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A Narrative Review of Converging Evidence addressing Developmental Toxicity of Pyrethroid Insecticides

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Abstract

Pyrethroid insecticides are broadly used in agriculture and household products throughout the world. Exposure to this class of insecticides is widespread, and while generally believed to be safe for use, there is increasing concern regarding their effects on neurodevelopment. Due to the critical roles that molecular targets of pyrethroids play in the regulation of neurodevelopment, particular focus has been placed on evaluating the effects of in utero and childhood pyrethroid exposure on child cognition and behavior. As such, this narrative review synthesizes an assessment of converging study types; we review reports of neonatal pyrethroid levels together with current epidemiological literature that convergently address the risk for developmental toxicity linked to exposure to pyrethroid insecticides. We first address studies that assess the degree of direct fetal exposure to pyrethroids in utero through measurements in cord blood, meconium, and amniotic fluid. We then focus on the links between prenatal exposure to these insecticides and child neurodevelopment, fetal growth, and other adverse birth outcomes. Furthermore, we assess the effects of postnatal exposure on child neurodevelopment through a review of the data on pediatric exposures and child cognitive and behavioral outcomes. Study quality was evaluated individually, and the weight of evidence was assessed broadly to characterize these effects. Overall, while definitive conclusions cannot be reached from the currently available literature, the available data suggest that the potential links between pyrethroid exposure and child neurodevelopmental effects deserve further investigation.

Keywords

Pyrethroid; Neurodevelopment; Review; Epidemiology; Developmental Toxicity; Insecticide; Attention Deficit Hyperactivity Disorder; Autism

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Introduction

Pyrethroids make up a significant percentage of the total market share for insecticides and are used widely in agricultural and household applications. They are a broad range of chemicals with high insect but low mammalian toxicity based on naturally occurring pyrethrins from the *Chrysanthemum cinerariaefolium* plant. Powdered derivatives of the pyrethrum plant were widely used for mosquito control even in the 1850's but were not stable in light and heat for long periods (Matsuo 2019). When the structure of pyrethrin I was discovered in 1945 and its stereochemistry in 1958 (LaForge and Barthel 1945; Ujihara 2019), potential modifications were investigated to increase its utility for agricultural applications by enhancing photostability (Matsuo 2019). Modification of pyrethroid structure—esters of chrysanthemum acid (ethyl 2,2-dimethyl-3-(1-isobutenyl)cyclopropane-1-carboxylate) and halogenated derivatives of their acids and alcohols—altered the safety margin of these chemicals (Chrustek et al. 2018). Some synthetic compounds were created and went into household use in the 1950's and 60's. However, halogenation of the vinyl group on the cyclopropane ring produced stability in light and resulted in 2nd generation pyrethroids such as permethrin, deltamethrin, and cypermethrin which have both agricultural and household applications (Elliott et al. 1973; Elliott et al. 1974). These pyrethroids have been assessed by manufacturers through many different rounds of safety testing, as with all insecticides, procedures required and reviewed in the US by the Environmental Protection Agency (EPA). Much of this information is collected prior to EPA registration when an insecticide comes on the market; however, reporting by the manufacturer of additional safety information is required after registration along with periodic EPA review of data on insecticide safety testing and reports. EPA registration of 2nd generation synthetic pyrethroids first occurred in 1979 and now includes commonly many used compounds: cypermethrin, deltamethrin, fenpropathrin, fenvalerate, bifenthrin, permethrin, λ-cyhalothrin, and cyfluthrin. The use of these more stable pyrethroids worldwide began in 1977 and is governed by the World Health Organization (WHO) and other governmental bodies which require similar safety margin testing (Palmquist 2012; Chrustek et al. 2018). The use of pyrethroids has been steadily increasing in terms of total amount and proportion of the insecticide market in subsequent decades: pyrethroids make up more than 80% of public health insecticides and had increased to 17% of agricultural insecticide market by 2015 (Tang et al. 2018; Matsuo 2019). This increase has occurred alongside EPA and other agencies gradually de-registering particular or general uses of other insecticide classes, most significantly organophosphates such as chlorpyrifos.

In general, the affinity of pyrethroids for the voltage-gated sodium channel (VGSC) is believed to be the primary insecticidal mode of action (Soderlund et al. 2002). Pyrethroids alter the kinetics of the VGSC by prolonging the channel's open-state conformation, which leads to increased influx of sodium into the neuron and slowing of the action potential falling phase. In addition, the 2nd generation pyrethroids used today interact with a broader range of molecular targets, including voltage-gated sodium channels, chloride channels, potassium channels, calcium channels, and ATPases (Soderlund et al. 2002). Affinity

for these molecular targets differs between individual chemicals within this broad class, particularly between those classified as type I vs. type II (Breckenridge et al. 2009).

Previous work has demonstrated that binding of type II pyrethroids to the VGSC leads to extended influx of sodium as compared to type I pyrethroids, which results in differences in effects on neuronal physiology between chemicals within this broad class. In general, increased sodium influx via the action of type I pyrethroids results in hyperexcitability of the neuron, whereas extended sodium influx induced by type II pyrethroids leads to membrane depolarization and conduction block (Field et al. 2017). In addition, type II pyrethroids have been demonstrated to have higher affinity than type I pyrethroids for other molecular targets in the human nervous system, including voltage-gated calcium channels, chloride channels, and potassium channels (Soderlund et al. 2002). Pyrethroids may therefore influence neuronal signaling through their effects on these channels in mature neurons and other cells in the brain; developing brain cells during development are also influenced by these same channels in their proliferation, migration, and differentiation (Pineda and Ribera 2008; Lepski et al. 2013; Malmersjo et al. 2013; Shen et al. 2016; Goyal et al. 2020). Disruptions in these cellular processes of development may have lasting impacts on emotional, cognitive, and behavioral brain functions in childhood and adulthood. The developing brain also interacts with the broader physiology of other systems in the body and, during prenatal periods, the placenta which also rely on channels and other cellular biochemistry sensitive to pyrethroids (Johansson et al. 2000; Bernucci et al. 2006; Vallejos and Riquelme 2007; Riquelme 2009; He et al. 2018; Feriani et al. 2021). Academic studies therefore support a hypothesis that the human nervous system may be affected in significant ways by pyrethroids during development.

Academic studies have also demonstrated a wide variety of adverse effects induced by early exposure to pyrethroids on rodent neurodevelopment; however, the relevance of these effects to human exposures and functional outcomes is less clear (Shafer et al. 2005). Regulatory studies submitted for product registration support a lack of risk for fetal malformations in response to prenatal pyrethroid exposure; however, effects on neurodevelopment are less clear. Given the sensitivity of neurodevelopment to chemical exposures and the relevance of many pyrethroid targets to neurodevelopmental processes, there is concern for the contribution of prenatal and juvenile exposures to cognitive and behavioral problems in children (Giordano and Costa 2012). Developmental neurotoxicity test (DNT) studies conducted by the industry in support of product registration have produced mixed results and generally support a lack of effect on measurements of brain morphometry and functional outcomes in response to low-dose exposures. However, as noted in a 2011 review by the EPA, these studies were limited in their sensitivity to detect the effects of pyrethroids on neurodevelopment, in part due to high variability observed in functional measurements of neurodevelopment and the lack of sensitivity for measures such as the functional observational battery (FOB). In fact, pup body weight decreases appeared to be the most reliable and sensitive marker of developmental toxicity observed in response to pyrethroid exposure in the DNT studies, with 4 out of 6 studies noting pup body weight effects at the lowest observed adverse effect level (LOAEL).

Given the insensitivity of regulatory guideline studies for detecting neurodevelopmental alterations and complexities of inter-species extrapolation during the time-sensitive process of development, it is critical to consider the epidemiological literature in humans to assess risk accurately. In 2018, the EPA reviewed epidemiologic studies assessing pyrethroid exposure and neurodevelopment alongside *in vitro* and *in vivo* studies to determine whether there is sufficient evidence to support increased sensitivity of juvenile and *in utero* exposures. In general, the literature review produced mixed results, and methodological issues were identified in many of the studies. The agency concluded that there was insufficient evidence to establish a clear causal relationship between pyrethroid exposure and adverse effects on child neurodevelopment. In addition, the EPA concluded that *in vitro* and *in vivo* studies did not provide sufficient evidence to support pharmacokinetic (PK) or pharmacodynamic (PD) differences in juveniles that may lead to increased sensitivity to pyrethroid exposures. As a result, it was determined that the Food Quality Protection Act (FQPA) safety factor for pyrethroids could be reduced to 1x, compared to the default 10x safety factor applied when evidence supports increased susceptibility to pre-and postnatal development due to PD/PK differences.

As noted in the EPA review, there are many methodological concerns with the epidemiological literature that prevent definitive conclusions from being reached at this time with regard to the safety of pyrethroids. However, it is worth examining these studies in line with the overall weight of evidence to determine appropriate paths forward for further research. In this scoping review that integrates convergent evidence, we summarize the human literature on health outcomes associated with pyrethroid exposure, specifically focusing on studies relevant to developmental toxicity. Our review approach complements the systematic literature on pyrethroid health effects by offering a combined assessment of studies of fetal pyrethroid levels (as measured in various samples at birth) and epidemiological studies assessing neurodevelopment, fetal growth, and major malformations. We addressed both study quality individually and summarized common findings across these studies more broadly to determine the current state of the literature and offer insight into further research needed to characterize these findings. In the following sections, we first address the literature on human fetal levels of pyrethroids to assess the degree to which direct exposure to the fetus may occur. We then address prenatal and pediatric exposure studies and discuss their findings relevant to infant and child growth, birth defects, and neurodevelopment.

