Environmental Human Health Effects of Chlorpyrifos in the Central Valley

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ABSTRACT

The use of pesticides, specifically chlorpyrifos (CPF), has been prevalent in the Central Valley for many decades due to its high effectiveness in combating agricultural pests. With the intensive use of pesticides, there has been a wide range of health problems for Central Valley residents. My research aims to study the human health impacts of CPF on brown adipose tissue, gut microbiota, and obesity caused by CPF. I used a systematic review approach, where I obtained and evaluated current scientific literature. Then, I applied the results to the Central Valley to see how they are affected. Similarly to in-vivo studies, where mice experience severe health problems, Central Valley children and workers also experience severe health problems. The health problems stemmed from many biological mechanisms, such as failure of acetylcholine degradation due to competing organophosphates (OPs) and acetylcholinesterases and poor thermoregulation and communication of brown adipose tissues with metabolic functions. In addition to biological mechanism malfunctions, socioeconomic factors play a huge role in the health burdens that workers and children face in the Central Valley. Many residents affected are often undocumented and are in the bottom percentiles in terms of economic wealth and many have inadequate access to healthcare and treatment when needed. Such inequities to resources result in high mortality rates and reduced lifespans. Moving forward, the health of workers and children must be addressed and work towards a future with less pesticide use and increased access to resources.

KEYWORDS

environmental justice, agriculture, obesity, brown adipose tissue, gut microbiota

INTRODUCTION

With rapid population growth in the past century, the demand for agricultural products has increased (Hazell and Wood 2012). In the United States, the Central Valley of California produces more than half of America's fruits, vegetables, and nuts. In order to sustain a massive scale of agricultural output, many farms use pesticides to control pests that decrease the yield (Tudi et al. 2021). Governmental organizations, such as the California Department of Agriculture, and private pesticide producers, such as Corteva, invest great amounts of resources towards pesticide research and development. From 2008 to 2012, the United States consumed 1.1 billion pounds on pesticides and spent around 797 billion dollars on pesticide consumption (Atwood and Paisley-Jones 2017). About sixty percent of all pesticide consumption is for agriculture (Atwood and Paisley-Jones 2017). Not only are pesticides used to increase yield, but they are also used to protect the inherent vulnerability of farms. Most of Central Valley's agriculture is monoculture, which makes its farms extremely vulnerable to pest invasions and disease (Cohen 2021). Within many broad categories of pesticides, chlorpyrifos (CPF) has been a popular choice due to its versatility in usage and broad applications in Central valley agriculture (Christensen et al. 2009).

CPF has been highly effective because it effectively targets conserved features of many pests, such as worms, rodents, and insects, which are all present in the Central Valley climate (Kross 2016). CPF has a wide application, both used for livestock, seasonal crops, and livestock feed (Christensen et al. 2009). Farmers do not have to apply a mix of pesticides for each individual pest, which means that agribusinesses are saving money and resources (John and Shaike 2015). CPF is more persistent in the environment in comparison to other popular pesticides, making it more effective for a lower price (John and Shaike 2015**).** In addition, CPF is relatively cheaper than many commercially available pesticides, making it an attractive option for many farmers (John and Shaike 2015). Due to its appealing qualities as a pesticide, farmers are drawn to using predominantly chlorpyrifos. In the United States alone, farmers use ten million pounds of chlorpyrifos, even after strict regulations imposed by the Environmental Protection Agency (EPA) (US Department of Health and Human Services 1997). The high use of CPF places the local ecosystem and population at risk, especially in the Central Valley.

Chlorpyrifos extensively damages the ecosystem health in the Central Valley, as well as the health and livelihoods of migrant workers and their families. In the Central Valley, where CPF exposure is great, many members, specifically low-income migrant families, face health issues directly correlated to chlorpyrifos exposure (Walton et al. 2021). CPF has a broad scope of toxicity, which means that there is a diversity of health issues. Some apparent health outcomes are obesity, which is caused by a variety of factors such as impaired brown adipose tissue and gut microbiota. Much of these health issues are passed down to the next generation, where many children are born with permanent disabilities (Harley et al. 2011). If children are fortunate enough to not inherit CPF related health illnesses, the constant exposure impairs their development, which causes problems throughout their childhood and their adulthood (Hicks 2020). Many low-income and migrant families do not understand the dangers of their exposure to CPF, because there is an educational and healthcare gap (Walton et al. 2021). Migrant families and low-income families do not have healthcare or the resources to get treatment, which is a big issue when it comes to pesticides and human health.

In this project, I will investigate how chlorpyrifos affects children and workers in the Central Valley. I aim to use data from experiments conducted on mice to demonstrate associations between chlorpyrifos exposure and health effects of people in this region. I will utilize a systematic review approach, where I hope to find appropriate studies and extrapolate their study methods and results. I will split my studies into three components. The first component focuses on how chlorpyrifos disrupts brown adipose tissue and its impacts on metabolism. The second component studies the effects of gut microbiota after its exposure to chlorpyrifos. The final component of obesity ties in the first two components by providing a framework to address the gaps in current literature. The goal of this project is to understand how we can mitigate the effects of chlorpyrifos and to see if there is a feasible solution that supports current agricultural demands and human health.

