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Review article

Pyrethroids and developmental neurotoxicity - A critical review of epidemiological studies and supporting mechanistic evidence

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ABSTRACT

Background: Pyrethroid metabolites are widely detectable in urine from the general population, including pregnant women and children. Pyrethroids are neurotoxic and suggested endocrine disruptors. Exposure during vulnerable developmental time windows may have long-term impacts on neurodevelopment.
Objective: To evaluate the epidemiological evidence for neurodevelopmental effects related to prenatal and childhood pyrethroid exposure in a systematic review and to assess biological plausibility by evaluating mechanistic evidence.
Methods: We searched PubMed and Web of Science up to September 1, 2021 and included original studies published in English in which pyrethroid exposure was measured or estimated during pregnancy or childhood and associations with neurodevelopmental outcomes in the children were investigated. The Navigation Guide Systematic Review Methodology was used to evaluate the epidemiological evidence. For mechanistic evidence, we focused on relevant key events (KEs) suggested in Adverse Outcome Pathways (AOPs) using the OECD-supported AOP-wiki platform. A systematic search combining the KEs with pyrethroids, including 26 individual compounds, was performed in the ToxCast database.
Results: Twenty-five epidemiological studies met the inclusion criteria, 17 presented findings on prenatal exposure, 10 on childhood exposure and two on both exposure windows. The overall body of evidence was rated as "moderate quality" with "sufficient evidence" for an association between prenatal pyrethroid exposure and adverse neurodevelopment. For childhood exposure, the overall rating was "low quality" with "limited evidence" because of cross-sectional study design. Regarding mechanistic evidence, we found that pyrethroids are able to interfere with neurodevelopmental KEs included in established AOPs for adverse neurodevelopmental. The evidence was strongest for interference with thyroid hormone (TH) function.
Conclusion: Pyrethroids are probably human developmental neurotoxicants and adverse impacts of pyrethroid exposure on neurodevelopment are likely at exposure levels occurring in the general population. Preventive measures to reduce exposure among pregnant women and children are warranted.

1. Introduction

Pyrethroids compose a large group of insecticides used both in agriculture and in biocidal products for residential use. The use of pyrethroids has been increasing during the last decade because they replace other insecticides, mainly cholinesterase inhibitors such as organophosphates with regulatory restrictions due to higher acute toxicity or concern for long-term health impacts including developmental neurotoxicity (EFSA, 2019). In 2015, pyrethroids represented approximately 38% of the world insecticide market (Li et al., 2017). Although

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pyrethroids have been used for decades, epidemiological studies on potential long-term adverse health effects at low environmental exposure levels are scarce but the concern is increasing (Bao et al., 2019; Demeneix et al., 2020). Thus, in the EU Human Biomonitoring program, HBM4EU, pyrethroids were prioritised as one of 18 substance groups of high concern by the EU authorities and partner countries, because of rising exposure levels and limited knowledge on potential adverse health impacts, especially among vulnerable population groups such as pregnant women and children.

The general population is mainly exposed to pyrethroids from residues in food but environmental exposure from neighbouring agricultural areas and indoor use of biocides are other important sources of exposure (Baudry et al., 2018; Dereumeaux et al., 2018; Glorennec et al., 2017; Morgan, 2012, 2020; Muñoz-Quezada et al., 2020). In addition, some individuals are occupationally exposed. Pyrethroids are readily absorbed after oral and inhalation exposure while the absorption rate is lower through the skin (Cote and Bouchard, 2018). After dietary exposure, pyrethroids are extensively absorbed from the gastrointestinal tract but, due to their high lipophilicity, a minor fraction is absorbed through the lymphatic pathway, thereby by-passing hepatic first pass metabolism (Mallick et al., 2020). Following daily low dose exposure, pyrethroids achieve approximately steady-state levels in internal tissues (Cote et al., 2014; European Food Safety Authority, 2011). They can also cross the human placenta as illustrated by detection of pyrethroids in umbilical cord blood and meconium (Berton et al., 2014; Silver et al., 2016). After absorption, pyrethroids are metabolized and excreted, primarily in the urine, within few days and urinary concentrations of pyrethroid metabolites are therefore useful as biomarkers for the internal exposure level integrating all exposure routes (Barr et al., 2010; Cote et al., 2014).