Methods

In our literature search, we utilized Pubmed using the following search terms: “pyrethroid” combined with either “prenatal,” “developmental toxicity,” “fetal exposure,” “fetal blood levels,” “fetal growth” “birth weight,” “child neurodevelopment,” “autism,” or “child behavior.” Citation lists of discovered articles were also reviewed for the inclusion of additional relevant articles. Authors with backgrounds in toxicology, child and adolescent psychiatry, neurodevelopment, and analytical chemistry reviewed all relevant studies. As the current literature on animal studies is well characterized in other reviews, this paper focused solely on studies performed in humans with outcomes relevant to birth defects, fetal growth, or neurodevelopment, since neurodevelopmental impacts often occur with

altered fetal growth or other adverse birth outcomes. Studies assessing effects on child neurodevelopment were separated based on the timing of exposure to account for differences in prenatal and postnatal brain development, as well as potential indirect effects in utero resulting from maternal exposure. When relevant, findings were discussed in the context of individual pyrethroids and their metabolites to account for mechanistic differences between chemicals within this broad class.

Details including location, sample size, time period, and methods of assessment for exposure and neurodevelopmental outcomes are included alongside results from all relevant papers in Supplementary Tables 1–5. Papers included in this review span the years of 2003 through 2022 and encompass the available literature as of August 2022. Relevant to prenatal pyrethroid exposures, our review discusses 14 papers that assess fetal exposure to pyrethroids, five that assess correlation with birth defects, 14 that assess correlation with birth weight, and 24 that assess correlation with child neurodevelopment. In addition, we include a discussion on a total of ten papers that evaluate the correlation between pediatric exposure and neurodevelopment. Papers included in our review assess exposure across multiple countries, including the USA, China, Japan, Bangladesh, Poland, Thailand, Denmark, Philippines, France, Canada, Spain, Costa Rica, and the Republic of Korea.

Evidence for placental transfer of pyrethroids

Understanding a compound's degree of placental transfer is critical for understanding its mechanism of action during pregnancy (Giordano and Costa 2012). Studies in pregnant rodents suggest pyrethroids are distributed across the placental barrier to varying degrees, however the degree to which transfer occurs in pregnant humans is currently unknown (Kaneko et al. 1984; Shiba et al. 1990; Bossi R. et al. 2013; Bossi Rossana et al. 2013; Liu et al. 2019; Personne et al. 2019). Current understanding of pyrethroid toxicokinetics in humans is limited in that studies assessing controlled exposure in human volunteers have primarily focused on the measurement of pyrethroid metabolite levels in urine, rather than direct measurement of the parent compounds in blood (Woollen et al. 1992; Tomalik-Scharte et al. 2005; Sams and Jones 2012; Ratelle et al. 2015; Quindroit et al. 2019). Toxicokinetic data on blood levels of parent pyrethroid compounds in humans is limited to an overdose case involving ingestion of the type I pyrethroid permethrin, which found that the parent compound reached a maximum blood concentration approximately 3 hours after oral exposure, with an elimination half-life of approximately 3–5 hours (Gotoh et al. 1998).

PBPK models have utilized the limited human exposure data alongside data from controlled exposure studies in rodents to estimate toxicokinetic parameters of pyrethroids in humans (Knaak et al. 2012; Quindroit et al. 2019). In support of potential fetal exposure, current PBPK models predict a relatively high degree of tissue perfusion consistent with the lipophilic properties of pyrethroids, with tissue:blood partition coefficients of approximately 1:1 to 5:1 for most tissues, and a partition coefficient of greater than 30:1 for adipose tissue (Quindroit et al. 2019). However, these models have yet to establish parameters for placental transfer and fetal tissue distribution in humans. To further characterize the degree of fetal exposure in humans resulting from environmental exposures, our review summarizes the currently available data on pyrethroid concentrations in umbilical cord

blood, amniotic fluid, and newborn meconium. In all but one study discussed in this review, pyrethroids or their metabolites were assessed as part of large-scale targeted analyses that included additional assessment of non-pyrethroid chemicals, including organophosphates, carbamates, organochlorines, and fungicides (Supplemental Table 1). While comparison of fetal pyrethroid exposure to other environmental exposures is outside of the scope of this review, most studies reported lower levels of detection for pyrethroids when compared to members of the organophosphate and carbamate classes (Whyatt et al. 2003; Corrion et al. 2005).

Correlation between levels of pyrethroids in maternal blood and cord blood at delivery offers the most precise assessment of fetal transfer of pyrethroids in humans. In our review of the literature, we found eight studies that investigated pyrethroid levels in cord blood (Table 1, Supplementary Table 1). Of these studies, three measured pyrethroid metabolites (Corrion et al. 2005; Silver et al. 2015; Wren et al. 2021) and six measured parent compounds (Whyatt et al. 2003; Williams Megan et al. 2006; Ostrea EM et al. 2008; Yan et al. 2009; Neta Gila et al. 2010; Silver et al. 2015). Furthermore, four included additional measurements in maternal blood for comparison to fetal levels (Whyatt et al. 2003; Corrion et al. 2005; Williams Megan et al. 2006; Yan et al. 2009).

The strongest evidence for significant placental transfer of permethrin was demonstrated in a study in a New Jersey, USA population, in which both maternal and cord blood were collected at delivery. Within this population, cis- and trans- permethrin were detected at higher concentrations in cord serum (Cis: 0.246 ± 0.469 pg/mL, Trans: 0.899 ± 0.783 pg/mL) as compared to maternal serum (Cis: 0.015 ± 0.090 pg/mL, Trans: 0.044 ± 0.257 pg/mL). While the overall rates of detection were relatively low, particularly for maternal serum (Maternal Serum: 1–2% detection frequency, Cord Serum: 21–58% detection frequency), higher levels in cord serum as compared to maternal serum suggest a significant degree of transfer for permethrin (Yan et al. 2009). Within another cohort of pregnant women from New York City, USA, cis- and trans-permethrin were detectable in the umbilical cord plasma only of 13% and 7% of the population, respectively (Cis-Permethrin Range: non-detectable (ND)-4.2 pg/g; Trans-Permethrin Range: ND-4.9 pg/g). Maternal plasma levels of permethrin in the pregnant women were also measured. They showed similar detection rates to cord plasma but at a wider range of concentrations (Cis-Permethrin: 10%>limit of detection (LOD), Range: ND-11.4 pg/g; Trans-Permethrin: 7%>LOD; Range: ND-27.0 pg/g). However, the utility of the matched samples in this study was limited in that maternal blood was collected up to 2 days after birth. Collecting samples across a range of days complicates comparisons between maternal and fetal plasma levels due to the short half-life of these compounds and variable sources of exposure (Whyatt et al. 2003).

In contrast to these previous two studies that suggest a significant degree of placental pyrethroid transfer, other studies have suggested a relatively low degree of transfer. For example, an investigation of pyrethroid exposure in a cohort of women living in inner-city New York City, USA found that levels of permethrin were undetectable in all umbilical cord plasma samples, despite mothers having detectable plasma levels at delivery of both cis (11.8%) and trans-permethrin (29.4%). While this study was potentially limited by a smaller cohort than the previously mentioned studies, the lower LOD in this work (0.5 pg/g versus

1.0 pg/g in Whyatt et al) adds confidence to their results (Williams Megan et al. 2006). In addition, further work investigating 3-PBA, a non-specific metabolite of many synthetic pyrethroids including permethrin, in almost 200 maternal-infant dyads from the Bulacan province outside of Manila in the Philippines found that levels were detectable in 3.5% of maternal whole blood samples, but were below the LOD in all cord whole blood samples (Corrion et al. 2005).

In addition to the previously mentioned work, several studies have also performed measurements in cord blood without comparison to maternal levels. For example, a group investigating exposure in a Baltimore, USA population measured levels of 10 different pyrethroids in cord serum and found that all but cyfluthrin (2%>LOD) and permethrin (52%>LOD) were below the limit of detection in all 185 samples (Neta Gila et al. 2010). However, in cord serum samples collected from a New Jersey, USA population (n=63), the non-specific pyrethroid metabolite 3-PBA was detectable in 29% of samples with an average concentration of 0.13 ± 0.34 ng/mL (Range: <LOD to 1.83 ng/mL). Of note, 3-PBA is not a metabolite of cyfluthrin, but is a metabolite of multiple other type I and II pyrethroids, including permethrin, cypermethrin, deltamethrin, allethrin, resmethrin, fenvalerate, cyhalothrin, fenpropathrin, and tralomethrin. Other pyrethroid metabolites with known specificity for particular parent compounds (DCCA, DBCA, F-3-PBA, CDCA) were detected at a much lower rate (<7%) than 3-PBA (Wren et al. 2021).

A more extensive study of cord blood samples taken from 336 newborns in China measured a range of commonly used pyrethroids and reported a relatively higher rate of pyrethroid detection. The type I pyrethroid cis-permethrin was detectable in 75% of samples (LOD: 2.19 ng/mL) with a median concentration of 6.92 ng/mL (Range: <LOD-470 ng/mL). Other commonly used pyrethroids were detected at lower concentrations, such as the type II pyrethroid cypermethrin, which was detectable in 42.6% of whole cord blood samples (LOD: 3.54 ng/mL, Range: <LOD-390.27 ng/mL) (Silver et al. 2015). Given that maternal blood samples were not collected during this study for comparison to fetal cord blood, it is helpful to compare the levels reported to another assessment of a Chinese population which investigated maternal blood levels of pyrethroids. In this cohort, cypermethrin was detected in 66.7% of maternal blood samples with an average concentration of 151.25 ng/mL. Permethrin was detectable in 17% of blood samples with an average concentration of 94.33 ng/mL. These levels corresponded to average urinary concentrations of 19.25 μg/L trans-DCCA (a metabolite of permethrin, cypermethrin and cyfluthrin) and 8.85 μg/L of the non-specific metabolite from permethrin, cypermethrin, and others, 3-PBA (Simaremare et al. 2019). While direct comparisons between levels reported in the Chinese studies cannot be made, they suggest that the concentrations reported in cord blood may be relatively low compared to those in maternal circulation within this population.

