THESIS

# STUDYING THE IMPACT OF AIR POLLUTION AND PESTICIDE MIXTURES ON RESPIRATORY HEALTH IN FRESNO AND TULARE COUNTIES OF CENTRAL CALIFORNIA

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In partial fulfillment of the requirements

For the Degree of Master of Science

Colorado State University

Fort Collins, Colorado

Spring 2022

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# ABSTRACT

## STUDYING THE IMPACT OF AIR POLLUTION AND PESTICIDE MIXTURES ON RESPIRATORY HEALTH IN FRESNO AND TULARE COUNTIES OF CENTRAL CALIFORNIA

Residents of California's Central Valley are exposed to some of the worst air quality in the United States, as well as high levels of pesticides owing to the region's large agricultural economy. There is ample evidence that exposure to air pollution is associated with adverse respiratory health outcomes, and some evidence from occupational and community-based studies that exposure to pesticides has negative impacts on respiratory health as well. Epidemiologic research on air pollution and pesticides often considers these exposures one at a time in relation to health outcomes, but humans are exposed to pollutants simultaneously in mixtures. In this study we used multiple linear regression models to look at linear relationships of three criteria air pollutants and biomarkers of organophosphates (dialkyl phosphates or DAPs) with urinary leukotriene E4 (LTE4), a biomarker of respiratory inflammation, in participants in four Central California communities (n=80). We then used Bayesian Kernel Machine Regression models to study these criteria air pollutants and DAPs as a mixture and determine if this mixture had a relationship with respiratory health in this population. We also studied these relationships at two different times of the year (January and June) to study whether and how this relationship between an air pollution-pesticide mixture and the respiratory health outcome changed seasonally. Our multiple linear regression

models revealed that dimethyl phosphates had a statistically significant association with respiratory health in January, which suggests that LTE4 can be used as a biomarker for respiratory inflammation in populations with low asthma prevalence. The results of our BKMR analysis were not statistically significant but did suggest interactions between the exposures in our air pollution-pesticide mixture. Despite a small sample size, this study adds to the limited research on environmental mixtures, and the effects of pesticide exposure on respiratory health.

# ACKNOWLEDGEMENTS

It would be incredibly remiss of me not to thank the many people who helped me write this thesis and earn my Master of Science degree in Environmental Health. The faculty and students at the College of Veterinary Medicine and Biomedical Science, as well as the Colorado School of Public Health have been such a pleasure to work with, and their commitment to public health and service makes me certain that I made the absolute best decision to study at Colorado State University.

I owe a tremendous amount of gratitude to my thesis advisor Dr. Sheryl Magzamen. Dr. Magzamen made me feel welcome in the ERHS department from the minute we first spoke over the phone, and has been a supportive, enthusiastic, and thoughtful mentor from the beginning. Not only has Dr. Magzamen shared her wealth of knowledge and expertise with me, but she has shown concern and interest for my own wellbeing as a colleague and friend. I'm very thankful for the other members of my thesis committee as well. It was a pleasure to be Dr. Joshua Schaeffer's teaching assistant for Environmental Health 220, and I thoroughly enjoyed learning the basics of environmental health this way. I am so glad to have met Dr. Angela Bosco-Lauth through my teaching assistantship as well and am thankful for the thoughtful insight she has provided to me regarding veterinary medicine in public health, and the One Health movement. And of course, I want to extend a huge thanks to Dr. Brooke Anderson, my second advisor. Dr. Anderson has not only exposed me to the exciting fields of weather, meteorology, and natural disaster epidemiology, but has greatly helped me to improve

my writing and communication skills, not to mention teaching me how to program in R. I'd be hard pressed to find a better thesis committee!

The entire Magzamen lab group has been a consistent sounding board for my thesis and other writings and presentations. I will miss seeing their faces over Microsoft Teams but am grateful for the time I had as a part of this group. I can't thank Grace Kuiper enough for the many hours she spent helping me to make sense of R code and the CMAQ data. Beth Lunsford also deserves recognition for helping me create maps of air pollutants over California. Sherry WeMott has supplied great moral support for writing, as she was completing her thesis at the same time as me. This thesis wouldn't have gotten off the ground without Lauren Hoskovec, who was kind enough to take the time to show me how to use the *bkmr* package in R and understand Bayesian Kernel Machine Regression. Dr. Shantanu Jathar supplied me with CMAQ datasets on air pollutants from the EPA, and his graduate student Ali Akherati also assisted with teaching the fine details of the data. Dr. Sheena Martenies supplied me with code to open and read the CMAQ files in R and met with me over Microsoft Teams to explain it. I must acknowledge Dr. Molly Gutilla for her role in helping me to hone practical professional skills that an epidemiologist needs in the workforce, including learning SAS and developing a public health leadership philosophy. Dr. Gutilla also got me involved in the MASCUP! study, where I assisted with mask surveillance, and she looked over my resume and cover letter and helped me to land my first public health job with the CDC. My mom, dad, and two sisters Ellen and Marianne have been encouraging and supportive of my education through everything, and of all my endeavors both personal and professional. I love them very much and look forward to spending time with them

after graduation. My friends Sulaiman Raja, Catherine Jaffe, Corey Gillette, Lucas Wiseman, Chase Metherd, and Tim Fischböck have been present through this entire process and have always reminded me that I have people to fall back on. Another good friend of mine, McKenna Considine from the University of Wyoming, is a big part of the reason I am here at all. Our phone conversations a little more than two years ago led to my sudden decision to become an epidemiologist and study environmental health.

Finally, I want to say thank you to the close friends I've made during my time in graduate school. Many thanks to my buddy Robert Fathke, not only for braving the statistics and epidemiology courses with me, but for being around to hike, fish, snowshoe and just hash things out over a beer when it was needed. Thanks a lot to Kat Kowalski for being supportive and encouraging, even after Covid-19 prevented us from being office mates. Thank you to Andrew Sustar, especially for providing some comic relief and for getting me out of the house to try new things like disc golf.

Being an environmental health graduate student has transformed the way I think about the planet, society, and service. It has also provided me with useful skills and understanding to forge a career in science. But the best part of it all has been the people. I'm thankful for meeting them and know that the bonds I made here will last well beyond school.

TABLE OF CONTENTS

# CHAPTER 1: LITERATURE REVIEW

In this chapter I will review the scientific literature on ambient air pollution, pesticides, multi-pollutant mixtures, and their associated effects on respiratory health. I will first describe the science of air pollution, the sources (both anthropogenic and biogenic), and the conditions that facilitate poorer air quality. This background is key to understanding the context of Central California's pollution exposures. I will then highlight some of the events that led to recognition of air pollution as a health hazard, and some of the steps that have been taken to limit exposure. After this I will describe the science of synthetic pesticides, how they came into use, and the documented health impacts. Next, I will explain the tools epidemiologists and other environmental science researchers use to measure exposure to air pollution as well as pesticides, before concluding with a review of the small body of literature surrounding multi-pollutant mixtures, a research direction that is gaining more traction as scientists consider how people are exposed to environmental exposures simultaneously that widely differ in composition.

## Air Pollution

### *Sources of Air Pollution*

Ambient air pollution is comprised of a mixture of different particles, gases, and vapors that result from both natural and anthropogenic activities.[1] Some examples of natural sources of air pollution include dust and gases from volcanic eruptions, smoke from forest fires, and biological materials such as mold spores, pollen, and other organic materials from animals and plants.[1] Chemical plants, incinerators, factories and manufacturing plants, oil refineries, and electric generating plants are stationary examples of

anthropogenic air pollution. A significant amount of anthropogenic air pollution is emitted from mobile sources such as motor vehicles, which contribute roughly half of volatile organic compounds and nitrous oxides (two large components of smog), nearly 75% of all manmade carbon monoxide, and more than 50% of emissions of toxic air pollutants in all air pollution.[1,2]

*Factors that Influence Air Pollution Severity*

There is an axiom in the environmental sciences that "the solution to pollution is dilution," and many of the factors that influence air pollution severity are related to the ways in which air pollutants either disperse throughout the atmosphere or accumulate at higher concentrations. Below I will discuss several of the meteorological and topographic factors that influence the dispersion and accumulation of air pollution.

*Precipitation and Relative Humidity*

Precipitation has been shown to have a cleansing effect on air quality, by washing away particulate matter and dissolving other pollutants that are soluble.[3] The raindrops attract aerosol particles as they fall through the atmosphere in a process known as coagulation.[4] Researchers at MIT observed that coagulation of rain drops and pollutants was most efficient when the rain drops were small and in relatively low humidity.[4,5]

Despite the findings of the MIT researchers, studies from India and China have found the relationship between relative humidity and air pollution less conclusive. [6,7]

*Inversions*

Temperature inversions are an atmospheric phenomenon that occur when warm air lies above cold air.[1,8] In the context of air pollution, an inversion acts as a lid that prevents air pollutants from rising and dispersing into the atmosphere, because the cooler air is more

dense and heavy than the warm air, thereby trapping pollutants underneath the layer of warm air.[8] This is the reverse of the more typical scenario in which solar radiation warms the earth's surface and creates a convection current of warm air below dispersing air pollutants into a cooler atmosphere above, away from the breathing zones of people.[1]

In an inversion the atmosphere is very stable, and this atmospheric stagnation contributes to poor air quality because the conditions are not conducive to the vertical mixing of air particles (including air pollutants) that helps to dilute them.[8] However, the region of air below the inversion, known as the mixing layer, is relatively unstable and allows for vertical mixing. The depth of the mixing layer (mixing depth) influences how well air pollutants can disperse.[8] The mixing depth becomes more shallow when the inversion lowers, and compresses the air pollutants into higher concentrations.[8] Conversely, the mixing depth increases when the inversion rises, and allows air pollutants to be dispersed throughout a wider volume of air, and thereby decrease their concentration.[8]

Radiation inversions (also called surface inversions) are typically short-lived inversions that form at night or in the early morning when the atmosphere is stable, wind is light and the sky is clear.[8] As the sun rises, it warms the earth's surface and leads to convection of warm air up into the atmosphere.[8] This convection causes the atmosphere to become more unstable and weakens the inversion, allowing pollutants to disperse more easily by early afternoon.[8] For these reasons, the levels of air pollution can fluctuate throughout the day in a single area.

Subsidence inversions, which form as the air above a deep anticyclone sinks (subsides), can last for much longer than radiation inversions, sometimes for days on

end, and they form when high atmospheric pressure causes air to sink over a wide area, and to heat up as it compresses.[8]

*Wind*

Wind influences the concentrations of air pollution by acting as a diluter. Air pollutants are dispersed more quickly by strong winds that create swirling eddies, which mix air pollutants with surrounding cleaner air and thereby lower the overall concentration of pollutants.[8] When winds are lighter, coupled with low vertical mixing, atmospheric stagnation can occur.[8]

However, while higher winds are associated with higher dispersion of air pollutants, wind can also transport air pollution from its original source to other areas downwind, sometimes over great distances. In the United States, the term interstate air pollution transport is used to describe the movement of air pollution across state borders, and this can contribute to the failure of states downwind of pollution sources to meet air quality standards.[9]

*Heat and Sunlight*

Clear days with sunshine are associated with the formation of smog because smog forming chemical reactions occur in the presence of sunlight, and heat speeds up the rate of these reactions.[3,8] For example, ground-level ozone (the main contributor to photochemical smog, sometimes known as Los Angeles-type smog), forms in the presence of sunlight when nitrogen oxides from industrial and vehicle emissions react with volatile organic compounds.[1,3,8,10]

Summertime, which is typically the hotter, sunnier season in the northern hemisphere, can increase the levels of ground-level ozone related air pollution. This is the case in the

Colorado Northern Front Range, which often experiences high ozone levels above what is deemed healthy by the National Ambient Air Quality Standards (NAAQS) in the summer months.[11]

*Topography*

Topography has a significant impact on the air quality of a geographic region, in many ways because topography influences the meteorological influences mentioned above. Air pollution tends to settle in valleys where surrounding mountains and hills prevent wind from dispersing pollutants, as is the case in cities like Los Angeles, Fresno, Salt Lake City, and Denver.[8,12,13]

Additionally, mountains and valleys collect cooler air and are often responsible for creating conditions ideal for the formation of temperature inversions, which occur when cool air is trapped under a layer of warmer air. Wintertime is often a season of temperature inversions in parts of the United States where mountains and valleys can collect cold air.[14] The Central Valley of California is prone to these winter temperature inversions, as is the Salt Lake Valley in Utah,[14] the inland valleys of Alaska where Fairbanks is situated,[15] and parts of the Mid-Atlantic Piedmont region in North Carolina and Virginia, where cold easterly winds are unable to disperse over the Appalachian mountains.[14]

Outside the United States, topography influences air quality in Beijing, which also sees increases in temperature inversions in the winter. The Chinese city of more than 20 million people is located in a region where two mountain ranges come together, making it difficult for incoming weather to disperse the already high levels of air pollution, and providing the ideal conditions for trapped cold air to create deadly inversions.[14]

*Historical Air Pollution Events*

Several historical environmental health crises led to the understanding of air pollution as a threat to human health. One of the notable 20th century cases occurred in the Meuse Valley of Belgium in 1930, near the city of Liège. This valley had a high concentration of smelters, foundries, coke ovens, and mills as part of the local steel industry operations, and levels of sulfur dioxide, sulfuric acid mists, and fluoride gases rose to unhealthy extremes that resulted in a mortality rate ten times that of what was normal.[16] Steel mills, along with iron mills, coal fired home stoves, and coal burning factories were similarly responsible for a catastrophic smog event in Donora, Pennsylvania in 1948, where an air inversion caused high levels of air pollution to cause illness in the about half of Donora's population.[1,17] This air pollution event, which lasted from October 27th, to October 30th, resulted in 400 hospitalizations and 20 deaths.[17] The London Fog of 1952, which resulted from coal and other fossil fuels being used to heat homes in London, England is the event that is thought to have catalyzed interest in air pollution research, after 3,000 excess deaths were reported from December 5th, to December 9th.[1,16]

*Health Effects of Air Pollution*

At present, the effects of air pollution on respiratory health are well documented. The landmark Harvard Six Cities study in 1993, documented an association between air pollution in the form of particulate matter, and increased risk of dying of all causes, including cardiovascular and respiratory health outcomes.[18] Prior to the Harvard Six Cities study, particulate matter ($PM_{2.5}$ and $PM_{10}$) were not criteria air pollutants, but in 1987 $PM_{10}$ began to be regulated by the National Ambient Air Quality Standards (NAAQS) set by the EPA, and $PM_{2.5}$ began to be regulated in 1997.[1,19] The US Environmental Protection

Agency's Integrated Science Assessment for Particulate Matter documents many of the known effects of inhaling particulate matter, which include decreased lung function and aggravated asthma.[20]

Some symptoms and health effects of acute exposure to ambient air pollution include irritation of the eyes, nose, and throat, aching of the lungs, coughing, wheezing, bronchitis, pneumonia, nausea, headaches, and difficulty breathing.[1,2,21] More chronic effects of exposure to air pollution include heart disease, chronic obstructive pulmonary disease (COPD), lung cancer, and death.[1]

*Disease Burden and Geographic Scope of Air Pollution*

Globally, air pollution is a leading contributor of disease burden and death, and levels of air pollution are high in many low and middle income countries.[22] Deaths attributable to particulate matter are particularly high in countries such as Egypt, Iran, Pakistan, India, Bangladesh, and China.[22] Despite positive air quality gains due to environmental regulations in many high income countries, air pollution remains a problem in the United States as well, with estimates from the American Lung Association that approximately half of Americans live in counties with unhealthy levels of particulate matter and ozone.[23] Levels of air pollution are especially high in California, with the Central Valley experiencing some of the United States' worst air quality.[24]

*Regulation of Air Pollution*

The US Environmental Protection Agency regulates certain common air pollutants known as criteria air pollutants, which include ozone, nitrogen dioxide, carbon monoxide, particulate matter, sulfur dioxide, and lead.[1,25,26] When present at high levels outdoors, these criteria pollutants have negative environmental impacts, particularly on vegetation

and waterways.[26] These air pollutants also have significant impacts on human health, especially respiratory health.[26]

In 1987, the World Health Organization set certain standards called the Air Quality Guidelines, for assessing air pollution exposure risk and mitigating health impacts of air pollution.[27,28] The 1990 Clean Air Amendment was passed in the United States in response to growing air pollution threats such as acid rain and the depletion of the ozone layer,[29] though the regulations set by the World Health Organization are more stringent.[19,28]

In summary, air pollution comes from a wide variety of anthropogenic (e.g., powerplants, automobiles) and naturally occurring sources (e.g., volcanoes, forest fires, pollen). Meteorologic and topographic factors such as sunlight, heat, wind, precipitation, and presence of mountains and valleys, influence the severity of air pollution and how well it either accumulates in areas or disperses into the environment. Air pollution has well documented associations with health impacts that include asthma, chronic pulmonary lung disease, lung cancer, and death, and though the disease burden of air pollution is high in low-income countries, certain parts of the United States also suffer from severe air pollution. In response to the increased awareness of air pollution's deleterious impact on human well-being, the US EPA and World Health Organization (among other organizations) now regulate criteria air pollutants and have established air quality guidelines. In the U.S. these regulatory programs and guidelines have seen success, as the total emissions of criteria pollutants have declined by 73% between 1980 and 2020, despite the U.S. experiencing an increase in population, GDP, energy consumption, and number of miles driven by vehicles in the same period.[30] Unfortunately, these programs

cannot regulate or enforce ambient air pollution deriving from natural sources such as volcanic eruptions and wildfires. This is likely to become an increasingly pressing environmental health problem as a warming climate catalyzes increasing wildfires in the Western US; in 2021 Denver and Salt Lake City ranked among the worst major cities in the world for poor air quality due to air pollution from wildfires in California and Oregon.[30,31]

