PENNINGTON BIOMEDICAL RESEARCH FOUNDATION LSU

Do Environmentally Persistent Free Radicals Induce Mutations in SARS CoV-2?

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OUTLINE

Particulate matter pollution

- Hazardous PM
- Environmentally persistent free radicals (EPFRs)

Exposure to EPFRs increases severity of RTVI (infant/pediatric models)

- Epithelial injury
  - Immunosuppression
  - Failure to repair

Does exposure to EPFRs enhance severity of SARS-CoV-2 (Ayaho/Sly) or induce genetic mutations in SARS-CoV-2?

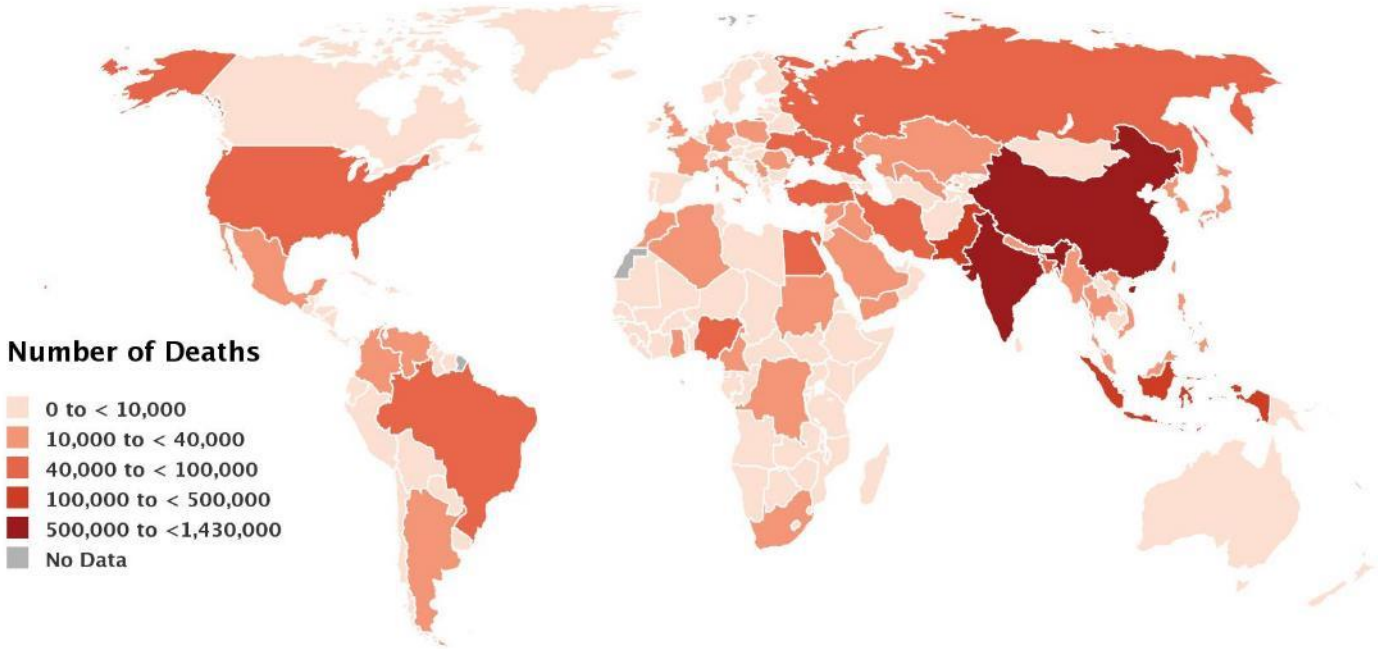
THE BURDEN OF AIR POLLUTION

- Ambient air pollution is the **5th leading cause of death** worldwide.

Contributing to:

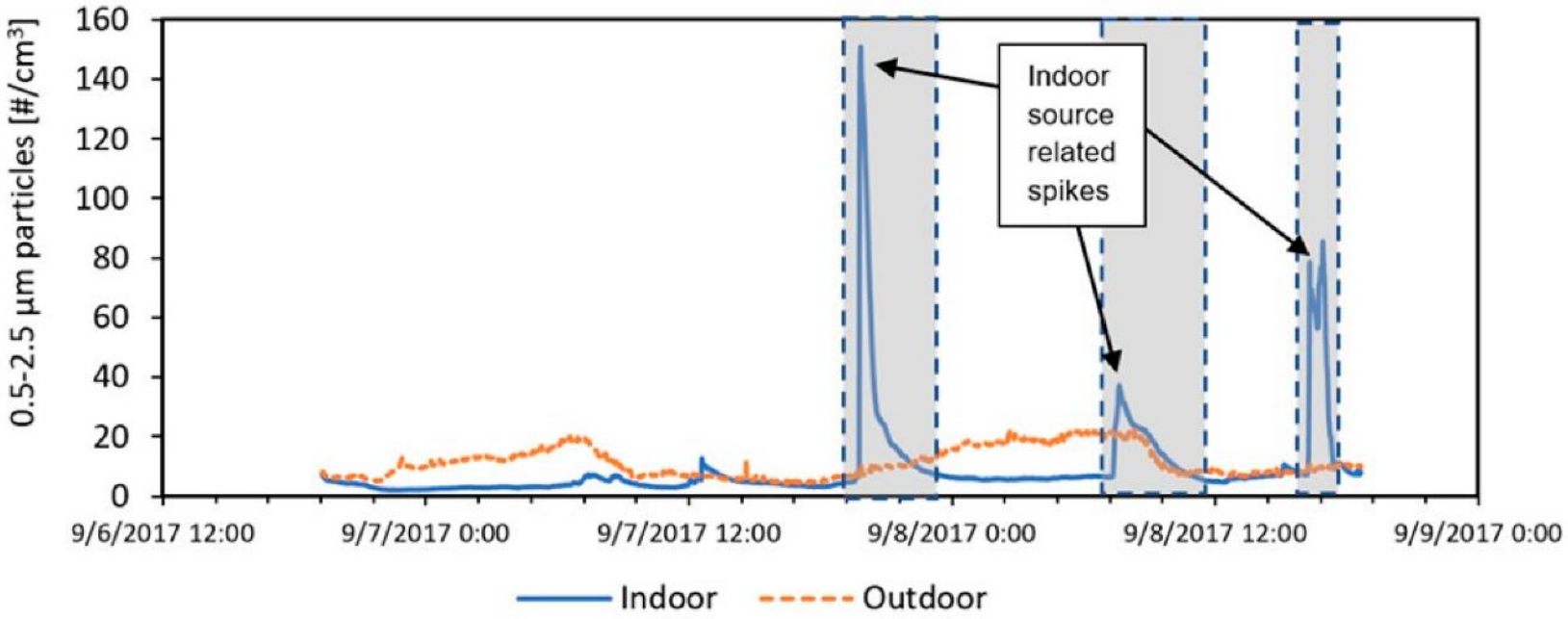
~ 4.2 million deaths worldwide

~400 000 deaths of children under five



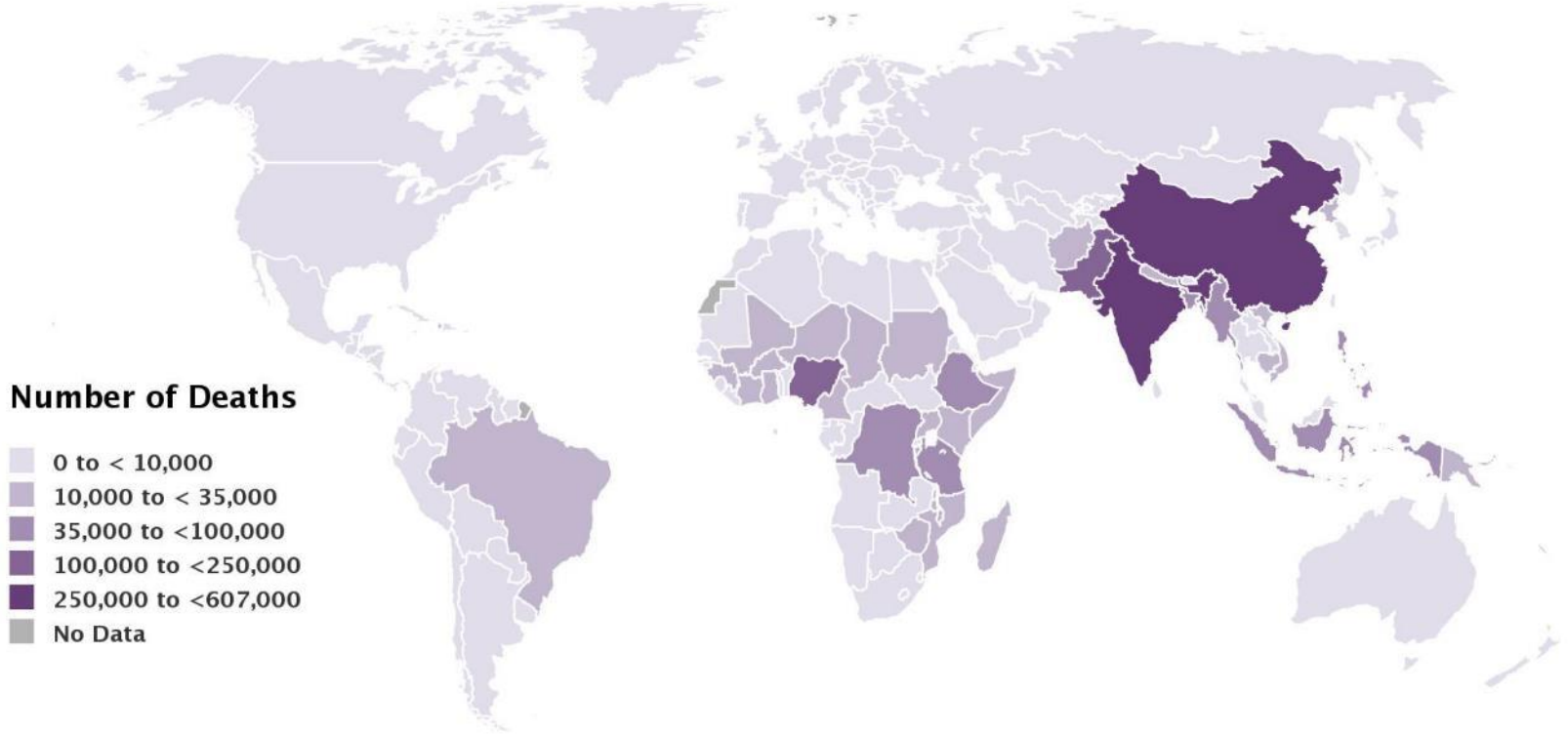
•Health Effects Institute. 2019. State of Global Air

