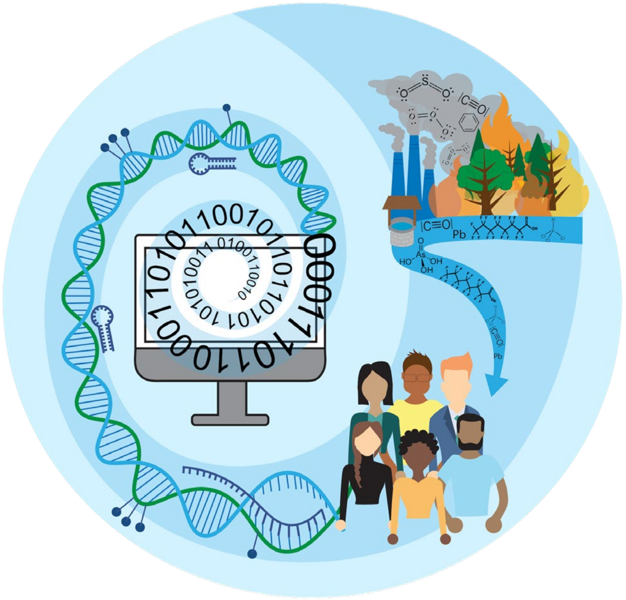
Wildfire Health Risks: Understanding the Chemical Drivers and Underlying Mechanisms of Highly Variable Smoke Exposure Conditions



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Center for Environmental Medicine and Lung Biology (CEMALB)

Curriculum in Toxicology and Environmental Medicine (CiTEM)

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Ragerlab

Climate Change Influences on the Environment

Flooding

ENVIRONMENT + CLIMATE

Climate change makes catastrophic flood twice as likely, study shows

Increased runoff could lead to devastating landslides and debris flows — particularly in hilly areas burned by wildfires

Flood damage will increase due to climate change, will disproportionately affect poor communities: Study

Annual flooding damage costs in the U.S. could increase 26% by 2050.

By Julia Jacobo
January 31, 2022, 11:52 AM

Drought

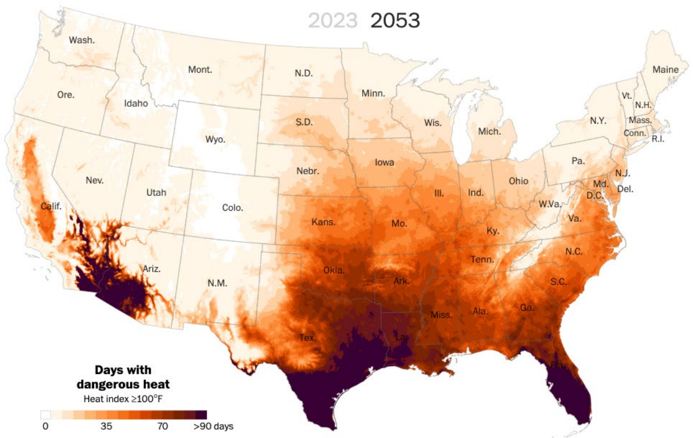
Climate crisis made summer drought 20 times more likely, scientists find

Record northern hemisphere drought in 2022 hit crops and power stations, worsening food and energy crises

Heat

More dangerous heat waves are on the way: See the impact by Zip code.

By mid-century, nearly two-thirds of Americans will experience perilous heat waves, with some regions in the South expected to endure more than 70 consecutive days over 100 degrees



Wildfire

The New York Times

Climate Scientists Warn of a 'Global Wildfire Crisis'

Worsening heat and dryness could lead to a 50 percent rise in off-the-charts fires, according to a United Nations report.

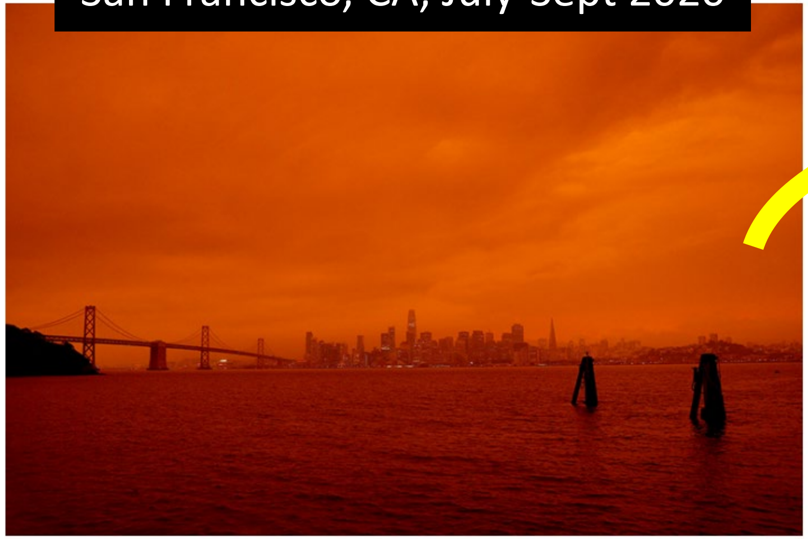
According to the National Interagency Fire Center, as of Oct 27th in the U.S., there have been **59,221 fires**, covering **>7 million acres** so far, this year – numbers that are well above the 10-y average

News sources: abcnews; newsroom.ucla; nytimes; theguardian; washingtonpost

Wildfires as a Growing Public Health Problem

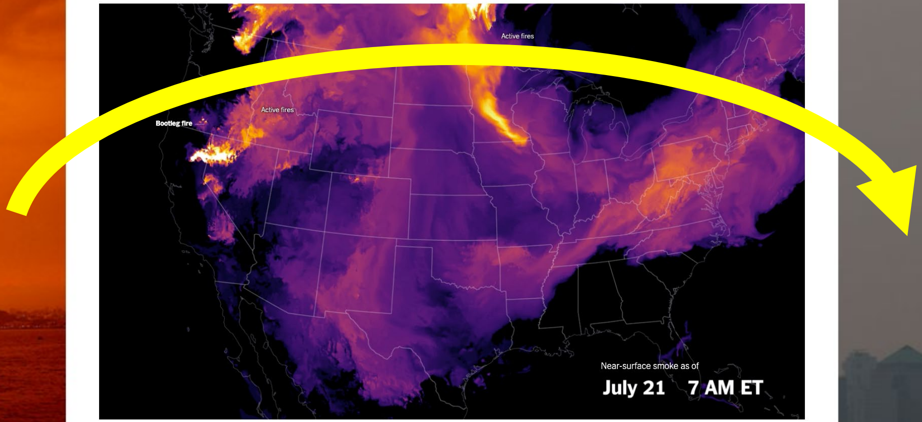
- **Wildfires are growing in prevalence and intensity, contributing to poor air quality**

San Francisco, CA, July-Sept 2020



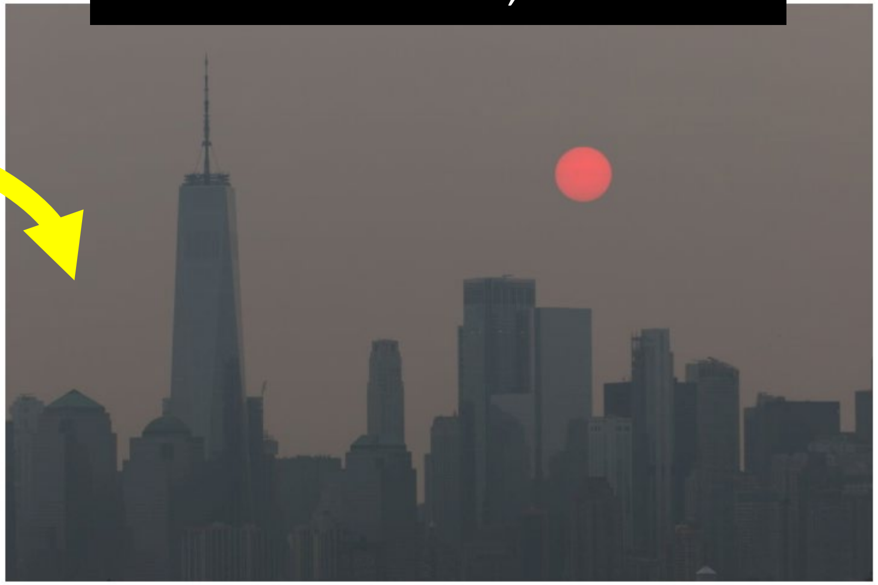
Smoke from wildfires shrouded the San Francisco Bay Area and blocked sunlight on September 9, 2020. Credit: Aaron Maizlish/Flickr/CC BY 2.0

https://climate.nasa.gov/ask-nasa-climate/3066/the-climate-connections-of-a-record-fire-year-in-the-us-west/



https://www.nytimes.com/interactive/2021/07/21/climate/wildfire-smoke-map.html

Manhattan, NY

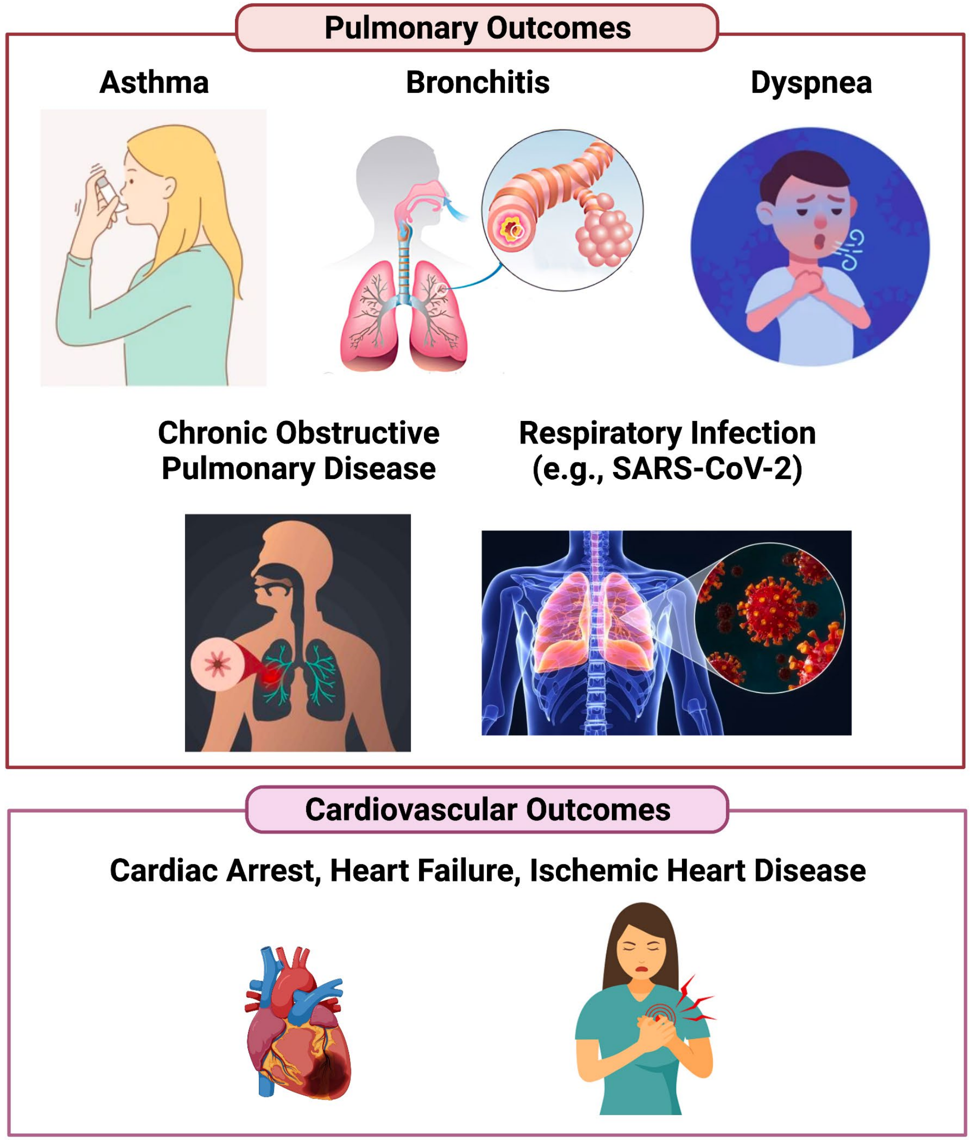


From Minnesota to Manhattan, the sun appeared orange because of haze from wildfire smoke.
Bjoern Kils/Reuters