## Pesticides

### *Uses and Taxonomy of Pesticides*

Pesticides are chemicals designed to deter or kill organismal pests, often to protect agricultural crops and control the spread of vector borne illnesses. For this purpose, pesticides have been highly effective, and it is estimated that agricultural pesticides have been responsible for 300 to 600% increases in yields for some food and fiber crops.[32] One of the world's most famous pesticides, dichlorodiphenyltrichloroethane (DDT) has been instrumental in saving many lives worldwide by controlling anopheline mosquitos and malaria and yellow fever.[32]

Pesticides have cytotoxic effects on the unwanted organisms they are designed to kill,[33] and are often classified and named after these organisms, such as herbicides (the most widely used pesticides globally), fungicides, rodenticides, insecticides, nematocides, acaricides, and molluscicides.[32–34] Pesticides are also classified based on their chemical structures. Chemical classes of pesticides include inorganic and organic metals, organochlorines, organophosphorus compounds, carbamates, pyrethroids, substituted phenols, and many others.[32–34]

*Environmental and Public Health Implications of Pesticide Use*

Despite the many advantages pesticides have conferred to modern civilization, there have been consequences to their widespread use, notably environmental contamination.[32] Rachel Carson's groundbreaking book *Silent Spring* sounded the alarm for the environmental effects of DDT on wildlife, agriculture, livestock, pets, and human health. DDT, an organochlorine, was banned in 1972 in the United States,[32] and was banned worldwide at the Stockholm Convention, though in countries where malaria is endemic such as South Africa, it has been grandfathered in for use.[35,36] Since then there has been more scrutiny on the toxicity of pesticides in use. Organochlorines have largely been phased out of agricultural and insect control operations, being replaced by organophosphates and carbamates, which have less persistence in the environment.[32] Generally, organophosphates, which are derived from phosphorus-containing acids,[37] are characterized by being applied at a low vapor pressure, having slight to moderate water solubility, moderate to high soil binding, and varying degrees of soil leaching.[38]

Organophosphates inhibit cholinesterase, an enzyme responsible for breaking down acetylcholine, a major neurotransmitter in the body [38,39] Humans generate two types of cholinesterase (RBC cholinesterase and plasma cholinesterase)[39] in the liver. When these enzymes are inhibited, the result is an excess of acetylcholine in the central and peripheral nervous systems, eventually leading to neurologic dysfunction.[38,40,41] In laboratory settings, a decrease in cholinesterase activity is used to confirm acute poisoning due to organophosphates.[39]

Due to acetylcholinesterase inhibition, organophosphates are considered more dangerous to human health than other pesticides, such as most herbicides, and a class of pesticides known as pyrethroids.[32]

Although the Food Quality Protection Act of 1996 began phasing out the residential use of organophosphates, pesticides are still widely used in the United States in agriculture, to protect crops from various insect pests.[38] Organophosphate insecticides are also still used in public health applications, for example making use of malathion and naled in mosquito control.[38] The United States Environmental Protection Agency lists roughly 40 different organophosphate pesticides for use.[38] In the United States, acceptable levels of organophosphates in the workplace, home, and on food, have been established by several federal agencies including the FDA, USDA, EPA and OSHA.[38] Routes of exposure to humans include ingestion (often on food or in drinking water),[38] dermal absorption (a common occupational exposure route for agricultural workers),[42] and inhalation.[42]

*Health Effects of Organophosphates*

Symptoms of moderate exposure to organophosphates include headache, dizziness, weakness, nausea, vomiting, fasciculations of the eyelids and skin, blurred vision, and sweating.[39,40]

Literature documenting the respiratory health effects of exposure to agricultural pesticides typically falls into two major categories. The first category is occupational exposures to pesticides. The second is pesticide exposure in the general population, which often includes studies investigating health effects in children. In this section I will describe what

each of these two categories of research has revealed about the association between pesticide exposure and respiratory health.

*Occupational/Agricultural Exposures*

Occupational studies on pesticides primarily focus on agricultural workers, who often have chronic exposure at high doses over extended periods of time. Farmers as an occupational group are at especially high risk for asthma and other respiratory diseases due to their frequent exposure to bioaerosols, dust, and pesticides.[43]

Understanding the role of pesticide exposures on respiratory health has been informed by the Agricultural Health Study, which is a cohort study of farmers and pesticide applicators in Iowa and North Carolina. Research from this cohort has suggested an association between pesticide application and self-reported wheezing symptoms.[43] In particular, chlorpyrifos, malathion, and parathion, which are all organophosphate pesticides, showed a dose-dependent relationship with wheeze.[43]

Using the same cohort data, researchers also discovered evidence of pesticide use in the Agricultural Health Study cohort, both on and off the farm, being associated with risk for chronic bronchitis.[44] It is of course important to note here that a particular limitation of data from the Agricultural Health Study is that it is derived from self-reported accounts of exposure, which introduces the possibility of recall bias.

*Community Exposures*

There is a large gap in the literature between occupational exposures to pesticides, and low-dose exposures that the general population experiences through the environment.[45] Low doses of many pesticides are hard to detect, and organophosphates, pyrethroid insecticides, and phenoxyl herbicides all have short half-lives, making the time frame for

detecting them smaller.[45] DDT, an organochlorine that is now banned in the USA, is an example of a pesticide that is easier to detect as it is slow to leave the body.[45]

Exposure to organophosphate pesticides *in utero* has been associated with decreased lung function in children.[46] A study based on a birth cohort of children born to women living in an agricultural study found that for every tenfold increase in organophosphate metabolites measured in urine, a 159 mL/second decrease in forced expiratory volume (FEV1) was observed, which is more than the decrease in FEV1 from passive pediatric exposure to maternal cigarette smoke.[46]

There is also evidence of a relationship between prenatal pesticide exposure and poor respiratory health outcomes in the first year of life.[47] This prospective birth cohort study of pregnant women and their children living near banana plantations in Costa Rica found that mancozeb measured by the urinary metabolite ethylenethiourea (ETU), was associated with lower respiratory tract infections in infants whose mothers were in the highest quartile of urinary ETU concentrations during the first half of pregnancy.[47]

Little is known about the impacts of pesticide exposures on respiratory health in rural areas,[33] despite the fact that people living close to agricultural fields where pesticides are sprayed are often in rural areas. A study in rural France sought to close this knowledge gap with a study on schoolchildren near vineyards that were sprayed with fungicides and insecticides.[33] This study was conducted over two periods, once in the winter, when the fields and vineyards were not sprayed, and once during the summer when the fields were treated with pesticides. The researchers discovered that even during the winter when the fields weren't sprayed, urinary levels of ETU, a biomarker of dithiocarbamates, was detected in a proportion of the children. Ultimately, results showed an association

between ETU and increased risk of asthma and rhinitis symptoms in the schoolchildren. Overall, children living near vineyards in rural areas were at a heightened risk for airborne dithiocarbamate exposure in the summer period.

In summary, pesticides have been developed to control, deter, and kill unwanted pests to protect agricultural products and protect humans from vector-borne disease. Because pesticides are cytotoxic, they have not been without their drawbacks, especially regarding human and environmental health. Although some of the most toxic pesticides like DDT have now been banned, other types of pesticides including organophosphates are largely still in production for agricultural purposes. The limited research on pesticides and respiratory health has revealed associations between coughing, wheeze, and decreased lung function among other impacts, largely gleaned from occupational studies of pesticide use, and studies of community exposure to pesticides in agricultural areas.

**Air Pollution Exposure Assessment**

Typically, humans are exposed to air pollution through the route of inhalation. Quantifying inhalation exposure to air pollution requires information about the concentration of pollutants in the air being breathed, and the duration this air is breathed by individuals. There are different methods and tools used for assessing this exposure, and in this section I will describe their uses, as well as the benefits and limitations. First, I will describe some of the different types of sensors and instruments used, which provide direct measurements of air pollution. Sensors produce direct measurements of air pollution at a particular place in time and space, often as part of large monitoring networks, but also as personal monitoring devices. I will also describe how certain biological processes can be used to infer indirect measurements or exposures to air

pollutants. Next, I will discuss modeling, which is another method of assessing air pollution, especially in situations where the density and/or location of air pollution sensors and measurements is not sufficient to assess exposure. While models do not give precise measurements, they do provide air quality predictions in time and space where measurements don't exist, which is particularly useful for assessing air pollution in regions without a lot of sensors, such as rural areas. Finally, I will discuss some of the methods of communicating air pollution and air quality data.

**Air Pollution Sensors and Instruments**

Measuring sensors and instruments often come from monitoring stations that are part of large monitoring networks, like the EPA Air Quality Monitoring Stations. The measurement instruments used by these air quality monitoring networks are usually in fixed locations with secure protections including air conditioning to prevent the sensors from overheating, but these monitoring stations are often not at densities sufficient for measuring personal air pollutant exposures, and they are often expensive.[48] However, in recent decades, a number of low-cost sensors have become available.[49] Some, like PurpleAir air quality monitoring sensors, have been installed worldwide and have provided data on ambient air quality that is more spatially-dense than regulatory monitoring networks.[50]

*Gravimetric Instruments*

Air quality instruments that utilize gravimetric methods, usually to measure particulate matter, involve the use of filters that are weighed before and after a given sampling period.[51] Gravimetric methods can also involve the use of impactors, which measure the size distribution of particles by their mass.[51] Impactors quantify particulate matter by

allowing aerosols to pass through a sequence of stages and at each stage particles larger than a certain diameter are collected, so that only the smallest particles remain by the final stages.[51]

Microbalances are another instrument that utilize gravimetric methods. Tapered Element Oscillation Microbalances and Quartz Crystal Microbalances are two popular instruments for this task, and they operate by collecting particles over the oscillatory microbalance element's surface and determine the particulate matter concentration from the alteration of the resonance frequency.[51]

*Instruments that Utilize Optical and Photometric Methods*

Many sensors and air quality instruments use optical methods such as dispersion photometers, which measure the intensity of scattered light due to suspended particles to estimate a measurement of concentration.[51] For certain particulates such as black carbon, light absorption is sometimes measured instead to calculate particulate concentration, and can be done so using instruments such as spot meters, aethalometers, photoacoustic soot sensors, and laser induced incandescence.[51] Opacity meters can be used to measure light extinction of particles.[51]

Photometric methods are similar to these optical methods, and operate by measuring light intensity through various chemical compositions, such as ozone analyzers, which measure UV light absorption to determine concentration of ozone.[48] The ozone analyzer works by using a pump on the top of a 10 meter tipping tower to draw air into a sampling inlet.[10] From here the air is split into two paths: one path is a sample of the ambient air that includes the ozone, and the other path has all of its ozone removed using ozone scrubbers.[10] Finally, the two samples of air including the ozone and the sample without

ozone are exposed to UV light and the intensity of the light that passes through the different air is measured.[10]

*Personal Air Pollution Monitors*

Personal air pollution monitors, which collect information on pollutant concentrations close to the breathing zones of study subjects, are considered one of the most accurate ways of measuring human exposure to air pollution.[52] Many personal monitors are designed to be worn by study participants, which means that the changes in air quality experienced by the study participant going about their daily activities in different places are captured. The size and weight of these monitors has decreased in recent years, and accuracy and efficiency have greatly improved as well.[27]

Personal air pollution monitors have been used in several studies of indoor air quality, particularly in low- and middle-income countries where wood, dung, and other biofuels are burned inside for cooking and heating. Researchers studying women's exposure to fine particulate matter in rural Honduras used lightweight gravimetric monitors called Ultra Personal Aerosol Samplers (UPAS).[53] Another study in Honduras assessed associations between biomass cookstove induced air pollution and blood pressure, by using exposure monitors clipped to the straps of bags they wore during the study, and also monitors installed in the kitchen near the stoves.[54]

Some of the disadvantages of using personal exposure monitors is that they are labor intensive, time consuming, costly, and limit the size of a study population.[27]

## Indirect Measurements of Air Pollution

*Biomarkers*

Biomarkers are a way to measure air pollution exposure because they reflect an interaction between an environmental agent (i.e., air pollution) and a biological system in the body. Numerous biomarkers have been used in studies. For example, volatile organic compounds (VOCs) were detected in condensation from exhaled breath to estimate personal exposure to ambient VOCs.[27] Malondialdehyde in condensation from exhaled breath has been associated with air pollution concentration and changes in lung function in children living in Mexico City.[55]

Some of the advantages of using biomarkers is that they are a safe and non-invasive technique for measuring exposure,[55] and they measure internal dose of air pollution, which is a composite of different exposure routes and mixtures within the body.[27] Some of the disadvantages of biomarkers are that the different pollutants and exposure pathways are difficult to differentiate and identify, since integrated exposure over time is what a biomarker measures.[56] This can sometimes result in levels of air pollution exposure much higher than what the actual exposure is.[56] Another disadvantage of using biomarkers in air pollution studies is that smoking is often a confounding factor.[56] Additionally, there are not biomarkers for every one of the criteria pollutants, so using biomarkers is not comprehensive. Lead is an example of a heavy metal that stays in the body for a long time and therefore acts as a reliable biomarker, both for assessing short term exposure (for example in the blood) and long-term exposure (for example lead deposits in bones and teeth). Air pollutants like $PM_{2.5}$ and ozone cannot be detected this

same way in the body, so the effects of pollutants are measured rather than the direct exposure to them.

*Biomonitoring*

Not to be confused with biomarkers, biomonitors are organisms (usually animals or plants) or materials from these organisms that are used to obtain quantitative information on conditions in the biosphere, such as air pollution.[57] Usually in studies utilizing biomonitoring, changes are observed, either in the organisms' behavior, or in the concentration of chemicals in their tissues.[57] Mosses and lichens are a widely used biomarker because they are thought to obtain minerals as well as pollutants through the air, since they lack root systems like vascular plants.[57] Ozone damage to plants is being used by the City of Fort Collins, Colorado at the to demonstrate the negative impacts of ozone to visitors.[58] Colorado State University and The Gardens on Spring Creek partnered with the city to install an ozone monitoring station that uses ultraviolet to measure ozone and display the levels to visitors.[59] The monitoring station is surrounded by ozone-sensitive plants.[58]

**Air Pollution Modeling**

The different sensors mentioned above give specific measurements, either directly (mechanical sensors) or indirectly (measuring biomarkers and biomonitors). These measurements will typically come from stationary sources, or in the case of personal monitoring stations; the specific locations the individual wearing it moves through. However, there are often times when researchers are interested in air quality in rural areas, or areas that may not have many air pollution monitors or sensors. Modeling air pollution is a way to predict air pollution values at times and places where we don't have

direct measurements. Models use measurements at other locations, chemical properties, meteorological conditions, and other factors as inputs to extrapolate air pollution data values where we do not have data.

*Proximity Models*

One of the most basic modeling techniques used for assessing air pollution exposure is proximity modeling, which relies on the assumption that the closer an individual is to a pollution source, the higher their exposure is going to be.[27,60] Proximity to roads and highways is a common way to assess exposure to air pollution in urban settings, and has been demonstrated by several studies to be an accurate proxy for measuring exposure to traffic related air pollution.[27] For example, a study in Ethiopia found a linear relationship between the risk of wheeze, and increased proximity to roads among individuals living within 150 meters of a road.[61] This relationship was stronger (though not significantly so) for proximity to roads with above average traffic volume. [61]

The main advantages of proximity models are the low cost nature of their implementation, and their simple and straightforward assignment of exposure, which makes them ideal for exploratory analysis when the etiology of an exposure is not well understood.[27,60] Proximity models can also be used to estimate a dose-response relationship between pollutant sources and health outcomes of interest, and by observing distance decay and the health outcome of interest.[60] For example, researchers in Hamilton, Canada observed declining risks of asthma with increased distance from roadways.[60] However, an important disadvantage of proximity models is that they are prone to misclassification, especially since meteorological and topographical parameters that influence dispersion

of pollutants are not considered by these models, nor are human behavior parameters that influence exposure.[27]

*Interpolation Models*

Proximity models consider exposure to air pollution (or other pollutants of interest) by measuring an individual or population's distance from the source, but interpolation models create pollution surfaces that can create predictions of pollution levels at specific points away from monitoring stations and measurement instruments. Interpolation surfaces are creating using deterministic and geostatistical techniques that take measurements from known monitoring stations in a study area as model inputs.[60] Kriging is a popular method of interpolating exposure surfaces, and is considered optimal by researchers because the best linear unbiased estimate of the pollutant's value at any point can be calculated.[60] Kriging was used to map a surface of outdoor sulfur dioxide ($SO_2$) concentrations in Prague, Czech Republic and Poznan, Poland, where elevated $SO_2$ levels were associated with wheeze and asthma in Czech and Polish schoolchildren.[62]

A strong advantage of interpolation modeling is that the predicted values on the interpolated surface also come with standard errors that can be used to quantify uncertainty in the predictions, and identify regions of the surface where the interpolation may be less reliable.[60] A disadvantage of interpolation models are that like proximity models, they do not take into account the topographic or meteorologic parameters that also influence values on the interpolated surface.[60]

*Land Use Regression Models*

Land use regression (LUR) models predict pollution concentrations at points on a surface by treating pollution concentrations as the response, and the geographic characteristics

of the study area (traffic volume, topography, etc.), as well as local data on air pollution, as the predictors in the model.[60] Least squares regression in combination with Geographic Information System (GIS) – based predictor data is used to create predictions of pollutants at areas that aren't measured.[63] A research team developed a LUR model to estimate the geographical distribution of $NO_2$ in Montréal, Canada and found that $NO_2$ in the city was associated with the distance to the nearest highway, the traffic count on the nearest highway, length of highways and roads within 100 meters, and population density.[64]

Advantages of LUR models are that they are cost effective, consider environmental factors beyond proximity to a source of pollution or a monitor, and are adaptable to local areas without having to acquire data or additional monitoring.[60] One of the limitations of LUR models is that they require accurate monitoring data at a large number of sites, as they are dependent on the concentration of observations.[60,65] Crucially, LUR models cannot be used for the design of this thesis, because they cannot address multi-pollutant mixtures; LUR models assess pollutants one at a time.[65]

*Dispersion Models and Chemical Transport Models*

Dispersion models are used to predict concentrations of air pollution over space and time by inputting emissions data (from stationary sources like homes, waste sites, and industry or from mobile sources such as vehicles and roadways) and meteorological data (from phenomena such as wind speed, ambient air temperature, etc.).[27] As monitoring data becomes more widely available to researchers, dispersion models have become much more widely used in epidemiologic studies, and have also been integrated with GIS to more accurately assign air pollution exposure. The Near-Road Exposures to Urban Air

Pollutant Study (NEXUS) used dispersion models to assess pollutant levels at varying distances from roads in Detroit, Michigan in order to investigate the relationship between childhood asthma and proximity to roadways.[66]

The main advantages of dispersion models are that they can provide more complete and high-resolution profiles of air pollution (and other environmental exposures).[27] Some of the disadvantages include the inability to require extensive model inputs,[27,60] are expensive to implement,[27] and are hard to implement over large geographic areas.[27]

*Community Multiscale Air Quality Modeling System*

The Community Multiscale Air Quality Modeling System (CMAQ), is a project of the U.S. Environmental Protection Agency that creates models of air pollution to understand and predict concentrations of common air pollutants, taking into account different sources of air pollution, and meteorological conditions like wind and precipitation.[67] Monitoring sites with air pollution monitors exist as point locations, but an advantage of the CMAQ models is that they create a smooth surface by estimating pollutant concentrations in places where there are not sensors or stations.