NOT JUST AN OUTDOOR CONCERN



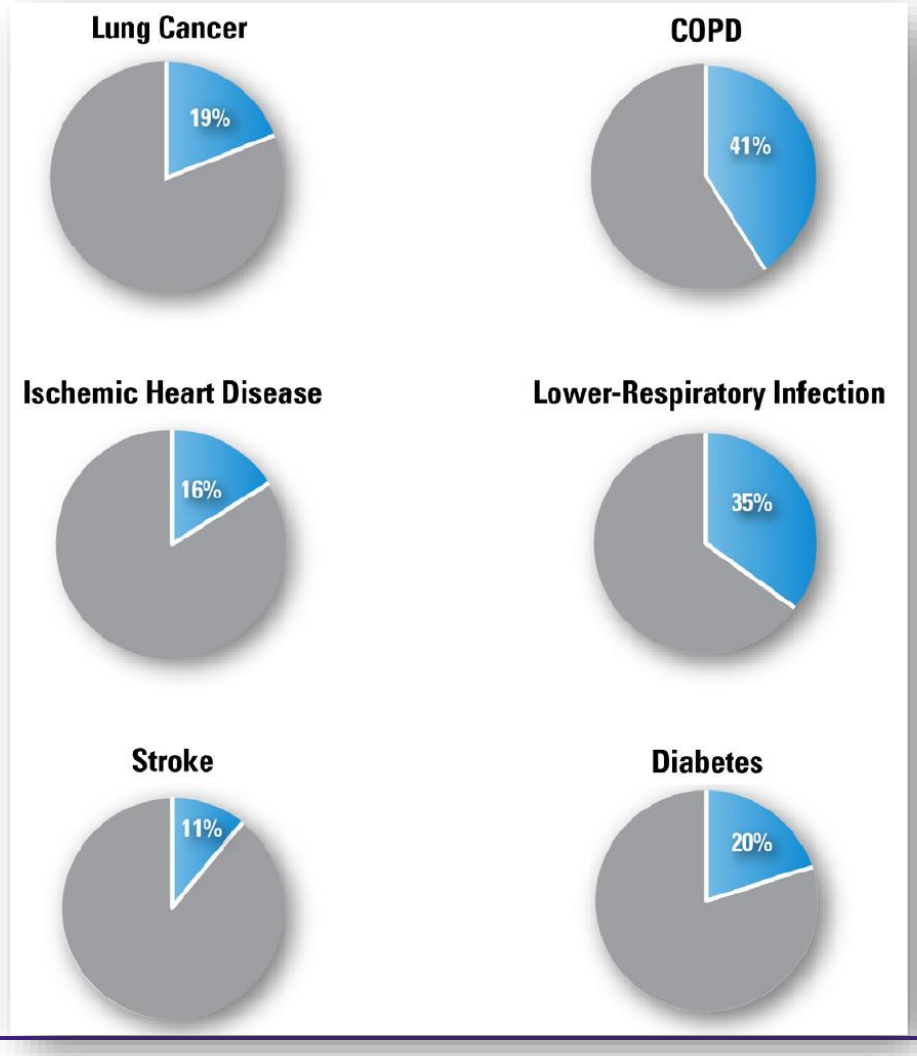
Shresta et al. Int J Environ Res Public Health. 2019

HOUSEHOLD AIR POLLUTION



•Health Effects Institute. 2019. State of Global Air

GLOBAL DEATHS FROM SPECIFIC DISEASES ATTRIBUTABLE TO AIR POLLUTION IN 2017



•Health Effects Institute. State of Global Air. 2019.

COMBUSTION DERIVED PARTICULATE MATTER (PM)

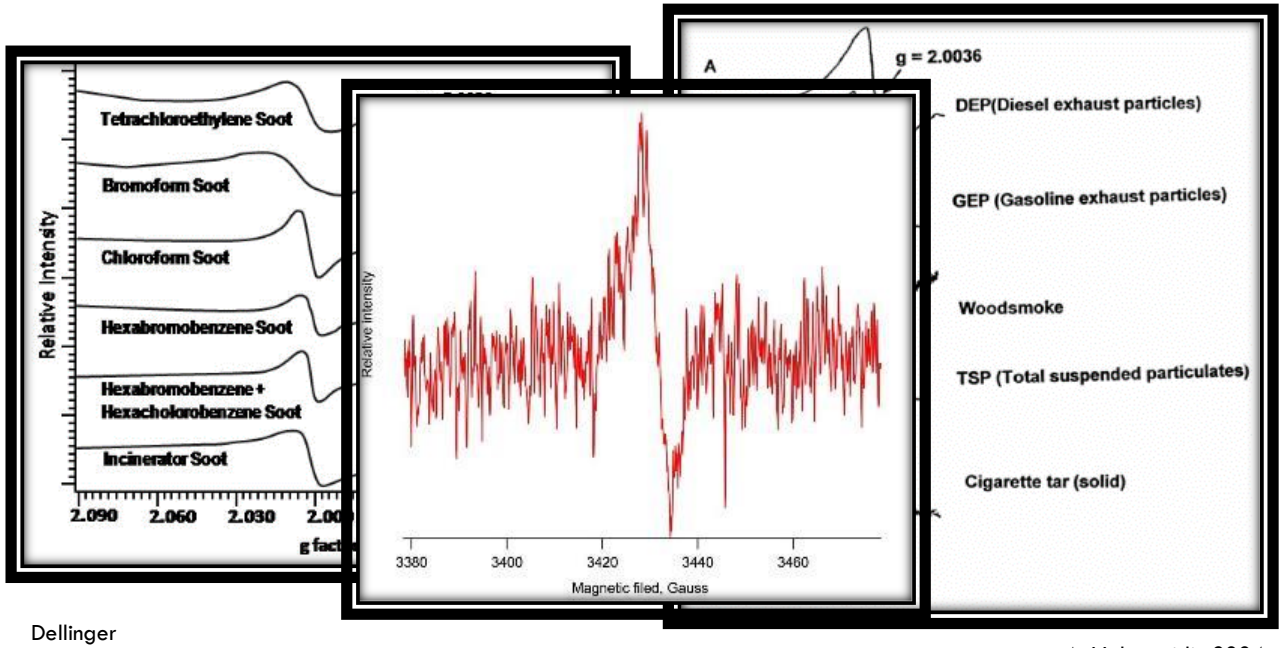
Mobile Sources
(vehicles)

Stationary Sources
(power plants, factories, fireplaces)

Personal Sources
(cigarettes)

Natural Sources
(forest fires, volcanoes)

COMBUSTION-GENERATED PM CONTAINS RADICALS



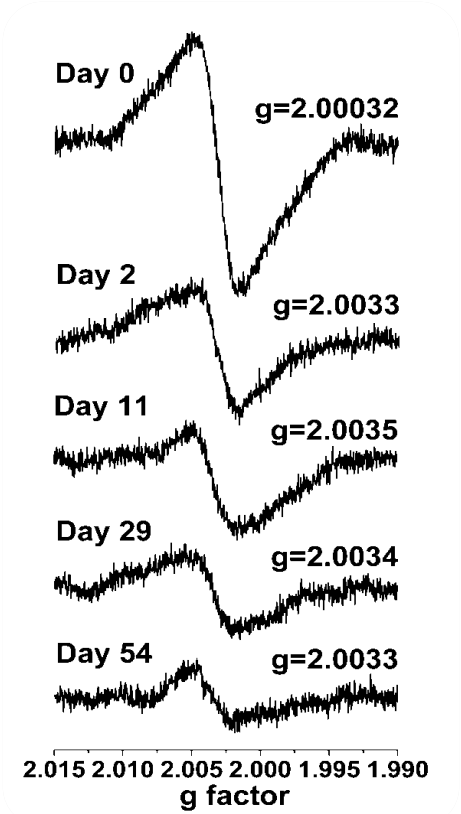
Dellinger

T.E. Sussan et al 2015

A. Valavanidis 2004

CS tar: 1e16 radicals/g
E-cig TPM: 2.6e15 radicals/g *T.E. Sussan et al PLOS One 2015*
$PM_{2.5}$:1e16 - 1e17 radicals/g (BR); 1e17 – 1e19 radicals/g (Memphis) *Oyana TJ et al. ES&T. 2017*