In addition to investigations of pyrethroids in cord blood, six studies have analyzed pyrethroids in meconium. Within a group of newborns in the Philippines, all four pyrethroids measured had very low detection rates, with cypermethrin showing the highest detection rate at 6% (LOD: 0.31 μg/g) and an average concentration of 1.2 μg/g (Bielawski et al. 2005). A 2008 study in the Philippines by the same group reported an even lower detection rate of three pyrethroids in meconium, with cypermethrin showing the

highest detection rate at 1.8% (LOD: 0.31 μg/g) (Ostrea EM et al. 2008). Similarly, low detection rates were also found in a French population, with cypermethrin showing the highest detection rate of 6.4% and two others ranging from 0–1.8% (Berton et al. 2014). Furthermore, an assessment of permethrin in the meconium of a Canadian population found that permethrin was undetectable in all 396 samples (LOD: 0.5 ng/g) (Cassoulet et al. 2019). In addition to meconium measurements, a study investigating amniotic fluid levels of specific and non-specific pyrethroid metabolites (3-PBA, cis-DCCA, trans-DCCA, 4-F-3-PBA, cis-DBCA) from a California, USA-based population also found that all metabolites were below the limit of detection (Bradman et al. 2003).

Overall, there is limited evidence supporting the significant transfer of pyrethroids into fetal tissue. In general, studies investigating levels in cord blood do suggest some transfer to fetal circulation. However, they are unclear about the degree to which this transfer happens. In addition, many of these studies only investigated the type I pyrethroid permethrin, and as such, there is arguably the most robust evidence for placental transfer of permethrin, specifically, but the type II pyrethroid cypermethrin also was detected in some studies, albeit at low levels. However, studies investigating levels in meconium, which may represent accumulated exposure to pyrethroids, have often found that over 90% of the time, levels are below the limit of detection for most pyrethroids and their metabolites assessed. Overall, a potential limitation of many of these studies is the generally low detection rates in both maternal and fetal samples, which may represent either low exposure/transfer or technical failure. Furthermore, studies that include both maternal and fetal blood measurements did not assess correlations between maternal and fetal pyrethroid levels for individual dyads likely due to limited sample numbers, which would provide additional data on the degree of transfer. An inherent limitation in these studies is the time-locked nature of fetal sample availability at the time of birth which may not reflect exposure/transfer at other time points. As such, it remains unclear as to the degree to which these compounds may enter fetal circulation to exert direct effects on fetal development in humans.

Prenatal pyrethroid exposure and birth defects

In general, academic and regulatory animal studies do not support a link between prenatal pyrethroid exposure and increased risk for embryo/fetal malformations (Syed et al. 2010). However, several studies in humans have reported correlations between pyrethroid exposure and increased incidence of birth defects (Table 2, Supplementary Table 2). These investigations generally have relied on characterizing exposure via maternal household proximity to pyrethroid application sites. For example, a case-control study in California, USA assessed the relationship between periconceptional proximity to pyrethroid application sites and congenital heart defects in over 1300 infants and over 400 individual chemicals. They found that higher predicted exposure to the type II pyrethroid lambda-cyhalothrin was associated with increased risk for secundum atrial septal defect (adjusted OR = 2.9, 95% CI: 1.1 to 7.9) (Carmichael et al. 2014). However, no significant association was reported for pyrethroids as a class for this deficit. In addition, the same group found that periconceptional maternal residential proximity to cyfluthrin application was associated with a substantially higher incidence of craniosynostosis (adjusted OR = 4.6, 95% CI: 1.5 to 14.0) (Carmichael et al. 2016). In general, these studies were limited by not fully correcting

statistically for multiple comparisons and the proximity-based prediction of exposure in a general periconceptional period, which has been utilized to understand population-level risks for these low-frequency events.

In a study with a more direct exposure assessment, topical application of a permethrin solution for hair lice during pregnancy was found to have no significant effect on rates of spontaneous abortion or major malformations (Kennedy et al. 2005). However, findings from this study are limited in that pyrethroids show poor skin absorption. In addition, the study only investigated the type I pyrethroid permethrin which is widely used but not reflective of broader pyrethroid exposures, did not distinguish the timing of exposure, and had a sample size of just over 200 cases and controls together, which is small for detection of low-frequency events such as malformations.

Due to concern about the potential endocrine-disrupting effects of pyrethroids reported in animal studies, the association between maternal pyrethroid exposure and incidence of hypospadias, a congenital malformation of the urethra, has also been investigated. In a study investigating hypospadias in the VHEMBE cohort in South Africa, a link with maternal urinary concentrations of cis- and trans-DCCA near the time of delivery was noted (adjusted RR = 1.58, 95% CI: 1.07 to 2.34, and adjusted RR = 1.61; 95% CI: 1.09 to 2.36, respectively) (Bornman et al. 2022). Of important note is that this study relied on the assessment of only 68 subjects due to a high rate of phimosis in the initial study population (291 out of 359 initial subjects, or 81%), and within the 68 subjects examined, an unusually high rate of hypospadias was noted (23 out of 68 boys, or 34%). Within this relatively small cohort, levels of cis and trans-DCCA were nearly twice as high in the mothers of boys with hypospadias. However, no significant link between other pyrethroid metabolites such as 3-PBA (adjusted RR = 1.48, 95% CI: 0.78 to 2.78) and cis-DBCA (adjusted RR = 0.88, 95% CI: 0.50 to 1.54) were noted. In general, while results from this study are strengthened by the use of direct pyrethroid metabolite measurements and the strong correlation observed, it is limited by the small sample size, as well as concerns regarding the unusually high level of hypospadias within this population.

In comparison to the findings in the VHEMBE cohort, a case-control study in Arkansas compared maternal proximity to pyrethroid application sites to the incidence of hypospadias in over 1000 infants and found no significant link between bifenthrin exposure and hypospadias. Interestingly, however, exposure to permethrin was associated with decreased incidence of this disorder (adjusted OR = 0.37, 95% CI: 0.16 to 0.86) (Meyer et al. 2006). While this study did benefit from a larger sample size relative to the VHEMBE cohort, a significant limitation was the lack of direct measurements of pyrethroid exposures. Overall, based on the limited number of studies assessing this endpoint, the risk between pyrethroid exposure and hypospadias is unclear.

Assessments of pyrethroid exposure and fetal growth defects

Our review of the literature found 15 studies that investigated the links between prenatal pyrethroid exposure and gestational size using a range of approaches and cohorts from multiple countries (Table 3, Supplementary Table 3). These investigations produced mixed

results, with four reporting negative associations, three reporting positive associations, and eight reporting no significant effects.

In a study assessing links between maternal pesticide use during pregnancy and infant birth weight in a cohort of 104 Polish women, maternal pyrethroid use was retrospectively assessed through a questionnaire and correlated to birth outcomes. This work found that any pyrethroid exposure from living on farms and/or with those applying pesticides during the first or second trimester was associated with a significant decrease in infant birth weight ($\beta = -233.3$, 95% CI: −4160 to −50, p=0.02) (Hanke et al. 2003). Within an investigation of birth outcomes in a group of 454 women in rural Northern China, pyrethroid metabolites were measured in maternal urine at delivery and correlated to birth outcomes. Similar to the Polish study, this work found a negative association; the sum of pyrethroid metabolites cis-DCCA, trans-DCCA, and 3-PBA predicted significantly lower infant birth weight ($\beta = -96.76$, 95% CI: −173.15 to −20.37). However, no significant association was reported between individual metabolites and birth weight, and no associations were found between total metabolite level and birth length or head circumference (Ding et al. 2015). These studies had limitations in their exposure assessment, including that a single measure of pyrethroid metabolites is not a strong classifier of consistent exposure (Verner et al. 2020).

In addition to effects on birth weight, lower birth length was associated with greater maternal use of pyrethroid-based mosquito coils/mats during pregnancy in a Japanese cohort of >90,000 women assessed prospectively with questionnaires during the 2nd and 3rd trimester (effect size: 0.00059, $q<0.01$). No significant effects on fetal body weight were found (Matsuki et al. 2020). Furthermore, an investigation of pyrethroid exposure in almost 900 women of the Odense Cohort in Denmark found that higher maternal urinary concentration of the non-specific pyrethroid metabolite 3-PBA at 28 weeks gestation was associated with a smaller abdominal circumference in female infants at birth ($\beta = -0.3$, 95% CI: −0.5 to −0.003 cm) (Dalsager Louise et al. 2018). These assessments of exposure have limitations in their accuracy, but since they were made prospectively or directly during pregnancy, they are relative strengths of these studies.

Compared to the previously described work that suggests a negative association between pyrethroid exposure and fetal growth impairments, several additional studies found a positive association (Xue et al. 2013; Zhang et al. 2013; Zhang et al. 2014; Jaacks et al. 2019) or did not find significant links (Dabrowski et al. 2003; Berkowitz et al. 2004; Kennedy et al. 2005; Mytton et al. 2007; Neta G. et al. 2011; Dalsager Louise et al. 2018; Ling et al. 2018). While this number of studies does challenge the relevance of the previously discussed work showing negative associations, the lack of significant negative correlation in certain studies may be due to a lack of statistical power. One study had a cohort of over 300,000 infants (Ling et al. 2018), but most assessed cohorts of 100–400. For example, a study assessing links between pesticide use and birth outcomes in 117 Polish women found that none of the individual pesticide classes, such as pyrethroids, were significantly associated with low birth weight, but general maternal exposure to pesticides was associated. In this case, the authors noted that the study was likely underpowered for analyses with specific classes, as only 6 mothers reported exposure to pyrethroids. In addition, another major limitation of this study was that exposure was assessed simply in

terms of ever/never use of the pesticides, which does not consider critical factors such as dose-response and timing/frequency of exposure (Dabrowski et al. 2003).