Air quality models like the ones produced by CMAQ, can be used to simulate hypothetical scenarios in the future, which can be used to explore questions about the impact emission regulations would have on air quality.[67]

**Communicating Air Pollution Exposure**

*Air Quality Index*

The Air Quality Index (AQI) is a way to categorize air quality on a scale from 0 to 500 divided into six groups.[68] When the AQI is between 0 and 50, air quality is considered good and is represented by the color green. Going down the scale, 51 to 100 is moderate

air quality represented by the color yellow, 101 to 150 is air quality that is unhealthy for sensitive groups (older adults and children) represented by the color orange, 151 to 200 is air quality that is unhealthy to the general public represented by the color red, 201 to 300 is very unhealthy air quality that poses increased risk for everyone represented by the color purple, and finally 301 to 500 is hazardous air quality represented by the color maroon.[68]

**Pesticide Exposure Assessment**

Humans are exposed to pesticides via inhalation, ingestion (food and water) , and dermal absorption (contact with skin, often an occupational exposure) exposure routes.[69] Food, water, dust and air can all contain pesticides that humans are exposed to upon contact. There are a wide variety of methods for assessing exposure to pesticides, and each of them come with different sets of advantages and disadvantages for use. Like I did in the section about air pollution exposure assessment, I will use this section to describe the different methods for assessing exposure to pesticides. I will first describe direct methods of assessing exposures to pesticides (biomarkers in urine samples, and personal monitors), and then I will describe more indirect methods of assessing pesticide exposure (questionnaires, surveys, home dust samples). I will then discuss the benefits and limitations of each of these methods.

**Direct Measurements of Pesticide Exposure**

Using direct measurements of pesticide exposure are the best way to gauge an individual's personal exposure to pesticides, which varies over time. Frequency and duration of exposure are used to determine cumulative dose over time.[70] Personal

monitoring devices, and samples taken from individuals are some of the main ways to take direct exposure measurements from individuals.

*Personal Measuring Devices*

Personal devices for monitoring airborne pesticide concentrations can be used to estimate exposure. Pumps and filters that are worn by study participants near their breathing zones are used to measure a point of contact between a person and the environmental medium through which they are exposed to pesticides.[70] To measure dermal exposure to pesticides, skin patch samples can be taken, but they operate using the same logic as the pump and filter personal samplers.[70] The advantage of this method is that it directly measures exposure during a specific monitoring period at the temporal scale of minutes, hours, and days.[70] However, there are several drawbacks to personal monitors, including the reality that they are often expensive and time consuming to use, burdensome to the study participants, and not always suitable for specific pesticides and routes of exposure.[70]

*Biomarkers*

Biomarkers and biological samples are a useful tool for assessing exposure to pesticides because they demonstrate that exposure and uptake of pesticides has indeed happened, and if information on intake, uptake, and metabolism are known for the individual being sampled, an exposure dose can be reconstructed.[70] However, there are some important disadvantages of relying on biological samples and biomarkers as well, including that they generally can't give information about the route of exposure, and often lack specificity for determining the type of pesticides the individual is exposed to.[70] Below I will briefly

describe two biomarkers of importance in assessing organophosphate pesticide exposure: cholinesterase and urinary dialkyl phosphates.

*Cholinesterase Surveillance*

Because organophosphates inhibit cholinesterase, cholinesterase surveillance was once a mainstay method for accessing pesticide exposures in occupational settings. Plasma cholinesterase in particular has been shown to be a great biomarker for organophosphate exposure in the body.[40] However, there are several limitations to this method including being generally inadequate, nonspecific, and unpredictable.[71]

*Dialkyl Phosphates (DAPs)*

Urinary metabolites are another method of detecting exposure to organophosphates that have been proven to be reliable for identifying subtle differences in occupational exposure to organophosphates, as well as detecting incidental exposures in the general population.[71] Results from Canada indicated that urinary DAP levels are associated with reductions in two measures of lung function: forced vital capacity (total amount of air exhaled)(FVC) and forced expiratory volume (FEV1),[72] which suggests that DAPs can be useful in studying the effects of organophosphate exposure on respiratory function. Dialkyl phosphates (DAPs) are urinary metabolites of organophosphates and are broken into six primary types: dimethyl phosphate (DMP), diethyl phosphate (DEP), dimethyl thio phosphate (DMTP), diethyl thio phosphate (DETP), dimethyl dithio phosphate (DMDTP), and diethyl dithio phosphate (DEDTP).[71]

Due to a short half-life, urinary DAPs typically reflect recent exposure in the past several hours or days due to the rapid metabolization and excretion of organophosphates by the body.[73] In general, detection of DAPs in the urine reflects exposure to organophosphates

within the previous two days.[38] This means that acute exposures can be detected easily if urine samples are obtained shortly after exposures, and also that chronic exposures to organophosphates (such as in an occupational setting) will be detected with this method. It has also been shown that in the case of chronic exposure to organophosphates, urinary elimination can reach a steady state and will cause the metabolite concentration to remain constant, indicating average exposure.[73] To rule out overdiluted or overconcentrated urine samples, creatinine or specific mass markers should be used, to normalize concentrations.[73]

There are some limitations of using DAPs as biomarkers of organophosphate pesticide exposure. These include the short half-life, which make it difficult to assess exposure to pesticides that isn't chronic or occurred more than several days prior to taking a urine sample.

Another limitation of using DAPs as a proxy for organophosphate exposure is that DAPs are commonly found in the environment.[74] A study looking at apple and orange fruit juices (both conventional and organic) found DAPs were present in both, with higher levels of DAPs observed in the conventional juice than the organic type.[75] It is thought by the researchers that organophosphates present in the juice were likely hydrolyzed into DAPs, and though DAPs metabolites are not known to be toxic,[38] it shows that urinary DAPs are not always an accurate way to measure direct exposure to organophosphates, since DAPs persist in the environment and humans can be exposed to the metabolites indirectly.[75]

Another limitation of using DAPs is that single measures of urinary metabolites cannot be considered dependable indicators of exposure for an individual because there is so much

variability in detection for each metabolite within and across individuals.[76] Additionally, relying on single measurements of DAPs is problematic because there is a lot of variability in DAPs excretion in a single day, and over several days.[74]

A study in Canada investigated exposure to organophosphates in the general population, and found that over 90% of Canadians in the study, who were a representative population of the entire nation, had at least one dialkyl phosphate metabolite (a biomarker for organophosphate exposure) in their urine.[72] Due to the short half-life of organophosphates in the environment, this suggests that Canadians are routinely exposed to pesticides.[72] If pesticide exposure is common and ongoing in the United States as well as in Canada, then studying the effects of pesticide exposure in the general population take on even more precedence.

**Indirect Measurements of Pesticide Exposure**

While there are many advantages to taking direct exposure measurements from individuals to assess their pesticide exposure, these methods are often infeasible due to resource constraints, costs, and the burden on study participants. There are many indirect methods for assessing pesticide exposure that typically involve making inferences on exposure based on samples taken from areas where individuals are likely to be exposed or based on information in surveys and registries that can give estimates of exposures. Dust, air, and food samples, as well as registries and surveys can estimate exposure by extracting information on the environment and exposure pathways that individuals are proximate to. A disadvantage is that these indirect methods make it harder to accurately estimate frequency and duration of exposure.

*Indoor Dust Samples*

Collecting dust samples from homes is another method of obtaining measurements to estimate pesticide exposure. This is called surface sampling, and has several different techniques including taking deposition pad samples, wipe sampling techniques (best for smooth surfaces such as windowsills, floors, and countertops), and vacuuming.[70] The advantage of these types of methods is that they can provide information on what residents are exposed to in their homes, which is a location many people spend a lot of time in.[70] Additionally, while pesticides often degrade quickly outside due to exposure to sunlight, precipitation, extreme temperatures, and microbial degradation, pesticides inside may persist longer, and so immediate exposure isn't as necessary.[70] Some disadvantages are that the dust samples don't represent all sources of pesticide exposures, and don't provide information on food related exposures or exposures related to direct pesticide application.[70]

*Air Samples*

Air samplers can be used to measure pesticides suspended in the air, both as particulates and as vapors. The state of matter of the pesticides in the air, as well as the particle size of the particulates are used to determine what kind of device is used for taking measurements; filter cassettes are usually used to collect pesticides that are solids or liquids, and solid sorbents are used for pesticides suspended as vapors.[70] Using a high volume or low volume airflow capture is another consideration. Typically, high volume airflow air samplers are used to measure ambient air pesticide exposure, with the disadvantages of being large, noisy, non-portable, and dependent on large amounts of electricity.[70] Low volume airflow samplers are a better choice for indoor air monitoring of

pesticides as they are quieter, smaller, portable, and can often be worn by study participants to measure personal pesticide exposures.[70]

*Food and Water Samples*

Because ingesting pesticide residues on food or drinking it in water is a common route of exposure to pesticides, numerous methods have been developed to assess exposure via food and water samples. Information on dietary habits and patterns of consumption coupled with measurements of pesticide residues in food and water can be used to construct mathematical models aimed at calculating exposure to pesticides via ingestion.[70] A limitation of this method is that it depends on the accuracy of the residue measurements.[70] Other limitations include the fact that collecting and storing food samples can be difficult, and that finding motivated participants for these types of studies is difficult.[70]

*Questionnaires and Surveys*

Because dermal exposure to pesticides is a common occupational health hazard, particularly for agricultural workers, questionnaires and surveys are often employed in occupational settings to ascertain frequency, duration, and intensity of exposure to pesticides. Researchers using data from the Agricultural Health Study rely on answers to questionnaires from farmers and pesticide applicators to assess exposure.[43] The questionnaire asks information about the types of pesticides used, the total amount used, and the frequency of application measured in days.[43]

Surveys and questionnaires are advantageous in that they can be cost-effective to implement.[77] In recent years online and mailed surveys have also allowed for more privacy and confidentiality to ensure survey respondents feel more comfortable answering

questions truthfully.[77] Certain limitations of relying on a questionnaire to assess exposure include recall bias (when participants don't remember events accurately), and response bias (when participants with certain types of exposures are more likely to respond to surveys than others).[77] For example, in a study by Hoppin *et al*., 2006, pesticide applicators from the Agricultural Health Study who handled pesticides were more likely to return the take home questionnaire than those that did not.[78] Additionally, surveys that are not in person lack the ability to probe interviewees for better clarification, and accurate responses may also depend on how literate the interviewees are on the subject matter of the survey.[77]

*Pesticide Registries*

The state of California has a comprehensive database called the California Pesticide Use Registry, which is a unique resource for assessing pesticide exposures. The database has information on specific types of pesticides, the amount in kilograms applied, the date applied, and the location of application (one square mile sections) quarterly in the state.[79] A study investigating air pollution and pesticide mixtures on children estimated exposure using this database and geolocated residential address to assign pesticide exposure.[79] An advantage of using the pesticide registries to estimate exposure is that it is inexpensive, and reliable data. The disadvantage is that it does not take into account duration or frequency of exposure since it is far from a direct measure.

**Respiratory Outcome Assessment**

As mentioned previously, both air pollution and pesticides have documented effects on respiratory health including increased risk of bronchitis, chronic obstructive pulmonary disease, asthma, and lung cancer. There are multiple different methods of assessing

respiratory outcomes regarding respiratory inflammation and function, and in this section, I will briefly outline two methods: spirometry and a biomarker known as leukotriene E4.

*Spirometry*

A common way to measure pulmonary function is to use spirometry. Spirometry measures how much air an individual can breathe in and out of their lungs, and at what speed and efficiency they can expel the air from their lungs.[80] There are several different measurements that can be used. Forced expiratory volume ($FEV_1$) measures the amount of air that can be pushed out of the lungs in one second, and gives an indication of the health of the large bronchioles.[79,81] Forced vital capacity (FVC) estimates how much air the lungs can hold by measuring the total amount of air breathed out after breathing as deeply as possible.[79,81] The forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75}$) serves as a good marker of the health of the small airways.[79] The $FEV_1$/FVC ratio measures forced expiration in the first second.[79]

The disadvantages of using spirometry to measure lung function is that it is difficult to quantify and standardize the effort undertaken by the individuals participating in the test. Because it requires that the participant expel air as forcefully as possible, differences will arise between individuals. However, the age, height, and gender of individuals participating in spirometry is taken into account.[81]

*Leukotriene E4*

Leukotrienes are biomarkers of inflammation that are detectable in urine samples. They are inflammatory molecules produced by mast cells and eosinophils that appear to have a key role in causing both acute asthma attacks and long-term hypersensitivity of the

airways in chronic asthma.[82] They also represent a non-invasive method of assessing respiratory inflammation.[79]

Urinary leukotriene E4 was used to assess levels of respiratory inflammation due to exposure, as a sign of asthma morbidity in asthmatic children living in the Yakima Valley of Washington State.[79] The final concentrations used in analysis were adjusted using creatinine.

**Mixtures of Environmental Exposures**

Much has been studied on the effects of different pollutants one at a time, and this is partly because the Clean Air Act originally sought to regulate a certain number of criteria air pollutants.[83] People are not exposed to air pollutants or pesticides one at a time, however, but instead are exposed to mixtures of these chemicals in the environment. It is important to study these mixtures because weather, sunlight, pollution sources, and other environmental factors impact the way that chemicals interact and affect the health of people exposed to these resulting mixtures.

Epidemiologists studying environmental mixtures of chemical pollutants can address several different research questions such as what the health effects of individual chemicals in a mixture are, what interactions exist between the chemicals in a mixture, and what impact cumulative exposure to such mixtures will have on human health.[84] Some of the methodological challenges involved with studying these mixtures are that chemicals within them are often correlated and act as co-pollutants, which leads to confounding.[84] Pollutants that are highly correlated will have to be analyzed in a way that elucidates the individual effects that they have on the outcome.[84]

Chemical mixtures result in different chemical exposure profiles that may have different effects on human health. A study in Colombia observing farmers' exposure to pesticide mixtures with paraquat, showed an association between paraquat exposure and asthma, but also that different chemical mixtures were associated with different respiratory disorders respectively, such as the flu, thoracic pain, allergic rhinitis, and obstructed patterns in spirometry.[85] Further, the previously cited study in Washington State that utilized urinary leukotriene E4 samples to assess asthma morbidity in asthmatic children found that simultaneous short term exposure to both criteria air pollutants and organophosphates elevated leukotriene E4, and presumably aggravated asthma morbidities and adversely impacted pediatric lung function.[79]

# CHAPTER 2: MANUSCRIPT

In this chapter I will describe the details of our environmental mixtures study. I will begin by providing background information on the high levels of pesticides and air pollution in Central California, and the need to study the health impacts of these pollutants as a mixture. I will then describe the research methods used to answer this objective, including the choice of location, study population, sampling methods, data collection, and data cleaning. After this I will describe the statistical analyses that were chosen, and our choice of statistical method for studying mixtures: Bayesian Kernel Machine Regression. Finally, I will explain the results of our data collection and analyses and conclude with some discussion on the interpretation of these results and the possible directions of future research.

## Introduction

California's Central Valley experiences some of the worst air quality in the United States.[24] Fresno County, which includes the City of Fresno, California's 5th largest city and the largest city by population in the Central Valley, has an average of 132 days a year of ozone levels that are considered hazardous to the health of sensitive groups.[86] California's Central Valley is also a critical agricultural region, domestically and globally, producing forty percent of the United States' fruits and nuts.[87] Extensive crop production contributes to comparatively high agricultural pesticide exposure for residents of Fresno County and the Central Valley.