The most used urinary biomarker is the generic pyrethroid metabolite, 3-PBA (3-phenoxybenzoic acid), representing exposure to most pyrethroids. In addition, some more specific pyrethroid metabolites are used: *cis*- and *trans*-DCCA (3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid) representing exposure to the *cis*- and *trans*-isomers of permethrin, cypermethrin, and cyfluthrin; F-3-PBA (4-fluoro-3-phenoxybenzoic acid) which is a specific metabolite of cyfluthrin; and *cis*-DBCA (*cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid) being a specific metabolite of deltamethrin. The metabolites are formed by ester cleavage of the parent compounds catalysed by carboxylesterase enzymes.

In populations exposed mainly from residues in the diet, the total exposure to pyrethroids can be assumed to be rather continuous, and urinary 3-PBA concentration will be a valid biomarker for aggregated exposure to dietary pyrethroid mixtures, although it may not capture peak exposures from e.g., indoor use (Needham and Sexton, 2000). The more specific metabolites (*trans*- and *cis*-DCCA, *cis*-DBCA and F-3-PBA) are dependent on recent exposure to the parent pyrethroid compounds and will therefore often have lower detection frequencies and higher intra-individual variation. For dietary exposure, the urinary biomarkers reflect exposure to the parent compounds since the content of pyrethroid degradates in food items was found to be very low (Morgan et al., 2018).

Exposure to pyrethroids is on the rise as demonstrated in human biomonitoring programs (NHANES) in the US (CDC, 2015) and Canada (HMSC, 2013), as well as in a recent study from Sweden (Noren et al., 2020). Thus, 3-PBA is now widely detectable in urine from the general population including pregnant women (Dalsager et al., 2019; Dereumeaux et al., 2018; Sokoloff et al., 2016; Yolton et al., 2013), although at lower concentrations in individuals who predominantly eat organic food (Baudry et al., 2018). Children are generally higher exposed to pesticide residues in food than adults because they eat more food per kg body weight. Accordingly, children showed the highest increase in urinary 3-PBA concentrations from 2001 to 2012 in the NHANES survey (Jain, 2016; Lehmler et al., 2020).

Pyrethroids target the nervous system of insects primarily by inhibiting voltage-gated sodium channels, VGSCs, but other ion channels are also affected (Soderlund, 2020). Due to similarities in neural function, pyrethroids also have neurotoxic properties in non-target organisms including humans (Abreu-Villaca and Levin, 2017). Since the brain is particularly vulnerable to neurotoxicants during development, exposure in foetal and early life may have long-lasting impacts on brain function (Grandjean and Landrigan, 2014; Rice and Barone, 2000). Although pyrethroids have rather low acute mammalian toxicity, long-lasting brain dysfunction after prenatal or early postnatal exposure have been demonstrated in animal models (Abreu-Villaca and Levin, 2017; Pitzer et al., 2021). The effects include neurochemical (e.g., alterations in dopamine function) and neurobehavioral alterations (e.g., hyperactivity, and deficits in learning and memory) sometimes with more pronounced effects in males (Laugeray et al., 2017; Pitzer et al., 2019; Richardson et al., 2015a). Furthermore, pyrethroids are suggested thyroid hormone (TH) disruptors (Leemans et al., 2019).THs are essential for normal brain development and since the human foetus is unable to synthesize THs during the first trimester of pregnancy, foetal brain development is dependent on maternal THs and it is well-known that even subtle changes in maternal THs function can affect foetal brain development (Jansen et al., 2019; Korevaar et al., 2018; Mughal et al., 2018). A few studies have investigated potential disturbance of THs related to pyrethroid exposure. In a Japanese birth-cohort study, no associations were seen between maternal urinary 3-PBA concentrations and TH concentrations in maternal serum (Zhang et al., 2013) or serum from their new-borns (Zhang et al., 2014). However, two recent studies found maternal 3-PBA to be associated with lower concentrations of free triiodothyronine (T3) concentrations in serum in third trimester (Hu et al., 2019) and increased concentrations of thyroid stimulating hormone (TSH) in new-borns (Chevrier et al., 2019), respectively, but potential associations with child neurodevelopment were not presented.