https://www.nytimes.com/interactive/2021/07/21/climate/wildfire-smoke-map.html

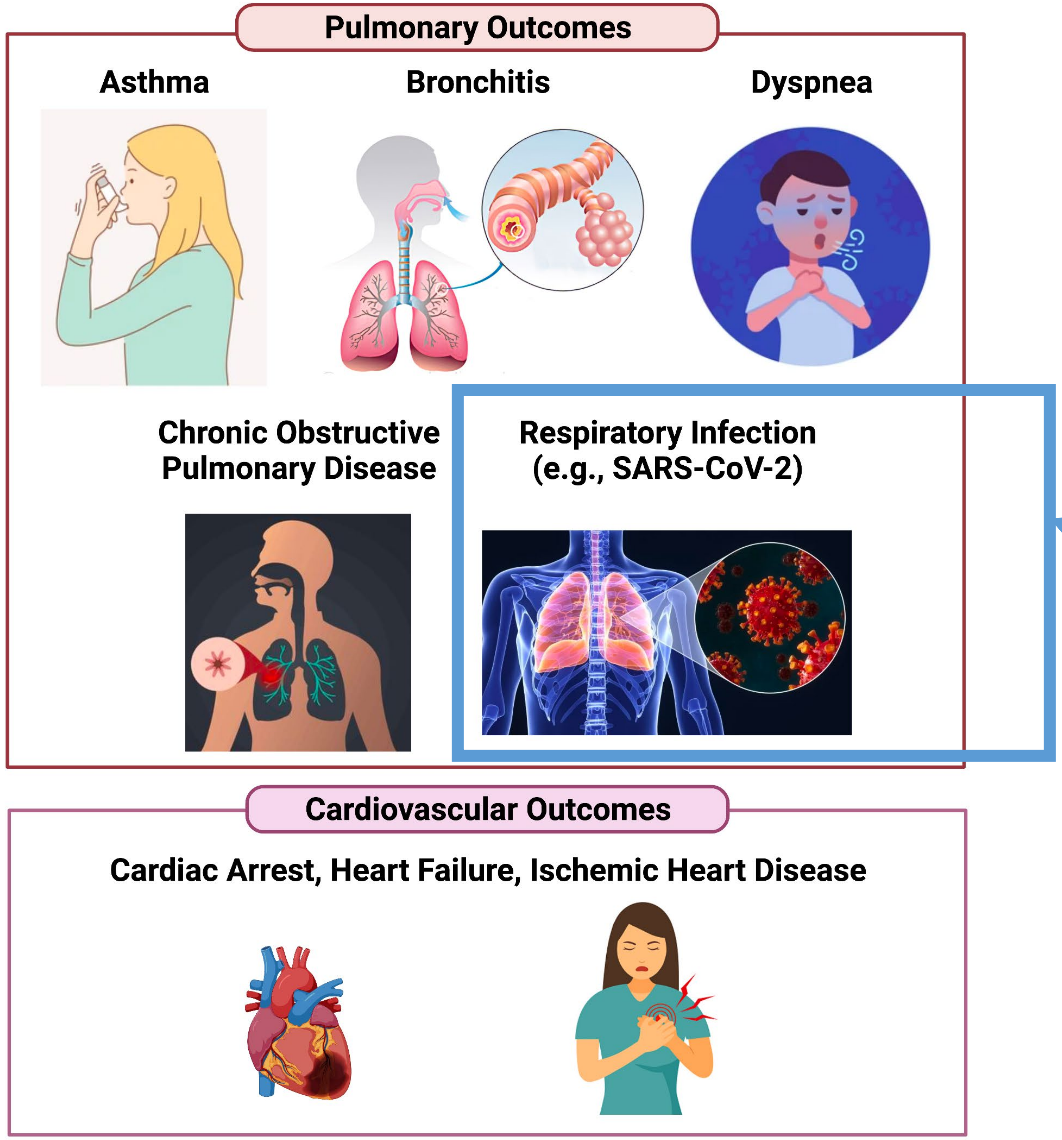
- **What is in wildfire smoke?** A mixture of compounds from tree combustion (e.g., particulate matter, acrolein, benzene, formaldehyde, PAHs, VOCs, metals, etc)
  - Can also be produced with other fuel sources, including variable biomasses and anthropogenic materials

Health Impacts of Wildfire Smoke Exposures



- Studies first carried out in firefighters
- Now finding similar relationships within the general public impacted by wildfire smoke exposures

Health Impacts of Wildfire Smoke Exposures



- Studies first carried out in firefighters
- Now finding similar relationships within the general public impacted by wildfire smoke exposures

Research at UNC is significantly contributing to data supporting wildfire relationships to increased respiratory infection

Wildfires and Mechanisms Supporting Increased Risk for Respiratory Pathogen Infection

Links to SARS-CoV-2 infection risk:

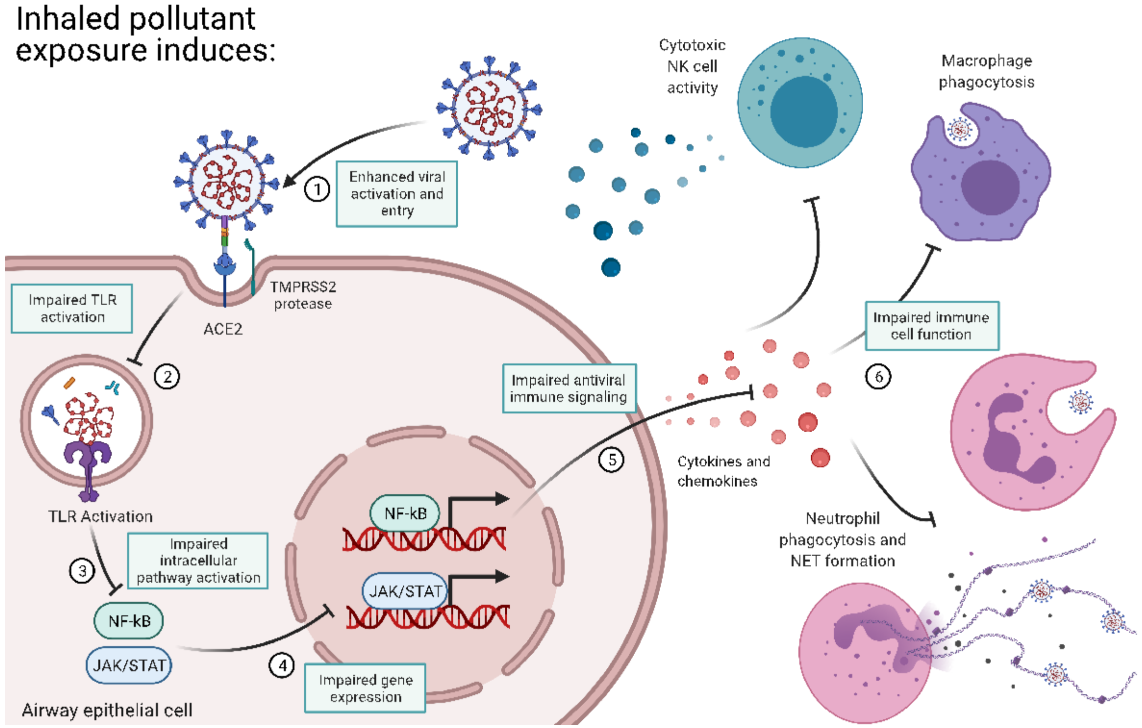
- Multiple studies point to a potential connection between wildfire smoke exposure and higher rates of COVID-19 infection and associated mortality (Kiser et al *Environ Health* 2020)

- Woodsmoke particles prior to SARS-CoV-2 infection alter antiviral response gene expression (Brocke et al *AJP-Lung* 2022)

Links to influenza infection risk:

- Winter influenza seasons in Montana were four to five times worse after bad wildfire seasons (Landguth et al *Environment International* 2020)

- Wood smoke exposure in vivo alters human inflammatory response to a model of influenza infection (Rebuli et al *AJRCCM* 2019)



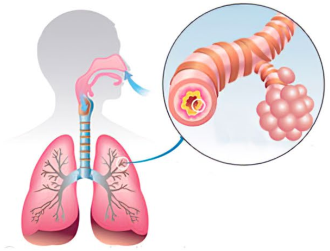
Slide credit: Meghan Rebuli, UNC

Health Impacts of Wildfire Smoke Exposures

Pulmonary Outcomes

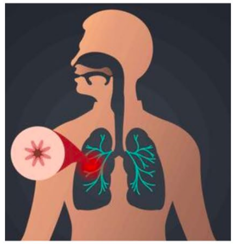
Asthma

Bronchitis



Dyspnea

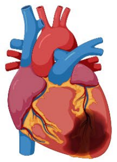
Chronic Obstructive Pulmonary Disease



Respiratory Infection (e.g., SARS-CoV-2)

Cardiovascular Outcomes

Cardiac Arrest, Heart Failure, Ischemic Heart Disease



Research Questions:

(1) Which chemicals drive toxicity?

(2) Which exposure conditions are sufficiently similar?

(3) What are the underlying biological mechanisms?

What Chemicals Drive Toxicity?

Difficulties in Wildfire Research

Variable and unpredictable exposure scenarios

https://www.economist.com/science-and-technology/2018/08/02/software-can-model-how-a-wildfire-will-spread

Epidemiology-based studies are often limited as retrospective analyses

- Where smoke exposures are difficult to quantify/characterize after the event

https://www.sfchronicle.com/california-wildfires/article/Bay-Area-awakens-to-smoky-skies-as-wildfires-rage-15495018.php

Lab-based studies are extremely difficult to carry out

- Exposure scenarios difficult to generate in the lab
- Biomass combustions are dangerous and can cause explosions
- It's difficult to analyze chemistry/PM conditions across wide span of chemistries occurring in wildfire simulations
- It's difficult to couple exposures with *in vitro/in vivo* test models

https://www.freepik.com/vectors/laboratory-microscope

Partnership with U.S. EPA Atmospheric Chemistry & Toxicology Lab – Ian Gilmour & Yong Ho Kim

Environmental Health Perspectives

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Ope

Vol. 126, No. 1 | Research

Mutagenicity and Lung Toxicity of Smoldering vs. Flaming Emissions from Various Biomass Fuels: Implications for Health Effects from Wildland Fires

is companion of

Yong Ho Kim, Sarah H. Warren, Q. Todd Krantz, Charly King, Richard Jaskot, William T. Preston, Barbara J. George, Michael D. Hays, Matthew S. Landis, Mark Higuchi, David M. DeMarini, and M. Ian Gilmour

Published: 26 January 2018 | CID: 017011 | https://doi.org/10.1289/EHP2200 | Cited by: 6