Overall, though, the mixed results concerning the effects of pyrethroids on fetal growth in humans suggest that the relationship is relatively unclear. As in all exposure studies, there is the possibility of residual confounding. Given the significant associations reported in some studies, it is worth further investigating whether alterations in fetal growth to the extent considered relevant to public health may occur following controlled exposure in animal models at exposure levels comparable to real-world scenarios in humans.

Prenatal pyrethroid exposure and neurodevelopment

In our review of the literature regarding prenatal pyrethroid exposure and neurodevelopment, we found a total of 18 studies that assessed this link with varied results (Table 4, Supplementary Table 4). Of the 18 studies, 10 reported negative correlations between prenatal pyrethroid exposure and neurodevelopment, five reported no significant effects, two reported positive effects, and one reported mixed effects (positive and negative effects for different pyrethroid metabolites). These studies utilized measures of exposure that were mostly non-specific for particular pyrethroid chemicals or types and investigated a wide range of neurodevelopmental outcomes in children, including assessment of motor control, cognitive development, behavioral regulation, and emotional control. In addition to these more generalized assessments of neurodevelopment, a total of five studies (one reported no significant effects, three negative effects, one mixed effects) have also investigated the specific relationship between prenatal pyrethroid exposure and diagnosis of autism spectrum disorder (ASD) in children.

Regarding the previously reviewed work on pyrethroid levels during pregnancy, several studies have investigated links between direct measures of prenatal pyrethroid exposure and assessments of neurodevelopmental delay in young children. For example, across almost 500 mother-child dyads within a Chinese population, levels of non-specific pyrethroid metabolites (cis-DCCA, trans-DCCA, and 3-PBA) were measured in a single maternal urine sample taken during pregnancy and correlated with child neurodevelopmental outcomes. Children at one year of age were evaluated using a standardized assessment widely used in China, the Developmental Screen Test (DST), which is appropriate for children under six years. From this work, the researchers found that prenatal pyrethroid exposure was negatively correlated with the development quotient of the DST ($\beta = -0.1527$, $p<0.05$), but not the mental index, suggesting lower infant motor or social development in those whose mothers had higher levels of pyrethroid exposure during pregnancy (Xue et al. 2013). This study had several limits, also noted in the EPA review, including the accuracy of a single urine sample, lack of adequate description of statistical methods, and limitations of the stepwise regression analysis utilized to select the statistical model.

Similar findings to the previously mentioned study were reported in a Chinese cohort of 301 women from Jiangsu Province, which also found that increased levels of non-specific pyrethroid metabolites in maternal urine were negatively associated with child neurodevelopment at one year of age as assessed through the same development quotient of the DST ($\beta = -0.1453$, $p<0.05$) (Qi X et al. 2011). In comparison to these findings,

a study in Mexico assessed links between the single non-specific pyrethroid metabolite 3-PBA in a sample of third-trimester maternal urine and scores on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) of the Bayley Scales for Infant Development (BSID), a broadly used tool in young children with predictive validity for later child neurobehavioral functioning. In general, this study did not establish significant effects of maternal 3-PBA on either outcome, outside of a potential effect of 3-PBA exposure on female MDI scores at 24 months of development (β = −6.2, 95% CI: −12.3 to −0.14). However, this effect was only established at the medium 3-PBA exposure level (not at the high), and no significant effects were found for MDI or PDI scores in the same children at 36 months of age (Watkins et al. 2016), perhaps demonstrating a lack of persistence or compensation for the earlier impact. A limitation of this study was the low rate of 3-PBA detection, in which over half of the samples were below the limit of detection.

In another cohort of almost 1000 women, maternal proximity to pyrethroid application sites in California, USA during the third trimester of pregnancy was associated with increased odds for clinically diagnosed developmental delay in 2–5-year-old children, as assessed through direct measure on two well-established tools for young child functioning -- the Mullen Scales of Early Learning and a parental survey on the Vineland Adaptive Behavioral Scale (Shelton et al. 2014). Given the small sample of children with developmental delay (n=168), results may have been limited by insufficient power. In addition, the EPA has noted a number of limitations with the statistical analysis on this study, including that statistical analysis were preformed separately across time periods, buffers, distances, and pesticide classes rather than combining these analysis and treating them as additional covariates.

In a study investigating child neurodevelopment within the VHEMBE cohort of 752 mother-child pairs in South Africa, researchers found that each 10-fold increase in maternal cis-DCCA, trans-DCCA, or 3-PBA was associated with decrements in Social-Emotional scores on the Bayley Scales for Infant Development (BSID-III) at 1 year of age of −0.70 (95% CI: −1.25 to −0.15), −0.49 (95% CI: −0.96 to −0.02), and −0.65 (95% CI: −1.23 to −0.06), respectively (Eskenazi Brenda et al. ; Eskenazi B. et al. 2018). Furthermore, each 10-fold increase in maternal cis-DBCA levels was associated with decrements in BSID-III Language Composite scores and Expressive Communication scores at 2-years of age (β = −1.90, 95% CI: −3.67 to −0.14, and β = −0.41, 95% CI: −0.8 to −0.01, respectively). In addition, relatively strong correlations prenatal pyrethroid exposure and neurodevelopmental delay were reported in a longitudinal cohort study in Xuanwei county in Southwest China, in which pyrethroid metabolites were measured throughout all three trimesters of pregnancy in 419 women and correlated to infant scores on the BSID-III at 1 year of age (Qi Z et al. 2022). In this study, the urinary concentration of 3-PBA during the second trimester, but not the first or third, was inversely associated with Cognition and Language scores on the BSID-III (β = −3.34, 95% CI: −6.11 to −0.57, and β = −2.90, 95% CI: −5.20 to −0.61, respectively). Furthermore, when BSID-III score cutoffs for developmental delay were applied to a binary logistic regression model (composite scores <80), 3-PBA during the second trimester was associated with a significantly increased risk for Cognition and Language developmental delay (OR = 1.64, 95% CI: 1.03 to 2.62, and OR = 1.52, 95% CI: 1.06 to 2.19, respectively). Interestingly, 4 F-3-PBA levels during the third trimester demonstrated an opposite effect on language development, with levels showing a positive

correlation to language scores on the BSID-III (β = 6.04, 95% CI: 1.84 to 10.23). When pyrethroid levels were stratified according to the 90th percentile of exposure, regression models demonstrated only the significant inverse correlations between the sum of pyrethroid metabolite levels during the 2nd trimester and BSID-III Cognition (β = −7.98, 95% CI: −13.84 to −2.12) and Language scores (β = −6.00, 95% CI: −10.91 to −1.10). In addition, total pyrethroid metabolite levels during the first trimester were inversely associated with BSID-III Motor scores (β = −6.53, 95% CI: −11.71 to −1.34). This study's strength was its size and repeated sampling of exposure which can reduce idiosyncrasies in exposure measures. Different findings arose from samples collected in different trimesters which may reflect stage-specific neurodevelopmental impacts or varied validity of maternal exposure measures; even more frequent assessments of exposure would be needed to address this.

In comparison to these results, a study investigating 327 mother-child pairs in Yunnan, China found no correlation between maternal urinary pyrethroid metabolites in the third trimester and language development in 2-year-old toddlers, as measured by the BSID-III (Chen et al. 2022). However, this study did report a significant correlation between language development delay at 2 years of age and pyrethroid metabolites in the infant's urine at 6–8 months of age (cis-DBCA as total pyrethroid metabolite levels), implicating a potential effect of juvenile exposure on language development. This study is discussed further in the following section on pediatric exposures.

Overall, it is difficult to generalize the outcomes of the studies that suggest links between pyrethroid pregnancy exposure and early childhood measures. In some studies, it appears that only cognitive abilities are significantly affected. Motor and other domains are affected in others, which may reflect varied developmental measures, populations, or other study differences. Correlation between pyrethroid levels and decrements in language development across three separate cohorts suggest that this may be an endpoint worth investigating further. Overall, the effect sizes are modest but relevant to children's population-level health. For example, at two years of age, Bayley MDI scores in girls whose mothers showed high and moderate urinary pyrethroid metabolite levels were 6 points below girls without these exposures (Watkins et al. 2016). These findings are similar to previous studies showing cognitive impacts in toddlers with a single standard deviation rise in prenatal lead levels (Hu et al. 2006).

In addition to work investigating early childhood developmental delay, there have also been several groups that have studied links between pyrethroid exposure and cognitive functioning and behavior in older children. For example, the relationship between pyrethroid application near prenatal residence and childhood IQ was investigated in children from California, USA as part of the CHAMACOS cohort. From this work, increased use of pyrethroids near the maternal residence during pregnancy was associated with significant decrements in the cognitive capabilities of their children at the age of 7, as determined by the widely used Wechsler Intelligence Scale for Children (WISC-IV). Effects of pyrethroids included significant decreases in Full Scale IQ (β = −2, 95% CI: −3.7 to −0.3, $p<0.05$), perceptual reasoning (β = −2.1, 95% CI: −4.0 to −0.2, $p<0.05$), and verbal comprehension (β = −1.8, 95% CI: −3.4 to −0.3, $p<0.05$) (Gunier Robert et al.). A noted limitation of this study was the relatively high correlation coefficients between pyrethroid use and other pesticide

groups, such as organophosphates (correlation coefficient of 0.82). Given that exposure was calculated based on the distance to these sites of use, this method may lack specificity for pyrethroids relative to other pesticides or combinations.