For direct neurotoxic mechanisms, the brain concentration of the neurotoxicant is central. The brain concentration depends on the concentration of unbound pyrethroid in plasma and the blood flow to the brain. According to a physiologically based pharmacokinetic (PBPK) model based on rats (Song et al., 2019), but taking into account differences in enzymatic metabolism of pyrethroids between rats and humans, the brain concentration between age 6 months and 25 years was similar for the same oral single dose of deltamethrin, cypermethrin or bifenthrin (Mallick et al., 2020). However, a PBPK model for deltamethrin predicted a considerably higher brain concentration in humans than rats due to an almost six-fold higher cardiac output to the brain in humans (Godin et al., 2010). Since children eat more per kg body weight, have faster breathing, and a larger relative surface area than adults, they tend to have higher exposure levels (Landrigan et al., 2004). Besides, young children have lower expression of carboxylesterase and CYP enzymes, as these enzymes are first expressed at adult levels at approx. 6 months of age and 10–15 years of age, respectively (Mallick et al., 2020). Further, plasma levels of albumin and total proteins are low at birth and increase during the first years of life causing a higher fraction of the plasma concentrations of pyrethroids to be unbound. Accordingly, the unbound fraction of deltamethrin in plasma was markedly higher (2–2.5 times) at birth but reached and remained at adult levels in infants and children older than 4 weeks (Sethi et al., 2016). Further, animal studies suggest a higher sensitivity to pyrethroid toxicity during the neonatal period due to expression of a more sensitive form of the VGSC (Meacham et al., 2008). Whether this is relevant for humans is unclear.

A limited number of epidemiological studies have investigated neurodevelopmental outcomes associated with pyrethroid exposure in human populations and the results seem conflicting. Some previous reviews within this topic have suggested a possible link between pyrethroid exposure and adverse neurodevelopment (Abreu-Villaca and Levin, 2017; Dorea, 2021; He et al., 2022; Lucero and Munoz-Quezada, 2021; Saillenfait et al., 2015; Tessari et al., 2020) but most of them were based on few included studies with focus on either exposure in agricultural settings (Lucero and Munoz-Quezada, 2021), selected countries in Latin America and Caribbean (Dorea, 2021), specific outcomes such

as Autism spectrum disorder (ASD) (He et al., 2022) and Attention deficit hyperactive disorder (ADHD) (Tessari et al., 2020), or were performed when only few studies were available (Saillenfait et al., 2015). Thus, the aim of this systematic review was to evaluate the strengths of the current epidemiological evidence for the potential impacts of prenatal and childhood exposure to pyrethroids on neurodevelopmental in humans. A systematic review of the mechanistic evidence from animal and *in vitro* bioassays was beyond the scope of this paper. Instead, we aimed to assess the biological plausibility by evaluating data from experimental studies with focus on mechanisms suggested for neurodevelopmental toxicity (DNT) in the OECD-supported Adverse Outcome Pathways (AOPs) platform (AOP-wiki). The findings from this review could be useful for decision-making and identification of research gaps.

2. Methods

2.1. Epidemiological evidence

2.1.1. Study question

The objective was to answer the question: Does foetal and/or childhood exposure to pyrethroids adversely affect neurodevelopment in humans? Our PECO (participants, exposure, comparator, and outcomes) statement was:

Participants: humans.

Exposure: exposure to pyrethroids during a) pregnancy (prenatal exposure) and 2) during childhood, between birth and up to 16 years of age (postnatal exposure).

Comparator: Humans exposed to lower levels of pyrethroids than more highly exposed humans.

Outcomes: Any clinical diagnosis or scale assessment of neurobehavioral problems (e.g., ADHD and ASD) and/or quantitative measures of intelligence (e.g., IQ) assessed in children or adolescents.

2.1.2. Data sources

The search for publications for this review was performed in the databases PubMed and Web of Science following the PRISMA guidelines (Moher et al., 2015) on September 1, 2021, without any limitation on initial publication date. The "All Fields" option was used to add the search terms: (pyrethroid*) AND (neuro* OR brain) AND (child* OR infant). To ensure accessibility for all authors, only full text publications in English were considered.

2.1.3. Study selection

The principal author (HRA) performed the search and selection of the studies. First, the reference lists were screened manually for duplicates and afterwards titles and abstracts of each reference was reviewed to determine eligibility. We included studies in which pyrethroid exposure was measured or estimated during pregnancy or childhood (up to 16 years of age) and associations with neurodevelopmental outcomes in the children were evaluated. Studies were excluded if they did not present original data, did not investigate human subjects, did not measure/estimate pyrethroid exposure during pregnancy or childhood, or did not assess neurodevelopmental outcomes according to the PECO statement above. Our search identified 121 publications from PubMed and 150 publications from Web of Science. After exclusion of 66 duplicates and 4 comments/erratums, 201 abstracts were reviewed for eligibility and a total of 23 original publications fulfilled the inclusion criteria. We also hand searched the reference lists of the included studies and used Web of Science to show articles that cited the included studies. In this way two additional studies were captured (Lee et al., 2020; Tanner et al., 2020). Thus, a total of 25 original epidemiological studies were included in this review. A flow diagram of the study selection is available in Supplementary Fig. 1.

