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Abstract

Purpose of Review: This review aims to summarize epidemiological literature published between May 15, 2018 and May 14, 2019 that examines the relationship between exposure to synthetic pesticides and health of agricultural workers.

Recent Findings: Current research suggests that exposure to synthetic pesticides may be associated with adverse health outcomes. Agricultural workers represent a potentially vulnerable population, due to a combination of unique social and cultural risk factors as well as exposure to hazards inherent in farm work. Pesticide exposure among agricultural workers has been linked to certain cancers, DNA damage, oxidative stress, neurological disorders, as well as respiratory, metabolic, and thyroid effects.

Summary: This review describes literature suggesting that agricultural workers exposed to synthetic pesticides are at an increased risk of certain cancers and neurological disorders. Recent research on respiratory effects is sparse, and more research is warranted regarding DNA damage, oxidative stress, metabolic outcomes and thyroid effects.

Keywords: farmworkers, pesticide exposure, synthetic pesticides, agricultural workers, cancer, DNA damage

Introduction

There are over 1 billion agricultural workers in the world[1]. In the US alone, there are more than 3 million seasonal and migrant workers, self-employed farmers, family members working on family farms, hired workers and contract laborers[2, 3]. In South Asia and Sub-Saharan Africa, more than half of all employment is in agriculture[1]. In many countries, including the US, farm working populations are becoming increasingly older and are comprised of a growing number of women[2]. Agricultural workers are among the most vulnerable working populations due to social and cultural risk factors frequently associated with their ethnicity, immigration status, social class and rural location, as well as disparities related to language barriers and lack of access to healthcare[4-7]. In addition, these potential risk factors can be exacerbated by occupational hazards associated with agricultural work, including exposure to environmental hazards such as synthetic pesticides and fertilizers, diesel exhaust, ultraviolet radiation, biologically active dusts, and zoonotic viruses and bacteria, all of which may put farm working populations at an increased risk for a variety of adverse health effects[8, 9].

This review summarizes recent epidemiological literature regarding potential health effects (specifically cancer, DNA damage and oxidative stress, neurological disorders, and respiratory, metabolic, and thyroid effects) of occupational exposure to synthetic pesticides among agricultural workers. In this review, we include descriptive, cross-sectional, cohort and case-control studies published over the past year, between May 15, 2018 and May 14, 2019. This relatively brief timeframe for review was selected for several reasons. First, this review considers exposures to all classes of agricultural pesticides and numerous diverse adverse health outcomes, creating a broad reach. Second, this year has seen the publication of several studies that include large agricultural cohorts and/or pooled analyses across multiple cohorts. Third, there has been a marked increase in the number of studies investigating exposures and health effects in previously understudied populations (e.g., Latin America and Asia) and employing emerging technologies (e.g., studies evaluating potential DNA damage). By focusing on just the last year, we are able to contribute a novel evaluation to the existing literature.

We define agricultural workers to include farmers, farm owners, farm workers, field workers, growers, harvesters, packers, graders and sorters, as well as agricultural pesticide handlers (mixers, loaders, cleaners and sprayers). This review did not consider take-home exposure among families of agricultural workers or spray drift in agricultural communities, nor did we include studies evaluating health effects exclusively among livestock workers, florists, pesticide manufacturers or commercial pesticide users. We also did not include animal toxicology studies, meta-analyses that do not represent novel investigations of pooled primary data, case reports, or acute poisonings.

Literature searches were conducted in PubMed, Google Scholar, and the Boise State University Alberton's Library System using a predetermined list of search words and fragments related to agriculture work, pesticide exposure and health outcomes. These searches resulted in a total of 508 articles, of which 484 were excluded due to inappropriate scope or focus on non-farm working populations. The results of the remaining 24 studies represent primary literature, are grouped according to health outcome and are discussed in the following sections.

Cancer

Several studies have identified that farmers have lower rates of mortality than the general population and lower rates of specific cancers, including those of the lung, esophagus, bladder, liver and colon, primarily attributed to low rates of smoking and high rates of physical activity in this population[9-11]. At the same time, farmers and other agricultural workers have demonstrated elevated rates of other types of cancer, including that of the prostate, brain, and lip, as well as melanoma and skin cancers, and lymphohematopoietic malignancies[8, 9, 12-17]. In this review, we identified six studies published in the last year that add to our existing understanding of the relationship between agricultural work and cancer.

The Agricultural Health Study (AHS) provides some of the most compelling insights into the relationship between agricultural work, pesticide exposures and cancer. This large prospective study was initiated in North Carolina and Iowa in 1993 with the express intention of identifying and quantifying cancer risks, and other non-cancer health outcomes, among a cohort of nearly 90,000 individuals including licensed private pesticide applicators (mostly farmers), their spouses, and commercial pesticide applicators[18]. The most recent evidence on overall cancer incidence in the AHS was published in April of 2019. Lerro et al. present age, year, sex, and race-adjusted standardized incidence ratios (SIRs) for cancer sites in the AHS relative to the general population for an extended period of follow-up, representing 20 years and 12,420 incident cancers[19] (Table 1). They found that while overall cancer incidence was indeed lower than in the general population – driven mainly by lower incidences of smoking, alcohol, or obesity-related cancers such as those of the respiratory, bladder and digestive systems – private pesticide applicators (primarily farmers) had higher incidence rates of lip and prostate cancer, B-cell lymphomas, chronic lymphocytic leukemia, acute myeloid leukemia, thyroid cancer, and testicular cancer. The authors speculated that the increases in lip cancer may be due to UV exposure and that the excess of thyroid and testicular cancer may be due to pesticide exposure in this population.

Other analyses among large cohort studies also provide insights into the relationship between agricultural work and cancer. In March of 2019, the Consortium of Agricultural Cohort Studies (AGRICOH) published a pooled analysis of the relationship between pesticide use and non-Hodgkin lymphoid malignancies (NHL) among participants in three agricultural cohorts[20] (Table 1). These cohorts included the AGRIculture and CANcer (AGRICAN) study, which enrolled over 180,000 individuals in France between 2005 and 2007 who were part of the national health insurance system of agricultural workers[21]; the Cancer in the Norwegian Agricultural Population (CNAP) study, from which this pooled analysis included nearly 150,000 farm owners and workers[22]; and the AHS study, described above. This

investigation included 2,430 cases of NHL among 316,270 farmers, and the researchers found almost no association between exposure to 4 pesticide chemical groups and 33 pesticide active ingredients with NHL overall or with any NHL subtype. However, the authors noted that associations may vary by cancer subtype and by pesticide, and they did observe weak to moderate positive associations between ever use of terbufos and NHL overall; ever use of deltamethrin and chronic lymphocytic leukemia/small lympocytic lymphoma; and ever use of glyphosate and diffuse large B-cell lymphoma.