Impacts like these on cognition may be linked with effects on behavior in older children, as the co-occurrence of clinical-level impairment in these two domains is common. Other studies have found that levels of clinically relevant, impairing behavior are also linked with prenatal pyrethroid exposure assessments. In the Mount Sinai Children's Environmental Health Center study, maternal urine pyrethroid metabolites were measured once during the third trimester (3-PBA, trans-DCCA, and cis-DCCA). Levels were examined in 162 mother-child dyads for their relationship to child behavior at 4, 6, and 7–9 years of age, as assessed by widely-used tools, the Behavioral Assessment System for Children (BASC) and the Behavior Rating Inventory of Executive Function (BRIEF). Although the study demonstrated a relatively low detection rate for pyrethroid metabolites (<30%), there were significant correlations between detectable levels of both 3-PBA and cis-DCCA in pregnant women and behavioral and executive functioning deficits in their children. For example, detectable levels of 3-PBA in maternal urine were associated with children's worse scores in Internalizing, Depression, Somatization, Behavioral Regulation, Emotional Control, Shifting, and Monitoring domains (Furlong et al. 2017). The latter two domains suggest cognitive effects of pyrethroid exposure. However, the others show that emotional impacts may also occur, which are critical for mental health at present and future stages.

In addition to behavioral evaluations, several studies have investigated potential links between prenatal pyrethroid exposure and attention-deficit hyperactivity disorder (ADHD) symptoms in children, including cognitive, motor, and complex behavior regulation domains. In a study investigating almost 1000 dyads in the Danish Odense Child Cohort, the researchers found that each doubling of maternal 3-PBA concentration was associated with a 3% increase in ADHD scale score as assessed by the well-validated Child Behavior Checklist (95% CI: 1.00 to 1.07). Furthermore, each doubling of maternal 3-PBA concentration was associated with a 13% increase in odds of having a clinically significant ADHD score greater than the 90^{th} percentile (OR = 1.13, 95% CI: 1.04 to 1.38) (Dalsager L. et al. 2019). Similar findings were reported in another study that investigated a cohort of 524 mother-child pairs in Seoul and Gyeonngi provinces of South Korea (Lee K-S et al. 2022). In this study, 3-PBA concentrations were measured in maternal urine samples collected between 14 and 27 weeks of gestation and from children at ages 2, 4, 6 and 8. ADHD symptoms were assessed in the children through parental evaluation using the ADHD Rating Scale IV (ARS). Within this cohort, the doubling of 3-PBA concentrations during pregnancy was associated with a 2.7% (95% CI: 0.3 to 5.2) increase in ARS scores at 6 years of age. Additional correlations between childhood exposures and ARS scores noted within this study are addressed in the following section pertaining to pediatric exposures.

In comparison to the previously mentioned work, five additional studies found no significant effect of prenatal pyrethroid exposure on neurodevelopment in cohorts of children from the USA, France, Philippines, and China (Horton et al. 2011; Ostrea EM, Jr. et al. 2014; Viel et al. 2015; Viel et al. 2017; Chen et al. 2022). These studies included measures of general and cognitive development in 2–6-year-old children and found that maternal pyrethroid

exposure did not predict these outcomes using a mixture of parent-reported measures and direct child assessments, as with the wider range of studies. Potential strengths of several of these studies include relatively large sample sizes and the use of direct measurements of pyrethroid exposure in a variety of matrices, such as mid-gestation maternal hair and blood, newborn infant hair, blood and meconium (n=696), urine metabolites in the first half of gestation (n=287), or maternal third-trimester air samples and maternal and infant plasma at delivery (n=342). However, as with many other studies, these were assessments from single time points. In addition, 6-year-old child behavioral problems assessed on the Strengths and Difficulties Questionnaire (SDQ) were not linked with pyrethroid metabolite levels in maternal urine from the first half of gestation.

When considering the variable outcomes of the studies investigating links between pyrethroid exposure and child neurodevelopment, it is important to note that most studies of childhood cognition and behavior outcomes with respect to exposures or genetic risks show overlapping and varied relationships across a range of measures, which may reflect the complexity of brain development. In addition, limitations in the measures of pyrethroid exposure and differing methodology and sample characteristics may also account for the varying associations reported for prenatal exposure on neurodevelopment in children. However, overall, these studies suggest that the links reported between prenatal pyrethroid exposure and adverse cognitive and behavioral outcomes in children deserve further evaluation epidemiologically and should also be studied further in controlled experiments using animal models and translationally relevant methods which can address mechanisms.

In addition to generalized assessments of cognition and behavior in children, pyrethroid exposure during gestation has also been assessed for its relationship to ASD in children (Table 4). In the CHARGE study, increased risk for ASD, as assessed by gold-standard ADOS testing, was found in 2–5-year-old children from mothers residing near agricultural pyrethroid application sites during the third trimester of pregnancy (OR = 1.87, 95% CI: 1.02 to 3.43) and during the preconception period (OR = 1.82, 95% CI: 1.00 to 3.31) (Shelton et al. 2014). In a follow-up analysis using the CHARGE dataset, the risk for ASD diagnosis in response to preconception and pregnancy exposure to pyrethroids was modified by maternal early-pregnancy folic acid intake (>800 μg) using proximity to agricultural application. Findings from this study, while not significant, suggest a protective role of folic acid that may be an effect modifier of links between pyrethroid exposure and ASD risk (Schmidt et al. 2017), as shown for other established ASD exposure risks (Bjørk et al. 2018). In another large California, USA-based study, maternal proximity to pyrethroid agricultural application sites during pregnancy was assessed in 465 children under the age of 10 with ASD, and almost 7,000 matched typically developing controls. The researchers reported a significant correlation between maternal proximity to the application of the type I pyrethroid bifenthrin and ASD risk ($\beta = 1.57$, p=0.049). However, no relationship was found for other pyrethroids investigated (Roberts Eric et al. 2007). Furthermore, another California, USA study investigating maternal residence during pregnancy and ASD found that prenatal exposure to agricultural use of permethrin, another type I pyrethroid, was correlated to a small but significant increase in risk for ASD through an examination of almost 3,000 individuals under the age of 10 with ASD and matched controls (OR = 1.10, 95% CI: 1.01 to 1.20). In addition, they reported a higher increase in risk between prenatal permethrin

exposure and ASD co-occurring with intellectual disability (OR = 1.46, 95% CI: 1.20 to 1.78) (von Ehrenstein et al. 2019). In contrast to the previously mentioned work all using proximity measures to agricultural pyrethroids, a more recent, smaller study in 200 dyads from California, USA, analyzed second trimester maternal urinary 3-PBA concentrations and risk for ASD diagnosis by direct assessment in their children at three years of age but did not find a significant relationship (RRR = 1.50, 95% CI = 0.89 to 2.51, p = 0.12) (Barkoski et al. 2021).

Overall, while definitive conclusions regarding ASD risk cannot be reached based on the currently available data, these studies suggesting positive correlation support further investigation into this link. However, a particular limitation of many studies assessing ASD risk is the reliance on proximity to pesticide application sites to measure exposure, rather than through direct measurement of pyrethroids or their metabolites in maternal blood or urine. As previously noted, the EPA has not validated this method, so there is some concern regarding its utility (Burns and Pastoor 2018). As such, additional studies utilizing direct exposure assessments with multiple time points of collection during pregnancy would be beneficial.

Pediatric pyrethroid exposure and neurodevelopment

In addition to the previously mentioned studies that investigated links between prenatal pyrethroid exposure and neurodevelopment, there have also been a number of studies investigating the effects of direct exposure in children (Table 5, Supplementary Table 5). This work has frequently focused on investigating links between pediatric pyrethroid exposure and ADHD symptoms and/or diagnosis in children. For example, an initial study using the 1999–2002 US National Health and Nutrition Examination Survey (NHANES) data found no significant associations between urinary pyrethroid metabolites in almost 1700 6 to 15-year-old children (3-PBA, cis-DCAA, trans-DCCA) and parental reports of ADHD or learning disability (Quirós-Alcalá et al. 2014); this study is limited by the reporting of diagnosis without confirmation with diagnostic scales. However, additional work in the following year assessed NHANES data from 2001–2002 and relied on an expanded assessment of 8–15-year-olds that included both caregiver reports of ADHD diagnosis and ADHD symptom counts determined by the Diagnostic Interview Schedule for Children (DISC). In this study, 687 children with detectable levels of the urinary non-specific 3-PBA metabolite of pyrethroids had a significantly higher rate of ADHD diagnosis than those without detectable levels (OR: 2.42, 95% CI: 1.06 to 5.57). Furthermore, while the associations of 3-PBA on inattention were not significant, hyperactive-impulsive symptoms increased by 50% for every 10-fold increase in urinary 3-PBA levels (adjusted count ratio 1.50; 95% CI: 1.03 to 2.19) (Wagner-Schuman et al. 2015). Potential limitations of this study include reporting bias due to the symptoms being identified by a single caregiver, as well as the cross-sectional study design.

Similar to findings reported from the NHANES database, two studies utilizing data obtained from the Environment and Development of Children (EDC) prospective cohort study in South Korea have reported significant correlations between pediatric pyrethroid exposure and ADHD symptoms in children. In the first study, residential use of pyrethroid-based

insecticide adhesives in almost 400 4-year-old Korean boys was associated with a 51.6% increase (95% CI: 6.3 to 116.1) in scores on the Korean attention-deficit/hyperactivity disorder rating scale (K-ARS). Within this cohort, use of insecticide adhesive was positively correlated with urinary 3-PBA levels (β = 0.42, 95% CI: 0.11 to 0.74). A similar 58% increase in K-ARS score was reported for boys with urinary 3-PBA ≥ 3.80 μg/g (95% CI: 0.1 to 150.5) (Lee W-S et al. 2020). In the second study, similar findings were reported, in which the doubling of 3-PBA concentrations at age 2 was associated with a 5.2% (95% CI: 0.5 to 10.2) increase in ARS scores at 6 years of age. In addition, doubling in 3-PBA concentrations at 2 and age 4 years of age was associated with 2.7% (95% CI: 0.3 to 5.3) and 3.3% (95% CI: 0.2 to 6.4) changes in ARS scores at 8 years of age, respectively (Lee K-S et al. 2022).