2.1.4. Rating of quality and strength of evidence

We evaluated the epidemiological evidence for adverse neurodevelopment related to pyrethroid exposure using the principles suggested in the Navigation Guide Systematic Review Methodology (Woodruff and Sutton, 2014). In this approach, a "moderate" quality rating is assigned *a priori,* and the overall rating may be down- or upgraded depending on the quality of the individual studies included. An initial rating was performed based on study design. Cross-sectional studies were by default down-regulated to "low" strength of evidence because the exposure assessment does not occur prior to development of the outcome and therefore an association could be the result of reverse causation (Rooney et al., 2014). For cohort studies and case-control studies a rating of "moderate" quality was kept as default. Next, the risk of bias for each of the studies was evaluated using eight different domains (recruitment strategy, blinding, exposure assessment, confounding, incomplete outcome data, selective reporting, conflict of interest, and other bias) as described in the Navigation Guide, see supplementary Material: "Instructions for making risk of bias determination" in Johnson et al. (2014). Risk of bias in each domain was rated as "low", "probably low", "probably high" or "high" according to the rating guidelines described in the Navigation Guide.

Regarding recruitment strategy, some selection bias related to socioeconomic status (SES) is difficult to avoid in observational studies because families with more resources often are more prone to participate. This might affect the representativeness of the study but if recruitment was unrelated to exposure, it is unlikely to affect the association between exposure and outcome. Thus, if data on the outcome were collected blinded to the exposure level, the risk of bias was rated low, because a potential misclassification would be random and thus, in most cases, bias the findings toward the null.

Regarding exposure assessment, studies without human biomonitoring (HBM) measurements of individual exposure were by default rated as "probably high" risk of bias. For HBM-studies, we used the urinary concentration of 3-PBA as the primary exposure estimate, except for one paper (Horton et al., 2011) that analysed piperonyl butoxide (PBO; pyrethroid synergist added to some biocide products) in maternal personal air samples collected during pregnancy as a marker of inhalation exposure to pyrethroids. Due to day-to-day variation in exposure to individual pyrethroids, the detection frequencies of specific urinary biomarkers, e.g., for deltamethrin, is often too low to allow health association studies. The risk of bias was rated as "low" if 3-PBA was analysed in repeated urine samples and as "probably low" if single spot urine samples were used. Pyrethroids are rapidly metabolized and excreted and combined with within-subject variability in exposure, some misclassification is likely, especially when single urine samples are used. However, such misclassification would, in most instances, be non-differential and tend to bias the findings toward the null and thereby hamper the possibility to detect a true association with the outcome. Besides, 3-PBA was detected with similar detection rates and median or geometric mean concentrations across pregnancy among women who provided repeated samples (Barkoski et al., 2018; Watkins et al., 2016) and in 24h urine samples collected repeatedly among 14 volunteers within a 1-year period (Klimowska et al., 2020). Thus, we considered 3-PBA concentrations in spot urine samples to be a valid biomarker for a continuous low dietary pyrethroid exposure. However, the accuracy of the measurement depends on the analytical method and quality assurance. To address this issue, we critically evaluated the analytical methods used to measure pyrethroid metabolites in urine, with a special focus on the deconjugation step (Supplementary Table 2). Like many non-persistent chemicals, pyrethroid metabolites such as 3-PBA are present mainly as phase II conjugates (glucuronide and/or sulfate) in urine (up to 85%), with a large inter-individual variability (Baker et al., 2004). Hence, omitting this deconjugation step can potentially lead to large underestimation of pyrethroid exposure in biomonitoring studies. The presence of a deconjugation step or not, but also the method used (i.e., enzymatic hydrolyses vs acidic hydrolyses)

were reported for each study. Since acidic hydrolyses is less specific than enzymatic deconjugation, other conjugates than glucuronide and sulfate ones can be released, as demonstrated for 3-PBA (Toshima et al., 2015). The deconjugation method was, however, not suspected to affect the contrast in 3-PBA concentrations within studies while the lack of a deconjugation step will underestimate the 3-PBA concentrations. Thus, if no deconjugation step was described, either directly or in a reference for the analytical method, the risk of bias was rated as "probably high" for the exposure assessment domain.