ENVIRONMENTALLY PERSISTENT FREE RADICALS (EPFRS)



Baton Rouge $PM_{2.5}$

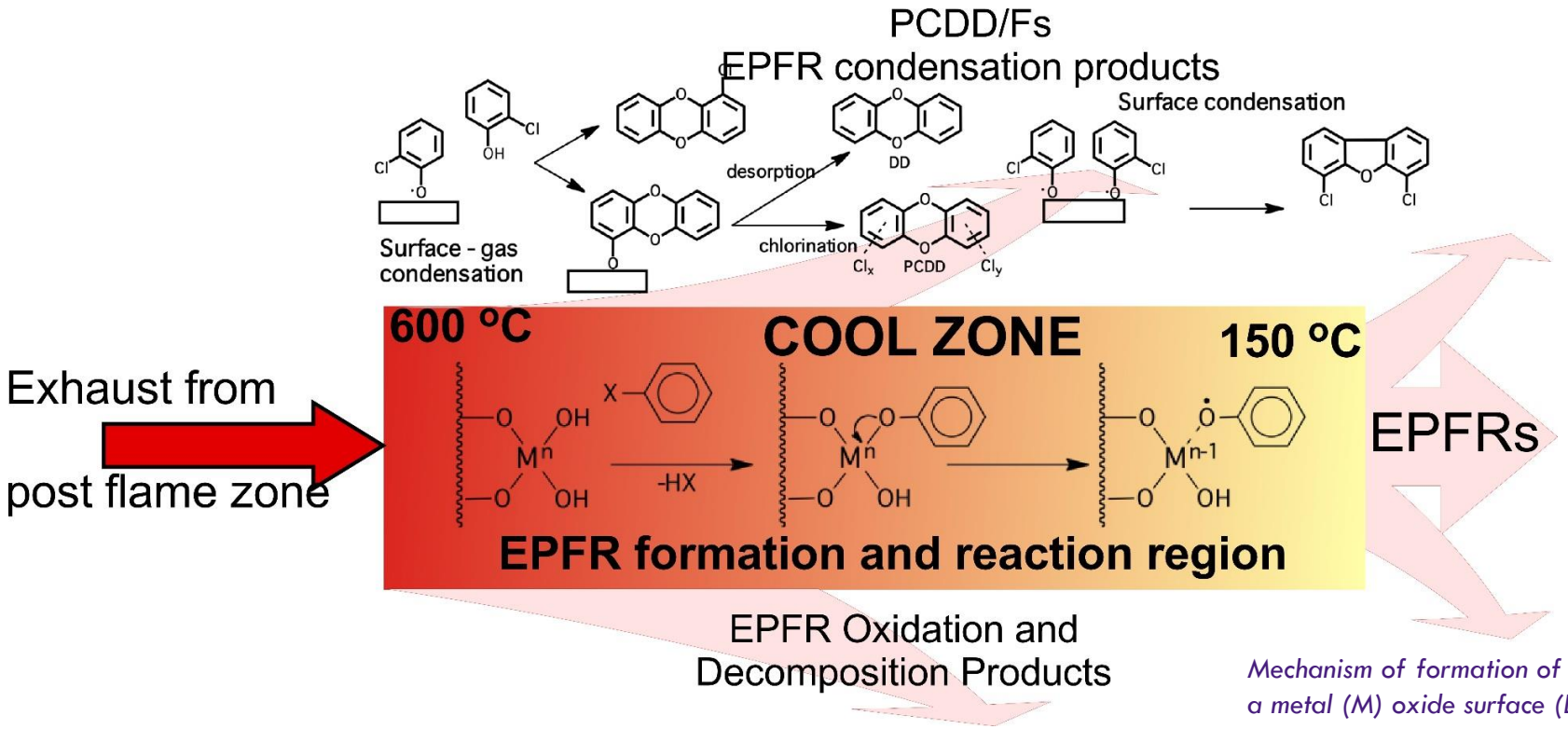
$T_{1/2}$ = 21d

CS tar: 1e16 radicals/g
E-cig TPM: 2.6e15 radicals/g
$PM_{2.5}$:1e16 - 1e17 radicals/g (BR); 1e17 – 1e19 radicals/g (Memphis)

Gehling et al. 2013

T.E. Sussan et al PLOS One 2015
Oyana TJ et al. ES&T. 2017

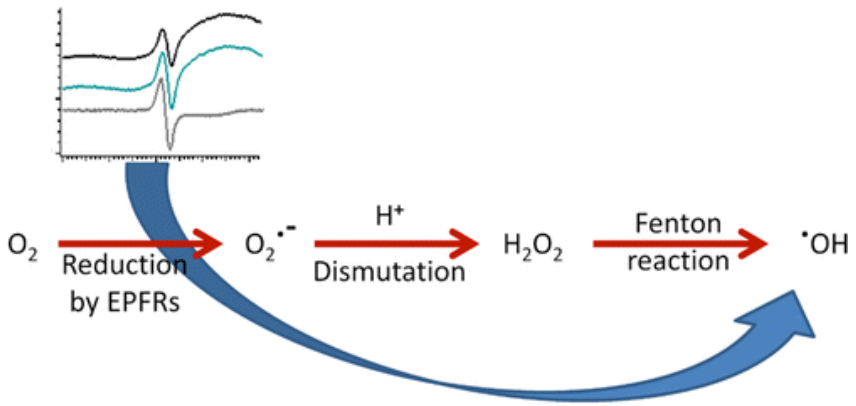
FORMATION OF EPFRS



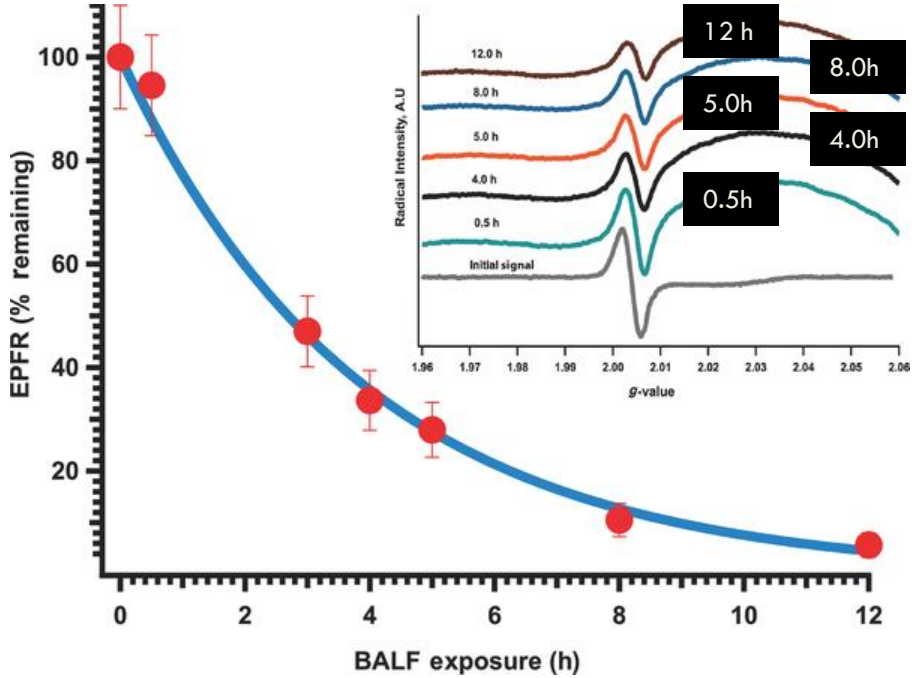
Mechanism of formation of a phenoxyl-type EPFR on a metal (M) oxide surface (Lomnicki et al 2008, Sly et al, 2019)

- EPFRs are pollutant particle systems that can be formed during combustion
- EPFRs are produced during thermal treatment (TT) of organic materials commonly found at Superfund sites
  - 30% of Superfund sites use TT to dispose of their waste (excludes groundwater)
- EPFRs are an understudied contaminant with the potential to impact human health