Compared to the previously mentioned work, a study assessing links between urinary 3-PBA and cognitive development in 6–9-year-old children living near banana plantations in Costa Rica found that higher 3-PBA concentrations were not associated with increased ADHD index. However, higher urinary 3-PBA was associated with lower processing scores, specifically in girls (β = −8.8, 95% CI: −16.1 to −1.4). In addition, this study of 140 children found no significant links between urinary 3-PBA and sensory function, behavioral problems, or psychomotor skills (van Wendel de Joode et al. 2016). Potential limitations of this study include the cross-sectional study design and lack of adjustment for multiple comparisons.

In addition to ADHD, several studies have investigated links between pediatric exposure and specific outcomes such as cognition and behavioral problems. In the PELAGIE cohort, increased levels of the common pyrethroid metabolite 3-PBA in children (>0.038 μg/L) at age six years were associated with a lower verbal comprehension index on the WISC-IV (β = −5.18, 95% CI: −9.5 to −1.11). In addition, increased levels of cis-DCCA (≥0.346 μg/L), a metabolite specific for deltamethrin, were also associated with a lower verbal comprehension index (β = −6.75, 95% CI: −11.17 to −2.32). No significant effects on verbal comprehension were reported for other pyrethroid metabolites assessed in this study (4-F-3-PBA, a metabolite specific for cyfluthrin; cis-DCCA; trans-DCCA), suggesting that these effects may be primarily associated with deltamethrin exposure (Viel et al. 2015).

Within a Chinese study of 3–6-year-old children, higher urinary 3-PBA demonstrated worse scores on standardized Intelligence tests (Chinese Binet Test: β=-3.47, 95% CI: −5.82 to −1.12, p ≤ 0.01; Arithmetic Test from the Weschler preschool scale of intelligence: β=-1.09, 95% CI: −1.78 to −0.41, p≤ 0.01). In addition, when urinary 3-PBA was treated as a continuous variable, higher urinary levels were significantly associated with lower scores on a cancellation task assessing attention, non-verbal comprehension, and motor coordination (β=-3.96, 95% CI: −7.06 to −0.86, p=0.01). Overall, results from this study suggest significant early childhood impairments in multiple cognitive domains with pediatric exposure. Interestingly, they also found a significant association between measured urinary 3-PBA levels and surveyed responses endorsing household proximity to agricultural fields as well as indoor mosquito repellant use, suggesting that these factors may be useful metrics for assessing exposure in young children when direct measurements are unattainable (Wang et al. 2016).

In another China-based population study, urinary samples from 327 pregnant women and 173 infants (80 boys and 93 girls) were analyzed for pyrethroid metabolites and correlated to scores on the BSID-III in the children at 2 years of age (Chen et al. 2022). Within this cohort, total pyrethroid metabolite levels in child urine at 6 to 8 months of age correlated with decrements in language composite scores ($\beta = -1.14$, 95 % CI: −2.25 to −0.04, p=0.042) and receptive communication scores ($\beta = -0.23$, 95 % CI: −0.44 to −0.01, p = 0.039) in boys.

In addition, links between behavioral problems and pyrethroid exposure have been found. For example, in a large cohort of 779 Canadian children, urinary cis-DCCA was associated with high scores for total behavioral difficulties (≥ 17) on the SDQ (OR for 10-fold increase = 2.0, 95% CI: 1.1 to 3.6), a level often representing clinically significant problems. However, no significant links were found for other pyrethroid metabolites, 3-PBA and trans-DCCA (Oulhote and Bouchard Maryse 2013). Another study examined the correlation between the aerial application of pyrethroid insecticides for mosquito control in New York, USA and rates of documented diagnosis with ASD or developmental delay in the medical record in individuals under the age 20 years old. From this analysis, zip codes with yearly aerial application of pyrethroid insecticides were found to have a 37% higher rate of these diagnoses, as compared to areas without aerial pyrethroid application (adjusted RR = 1.37, 95% CI: 1.06 to 1.78, p=0.02) (Hicks et al. 2017).

In comparison to these findings, an investigation utilizing the PELAGIE cohort at age six produced mixed results regarding links between childhood pyrethroid exposure and behavioral symptoms on the SDQ. While higher levels of urinary 3-PBA in children were positively associated with externalizing symptoms (Cox p-value=0.04), higher levels of another common metabolite, trans-DCCA, were negatively associated with externalizing symptoms (Cox p-value=0.03) (Viel et al. 2017). Additionally, a study in Thai children found no significant effect of 3-PBA or DCCA on performance in neurobehavioral tests conducted using the computerized Behavioral Assessment and Research System (BARS), which assesses attention, memory and learning, psychomotor response speed and coordination, and motivation. However, the study was limited by a small sample size (n = 54 children), in which there was likely a low rate of neurobehavioral problems. Additional limitations of this study include the cross-sectional study design, reporting of only p-values rather than risk or effect size, and lack of adjustment for multiple comparisons (Fiedler et al. 2015).

From this set of studies, which examined different populations using a range of exposure measures and varied neurodevelopmental tests, pyrethroid exposure in childhood was linked with simultaneous altered cognitive and behavioral deficits. Most of these studies assess single-point child urinary non-specific metabolite levels that capture exposures from multiple sources (agricultural drift, residential, personal). When viewed individually, these studies certainly have limitations; however, they generally suggest that the brain development occurring during the first two decades of life may be sensitive to pyrethroids and that further research is warranted. Therefore, particular focus should be placed on specific pyrethroids, through particular routes and ages of exposure, and the mechanisms that may be the most critical to neurodevelopmental processes.

Conclusion

Across both prenatal and childhood stages, studies in humans have produced variable results with regard to associations between environmental pyrethroid exposures and adverse outcomes in children. Overall, the majority of studies outlined in this review suggest a relatively small, but potentially significant, increase in risk in some populations for neurodevelopmental delay, lower cognitive capabilities, and rates of adverse behavioral outcomes following both prenatal and childhood pyrethroid exposures. However, many of these studies were subject to significant limitations as discussed in the recent EPA review of the literature. As such, more research is needed to make definitive conclusions regarding the potential neurodevelopmental effects of pyrethroids in children.

Compared to the findings regarding neurodevelopment, links between pyrethroid exposure and fetal growth outcomes are more mixed within the epidemiological literature. While the correlation between pyrethroid exposure and low birth weight has also been noted in academic and regulatory studies, these effects often occur at doses that either exceed relevant human exposures or co-occur with maternal toxicity. In the DNT studies for beta-cyfluthrin and zeta-cypermethrin, reductions in fetal weight were noted at doses below that which induce decreases in maternal body weight and food consumption, suggesting an effect independent of maternal toxicity that deserves additional investigation. In general, though, the lack of correlation between birth weight and neurodevelopmental outcomes in the epidemiological literature suggests that any potential effects on the developing brain are unlikely to be secondary to general fetal growth effects. However, for such mediator questions, larger-scale studies would be needed. Furthermore, although several epidemiological studies have suggested a risk for birth defects, the small number of studies finding significant outcomes and the lack of supporting data from animal studies suggest that these may be of less concern.

Given the reported effects on fetal development following prenatal exposure, it is interesting to examine the current evidence addressing placental transfer. Studies investigating direct fetal exposure to pyrethroids through measurements in cord blood show relatively low levels of direct exposure and even lower levels detected in meconium. Given that many of the studies were limited by low rates of maternal exposure, there is a need for additional studies in animals to investigate the tissue distribution of these compounds during pregnancy.

Overall, it is worth reiterating that most of these studies should be interpreted with caution, as there are concerns about specific limitations of each that may diminish their predictive utility (Burns and Pastoor 2018). As noted in the 2018 EPA literature review, many of the studies that either supported a correlation or found no correlation were considered to be of relatively low quality due to methodological concerns, in turn preventing a clear assessment of risk. A primary concern of the EPA is the validity of estimating maternal exposure based on proximity to pesticide application sites identified through state databases (Burns and Pastoor 2018). However, there are a number of studies that have demonstrated elevated levels of pesticides in households with close proximity to agricultural application sites, suggesting that pesticide drift from nearby application sites may be a relevant source of exposure (Lu et al. 2000; Fenske Richard et al. 2002; Harnly et al. 2005; Ward Mary et

al. 2006; Gunier Robert et al. 2011). These measurement methods do not account for civic, residential, or personal pesticide use, which can involve a range of pyrethroids.

For studies where measurement of pyrethroid metabolites in urine was conducted, most were limited by a single urine spot collection. As such, there is a legitimate concern regarding the validity of a single urine measurement in representing long-term exposures (Attfield Kathleen et al. 2014; Morgan et al. 2016). Due to the short half-life of pyrethroids in the body, urinary metabolites are subject to variation depending on the timing of the most recent exposure and other aspects of urinary excretion (Ferland et al. 2015). However, a recent study demonstrated relatively low variability between urinary pyrethroid metabolites across the span of a year, suggesting that a single urinary measurement may be sufficient for accurately assessing long-term exposure (Klimowska et al. 2020).