Andreotti et al. (2018) specifically examined the relationship between use of the common herbicide, glyphosate, and cancer incidence in the AHS and found no relationship between glyphosate and cancer at any site, with the exception of an elevated but non-significant association between applicators in the highest exposure quartile (compared with never users) and acute myeloid leukemia[23] (Table 1). This analysis included 5,779 incident cancer cases among 54,521 licensed pesticide applicators. This finding differs somewhat from that observed in the AGRICOH analysis described above, of which the AHS was a part, where glyphosate exposure was associated with diffuse large B-cell lymphoma. It may be worth noting that the analysis described by Andreotti et al. was limited by incomplete follow-up; 20,968 participants (37% of the cohort) did not complete the follow-up questionnaire, and it has been suggested that the method by which the researchers imputed the missing data may have biased the results towards the null[24].

In another chemical-specific study within the AHS cohort published in the past year, Lerro et al. (2018) investigated the relationship between use of another common herbicide, alachlor, and cancer incidence[25] (Table 1). This analysis included 48,685 licensed pesticide applicators, among whom 51.6% reported use of alachlor. Although the researchers in this study also were limited by incomplete follow-up data, they observed a strong positive association and exposure-response trend between alachlor use and laryngeal cancer. They also observed an elevated, but non-significant, relationship between alachlor use and myeloid leukemia among the most highly exposed participants. No significant associations were observed between exposure to alachlor and lymphohematopoietic cancers overall nor specifically with NHL.

While multiple studies have shown that farmers are at relatively low risk of lung cancer[10, 12, 16, 26], a recent analysis in the AGRICAN cohort found trends suggesting that winegrowers may be at a slightly higher risk of adenocarcinoma compared to non-winegrowing farmers, possibly attributable to the historic use of arsenical pesticides in vineyards[27] (Table 1). This same study also found pea growers, harvesters, and pesticide applicators to be at increased risk of small cell lung cancer, though there was a low number of exposed cases and the results were not statistically significant. In contrast, these researchers observed a negative association between lung cancer and production of corn and wheat/barley, which is more consistent with previous studies of the relationship between farming and lung cancer. Also in the AGRICAN cohort, Piel et al. (2018) described a positive association between central nervous system (CNS) tumors, particularly gliomas and meningiomas, and use of carbamate insecticides[28] (Table 1). Confidence in these results are strengthened by the consistency in findings across multiple individual carbamates.

In summary, most studies published in the past year consistently show that agricultural workers are at increased risk of some cancers, but the risk varies by cancer subtype and pesticide exposure. These studies, and particularly the study including 20 years of follow-up in the AHS[19], confirmed previous evidence that the incidence of some cancers is lower among agricultural workers compared to the general population. However, it is possible that individuals whose health status may have rendered them unable to work may be underrepresented in agricultural cohorts, suggesting that the healthy worker effect could potentially be a factor to consider when interpreting these results.

Other cancers such as prostate, lip and certain lymphomas, as well as acute myeloid leukemia, are higher among those working in agriculture compared to the general population, which may reflect differences in lifestyle and behavior, as well as potential exposures to agricultural chemicals. In terms of effects of individual pesticides or classes of pesticides, some of the most compelling relationships were between exposure to alachlor and laryngeal cancer within the AHS study[25] and exposure to carbamates and gliomas and meningiomas within the AGRICAN study[28]. Evidence was inconsistent regarding the relationship between glyphosate and cancer. One study found a slight increase in diffuse large B-cell lymphoma among those exposed to glyphosate[20] – which supports the results of a recent meta-analysis of six studies that found an overall increased risk of NHL among individuals in the highest exposure groups[29] – while another showed no such association[23].

DNA Damage and Oxidative Stress

Exposure to cytotoxic and genotoxic substances can result in chromosomal aberrations and DNA damage, which may be early precursors for the onset of clinical health effects, particularly cancer[30, 31]. We reviewed eight publications from the past year that investigated potential chromosomal aberrations and DNA damage related to pesticide exposure among agricultural workers. While there is no single standardized test for chromosomal aberrations and DNA damage, and measurements involve a range of molecular biomarkers and endpoints, the most widely used and accepted procedures are comet and micronucleus assays[32, 33]. Comet assays, which provide measurements such as comet tail length, shape, and/or intensity (known as comet tail moment), can detect various types of DNA damage including single and double DNA strand breaks. A longer tail, increased moment, or increased percent DNA in the tail are considered indicators of DNA damage[32, 34, 35]. Micronucleus assays measure the presence of micronuclei, as well as the presence of DNA damage biomarkers such as nuclear buds. Micronuclei are whole chromosomes or damaged chromosome fragments that are not incorporated into the daughter nuclei during mitosis and are thus can be used as an indication of chromosomal abnormalities[33, 36] The majority, but not all, of the studies in this section report an increase in chromosomal aberrations and DNA damage among agricultural workers exposed to pesticides compared to control populations [37-42] (Table 2).

Hutter et al. (2018) compared buccal cells from 38 pesticide applicators who were exposed to a complex mixture of pesticides and 33 organic farmers, presumably unexposed to pesticides, in the Jarabacoa coffee production region in the Dominican Republic. After adjusting for age, body mass index, smoking, tobacco chewing, alcohol consumption, dental x-rays in the past month, and frequency of eating spicy foods, these researchers concluded that pesticide applicators had significantly increased odds for all micronucleus assay endpoints evaluated, including the following: total number of micronuclei cells, total number of micronuclei, nuclear buds, broken eggs, and binucleated cells[37]. Of note, fewer than 14% of pesticide applicators in this study reported wearing personal protective equipment (PPE) while spraying. This is consistent with previous studies that report chromosomal damage among agricultural workers who predominately did not use PPE[43, 44]. Further, a similar study among agricultural workers who *did* utilize PPE showed the converse -- no significant increases in genotoxic outcomes were observed[45].

Results comparable to Hutter et al. were observed by Kahl and colleagues[38], who enrolled 121 tobacco field workers exposed to nicotine and complex pesticide mixtures and 121 non-exposed individuals working in offices and retail in Brazil, matched by sex and age, and excluding participants who were smokers or had chronic health conditions. Comet assay on whole blood cells showed that agricultural workers had significantly increased DNA damage based on tail size and shape, and micronucleus assay on buccal cells showed significantly increased mean levels of micronuclei, nuclear buds, and binucleated cells.

