The effect of pesticides on prenatal and postnatal children toward developing autism spectrum disorder

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Autistic Spectrum Disorder (ASD) is defined as a complex neurodevelopmental disorder characterized by abnormalities in social communication, unusual and repetitive behaviors. According to Centers for Disease Control and Prevention (CDC), in 2014, an average of 1 in 59 8-year-old children were identified as being on the autistic spectrum (Baio, 2014).

ASD is a multi-factor disorder, thought to be partially genetic, and partially environmental. As such it is impossible to define a single cause for the disorder, however, since there are so many environmental factors that have been created, discovered, or changed over the last few generations, it is difficult to narrow down possible contributing environmental factors involved with the disorder. It is similarly not yet known exactly at which point the contributing environmental factors come into play, whether prior to conception, prenatal, or postnatally. There are also problems in even diagnosing the disorder, and since the disorder is on a spectrum, it is feasible that there may be some factors that affect some people and other factors affecting others, which may lead to differences within the spectrum of the disorder.

This study is seeking to answer the question, “are pesticides a contributing factor towards development of Autism Spectrum Disorder?” This will include a review of several recent studies going over the current state of knowledge regarding what is known about how pesticide usage may be a contributing factor toward development of ASD. This will hopefully allow us to determine what role pesticides play as a contributing factor in ASD, and if so, how the use of these may be changed in order to prevent the rise of ASD within the general population.

The first article being reviewed is “Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population-based case-control study” (von Ehrenstein et al., 2019). The authors started the article by going over previous research, specifically mentioning how pesticides have previously been linked to neurodevelopmental problems. Von Ehrenstein et al. (2019) goes on to state that not enough is known about the environmental factors in play regarding Autistic Spectrum Disorder (ASD), which is the reasoning behind the study. The study consisted of a large population study, assessing prenatal and infant exposure to various pesticides. The authors used data from the Department of Developmental Services (DDS), and the California state-mandated Pesticide Use Reporting (CA-PUR) program within an agriculturally intensive region of California. From the DDS data, they matched birth data of those classified under “autistic disorder” by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) diagnostic criteria along with California birth records from the Office of Vital Statistics to determine ASD sufferers and their residence at birth. From this information the authors were able to create a record of how much of each pesticide was used within 2000m of a subject’s address, averaged over specific periods. Those periods consisted of three months before gestation, each month of gestation, and the first year of life.

Von Ehrenstein et al. (2019) chose 11 pesticides within their analysis (based upon previous studies that had shown some links between these high-use substances and developmental problems): glyphosate, chlorpyrifos (an organophosphate pesticide), diazinon, acephate, malathion, permethrin, bifenthrin, methyl bromide, imidacloprid, avermectin, and myclobutanil. They specifically disregarded organochlorines, as despite their apparent link to developmental issues, they have been banned in California for a long time, and therefore data was not available on those.

Results of the study showed that for all periods of exposure around developmental periods (3 months before, during, and during first year after birth), ratios of exposure to most substances increased, but associations were strongest for chlorpyrifos, diazinon, and avermectin. However, unlike some previous studies, the authors discerned no clear patterns per-trimester. The authors also considered ASD with comorbid intellectual disability, which showed clearer risks during the first year after birth. They concluded that the risk of ASD increased with the prenatal and early infant exposure to these common pesticides shown to affect neurodevelopment within previous studies.

This study had multiple strengths and weaknesses. The strengths included avoiding participation bias, since they did not rely upon reports on past exposure from the parents themselves, however it had a few limitations as well. Specifically, von Ehrenstein et al. (2019) had to rely upon gestational age and birth date to construct developmental periods, they had to assume that the subjects were present at their residence during the entirety of the exposure time, and they had to assume that substances only stayed in their home for the targeted periods and did not get trapped in the home, through dust or any other means.

The second article being reviewed is “Neurodevelopmental Delay Diagnosis Rates Are Increased in a Region with Aerial Pesticide Application”, by Hicks, Wang, Fry, Doraiswamy, and Wohlford (2017). In this study, Hicks et al. examined ASD and childhood Developmental Delay (DD) in an area that has yearly aerial pesticide application to combat encephalitis from infected mosquitos, in upstate New York. In this study, there was only a single pesticide of concern being used, “pyrethroid” (PP), though it was explained that this is common within household insecticides. Hicks et al. were testing “the hypothesis that rates of regional ASD/DD diagnoses are related to route (aerial application) of PP exposure” (2017). The authors explained that between 2007 and 2009, the yearly average exposure to pesticides for the aerial-exposed zip codes was 11,299 kg, whereas it was only 4,164 kg for the surrounding 16 zip codes.