Additional limitations noted by EPA for some of the studies investigating links between pyrethroid exposure and neurodevelopment include: limited details on the statistical approach (Xue et al. 2013), lack of details in regard to QA/QC procedures (Xue et al. 2013; Fiedler et al. 2015; Viel et al. 2015; Domingues et al. 2016; van Wendel de Joode et al. 2016; Wang et al. 2016; Watkins et al. 2016; Furlong et al. 2017; Hisada et al. 2017; Viel et al. 2017), use of automated stepwise regression methods to select a final regression model (Xue et al. 2013; Hisada et al. 2017), use of cross-sectional study designs (Oulhote and Bouchard Maryse 2013; Quirós-Alcalá et al. 2014; Fiedler et al. 2015; Wagner-Schuman et al. 2015; Domingues et al. 2016; van Wendel de Joode et al. 2016; Wang et al. 2016), potential bias in parental evaluations of endpoints such as ADHD (Quirós-Alcalá et al. 2014; Wagner-Schuman et al. 2015), no adjustment for multiple comparisons (Fiedler et al. 2015; van Wendel de Joode et al. 2016), low detection rates of pyrethroid metabolites (Watkins et al. 2016), relatively high study dropout rates (Gunier Robert et al. ; Furlong et al. 2017), and small sample size (Domingues et al. 2016).

Given the discrepancy in findings across multiple studies for most of the discussed endpoints, it is also worth noting that many of the studies characterized exposure using metabolites such as 3-PBA, which is common to various chemicals within the pyrethroid class. In this respect, these techniques obscure the relative contributions of different chemicals within this class and impede identifying chemical-specific health outcomes. As previously discussed, there are notable mechanistic differences between chemicals within this broad class that result in a wide range of relative toxicities (Breckenridge et al. 2009; Ravula and Yenugu 2021). As such, health effects may be better understood by investigating these chemicals individually.

It is also worth considering other interacting factors that may influence pyrethroid toxicity, such as concomitant stress, individual child and maternal genetics, and chemical mixture effects (Elser et al. 2020). Mixture effects with regard to other pesticides, such as organophosphates, may be of particular interest, as these compounds have also been investigated for potential links to neurodevelopmental disorders. In this respect, several studies have suggested potential mechanisms of synergistic toxicity associated with combined exposure to organophosphates and pyrethroids (Gaughan et al. 1980; Zhou et al.

2011; Iyyadurai et al. 2014). As such, future studies may benefit from investigating potential interactions between pesticide exposures and effects on neurodevelopment and fetal growth.

In summary, the consideration of epidemiological studies alongside *in vivo* data from animal studies supports further investigation into the potential mechanisms by which pyrethroids may alter neurodevelopment and fetal growth. As noted in the recent EPA review, the current pyrethroid literature does not establish a clear causal relationship. However, correlating environmental exposures to relatively subtle neurodevelopmental changes is difficult to achieve, especially in the case of compounds with short biological half-lives such as pyrethroids. Given the significant number of studies that have reported relatively weak, but statistically significant, correlations between pyrethroid exposure and effects on child neurodevelopment, there is a need to investigate these findings further. A combined approach of higher-quality epidemiological studies alongside targeted animal models to investigate potential mechanisms will likely provide the best approach to solving this question. Particular emphasis should be placed on investigations of neurodevelopmental processes implicated in developmental delay and ASD using exposure levels translatable to real-word scenarios for pregnant women and children. Accurate assessment of these endpoints will likely require a more thorough assessment of neurodevelopmental processes beyond the standard testing batteries utilized in regulatory studies. In addition, assessments of tissue distribution within pregnant mammals would provide helpful information on the relevance of direct and indirect modes of action *in utero*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Studies assessing maternal and fetal levels of pyrethroids and their metabolites

Tissue	Pesticide Detected	Substance Detected	Detection Frequency	References
Cord blood and Maternal blood	Yes (maternal blood only)	Metabolites	Maternal Blood 3-PBA: 3.5%, Cord Blood 3-PBA: 0%	Corrion, 2005
	Yes (maternal blood only)	Parent compounds	Control Group Maternal Blood: Cis-Permethrin (11.8%) and Trans-Permethrin (29.4%). All cord blood samples in the control group were < limit of detection.	Williams, 2006
	Yes	Parent compounds	Maternal Serum: 7% Trans-Permethrin, 10% Cis-Permethrin. Cord Serum: 7% Trans-Permethrin, 13% Cis-Permethrin.	Whyatt, 2003
	Yes	Parent compounds	Maternal Serum: 1% Cis-Permethrin, 2% Trans-Permethrin. Cord Serum: 21% Cis-Permethrin, 58% Trans-Permethrin	Yan, 2009
Cord Blood	Yes	Parent compounds/ Metabolites	Cypermethrin: 42.6%, Cis-Permethrin: 75%, Trans-Permethrin: 71.1%, 3-PBA: 88.4%, Cyfluthrin: 33.9%, Cyhalothrin: 53.6%, Etofenoprox: 77.4%, Fenpropathrin: 44.6%, Fenvalerate: 11.9%, Flucythrinate: 2.4%, Fluvalinate: 13.7%, Tefluthrin:2.1%, Tetramethrin: 17.6%.	Silver, 2015
	Yes	Parent compounds	Cyfluthrin: 2%, Cis-Permethrin: 41%, Trans-Permethrin: 52%.	Neta, 2010
	Yes	Metabolites	3-PBA: 29%, t-DCCA: 6.3%, t-CDCA: 6.3%, c-DCCA: 4.7%, F-PBA: 1.6%, and c-DBCA: 0%.	Wren, 2021
Meconium, cord blood and infant hair	Yes (meconium only)	Parent compounds	Meconium: Cypermethrin (1.9%), Cyfluthrin (0.8%), Bioallethrin (0.3%). Below limit of detection in all cord blood and infant hair samples.	Ostrea, 2008
Meconium	Yes	Parent compounds	Deltamethrin: 0%, Cypermethrin: 6.4%, Cyfluthrin: 1.8%, DCCA: 4.7%.	Berton, 2014
	Yes	Parent compounds	Cypermethrin: 6.0%, Cyfluthrin: 0.6%, Bioallethrin: 0.6%, Transfluthrin: 0%.	Bielawski, 2005
	No	Parent compounds	Permethrin below limit of detection in all samples	Cassoulet, 2019
Maternal hair and meconium	Yes	Parent compounds	Grouped Pyrethroids: 13.9% in Maternal Hair, 2.5% in meconium.	Ostrea, 2012
Placenta and meconium	Yes	Parent compounds	Grouped Pyrethroids: 90% in placenta. Deltamethrin: 26% in meconium.	Fernandez-Cruz, 2020
Amniotic fluid	No	Metabolites	All metabolites were below the limit of detection.	Bradman, 2003

Additional information pertaining to time period, location, sample size, limits of detection, average/median concentrations, and non-pyrethroid analytes are located in Supplementary Table 1.

Table 2.

Studies assessing links between prenatal pyrethroid exposure and birth defects

Observations	Authors
Permethrin exposure associated with decreased incidence of hypospadias (OR = 0.37, 95% CI: 0.16 to 0.86).	Meyer, 2006
Maternal proximity to lambda-cyhalothrin application associated with increased risk for secundum atrial septal defect (OR = 2.9, 95% CI: 1.1 to 7.9).	Carmichael, 2014
Maternal proximity to cyfluthrin application was associated with increased incidence of craniosynostosis (OR = 4.6, 95% CI: 1.5 to 14.0).	Carmichael, 2016
No effect	Kennedy, 2005
Maternal cis-DCCA and trans-DCCA urinary concentrations were associated with an increased risk of hypospadias (aRR = 1.58; 95 % CI: 1.07, 2.34 and aRR = 1.61; 95 % CI: 1.09, 2.36, respectively)	Bornman, 2022

Additional information pertaining to time period, location, population, exposure metric, and method of assessment are located in Supplementary Table 2.

Table 3.

Studies assessing links between prenatal pyrethroid exposure and fetal growth

Outcome	Country	Findings	Authors
Negative Association	Poland	Association between exposure during first or second trimester and significant decrease in infant birth weight (β: −233.3, 95% CI: −4160 to −50, p=0.02).	Hanke, 2003
	China	Negative association between sum of metabolites and birth weight.	Ding, 2015
	Japan	Use of pyrethroid-based mosquito coils/mats associated with decreased birth length (effect size: 0.00059, q<0.01). No significant effect on birth weight.	Matsuki, 2020
	Odense, Denmark	Higher maternal 3-PBA concentrations associated with smaller abdominal circumference in females (β: −0.3, 95% CI: −0.5 to −0.003 cm).	Dalsager, 2018
Positive Association	Tokyo, Japan	Positive association between maternal urine 3-PBA and birth weight and head circumference.	Zhang, 2013
	Tokyo, Japan	Positive association between maternal urine 3-PBA and birth weight and head circumference. No effect of 3-PBA on thyroid hormones.	Zhang, 2014
	Bangladesh	Maternal urinary 3-PBA associated with lower risk for small for gestational age (OR:0.13, 95% CI: 0.02 to 0.95). However, women with detectable 3-PBA were also more likely to be overweight (p=0.04).	Jaaks, 2019
	Southwest China	Sum of pyrethroid metabolites associated with increased birth weight, length, and gestational age, and with decreased risk for small for gestational age and/or premature birth.	Xu, 2020
No association	Central Poland	No significant effect of pyrethroids on birth weight (p=0.286) (limited by small sample size).	Dabrowski, 2003
	Thailand	No effect	Mytton, 2007
	Canada	No effect	Kennedy, 2005
	New York, USA	No effect	Berkowitz, 2004
	Baltimore, MD	Negative association between permethrin and IL-10 (B=-0.14, 95% CI: −0.22 to −0.05). No effect on other endpoints.	Neta, 2011
	California	Non-significant effect on birth weight in infants exposed to two or more pyrethroids. OR (1st trimester): 1.05; 95% CI: 0.98, 1.13. OR (2nd trimester): 1.06; 95% CI: 0.99 to 1.13).	Ling, 2018

Additional information pertaining to time period, location, population, exposure metric, and methods/timepoints of assessment are located in Supplementary Table 3.

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Table 4.