Regarding confounding, the appropriateness of methods used for selection of confounding variables was assessed, including whether inclusion of probably mediating variables was avoided and the risk of 'overadjustment' for variables that did not satisfy the criteria for potential confounders.

Based on existing knowledge about the exposure and outcome of interest, SES and/or parental education or intelligence scores were considered to be the most important potential confounders, and studies that did not adjust for these variables (or a valid proxy) or did not investigate whether they affected the association between exposure and outcome, were considered *a priori* to be at "high risk of bias" for confounding.

Since neurodevelopmental outcomes are dependent on the child age, studies that did not control for the age of the child at examination, e.g., by using age-standardised outcomes or including child age at examination as a covariate in the regression models, are likely to have lower precision in the outcome measurements. Urinary biomarkers are often corrected for sample dilution using creatinine. Since creatinine is influenced by different factors e.g., age and BMI, it is suggested to include creatinine as a covariate in the data-analysis to avoid introduction of bias (Barr et al., 2005). Thus, studies that did not control for child age at examination and studies using creatinine corrected biomarker concentrations without including creatinine as a covariate were rated one step higher for risk of bias (e.g., "probably low" instead of "low") or these limitations were included in the overall rating of the confounding domain for the study, if other potential risks of bias were identified.

Ratings of risk-of-bias for each study were performed independently by three review authors (HRA, CF, MFF) after consensus on the rationale for all ratings as described above. For three studies, there were some minor differences in judgement and consensus was reached after discussion and in all three cases the most conservative rating (e.g., "probably high risk" compared to "probably low risk") was used. Besides study design and risk of bias, the confidence in the results of the individual studies was assessed in relation to the size of the study population and if the exposure contrast was sufficient to obtain a reliable estimate of the association, and the validity of methods used to estimate exposure and outcome.

Based on the risk of bias ratings of the individual studies, the overall quality of evidence across the studies was rated. According to the Navigation Guide, a "moderate" quality rating is assigned *a priori* (Johnson et al., 2014; Woodruff and Sutton, 2014). This rating was evaluated and eventually down or upgraded using criteria guided by the GRADE method (Guyatt et al., 2008) and described in previous structural reviews using the Navigation Guide methodology (Johnson et al., 2014; Lam et al., 2014, 2017). For downgrading five factors were considered: risk of bias across studies, indirectness, inconsistency, imprecision, and publication bias. The overall quality was upgraded according to evaluation of three factors: large magnitude of effects, dose-response, and whether confounding minimized the effect. This rating combined with confidence in the results obtained in the included studies was used to assess the strength of epidemiological evidence for developmental neurotoxicity of pyrethroids as sufficient, limited, inadequate or evidence of lack of toxicity as specified in the Navigation Guide (Johnson et al., 2014; Woodruff and Sutton, 2014). These ratings were discussed until consensus was reached by all authors.

2.2. Mechanistic evidence

To make a structure for evaluating the mechanistic evidence, we utilized primarily the OECD-supported Adverse Outcome Pathways (AOPs) platform (AOP-wiki) and searched for relevant key events (KEs) suggested in the existing AOPs. The search focused on impaired cognition and behavioural disorders, such as ADHD and ASD, related to exposure during development.

Three AOPs for impaired cognitive function were identified and are listed below. All three AOPs are currently endorsed by the OECD Task Force on Hazard Assessment/Working Group of the National Coordinators of the Test Guidelines Programme (TFHA/WNT). This endorsement (in comparison to other AOPs that are mostly under development) indicates higher level of quality and validity of the biological information captured in the AOP. The relevant AOPs were:

AOP 13 Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities.
AOP 42 Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.
AOP 54 Inhibition of Na+/I- symporter (NIS) leads to learning and memory impairment.

For AOPs 42 and 54, reduced TH synthesis (KE 277), decreased thyroxine (T4) in serum (KE 281) and decreased T4 in neuronal tissue (KE 280) are shared KEs. A shared KE between AOP 13 and 54 is reduced level of brain-derived neurotrophic factor (BDNF) (KE 381) which in AOP 54 is suggested to mediate the link between reduced TH and impaired neurodevelopment. Another relevant AOP for DNT health outcomes is AOP 17, which is currently under EAGMST review (i.e., advanced AOP but not fully validated and citing is not recommended yet). This AOP contains a key event "Neuroinflammation" (KE 188), which is shared with several other AOPs for adult or aging neurodegenerative outcomes (AOP 3, AOP 12 or AOP 48).