A 2019 study in Punjab, Pakistan found significantly increased comet tail length and comet frequency measured using whole blood DNA from pesticide industry workers and pesticide sprayers compared to controls, matched by age, location, and smoking status[39]. Similarly, researchers in Egypt found that several comet assay parameters including tail length, percent DNA in tail, and tail moment in whole blood DNA were significantly elevated among rural pesticide sprayers and urban researchers using pesticides in laboratories (exposed mostly to the insecticides malathion, chlorpyrifos, dimethoate, and carbofuran), compared to researchers and rural controls not occupationally exposed to pesticides[40]. While this study did match on age and smoking status, it did not adjust for sex or consider the use of PPE. A cross-sectional study conducted in tea gardens in India found that women who plucked tea leaves (considered occupationally exposed to pesticides, n=77), had significantly increased mean comet tail length, percent DNA in tail, and tail moment in peripheral lymphocyte DNA compared to women with no occupational exposure to pesticides (n=66). Important for the interpretation of this data, almost 80% of exposed women reported not using PPE and information regarding quantity and frequency of pesticide mixture application at the tea garden was unknown[41].

Finally, a case-control study by Intranuovo et al. (2018) in Italian farming regions compared 2,374 comet assay images from peripheral lymphocytes from 22 agricultural workers involved in the production of vegetables, grapes, and olive trees (with exposure mainly to chlorpyrifos, deltamethrin, glyphosate, dimethoate, mancozeb, and fosetyl) and 24 non-exposed individuals. These researchers observed significantly increased odds of tail moment and tail length measurements above the 75th percentile among those occupationally exposed to pesticides, after adjusting for age and smoking status. Of note, all exposed agricultural workers in this study reported using PPE (masks, gloves, and suits)[42].

However, not all studies we reviewed were consistent[46, 47] (Table 2). Cattelan et al. (2018) compared whole blood DNA damage between farmers in Brazil who reported occupational use of various pesticide combinations and farmers who did not report occupational pesticide use, and found no significant differences in micronucleus frequency[46]. In this study, over 60% of farmers reported using some form of PPE, though exact pesticide combinations and frequency of pesticide use could not be determined due to different agrochemical requirements for various crops. Likewise, Sapbamrer et al. (2019) compared pre- and post-application season exposures among 56 farmers in Thailand and also found no statistically significant differences in tail length or tail moment in comet assay of peripheral lymphocyte samples[47]. Of note, this is the only study in this review section that examined DNA damage intra-individually and not between individuals.

Despite some inconsistencies, six of the eight epidemiological studies published in the past year examining genotoxic effects of pesticides identified increases in DNA damage among occupationally exposed agricultural workers compared to unexposed populations. While all of these studies utilized widely accepted assays for chromosomal aberrations and DNA damage, assessment of causality remains difficult for numerous reasons. Age, tobacco smoke, gender, diet, physical activity, and exposure to ultraviolet radiation have been shown to effect comet assay results[42], but not all studies in this review adjusted for these potential confounders. Differences in accounting for PPE use, doses, types, combinations, duration, and frequency of pesticide use among studies make it difficult to generalize results to all agricultural occupations. In addition, the comet assay in particular does not inclusively detect all types of cell damage nor is this assay on its own considered predictive of cancer risk[42]. Micronucleus assays are also limited by scorer bias, variability, and fatigue[48]. Finally, while it is outside the scope of this review to discuss the appropriateness of cell type selection, it must be noted that studies listed here were not consistent in their selection, ranging from buccal cells to whole blood to separated peripheral lymphocytes. This is problematic given that DNA repair capacity can vary by cell type[49]. Moreover, studies have identified that peripheral lymphocytes relative to whole blood may be more resilient to DNA damage[50], and this could impact the interpretability of the results reviewed here.

Four studies published in the past year – including three that also investigated DNA damage – evaluated the relationship between occupational pesticide exposure and markers of oxidative stress [38, 46, 47, 51] (Table 2). Oxidative stress results from an imbalance between free radicals/reactive oxygen species (ROS), and antioxidant species. When this imbalance favors ROS over antioxidants, oxidative damage may occur, resulting in cellular adaption, damage to cellular lipids, DNA, proteins, and carbohydrates, and/or cellular death[52, 53]. Studies have shown that oxidative damage may contribute to the development of a range of chronic conditions, including Alzheimer's disease and other neurodegenerative disorders, cancers, and diabetes[52, 54-57].

There are many cellular and molecular targets of ROS, and as such, measurements of oxidative stress and damage in humans are complex. Biological markers of oxidative stress can be non-specific to a single oxidative pathway, and methods and markers are often not standardized across studies, making comparisons difficult[52, 53]. Most studies measure the presence of biomarkers formed from reactions between ROS and other biological molecules and/or the disruption in antioxidative enzymatic activities[52, 53, 58]. Examples of oxidative stress biomarkers include thiobarbituric acid reactive substances (TBARS), 8-hydroxy-2'-deoxyguanosine (8-Oxo-dG), and total equivalent antioxidant capacity (TEAC). Examples of antioxidant enzymes include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and paraoxonase-1 (PON1).

Regarding oxidative stress biomarkers, Cattelan et al. (2018) found that farmers who used pesticides had significantly lower levels of TBARS, suggesting less oxidative stress, compared to farmers who did not use pesticides [46]. Sapbamrer et al.(2019) found no difference in 8-Oxo-dG among pesticide applicators pre- and post- pesticide application seasons[47]. In contrast, both Kahl et al. (2018) and Lozano-Panigua et al. (2018) found agricultural workers occupationally exposed to pesticides had significantly increased levels of oxidative stress biomarkers, including increased TBARS and TEAC[38], and ferric reducing ability of serum (FRAS) and total thiol groups (SHT) [51]. These inconsistent results make it difficult to draw conclusions about the relationship between agricultural work and biomarkers of oxidative stress.

Regarding antioxidant enzyme activity, Cattelan et al. (2018) observed that farmers who used pesticides had significantly reduced levels of SOD, GPx, and glutathione reductase (GSH) compared to farmers who did not use pesticides[46]. The authors note that this effect may represent a reduced antioxidant defense system in response to an increase in ROS. Other recent studies suggest occupational pesticide exposure is associated with elevations, rather than reductions, in antioxidant enzyme activity. Sapbamrer and colleagues found significantly increased SOD activity

post-pesticide application season compared to pre-pesticide application season[47]. In addition, Lozano-Paniagua et al. (2018) found an elevated but non-significant increase in PON1 activity in greenhouse workers compared to controls[51]. This increase in antioxidant enzymatic activity may represent an adaptive response to an increase in the generation of free radicals[47].

The inconsistencies seen among these studies could be due to different doses, types, combinations, and duration of pesticides use, limitations inherent in cross-sectional study designs, and the difficulty in making meaningful measurements of oxidative stress. The latter point likely being exacerbated by nonuniform biological sample collection, storage, and assessment protocols between studies. It is worth noting that many of these studies were unable to determine exposure to specific pesticides and instead analyzed exposure to various complex pesticide mixtures used on a variety of crops. In addition, agricultural pesticide bans vary by country, and most of these studies were conducted in different countries with different types and levels of pesticide usage. While the papers included in this review observed conflicting results regarding oxidative stress biomarkers, most studies agreed that pesticide exposure may lead to disruptions in antioxidant enzyme homeostasis, though the direction of this disruption and possible underlying biological mechanisms are unclear and warrant further investigation.