BACKGROUND

Central Valley Geography and Agricultural History

The Central Valley of California is a 450 mile long region in Central California that produces 25% of the nation's food supply. The region extends from Bakersfield (Tulare Basin) at its southern tip to Redding (Sacramento Valley) at its northern end (USGS n.d.). The Central Valley is a great place for agriculture mainly due to two reasons. Its geography next to the Sierra Nevada mountains is critical. Over thousands of years, rich sediment and nutritious soil have been deposited throughout this area due to its expansive systems of rivers (Katibah 1984) (Figure 1). This reduces the cost of transporting synthetic fertilizers in its early stages of development. The Central Valley also has a consistent, dry climate. Such a dry climate provides consistent temperature, but it places the Central Valley at a high risk of drought during the summer (Thomas 2017). Despite such vulnerabilities in temperature in the summer, the Central Valley's ability to support crop growth for three seasons makes this area a highly desirable place for farming.

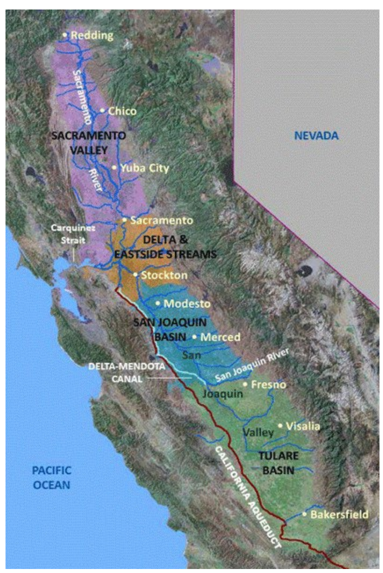

Figure 1. California's Central Valley is divided into its main regions (USGS n.d.). The Central Valley has many geographical qualities that make it ideal for agriculture. In the Sacramento Valley region, the Sacramento River has many tributaries that branch out, allowing for water to reach many different parts of the valley. In the San Joaquin and Tulare Basins, the San Joaquin River flows to provide water to communities and farms. In addition, the development of the California Aqueduct (near the I-5 freeway) is critical to delivering water to the Central Valley. The California Aqueduct brings water from the high elevation Sierra Nevada mountain ranges to the low elevation Central Valley for agriculture.

With such agricultural development in the Central Valley, many jobs pertaining to the agricultural sector have been developed over the numerous decades following World War II. This is due to the development of irrigation and pesticides in the region (California Agriculture 1996). With such development, many jobs in the agricultural sector have been created (California Agriculture 1996). With many opportunities in the market, farmer families, many of them undocumented, made their way to the Central Valley to find employment. About 92 percent of all farmworkers are of Hispanic descent, and 77 percent of farmworkers are non-citizens (Rogers and Buttice 2013). Farm owners know that most workers have no other employment option, so they require migrant families to invest long hours with very low pay and no benefits (Lopez 2007). Due to the laborious circumstances and high exposure to pesticides, many migrant families faced pesticide-related health issues without getting the necessary treatment and rest they needed (Hicks 2020). This socioeconomic disparity in the Central Valley with migrant families has been prevalent for many decades and continues to be a problem from a public health standpoint.

Chemical Properties of Chlorpyrifos

Chlorpyrifos is an organophosphate (OP) sold in white or colorless crystals (Christensen et al. 2009). CPF has a relatively potent smell similar to rotting eggs or garlic (Christensen et al. 2009). CPF has lipophilic (hydrophobic) properties that make it persistent in the human body. The nonpolar aromatic ring, as well as the two attached methyl groups contribute to its nonpolar structure (Figure 2). Such compounds have affinity towards carbon and hydrogen based compounds, which are foundational structures to lipids (Zhang et al 2021). When CPF enters the body, it is very hard to diagnose initial exposures of the pesticide. CPF is not excreted as easily; although Phase I metabolites like Cytochrome P450 (CYP450) can metabolize chlorpyrifos into its oxon form, CYP450 and other Phase I/II metabolites struggle to excrete chlorpyrifos out of the system (Zhang et al 2021). As workers continually get exposed to CPF, it accumulates in fat cells and causes problems over a long period of time. The accumulation of chlorpyrifos is the precursor to obesity and brown adipose tissue dysfunction (Audelo 2016).

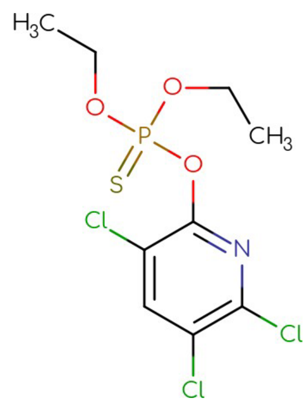

Figure 2: Structure of chlorpyrifos, generated by ChemDraw. The primary nonpolar components are labeled in black. The $-CH_3$ (methyl) groups and the aromatic structure at the bottom of the structure contributes to its hydrophobic behavior.

Chlorpyrifos affects human health through several different biological mechanisms. CPF is metabolized by Cytochrome P450, a Phase I metabolite, which is then turned into a chlorpyrifos oxon (Zhang et al 2021). When CPF is in this state, it is highly reactive with nervous system agents. The CPF oxon, labeled OP (organophosphates in Figure 3), would block the decomposition reaction of acetylcholine to acetate and choline. The CPF oxon state would outcompete and/or degrade acetylcholinesterase (AchE), which is responsible for degrading acetylcholine (Ach). Ach degradation is vital to a functioning nervous system, as a high concentration of acetylcholine will cause various short and long term problems. Short term problems include muscle spasms, blurry vision, and weakness, while long term issues include Parkinson's and other chronic illnesses (Costello 2009). In addition, the improper degradation of Ach is linked with brown adipose tissue signaling problems and gut microbiota communication with cells (Conceicao 2017).