PERSISTENCE OF EPFRS IN BIOLOGICAL SOLUTIONS



Kelley et al., Chem Res Toxicol, 2013



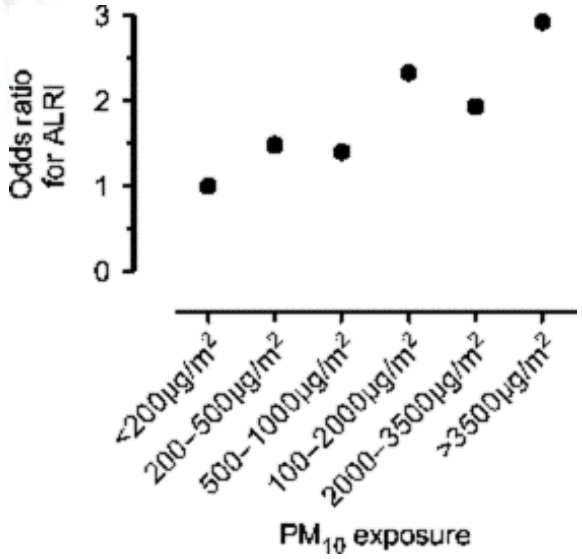
Saravia *et al.*, 2012

Dugas

Cormier

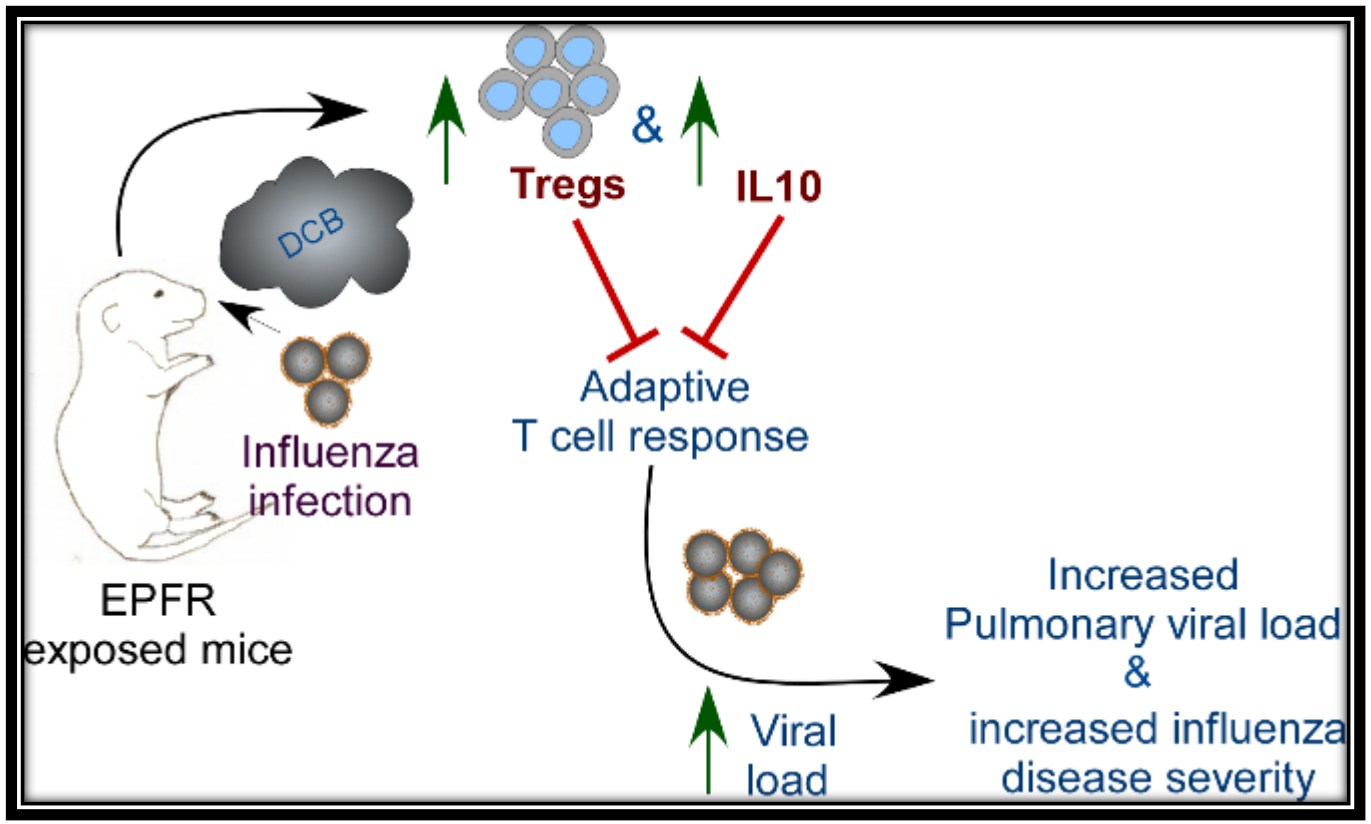
Every year, 1.96 million people die from ARIs as a result of indoor air pollution

Source: ARIAtlas.org, World Lung Foundation 2010



Grigg. 2011. Clinical & Experimental Allergy. 41: 1072-1075

SUMMARY



- Depletion of Tregs/IL10 in PM exposed mice increases protective T cell responses and reduces influenza morbidity & mortality
- IL10 alone recapitulates PM enhanced influenza morbidity