Neurologic Disorders

Numerous studies have documented neurologic effects of pesticide exposure. These effects include disruption of cholinergic function as well as various neurological disorders including Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), affective disorders, anxiety, depression, lower intelligence quotient, and delayed mental development[59-65]. These studies have primarily focused on organophosphate (OP) insecticides, although such effects have also been noted in conjunction with exposure to other pesticides as well.

This review describes four studies published in the past year regarding the relationship between occupational exposure to agricultural pesticides and neurological effects. A recent longitudinal study evaluated the frequency of ADHD symptoms in relation to biomarkers of exposure to chlorpyrifos, a common OP insecticide, among adolescents in Egypt[66] (Table 2). In this study, researchers measured urinary levels of tricholoro-2-pyridinol (TCPy – a metabolic product of chlorpyrifos exposure) and blood levels of acetylcholinesterase and butyrylcholinesterase (AChE and BChE – which indicate cholinergic response to OP exposure) among 59 participants who either did or did not work as pesticide applicators. The researchers found that those adolescents who worked as pesticide applicators were significantly more likely to demonstrate ADHD symptoms than non-applicators. They also observed a dose-response relationship between increasing levels of all three exposure biomarkers (TCPy, AChE, and BChE) and ADHD symptoms. Despite the small sample size, this study provides compelling evidence of a relationship between chlorpyrifos exposure and ADHD among adolescent pesticide applicators.

AChE inhibition was also measured as a marker of cholinergic disruption among a cohort of agricultural workers in the Trang Province of Thailand[67] (Table 2). Guytingco et al. (2018) conducted a cross-sectional study in which they surveyed 6,118 agricultural workers regarding pesticide-related symptoms. Blood samples were collected from 3,431 of these workers and analyzed for AChE. Low AChE levels were measured in 12.5% of the cohort, most commonly among those who reported spraying and mixing pesticides. Individuals with low AChE were significantly more likely to report experiencing neurological symptoms associated with pesticide exposure, such as dizziness and headaches.

Exposure to pesticides and agricultural work has also been linked to anxiety, depression and suicide, although epidemiological studies on this are limited[68-71]. Serrano-Medina et al. (2019) conducted a cross-sectional study of AChE inhibition and neuropsychiatric disorders among agricultural workers in a rural village of Mexico[72] (Table 2). They found that agricultural workers (n=140) had significantly more psychiatric disorders than control participants recruited from an urban area (n=100), including more frequent depression, major depression with suicidal risk, and depression-generalized anxiety. They also found a significant relationship between AChE inhibition and suicide risk.

Finally, in the AHS cohort, researchers investigated the association between high pesticide exposure events (HPEE), as a surrogate for acute, high-dose exposures, and olfactory impairment[73] (Table 2). This relationship was of interest because pesticides may affect the sense of smell by affecting peripheral olfactory structures and/or the central nervous system, and olfactory impairment has been recognized as one of the earliest symptoms of neurological disorders like Parkinson's disease and Alzheimer's disease[74, 75]. These researchers found that a history of self-reported HPEEs was significantly associated with olfactory impairment measured two decades later.

Overall, recent research is consistent regarding the relationship between pesticide exposure and neurological effects in agricultural workers. It is worth noting that all four of the relevant studies identified in the past year were focused on relatively high pesticide exposures, either self-identified as such, or sufficient to result in cholinergic inhibition. Together, these studies suggest that occupational exposure to synthetic pesticides – particularly OPs – is associated with neurological effects including dizziness and fatigue, ADHD, neuropsychiatric disorders, and olfactory impairment, a potential early predictor of neurodegeneration.

Respiratory Effects

In addition to dermal absorption and ingestion, inhalation is an another pathway by which agricultural workers may be exposed to synthetic pesticides[76]. Such exposures are hypothesized to cause or exacerbate adverse respiratory symptoms in these workers[77, 78]. One publication in the past year investigated the relationship between occupational exposure to synthetic pesticides among agricultural workers and respiratory symptoms (Table 2). In this study, Buralli et al. (2018) investigated the prevalence of respiratory impairment in a cohort of family farmers (n=82) who had been exposed to multiple pesticides from an early age[79]. The prevalence of cough, nasal allergies, hay fever, breathlessness, and chest tightness were reported more frequently during the season in which the farmers were actively working in agriculture compared to the off-season. However, due to the small sample size, the confidence intervals around these estimates were wide and rarely reached statistical significance. The authors did report significant associations between lung function, as assessed by various spirometry variables, and self-reported pesticide exposure. Though limited by a lack of an unexposed control group, the results of this study are suggestive of a relationship between pesticide exposure and respiratory symptoms and pulmonary function impairment.

Metabolic Effects

Previous research has suggested that pesticide exposure, particularly exposure to organochlorine insecticides and some OPs, may be associated with type II diabetes mellitus[80-82]. Two epidemiologic studies published in the past year add to our knowledge of the relationship between occupational exposure to pesticides and metabolic diseases including diabetes.

One cross-sectional study analyzing data from participants of the Korea Farmers Cohort study found that the prevalence of diabetes was significantly higher in study participants who had ever been a farmer or had ever used any pesticides, compared to those who had not[83] (Table 2). Further, the odds of diabetes were significantly elevated with ever use of pesticides, years of pesticide use, frequency of pesticide use, volume/intensity of use, and cumulative exposure index of pesticide use, and this remained true among the overweight and obese groups when stratified by body mass index (BMI).

Another study among farmers in Thailand investigated differences in levels of adverse metabolic biomarkers between organic and conventional farmers[84] (Table 2). In this study, the authors investigated the role of pesticide use in metabolic pathways by considering employment as a conventional farmer to be a proxy for pesticide exposure, while organic farmers were considered unexposed. These researchers found significantly higher BMI, waist circumference, percent body fat, triglycerides, total cholesterol, and low-density lipoproteins among conventional farmers, compared to organic farmers. No significant differences were seen between type of farm work and blood glucose, blood pressure, or metabolic syndrome. While the researchers collected and controlled for multiple confounding variables, including alcohol intake, smoking, exercise, diet, stress and socioeconomics, there were significant differences in demographics and behavior between the organic and conventional farmers, and the authors acknowledge that their study results may still reflect uncontrolled confounding. Between this possibility and the cross-sectional study design, it is difficult to make a causal argument based on the results of this study.

Overall, research over the past year contributes to the weight of evidence suggesting a relationship between occupational exposure to synthetic pesticides and metabolic effects among agricultural workers. However, research in this area remains sparse and additional work will be required to confirm this relationship.