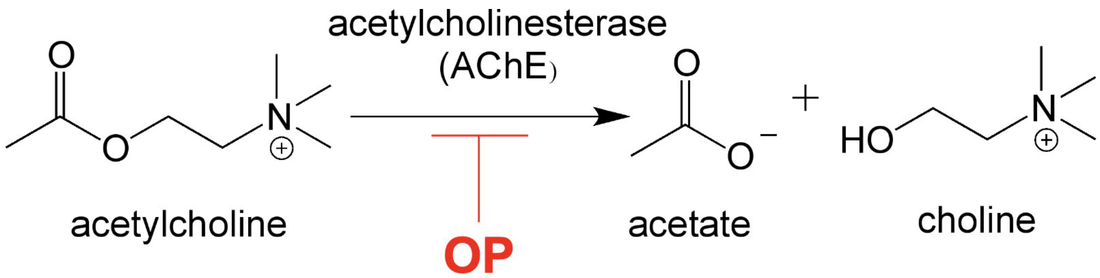

Figure 3. Degradation of acetylcholine blocked due to chlorpyrifos (Nomura 2022). AChE catalyzes the degradation of Ach, which is a critical function of the central and the peripheral nervous systems. CPF will form an acetylcholinesterase-inhibitor complex, effectively blocking AchE from performing its normal function of decomposing Ach to acetate and choline.

Due to its chemical properties, CPF is well-known to target conserved features of pests and has high resistance to biodegrading. A conserved feature is often a biological function that is prevalent in almost any species (Lu et al. 2020). For example, most insects utilize lipid reserves to support energy intensive functions like myogenic flight. Pesticides target lipid metabolism by increasing toxicity when lipids are released for energy use, or pesticides halt lipid metabolism completely (Arrese and Soulages 2010). Humans are not exempt from the effects of chlorpyrifos, as humans also have lipid reserves for energy storage (Lu et al. 2020). When exposed to pesticides in large quantities and/or long durations of time, humans will face health repercussions that are permanent (Casida and Durkin 2016).

METHODS

General Study Design

My study design for this systematic review was supported by multiple sources from various PubMed searches listed in the reference section. I initially adapted a meta-analysis model to push forward my analysis, but I changed my approach to be a systematic review to capture more literature in my studies. Outlined below were the steps:

1. I created a study question and subquestions. This was one of the first steps to my research. My study questions and subquestions were modified throughout Fall 2022 and Spring 2023.

2. I formulated a search strategy. This included searching papers using specific keywords (called an inclusion criteria) and specific words to omit (called exclusion criteria). I kept my search terms broad so that I have many options when evaluating papers. More information can be found under the search strategy section.
3. I created an organized table of papers that I potentially wanted to use from the collected papers. Not all papers from this table ended up in the results section for analysis.

Search Strategy

I approached this systematic review in a very structural way. The very first step to any searching would be to make a concept map of things that I want to search. I would start by listing a broad term (e.g., pesticides) and then branch out to more specific details (e.g., DDT, chlorpyrifos, etc). Then, I searched for papers with the keywords that I wrote out. I went to websites such as PubMed, Science Direct, and Multidisciplinary Digital Publishing Institute (MDPI) to insert my keywords. These keywords are important, because they will become my inclusion and exclusion criteria as my project develops. Any paper that fits the criteria was saved through Zotero, a citation software that saves literature. Once I accumulated many papers, I rereviewed them to see if they fitted my analysis. The study tables below show papers that meet the inclusion criteria and are papers that may be used in interpreting the results.

Organized Tables

I decided to organize my study tables by subquestion. The study tables include the name of the article, authors, publication date, observations, and results. I added the inclusion and exclusion criteria for each subquestion above the tables.

How does chlorpyrifos affect brown adipose tissue behavior?

The inclusion criteria included brown adipose tissue, chlorpyrifos, and thermogenic mechanisms related to cell signaling and coupling reactions. The exclusion criteria were strictly to not include pesticides that were not chlorpyrifos. Table 1 below shows potential candidates for papers to use for my study.

Table 1. Summary tables based on searched literature for brown adipose tissue behavior. Summary of articles for potential use in systematic review analysis.

Article Name	Authors and Publication Date	Experimental Approach	Results
The pesticide chlorpyrifos promotes obesity by inhibiting diet-induced thermogenesis in brown adipose tissue	Wang et al. 2021	Tested 34 different proteins when exposed to chlorpyrifos under different temperatures	6 of 34 were related to being affected by chlorpyrifos. The proteins affected lead to the development of obesity and other lipid related health issues.
Environmental toxicants, brown adipose tissue, and potential links to obesity and metabolic disease	Wang et al. 2022	Investigated potential environmental health issues related to chlorpyrifos	Chlorpyrifos is related to inhibiting the brown adipose tissue (BAT) pathway responsible for lipid thermogenesis under very low doses.

How does chlorpyrifos affect gut microbiota behavior?

The inclusion criteria included chlorpyrifos, gut microbiota, gastrointestinal behavior, and lipopolysaccharide (LPS) mechanisms in the small intestine. The exclusion criteria was strictly to not include pesticides that were not chlorpyrifos. Table 2 below shows potential candidates of papers used for my study.