Jaligama et al. RR 2017

EXPANDING TO COMMUNITY HEALTH

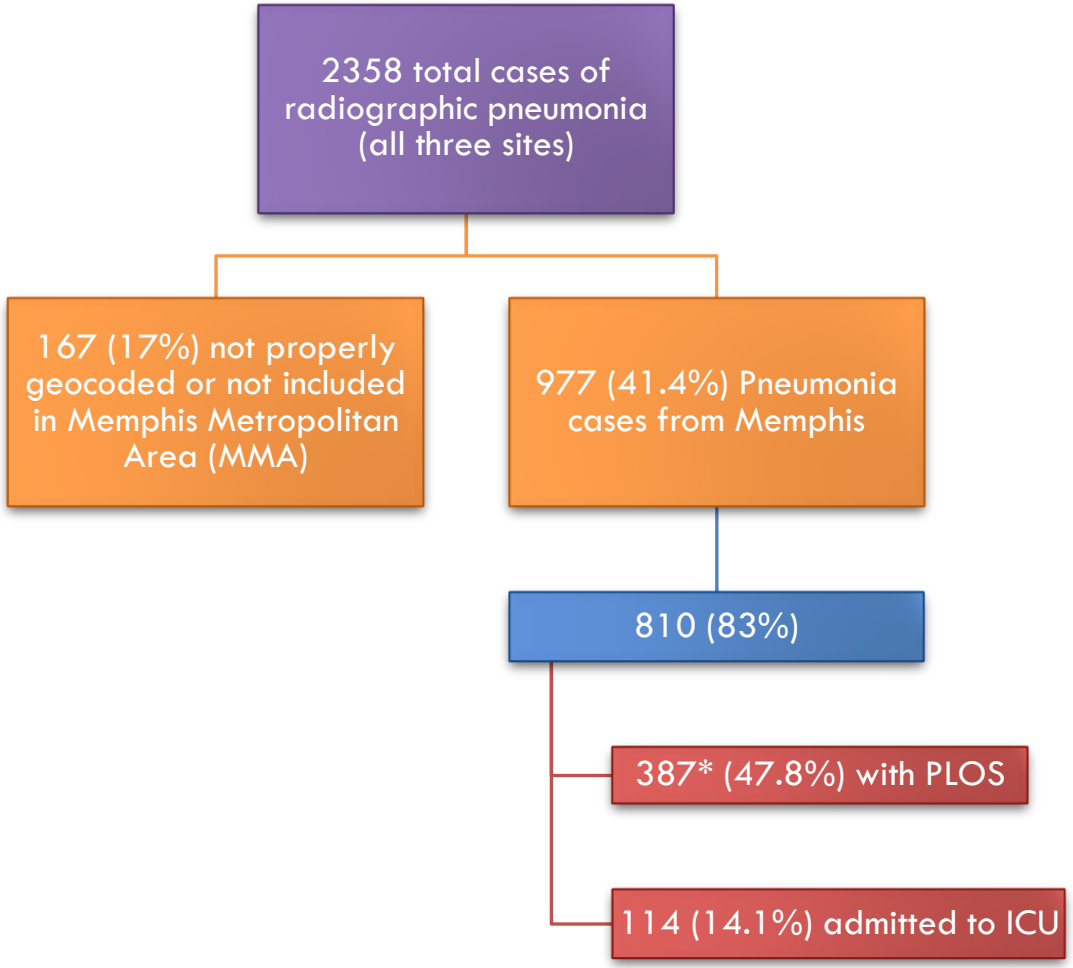
LeBonheur Children's Hospital

EPIC

LOUISIANA DEPARTMENT OF HEALTH
Environmental Public Health Tracking

Arundhati Bakshi, PhD
Kathleen Aubin, MSPH
Kate Friedman, MNS

POPULATION BASED PNEUMONIA STUDY



CDC EPIC Cohort

Oyana et al., EBM 2021

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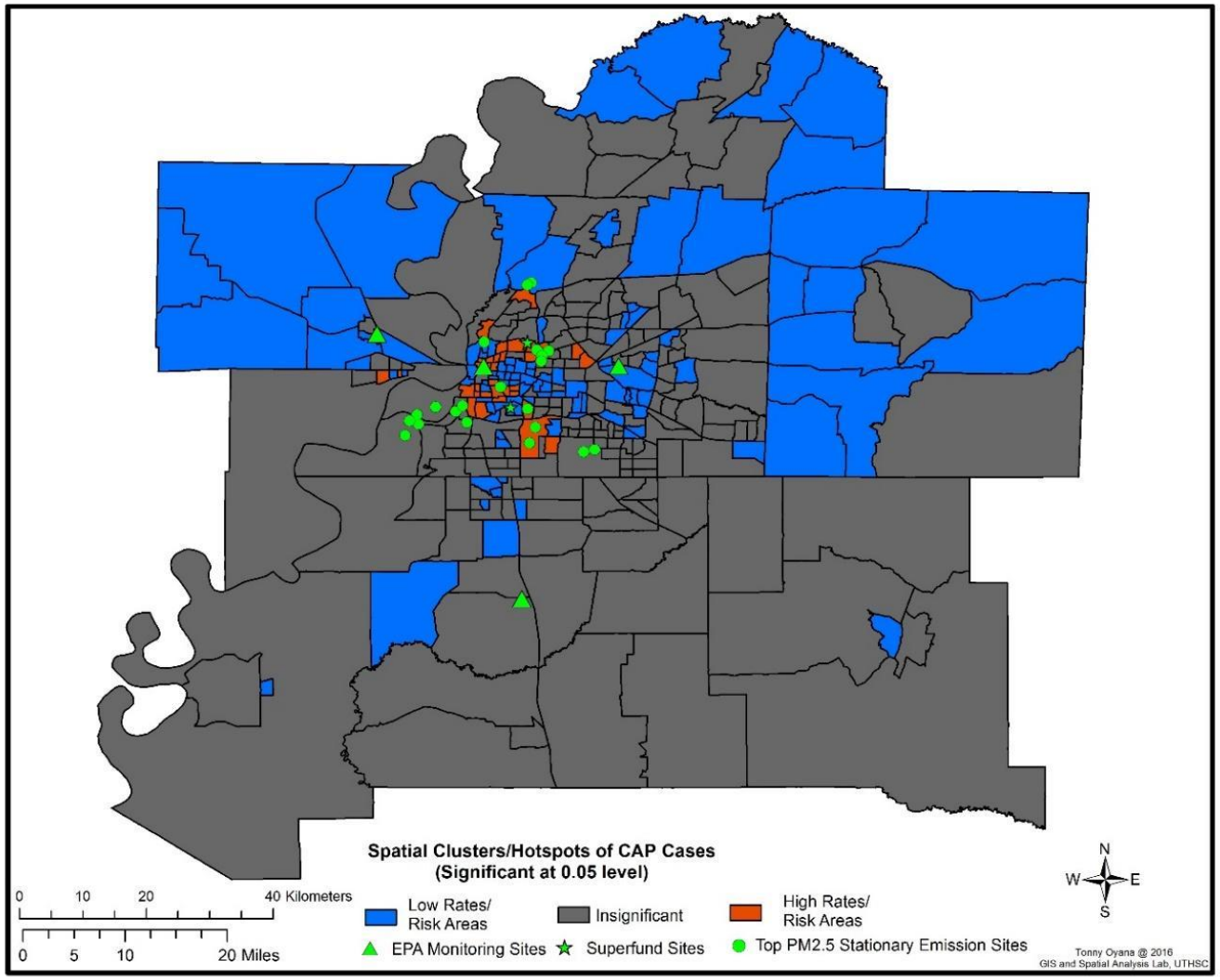
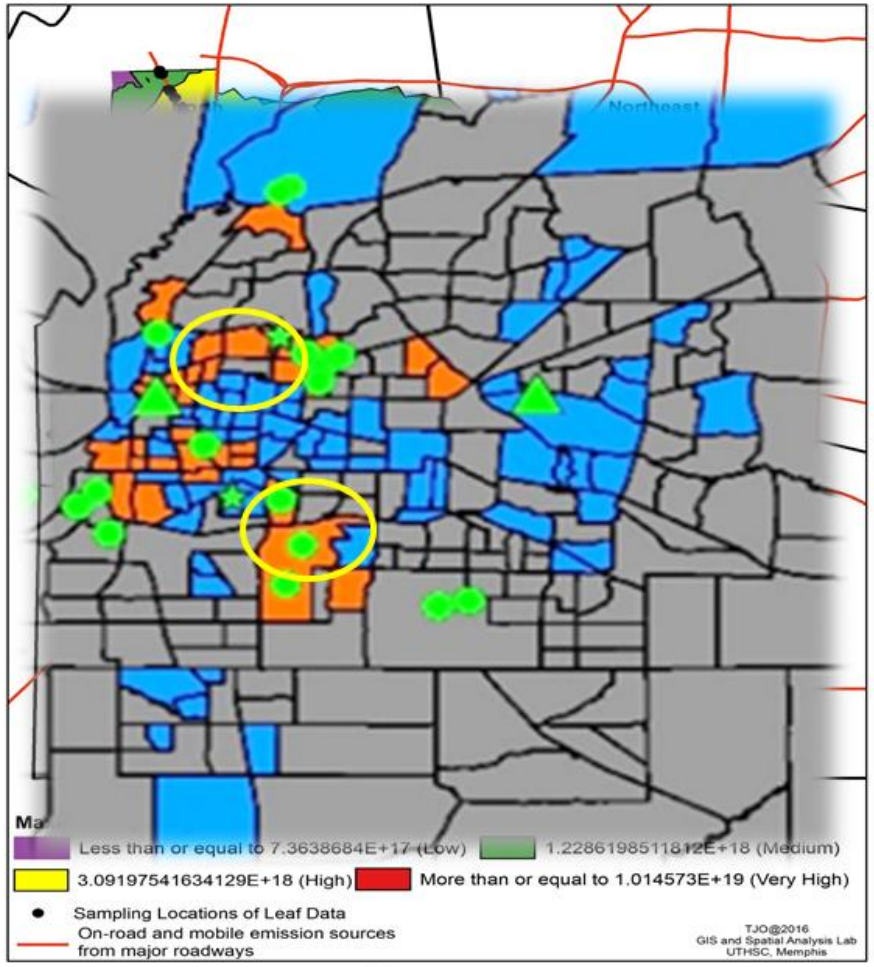
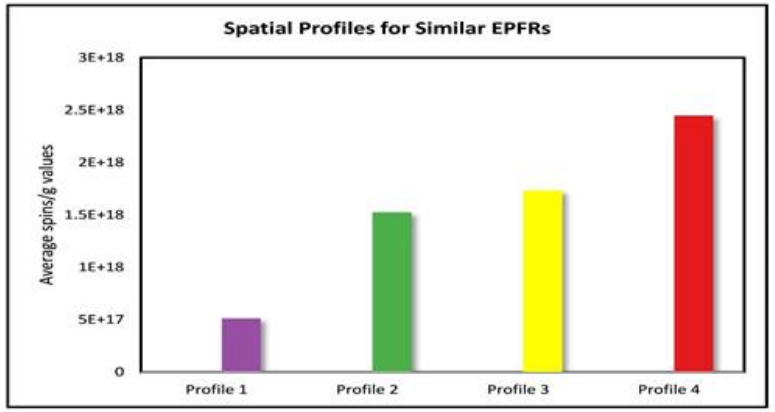
COMMUNITY ACQUIRED PNEUMONIA (CAP) "HOTSPOTS"



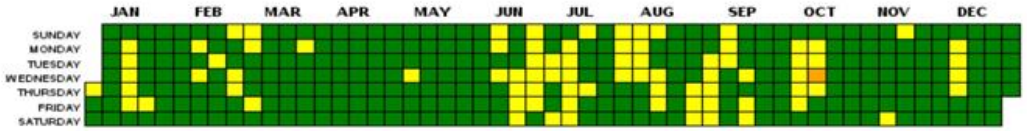
SPATIAL PROFILES OF EPFRS IN MEMPHIS, TN



(a)



(b)



Good (≤ 12.0 ug/m³) 282 days

Moderate (12.0–35.4 ug/m³) 82 days

Very Unhealthy (≥ 150 ug/m³) 0 day

Unhealthy for Sensitive Groups (35.5–55.4 ug/m³) 1 day

Unhealthy (55.5–150.4 ug/m³) 0 day

EPA Tile Plot for $PM_{2.5}$ Daily Air Quality Index
Early November 2015 when leaf data was collected,
it was rated moderate (12.0 to 35.4 ug/m³) 82 days.
Source: U.S. EPA AirData https://www.epa.gov/air-data
Created on December 6, 2016.

(c)

PROXIMITY TO $PM_{2.5}$ SOURCES PREDICTS PNEUMONIA SEVERITY IN CHILDREN

- CAP has a non-homogenous geospatial distribution
- Higher than the mean $PM_{2.5}$ was associated with living in a high-risk area for CAP [adjusted odds ratio (aOR) 2.47, 95% confidence interval (CI) 1.31–4.66]
  - Mean $PM_{2.5}$ (10.75 μg/m^3)
- Increased risk for CAP associated with
  - Viral vs bacterial infection
- 1st to show possible $PM_{2.5}$ effects at exposure levels lower than the current EPA limit

- Possible spatial overlap with high environmental EPFR concentration *Oyana et al. 2017, EST*

COLFAX, LOUISIANA

Seat of **Grant Parish**, Louisiana

- 2019 Population: 2456
- Demographics: 60% African-American, 32% white
- Median income: $20,048