Thyroid Effects

There is some increasing evidence, though from a limited number of studies, to suggest that pesticide exposure may affect thyroid function[85]. Three initial studies in the AHS suggested a relationship between pesticide exposure and thyroid dysfunction[86-88]. Most recently, Shrestha et al. (2018) followed up on this work by analyzing data from

35,150 pesticide applicators in this cohort, among whom 829 had self-reported hypothyroidism[89] (Table 2). The researchers observed an increased risk of hypothyroidism with ever use of several specific pesticides, including chlordane, diazinon, dichlorvos, malathion, dicamba, glyphosate, and 2,4-D. However, results from this study are limited, as self-reported hypothyroidism may have low validity and diagnoses pulled from medical records are considered a more reliable measurement[90]. In a much smaller study, Bernieri et al. (2019) observed significant decreases in serum levels of thyroid stimulating hormone (TSH) and significant increases in free thyroxin (FT4) and total triiodothyronine (TT3) among 46 Brazilian soybean growers compared to 27 unexposed participants from urban regions[91] (Table 2).

These two studies add to the limited existing epidemiological literature suggesting that occupational exposure to synthetic agricultural pesticides may affect thyroid function. It is important to note that there is a variable course to thyroid disease, where hypothyroidism can develop after hyperthyroidism[92]. There are also many hormones, antibodies, and proteins involved in thyroid homeostasis, and pesticides have the potential to alter thyroid function via several mechanisms[89]. The specific types of pesticides, thyroid targets, and mechanisms that might underlie this relationship are complex, and as such additional toxicological and epidemiologic studies are warranted to further evaluate this relationship.

Conclusions

This review summarized epidemiological literature published between May 15, 2018 and May 14, 2019 examining the relationship between occupational exposure to agricultural pesticides and health outcomes including cancer, DNA damage and oxidative stress, neurological disorders, and respiratory, metabolic, and thyroid effects. Most studies published in the past year confirm that, while agricultural workers occupationally exposed to pesticides have a decreased incidence of some cancers, they are at an increased risk for others, such as prostate, lip and certain lymphomas, as well as acute myeloid leukemia, but the risk varies by cancer subtype and the specific pesticides. Studies also confirm that occupational exposure to synthetic pesticides – particularly organophosphates – is associated with neurological and neuropsychiatric effects and disorders. Results regarding respiratory function are limited but do suggest a relationship between agricultural pesticide exposure and adverse pulmonary function. Studies of DNA damage, oxidative stress, metabolic effects and thyroid effects suggest pesticide exposure among agricultural workers may be deleterious, but additional research in these areas is warranted.

Overall, agricultural workers may be at risk for various adverse outcomes due to synthetic pesticide exposure. However, further research is warranted to better inform causality, as there are many factors to consider when evaluating occupational pesticide exposure. Studies on pesticide exposure are often limited by their cross-sectional design, and consideration of the use of PPE and adjusting for the appropriate confounders is necessary. In addition, exposure to pesticides can occur via various routes (i.e. inhalation, dermal), is often not limited to one single pesticide, and may depend on frequency of application, creating difficulties in exposure assessment and the interpretation of results. Given the difficulty of controlling for confounding and establishing causality, animal studies, in addition to human studies, could help elucidate the relationship between exposure to pesticides and health outcomes. Worldwide pesticide consumption remains highest in South Asia and Latin America, and there has been a marked increase in the number of studies investigating occupational pesticide exposures and health effects in these previously understudied populations. While generalizations between studies is difficult due to geographic differences and agrochemical practices that vary between crops and countries this work indicates the importance of continued focus on the health of this vulnerable population.

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Table 1. Studies regarding agricultural occupational pesticide exposure and cancer: May 15, 2018 - May 14, 2019

Author	Participants	Exposures and Assessments	Outcomes and Assessments	Key Results (all confidence intervals at 95%)
		Cancer		
Lerro CC et al. April 2019 [19]	Agricultural Health Study (AHS): 89,565 private and commercial pesticide applicators and spouses, from North Carolina and Iowa, recruited from 1993 to 1997	Self-administered questionnaires on farm life & agricultural practices, types of crops & livestock, pesticide use/use of >50 individual pesticide active ingredients	Incident cancer cases from NC and IA state cancer registries	All cancer sites: SIR (private applicators)=0.91, CI 0.89 - 0.93 SIR (commercial applicators)=0.83, CI 0.76 - 0.92 Lip cancer: SIR (private applicators)=2.22, CI 1.71 - 2.84 Prostate cancer: SIR (private applicators)=1.15, CI 1.11 - 1.19 B-cell lymphomas overall: SIR (private applicators)=1.12, CI 1.03 - 1.21 Chronic lymphocytic leukemia: SIR (private applicators)=1.17, CI 1.00 - 1.36 Acute myeloid leukemia: SIR (private applicators)=1.29, CI 1.03 - 1.59
Leon ME et al. March 2019 [20]	Subset of the Agricultural Health Study (AHS), including: 57,310 private and commercial pesticide applicators from North Carolina and Iowa, recruited from 1993 to 1997 Agriculture and Cancer (AGRICAN): 181,747 active and retired farm workers in France, recruited from 2005-2007 Subset of the Cancer in the Norwegian Agricultural Population (CNAP), including: 147,134 farm holders in Norway, based on censuses in 1969, 1974, 1979, 1985, 1989	AHS: self-administered enrollment questionnaires on farm life & agricultural practices, types of crops & livestock, pesticide use/use of >50 individual pesticide active ingredients, 5 year follow-up questionnaires on pesticide use since enrollment AGRICAN: self-administered questionnaires on cultivating 13 crops and raising 5 animal species and performance of pesticide treatment tasks, crossed with country-specific-crop-exposure matrices CNAP: census data on type of crops and livestock produced the preceding year, acreage, technology, pesticide expenses and pesticide spraying equipment, crossed with country-specific-crop-exposure-matrices	First incident non-Hodgkin's lymphoma (NHL) during follow-up: AHS: North Carolina and Iowa cancer and mortality registries and the National Death Index AGRICAN: French cancer and mortality registries and the National Death Index CNAP: National Cancer Registry of Norway	NHL overall & ever use of terbufos: mHR(AGRICAN and AHS)=1.18, CI 1.00 - 1.39; Chronic lymphocytic leukemia/small lymphocytic lymphoma & ever use of deltamethrin: mHR (AGRICAN and CNAP)=1.48, CI 1.06 -2.07 Diffuse large B-cell lymphoma & ever use of glyphosate: mHR=1.36, CI 1.00 - 1.85