Table 2. Summary tables based on searched literature for gut microbiota behavior. Summary of articles for potential use in systematic review analysis.

Article Name	Authors and Publication Date	Experiment Approach	Results
Chronic Perigestational Exposure to Chlorpyrifos Induces Perturbations in Gut Bacteria and Glucose and Lipid Markers in Female Rats and Their Offspring	Djekkoun et al. 2022	Four mice groups (n=4): ● Control (no chlorpyrifos) ● Chlorpyrifos with rapeseed oil ● Control inulin (sugar solution) ● Inulin with chlorpyrifos Four groups for offspring using the same categories above.	Results imply that CPF has an impact on lipid and glucose metabolism because it kills off good microbiota. Microbiota are in charge of doing many lipid metabolic functions.
Organophosphorus pesticide chlorpyrifos intake promotes obesity and insulin resistance through impacting gut and gut microbiota	Liang et al. 2019	Four different groups (n=8), study over 90 days: ● HFD (high fat diet) ● HCPF (high fat diet + pesticide) ● NFD (no fat diet) ● NCPF (no fat diet + pesticide) The experimental groups were treated with 5 mg/kg/day.	Chlorpyrifos impairs intestinal function which allows LPS (gram negative bacteria) to more easily enter the intestine. Gram negative bacteria compete with commensal bacteria in the gut and ultimately outcompete them. This causes low-grade inflammation, which is directly correlated with obesity.
Chronic chlorpyrifos exposure elicits diet-specific effects on metabolism and the gut microbiome in rats	Fang et al. 2018	Groups (n=6) categorized by: *Category 1:* NF= Normal fat diet HF= high fat diet *Category 2:* C=control (no CPF) L= low amount of pesticide; 0.3mg/kg H= high amount of pesticide; 3 mg/kg	There is a strong correlation that indicates that CPF is responsible for killing good microbiota.

How does chlorpyrifos affect weight gain?

The inclusion criteria included chlorpyrifos, weight gain, in vivo studies (preferably mice/rat studies), and a response variable that measures weight gain. The exclusion criteria were strictly to not include pesticides that were not chlorpyrifos. Table 3 below shows potential candidate papers to use for my study.

Table 3. Summary tables based on searched literature for obesity. Summary of articles for potential use in systematic review analysis.

Article Name	Authors and Publication Date	Experiment Approach	Results
Weight Gain Associated with Chronic Exposure to Chlorpyrifos in Rats	Meggs and Brewer 2007	Two main groups (n=10): the control group and the experimental group (treated 5 mg/kg/day). Approach: Measure weight over time=0 months, 2 months, 3 months, and 4 months.	Control group weight and experimental group weights are shown, respectfully, for three time intervals. 2 months: (335.7+/- 16.7 g vs. 318.6+/- 15.8 g; p=0.034). 3 months: (350.1+/-16.4 g vs. 322.3+/-21.3 g p=0.006) . 4 months (374.4+/-22.2 g vs. 340.2+/-25.2 g p=0.006) *Significant weight increase as seen in the 95% confidence interval above. Low p-value indicates statistically significant results.
Rats gain excess weight after developmental exposure to the organophosphorothionate pesticide, chlorpyrifos	Lassiter and Brimijoin 2007	Two main groups: the control group and the experimental group (dosed with 2.5 mg/kg/day).	Did not prove CPF was a definite source for obesity. However, data shows significant changes in weight of the mice exposed to CPF.
The mechanistic basis for the toxicity difference between juvenile rats and mice following exposure to the agricultural insecticide chlorpyrifos	Sette et al. 2022	Approach (n=8-16): ● First study with weight gain ● Second study with brain AChE ● Third study with CES (CES removes CPF-oxon, which inhibits AChE)	There is a difference between mice and rats when affected by CPF (rats are more affected) Useful to know because rats have higher levels of CYP450 and CES activity. It seems like CPF is affecting these metabolic process the most, which is linked with AChE degradation

RESULTS

Results Overview

I conducted a systematic review of the existing literature on lipid metabolism and chlorpyrifos. Here is an outline on how I approached my analysis of my findings. This five step outline is a general format that most biostatisticians and researchers use to conduct a systematic review:

1. I created a table that summarizes my papers in an organized manner
2. The table contained critical study information, such as sample size, study design, and results.
3. I wrote a general narrative that highlights the main findings of my review.
4. I mentioned the biases involved in the study.
5. I addressed the limitations that are present in the study.

General Context of the Study

At the beginning of the year, I created a central research question with three detailed sub questions that address chlorpyrifos affecting human health. Then, I constructed a basic inclusion and exclusion criteria that fit the objective of my research. I explored the relationships between the pesticide and health effects to see if current research is sufficient to understand the pesticide's interaction. I organized all the papers I collected into a study table, which includes detailed information about the statistics, methodology, and graphics presented in the study. Overall, I identified that there were many studies that did show the correlation between chlorpyrifos and lipid dysfunction. However, I found that almost all of the open access studies were oriented towards in vivo studies (mice studies). There were very few studies related to humans, and if there were, they either covered very broad categories of human health effects or were exclusive to a very specific group of people.

Study Table

I listed studies organized by sub question and inclusion and exclusion criteria. I included the article name/link, the associated authors, the experimental approach, and the results. This table is a more refined and finalized version from the methods section.

How does chlorpyrifos affect brown adipose tissue behavior?