There is clear evidence that ambient air pollution is associated with negative respiratory health outcomes such as decreased lung function and asthma,[20] as well as overall risk of

mortality, including from respiratory outcomes.[18] Though pesticides are considered an inhalation hazard, there is limited information on the impacts of pesticide exposures on respiratory health outcomes. Occupational studies have shown an association between pesticide exposure, and wheeze and bronchitis.[43,44] Recently, a number of analyses have been conducted on the effects of pesticide exposure on respiratory health outcomes in community-based studies and non-occupational populations. Previous work has linked pesticide exposure with decreased lung function in children with asthma in Fresno, California.[46] Researchers in Canada also documented decreased lung function in the general Canadian adult population associated with pesticide metabolites detected in urine samples.[45]

Traditionally, the effects of air pollutants and pesticides on respiratory health have been studied as distinct domains of exposure. However, humans are not exposed to pollutants and chemicals one at a time, but rather simultaneously as mixtures. Implementing statistical models to evaluate the health effects of environmental mixtures can elucidate both the individual effects of pollutants on the health outcome as well as the interactions that exist between chemicals in the mixture, with the overall goal of understanding cumulative impacts that environmental mixtures have on health endpoints.[84]

The Central Valley of California provides an ideal study area to explore environmental mixtures as residents here are exposed to high levels of air pollution and high levels of pesticides. However, because pollution mixtures are influenced by the sources of pollution, topography, meteorology, sunlight, and other environmental factors, the exposure patterns of environmental mixtures are also constantly changing over time.[1,8] Therefore, this study has two aims. The first is to understand the relationship between the

ambient air pollution and agricultural pesticide mixture and respiratory health outcomes in a community-based study. The second aim is to see how this relationship changes seasonally, by taking measurements from two different times of the year when the pollution mixtures are likely to have different compositions and properties.

**Research Question**

This study seeks to understand the relationship between air pollution-pesticide mixtures and respiratory health. More specifically, what is the relationship between a mixture of criteria air pollutants and other airborne chemicals, specifically organophosphate pesticides, measured by urinary dialkyl phosphate (DAP) concentrations, which are metabolites of organophosphates? Second, how does this observed relationship differ between samples taken in January, which has low pesticide and ozone exposure and high particulate matter (PM), and samples taken in June, which has high pesticide and ozone exposure and relatively lower PM?

**Methods**

*Study Location*

The Study of Environmental Mixtures in Periurban Respiratory Outcomes (SEMIPRO) seeks to understand the relation of ambient environmental and chemical pollutant (ECP) exposures on the respiratory health endpoints among residents of the Central Valley of California. Four agricultural communities were selected in Fresno and Tulare Counties in California for this study. Agriculture is a major economic sector in Fresno and Tulare counties. Fresno County ranks as number one in the state for production of fruits, tree nuts, and berries, and second for vegetables, melons, potatoes, and sweet potatoes, while Tulare County ranks as the third largest producer of fruits, tree nuts, and berries in

the state, according to the 2017 USDA Census of Agriculture.[88]

We partnered with the Central California Environmental Justice Network (CCEJN) to identify the study communities and households that were eligible for enrollment. Eligible households were located approximately within 61 meters of cropland or orchards (i.e., agricultural fields). Residences were identified using Google Earth and data from the California Pesticide Use Registry was used to confirm that these communities were located near agricultural areas where large quantities of pesticides were applied.

*Study Population*

In the four communities selected for this study, CCEJN conducted a door knocking campaign to communicate face-to-face with eligible households and enroll participants in the study. Inclusion criteria included living in their residence for at least a year, English or Spanish speaking, and be older than 7 years of age. Consent of participants over 18 and assent of all participants under 18 were completed prior to participation in the study. Study visits were conducted in January 2019, considered to be the low pesticide application season, and again in June 2019, considered to be the high pesticide application season. All study procedures were approved by the Colorado State University Institutional Review Board.

*Survey and Sampling Methods*

Study participants were asked to respond to the SEMIPRO survey, administered by researchers in their home that gathered information on built environment features of the household (e.g,, ventilation, number of windows, number of doors), socioeconomic status (e.g., level of educational attainment), health status, and workplace exposures. Household features were only asked of the first participant interviewed in the household;

all subsequent participants only answered questions of individual factors. The responses to these surveys were entered into a REDCap database.

Dust samples were collected for each household and urine samples were collected from each consenting and assenting participant in the household. Urine samples, the focus of this analysis, were collected in urine collection cups at the participants' homes. Instructions were given for participants to wash their hands, use a sanitation wipe to clean the perineal area, attempt to fill the cup halfway, and return the sample to study staff in biohazard bags. After collection, the urine cups were stored at Fresno State University in freezers at -80 degrees Celsius. At the end of each campaign, samples were shipped overnight on dry ice to Colorado State University. The samples remained frozen until aliquoted for analysis.

*Variables of Interest*

*Pesticide Exposure*

Dialkyl phosphate metabolites (DAPs), biomarkers for organophosphate exposure, were represented as concentrations (ng/mL) in urinary samples and were the primary pesticide exposure of interest. Though there are six DAPs metabolites, we investigated the total DAPs concentrations, as a continuous exposure variable in the model. We also evaluated two classes of DAPs, diethyl phosphates and dimethyl phosphates.

The CSU Analytical Toxicology lab followed published methods and protocols for analysis. First, 3 mL of urine from each individual sample were lyophilized to remove water before extracting into 5 mL of acetonitrile and sonication for 30 minutes. After this, the acetonitrile extracts were put under nitrogen to dry to 500 µL and then water was added to reconstitute to 1 mL. After this, reverse phase liquid chromatography and

tandem mass spectrometry were used to analyze the urine extracts for DAPs. The retention time and product ion ratio correlation to DAPs standards were then used to identify analytes. Finally, the urinary concentrations of DAPs were quantified using isotope dilution and linear regression.

*Air Pollution Exposures*

The data used to analyze air pollution as a component of an air pollution-pesticide mixture were obtained from the Community Multiscale Air Quality Modeling System (CMAQ). CMAQ, a project of the U.S. Environmental Protection Agency, provides open source development of programs used to model air quality simulations.[67] CMAQ models are numerical air quality models that predict estimates of ozone, particulate matter, and other pollution concentrations from simulations that use meteorological conditions and emission rates from known sources of pollution as the main inputs.[67]

The CMAQ models consist of gridded data that identify pollutant concentrations at specific points in time and space using latitude, longitude, the hour of the day, and the date. The gridded location is used to assign air pollutant concentrations to participant residential addresses. Grids are 12x12 kilometer squares, four of which such squares correspond to the four different communities. Thus, each of the four communities will be assigned an air pollution exposure value for $O_3$, $NO_2$, and $PM_{2.5}$. Seasonal values for all pollutants were assigned by community, as each community was contained within the same 12x12 grid in the CMAQ dataset.

The US EPA provided CMAQ data on air pollution concentrations via netCDF files, with the latitude and longitude coordinates corresponding to these home communities for the participants.

*Response Variable*

Leukotriene E4 (LTE4) urinary concentration (pg/mg) is the outcome variable of interest in this study. LTE4 is a metabolite of cysteinyl leukotrienes, which are produced by eosinophils, mast cells, and basophils, cells associated with asthma and/or allergen induced respiratory inflammation.[82,89] LTE4 has been well established as a biomarker for respiratory inflammation in asthmatic patients, but there is less known about its usefulness as a biomarker in studying acute respiratory inflammation in community settings among individuals without asthma.

Using the urine samples collected in January and June of 2019, LTE4 concentrations were measured using ELISA kits from Cayman Chemical (Ann Arbor, MI) Kit #501060, and normalized with creatinine.

*Covariates*

Covariates for this analysis were selected via directed acyclic graphs (DAGs) and bivariate analyses between the potential covariate and the exposure, and the potential covariate and the outcome using Wilcoxon sign-rank test. To control for confounding we considered seven covariates: age (continuous), sex (categorical), whether the individual worked in agriculture (categorical), whether or not a person in the individual's household worked in agriculture (categorical), whether or not the individual had an asthma diagnosis (categorical), ambient air temperature (continuous), and relative humidity (continuous). The data for the first four covariates were gathered from the SEMIPRO surveys administered in each household. The air temperature and relative humidity covariates came from weather data taken from the Automated Surface Observing Systems (ASOS) in California provided by the Iowa Environment Mesonet website.[90]

*Data Cleaning*

All data cleaning and statistical analysis were performed in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). The SEMIPRO dataset contained the urinary concentrations of DAPs, urinary concentration of LTE4, and the demographic data of each participant. This dataset was read into R and was joined with data frames describing air pollutant concentrations that were extracted from the netCDF files provided by the US EPA. These air pollutant data frames were joined to the SEMIPRO dataset to correspond with the latitude and longitude of the participant communities. Thus, air pollution values were assigned to the participants in the respective communities corresponding to each of four 12x12 kilometer grids that were used to calculate an air pollution concentration using the CMAQ models.

To clean the air pollution data from the CMAQ models and create data frames that were compatible to join with the SEMIPRO dataset took several steps. First, the data on air pollutants came in netCDF files in the form of arrays and had to be converted into data frames. Data frames were created that contained latitudes, longitudes, pollutant concentration values, and time in hours for $O_3$, $NO_2$, and $PM_{2.5}$ for January and also for June. The time in hours meant that a value was recorded for every hour in the entire month of January (744 hours), and June (720 hours). In order to match the correctly timed pollution concentration value with the closest period of time that samples were taken, these hours had to be converted into days of the month. NAAQS standards were used to pick times to extract pollution concentrations. For $O_3$, this was the monthly average of the maximum daily 8-hour concentration (the average of the 8 hours in a day that provided the highest level of $O_3$). For $PM_{2.5}$ this was the mean of the hourly concentrations over the

month. For $NO_2$, this was the one hour daily maximum value, averaged over the month. Once the correct times were specified to extract pollutant concentration values, these values were assigned to the entire community. So, for example, the January value of $O_3$ for community 1, was the same exposure that we considered everybody in community 1 to have.

Once the pollutant data frames were created, they were added to the SEMIPRO dataset, so that relationships between the air pollutants and our health outcome (urinary LTE4 concentrations) and the other exposures (DAPs) could be assessed. This dataset was further divided into samples taken from January (80 samples) and June (77 samples).

To assign air temperature and relative humidity values as covariates in the model, the *riem* package in R was used. First, Automated Surface Observing Systems (ASOS) were identified based on their closest proximity to the four communities being studied in Fresno and Tulare Counties. Because the closest stations lacked the data needed, several of these ASOS stations had to be excluded before finding the next closest stations that had data on air temperature and relative humidity. Air temperature and relative humidity was then averaged for each day of the month (January and June respectively), and then the monthly average of all the daily averages was taken and assigned to each community for month.

*Descriptive Analysis*

Wilcoxon (Paired) Signed-Rank tests were also performed on each of the exposure variables to assess differences in levels between January and June. The Wilcoxon signed-rank test is a nonparametric test that compares non-independent samples and gives an assessment of the difference between their population means. The null

hypothesis of a Wilcoxon signed-rank test is that true location shift (of the sample mean) is equal to zero, and consequently the alternative hypothesis of this test is that the true location shift is not equal to zero.

*Univariable Analysis*

$O_3$, $NO_2$, $PM_{2.5}$, diethyl phosphates, and dimethyl phosphates were all analyzed individually as the main exposure variable in multiple linear regression models, with log-transformed LTE4 as the response variable. For each pollutant, three models were run. The first model only included the main predictor variable, and the response variable. The second model added five covariate variables: age, sex, working in agriculture, being in a household with somebody who works in agriculture, and having asthma. The third model added temperature and relative humidity to these models as well.

*Bayesian Kernel Machine Regression*

Bayesian Kernel Machine Regression (BKMR) is the statistical method that we applied to our air pollution – pesticide mixture exposure and respiratory health outcome to estimate an association. BKMR is an advantageous method for analyzing mixtures because it estimates an exposure-response association by utilizing a flexible surface that allows for non-linear and non-additive interactions between mixture components.[91] It also performs a hierarchical variable selection (HVS) using prior knowledge of the pollution mixture's structure.[79,91]

BKMR allows us to estimate the effects of individual pollutants in the mixture, as well as interactions between those pollutants in the mixture, which may or may not be linear. Thus, both individual and joint effects of pollutants in the mixture can be assessed. BKMR estimates the amount that each pollutant in the pollutant mixture contributes to the

outcome through variable selection. A partitioning of the exposures into groups is provided by the user in hierarchical variable selection. BKMR estimates both the group-wise posterior inclusion probability and, conditional on group inclusion, the component-wise posterior inclusion probability for exposure.

Taking into account the possible correlations between exposure variables and the overall structure of a mixture, hierarchical variable selection estimates posterior inclusion probabilities (PIPs), which give the probability that exposure variables (in this case our different air pollutants and pesticides) are associated with the outcome (LTE4 concentrations).[79,91] This is done first by estimating the probability that a group (or domain) of pollutants should be included in the model, and then assessing how each component of that group/domain drives the association with the outcome.[79]

A disadvantage of BKMR is that it is unable to accommodate a large number of variables, usually being an ineffective model. This shouldn't be a problem with our analysis because only three air pollutants ($O_3$, $NO_2$, and $PM_{2.5}$) and two DAPs categories (diethyl phosphates and dimethyl) are included as exposures.

The BKMR model is represented by this function:

$$y_i = h(x_{i1},\ldots,x_{iM}) + z_i^T\beta + \varepsilon_i$$

where $y_i$ is the health outcome (LTE4 concentration), $M$ is the number of components in the exposure mixture, $x_i$ represents components of the exposure mixture (air pollutants and/or pesticides), $h()$ is a smooth exposure-response function allowing for non-linearity and/or interaction between mixture components, $z_i$ are model covariates, and $\varepsilon_i$ are normally distributed residuals.[79]

The BKMR analysis was performed using the *bkmr* package in R version 3.6.3 (Bobb,

2017). The BKMR analysis was run for the air pollution concentrations, DAPs concentrations, and LTE4 concentrations once in January, and again separately for those in June.

The BKMR model was fit using the *kmbayes()* function, which uses the Markov chain Monte Carlo algorithm[92] in the *bkmr* R package, and running 10,000 iterations, which proved to be enough for the parameters to converge after inspecting trace plots. The model was fit with variable selection, and all the exposures were scaled. Posterior means were calculated for $O_3$, $NO_2$, $PM_{2.5}$, and DAPs. Posterior means in BKMR analysis can be thought of as analogous to the beta coefficients in linear regression analysis.

Posterior inclusion probabilities were extracted from the fitted BKMR model, and provide a measure of variable importance for each exposure, or in other words how much this variable contributes to the model.[93]

After fitting the BKMR model, we wanted to visualize the smooth exposure-response function h() but we can't view a high dimensional surface so we had to instead look at different cross sections of the surface by looking at the relationship between one or two exposures and the outcome, while holding the other exposures at a fixed percentile.[92] First, we looked at the univariate relationship between each exposure and the outcome, and held all the other exposures at percentiles of 0.25, 0.5, and 0.75. Then, we looked at the bivariate exposure-response relationship for two exposures, where all the other exposures were held at fixed percentiles.

## Results

*Descriptive Statistics*

Study population data are presented in Table 1. At the start of the study in January, 34 households, with an average of 2.5 residents per household, were enrolled. This

encompassed a total of 80 participants recruited by the Central California Environmental Justice Network. Three were lost to follow up and did not participate in the June campaign. A combined total of 157 urine samples were salvaged from the participants in January and June. The majority of study participants were male (57.1%), and the mean age was 42.4 years old. Prevalence of asthma was above average in this study population, with 11 individuals reporting asthma (14.3% of the population). For context, the national incidence of asthma is about 8% for adults, and 7% for children.[94] Almost a third of the study participants were directly employed in agriculture, with a total of 24 individuals working in this industry (31.2% of the study population). Furthermore, 63 of the participants (81.8% of the study population) live in a household where at least one person works in agriculture.

*Exposure Statistics*

Concentrations of air pollutant and pesticide exposures are summarized in Table 2. Among the air pollutants, particulate matter ($PM_{2.5}$) and ozone ($O_3$) had higher concentrations measured in June than in January. Nitrogen dioxide ($NO_2$) was different from $PM_{2.5}$ and $O_3$ in that it had higher concentrations in January than in June.

Urinary DAP concentrations were highly skewed, with the majority of the sample concentrations being so low that they registered as zero. Dialkyl phosphate (DAP) concentrations were higher in urine samples taken in January (maximum of 332.56 ng/mg of creatine) than in June (maximum of 106.02 ng/mg of creatine), mostly owing to dimethyl phosphates, which constituted the majority of the total dialkyl phosphates detected. Diethyl phosphates were detected at higher levels from urine samples collected in June (maximum of 29.47 ng/mg of creatine in June vs. a maximum of 23.07ng/mg of creatine

in January), while dimethyl phosphates were detected at higher levels from urine samples collected in January (maximum of 332.56 ng/mg of creatine in January vs. 106.02 ng/mg of creatine in June).

The results of the Wilcoxon signed-rank paired tests showed significant seasonal differences in the concentrations of the air pollutants measured, and the results of these tests are summarized in Table 3. Wilcoxon signed-rank tests for particulate matter ($PM_{2.5}$), ozone ($O_3$) and nitrogen dioxide ($NO_2$) all yielded p-values less than 0.05. This means there is a significant difference between the levels of these air pollutants in January and June. Wilcoxon signed-rank tests for concentrations of dialkyl phosphate concentrations in January and June did not reveal significant results, indicating that the different levels of pesticides observed in different seasons were not meaningful.