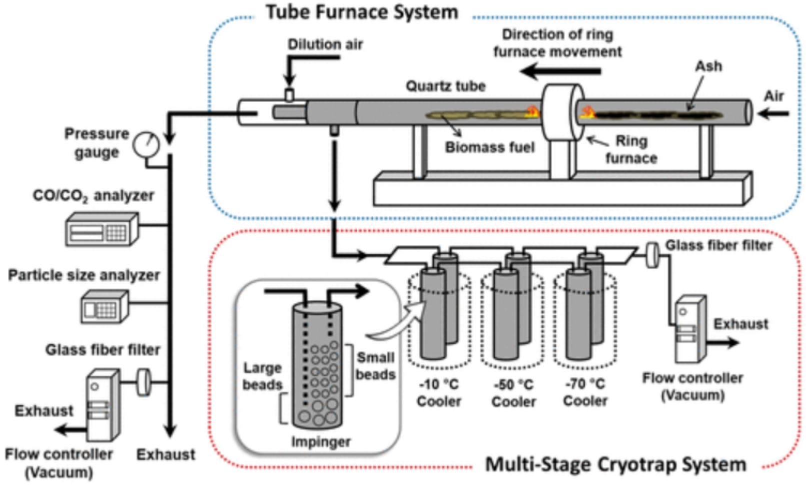
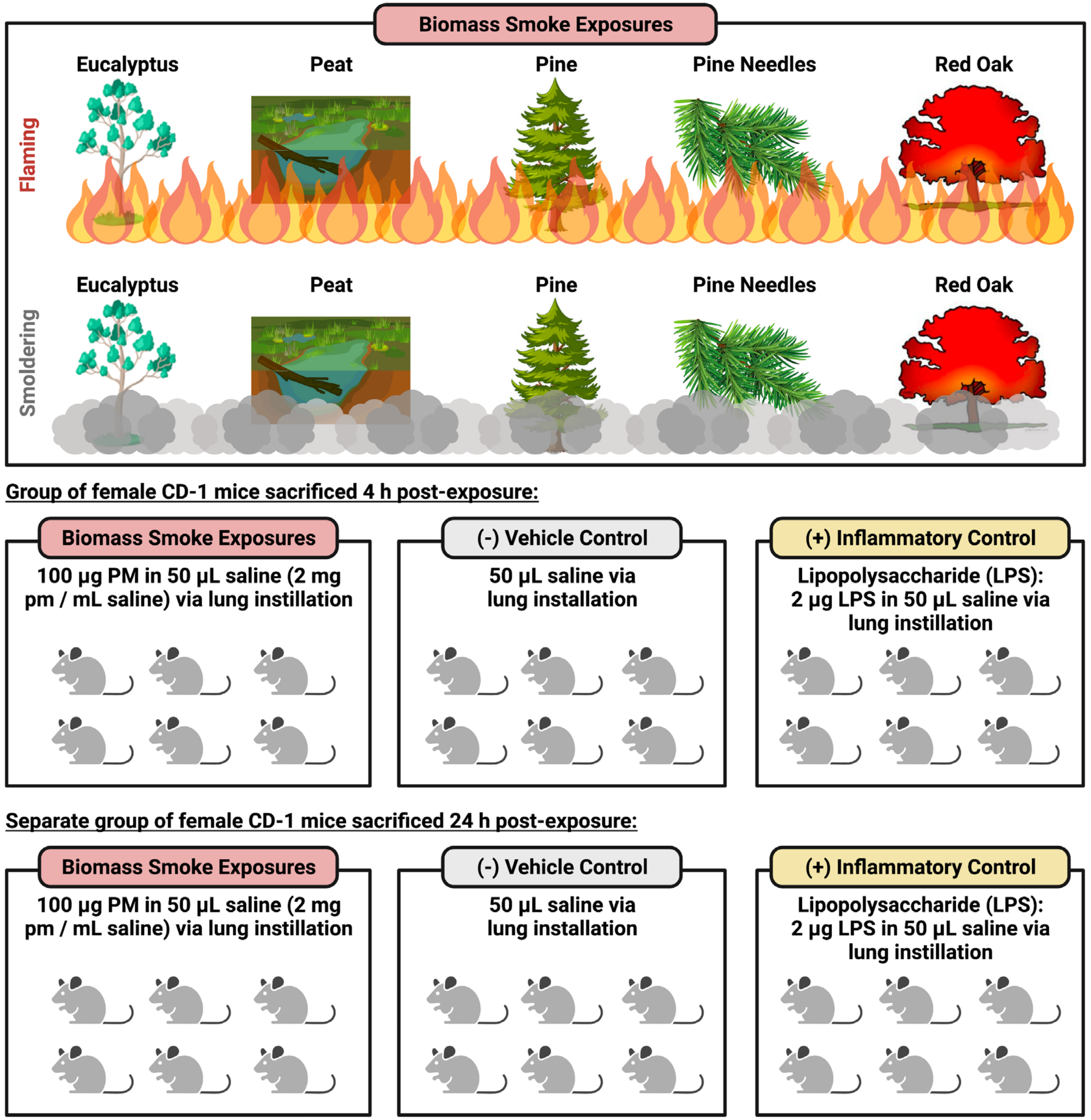
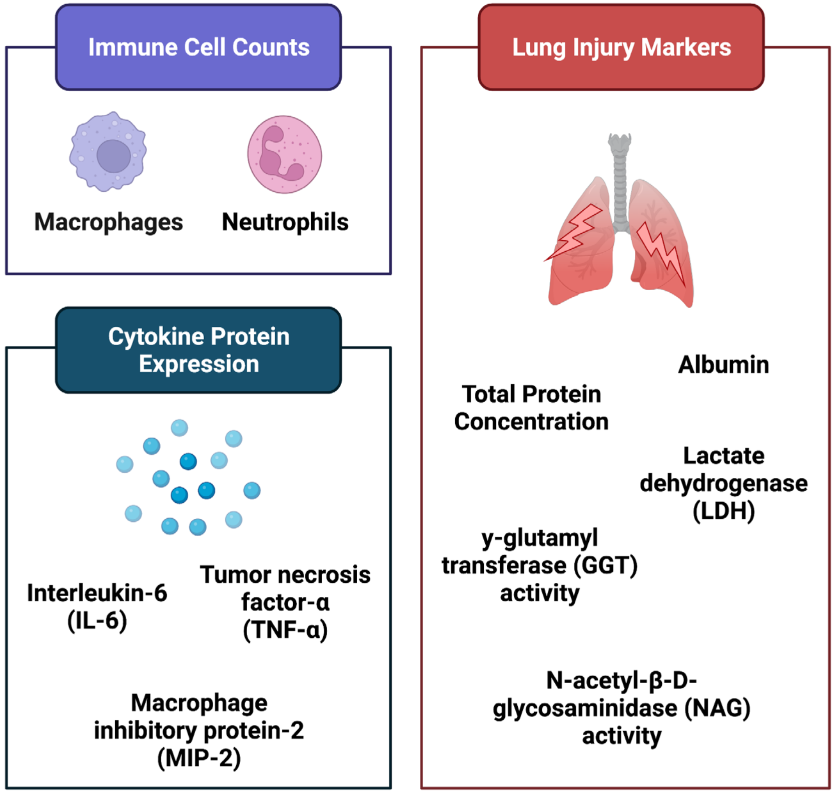


Figure 1. Diagram of the biomass combustion and smoke collection system. The tube furnace system consisted of a quartz tube and a ring furnace that traversed along the length of the quartz tube and was able to sustain stable flaming or smoldering phases consistently for 60 min. The multistage cryotrap system had three sequential impingers that were cooled cryogenically at –10, –50, and –70°C, permitting the capture of PM and semivolatile organic compounds from the biomass smoke emissions.

Exposure Design



Toxicity Markers



Which Chemicals may be Driving Wildfire-Associated Toxicity?

Science of the Total Environment 775 (2021) 145759

Contents lists available at ScienceDirect

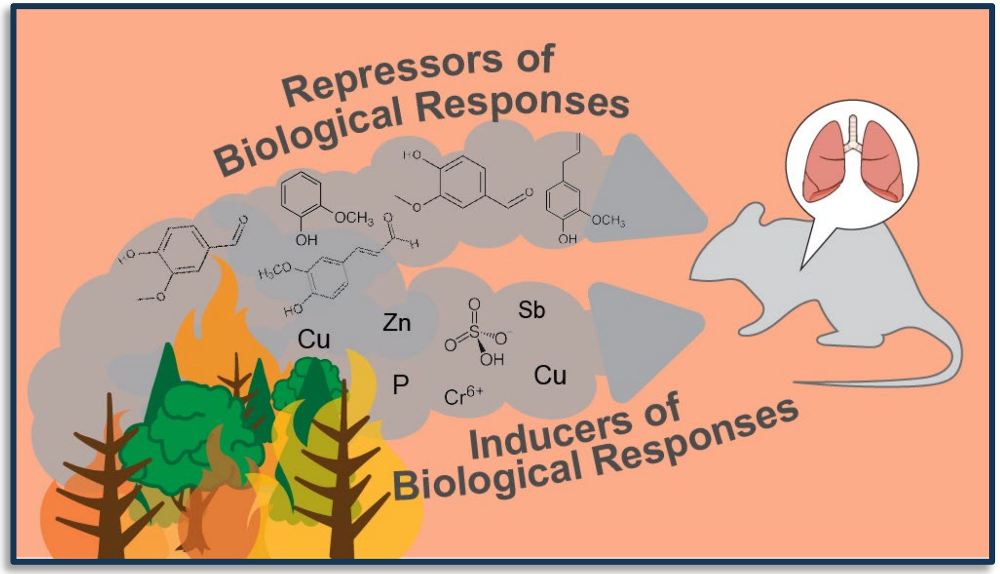
Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Mixtures modeling identifies chemical inducers versus repressors of toxicity associated with wildfire smoke

Julia E. Rager[a,b,c,*], Jeliyah Clark[a,b], Lauren A. Eaves[a,b], Vennela Avula[a,b], Nicole M. Niehoff[d], Yong Ho Kim[e], Ilona Jaspers[b,c,e,f], M. Ian Gilmour[g]

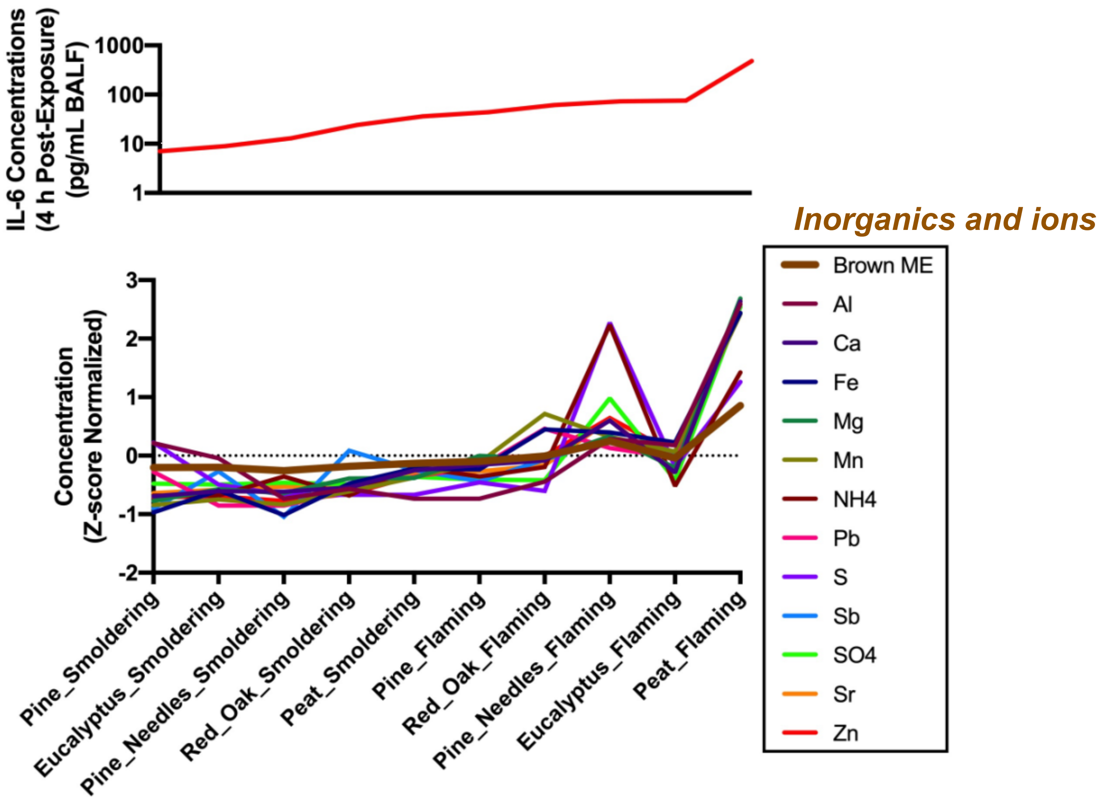
[a] Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[b] The Institute for Environmental Health Solutions, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[c] Curriculum in Toxicology, School of Medicine, University of North Carolina, Chapel Hill, NC, USA
[d] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA
[e] The Center for Environmental Medicine, Asthma and Lung Biology, School of Medicine, The University of North Carolina, Chapel Hill, NC, USA
[f] Department of Pediatrics, School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[g] Public Health and Integrated Toxicology Division, Center for Public Health and Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC, USA



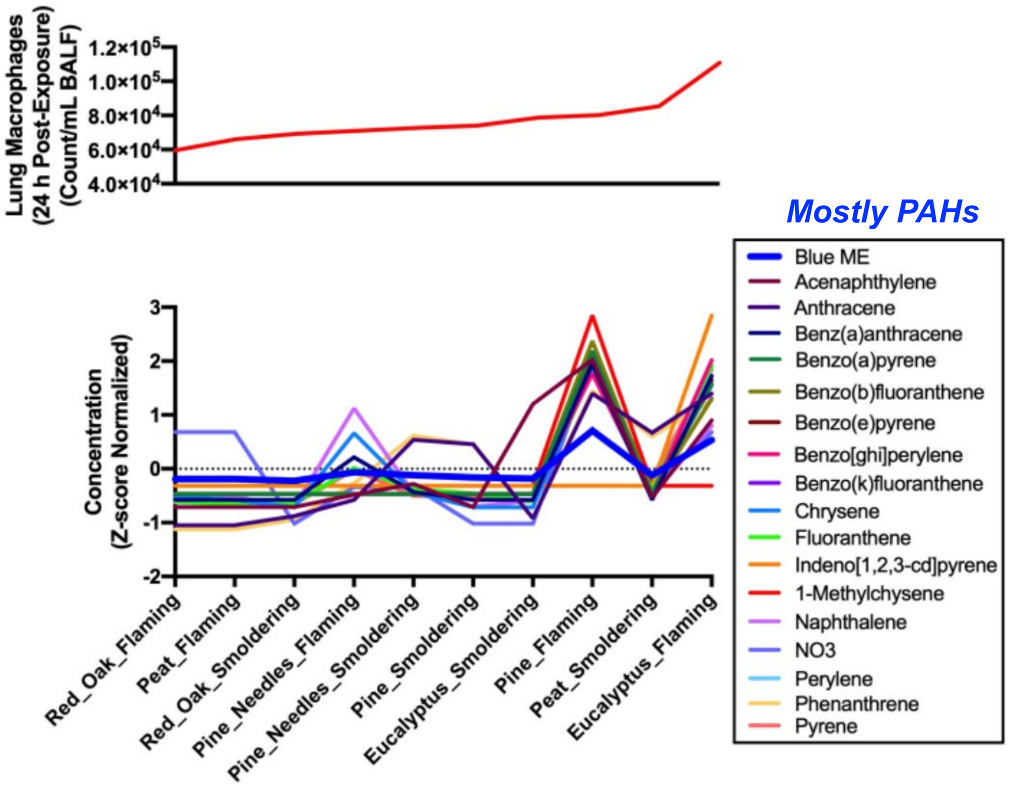
- This study utilized a suite of computational mixtures approaches to identify groups of chemicals induced by variable biomass burn conditions associated with biological responses in the mouse lung