Studies assessing links between prenatal pyrethroid exposure and child neurodevelopment

Outcome	Findings	Authors
ASD	ASD OR at 1.5km distance during 3rd trimester: 1.87 (1.02, 3.43). Note: OR's did not increase with increased distance to pyrethroid application sites (ie. not significant at 1.25km or 1.75km distance).	Shelton, 2014
	Closer distance to bifenthrin use associated with higher risk for ASD (B=1.570, p=0.0485, adjusted alpha=0.0047).	Roberts, 2007
	Non-significant OR = 2.1 (95% CI: 0.9, 4.8) for pyrethroids. High folic acid attenuated increase.	Schmidt, 2017
	Maternal permethrin exposure increased risk for both ASD (OR: 1.10, 95% CI: 1.01 to 1.20) and ASD with intellectual disability (OR: 1.46, 95% CI: 1.20 to 1.78).	von Ehrenstein, 2019
	No significant association between second trimester 3-PBA concentrations and ASD (RRR: 1.50, 95% CI: 0.89 to 2.51, p = 0.12).	Barkoski, 2021
Neurodevelopment: Negative Association	Pyrethroid exposure was negatively correlated with neural and mental development of infants (β = −0.1527, P < 0.05).	Xue, 2013
	Pyrethroid use near residence associated with decreased Full-Scale IQ (β=-2, 95% CI: −3.7 to −0.3, p<0.05), perceptual reasoning (β=-2.1, 95% CI: −4.0 to −0.2, p<0.05), and verbal comprehension (β=-1.8, 95% CI: −3.4 to −0.3, p<0.05).	Gunier, 2017
	3-PBA and cis-DCCA associated with behavioral and executive functioning deficits (worse scales for Internalizing, Depression, Somatization, Behavioral Regulation, Emotional Control, Shifting, and Monitoring).	Furlong, 2017
	1.75 km distance between pyrethroid application site and maternal residence during 3rd trimester associated with increased odds for developmental delay diagnosis (OR: 2.31, 95% CI: 1.15 to 4.66). OR not significant at 1.25 km or 1.5 km distance.	Shelton, 2014
	Increased odds for ADHD.	Dalsager, 2019
	Negative association between pyrethroid exposure and neurodevelopment index (B = - 0.1453, P < 0.05).	Qi, 2011
	Potential effect of 3-PBA exposure on female MDI scores at 24 months of development (β = −6.2, 95% CI = −12.3 to −0.14). Effect only established at the medium 3-PBA exposure level (not at the high). No significant effects were found for MDI scores at 36 months of age.	Watkins, 2016
	At second trimester, cognition inversely associated with 3-PBA [β = − 3.34 (95% CI = − 6.11, − 0.57)], Language scores inversely associated with 3-PBA [β = − 2.90 (95% CI = − 5.20, − 0.61)], and Adaptive Behavior scores inversely associated with cis-DBCA [β = − 0.73 (95% CI = − 1.27, − 0.19)].	Qi, 2022
	Each 10-fold increase in cis-DCCA, trans-DCCA, and 3-PBA were associated, respectively, with −0:70 (95% CI: −1:25, −0:15), −0:49 (95% CI: −0:96, −0:02), and −0:65 (−1:23, −0:06) decrement in Social-Emotional scores at 1 year of age. Each 10-fold increase in maternal cis-DBCA levels was associated with significant decrements at 2 years of age in Language Composite scores and Expressive Communication scores [b = −1:90; 95% CI: −3:67, −0:14 and b = −0:41; 95% CI: −0:81, −0:01, respectively, for a 10-fold increase].	Eskenazi, 2018
	Doubling of 3-PBA concentrations during pregnancy was associated with 2.7% (95% CI: 0.3, 5.2) increase in ADHD (ARS) scores at 6 years of age. Doubling of 3-PBA concentrations at age 2 was also associated with 5.2% (95% CI: 0.5, 10.2) increase in ARS scores at 6 years of age. Doubling in 3-PBA concentrations at 2 and age 4 years of age was associated with increased ARS scores at 8 years (2.7% change [95% CI: 0.3, 5.3]; 3.3% change [95% CI: 0.2, 6.4], respectively).	Lee, 2022
Neurodevelopment: No Association	No effect of prenatal exposure. Negative association between child urinary 3-PBA & cis-DBCA and verbal comprehension/working memory.	Viel, 2015
	Increased prenatal DCCA associated with internalizing difficulties (Cox-p=0.05). Childhood 3-PBA associated with externalizing difficulties (Cox-p=0.04). High ORs were found for abnormal or borderline social behavior (OR 2.93, 95% CI 1.27 to 6.78, and OR 1.91, 95% CI 0.80 to 4.57, for the intermediate and highest metabolite categories, respectively).	Viel, 2017
	No effect of pyrethroids on mental development.	Ostrea, 2012

Outcome	Findings	Authors
	No effect.	Horton, 2011
	No effect of prenatal third trimester 3PBA, 4F3PBA or DBCA on language development	Chen, 2022
Neurodevelopment: Positive Association	3-PBA positively associated with Kinder Infants Development Scale score.	Hisada, 2017
	No association between pyrethroid exposure and impaired language development. However, highest tertile of 3-PBA in boys associated with lower odds of scoring below 15th percentile (OR:0.30, 95% CI:0.12 to 0.72, p-trend=0.007).	Anderson, 2021
	At third trimester, language scores were positively associated with 4 F-3-PBA [β = 6.04 (95% CI = 1.84, 10.23)], Adaptive Behavior scores were positively associated with cis-DBCA [β = 0.73 (95% CI = 0.29, 1.17)] and ∑Pyrethroids [β = 0.10 (95% CI = 0.01, 0.20)].	Qi, 2022
Neurodevelopment: Mixed Effects	3-PBA and DCCA had opposing effects on child mental functioning.	Fluegge, 2016

Additional information pertaining to time period, location, population, exposure metric, and methods/timepoints of assessment are located in Supplementary Table 4.

Table 5.

Studies assessing childhood pyrethroid exposure and neurodevelopment

Association	Findings	Authors
Negative	Cis-DCCA associated with high scores for total difficulties on the Strengths and Difficulties Questionnaire (OR for a 10-fold increase = 2.0; 95% CI: 1.1 to 3.6).	Oulhote, 2013
	3-PBA associated with increased odds for ADHD (OR: 2.42, CI:1.06,5.57). Hyperactive-impulsive symptoms increased by 50 % for every 10-fold increase in 3-PBA levels (adjusted count ratio 1.50; 95 % CI 1.03 to 2.19).	Wagner-Schulman, 2015
	Higher urinary 3-PBA was associated with lower processing scores, specifically in girls (β = −8.8, 95% CI: −16.1 to −1.4).	van Wendel de Joode, 2016
	Increased level of 3-PBA in child urine was associated with lower verbal comprehension index (β = −5.18, 95% CI: −9.5 to −1.11). Increased level of cis-DBCA, a metabolite specific for deltamethrin, was associated with a lower verbal comprehension index (β = −6.75, 95% CI: −11.17 to −2.32).	Viel, 2015
	Higher levels of urinary 3-PBA in children were positively associated with externalizing disorders (Cox p-value = 0.04). However, higher levels of trans-DCCA were negatively associated with externalizing disorders (Cox p-value = 0.03).	Viel, 2017
	Children with higher urinary 3-PBA demonstrated worse scores on Intelligence tests (Chinese Binet Test: β = −3.47, 95% CI: −5.82 to −1.12, p ≤ 0.01; Arithmetic Test: β = −1.09, 95% CI: −1.78 to −0.41, p≤ 0.01) and lower scores on the cancellation test (β = −3.96, 95% CI: −7.06 to −0.86, p=0.01).	Wang, 2016
	ASD children trended towards higher urinary 3-PBA than in the control group, but not statistically significant (p = 0.054). No correlation between Childhood Autism Rating Scale total score and 3-PBA in urine (R^2 = 0.0539; p > 0.05).	Domingues, 2016
	Use of insecticide adhesives was associated with a 51.6% increase (95% CI: 6.3 to 116.1) in scores on the Korean ADHD rating scale (K-ARS) for boys. Use of insecticide adhesive was positively correlated with urinary 3-PBA levels (β = 0.42, 95% CI: 0.11, 0.74), and a similar 58% increase in K-ARS score was reported for boys with urinary 3-PBA ≥ 3.80 μg/g (95% CI: 0.1 to 150.5).	Lee, 2020
	Zip-codes with yearly aerial pyrethroid application had a 37% higher rate of ASD or developmental delay diagnosis (adj R.R. = 1.37, 95% CI: 1.06–1.78, p = 0.02).	Hicks, 2017
	Negative correlation between 4F3PBA in infancy and toddlers' receptive communication [β = − 0.43 (95 % CI: − 0.85, − 0.01), p = 0.046]. Negative correlation between total PYRs metabolites in infancy with boys' language composite [β = − 1.14 (95 % CI: − 2.25, − 0.04, p = 0.042] and RC scores [β = − 0.23 (95 % CI: − 0.44, − 0.01), p = 0.039]. Higher DBCA in infancy increased risk of language development delay by 4.58 times (OR = 5.58, 95 % CI: 1.76–17.68, p = 0.004) and 21 % risk expressive communication failures (OR = 1.21, 95 % CI: 1.01–1.45, p = 0.040). The risk of receptive communication failures increased 9 % with 4F3PBA increasing per 1 μg/g in infancy (OR = 1.09, 95 % CI: 1.02–1.15, p = 0.007).	Chen, 2022
No Association	No significant associations between urinary pyrethroid metabolites in children (3-PBA, cis-DCAA, trans-DCCA) and parental reports of ADHD or learning disability.	Quiros-Alcala, 2014
	No significant effect of 3-PBA or DCCA on performance in neurobehavioral tests.	Fiedler, 2015

Additional information pertaining to time period, location, population, exposure metric, and methods/timepoints of assessment are located in Supplementary Table 5.