*Leukotriene E4 Statistics*

Table 4 summarizes the concentrations of Leukotriene E4 (LTE4) in January and June. January concentrations of LTE4 ranged from 175.69 pg/mg of creatinine to 10399.24 pg/mg of creatinine and had a median concentration of 1006.25 pg/mg of creatinine. The June concentrations of LTE4 ranged from 313.11 pg/mg of creatinine to 11403.53 pg/mg of creatinine and had a median concentration of 1379.08 pg/mg of creatinine. The results of the Wilcoxon signed-rank test for LTE4 yielded a p-value of 0.10 indicating that these differences between seasons were not statistically significant.

*Multiple Linear Regression Analysis*

Multiple linear regression analysis was performed using each of the exposures of interest (particulate matter, nitrogen dioxide, ozone, and dialkyl phosphates) as the main predictor variables, and using log transformed leukotriene E4 concentration as the outcome

variable. The linear models examined each of these exposures one at a time, and adjusted for age, sex, asthma status, whether or not the individual worked in agriculture, and whether or not a person in the individual's household worked in agriculture. Table 5 provides the β1 values and 95% confidence intervals for each of the exposures and covariates.

Results from the multiple linear regression analysis did not reveal any conclusive associations between any of the air pollutants and an elevated urinary concentration of leukotriene E4. However, dimethyl phosphate concentration in January showed a positive association and a β1 value of 0.01 (95% CI: 0.001, 0.010) in models 1, 2, and 3. This means that for every one unit increase in the concentration of dimethyl phosphate, there is a 0.01 unit increase in log-transformed leukotriene E4 concentration. We multiplied the β-coefficients of all the exposure variables by the interquartile range (IQR) to observe a larger change. The IQR represents the middle 50% of the values in a distribution, in this case the distributions being the values of each exposure variable for January and June. With an IQR change of 0.06 for dimethyl phosphate, we say that for every one unit increase in the concentration of dimethyl phosphate, there is a 0.06 increase in the IQR of the log-transformed leukotriene E4 concentration.

*Bayesian Kernel Machine Regression Analysis*

We fit the BKMR model and extracted the group and conditional PIPs for each exposure. Two groups were used for hierarchical variable selection: air pollutants ($O_3$, $PM_{2.5}$, and $NO_2$) and pesticides (diethyl phosphates and dimethyl phosphates), as seen in Table 5. We observed differences in the group PIPs by season, with the pesticides group driving

the mixture the most in January (group PIP: 0.80), and air pollutants driving the mixture in June (group PIP: 0.73).

Among the exposures in the air pollutant group, $O_3$ and $PM_{2.5}$ were the most important components in January (conditional PIP: 0.35 for both), and $O_3$ was the most important component in June (conditional PIP: 0.36). In the pesticides group, dimethyl phosphates were the most important component in January (conditional PIP: 0.82), but in June diethyl phosphate was the component that contributed the most to the outcome (conditional PIP: 0.54).

Figures 1-6 display different plots of the predictor response functions. The function is a high dimensional surface, and because we can't view this, we observe it as different cross sections.[92] Each cross section explores the relationship between one two exposure variables with the outcome, while setting the other exposure variables to a particular percentile.[92]

Figures 1 and 2 display the univariate relationship between each exposure variable and the outcome of urinary concentration of LTE4. In January, $O_3$, $PM_{2.5}$, $NO_2$, have a slightly negative relationship with LTE4. Diethyl phosphates have a positive relationship with urinary LTE4. In other words, as the levels of these diethyl phosphates exposures increase, the LTE4 concentration also increases. Dimethyl phosphates in January show a non-linear relationship with LTE4 concentration. At first, LTE4 increases as dimethyl phosphates increase, but at about a dimethyl phosphate z-score of 5 this relationship peaks and becomes negative.

In June, $O_3$, exhibits a slightly negative relationship with LTE4. In other words, as $O_3$ increases, the concentration of LTE4 decreases. $PM_{2.5}$ and $NO_2$ don't appear to have a

positive or negative relationship with LTE4. As concentrations of diethyl phosphates increase, the levels of LTE4 remain constant. And finally, dimethyl phosphates displayed a positive relationship with LTE4 in June, with LTE4 increasing as dimethyl phosphates increased. All these relationships are observed while holding the other exposure variables at their median values.

In Figures 1 and 2, the shaded areas represent 95% confidence bands. The confidence bands for all exposures includes the null value, which indicates that none of the relationships with LTE4 are statistically significant.

Figures 3 and 4 display the bivariate relationship between two exposures and the outcome of urinary concentration of LTE4. These plots are harder to interpret than the univariate exposure-response cross sections, and there are no parameters in the model that allow for statistical uncertainty (such as a confidence interval) to be displayed, since the h function is non-parametric. Dark red represents high levels of urinary LTE4, and blue represents low levels of LTE4. Gray is where the model is missing data. Each plot shows how LTE4 changes as one exposure increases at different levels of another exposure. For example, in June the levels of urinary LTE4 decrease as $O_3$, $PM_{2.5}$, and $NO_2$ increase (which is consistent with the univariate relationships we observed in Figures 1 and 2), but we see that this happens differently at different concentration levels of dimethyl phosphates.

Figures 5 and 6 show the relationship of the exposure and outcome, given a quantile of another one of a second exposures When the quantile lines intersect each other or have different slopes, this indicates interaction between the two exposure variables. When the quantile lines are on top of each other, as in Figure 5 $O_3$ and $NO_2$, this indicates no

interaction, because the relationship between the exposure and outcome does not vary depending on the quantile of the other exposure. For example, we can see in January (Figure 5) that the response of LTE4 concentration to $PM_{2.5}$ is different depending on the quantile of $O_3$, with a different response being observed at the 75$^{th}$ percentile of $O_3$ than at the 25$^{th}$ percentile. In June (Figure 6) we see LTE4 increasing in response to increasing dimethyl phosphate and $NO_2$ exposure at all quantiles of every other exposure, while LTE4 decreases in response to increasing levels of $O_3$, and $PM_{2.5}$ at every quantile of every exposure. In June, diethyl phosphate is different from all these exposures, in that LTE4 decreases at a certain rate with increasing concentrations of diethyl phosphates at the 25$^{th}$ percentile of $O_3$, $NO_2$, and $PM_{2.5}$, and at a different rate than at the 50$^{th}$ and 75$^{th}$ percentiles of $O_3$, $NO_2$, and $PM_{2.5}$.

Figures 7 and 8 display the change in risk of the outcome when the specific exposure on the y-axis moves from its 75$^{th}$ to 25$^{th}$ percentile, while the other exposures are held at either their 25$^{th}$, 50$^{th}$, or 75$^{th}$ percentiles. For example, in Figure 7 we see that in January when levels of dimethyl phosphate move from their 75$^{th}$ to 25$^{th}$ percentiles, there is a slight (but not significant) change in the risk. The values are to the right of the null when all other exposures are at their 25$^{th}$, 50$^{th}$, and 75$^{th}$ percentiles which is congruent with the previously mentioned plots that showed dimethyl phosphates to have a positive association with LTE4. However, the magnitude of the difference in risk when dimethyl phosphate levels move from their 75$^{th}$ to 25$^{th}$ percentiles does not change when all other exposures are at their 25$^{th}$, 50$^{th}$, and 75$^{th}$ percentiles. For all predictors, the values on these plots that overlap the null, indicating that none of the relationships between any of the predictors and the response are statistically significant.

## Discussion

Before discussing the results, I will reiterate the aims of this study. The first was to understand the relationship between the air pollution and pesticide mixture, and respiratory health outcomes. The second aim was to see how this relationship changes seasonally, by taking measurements from two different times of the year when the pollution mixtures are likely to have different compositions and properties.

The results from analyses investigating the first aim were complicated. The relationship between the air pollutants and pesticide and the concentration of urinary LTE4 was different when we used multiple linear regression and BKMR analysis to assess this relationship. Multiple linear regression revealed little evidence of a relationship between the levels of criteria air pollutants ($PM_{2.5}$, $NO_2$, and $O_3$) in both January and June. There was however a significant association between the levels of total DAPs and urinary LTE4 in January, as well as dimethyl phosphates and urinary LTE4 in January. The Wilcoxon signed-rank tests did not suggest statistically different levels of DAPs in the two months, although June is the spraying season.

One potential reason for the statistically significant relationship between urinary LTE4 and total DAPs (and urinary LTE4 and dimethyl phosphates) is that the DAPs came from individual study participants, whereas a single air pollutant concentration was broadly assigned to each community, and so each person in that community was assigned the same exposure. In other words, we estimated exposure to pesticides using individual measurements, and thus had a higher number of measurements using a larger sample size (based off the study population), while we only had four air

pollutant measurements per month (one for each community). Finding statistical sample size from a smaller number of measurements is much harder.

It is possible that the individual measurements of pesticides are subject to classical error, which occurs when individual measurements vary from the true value being measured.[95] In contrast, the measurements of air pollution could be subject to Berkson error, which occurs when an aggregate measure is assigned to a group of participants, who may vary in their exposure with respect to this value.[95]

Regarding bias, we do not know if there is non-differential or differential misclassification, but it is possible that there could be differential misclassification occurring due to different exposure profiles for people who work inside or outside. Additionally, people who are more sensitive to respiratory irritants, such as people with asthma, may be more likely to adjust their behavior accordingly which could potentially change their exposure to air pollutants and pesticides relative to other members of the community.

While the multiple linear regression did not reveal conclusive results for most of the exposures (except for total DAPs and dimethyl phosphates), the BKMR analyses did reveal interesting interactions between the different pollutants. While most of these relationships in January appeared to be somewhat linear, the relationship between dimethyl phosphates and LTE4 was not. Instead, dimethyl phosphates showed a positive association with LTE4 until about 5 standard deviations, whereby the relationship became negative.

The univariate exposure-response function in June showed little to no relationship between air pollutants and LTE4 but showed more linear relationships between the DAPs and LTE4 (negative for diethyl phosphates and positive for dimethyl phosphates).

It should be noted that all the graphical displays of these relationships for both January and June showed very large confidence intervals. This is probably due to the relatively small concentrations of DAPs that were extracted from the urine samples, and the fact that all air pollutant exposures were assigned to every individual in the community. The strongest association between an exposure and urinary LTE4 in the univariate exposure-response function was dimethyl phosphates in January, which is very similar to the results we saw from the multiple-linear regression. This is different from what we would otherwise expect given that June is the season when spraying occurs in California.

Though harder to interpret, and though they don't account for statistical uncertainty, these bivariate exposure response functions showed that there were interactions happening between the pollutants in the mixture. A lot of data is missing, but it is possible to see that urinary LTE4 increases or decreases as the various exposures decrease, but at different rates depending on the level of the other exposure.

Figures 5 and 6 also show that interactions are occurring between the different exposures in the mixture. Figure 5, which shows the relationship between an exposure and urinary LTE4 given a second exposure in January, shows that urinary LTE4 increases as diethyl phosphates and dimethyl phosphates increase, but these increases don't appear to depend much on quantiles of other exposures.

In June, urinary LTE4 increases as $NO_2$ and dimethyl phosphates increase, at all measured quantile levels of all exposures. Diethyl phosphates show a more complex interaction in June, because as diethyl phosphates increase at the 0.5 and 0.75 quantiles of $O_3$, $NO_2$ and $PM_{2.5}$, urinary LTE4 decreases, but LTE4 decreases at a steeper rate at the 0.25 levels of $O_3$, $PM_{2.5}$, and $NO_2$.

These different interactions between the components of the pollution mixture are not well understood and should be the subject of future research in this field. While none of the results of the BKMR analysis were statistically significant, they still pointed to complex interactions between the mixture components that the multiple linear regression could not detect. A similar study conducted in Washington State by Benka-Coker *et al.* observed that increasing total mixture levels of $PM_{2.5}$, ozone, and organophosphates was associated with increased levels of urinary LTE4. (Benka-Coker *et al.* 2019)

To wrap things up, I want to summarize the main findings of this study, and the limitations and strengths.

First, there are several strengths to this study. One of them is that this study adds to the currently small volume of literature on environmental mixtures. Although the need to study environmental mixtures is becoming more acknowledged by the scientific community, little work has been done to date, particularly on mixtures between different environmental domains (e.g., air pollution and pesticides). Because the BKMR mixture analysis revealed associations that the linear regression models could not detect, this could be a sign for future research that linear models may not always be appropriate for studying joint environmental exposures.

A particular strength of using BKMR is that it allows for non-linearity and more flexibility in the relationships between air pollutants, pesticides, and respiratory health outcomes.

Another strength of this study is that we demonstrated a positive association between total urinary DAPs and urinary LTE4 in a population with relatively low asthma prevalence. There is limited research to date on the effectiveness of LTE4 as a marker for respiratory inflammation in populations that do not have asthma. This research also

builds on the literature establishing a link between exposure to pesticides and respiratory health.

There are some important limitations to discuss in this study as well. One is that the sample size is very small; 80 participants in January gave samples, and this was reduced to 77 in June. Another limitation is that as mentioned before, we used an ecological measure for air pollution exposure, but an individual measurement for pesticide exposure. This had the potential to introduce Berkson error for the former. Classical error is also probable in our individual pesticide samples, because DAPs represent short term exposure. They also do not tell us the route of exposure, or the specific types of organophosphates that the individuals in the study were exposed to.

In summary, in a community-based study of residents of communities where ambient air pollution and pesticide application was high, we found that urinary markers of organophosphate pesticides were positively associated with a urinary marker of respiratory inflammation. Since the prevalence of asthma was low in this population, we also recognized that LTE4 has the potential to be used as a biomarker for respiratory inflammation in individuals who do not have asthma. We also discovered that interactions between different air pollution and pesticide exposures exist, at least one of which was non-linear, and that these mixtures had different relationships with the health outcome in January and June. To effectively study an environmental mixture of air pollutants and pesticides, much larger sample sizes should be used in future research, and more individual air pollutant measurements should also be considered.

# CHAPTER 3: CONCLUSION

## Study Findings

The field of environmental mixtures is still very new, despite growing consensus among researchers that the complex interactions and exposure pathways of environmental exposures warrant the use of mixtures analysis.

We conducted this study with an interest in several specific questions. First, we wanted to know if there were associations between the air pollution and pesticide mixtures and the respiratory health outcomes, and whether or not these associations were different seasonally. The mixture in question included air pollution and organophosphate pesticides, and while a lot is known about the respiratory health impacts of air pollution, much less is known about the relationship between pesticides and respiratory health. Since we ran multiple linear regression models on each exposure separately before running them all together in a mixture using BKMR, we were able to look at the effect of a pesticide biomarker and see if there was an association with a biomarker of respiratory inflammation. We also wanted to use the study population as an opportunity to investigate whether LTE4 could be used as a marker for respiratory inflammation in a population with a low prevalence of asthma.

All these questions were answered to some extent in our study. First, BKMR analysis revealed that there were indeed associations between the different air pollutants and markers of pesticide exposure, although none of them were statistically significant. By running BKMR analysis separately in both January and June we were also able to see that these relationships changed from winter to summer.  Regarding our interest in

pesticide exposure and respiratory health, our multiple linear regression analysis revealed a small but statistically significant association between urinary dimethyl phosphates and urinary LTE4 (our respiratory health marker) in January. Though small, this points to a connection between pesticides and respiratory health that should be studied further. And finally, this association revealed that LTE4 has some utility as a marker for respiratory inflammation in populations that don't have high prevalence of asthma.

**Future Research**

Future research on this topic is necessary. I think a similar study with the same main objectives (studying the impact of air pollution and pesticide mixtures on respiratory health, and in two different seasons) with a much larger sample size would be a logical next step. For the current study, 80 participants dropping to 77 participants in a study probably isn't adequate to take full advantage of a BKMR analysis. I think that with a large sample size we could lower our credible intervals and understand more complexity in the associations. We could see more non-linear relationships between exposures and the outcome.

Future studies on air pollution mixtures and pesticide mixtures should also attempt to gather more individual level measurements of air pollution exposure. In this study everybody in the same community had the same level of air pollution assigned to them as an exposure and this is a very big assumption to make. Most likely, the residents of a certain community had wildly different levels of exposure based on how much time they spent outside, and where outside they were. Installing more low-cost monitors at households or asking participants to wear personal air pollution monitors could be a way

to gather more individual air pollution data in the future, although this could be invasive and cumbersome to some participants and overall expensive to implement.

Another direction of future research on environmental mixtures should also include different exposures to the mixture. Pesticides and air pollution are two very important health hazards that residents of the California Central Valley are routinely exposed to, but there are many other environmental risk factors in this area that could also be added to a mixture model. For example, with increasingly hot days in California, adding heat temperatures to a mixtures model (instead of something to control for as we did in our multiple linear regression analysis) would be useful to understand mixtures.

**Post Thesis Reflections**

I've mentioned this to my thesis advisor Dr. Sheryl Magzamen, and I want to make sure my other advisor Dr. Brooke Anderson knows as well, but I've gotten "the bug" so to speak, in terms of interest in air pollution, meteorology, weather, and the resulting public health implications. I had a brief career as a field ecologist before graduate school, and so I've always had a special love for the natural world, which is what helped lead me to this field. Yet writing this thesis, and also helping with research on tropical cyclones with Dr. Anderson, has made many environmental issues seem to me more consequential and urgent than ever before.