Clusters (called 'Modules') of Co-Occurring Chemicals were Identified across Biomass Burns

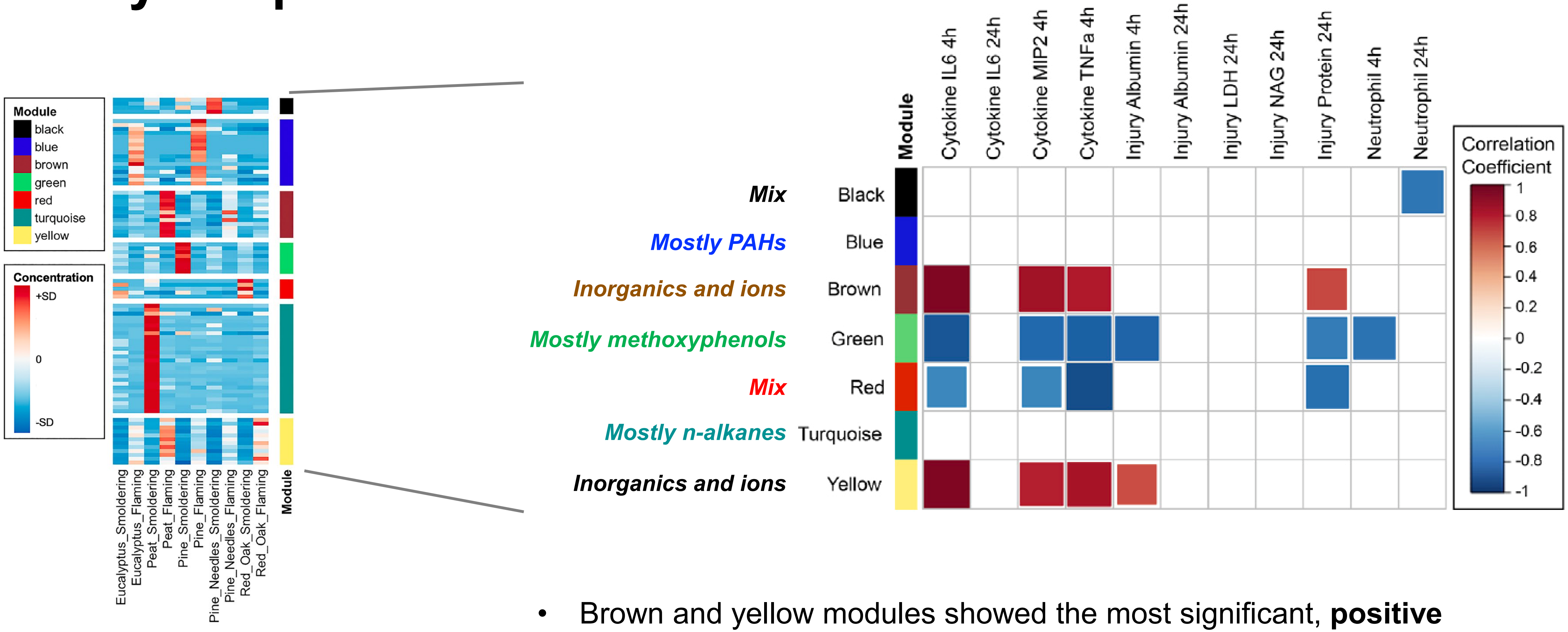
"Brown" Module and its Eigenvector



"Blue" Module and its Eigenvector

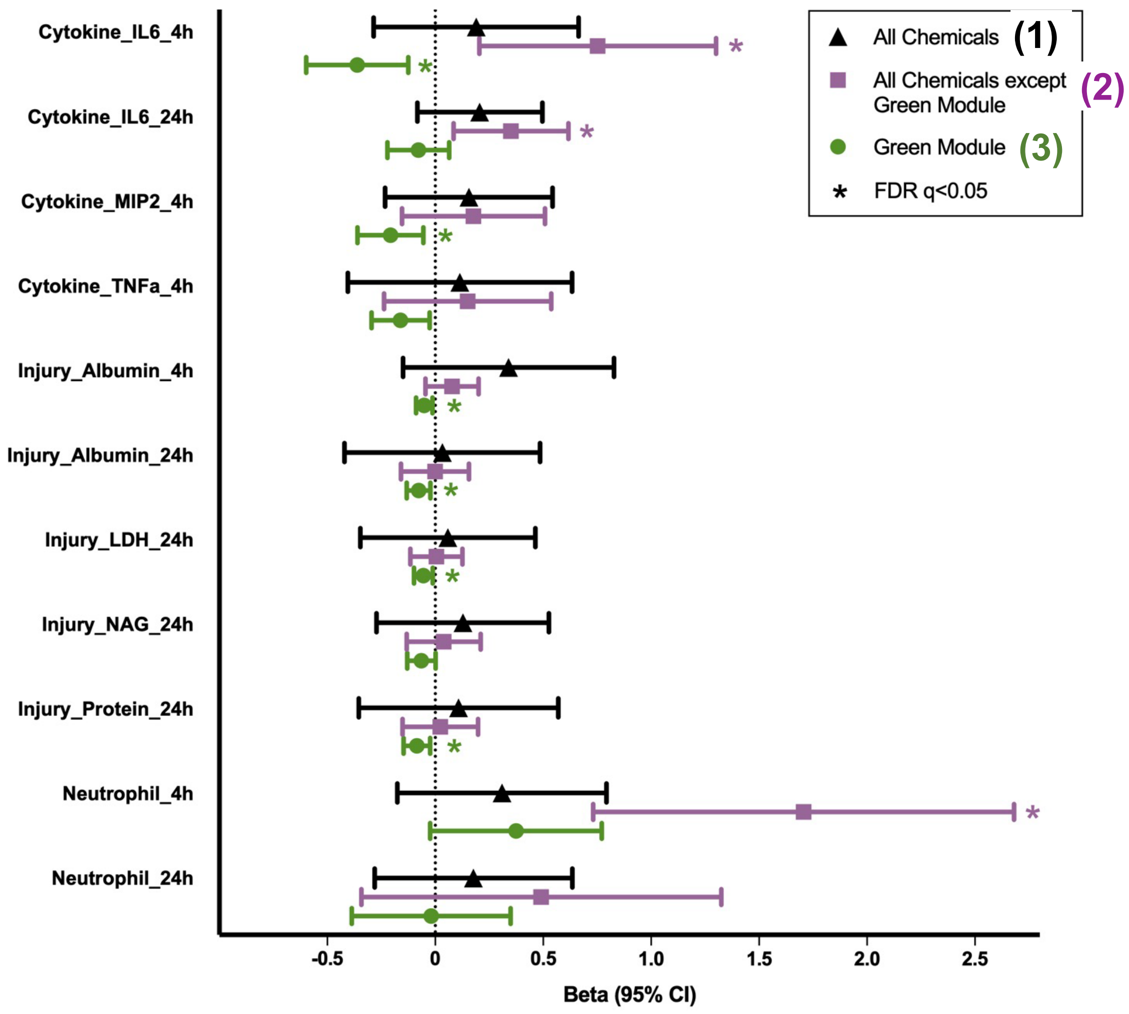


Select Chemical Groups Correlated with Cardiopulmonary Toxicity Endpoints



- Brown and yellow modules showed the most significant, **positive associations** across the largest number of biological responses
- Green module showed the largest number of negative associations -> **potential protective effects? Let's evaluate further!**

Mixtures Modeling through Quantile g-Computation



Ran models individually for each outcome (i.e., each cardiopulmonary toxicity marker)

Three models per outcome:

(1) All chemicals

(2) All chemicals except those in the 'green module'

(3) Just the chemicals in the 'green module'

General findings:

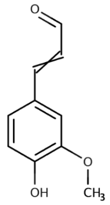
- Toxicity endpoints increased in **(2)** vs **(1)**
- **Green is good!**

Alex Keil and Nicole Niehoff (NIH)

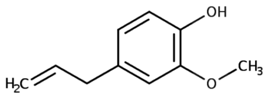
What's in the 'Good' Module?

Methoxyphenols

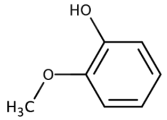
Coniferyl Aldehyde
458-36-6



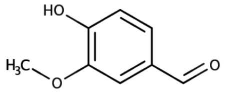
Eugenol
97-53-0



Guaiacol
90-05-1



Vanillin
121-33-5



There is evidence for these individual chemicals decreasing DNA damage and/or inflammation after an exogenous insult

What's in the 'Bad' Modules?