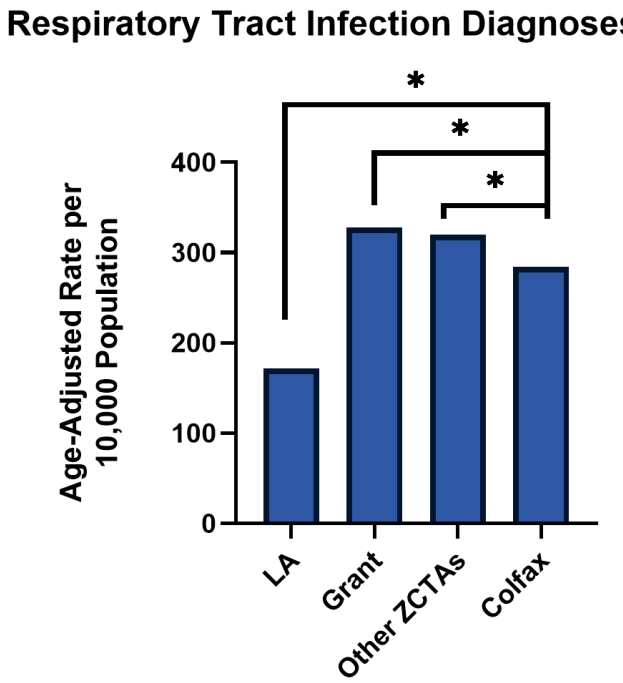
The Colfax Clean Harbors site conducts **open burning** of munitions and old explosives

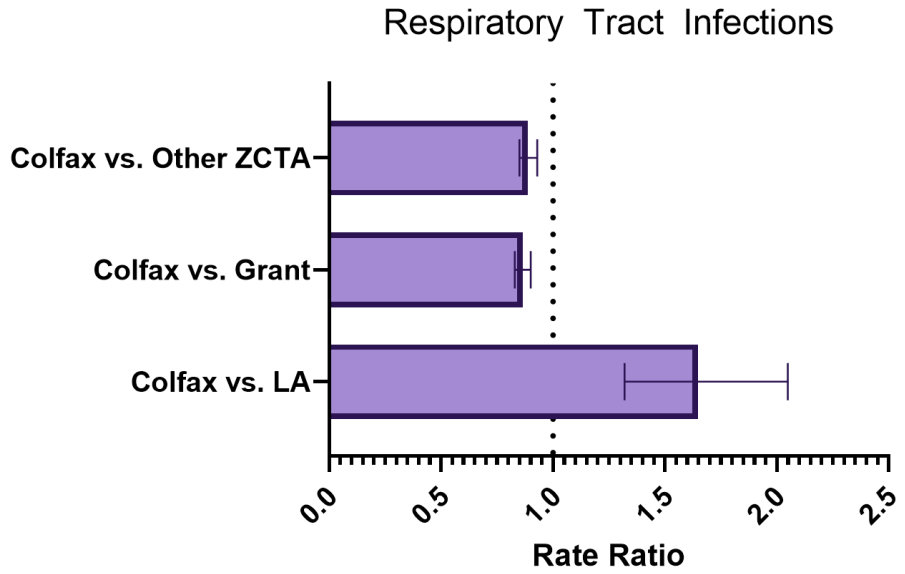
2015 alone 700,000 lbs burned

This process causes community disturbance:

- Consistent smoke plumes, noise and air pollution, rattling of homes
- Increased levels of acrolein and benzene in the air; perchlorate, dioxin, and lead in soil and water
- Residents reported a large number of **health impacts**.