While Covid-19 will probably always remain the most memorable and traumatizing public health issue of this current time period, for me the endless weeks of air pollution we experienced in 2020 and 2021 in Fort Collins were just as memorable and had a major impact on my environmental mindset. Living with the constant smell of smoke, cancelling outdoor plans because of poor air quality, and looking outside certain days to

see apocalyptic looking red skies brought the issue of my thesis into stark focus. It wasn't theoretical or academic, it was right outside. I remember walking on campus one day, and seeing the sky look like something straight out of *The Wump World*, by Bill Peet. Aside from fires and smoke, the past summer was also full of extreme heat advisories, devastating hurricanes and flooding, and extreme drought. Like air pollution, climate change no longer seems like an abstract phenomenon that affects different people somewhere else, it is knocking on all of our doors right this moment.

And this is where I want to take a hard turn. It is easy to panic and despair about the state of things. And to be clear, the prognosis for many environmental problems is not great. But what the headlines don't do a good job of acknowledging is the many researchers, public health professionals, and environmental scientists who understand the concerns and pressing challenges but don't shy away from the challenge of hunting for solutions. That is one of the things about environmental health that I think is so uplifting: we are actively working to find ways to live with our new paradigm. Though my thesis was a pilot study, I really hope that it can help to further the understanding of air pollution and pesticide mixtures. And hopefully that understanding can lead to better environmental and public health policies that protect people in an increasingly hotter world.

Going forward in my career, there are many skills and important things I've learned as a student that I believe will serve me well. Though I have a lot of room for improvement, my ability to program in R and SAS would never have taken off without being a student here. And I have come to understand and appreciate a whole new way of writing and communicating. Where my career leads from here is still murky but I know that I want to

remain focused on environmental health, especially with a focus on climate change. Working at the CDC in the Arboviral Disease Branch is a good start since vector borne illnesses are certainly poised to expand with increasingly warm climates around the globe. I have recently gotten involved in the ISeeChange project, which is a citizen science community journal for reporting weather and climate change related events. I have been in contact with ISeeChange's CEO and hope to contribute written pieces on climate change (either about air pollution, pesticides, or hurricanes) to the organization. Finishing this thesis and completing my degree at Colorado State University is hopefully the beginning of a long and varied career studying and writing about the health impacts of environmental exposure in response to climate change, extreme weather events, and exposures to pollution. By focusing on public health with insights from ecology and meteorology, I hope to also advance conservation of our planet's natural resources, by facilitating understanding of practices that are good for the health of our communities but also the biodiversity with which we share our homes.

# TABLES & FIGURES

Table 1. Study Population & Demographics of Study Population in June

| | Community 1 (N = 33) | Community 2 (N = 5) | Community 3 (N = 24) | Community 4 (N = 15) | Total (N = 77) |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| **Male** | 13.0 (39.4%) | 3.00 (60.0%) | 10.0 (41.7%) | 7.0 (46.7%) | 33.0 (42.9%) |
| **Female** | 20.0 (60.6%) | 2.00 (40.0%) | 14.0 (58.3%) | 8.0 (53.3%) | 44.0 (57.1%) |
| **Age (years)** | | | | | |
| **Mean (SD)** | 41.7 (23.4) | 53.2 (19.7) | 41.3 (19.1) | 42.0 (19.9) | 42.4 (21.1) |
| **Median [Min, Max]** | 36.1 [7.09, 87.8] | 59.3 [18.9, 68.2] | 47.2 [11.7, 81.3] | 46.0 [13.7, 71.7] | 46.3 [7.09, 87.8] |
| **Asthma** | | | | | |
| **Yes** | 5.0 (15.2%) | 0 (0%) | 2.00 (8.3%) | 4.00 (26.7%) | 11.0 (14.3%) |
| **No** | 28.0 (84.8%) | 5.0 (100%) | 22.0 (91.7%) | 11.0 (73.3%) | 66.0 (85.7%) |
| **Don't Know** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Individual Works in Agriculture** | | | | | |
| **Yes** | 8.0 (24.2%) | 1.00 (20.0%) | 10.0 (41.7%) | 5.00 (33.3%) | 24.0 (31.2%) |
| **No** | 25.0 (75.8%) | 3.00 (60.0%) | 14.0 (58.3%) | 9.0 (60.0%) | 51 (66.2%) |
| **Don't Know** | 0 (0%) | 1.00 (20.0%) | 0 (0%) | 1.00 (6.7%) | 2.00 (2.6%) |
| **Somebody in Household Works in Agriculture** | | | | | |
| **Yes** | 31.0 (93.9%) | 2.00 (40.0%) | 16.0 (66.7%) | 14.0 (93.3%) | 63.0 (81.8%) |
| **No** | 2.00 (6.1%) | 0 (0%) | 8.0 (33.3%) | 1.00 (6.7%) | 11.0 (14.3%) |
| **Don't Know** | 0 (0%) | 3.00 (60%) | 0 (0%) | 0 (0%) | 3.00 (3.9%) |

Table 2. Environmental exposure values per season based off SEMIPRO collection and CMAQ derived estimates.

| Month | Exposure | Std. Dev | Minimum | 1st Quartile | Median | 3rd Quartile | Maximum |
|---|---|---|---|---|---|---|---|
| **January** | Particulate Matter < 2.5 µm ($PM_{2.5}$)(µg/$m^3$) | 1.01 | 3.33 | 3.33 | 3.80 | 5.63 | 5.63 |
| **June** | Particulate Matter < 2.5 µm ($PM_{2.5}$)(µg/$m^3$) | 1.54 | 4.93 | 4.93 | 7.36 | 8.31 | 8.31 |
| **January** | Ozone ($O_3$)(ppb) | 0.97 | 26.84 | 26.95 | 27.76 | 29.07 | 29.07 |
| **June** | Ozone ($O_3$)(ppb) | 4.21 | 44.51 | 44.51 | 51.61 | 53.63 | 53.63 |
| **January** | Nitrogen dioxide ($NO_2$)(ppb) | 1.01 | 4.25 | 4.25 | 4.70 | 6.46 | 6.46 |
| **June** | Nitrogen dioxide ($NO_2$)(ppb) | 1.53 | 2.14 | 2.14 | 4.37 | 5.47 | 5.54 |
| **January** | Diethyl (ng/mg of creatine) | 2.66 | 0 | 0 | 0 | 0 | 23.07 |
| **June** | Diethyl (ng/mg of creatine) | 4.33 | 0 | 0 | 0 | 0 | 29.47 |
| **January** | Dimethyl (ng/mg of creatine) | 39.47 | 0 | 0 | 0 | 5.58 | 332.56 |
| **June** | Dimethyl (ng/mg of creatine) | 21.02 | 0 | 0 | 0 | 3.71 | 106.02 |

Table 3. Wilcoxon (Paired) Signed-Rank Test between January and June exposures

| Exposure | p-value |
|---|---|
| **Nitrogen dioxide ($NO_2$)** | |
| **Winter – Summer** | 1.78e-08 |
| **Ozone ($O_3$)** | |
| **Winter – Summer** | 2.10e-14 |
| **Particulate Matter ($PM_{2.5}$)** | |
| **Winter – Summer** | 1.22e-13 |
| **Total DAPs** | |
| **Winter – Summer** | 0.89 |
| **Diethyl phosphate** | |
| **Winter – Summer** | 0.20 |
| **Dimethyl phosphate** | |
| **Winter – Summer** | 0.57 |

Table 4. Summary statistics of urinary dialkyl phosphate concentrations (pg/mg of creatinine) for January (n=80) and June (n=77).

| Month | Std. Dev | Minimum | 1st Quartile | Median | 3rd Quartile | Maximum |
|---|---|---|---|---|---|---|
| **January** | 1903.98 | 175.69 | 637.07 | 1006.25 | 1590.57 | 10399.24 |
| **June** | 1484.39 | 313.10 | 943.55 | 1379.08 | 1906.65 | 11403.53 |

Tables 5 a.- d. Multiple Linear Regression β1 Coefficients and 95% Confidence intervals. Model 1 is only the exposure and response, Model 2 is the exposure and response plus demographic covariates, and Model 3 is exposure and response plus demographic covariates, and meteorological covariates.

Table 5 a. Model 1

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | NO2 | -0.12 | -0.27 | [-0.302, 0.070] |
| **June** | NO2 | -0.08 | -0.27 | [-0.179, 0.013] |

Table 5 a. Model 2

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | NO2 | -0.01 | -0.02 | [-0.316, 0.118] |
| | Age | -0.01 | | [-0.019, <0.001] |
| | Sex | 0.04 | | [-0.364, 0.434] |
| | Asthma | -0.18 | | [-0.741, 0.374] |
| | Agself | -0.07 | | [-0.547, 0.404] |
| | Agany | 0.01 | | [-0.553, 0.571] |
| **June** | NO2 | -0.07 | -0.23 | [-0.184, 0.034] |
| | Age | <0.01 | | [-0.005, 0.010] |
| | Sex | -0.13 | | [-0.439, 0.186] |
| | Asthma | -0.10 | | [-0.529, 0.336] |
| | Agself | -0.05 | | [-0.405, 0.308] |
| | Agany | -0.01 | | [-0.488, 0.460] |

Table 5 a. Model 3

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | NO2 | -0.15 | -0.33 | [-0.692, 0.394] |
| | Age | -0.01 | | [-0.018, 0.001] |
| | Sex | <0.01 | | [-0.398, 0.407] |
| | Asthma | -0.22 | | [-0.790, 0.341] |
| | Agself | -0.05 | | [-0.533, 0.425] |
| | Agany | 0.07 | | [-0.516, 0.653] |
| | Temperature | -0.09 | | [-0.396, 0.211] |
| | Relative Humidity | -0.01 | | [-0.275, 0.261] |
| **June** | NO2 | 0.09 | -0.30 | [-0.789, 0.966] |
| | Age | <0.01 | | [-0.006, 0.010] |
| | Sex | -0.12 | | [-0.443, 0.201] |
| | Asthma | -0.11 | | [-0.559, 0.335] |
| | Agself | -0.05 | | [-0.411, 0.317] |
| | Agany | -0.02 | | [-0.517, 0.477] |
| | Temperature | 2.26 | | [-9.568, 14.096] |
| | Relative Humidity | -1.90 | | [-11.777, 7.967] |

Table 5 b. Model 1

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | O3 | 0.15 | 0.32 | [-0.042, 0.345] |
| **June** | O3 | -0.03 | -0.27 | [-0.064, 0.006] |

Table 5 b. Model 2

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | O3 | 0.14 | 0.30 | [-0.081, 0.364] |
| | Age | -0.01 | | [-0.019, <0.001] |
| | Sex | 0.02 | | [-0.374, 0.421] |
| | Asthma | -0.20 | | [-0.749, 0.354] |
| | Agself | -0.07 | | [-0.542, 0.398] |
| | Agany | 0.04 | | [-0.511, 0.591] |
| **June** | O3 | -0.03 | -0.27 | [-0.067, 0.012] |
| | Age | <0.01 | | [-0.005, 0.010] |
| | Sex | -0.13 | | [-0.438, 0.186] |
| | Asthma | -0.10 | | [-0.534, 0.329] |
| | Agself | -0.05 | | [-0.405, 0.307] |
| | Agany | -0.02 | | [-0.487, 0.456] |

Table 5 b. Model 3

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | O3 | 0.29 | 0.62 | [-0.754, 1.326] |
| | Age | -0.01 | | [-0.018, 0.001] |
| | Sex | <0.01 | | [-0.398, 0.407] |
| | Asthma | -0.22 | | [-0.790, 0.341] |
| | Agself | -0.05 | | [-0.533, 0.425] |
| | Agany | 0.07 | | [-0.516, 0.653] |
| | Temperature | 0.04 | | [-0.691, 0.767] |
| | Relative Humidity | -0.08 | | [-0.588, 0.434] |
| **June** | O3 | 0.10 | 0.91 | [-0.870, 1.064] |
| | Age | <0.01 | | [-0.006, 0.010] |
| | Sex | -0.12 | | [-0.443, 0.201] |
| | Asthma | -0.11 | | [-0.559, 0.335] |
| | Agself | -0.05 | | [-0.411, 0.317] |
| | Agany | -0.02 | | [-0.516, 4.774] |
| | Temperature | 4.82 | | [-32.377, 42.023] |
| | Relative Humidity | -4.07 | | [-35.379, 27.244] |

Table 5 c. Model 1

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | PM2.5 | -0.10 | -0.23 | [-0.287, 0.088] |
| **June** | PM2.5 | -0.08 | -0.27 | [-0.175, 0.015] |

Table 5 c. Model 2

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | PM2.5 | -0.08 | -0.18 | [-0.296, 0.130] |
| | Age | -0.01 | | [-0.019, <0.001] |
| | Sex | 0.04 | | [-0.359, 0.439] |
| | Asthma | -0.19 | | [-0.746, 0.370] |
| | Agself | -0.07 | | [-0.542, 0.411] |
| | Agany | -0.02 | | [-0.570, 0.533] |
| **June** | PM2.5 | -0.07 | -0.24 | [-0.182, 0.032] |
| | Age | <0.01 | | [-0.005, 0.010] |
| | Sex | -0.13 | | [-0.438, 0.186] |
| | Asthma | -0.10 | | [-0.532, 0.332] |
| | Agself | -0.05 | | [-0.406, 0.307] |
| | Agany | -0.01 | | [-0.486, 0.460] |

Table 5 c. Model 3

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | PM2.5 | -0.22 | -0.51 | [-1.017, 0.579] |
| | Age | -0.01 | | [-0.018, 0.001] |
| | Sex | <0.01 | | [-0.398, 0.407] |
| | Asthma | -0.22 | | [-0.790, 0.341] |
| | Agself | -0.05 | | [-0.533, 0.425] |
| | Agany | 0.07 | | [-0.516, 0.653] |
| | Temperature | -0.07 | | [-0.437, 0.295] |
| | Relative Humidity | -0.04 | | [-0.434, 0.348] |
| **June** | PM2.5 | 0.16 | 0.54 | [-1.387, 1.697] |
| | Age | <0.01 | | [-0.006, 0.010] |
| | Sex | -0.12 | | [-0.443, 0.201] |
| | Asthma | -0.11 | | [-0.559, 0.335] |
| | Agself | -0.05 | | [-0.411, 0.317] |
| | Agany | -0.02 | | [-0.516, 0.477] |
| | Temperature | 3.22 | | [-18.010, 24.546] |
| | Relative Humidity | -2.71 | | [-20.556, 15.134] |

Table 5 d. Model 1

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | Diethyl phosphate | <0.01 | 0 | [-0.070, 0.072] |
| **June** | Diethyl phosphate | -0.01 | | [-0.042, 0.028] |

Table 5 d. Model 2

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | Diethyl phosphate | 0.01 | 0 | [-0.065, 0.084] |
| | Age | -0.01 | | [-0.019, <0.001] |
| | Sex | 0.06 | | [-0.345, 0.458] |
| | Asthma | -0.21 | | [-0.769, 0.348] |
| | Agself | -0.03 | | [-0.504, 0.452] |
| | Agany | -0.10 | | [-0.611, 0.406] |
| **June** | Diethyl phosphate | -0.01 | | [-0.048, 0.028] |
| | Age | <0.01 | | [-0.005, 0.010] |
| | Sex | -0.08 | | [-0.405, 0.242] |
| | Asthma | -0.12 | | [-0.561, 0.323] |
| | Agself | -0.03 | | [-0.405, 0.345] |
| | Agany | -0.12 | | [-0.576, 0.332] |

Table 5 d. Model 3

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | Diethyl phosphate | 0.01 | 0 | [-0.064, 17.473] |
| | Age | -0.01 | | [-0.019, <0.001] |
| | Sex | 0.02 | | [-0.384, 0.424] |
| | Asthma | -0.25 | | [-0.808, 0.317] |
| | Agself | -0.03 | | [-0.509, 0.452] |
| | Agany | 0.01 | | [-0.530, 0.552] |
| | Temperature | -0.16 | | [-0.360, 0.049] |
| | Relative Humidity | 0.06 | | [-0.050, 0.174] |
| **June** | Diethyl phosphate | -0.02 | 0 | [-0.057, 0.022] |
| | Age | <0.01 | | [-0.005, 0.010] |
| | Sex | -0.10 | | [-0.427, 0.224] |
| | Asthma | -0.11 | | [-0.561, 0.334] |
| | Agself | -0.11 | | [-0.510, 0.279] |
| | Agany | <0.01 | | [-0.499, 0.502] |
| | Temperature | 1.21 | | [-0.406, 2.834] |
| | Relative Humidity | -1.02 | | [-2.432, 0.385] |

Table 5 e. Model 1

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | Dimethyl phosphate | 0.01 | 0.06 | [0.001, 0.010] |
| **June** | Dimethyl phosphate | <0.01 | <0.04 | [-0.001, 0.011] |

Table 5 e. Model 2

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | Dimethyl phosphate | 0.01 | 0.06 | [0.001, 0.011] |
| | Age | -0.01 | | [-0.019, <-0.001] |
| | Sex | -0.01 | | [-0.394, 0.377] |
| | Asthma | -0.21 | | [-0.742, 0.326] |
| | Agself | 0.05 | | [-0.406, 0.509] |
| | Agany | -0.12 | | [-0.596, 0.377] |
| **June** | Dimethyl phosphate | <0.01 | <0.04 | [-0.005, 0.011] |
| | Age | <0.01 | | [-0.007, 0.009] |
| | Sex | -0.07 | | [-0.395, 0.254] |
| | Asthma | -0.08 | | [-0.532, 0.364] |
| | Agself | 0.01 | | [-0.346, 0.362] |
| | Agany | -0.14 | | [-0.597, 0.314] |