Inorganics

Copper (Cu)
7440-50-8
Cu

Hexavalent chromium (CrVI)
18540-29-9
Cr^{6+}

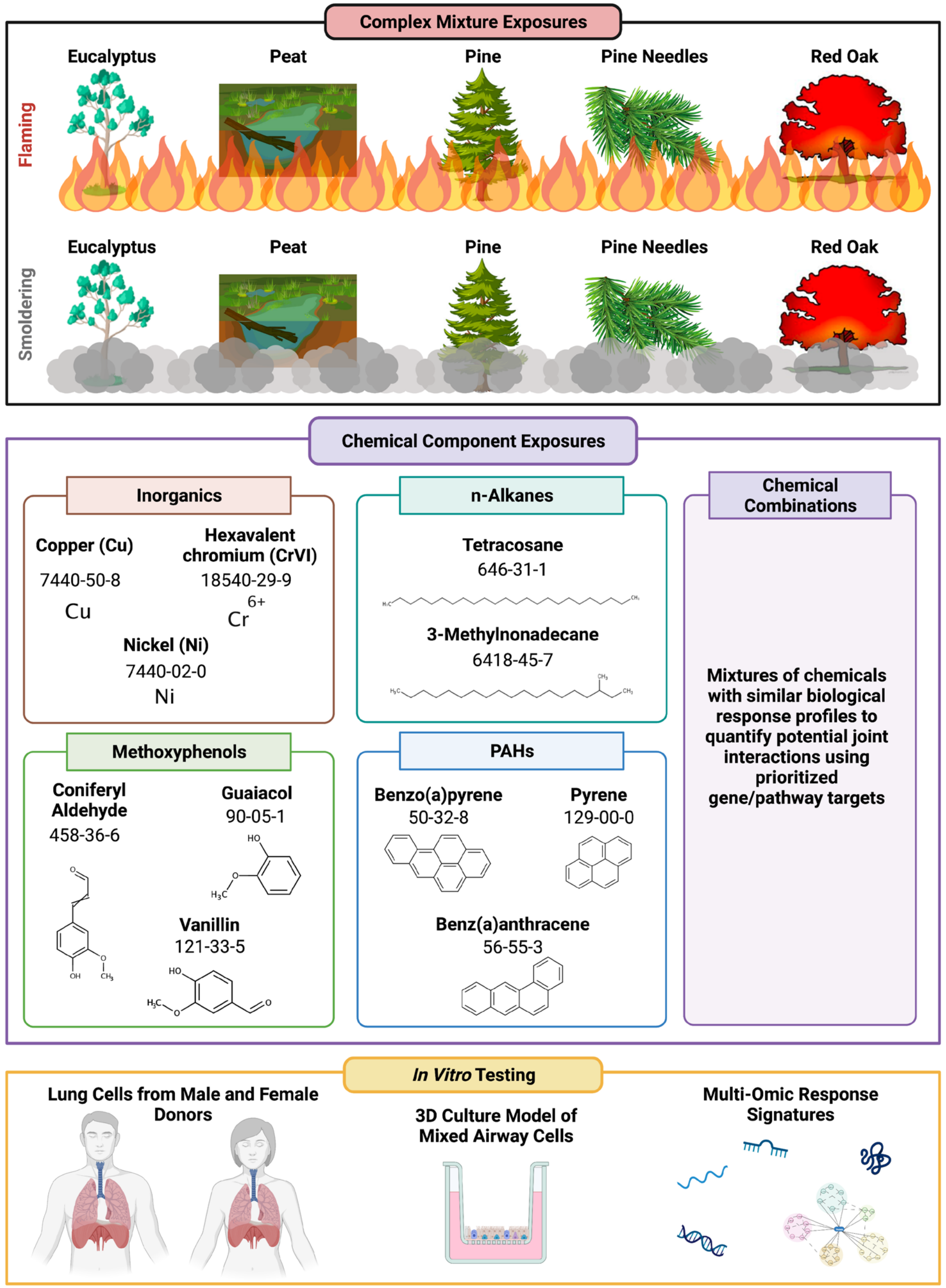
Nickel (Ni)
7440-02-0
Ni

Ionic Constituents

SO4 **NO3** **PO4**

Individual Chemicals vs Potential Joint Relationships

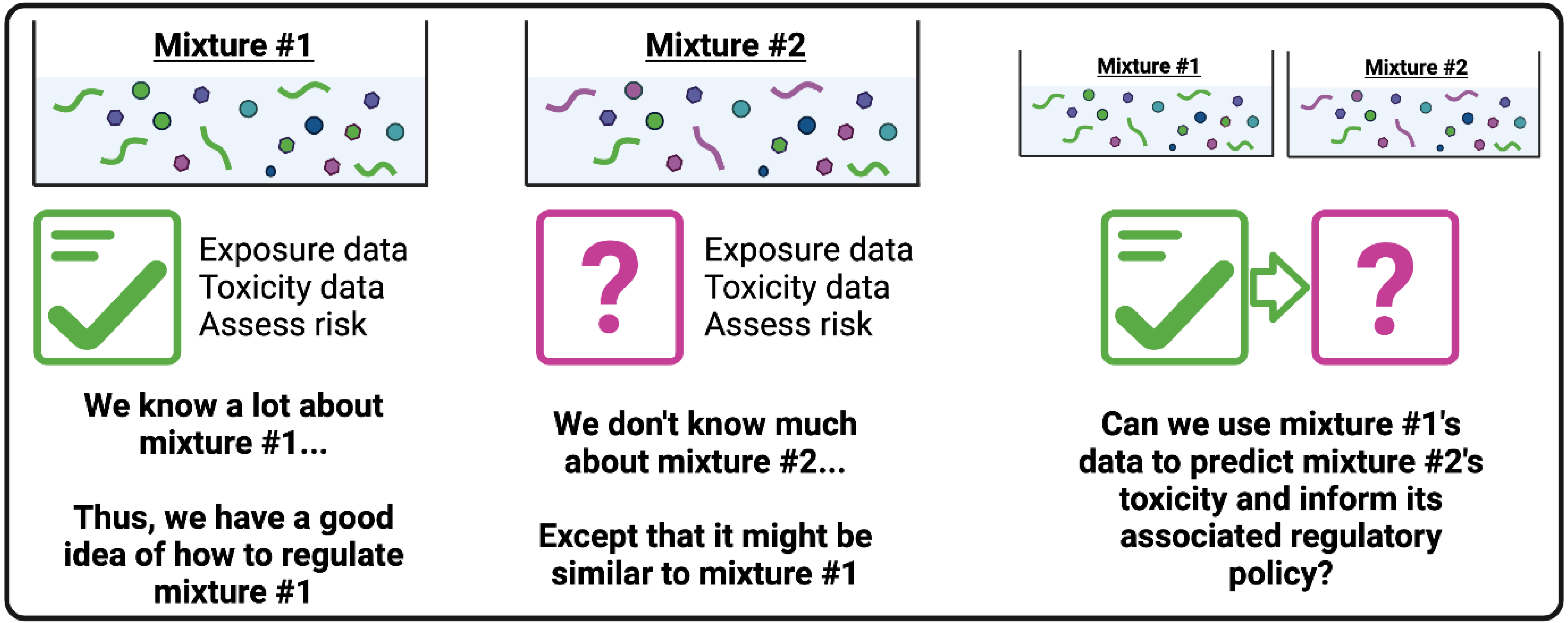
- **Many of the relationships identified through mixtures modeling were not captured through individual chemical analyses**
  - Demonstrates the utility of mixtures-based statistical approaches!
- Findings are now informing the design of future *in vitro* testing (shown on right)
- *Goal: Quantify & model the potential relationships between major chemical drivers of wildfire-associated outcomes*



What Exposure Conditions are Sufficiently Similar?

Introduction to Evaluating Exposure / Toxicity Similarities across Complex Mixtures

- Sufficient similarity methods are used to generally determine groups of exposure conditions that are chemically/biologically similar enough to be regulated together for safety assessments



Examples of Research on Sufficient Similarity

Journal of Toxicology and Environmental Health, Part A, 72: 429–436, 2009
This article is not subject to U.S. copyright
ISSN: 1528-7394 print / 1087-2620 online
DOI: 10.1080/15287390802608890

Evaluating the Similarity of Complex Drinking-Water Disinfection By-Product Mixtures: Overview of the Issues

Glenn E. Rice[1], Linda K. Teuschler[1], Richard J. Bull[2], Jane E. Simmons[3], and Paul I. Feder[4]
[1]U.S. Environmental Protection Agency, Cincinnati, Ohio, [2]MoBull Consulting Richland, Was
[3]National Health and Environmental Effects Research Laboratory, Office of Research and Dev
U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, and [4]Battell
Statistics and Information Analysis, Columbus, Ohio, USA

Analytical and Bioanalytical Chemistry (2020) 412:6789–6809
https://doi.org/10.1007/s00216-020-02839-7

PAPER IN FOREFRONT

Check for updates

Comparison of phytochemical composition of *Ginkgo biloba* extracts using a combination of non-targeted and targeted analytical approaches

Bradley J. Collins[1] · Season P. Kerns[2] · Kristin Aillon[2] · Geoffrey Mueller[3] · Cynthia V. Rider[1] · Eugene F. DeRose[3] · Robert E. London[3] · James M. Harnly[4] · Suramya Waidyanatha[1]

Food and Chemical Toxicology 118 (2018) 328–339

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

ELSEVIER

Check for updates

How similar is similar enough? A sufficient similarity case study with *Ginkgo biloba* extract

Natasha R. Catlin[a,1], Bradley J. Collins[a], Scott S. Auerbach[a], Stephen S. Ferguson[a], James M. Harnly[b], Chris Gennings[c], Suramya Waidyanatha[a], Glenn E. Rice[d], Stephanie L. Smith-Roe[a], Kristine L. Witt[a], Cynthia V. Rider[a,*]

[a] *Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA*
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[d] *U.S. Environmental Protection Agency, Cincinnati, OH, USA*

Risk Analysis
AN INTERNATIONAL JOURNAL
An Official Publication of the Society for Risk Analysis

Original Research Article

An Empirical Approach to Sufficient Similarity: Combining Exposure Data and Mixtures Toxicology Data

Scott Marshall, Chris Gennings, Linda K. Teuschler, LeAnna G. Stork, Rogelio Tornero-Velez, Kevin M. Crofton, Glenn E. Rice

First published: 11 February 2013 | https://doi.org/10.1111/risa.12015 | Citations: 10

OXFORD
SOT Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 172(2), 2019, 316–329
doi: 10.1093/toxsci/kfz189
Advance Access Publication Date: August 27, 2019
Research Article

Evaluating Sufficient Similarity of Botanical Dietary Supplements: Combining Chemical and *In Vitro* Biological Data

Kristen R. Ryan,*,[1] Madelyn C. Huang,*,[1] Stephen S. Ferguson ,* Suramya Waidyanatha,* Sreenivasa Ramaiahgari,* Julie R. Rice,* Paul E. Dunlap,* Scott S. Auerbach,* Esra Mutlu,* Tim Cristy,† Jessica Peirfelice,† Michael J. DeVito,* Stephanie L. Smith-Roe,* and Cynthia V. Rider*,[2]

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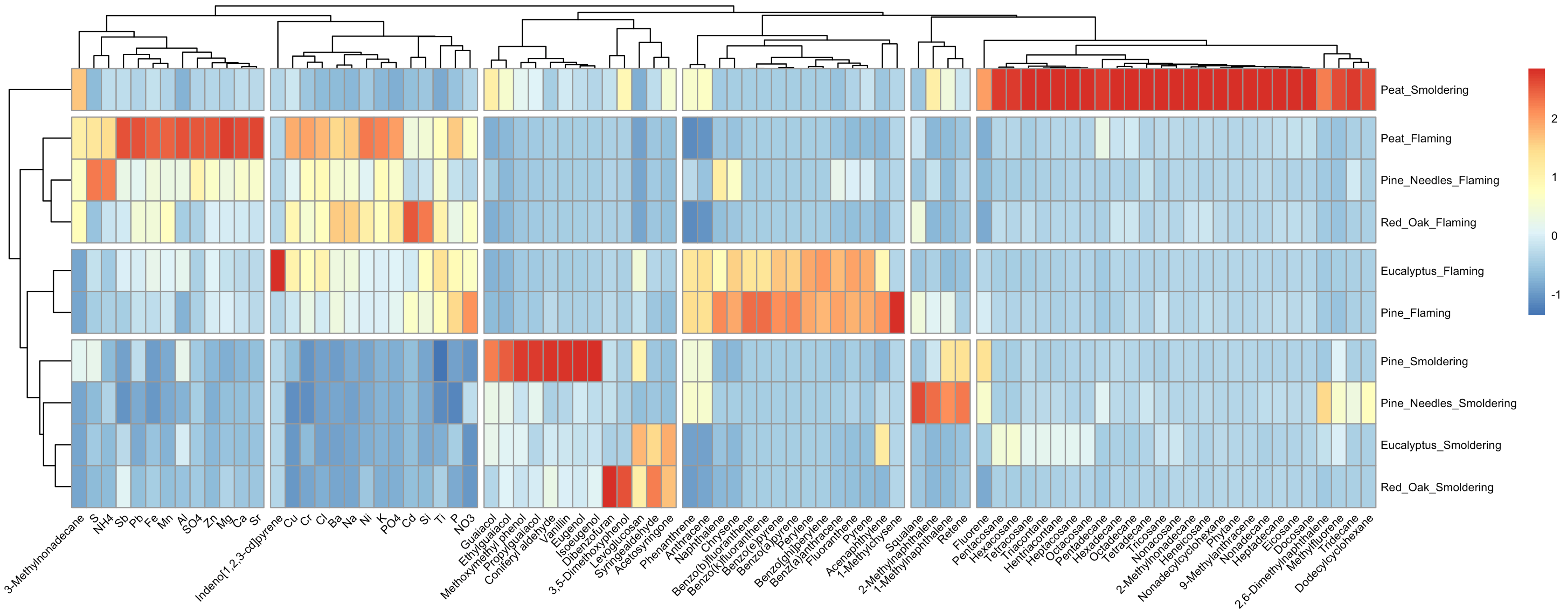
[1]These authors contributed equally to this study.
[2]To whom correspondence should be addressed at Cynthia Rider at National Institute of Environmental Health Sciences, PO Box 12233, K2-12, Research Triangle Park, NC 27709. Fax: 919-541-1019; E-mail: cynthia.rider@nih.gov.

Which Wildfire-Relevant Exposure Conditions are Similar?

Each exposure condition produced a different set of emission chemistries:

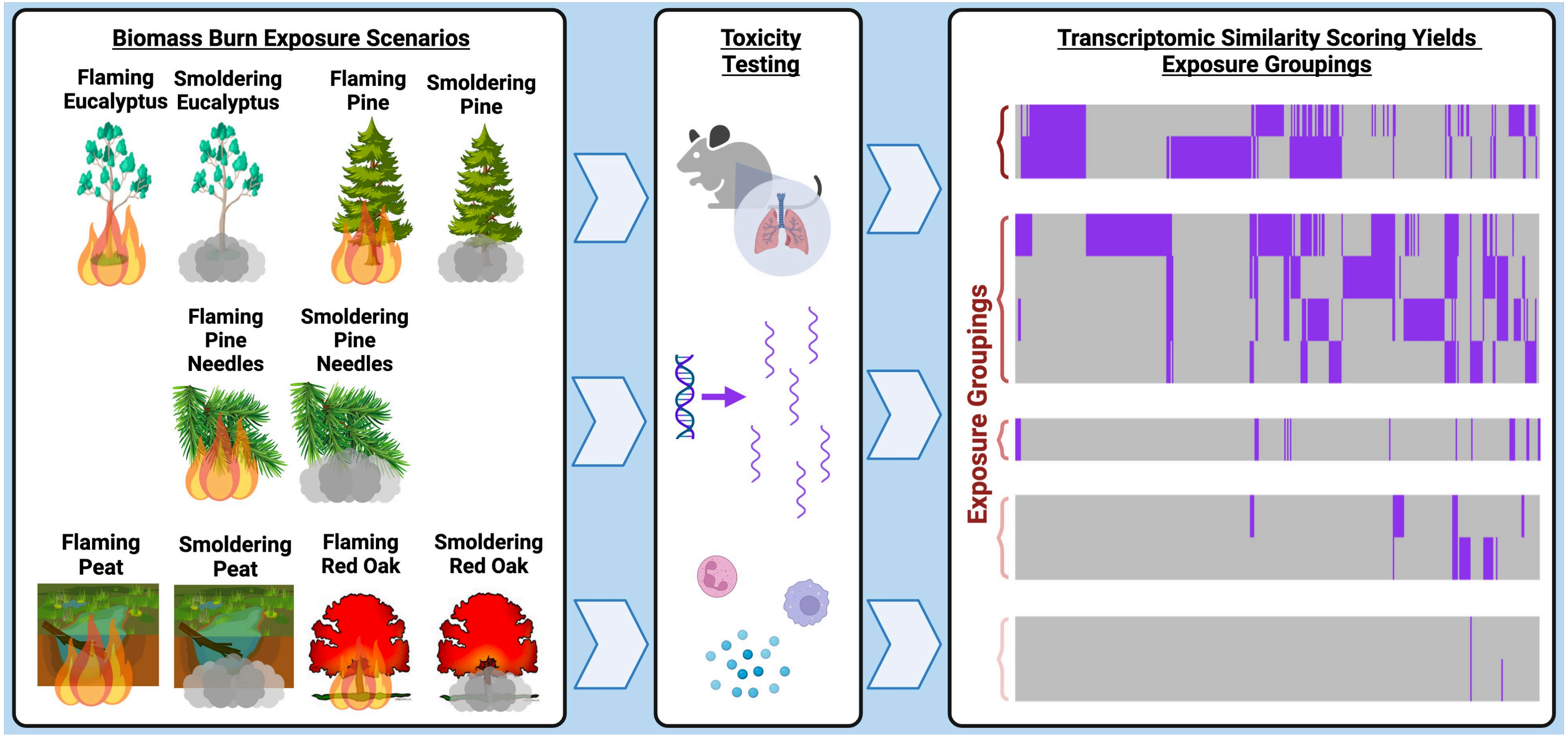


If we are just looking at the chemistry, we may conclude that:

- Flaming conditions group together
- Smoldering conditions group together
- Except smoldering peat, which is pretty distinct

Is this true of the biology?