Hicks et al. (2017) found that within zip codes with aerial pesticide exposure, the rate of ASD diagnosis was 1 in 115, compared to 1 in 196 in the control zip codes, and the authors found a significant correlation between aerial exposure of pyrethroid and ASD/DD prevalence, as well as total pesticide exposure and prevalence of ASD/DD.

Hicks et al. (2017) did explain that every year, precautions are taken to advise people in the affected every year prior to the aerial pesticides, but also explained how these would be difficult to follow, even if the people are aware of them.

The authors also explained some of the limitations of this study, especially since the prevalence of ASD diagnoses were well below the national average. The suggested reasoning behind this is that the children’s hospital that would make the clinical diagnosis was the only such hospital within an 80-mile radius, and therefore data may have been missing around ASD and DD due to informal diagnosis, being managed by local pediatricians without a referral. Even without this data though, the authors found that there was a 37% higher rate of ASD/DD within areas exposed by aerial pesticides.

The third study reviewed was “Polychlorinated Biphenyl and Organochlorine Pesticide Concentrations in Maternal Mid-Pregnancy Serum Samples: Association with Autism Spectrum Disorder and Intellectual Disability”, by Lyall et al. (2016). This particular study was checking for any association between polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), and ASD, as well as intellectual disability without autism (ID). This study used data from the Early Markers for Autism (EMA) study, a California statewide screening program that took blood from both the pregnant mothers during the second trimester and later their babies after birth. This consisted of a total of 1144 children, of which 545 children had ASD, 181 children had ID without ASD, and 418 control children.

Lyall et al. (2016) compared the amount of OCPs and PCBs found in the blood of both the mother and child separately with the children that had developed ASD. The authors found generally an increased risk of ASD with higher levels of PCBs, however they did not find an association between OCPs and ASD, although there are other previous studies that have, along with animal models that would provide some biological basis for this. It is worth noting however, that most of the other studies in this review did not take into consideration OCPs, since they have been largely banned within the US for a long time.

The fourth study reviewed was “Prenatal Organophosphate Pesticide Exposure and Traits Related to Autism Spectrum Disorders in a Population Living in Proximity to Agriculture” by Sagiv et al. (2018). This studied use data from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) longitudinal study. The objective of this study was to investigate the link between exposure to organophosphate (OP) pesticides during pregnancy and ASD. The CHAMACOS study included taking the mother’s urine twice during the pregnancy, once during the first interview at 13 weeks, and the next during an interview at the 26-week period. Within this study Sagiv et al. (2018) were measuring how much dialkyl phosphate (DAP) metabolites there were in the urine in order to assess the amount of exposure to OP pesticides. Similar to von Ehrenstein et al. (2019), Sagiv et al. used data from CA-PUR, but combined them with coordinates of the mother’s residence during pregnancy in order to determine how much OP pesticides were used within a 1km radius.

Combined data from CA-PUR data with coordinates of residence of the expectant mother during her pregnancy in order to determine how much OP pesticides were used within a 1km radius. In this study the authors used mother-children pairs where they knew the residence of the mother for at least 75 days per trimester, for 2 or more of the trimesters, and used this information to average the pesticide exposure.

Sagiv et al. (2018) examined pesticide in multiple ways within this study. They examined the 4 most common OP pesticides: chlorpyrifos, diazinon, malathion, and oxydemeton-methyl, then examined the sum of all OP pesticides use (15 total pesticides), and then also examined the weighted sum of relative toxicities. In this study there was not a formal diagnosis of ASD, but participants were “administered several instruments to directly assess or capture parent or teacher reports on children’s traits related to ASD” (Sagiv et al., 2018)

Within this study, the authors found associations between DAP metabolites in urine with ASD-related behavior at 14 years using the SRS-2 test, but did not find association between urine levels and facial affect recognition tests. Similarly, the authors were unable to identify an association between ASD traits and proximity to places pesticides were used for agricultural reasons.

The primary limitation to this study compared to others is that a clinical diagnosis of ASD was not performed, and instead it was identified by traits of ASD found using tests submitted by parents and teachers. However, there was also a limited variability of exposure, as most participants lived near agricultural fields, and so most were exposed to a lot of pesticides. Due to this, it could be that a limit in the variation may have limited the ability to detect differences in ASD traits. Since von Ehrenstein et al. (2019) similarly used CA-PUR data, it is logical to first make comparisons to this, especially since the results were completely different. Regarding the differences in the studies, apart from the limitations noted above, a strength of this study is that the authors were able to identify which parents were at the residence throughout the study, with a higher degree of accuracy of determining how far away they were from agricultural fields, and similarly used a narrower field (1km from agricultural fields compared to 2km). Both however, have the limitations the CA-PUR data implicitly has, in that it cannot account for consumption through diet, pesticide use within the home, and proximity to transportation of pesticides.