Andreotti G et al. May 2018 [23]	Subset of the Agricultural Health Study (AHS): 54,251 pesticide applicators from North Carolina and Iowa, recruited from 1993-1997, 63% of whom participated in a follow up phone interview 5 years after enrollment	Ever/never use, lifetime days of use (days per year × number of years), and intensity-weighted lifetime days (lifetime days × intensity score) use of glyphosate from questionnaires at enrollment and follow-up	Incident cancer cases from North Carolina and Iowa state cancer registries	Highest quartile of glyphosate exposure to no exposure: Total cancer: RR=0.99, CI 0.91 - 1.08 Hematopoietic or lymphatic malignancies: RR=1.00, CI 0.74 - 1.34 Non-Hodgkin lymphoma: RR=0.87, CI 0.64 - 1.20 Multiple myeloma: RR=0.87, CI 0.45 - 1.69
Lerro CC et al. Sept 2018 [25]	Subset of the Agricultural Health Study (AHS): 49,685 pesticide applicators from North Carolina and Iowa, recruited from 1993-1997, 63% of whom participated in a follow up phone interview 5 years after enrollment	Cumulative lifetime days (sum of days of alachlor use reported at enrollment through the year last farmed reported at follow-up) and intensity-weighted days (cumulative lifetime days multiplied by an intensity-weighting factor) from questionnaires at enrollment and follow-up on alachlor use	Incident cancer cases from North Carolina and Iowa state cancer registries	Laryngeal cancer & alachlor exposure: RR (Quartile 2, 661-1762 intensity-weighted days compared to no exposure)=4.68, CI 1.95 - 11.23 RR (Quartile 3, 1763–5075 intensity-weighted days compared to no exposure)=6.04, CI 2.44 - 14.99 RR (Quartile 4, >5075 intensity-weighted days compared to no exposure)=7.10, 2.58 - 19.53
Boulanger M et al. May 2018 [27]	Agriculture and Cancer (AGRICAN): 148,044 active and retired farm workers in France, recruited from 2005-2007	Self-administered questionnaires on lifetime history of agricultural activities, cultivating 13 crops and raising 5 animal species, performance of harvesting, pesticide application, seed treatment, seedling, and/or re-entry tasks	Incident lung cancer cases from French cancer registries	Adenocarcinomas & winegrowing: HR (Ever vineyard farm work to never vineyard farm work)=1.27, CI 0.94 - 1.72 Small cell lung cancers & pea/field beans: HR (Ever pesticide application to never pesticide application)=2.38, CI 1.07 - 5.28 Squamous cell carcinomas & beets: HR (Ever pesticide application to never pesticide application)=1.47, CI 0.92 - 2.34 Squamous cell carcinomas & sunflowers: HR (Ever harvester to never harvester)=1.61, CI 0.91 - 2.86 Squamous cell carcinomas & fruit-trees: HR (Ever pruner to never pruner)=1.44, CI 0.92 - 2.27 Overall lung cancer & corn: HR (Ever grower to never grower)=0.76, CI 0.62 - 0.92 Overall lung cancer & wheat/barley: HR (Ever grower to never grower)=0.85, CI 0.70 - 1.04
Peil C et al. November 2018 [28]	Agriculture and Cancer (AGRICAN): 181,842 active and retired farm workers in France, recruited from 2005-2007	Self-administered questionnaires on cultivating 13 crops and raising 5 animal species and occupational activities	Incident central nervous system cancer cases (gliomas and meningiomas) from French cancer registries and the National Death Index	CNS tumors & exposure to all carbamates: HR=1.47, CI 1.03 - 2.10

Table 2. Studies regarding agricultural occupational pesticide exposure and other health outcomes: May 15, 2018 - May 14, 2019

Author	Participants	Exposures and Assessments	Outcomes and Assessments	Key Results (all confidence intervals at 95%)
		DNA Damage and Oxidative Stress		
Hutter HP et al. August 2018 [37]	38 pesticide sprayers and 33 farmers not exposed to pesticides from coffee production farms in the Dominican Republic	Pesticide sprayers were considered exposed, additional information was collected from a questionnaire on demographics and indicators of pesticide exposure including type and duration	Buccal cell samples analyzed for genotoxic and cytotoxic effects: micronuclei cells, total micronuclei, nuclear buds & broken eggs, binucleated cells, condensed chromatin, karyorrhectic cells, karyolitic cells, and pyknosis	Micronuclei cells: OR=3.098, CI 1.297 - 7.404 Total micronuclei: OR=2.534, CI 1.219 - 5.226 Nuclear buds & broken eggs: OR=1.916, CI 1.448 - 2.536 Binucleated cells: OR=1.412, CI 1.207 - 1.650
Kahl SVF et al. September 2018 [38]	121 tobacco farm workers occupationally exposed to pesticide mixtures and 121 non-exposed non-farm workers in Brazil	Those with an occupation as a tobacco farmer were considered exposed to pesticides and completed a questionnaire adapted from the International Commission for Protection against Environmental Mutagens and Carcinogens	Whole blood comet assay as well as buccal cell micronucleus cytome assay for damage index, micronucleus, nuclear buds, binucleated cells, and telomere length; blood cotinine levels and inorganic elements; thiobarbituric acid reactive substances (TBARS) and total equivalent antioxidant capacity (TEAC); and various polymorphisms	Increased frequency of: Damage index: 22.1 ± 1.6 (exposed) vs. 4.6 ± 0.4 (unexposed), p=<0.001 Micronucleus: 25.3 ± 2.9 (exposed) vs. 5.8 ± 0.7 (unexposed), p=<0.001 Nuclear buds: 3.3 ± 0.3 (exposed) vs. 1.1 ± 0.1 (unexposed), p=<0.001 Binucleated cells: 7.2 ± 0.5 (exposed) vs 5.4 ± 0.4 (unexposed), p=0.010 Exposed vs. non-exposed increased levels of oxidative stress biomarkers: TBARS: p=<0.001 TEAC: p=<0.001
Hayat K et al. November 2018 [39]	Pesticide industry workers (formulators and packers), pesticide sprayers, and controls with no occupational exposure to pesticides	Pesticide industry workers and sprayers were considered exposed to pesticides	Whole blood comet assay for tail length and comet frequency, pesticide residues in blood samples, and hepatic and nervous system enzymes	Tail length (μm): 16.88 ± 8.57 (industry workers) vs. 16.33 ± 3.78 (sprayers) vs. 6.53 ± 2.75 (controls), p=<0.01 Comet frequency: 17.56 ± 11.55 (industry workers) vs. 15.76 ± 9.37 (sprayers) vs. 3.25 ± 1.42 (controls), p=<0.01
Saad-Hussein A et al. February 2019 [40]	50 urban researchers using pesticides in laboratories, 50 rural pesticide sprayers, and 50 urban researchers not occupationally exposed to pesticides and 50 rural controls not occupationally exposed to pesticides	Urban researchers exposed to pesticides in laboratories and rural pesticide sprayers were considered exposed	Whole blood telomere length, telomerase activity, comet assay for tail length, percent DNA in tail, and tail moment; GST genotypes; liver tumor markers	Comet tail length: 17.84 ± 1.07 (rural exposed) vs. 8.4 ± 0.72 (rural controls), p=<0.0001 Percent DNA in tail: 4.57 ± 0.40 (rural exposed) vs. 0.84 ± 0.19 (rural controls), p=<0.0001 Tail moment: 0.73 ± 0.05 (rural exposed) vs. 0.08 ± 0.001 (rural controls), p=<0.0001