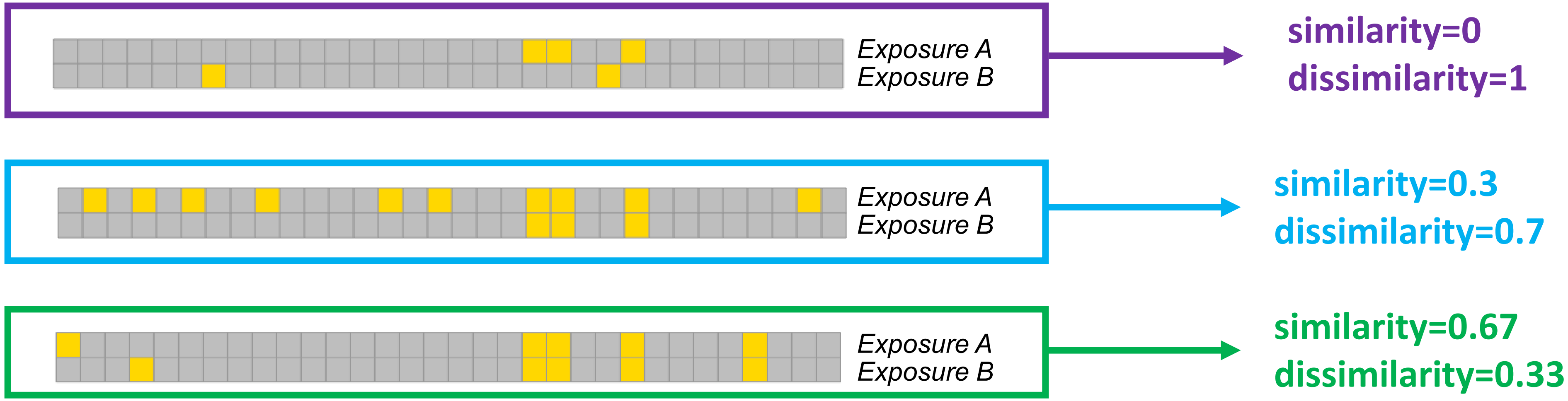
Transcriptomic Similarity Scoring



Transcriptomic Similarity Scoring

For hypothetical exposures A and B, the Jaccard distance, or dissimilarity, is defined as:

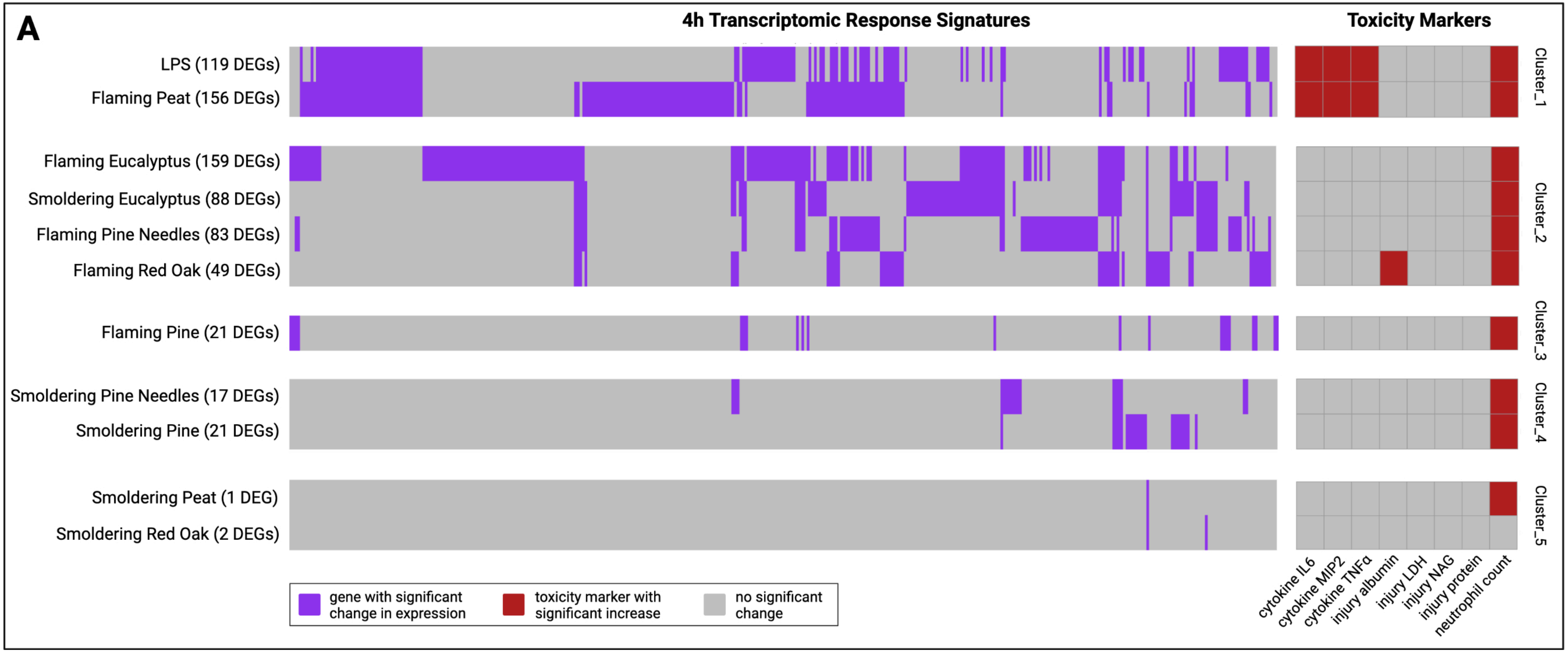
$$D(A,B) = 1 - \frac{|A \cap B|}{|A \cup B|} = 1 - \frac{\text{number of altered genes in common between exposures A and B}}{\text{total number of altered genes between exposures A and/or B}}$$



Hypothetical gene without an exposure-induced expression change

Hypothetical gene with exposure-induced expression change

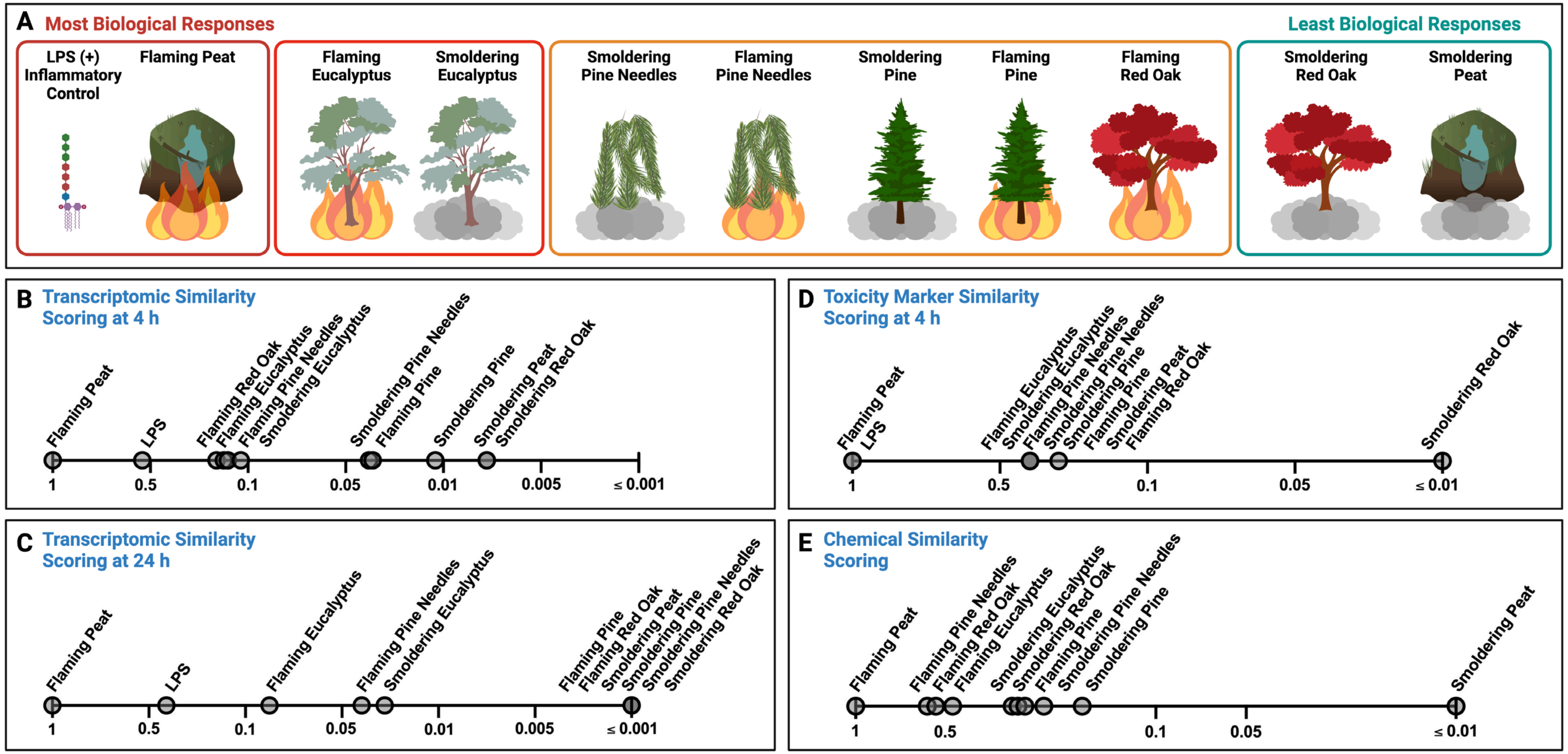
Clustering of Transcriptomic Similarity Scores (4h)



Clustering of Transcriptomic Similarity Scores (24h)

-> Overall, responses are more muted in comparison to 4 h post-exposure, with the same exposures grouping together at the top

Grouping Results Summary



-> Largely consistent groupings across transcriptomics, toxicity phenotypes, and post-exposure time periods

-> Largely inconsistent groupings with the chemical exposure profiles (though targeted methods were employed)

Differences between Chemical vs. Biological-based Groupings is Consistent with Previous Studies

Example: Black Cohosh (BC) sample similarity 'calls' on whether or not each sample aliquot was similar to a NTP test article (Ryan et al. 2019)

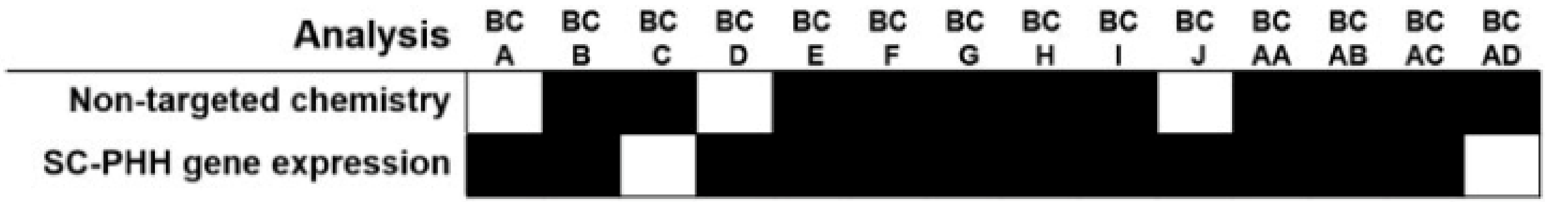


Figure 6. Summary of total sufficient similarity findings for black cohosh (BC) samples. Conclusions of sufficient similarity for the different data streams are shown. A black box indicates the result for each data stream is "similar" to the NTP test article (BC 1) and a white box indicates "different." Only samples used in all analyses are presented. SC-PHH = sandwich culture of primary human hepatocytes.

