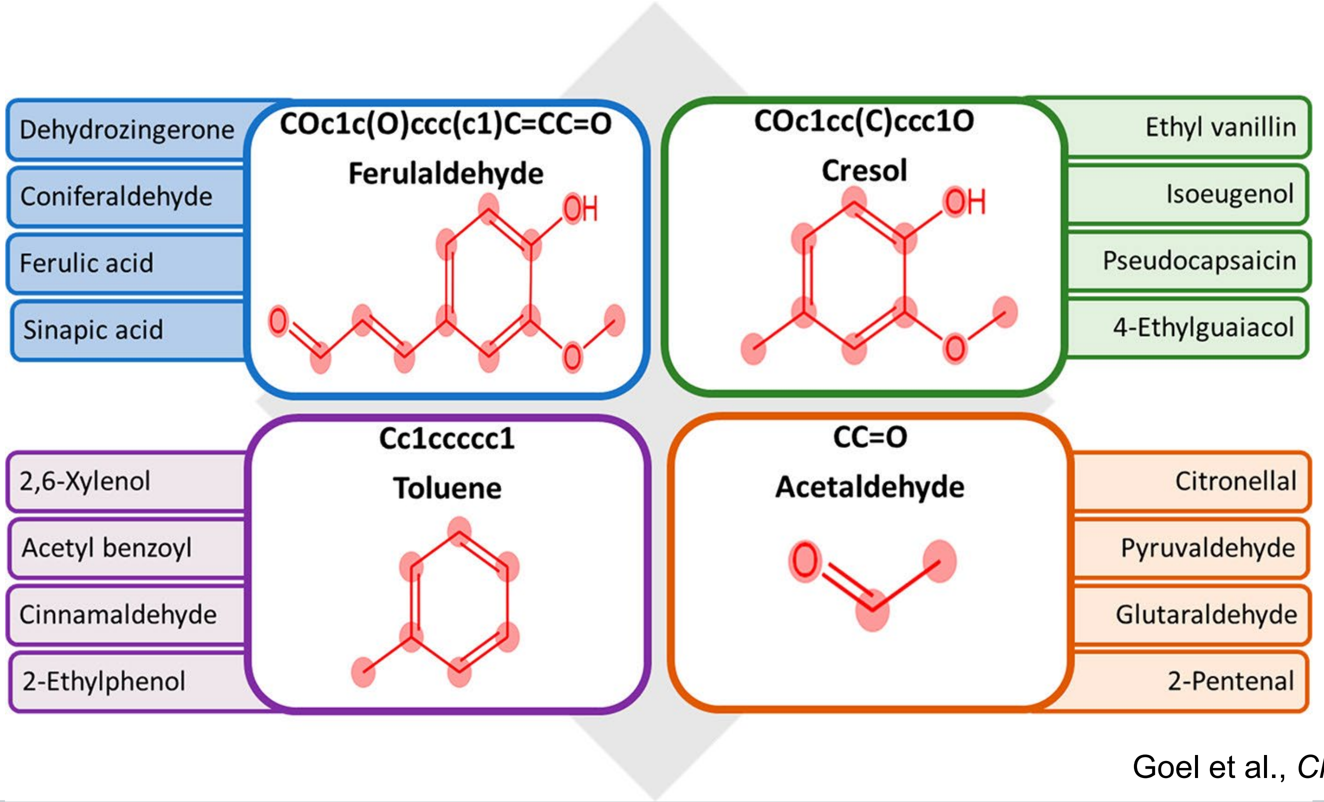
- Illustrative examples to show shared substructures of three flavors documented as respiratory toxicants with other flavors from the flavor compound library