Based on these AOPs, a systematic search combining the KEs and „pyrethroid*", as well as specific search for 26 individual pyrethroid compounds was performed in the ToxCast database (Supplementary Table 3). Supporting literature was searched in the PubMed database.

3. Results

3.1. Epidemiological evidence

Our search identified 201 unique publications of which 23 met the inclusion criteria. Two additional publications were identified by hand search of references or citation of the identified studies (Supplementary Fig. 1). Among the 25 original publications included, the potential impact of prenatal exposure was reported in 17 (Table 1), while childhood exposure was addressed in 10 publications (Table 2) and two studies presented findings on both pre- and postnatal pyrethroid exposure (Viel et al., 2015, 2017). The selected studies were published between 2011 and 2021 and included populations from 12 different countries. Twenty of the studies used urinary concentrations of pyrethroid metabolites to quantify exposure. Of these, 11 studies reported an enzymatic deconjugation step using β-glucuronidase and/or sulfatase, four studies reported an acidic hydrolysis deconjugation step and five did not report any deconjugation steps (Supplementary Table 2). This step was usually very briefly described, with a lot of variability between the laboratories. Among those who did not mention any deconjugation steps, one referred to a method including this step (Lee et al., 2020) but for the other four studies it was not possible to determine if this was an omission in the description of the analytical method or if it was not performed at all. Hence, exposure assessment in these studies was evaluated as "probably high risk of bias" for this domain (Viel et al., 2015, 2017; Wang et al., 2016; Xue et al., 2013). Overall, the studies

Table 1
Association between prenatal pyrethroid exposure and child neurodevelopment.

Study			Exposure			Outcome			Main findings
Reference, Study name and design	**Location**	**Sample size**	**Sampling year and method**	**LOD, µg/L (%>LOD)**	**Urinary conc., unit**	**Child age**	**Outcome and Examination method**	**Covariates included in adjusted analyses**	
Andersen et al. (2021), OCC, prospective cohort	Denmark	755	2010–12, morning spot urine (after overnight fasting), GW 28	3-PBA 0.03 (94.3) 4F-3PBA 0.2 (0.1) *Trans*-DCCA 0.4 (12.2) *Cis*-DCCA 0.5 (2.6) *Cis*-DBCA 0.5 (3.2)	M (75p): 3-PBA 0.24 (0.45) µg/g crea	20–36 mo	Early language development, MacArthur-Bates Communicative Development Inventories (MB-CDI), parent-reported, Vocabulary and Complexity scores reported as age and sex-standardized z-scores	U-crea, maternal education, breastfeeding duration, and child sex	↔ Maternal 3-PBA associated with lower odds of scoring below the 15th percentile MB-CDI vocabulary score among boys.
Barkoski et al. (2021), MARBLES, prospective cohort	USA, California	201	2007–14, First morning voids, 3 in each trimester (pooled per trimester)	3-PBA 0.10 (97)	M (75p): 3-PBA 2.06 (3.50), µg/L, specific gravity corrected	3 y	Cognitive and behavioural (ASD) function, The Mullen Scales of Early Learning (MSEL) and Autism Diagnostic Observation Scale (ADOS)	U-specific gravity, pre-pregnancy BMI, birth year, homeownership, prenatal vitamin use, maternal TCPy	↔ No differences in maternal 3-PBA between typically developing (TD) and non-TD children. Modest non-significant association between 3-PBA and risk for ASD
Guo et al. (2020), SMBCS, Prospective cohort	China, Sheyang,	326	2009-10 spot urine at delivery	3-PBA 0.10 (98) *Trans*-DCCA 0.10 (98.4) *Cis*-DCCA 0.10 (91.8)	M (75p): 3-PBA 1.11 (2.12) *Trans*-DCCA 1.26 (3.22) *Cis*-DCCA 0.48 (1.11), µg/L	7 y	Cognitive function, Wechsler Intelligence Scale for Children, fourth edition (WISC-IV) Chinese version, full IQ (FIQ) scores	U-crea, maternal age at delivery, maternal education, family annual income, passive smoking in pregnancy, breastfeeding duration ($<$ or $\geq$ 6 mo), child sex, physicians administering IQ assessment, marital status at assessment	↔ No association between maternal 3-PBA and FIQ scores
Tanner et al. (2020) SELMA, Prospective cohort	Sweden	718	2007–10 First morning voids, 1. Trimester (median GW 10),	3-PBA 0.017 (99)	GM (GSD): 3-PBA 0.16 (2.7), µg/L	7 y	Cognitive function, WISC -IV, FIQ scores	U-crea, child sex, maternal IQ (RAVEN), education, weight, and smoking status (GA mentioned in the abstract but according to the method section it was not included)	(↑) FIQ scores were 1.9-points (95% CI: −3.6, −0.2) lower among boys for an inter-quartile-range change in the Weighted Quantile Sum index for 26 EDCs included. Maternal 3-PBA was estimated to contribute with a weight of 9% to the index but separate results for 3-PBA not provided
Dalsager et al. (2019), OCC, prospective cohort	Denmark	948	2010–12, morning spot urine (after overnight fasting), GW 28	3PBA 0.03 (94.3) 4F-3PBA 0.2 (0.1) *Trans*-DCCA 0.4 (11.4) *Cis*-DCCA 0.5 (2.8) *Cis*-DBCA 0.5 (3.0)	M (75p): PBA 0.24 (0.46), µg/L	2-4 y	Behavioural function, Child Behaviour Checklist (CBCL) for ages 1.5–5 y, parent reported, ADHD-scale scores	U-crea, maternal educational, parental psychiatric diagnosis, child age and sex	↑ Maternal 3-PBA associated with higher ADHD score, 3-PBA and *trans*-DCCA associated with higher odds of scoring above the 90-percentile on the ADH-scale score.