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Dhananjayan V et al. March 2019 [41]	77 tea garden workers exposed to pesticide and 66 individuals with no occupational exposure to pesticides in India, recruited from December 2013 to February 2014	Women who had worked in tea gardens for at least 3 years were considered exposed to pesticides. Participants completed a questionnaire on demographics, health, lifestyle, and occupational details	Peripheral lymphocyte comet assay for percent DNA in tail, tail length, tail moment, and olive tail moment; and cholinesterase activity in erythrocytes and blood plasma	Mean tail length (µm): 9.45 ± 5.28 (exposed) vs. 2.09 ± 0.95 (unexposed), p=<0.05 Percent DNA in tail: 13.1 ± 8.17 (exposed) vs. 2.26 ± 1.63 (unexposed), p=<0.05 Tail moment (µm): 3.19 ± 2.29 (exposed) vs. 0.20 ± 0.12 (unexposed), p=<0.05 Olive tail moment (µm): 4.15 ± 2.18 (exposed) vs. 0.59 ± 0.44 (unexposed), p=<0.05
Intranuovo G et al. July 2018 [42]	22 agricultural workers exposed to pesticides and 24 non-agricultural hematologic outpatients from the provinces of Bari and Taranto, Italy	Agricultural workers were considered exposed to pesticides. Intensity level score for pesticide exposure calculated based on questionnaire responses regarding pesticide mixing, application, personal hygiene, use of protective equipment, repair of pesticide tanks, and use of tractors with cabins	Peripheral lymphocyte comet assay for tail moment, tail area, head DNA, tail DNA, integral intensity, head radius, tail length, olive movement, and head area	Odds of tail moment above 75th percentile in exposed to unexposed: OR=5.77, CI 4.63 - 7.21 Odds of tail length above 75th percentile in exposed to unexposed: OR=6.36, CI 5.1 - 7.95
Cattelan MDP et al. June 2018 [46]	84 farmers reporting occupational pesticide use and 68 farmers not reporting occupational pesticide use in Brazil	Farmers reporting pesticide use were considered exposed, based on a questionnaire regarding pesticide use and occupational practices	Blood samples to measure thiobarbituric acid reactive substances (TBARS) and carbonylation of proteins (Carbonyl); superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSH), and glutathione peroxidase (GPx); and frequency of micronuclei in leukocytes	Micronuclei frequency: 0.24% (exposed) vs. 0.12% (unexposed), p=0.288 SOD activity: decreased in exposed vs. unexposed, p=< 0.01 GSH activity: decreased in exposed vs. unexposed, p=<0.01 GPx activity: decreased in exposed vs. unexposed, p=< 0.01 TBARS: decreased in exposed vs. unexposed, p=0.02
Sapbamrer R et al. May 2019 [47]	56 male farmers in Thailand	In-person interview on demographics and occupational exposures, and blood samples collected pre- and post- pesticide application seasons	Peripheral leukocyte comet assay for tail length and tail moment;, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels; superoxide dismutase (SOD) activity	Median tail length (µm): 5.66 (pre-pesticide application season) vs. 5.67 (post-pesticide application season) , p=0.867 Median tail moment (µm): 2.84 (pre-pesticide application season) vs. 2.83 (post-pesticide application season), p=0.729 Median 8-OHdG (ŋg/mL): 8.31 (pre-pesticide application season) vs. 7.20 (post-pesticide application season), p=0.757 Median SOD (U/mL): 0.94 (pre-pesticide application season) vs. 1.35 (post-pesticide application season), p=< 0.001

Lozano-Paniagua D et al. October 2018 [51]	175 greenhouse workers carrying out farming activities (pruning, weeding, thinning, and applying pesticides) and 91 healthy individuals without occupational exposure to pesticides in Almeria, Spain	Greenhouse workers were considered exposed to pesticides. Analyses was conducted for two crop seasons: low pesticide exposure season (one to two pesticide applications per month) and high pesticide exposure season (weekly pesticide applications)	Blood samples to measure thiobarbituric acid reactive substances (TBARS), ferric reducing ability of serum (FRAS), total thiol groups (SHT), and gamma-glutamyl transpeptidase (GGT) and Paraoxonase 1 (PON1)	Mean FRAS (µmol/l): High exposure season: 2.800 ± 0.017 (greenhouse workers) vs. 2.664 ± 0.020 (unexposed), p=< 0.001 Mean SHT (µmol/l): High exposure season: -0.250 ± 0.015 (greenhouse workers) vs. -0.396 ± 0.019 (unexposed), p=<0.001 Low exposure season: -0.366 ± 0.019 (greenhouse workers) vs. -0.387 ± 0.126 (unexposed), p=<0.001 Mean PON1 (U/l): High exposure season: 2.276 ± 0.036 (greenhouse workers) vs. 2.206 ± 0.047 (unexposed), p=0.069 Low exposure season: 2.231 ± 0.033 (greenhouse workers) vs. 2.115 ± 0.046 (unexposed), p=0.069
		Neurological Disorders		
Rohlman DS et al. May 2019 [66]	98 adolescents aged 12-21 years, comprised of 59 pesticide applicators working for the Ministry of Agriculture in Egypt and 39 non-applicators	Pesticide applicated were considered exposed to pesticides, measurements were also done for urinary 3,5,6-trichloro-2-pyridinol (TCPy) levels, a biomarker of chlorpyrifos exposure, and blood acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity, biomarkers of organophosphate exposure	Symptoms of attention deficit hyperactivity disorder (ADHD) assessed by parental completion of the Revised Short Form of Conners' Parent Rating Scale	ADHD symptoms: 4.46 ± 4.95 (applicators) vs. 1.44 ± 2.18 (non-applicators), p=< .001 Positive dose-response effect for number of ADHD symptoms and TCPy level: p=<0.001 Positive dose-response effect for number of ADHD symptoms and AChE: p=<0.001 Positive dose-response effect for number of ADHD symptoms and BChE: p=<0.001
Guytingco A et al. July 2018 [67]	6,118 agricultural workers in Thailand completing a questionnaire on occupational pesticide use and pesticide behavioral patterns, and symptoms, among those 3,431 providing a blood sample	Blood acetylcholinesterase (AChE) levels, a biomarker of organophosphate pesticide exposure	Self-reported symptoms of dizziness, dry skin & irritation, fatigue, burning sensation in nose, sore throat, cough, rash, sweating, headache, conjunctivitis, heart palpitations	12.5% of participants had low AChE levels; Prevalence of dizziness: 12.4% (abnormal AChE) vs. 4.0 % (normal AChE), p=<0.001 Prevalence of headache: 3.3% (abnormal AChE) vs. 1.3% (normal AChE), p=0.010 Prevalence dry skin and irritation: 10.5% (abnormal AChE) vs. 4.0% (normal AChE), p=<0.001