Table 5 e. Model 3

| Month | Exposure/Covariate | β Coefficient | IQR Change | 95% CI |
|---|---|---|---|---|
| **January** | Dimethyl phosphate | 0.01 | 0.06 | [0.001, 0.010] |
| | Age | -0.01 | | [-0.018, 0.001] |
| | Sex | -0.04 | | [-0.425, 0.353] |
| | Asthma | -0.24 | | [-0.785, 0.297] |
| | Agself | 0.05 | | [-0.412, 0.518] |
| | Agany | -0.03 | | [-0.553, 0.488] |
| | Temperature | -0.13 | | [-0.325, 0.071] |
| | Relative Humidity | 0.04 | | [-0.068, 0.148] |
| **June** | Dimethyl phosphate | <0.01 | <0.04 | [-0.005, 0.012] |
| | Age | <0.01 | | [-0.007, 0.010] |
| | Sex | -0.10 | | [-0.427, 0.270] |
| | Asthma | -0.09 | | [-0.540, 0.366] |
| | Agself | -0.04 | | [-0.407, 0.327] |
| | Agany | -0.05 | | [-0.562, 0.453] |
| | Temperature | 1.07 | | [-0.520, 2.652] |
| | Relative Humidity | -0.92 | | [-2.305, 0.464] |

Table 6. Group and conditional posterior inclusion probabilities (PIPs), with air pollutants and pesticides as separate groups.

| **Exposure** | **January** | | **June** | |
|---|---|---|---|---|
| | Group | Conditional | Group | Conditional |
| **$O_3$** | 0.61 | 0.35 | 0.73 | 0.36 |
| **$PM_{2.5}$** | 0.61 | 0.35 | 0.73 | 0.31 |
| **$NO_2$** | 0.61 | 0.30 | 0.73 | 0.33 |
| **Diethyl phosphate** | 0.80 | 0.18 | 0.54 | 0.54 |
| **Dimethyl phosphate** | 0.80 | 0.82 | 0.54 | 0.46 |

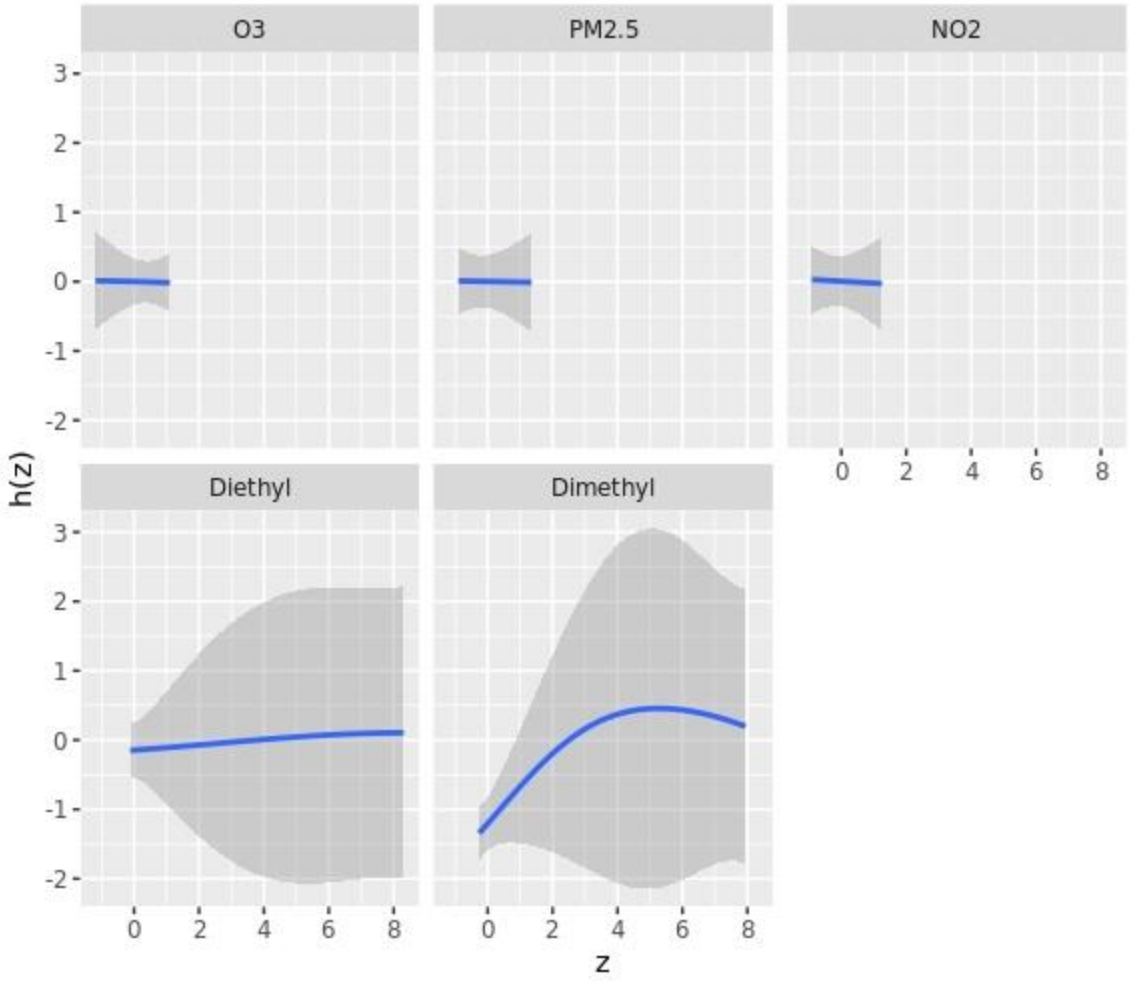


Figure 1. Cross section of univariate relationship between each exposure and log-transformed LTE4, while holding all other exposures at their 50$^{th}$ percentile in January.

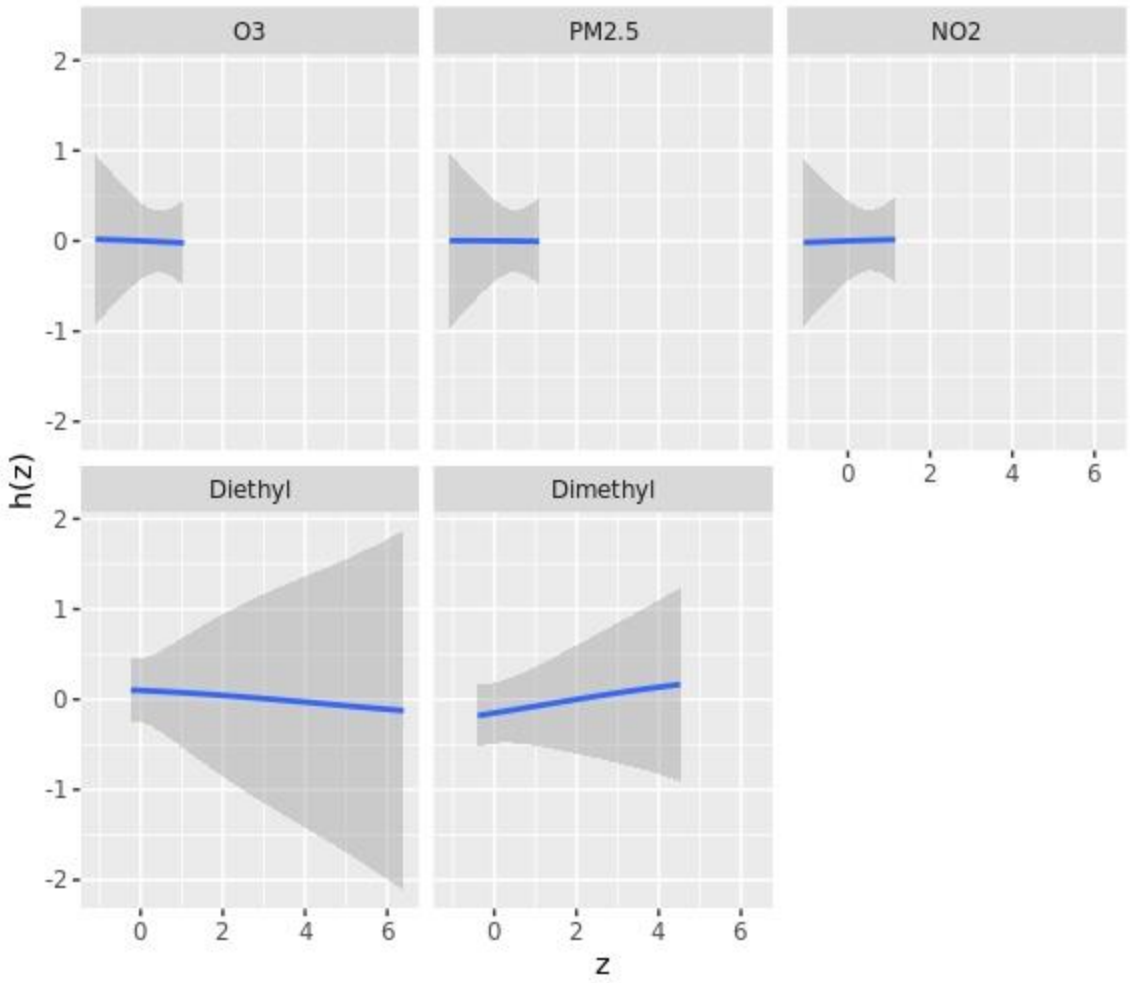


Figure 2. Cross section of univariate relationship between each exposure and log-transformed LTE4, while holding all other exposures at their 50$^{th}$ percentile in June.

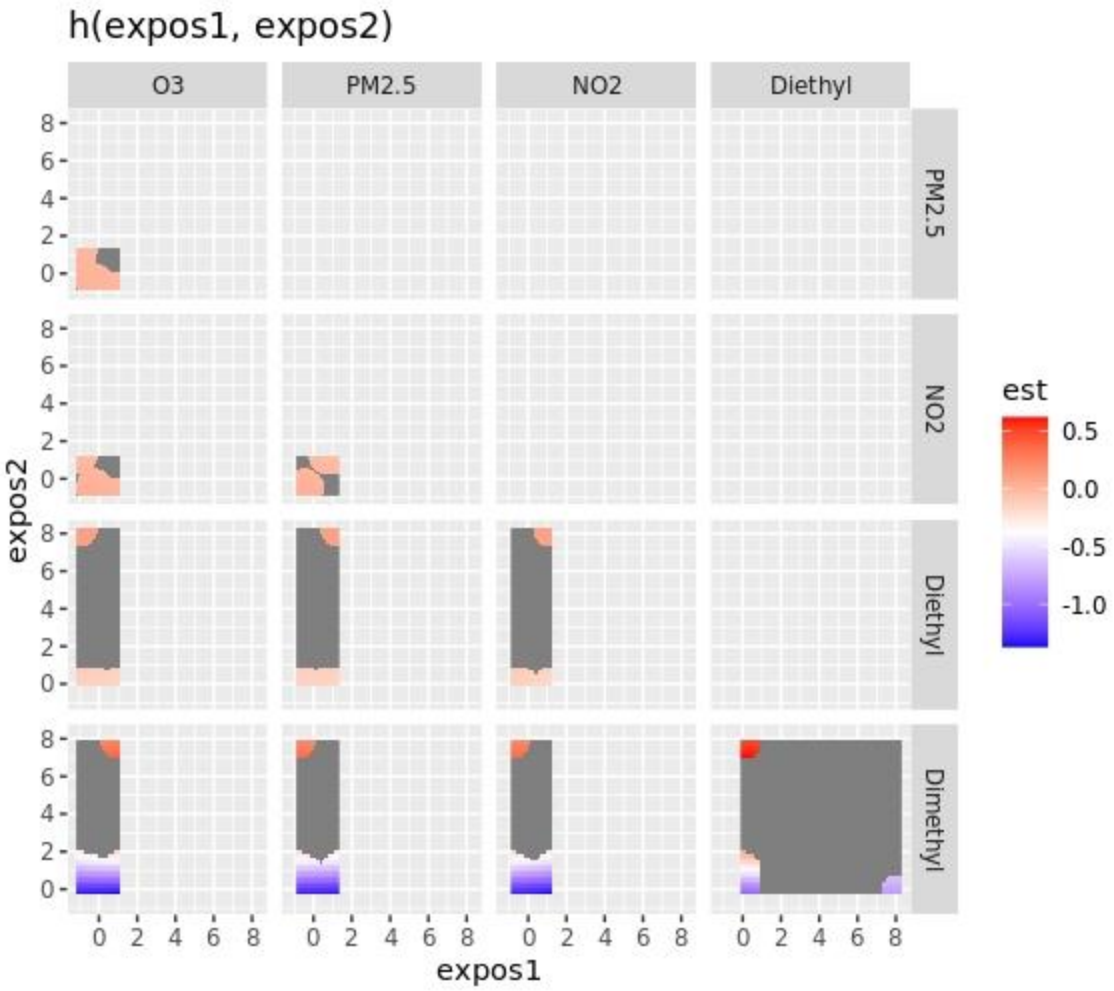


Figure 3. Exposure response pattern between two air pollutant and/or DAP exposures at the same time, and log-transformed leukotriene E4 in January. Legend shows the change in concentration of log-transformed LTE4. Red=log-transformed LTE4 increasing. Blue=log-transformed LTE4 decreasing.

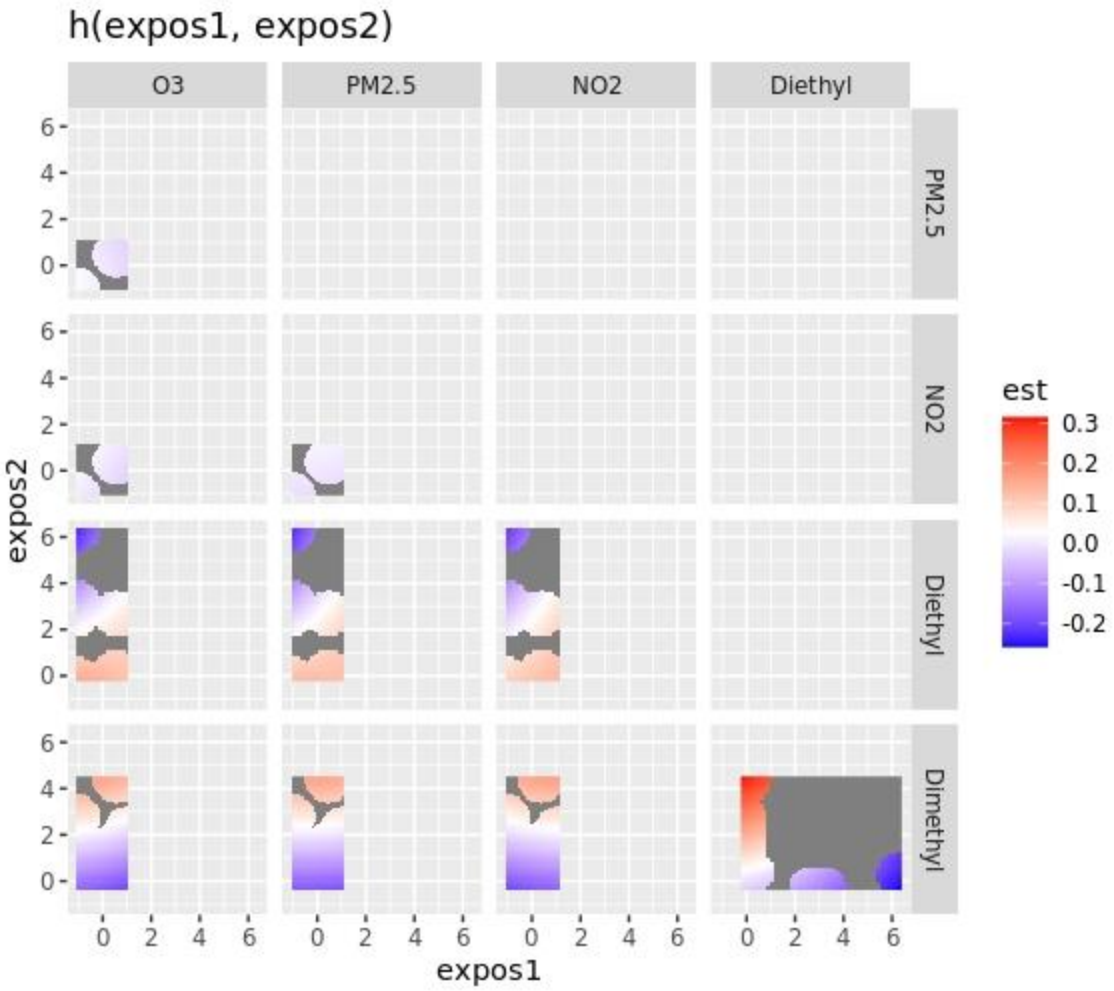


Figure 4. Exposure response pattern between two air pollutant and/or DAP exposures at the same time, and log-transformed leukotriene E4 in June. Legend shows the change in concentration of log-transformed LTE4. Red=log-transformed LTE4 increasing. Blue=log-transformed LTE4 decreasing.