Goel et al., *Chem. Res. Toxicol.* 2022, 35(3):450-450

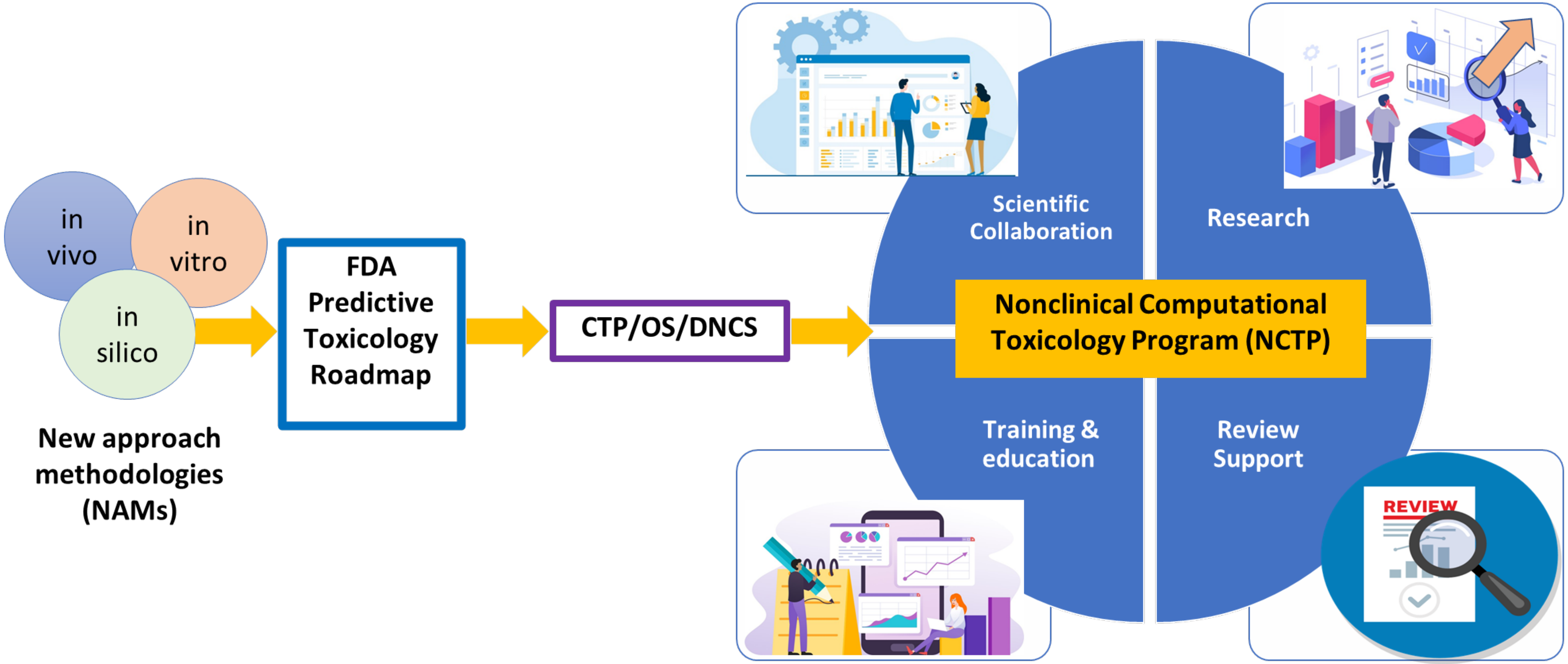
STUDY RESULTS: RESPIRATORY TOXICOPHORES IDENTIFIED IN FLAVOR LIBRARY

- Used maximum common substructure computational technique
- Four toxicophores and the SMART (SMILES Arbitrary Target Specification) patterns identified in this study that are potentially associated with respiratory toxicity.