The fifth article reviewed was “Prenatal exposure to organophosphate pesticides and risk of autism spectrum disorders and other non-typical development at 3 years in a high-risk cohort”, by Philippat et al. (2018). Similar to the CHAMACOS study used by Sagiv et al. (2018), Philippat et al. used urine samples during pregnancy to determine levels of pesticides. This study in particular was examining prenatal exposure to organophosphate (OP) pesticides in relation to diagnosis of ASD and non-typical development (NTD).

Philippat et al. (2018) used the Markers for Autism Risk in Babies – Learning Early Signs (MARBLES) mother-child cohort, which includes women who are pregnant or planning to become pregnant if they have an elevated risk for their child developing ASD. Of the children assessed at 3 years of age, they were categorized as follows: 46 children were diagnosed with ASD, 55 had non-typical development (NTD), and 102 had typical development (TD).

The authors in this study found an association between girls and one of the chemicals tested, but not boys, however there was only a small number of girls with ASD within the study, so further analysis would need to be done to come to any more concrete findings. Some limitations that may have affected results within this study include the fact that the study consisted of mothers who were at high-risk of having a child with ASD, since they either already had a child with ASD, or had a twin that had a child with ASD, therefore there may have been more genetic factors involved here compared to the general population.

The final study reviewed was “Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration” by Pearson et al. (2016). This study was the only experimental study reviewed and consisted of studying how various pesticide chemicals may lead to brain transcriptional changes associated with ASD. The authors used mouse cortical neuron-enriched cultures, to measure the cytotoxicity of 294 pesticide chemicals (primarily found within food production) within the EPA ToxCast Phase I library and identify a non-toxic level for RNA sequencing.

Pearson et al. (2016) were able to identify a group of 8 chemicals that mimicked ASD, brain aging and neurodegeneration transcriptionally, which the authors were surprised at, as it may indicate an overlapping pathological process behind all of these. This study gives a somewhat of a possible biological reason for why pesticides may lead to ASD, however since the testing was performed on mouse cortical neuron-enriched cultures, further live animal studies would need to be performed to determine effectiveness.

The articles reviewed within this study show varying results, but also a lot of differences and similarities among pesticides tested, methods of data retrieval, and data analysis methods performed. This all combines to show that it is very difficult to determine cause and effect for ASD, especially considering it is a multi-factor disorder, environmental factors are only likely one part of the puzzle, and so it is not clear whether we will ever have a single substance that can be pointed to that leads to an increased risk in ASD. Some of these studies used public data, some used general longitudinal studies that were not specifically designed for their needs, and some used a cross-section of the two. Most of the epidemiological studies required a clinical diagnosis of ASD, except for Sagiv et al. (2018), a clear limitation compared to the others, but the same study also included some strengths improving over other studies, such as the ability to know that the expectant mother actually lived at the residence for the given parts of pregnancy.

There was also a discrepancy across the studies about how to measure pesticide exposure. Von Ehrenstein et al. (2019) and Hicks et al. (2017) focused on pesticide exposure via proximity in the air and found an association, Lyall et al. (2016) focused on levels of pesticides within blood samples and found an association, whereas Sagiv et al. (2018) and Philippat et al. (2018) both focused on urine samples and did not find any significant association. It would have to be questioned whether all these data retrieval methods are similarly effective.

In conclusion, there are findings that both support the hypothesis of this paper, as well as some that do not find an association, but there needs to be further experimental and epidemiological studies performed to further confirm either way.

There are a lot of differences between studies, with a lot of different methods being used to determine associations, and different data retrievals. It is first imperative to understand the most accurate ways to retrieve data regarding pesticide exposure to humans, preferably using experimental studies, as well as understanding how this may differ between different chemicals within the environment. This needs to be determined so that we can come to a consensus regarding ways to retrieve this data, whether it be taking public data from the CA-PUR program, finding this information from blood samples, or retrieving it from urine samples. This will allow us to further narrow down whether pesticides, and which ones, may have a causal contributing factor toward ASD. There is also a need for having large longitudinal studies, covering a larger, varying population, as most studies were narrowed down to similar areas, where the socioeconomic status, race, and exposure to pesticides may not have as varied as much as they would have on a larger scale study. Unfortunately, it is very expensive and time consuming to be able to create large longitudinal studies, especially those involving expectant mothers and their children over many months and years, and so there likely needs a greater buy-in from the public, government and private firms in order to be able to determine more specifically what are and are not contributing factors toward children developing ASD.

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