INCREASED RESPIRATORY TRACT INFECTION DIAGNOSES IN COLFAX, LA

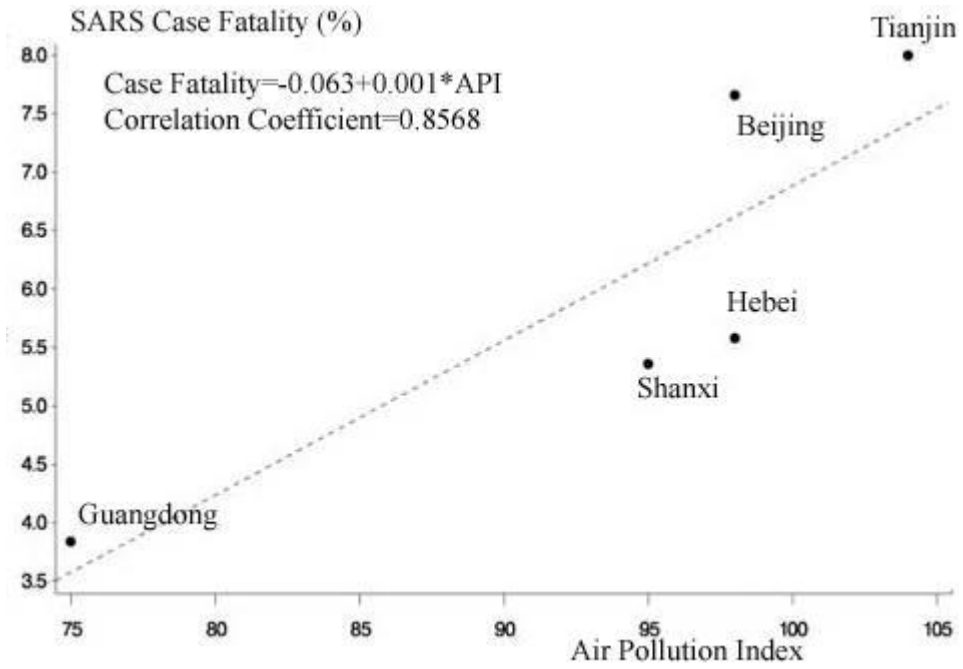




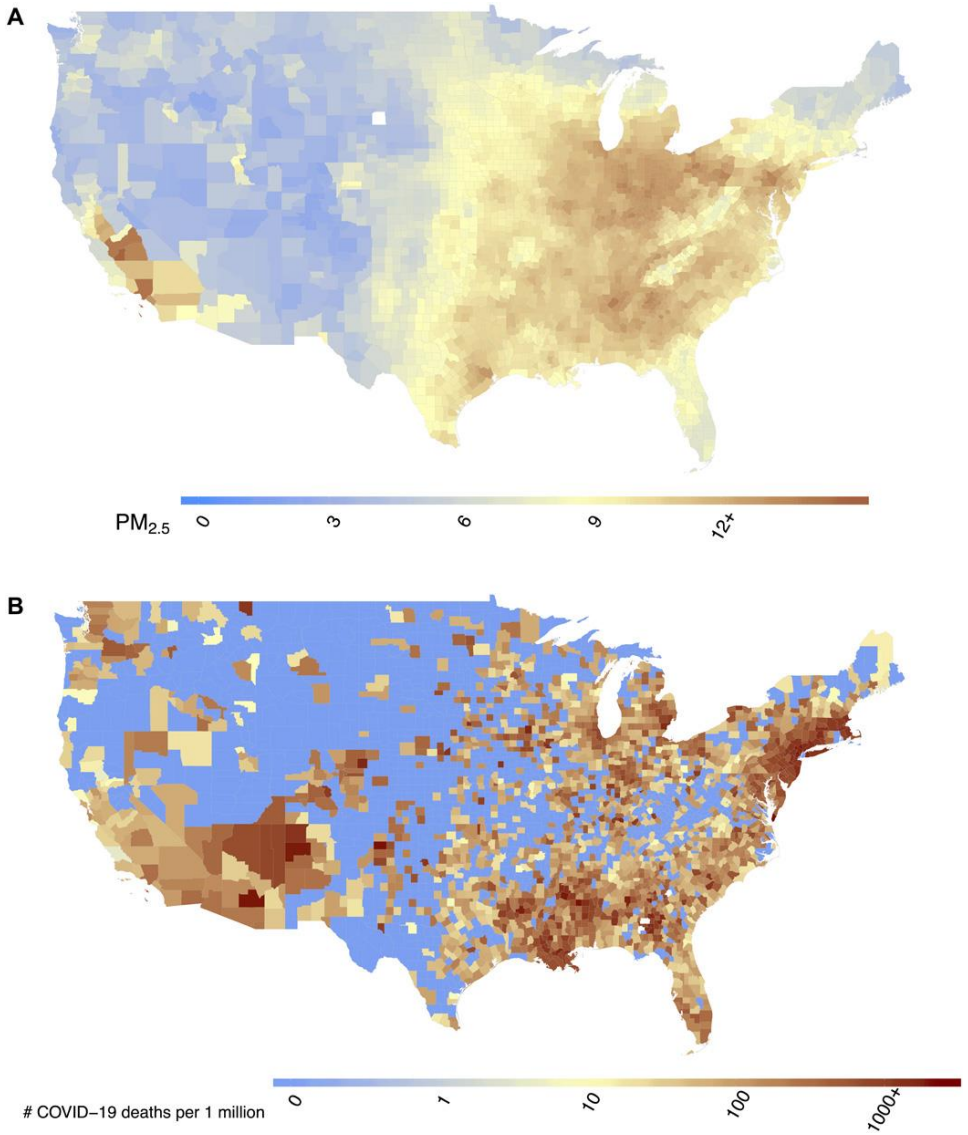
EXPOSURE TO PM INCREASES SEVERITY OF COVID

2021/08/19
https://coronavirus.jhu.edu/map.html

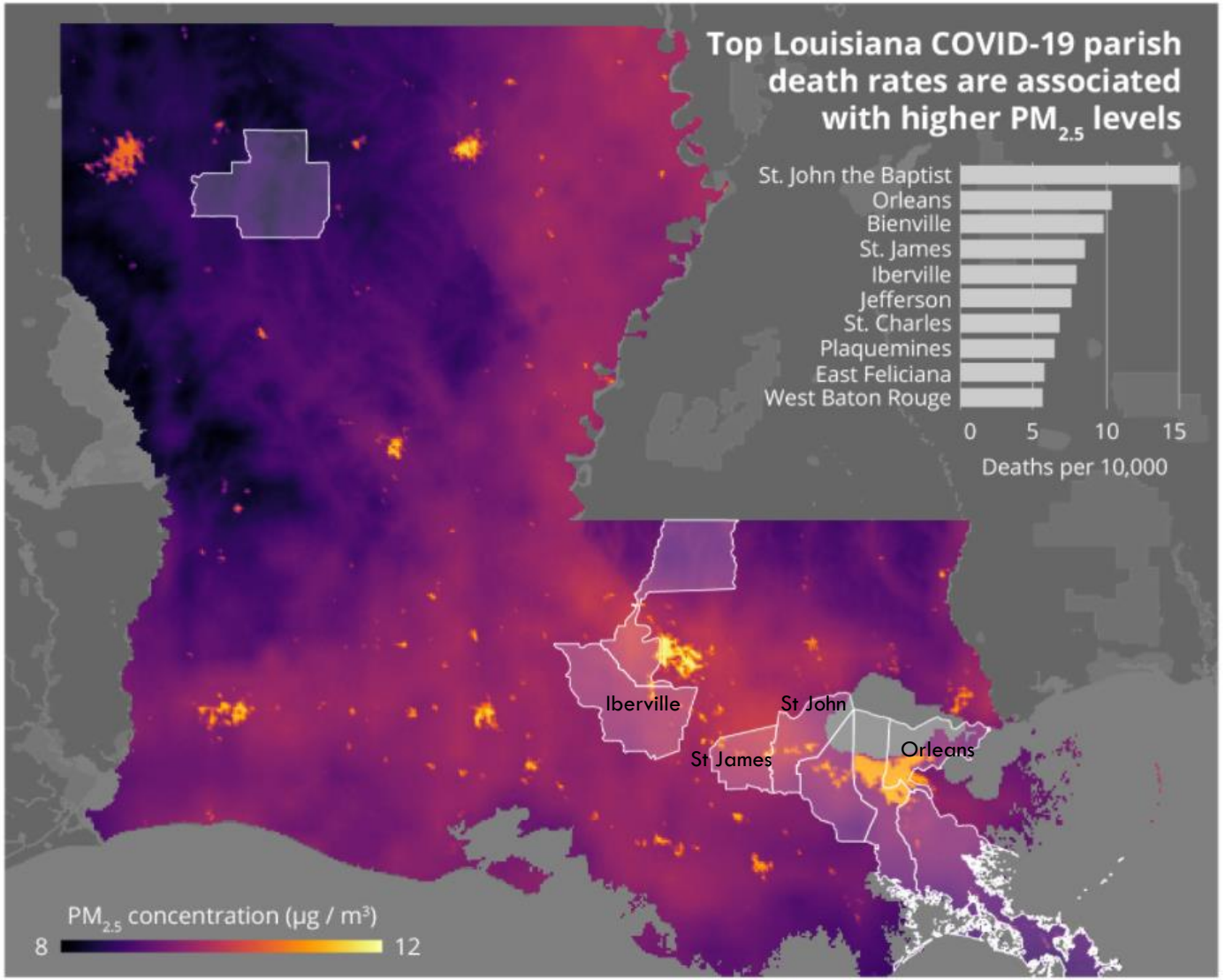
SARS PATIENTS FROM REGIONS WITH MODERATE APIS HAD AN 84% INCREASED RISK OF DYING



PM2.5 CONCENTRATIONS AND COVID-19 DEATHS



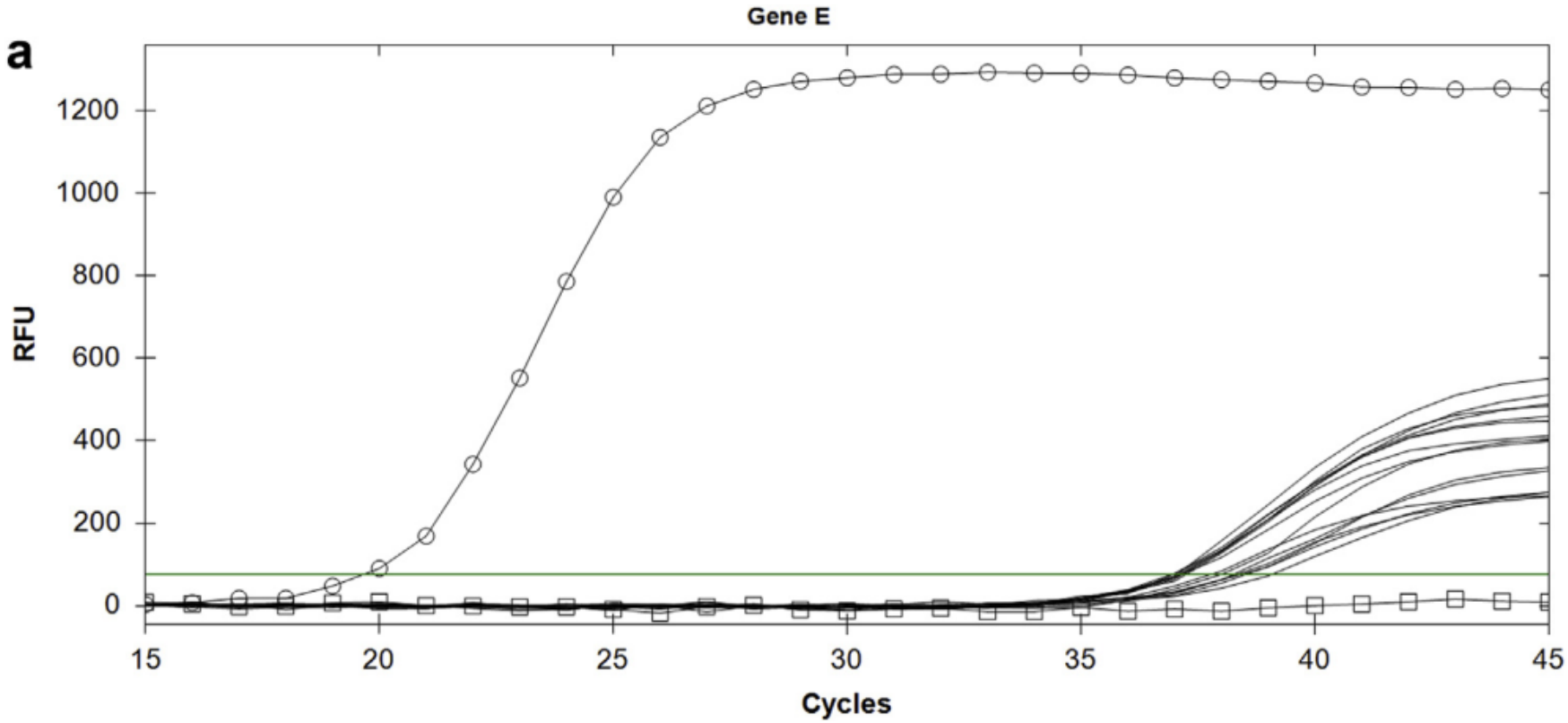
X. Wu et al. Sci Adv 2020;6:eabd4049



Source: K. Terrell / U.S. Census / Louisiana Department of Health / van Donkelaar et al. 2019
Data as of April 26, 2020. Particulate matter concentrations represent 17-year averages (2000–2016).

grist

VIRAL HITCHHIKING?