Goel et al., *Chem. Res. Toxicol.* 2022, 35(3):450-450

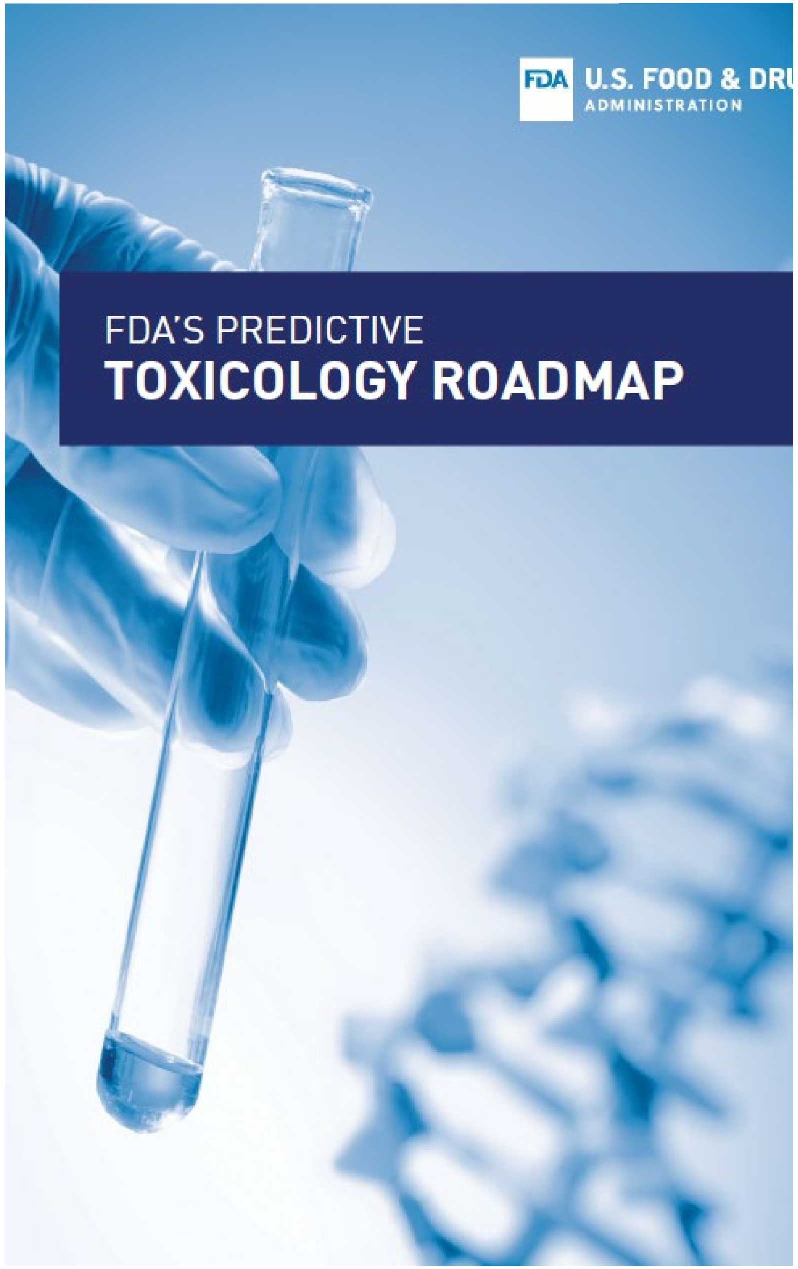
NONCLINICAL COMPUTATIONAL TOXICOLOGY PROGRAM TEAM SUPPORTS TOBACCO REGULATORY SCIENCE



COMPUTATIONAL TOXICOLOGY AT CTP REFLECTS THE GOALS OF FDA'S PREDICTIVE TOXICOLOGY ROADMAP

1. Application of computerized predictive models to better understand and predict potential toxicological hazards of chemicals in or emitted by tobacco products
   - ❑ Efficient: provides timely results
   - ❑ Machine learning to discover patterns in the data
   - ❑ Predictions to produce actionable intel
   - ❑ Scientific rigor and reliability to help make better decisions
   - ❑ Versatile
   - ❑ High throughput
   - ❑ Strategy to support prioritization for follow-up

2. Leverages existing knowledge
   - ❑ Reduce animal testing in cases of in vivo toxicity endpoints
   - ❑ Maximizes resources
   - ❑ Machine learning uses training sets of existing in vitro and in vivo data