The inclusion criteria included brown adipose tissue, chlorpyrifos, and thermogenic mechanisms related to cell signaling and coupling reactions. The exclusion criteria was strictly to not include pesticides that were not chlorpyrifos. Table 4 below shows articles used for analysis.

Table 4. Summary table based on searched literature for brown adipose tissue behavior. Summary of articles used in systematic review analysis.

Article Name	Authors and Publish Date	Experimental Approach	Results
The pesticide chlorpyrifos promotes obesity by inhibiting diet-induced thermogenesis in brown adipose tissue	Wang et al. 2021	Tested 34 different proteins when exposed to chlorpyrifos under different temperatures	6 of 34 were related to being affected by chlorpyrifos. The proteins affected lead to the development of obesity and other lipid related health issues.
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How does chlorpyrifos affect gut microbiota behavior?

The inclusion criteria included chlorpyrifos, gut microbiota, gastrointestinal behavior, and lipopolysaccharide (LPS) mechanisms in the small intestine. The exclusion criteria were strictly to not include pesticides that were not chlorpyrifos. Table 5 below shows articles used for analysis.

Table 5. Summary tables based on searched literature for gut microbiota behavior. Summary of articles used in systematic review analysis.

Article Name	Authors and Publish Date	Experiment Approach	Results
Chronic Perigestational Exposure to Chlorpyrifos Induces Perturbations in Gut Bacteria and Glucose and Lipid Markers in Female Rats and Their Offspring	Djekkoun et al. 2022	Four mice groups: ● Control (no chlorpyrifos) ● Chlorpyrifos with rapeseed oil ● Control inulin (sugar solution) ● Inulin with chlorpyrifos Four groups for offspring using the same categories above.	Results imply that CPF has an impact on lipid and glucose metabolism because it kills off good microbiota. Microbiota are in charge of doing many lipid metabolic functions.
Organophosphorus pesticide chlorpyrifos intake promotes obesity and insulin resistance through impacting gut and gut microbiota	Liang et al. 2019	Four different groups (n=8), study over 90 days: ● HFD (high fat diet) ● HCPF (high fat diet + pesticide) ● NFD (no fat diet) ● NCPF (no fat diet + pesticide) The experimental groups were treated with 5 mg/kg/day.	Chlorpyrifos impairs intestinal function which promotes LPS (gram negative bacteria) to more easily enter the intestine. Gram negative bacteria compete with commensal bacteria in the gut and ultimately outcompete them. This causes low-grade inflammation, which is directly correlated with obesity.

How does chlorpyrifos affect weight gain?

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Table 6. Summary tables based on searched literature for obesity. Summary of articles used in systematic review analysis.

Article Name	Authors and Publish Date	Experiment Approach	Results
Weight Gain Associated with Chronic Exposure to Chlorpyrifos in Rats	Meggs and Brewer 2007	Two main groups (n=10): the control group and the experimental group (treated 5 mg/kg/day). Approach: Measure weight over time=0 months, 2 months, 3 months, and 4 months.	Control group by 2 months (335.7+/- 16.7 g vs. 318.6+/- 15.8 g; p=0.034). This difference increased at 3 months (350.1+/-16.4 g vs. 322.3+/-21.3 g p=0.006) . At 4 months (374.4+/-22.2 g vs. 340.2+/-25.2 g p=0.006) *Significant weight increase as seen in the 95% confidence interval above
Rats gain excess weight after developmental exposure to the organophosphorothionate pesticide, chlorpyrifos	Lassiter and Brimijoin 2007	Two main groups: the control group and the experimental group (dosed with 2.5 mg/kg/day).	Did not prove CPF was a definite source for obesity. However, data shows significant changes in weight of the mice exposed to CPF.

Brief Summaries of Studies

In general, most of the studies (shown in Tables 4 and 5) summarized the effects of chlorpyrifos on different metabolic functions of rats. The first component of this paper talked about how chlorpyrifos affects brown adipose tissue. Both studies concluded that brown adipose tissue function falters with chlorpyrifos; the first study talked about how it is correlated with obesity while the second study talked about how it affects lipid thermogenesis. The second component talks about how chlorpyrifos affects microbiota behavior. All studies concluded that chlorpyrifos restricts the resource of beneficial bacteria. Chlorpyrifos exposure decimated the population of beneficial bacteria, which are correlated with many metabolic disorders and gastrointestinal issues. The last component of this paper tied in the ideas from the first two components. The studies about obesity talked about notable weight changes that the chlorpyrifos exposed mice experienced. Though both studies do not conclude that chlorpyrifos is directly related to obesity, both strongly suggested that further experiments were needed to make the correlation between chlorpyrifos and obesity more visible.

Limitations of Studies Reviewed

There were many limitations in the studies. I wanted to highlight two major limitations that I found and will explain them in detail:

1. Studies exclusively used rats, mice, or zebrafish
2. Limited access to human studies

Studies with rats and zebrafish were quite critical to understanding how chlorpyrifos works without harming human subjects. In addition, in vivo studies were replicable and less expensive. Such characteristics of in vivo studies made them extremely powerful and efficient for many scientists. However, due to the fact that in vivo studies were so convenient in comparison to human studies, I found that in vivo studies dominate the literature so far. During my search, it was difficult to find human studies, and after looking through many research databases, I was only able to find a handful of them. All of my results were drawn from in vivo studies, due to their easy accessibility and connectivity with each other.