Setti et al. 2020. Environmental Research

FREE RADICAL INDUCED VIRAL MUTATION

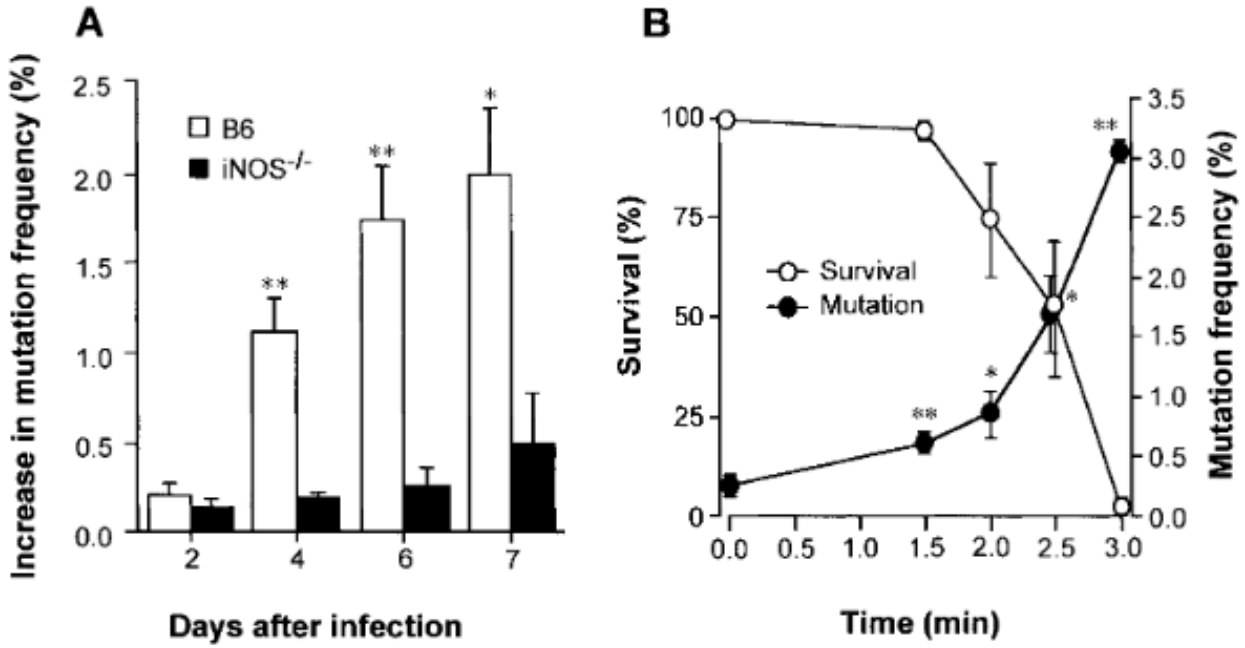
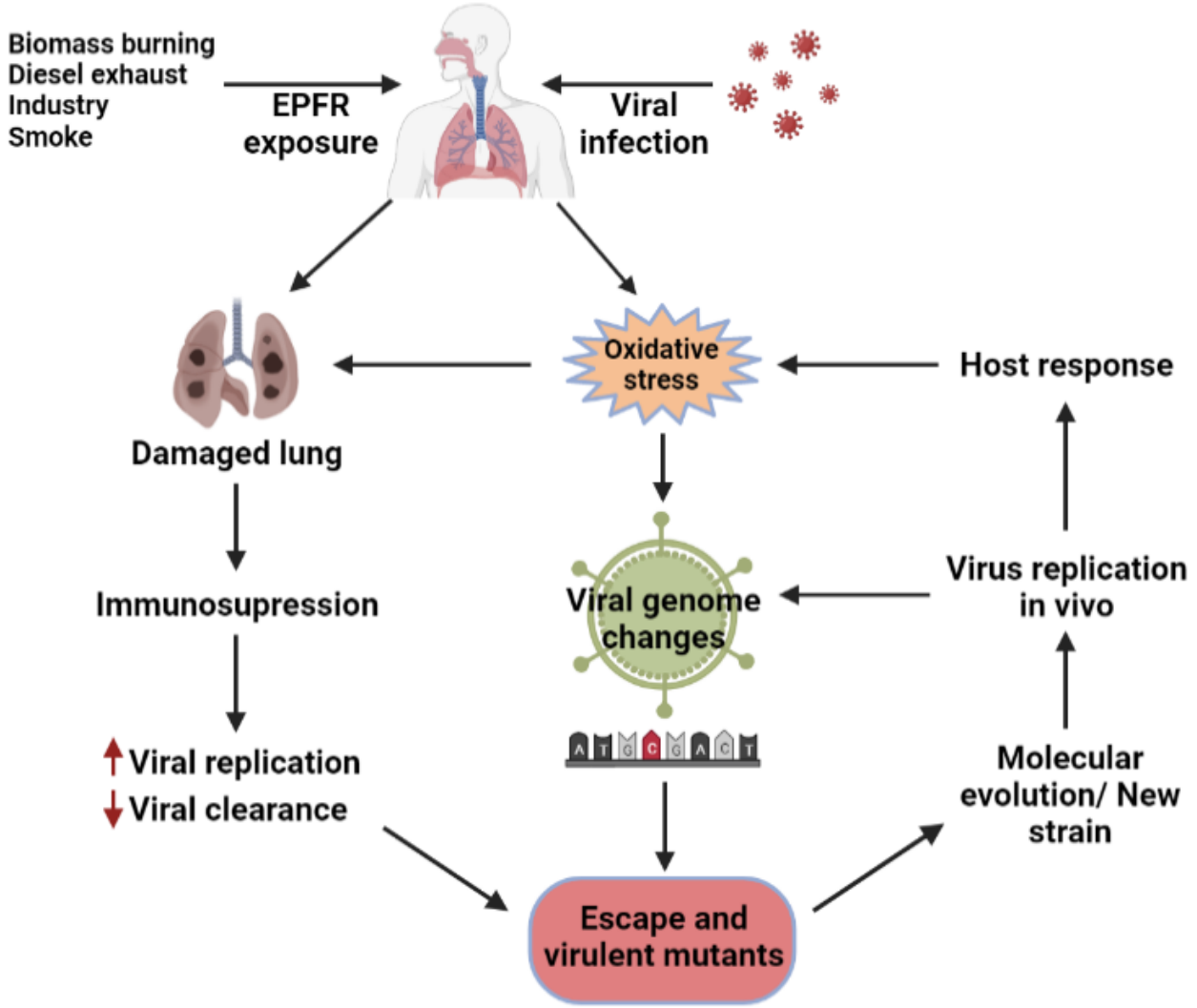
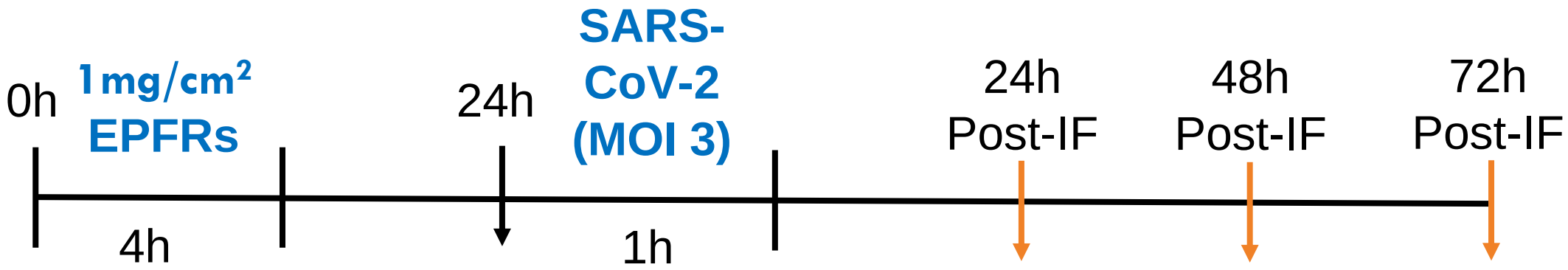


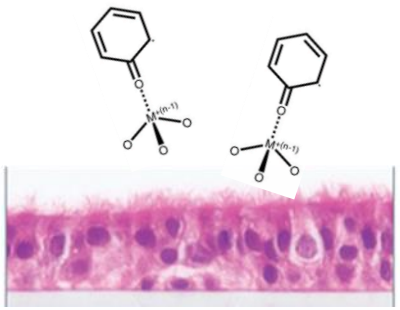
Figure 5. NO-dependent SeV mutation as revealed by genetic mutation of GFP in a recombinant SeV (GFP-constructed SeV, GFP-SeV). (A) The mutation frequency of the virus (GFP-SeV) isolated from the lung of wild-type B6 mice and iNOS$^{-/-}$ mice was quantified by use of the GFP-based mutation assay. (B) Increase in mutation frequency of SeV by $ONOO^-$. GFP-SeV was treated in a constant-flux $ONOO^-$ (0.8 μM) system, and the mutation frequency was determined by the GFP-based mutation assay. Data are mean ± SEM ($n = 4$). *$p < .05$, **$p < .01$, compared with controls or iNOS$^{-/-}$ mice (t-test). Adapted from Akaike *et al.* [45] by copyright permission from Federation of American Societies for Experimental Biology

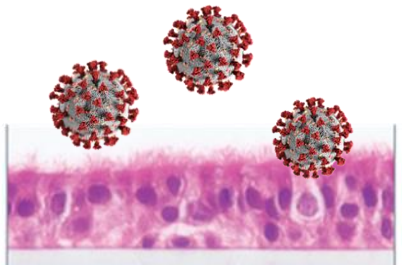
POSSIBLE ROLES OF FREE RADICALS IN VIRAL MUTATION/EVOLUTION



EXPOSURE SCHEMATIC & PROTOCOL – AYAHO/SLY







- Supernatant collection
- Viral RNA extraction
- RNA sequencing

Unpublished data removed

Gordon, D.E., et al. Nature 2020

Unpublished data removed

Unpublished data removed

Unpublished data removed

Unpublished data removed

KEY RESULTS

Exposure to EPFR containing PM

- Increased morbidity and mortality from influenza virus infection
  - Oxidative stress required
  - Supplementation with antioxidants reduced lung injury and improved survival
- Correlates with
  - Enhanced pneumonia risk in a pediatric population
  - Increased incidence respiratory tract infections in exposed communities

- COVID
  - Rapid changes in SARS-CoV-2 viral genome (evolution)
    - Increase in variants
    - Increased risk of vaccine escape
  - Increased morbidity and mortality in areas of high PM

Thevenot P, et al. AJRCMB. 2013. 48:188-97.
Balakrishna S, et al. PFT. 2011;8:11.
Wang P, et al. AJRCMB. 2011. 45: 977-983

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LSU SUPERFUND Research Center

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  - Early programing in RSV Infection in infants
- NIGMS: U54 GM104940-05S3 (Kirwan - PI)
  - TEST UP-BR:Transforming Community Engagement to Increase SARS-CoV-2 Testing in Underserved Populations in Baton Rouge
- LAGOV: 2000501266
  - School Surveillance Testing – special needs elementary school
- Merck Investigators Studies Program
  - Targeting the viral and human host factors governing COVID19 disease to inform individual and population biomarkers of immunity and therapeutic development

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QUESTIONS?

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