Serrano-Medina A et al. February 2019 [72]	140 agricultural workers and 100 individuals not exposed to pesticides in Mexico	Agricultural workers were considered exposed to pesticides, measurements were also done for blood acetylcholinesterase levels, a biomarker of organophosphate pesticide exposure	Symptoms of neuropsychiatric disorders as assessed by the Mini International Neuropsychiatric Interview Diagnostic Test (MINI)	Depression diagnosis frequency: 14.3% (exposed) vs. 3.0% (unexposed) Major depression with suicidal risk diagnosis frequency: 31.4% (exposed) vs. 8.0% (unexposed) Generalized anxiety diagnosis frequency: 14.3% (exposed) vs. 18.0% (unexposed) No psychiatric disorder diagnosis frequency: 36% (exposed) vs. 64% (unexposed) Positive association between AChE activity & psychiatric disorders such as suicide risk: $p=0.006$
Shrestha S et al. January 2019 [73]	Subset of the Agricultural Health Study (AHS) who completed the third AHS follow-up and met all study inclusion criteria: 11,232 pesticide applicators from North Carolina and Iowa	Self-reported experience of a high pesticide exposure event (HPEE)	Self-reported olfactory impairment	Olfactory impairment and: History of HPEE reported at enrollment: OR=1.49, CI 1.28 - 1.73 HPEE involving the respiratory or digestive track: OR=1.53, CI 1.22 - 1.92 HPEE involving dermal contact: OR=1.47, CI 1.22 - 1.78
Respiratory Effects				
Buralli RJ et al. June 2018 [79]	48 farm workers in tomato cultivation in Brazil and 34 relatives residing in the same area who also may have helped in agricultural activities	Rural workers and relatives were considered exposed to pesticides, specifically 49 pesticides from 31 chemical groups based on self-reported use Crop season (active work in tomato cultivation) and off-season (not working in agriculture) were compared, blood acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity was also measured	Self-reported respiratory symptoms based on the European Community Respiratory Health Survey (ECRHS) and spirometry testing	Crop season and: Wheeze or chest tightness: OR=2.25, CI 0.63 - 10 Wheeze with breathlessness: OR=0.67, CI 0.06 - 5.82 Wheeze without cold: OR=1.5, CI 0.17 - 17.96 Waking with chest tightness: OR=6, CI 0.73 - 275.99 Waking with cough: OR=5.5, CI 1.20 - 51.07 Nasal allergies and hay fever: OR=2.4, CI 0.79 - 8.70

Metabolic Effects				
Park S et al. January 2019 [83]	Korea Farmers Cohort Study: 2,559 farmers and farm managers from rural areas of Wonju and Pyeongchang, Gangwon-do, Korea, recruited from 2005 - 2008	Intensity level [(mixing status+application method+repair status) × Personal Protective Equipment] and Cumulative Exposure Index (CEI) [intensity level×duration (number of years) × frequency (average days per year)], from questionnaires on occupation as a farmer, mixing or applying pesticides, and specifics of pesticide use	Prevalence of diabetes defined by fasting plasma glucose ≥ 126mg/dL, or 2-hour plasma glucose ≥ 200mg/dL during oral glucose tolerance test, or HbA1c ≥ 6.5%, or reported current use of insulin or antidiabetic medication	Diabetes and: Ever pesticide use: OR=1.58, CI 1.13 - 2.21 ≥ 20 years of pesticide use: OR=1.51, CI 1.07 - 2.14 ≥ 10 days of pesticide use per year: OR=1.53, CI 1.09 - 2.15 Pesticide exposure at lower intensity level: OR=1.55, CI 1.07 - 2.24 Pesticide exposure at higher intensity level: OR=1.53, CI 1.06 - 2.22 Higher CEI: OR=1.54, CI 1.03 - 2.30
Kongtip P et al. November 2018 [84]	243 conventional farmers and 235 organic farmers in Thailand	Work as a conventional farmer was considered exposed, work as an organic farmer was considered non-exposed	Body mass index (BMI), waist circumference, percent body fat, blood pressure, metabolic syndrome, and blood sample analysis of serum glucose, triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)	Conventional farm work to organic farm work: BMI: RR=1.83, CI 1.20 - 2.78 Waist circumference: RR=1.69, CI 1.13 - 2.51 Percent body fat: RR=1.31, CI 1.05 - 1.64 TGs: RR=1.51, CI 1.01 - 2.27 TC: RR=2.20, CI 1.69 - 2.86 LDL: RR=1.34, CI 1.14 - 1.57 HDL: RR=0.83, CI 0.37 - 0.95

Thyroid Effects				
Shrestha S et al. Sept 2018 [89]	Subset of the Agricultural Health Study (AHS) who completed at least one follow-up survey between 1999 and 2016: 38,698 pesticide applicators from North Carolina and Iowa	Ever/never use of pesticides and intensity-weighted cumulative days of pesticide use based on self-administered questionnaires on farm life & agricultural practices, types of crops & livestock, and pesticide use/use of >50 individual pesticide active ingredients	Self-reported hypothyroidism	Hypothyroidism and: Ever use of chlordane: HR=1.21, CI 1.04 - 1.41 Ever use of diazinon: HR=1.27, CI 1.10 - 1.48 Ever use of dichlorvos: HR=1.42, CI 1.17 - 1.72 Ever use of malathion: HR=1.23, CI 1.04 - 1.46 Ever use of dicamba: HR=1.27, CI 1.08 - 1.50 Ever use of glyphosate: HR=1.28, CI 1.07 - 1.52 Ever use of 2,4-D: HR=1.30, CI 1.07 - 1.58
Bernieri T et al. March 2019 [91]	46 soybean growers and 27 individuals not exposed to pesticides an urban area of Brazil	Employment as a soybean grower was considered exposed to pesticides, blood butyrylcholinesterase (BChE) activity was also measured	Serum levels of free thyroxin (FT4), total triiodothyronine (TT3) and thyroid-stimulating hormone (TSH)	Activity of BChE (U/L): 7969.8 ± 1582.3 (exposed) vs. 9140.2 ± 2032.3 (unexposed) U/L, p=0.006 TT3 (ng/dL): 139.0 ± 28.6 (exposed) vs. 104.5 ± 20.0 (unexposed) ng/dL, p=<0.001 FT4 (ng/dL): 0.78 ± 0.15 (exposed) vs. 0.66 ± 0.09 (unexposed) ng/dL, p=<0.001 TSH (µUI/mL): 2.15 ± 1.09 (exposed) vs. 2.91 ± 1.35 (unexposed) µUl/mL, p=0.007