Another problem I ran into was the limited amount of human studies accessible. Sources like PubMed, MDPI, Science Direct, and Google Scholars had less than five articles combined that specifically fit my search criteria. Much of the minute CHAMACOS data and human studies were exclusive to graduate students and/or CHAMACOS affiliated faculty and obtaining permission was very difficult. This meant that there was insufficient information to draw conclusions from human studies, besides the broad overview provided in some select papers. CHAMACOS data is highly valuable, as this partnership provides researchers with many decades of longitudinal data and insight into how chlorpyrifos affects human health.

Biases Present in Study

I had a very small exclusion criteria in comparison to other systematic reviews. This was due to the broad nature of articles presented by the scientific community. Many studies about chlorpyrifos and lipid metabolism often presented on topics that were overlapping with other biological mechanisms, so it was inherently difficult to have a focused exclusion criteria. Having a broad exclusion criteria meant that there was other external information that influenced the overall systematic review. In addition, it was common for many systematic reviews to have multiple article reviewers. Most of the article work and article selection was done by me, with very little intervention from outside sources. This means that there was potential bias when articles were selected for this study, since there were less people looking at the papers.

DISCUSSION

Discussion Introduction

The lack of epidemiological studies focused on specific human health outcomes is a concerning issue in the pesticide research community. My findings from existing literature are critical to understanding how chlorpyrifos affects human health. With limited research on humans, animal studies provide an important framework for epidemiological studies. In this discussion, I will apply what is currently known about chlorpyrifos to the residents of the Central Valley. My goal is to understand how human health is altered through pesticide exposure by exploring mechanisms in brown adipose tissue behavior, gut microbiota, and obesity. Then, I address how we can balance the interests between human health and agricultural production.

The issue of pesticides, agriculture, and human health is not a clear-cut matter. There are multiple elements and nuances to this problem, yet current literature seems to neglect many elements that are critical to understanding. Some of these issues lie in children's health and worker's health, which are the focus of this discussion. Children and workers who are affected by chlorpyrifos are typically from lower socioeconomic groups, which means that there are significantly less groups, such as profit-based corporations, interested in studying them (Robinson and Carson 2015). It takes a lot of money and resources to work with these communities, and firms with money would rather spend that money on corporate development (Robinson and Carson 2015). Obtaining permission to collect data is challenging because workers may not be able to stick with research programs or may face language barriers from research programs (Lopez 2007). The paper will further investigate these issues in relation to both children's and worker's health based on past research.

Application of Experimental Studies to the Central Valley Population

Children's Health and Brown Adipose Tissue

Children are one of the most vulnerable populations, because much of their cellular processes (e.g., their metabolic processes, such as lipogenesis and gluconeogenesis) are still developing. Chlorpyrifos inhibits acetylcholinesterase, which leads to the excessive buildup of acetylcholine. With excess acetylcholine buildup, there is an excessive release of calcium ions, which inhibit brown adipose tissue function (Gutgesell et al. 2020). Brown adipose tissue works closely with the mitochondria to prevent hypothermia, increase insulin sensitivity, and circulate triglycerides (fats) in the circulatory system (Wang et al 2021**)**. From my investigation, there are clear research to how chlorpyrifos affects brown adipose tissue and acetylcholinesterase function. What I did not find in my research was any study of how it affects children long term.

Brown adipose tissue dysfunction in children causes many other off-target developmental problems. Current research suggests that brown adipose tissue is generally associated with insulin sensitivity and thermogenesis (Wang et al 2022). There are mechanisms where brown adipose tissue works with acetylcholinesterase to regulate lipogenesis and thermogenesis (Gutgesell et al. 2020). Without proper cellular communication with AchE and Ach levels, there will be many neurological developmental problems (Raanan et al. 2015). Research that focuses on neurological problems, such as fetal development, may trace back to brown adipose tissue dysfunction (Harley et al. 2011). PON1 is a gene that helps detoxify organophosphates (OPs), and when PON 1 mutates, there will be a higher concentration of OPs like chlorpyrifos in the body (Harley et al. 2011). CPF and other OPs contribute to mutated PON1 genes; this mutation acts as a positive feedback loop which reduces the effectiveness of CPF detoxification. Eventually, children will have very little/no tolerance against CPF (Harley et al. 2011).

Children's Health on Gut Microbiota

Chlorpyrifos disrupts gut microbiota in children by inhibiting nutrients (e.g., passively transported ions in the gut) to certain commensal bacteria that are beneficial to digestive tasks, lipid metabolism, gluconeogenesis, and many more functions (Djeukkoun et al. 2019). Without these bacteria, the human body cannot do such tasks and will face health complications. For children, it is critical that a proper gut microbiome is built. Gut microbiome is in charge of many lipid metabolic functions. When CPF inhibits beneficial bacteria, pathogenic bacteria can easily outcompete the helpful bacteria (Liang et al. 2019). The competition leads to many complicated health problems, including low grade inflammation, which recruits an abnormal amount of macrophages (Liang et al. 2019).