(*continued on next page*)

Table 1 (*continued*)

Study			Exposure			Outcome			Main findings
Reference, Study name and design	**Location**	**Sample size**	**Sampling year and method**	**LOD, μg/L (%>LOD)**	**Urinary conc., unit**	**Child age**	**Outcome and Examination method**	**Covariates included in adjusted analyses**	
									These associations were not modified by child sex.
Eskenazi et al. (2018) VHEMBE, Prospective cohort	South Africa	705	2012-13 peripartum urine samples,	3-PBA 0.0047 (100) 4F-3PBA 0.005 (12.5) *Trans*-DCCA 0.0038 (100) *Cis*-DCCA 0.0045 (100) *Cis*-DBCA 0.0025 (100)	M (75p): 3-PBA 0.700 (1.372) *Trans*-DCCA 0.340 (0.785) *Cis*-DCCA 0.301 (0.601) *Cis*-DBCA 0.223 (0.475), μg/L, specific gravity corrected	1 and 2 y	Behavioural and cognitive function. Bayley Scales of Infant Development (BSID), At age 1 and 2 y: Cognitive, language (Receptive and Expressive), and Motor (Fine and Gross) subtests; At age 1 y: the Social-Emotional subtest, maternal reported, data reported as age standardized z-scores	Maternal age, education, poverty status, and marital status at delivery; breastfeeding status, Raven's Coloured Progressive Matrices z-score for the mother/ caregiver, preterm birth, birthweight z-scores, maternal depression risk score, USDA Food Insecurity Score, modified HOME z-score, and the psychometrician administering the BSID-III	↑ Maternal 3-PBA, *cis*-and *trans*-DCCA associated with decrement in Social-Emotional scores at age 1 y. *Cis*-DBCA associated with decrements in Language Composite/ Expressive Communication scores at age 2 y. These associations were not modified by child sex
Furlong et al. (2017), MSCEHC, prospective cohort	USA	162	1998–2002 spot urine, third trimester	3-PBA 0.25 (29.6); *Trans*-DCCA 0.20 (21.6); *Cis*-DCCA 0.20 (14.4)	M (75pct): 3-PBA <LOD (0.34) *Trans*-DCCA <LOD (<LOD) *Cis*-DCCA <LOD (<LOD), μg/L	4, 6, and 7–9 y	Behavioural function, The Behaviour Assessment System for Children (BASC) and The Behaviour Rating Inventory of Executive Functioning (BRIEF), both were parent reported, repeated measures at age 4, 6 and 7–9 y	U-crea, race/ ethnicity, HOME scores, DMPs (organophosphate metabolites), maternal marital status and education at follow-up, visit, and child sex	↑ Maternal 3-PBA > LOD associated with worse scores for internalizing behaviours and behavioural regulation. DCCA > LOD associated with worse scores for externalising behaviours and behavioural regulation. These associations were not modified by child sex
Hisada et al. (2017), Prospective cohort	Japan, Tokyo	102	2009–11 Spot urine, GW 10–12,	3-PBA NI	M: 3-PBA 0.389, μg/L, specific gravity corrected	18 mo	Cognitive function/mental development. Kinder Infants Development Scale (KIDS), caretaker-reported, Development Quotient scores	Maternal age, maternal BMI, parity, infant sex, birth weight, GW, infant blood TSH 5 days postpartum, breast-feeding duration, infant age at examination, and Index of Child Care Environment score. In a second model fish consumption was also included.	↔ Maternal 3-PBA associated with a higher Development Quotient score, not significant after adjusting for dietary fish intake
Viel et al. (2017), PELAGIE, prospective cohort	France	205	2002–06, maternal urine, before GW 19, single first morning void	3-PBA 0.008 (30.2); 4F-3PBA 0.003 (8.8); *Trans*-DCCA 0.01 (98.0); *Cis*-DCCA 0.07 (64.9); *Cis*-DBCA 0.07 (68.3)	M (75pct): 3-PBA <LOD (0.02) *Trans*-DCCA 0.14 (0.27) *Cis*-DCCA 0.09 (0.17) *Cis*-DBCA 0.011(0.18), μg/L	6 y	Behavioural function, Strengths and Difficulties Questionnaire (SDQ) parent reported, subscale scores for prosocial behaviour, internalizing disorders, and externalising disorders	Maternal education, child sex, childhood pyrethroid metabolite concentration, U-crea (mother and child), and maternal organophosphate metabolite concentrations	**↑ (↔ for 3-PBA)** Maternal *cis*-DCCA associated with internalizing difficulties, the association was stronger for females than males, no associations were seen for *trans*-DCCA or for 3PBA (below vs above LOD)