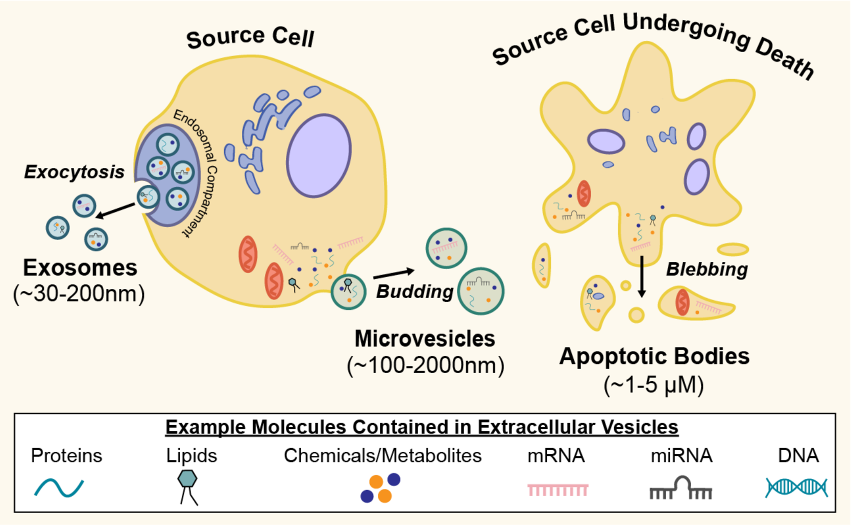
Though our future wildfire research will incorporate more global chemistry approaches (e.g., NTA) to more holistically capture exposure signatures

What are the Underlying Biological Mechanisms?

Extracellular Vesicles (EVs) are Extremely Understudied in Relation to Chemical Safety and Risk

<u>**What are EVs?**</u>
Particles released from cells with an outer lipid bilayer that contain (and transport) molecules - are distinguished from cells because they cannot replicate

EVs carry different molecular content and then impart beneficial, neutral, or detrimental effects to nearby or distant target tissues



Journal of Exposure Science & Environmental Epidemiology

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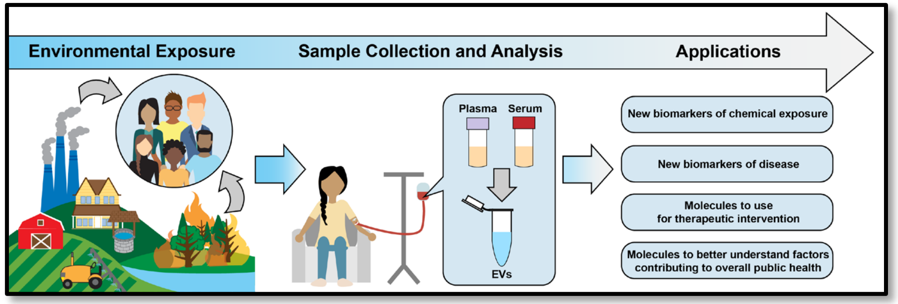
Review Article | Published: 25 February 2022

Approaches to incorporate extracellular vesicles into exposure science, toxicology, and public health research

Celeste K. Carberry, Deepak Keshava, Alexis Payton, Gregory J. Smith & Julia E. Rager

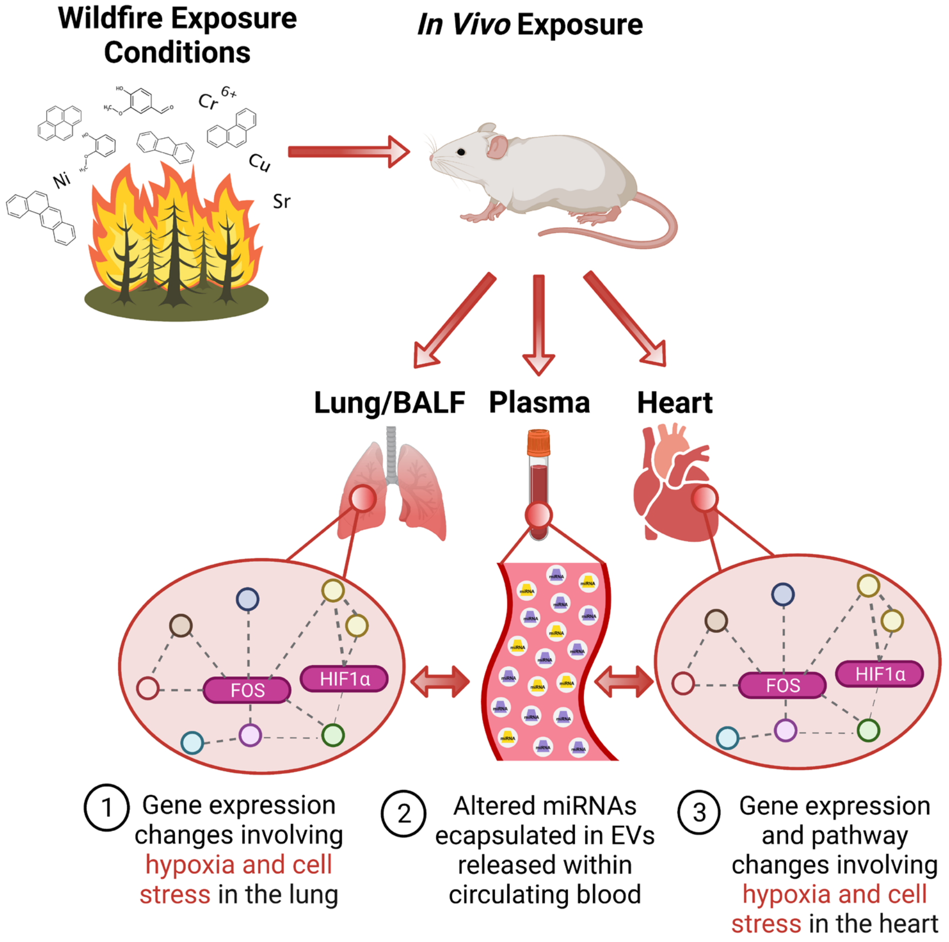
Journal of Exposure Science & Environmental Epidemiology (2022) | Cite this article

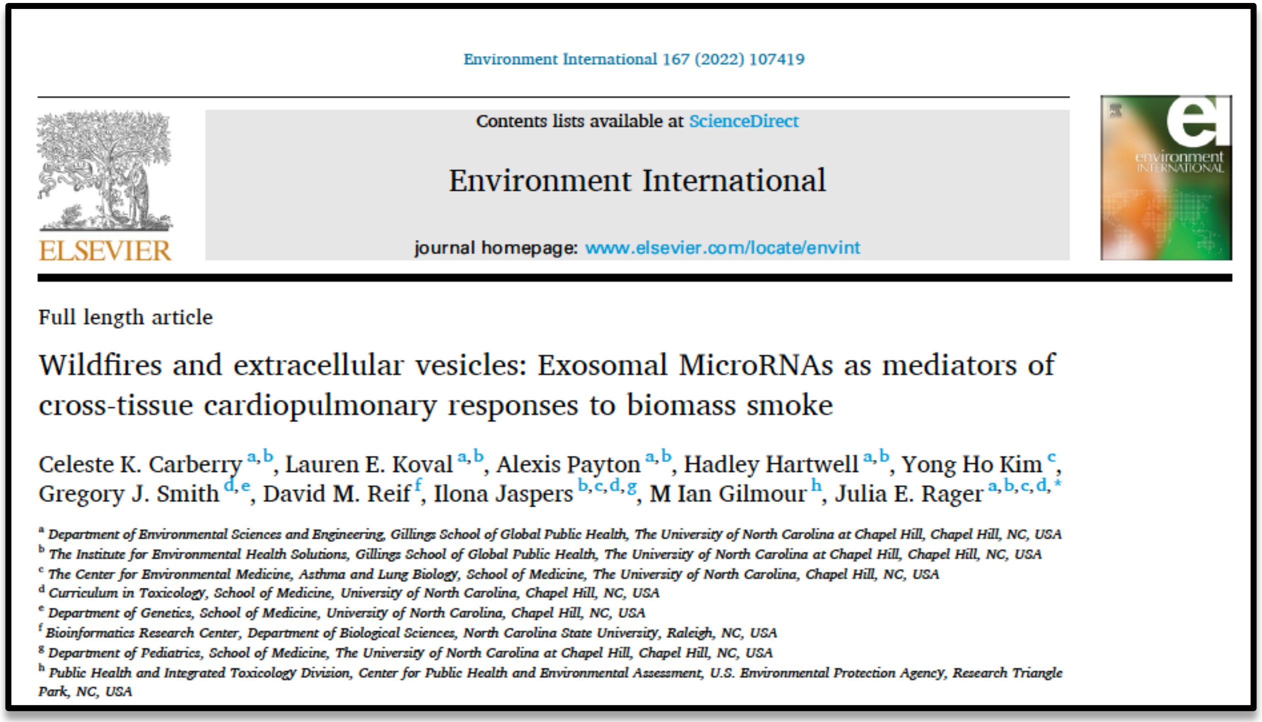
43 Accesses | 7 Altmetric | Metrics



(Carberry et al. 2022)

EVs as Cross-Tissue Mediators of Wildfire Toxicity

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Full length article

Wildfires and extracellular vesicles: Exosomal MicroRNAs as mediators of cross-tissue cardiopulmonary responses to biomass smoke