Some metabolic functions affected include obesity and diabetes (Djekkoun et al. 2019). Chlorpyrifos research with gut microbiota is currently difficult since current literature is unaware of much of the functions of the microbiome. The microbiome is a complex, dynamic system that is changing. As children develop, a variety of commensal bacteria are recruited over time. The growth of specific bacteria stems from many environmental factors, such as diet and exposure. Many in-vivo studies provide groundwork for mechanisms to investigate. In the in-vivo studies, many bacteria are highly dependent on the amount of nutrients that are available for consumption (Scott et al. 2013). Children who are exposed to pesticides have issues with nutrient distribution in the gut microbiota due to cell signaling abnormalities between the intestines and the bacteria that communicate with the intestinal cells (Scott et al. 2013). Scientific literature should focus on how we can track the development of commensal bacteria in children. In children, we can measure the cell neurotransmitters or check nutritional flow with the gastrointestinal systems. Then, we can find the metabolic functions associated with different nutrients and work on studies related to gut microbiota nutrition by measuring urine samples (Zhao et al. 2016). From urine samples, researchers can spot differences from people exposed to different levels of chlorpyrifos and see how people's gut microbiota are affected from chlorpyrifos (Zhao et al. 2016).

Children's Health and Obesity

Obesity is a critical disorder that must be studied in the context of chlorpyrifos. Brown adipose tissue and gut bacteria are closely associated with outcomes of obesity. If either fails to work properly, then the victim's probability of getting obesity is very high; this probability in children is higher than an adult because many parts of their body are developing (Sagar and Gupta 2018). Unfortunately, much of the literature on obesity is studied in mice. In the laboratory, mice exposed to chlorpyrifos show visible weight gain within a short span of three months compared to mice that were not exposed (Meggs and Brewer 2007). Children who live in the Central Valley are exposed to chlorpyrifos for longer than three months, which means the effects are more devastating. Literature from CHAMACOS studies emphasize that persistent OP exposure in children has significant contributing events towards obesity (Warner et al. 2013). Despite having studies emphasizing the effects of chlorpyrifos on weight gain, there is still a need for more studies to be published (Lassiter and Brimijoin 2007).

More systematic reviews and meta analyses are required that evaluate current literature due to the little research that measures the extent of pesticide poisoning by chlorpyrifos on children. Studies should focus on specific groups of people affected by obesity. Studying obesity with children is absolutely critical to understanding the progression of obesity in the body. Obesity is a disease that has a long lasting impact and is progressive (Sagar and Gupta 2018). Studying the disease in younger individuals allows researchers to get specific details on its progression throughout a lifetime. By understanding how the disease progresses and affects the body, researchers can provide more accurate recommendations to remediate the impacts of this disease. This knowledge is helpful because more updated research can be implemented in educational curriculums and medical practices. The goal is to apply experimental data from mice to allow for a starting point to what further research needs to be done.

Worker's Health and Brown Adipose Tissue

Agricultural workers are also heavily affected by pesticides and face drastic health consequences. In comparison to children, workers have a longer exposure time to pesticides, many of them working for over ten hours, five to six days a week (Lopez 2007). Just by exposure alone, it is expected that workers will face drastic health consequences the longer they work in the work fields (Hicks 2020). High exposure time gives chlorpyrifos more chances to change the normal function of brown adipose tissues. Altered brown adipose tissue function leads to many health problems, which can reduce longevity, be a precursor to other chronic illnesses, and contribute to other progressive diseases like Alzheimers and Parkinson's (Costello et al. 2009). Problems with brown adipose tissue function leads to issues with the proper functioning acetylcholinesterase, insulin sensitivity, and general lipid metabolism.

Worker's Health and Gut Microbiota

The adult gut microbiota is extremely dynamic, meaning that it will change depending on environmental factors. Because pesticides, especially chlorpyrifos, directly and indirectly cause problems in commensal bacteria by restricting their nutritional intake, opportunistic bacteria will often dominate the gut (Liang et al. 2019). These opportunistic bacteria are precursors to many chronic illnesses, such as obesity. The metabolism of gut-specific nutrients will fail, and workers in the Central Valley will not be able to absorb critical nutrients (Djekkoun et al. 2022). For example, gut microbiota can metabolize complex carbohydrates, proteins, lipids, and vitamins that the body cannot naturally produce (Fang et al. 2018). This will cause many short term issues, such as a weakened gastrointestinal immune system and long term issues, such as metabolic disorders. These negative effects compound and are exacerbated over time.

Worker's Health and Obesity

Obesity is of high concern when it comes to worker's health. With complications in brown adipose tissue function and gut bacteria, the probability of expressing obesity in chlorpyrifos intensive areas is higher than the national average, which is 41.9% (CDC 2022). Obesity has precursors from many different health complications, and further serves as the precursor to many other health problems. Obesity in the Central Valley is dangerous because it is linked to epigenetics. This means that one can pass on obesity to the next generation. Children born to workers exposed to pesticides are more likely to become obese not only due to their own exposure to the pesticides, but children inherit mutated genes from their working parents that make them at a higher risk for obesity (Rohde et al. 2019).

The obesity problem in the Central Valley is difficult to address because there are so many factors related to obesity, so there is no universal solution (CDC 2022). There are different approaches to this issue, which makes this problem very difficult to solve in an upstream (societal/public health) approach. At the downstream (individual) level, many workers cannot afford a doctor, dietitian, or professional that will provide one-on-one assistance to mitigate their obesity, let alone if they have the time to get counseling or have an affordable healthcare plan (Legido-Quigley et al. 2019). The obesity problem with workers stretches beyond blaming individuals on their lifestyles. Pesticides play such a large role in promoting obesity, and reducing pesticides will be a great factor that will lower the demographics of people that get obesity (Audelo et al. 2016). There is much progress to be done to help workers exit the generational trap of health problems.