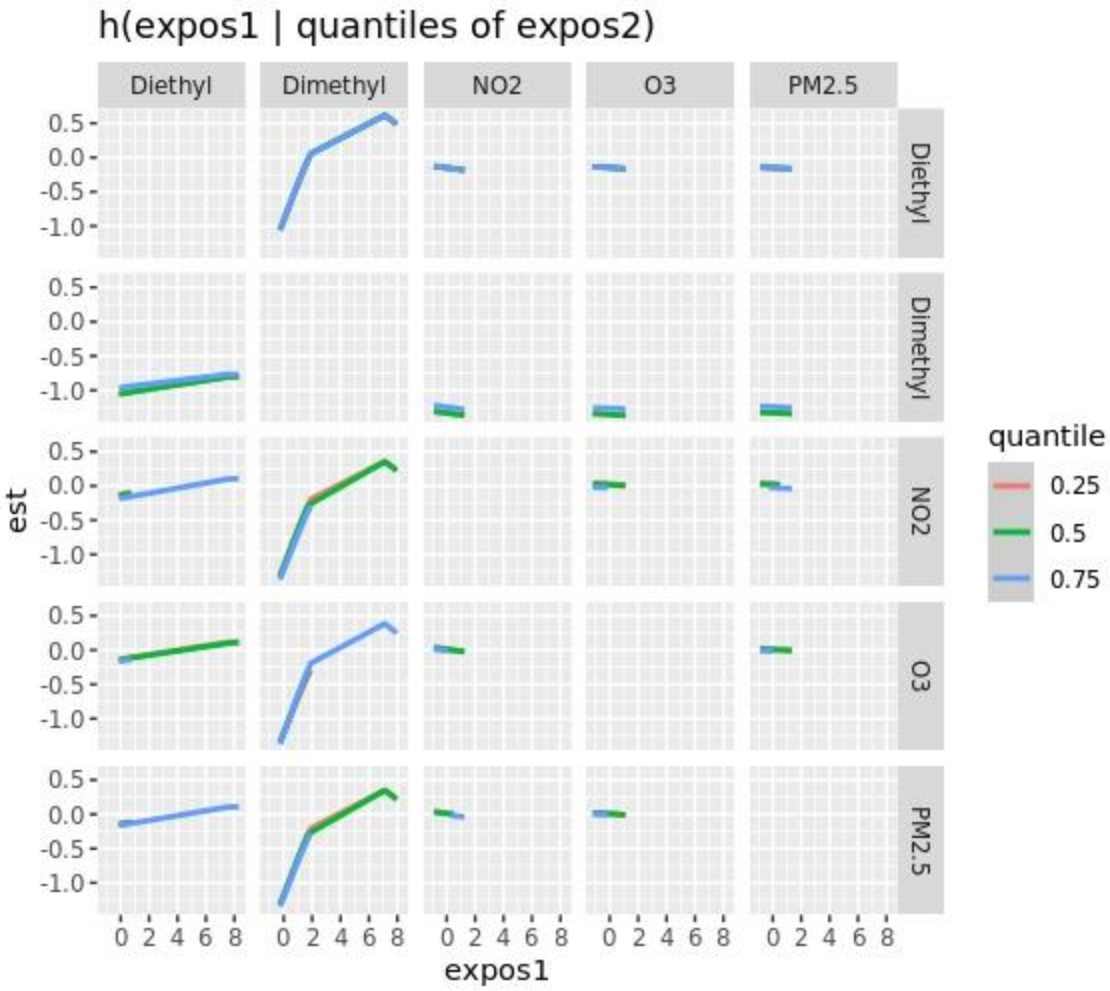


Figure 5. Relationship between exposure 1 and the outcome of urinary LTE4 given quantiles of exposure 2 in January.

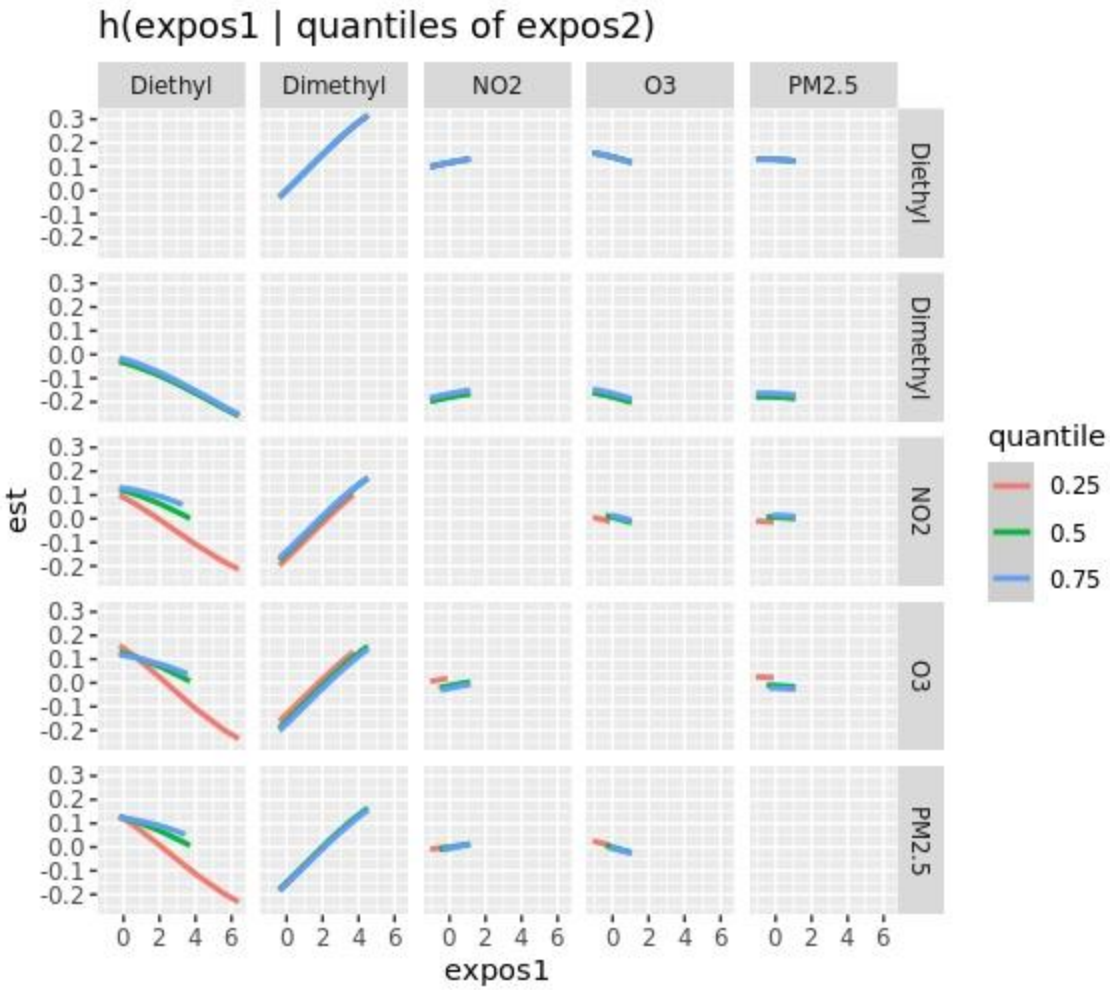


Figure 6. Relationship between exposure 1 and the outcome of urinary LTE4 given quantiles of exposure 2 in June.

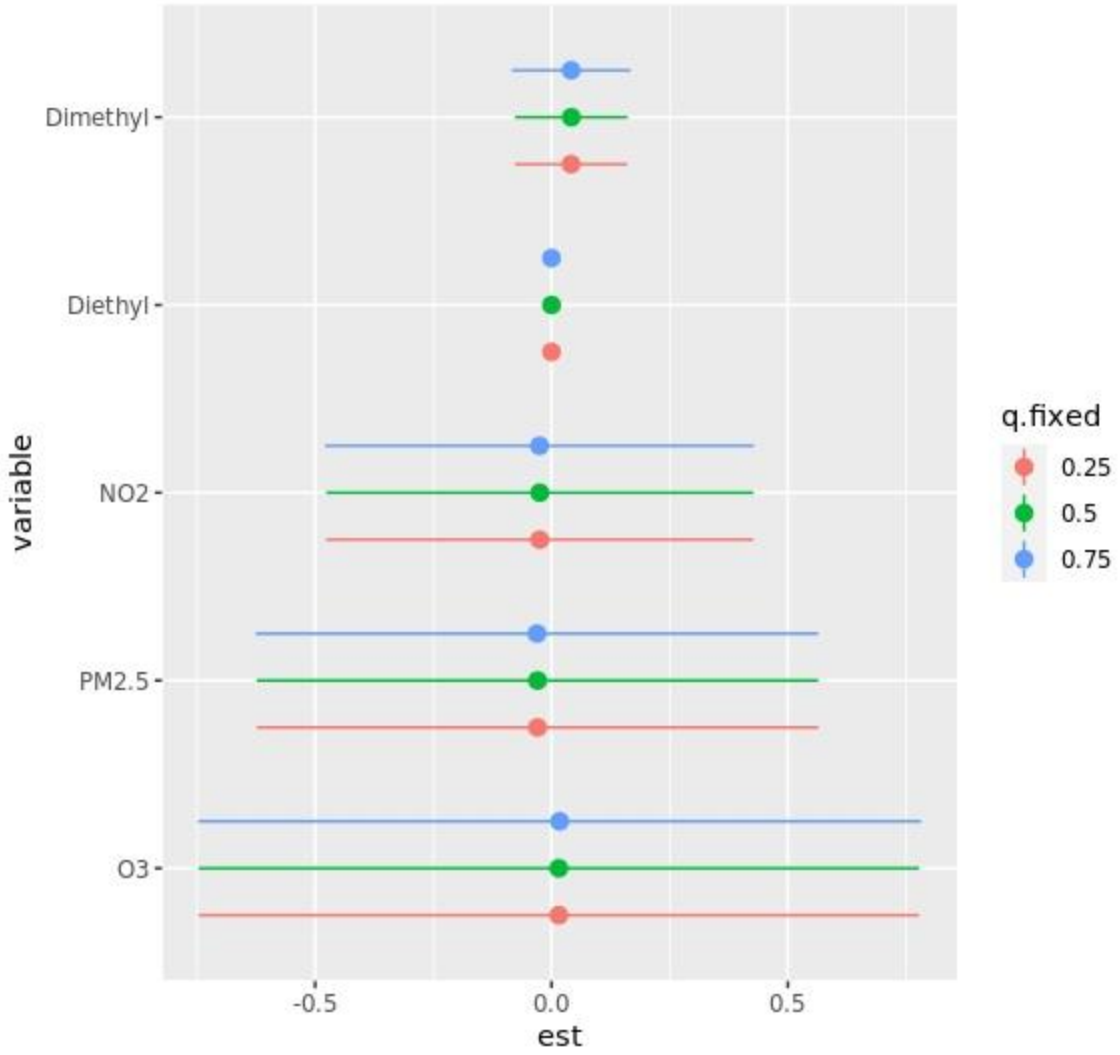


Figure 7. The effect of each exposure on LTE4 when it is at its 75th percentile compared to its 25th percentile when the other exposures are fixed at the 0.25$^{th}$, 0.5$^{th}$, 0.75$^{th}$ percentiles, in the month of January.

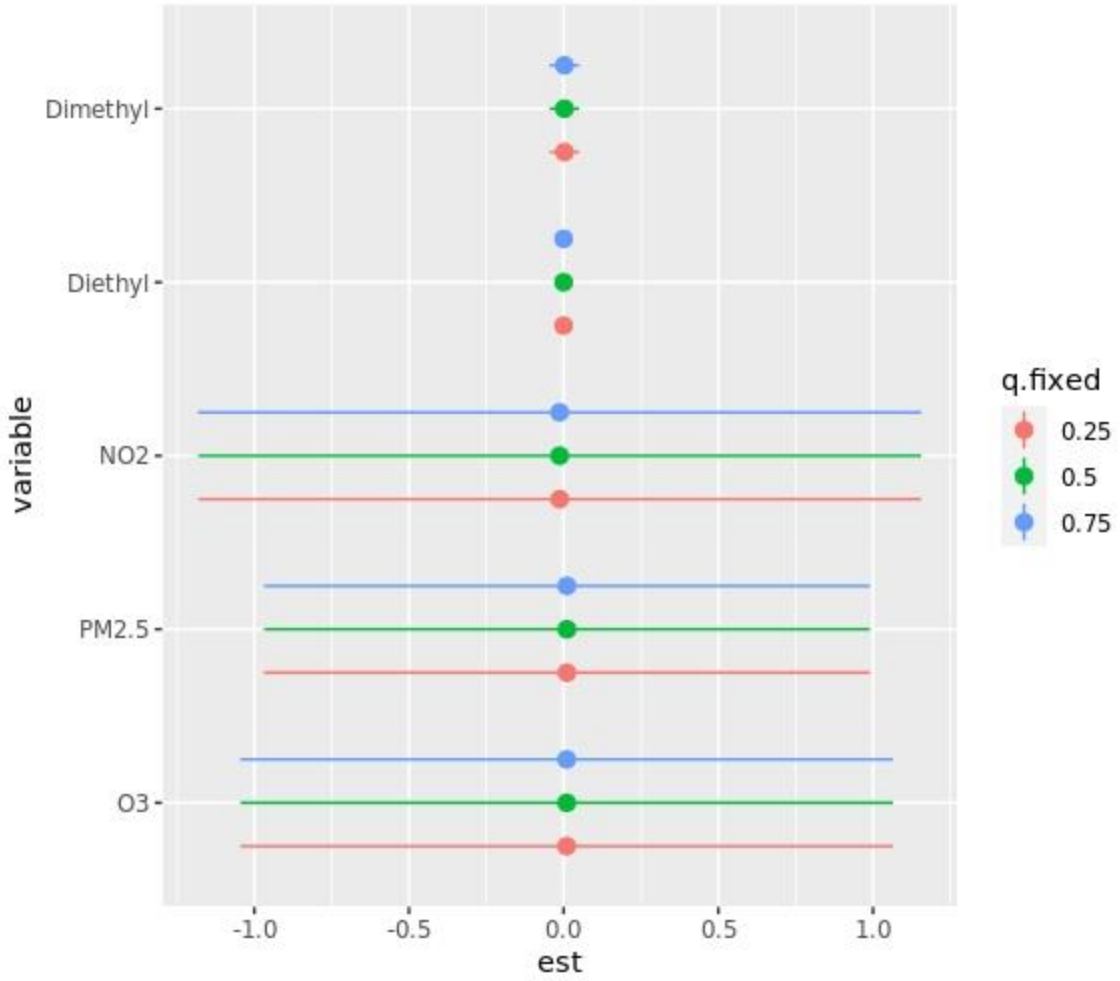


Figure 8. The effect of each exposure on LTE4 when it is at its 75th percentile compared to its 25th percentile when the other exposures are fixed at the $0.25^{th}$, $0.5^{th}$, $0.75^{th}$ percentiles, in the month of June.

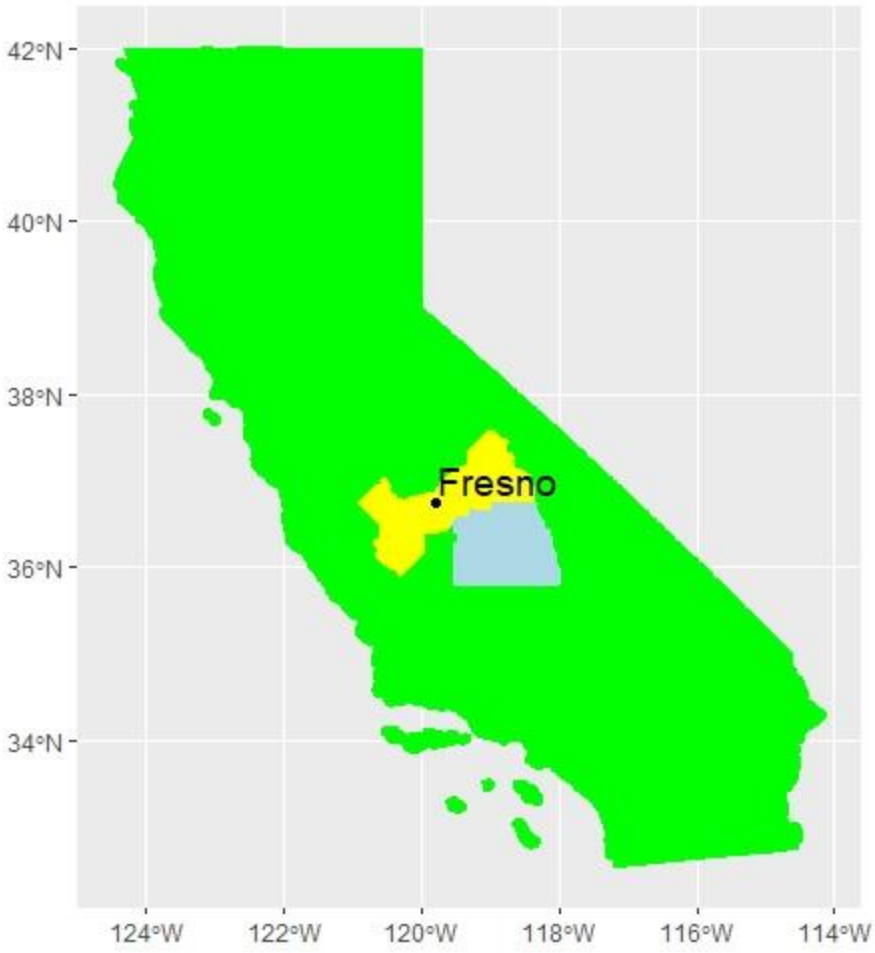

Figure 9. Fresno and Tulare Counties in Central California. Yellow indicates Fresno County, and blue indicates Tulare County.

Figure 10. Poor air quality on Colorado State University campus on October 5, 2020 due to the Cameron Peak wildfire, and wildfires burning in the West Coast. An example of a naturally occurring source of air pollution.

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