KEY CONSIDERATIONS

- Best practices framework, caveats, and important considerations
  - ❑ What available data already exists for the subject chemical?
  - ❑ Is the model fit for the context of use?
    - ❑ what is the specific regulatory science question or technical need?
  - ❑ Model selection depends on goals
    - ❑ understand how the model was built, it is often difficult to generalize a model
  - ❑ Models are not perfect
  - ❑ Evaluate the prediction with **human expert knowledge/review**
  - ❑ Model documentation: Consider the quality of data used to construct the model, criteria used for training set, rigor of validation testing
  - ❑ Is the prediction explained by the model output data?
  - ❑ Efficiency, but not at the expense of scientific rigor; reliability, quality, integrity to the technical question at hand

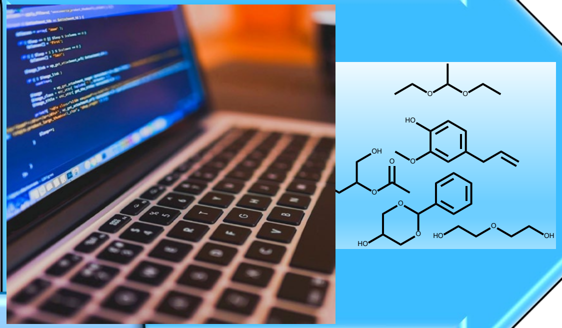
COMPUTATIONAL TOXICOLOGY MODEL PREDICTIONS FOR GENETIC TOXICITY AND RODENT CARCINOGENICITY

FDA

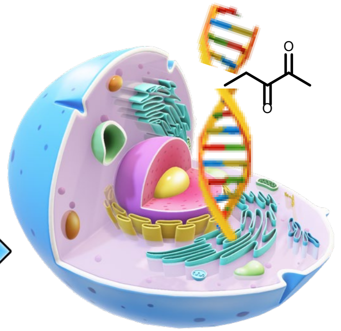
In Vitro Mutagenicity (Ames)
In Vitro Genotoxicity
Rodent Carcinogenicity

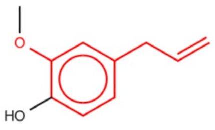
In Silico Models

Machine Learning



DNA Damage





Predictive data

QSAR Prediction

Sum of Factors = 1.276 - 0.976 = 0.300

Calculated probability using the global QSAR = $1/(1+e^{-1*0.300})$ = 0.575 (57.5%)

Human Expert Knowledge/Analysis

Weight-of-Evidence

PREDICTION CALLS

Mutagenicity
Genotoxicity
Rodent Carcinogenicity

PREDICTIVE KNOWLEDGE

PREDICTIONS

Chemical-induced
Mutagenicity
Genotoxicity
Rodent Carcinogenicity

Chemical Hazard Identification

Context of Use

Is there a concern for hazard?
Set Priorities for Follow-up and Risk

Better decision-making

MOVING FORWARD

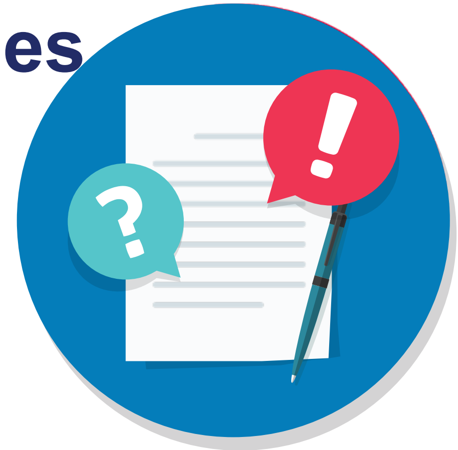
TOBACCO PRODUCT APPLICATIONS

Context of Use of Evidence from NAMs

Regulatory Toxicology Review Evaluations

Common Issues

-Analysis of prediction data from computational models
-Is model fit and is it fit for the particular question?
-Prediction narrative



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- Prabha Kc PhD, Chad Brocker PhD