Application of Human Health in a Public Health Perspective

From an upstream (public health/societal) level, a large number of people with various health problems is extremely concerning. Most of the Central Valley workers do not have access to or are ineligible to healthcare, which means it is very difficult to get treatment once they are finally diagnosed (Yoshikawa et al. 2014). This issue stems from societal barriers that make healthcare exclusive to English speaking citizens. Even if workers reach out for help, resources in the Central Valley are limited for migrant families and difficult for those who speak only Spanish or another language (Lopez 2007). At a downstream (individual) level, many workers are not in the financial position to quit their job. The workers are essentially trapped in their dangerous jobs, and their exposures to pesticides contribute to exacerbating their health (Lopez 2007). Such health problems and deaths are devastating to worker's families, as they have to witness their friends and family pass away. This brings into question the quality of life of the workers, as most workers face very long work hours and emotionally traumatic events in their lives. Such upstream societal issues have to be addressed at a downstream level, where workers are provided with better personal protective equipment (PPE), less working hours to reduce exposure, and healthcare that is more accessible.

Conflicts Between Agricultural Corporations and Human Health in the Central Valley

The pesticide and human health issue is challenging and requires finding a proper balance that would take into account the interests of both agricultural corporations and human health. The current situation heavily favors the agricultural corporations, due to intense lobbying and the backing of other powerful corporations (Bellemare and Carnes 2015). Laws have been in place to secure the health and rights of people in the Central Valley, which started with regulations for pesticide application (Coupe and Capel 2022). Despite the regulations, there are still too many cases where community members suffer from pesticide-related activity.

Current pesticide practices are extremely insufficient and dangerous as chlorpyrifos is directly sprayed on plants. Chlorpyrifos is extremely volatile, which means that it is likely to linger in the air after its release; however, its persistence and high absorptivity in the environment makes it extremely lethal (US Department of Health and Human Services 1997). Most of the pesticides are not directed towards the plant; the pesticides just float off and affect nearby workers and communities (Christensen et al. 2009). Workers will directly inhale the volatile chlorpyrifos, irritating their respiratory tracts and degrading their health (Christensen et al. 2009). If pesticide application were more efficient, farms could spray less pesticides on plants. Instead, big agricultural corporations do not consider such factors and will spray potent pesticides in higher frequencies/concentrations to compensate for the yield loss (Coupe and Capel 2022).

The future in agriculture does not lie in creating pesticides to defeat pests that live near plants. Instead, we need to take more organic approaches to agriculture. This includes moving away from intense monoculture in the Central Valley and efficiently rotating crops for farming. Polyculture will help because different agricultural products provide natural resistance towards pests and invasive species (Finney and Kaye 2017). Rotating crops and leaving land fallow will allow land to heal, which provides more resistance towards pests (Finney and Kaye 2017). It is expected that we may lose some yield in production in the short term, but the positive, long term externalities are greater (Iverson et al. 2014). Farmland managers can protect community members from being exposed to unhealthy amounts of pesticides (and protect them from getting chronic illnesses), and we can establish a healthier relationship with our ecosystem. With greatly reduced amounts of pesticides, farmers are not constantly fighting a battle against genetic mutation and resistance of pests (Govindaraj et al. 2015).

It is critical that all the stakeholders involved with the pesticide businesses are addressed. Ironically, the very own pesticides that kill workers are the main source of income for many workers. There are many employment opportunities for workers for pesticide manufacturing and pesticide application. In addition, many workers have families and houses near fields sprayed with pesticides. Many pesticide manufacturers intentionally trap workers in situations where they are reliant on pesticide specific industries (Apgar 2015). Big agriculture companies know that their workers are undocumented, which means they are not protected by the law (Sherman et al. 2019). It is easy for companies to exploit their workers and put them under harsher work conditions (Apgar 2015). Businesses know that workers will still take the occupation because working on the fields are workers' only options (Sherman et al. 2019). This makes the issue of protecting worker's health tricky without trying to take away their economic opportunities or establishments.

The goal would be for alternative industries that use safer and more efficient agricultural practices to slowly replace the existing pesticide manufacturers. Current pesticide manufacturers are profitable because of economies of scale, where mass producing one specialized item would make each unit price cheaper (Martin and Kassel 2023). In addition, many farms have existing capital that support technology for pesticides (Martin and Kassel 2023). However, there are so many safer alternatives that are cheaper and more efficient if economies of scale did not apply. The goal would be policy changes that limit pesticide manufacturers from having such a massive presence in the agricultural legislation, and for the California state government to spend more money to push companies that promote safer and more efficient agricultural companies to implement their technology in Central Valley's agriculture. This plan is projecting towards California's future for many decades, and as more eco-friendly agricultural companies expand, they will have more opportunities for workers that provide safer working conditions. The government of California can provide subsidies for farms to specifically purchase equipment that is compatible for eco-friendly agriculture (Jacquet et al. 2022). The government can also provide supplementary programs that will help farmers understand the eco-friendly and safe technology that can be passed onto workers.

Moving Forward

There is much work to be done in terms of balancing the interests of human health and agriculture. Even though the demand for agriculture is pressing, it is absolutely critical to protect human health and regulate pesticides. The issue of pesticides, agriculture, and human health is very nuanced and complicated, but I am optimistic that we are moving forward in the right direction. More aggressive eco-friendly management practices and policy changes are necessary to create a balanced future where agricultural interests and human health interests are honored.

We must continue our endeavors of pushing forward our support to the Central Valley community and create a more sustainable future for global agriculture.

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