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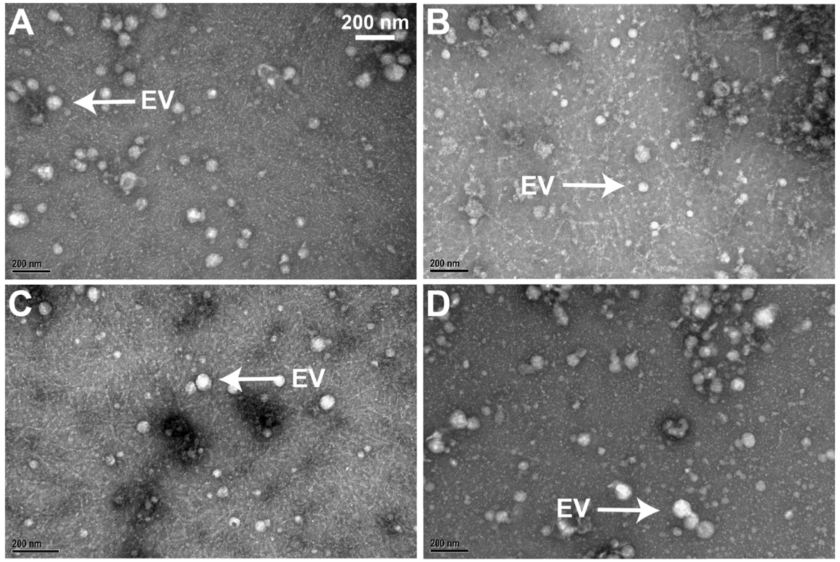
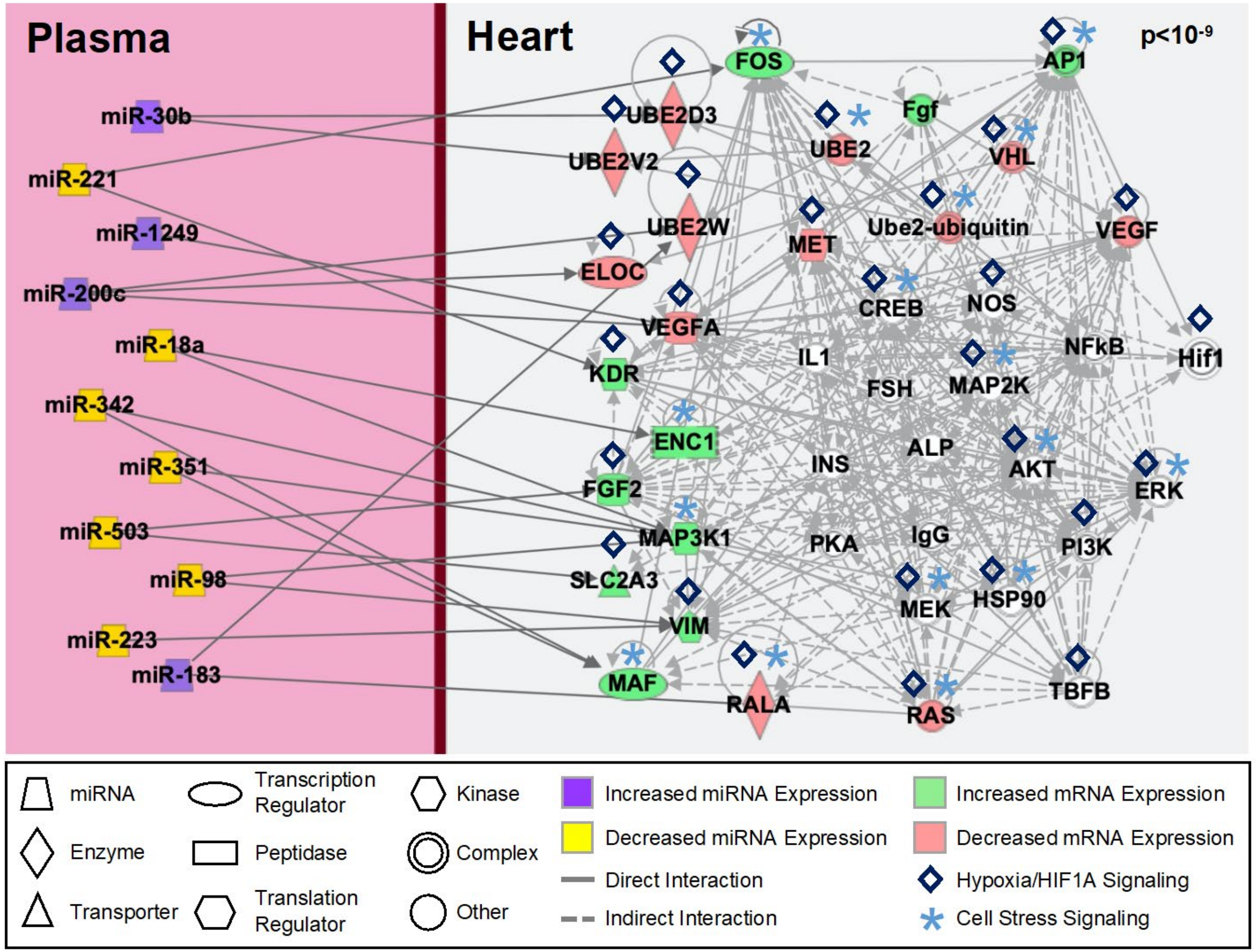
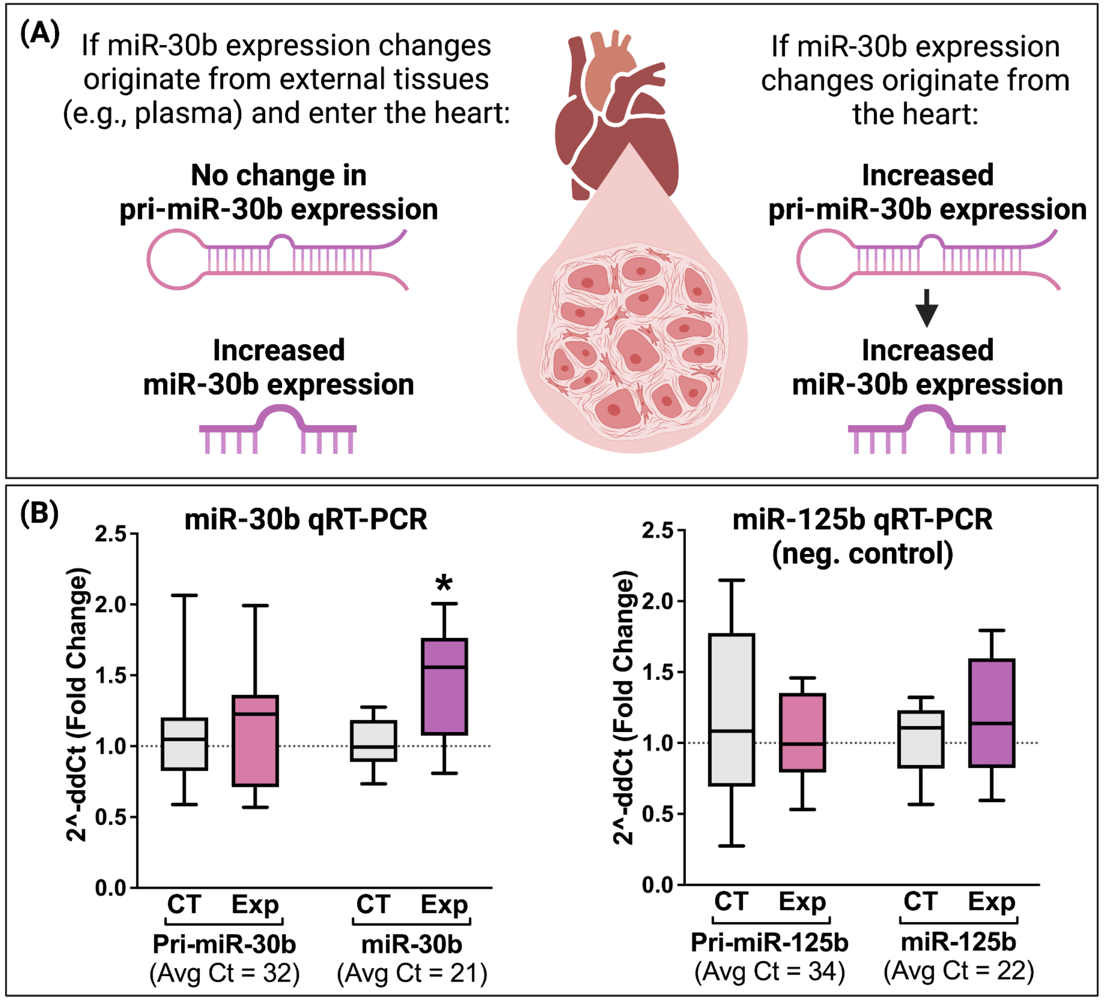
Evaluated EV-encapsulated MicroRNAs in Mouse Plasma





Evidence Supporting Possible Transfer of miR-30b from Plasma to Heart after Biomass Smoke Exposure



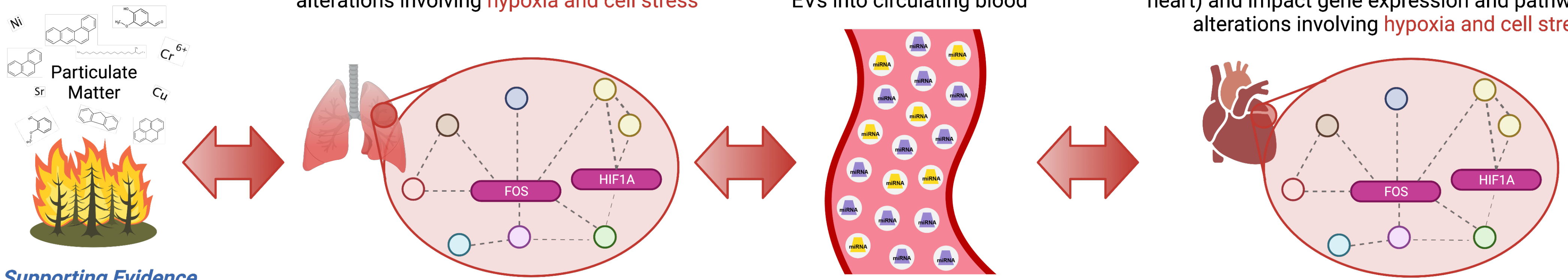
EVs as Cross-Tissue Mediators of Wildfire Toxicity

Wildfire Exposure Conditions

Key Event 1: Lung Cell Responses
Gene expression changes & pathway-level alterations involving hypoxia and cell stress

Key Event 2: EV miRNAs
Release of miRNAs encapsulated in EVs into circulating blood

Key Event 3: Communication with Distal Tissues
EV miRNAs circulating in blood reach target tissues (e.g., heart) and impact gene expression and pathway-level alterations involving hypoxia and cell stress



Supporting Evidence

Current study supports association between biomass smoke exposures and lung hypoxia/cell stress pathway changes

Current study supports association between lung hypoxia/cell stress pathway changes coinciding with changes in plasma EV miRNAs

Additional mechanistic evidence from published articles: Chen et al. 2017, Su et al. 2020, Zhang et al. 2021

Current study supports association between changes in plasma EV miRNAs coinciding with changes in heart hypoxia/cell stress pathway changes

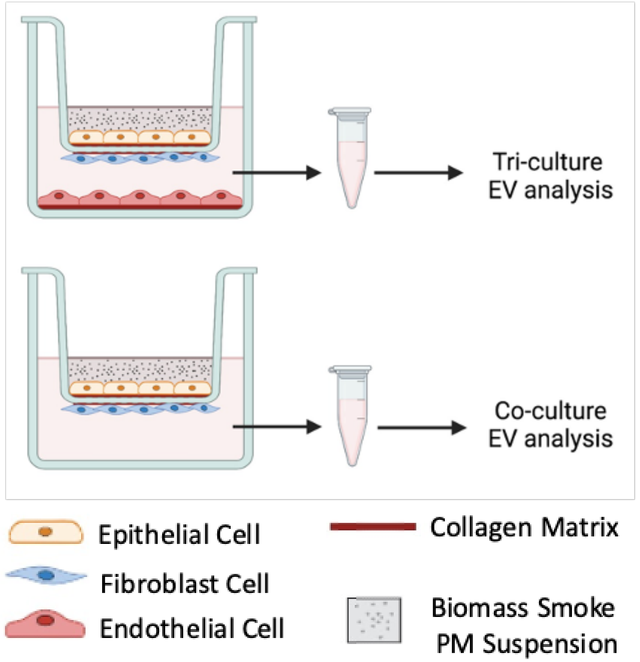
Current study supports association between changes in plasma EV miRNAs coinciding with changes in the same miRNAs (e.g., miR-30b) in heart tissue

Additional mechanistic evidence from published articles: Das and Halushka et al. 2015, Davidson et al. 2019, Emanueli et al. 2016, Gong et al. 2017, Minghua et al. 2018

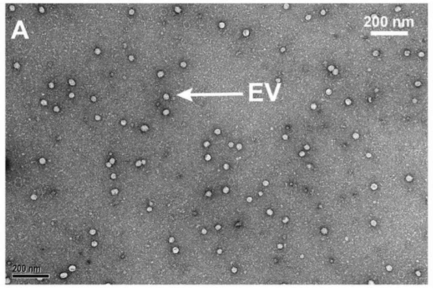
Currently Developing Methods to Evaluate EVs within *In Vitro* Models

In Vitro Wildfire Studies

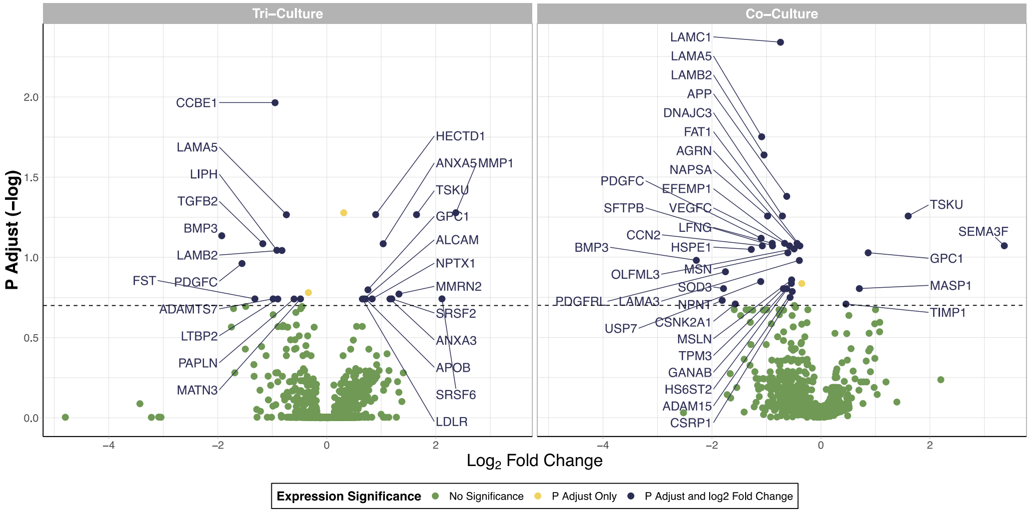
1. 3D Organotypic Models of the Airway Epithelium + Biomass Smoke Exposure



2. EV Isolation from Conditioned Media



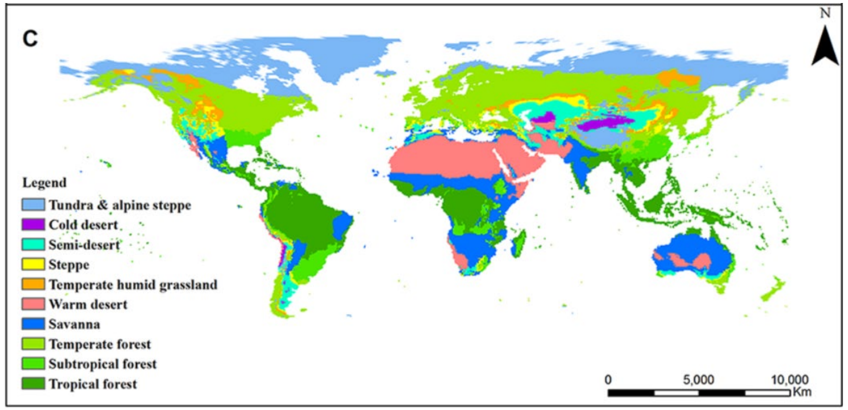
3. Differential EV Proteomic Landscape



Shaun McCullough (EPA), Eva Vitucci (UNC), Celeste Carberry (UNC), Alexis Payton (UNC)

Overall Impact

- It's impossible to test every chemical in wildfires (individually or across combinations)
- Leveraging *in silico* mixtures modeling has great utility towards decreasing reliance upon animal testing and informing future *in vitro/in vivo* study designs



https://www.researchgate.net/figure/Spatial-distribution-of-global-natural-vegetaiton-biomes-in-the-period-1911-2000-a-T1_fig10_258956265

Real-world solutions: What can we do with these findings?

- Improve risk characterizations of these complex exposure conditions by identifying major toxicity drivers
- Identifying the 'bad actors' in these exposures can inform geographical regions that may be more at risk of wildfire smoke-induced health impacts, based on their prevalent biomass species

Collaborations and Funding

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Trainees in italics

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