(*continued on next page*)

Table 1 (*continued*)

Study			Exposure			Outcome			Main findings
Reference, Study name and design	**Location**	**Sample size**	**Sampling year and method**	**LOD, µg/L (%>LOD)**	**Urinary conc., unit**	**Child age**	**Outcome and Examination method**	**Covariates included in adjusted analyses**	
Fluegge et al. (2016), prospective cohort	Ohio, USA	118	2002–05 First morning voids in 2. and 3. trimester and postnatal at age 2 mo	3-PBA 0.1 (92) *Trans*-DCCA: 0.2 (58) *Cis*- DCCA 0.2 (50); *cis*-DBCA: 0.1 (100)	Urinary concentrations not presented, but used to estimate daily excretion per kg body weight	3 mo	Cognitive function/mental development. BSID (II), Mental Development Index (MDI) and Psychomotor Development Index (PDI). scores	birth weight, gestational age and maternal education status, in some models also TCPY (metabolite of chlorpyrifos)	↑ Maternal 3-PBA associated with lower MDI scores, No association with PDI scores
Watkins et al. (2016), ELEMENT, prospective cohort	Mexico City	187	1997–2001, Spot urine in third trimester	3-PBA 0.25 (44.9)	M (75pct): 3-PBA <LOD (0.34), µg/L 21 women provided repeated samples	2-3 y	Cognitive function/mental development. BSID (II, Spanish version) Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores.	urinary specific gravity, maternal IQ, education, SES, blood lead, and child sex	↑ Maternal 3-PBA > LOD associated with lower MDI scores at 2 y, slightly stronger associations among females, no association between 3-PBA and MDI at 3 y, or with PDI scores at either 2 or 3 y
Viel et al. (2015), PELAGIE, prospective cohort	France	205	2002–06, maternal urine, before GW 19, single first morning void	3-PBA 0.008 (30.2); 4F-3PBA 0.003 (8.8); *Trans*-DCCA 0.01 (98.0) *Cis*-DCCA 0.07 (64.9); *Cis*-DBCA 0.07 (68.3)	M (75pct): 3-PBA <LOD (0.02) *Trans*-DCCA 0.14 (0.27) *Cis*-DCCA 0.09 (0.17) *Cis*-DBCA 0.011(0.18), µg/L	6 y	Cognitive function, WISC-IV, Verbal Comprehension Index scores and Working Memory Index scores	Maternal education, child sex, childhood pyrethroid metabolite concentration, U-crea (mother and child), and maternal organophosphate metabolite concentrations, maternal IQ, and Home Observation for Measurement of the Environment score	↔ No significant associations with cognitive function but a tendency to lower score for working memory for higher maternal *trans*-DCCA and *cis*-DCCA.
Xue et al. (2013), prospective cohort	China, Henan, Jiaozuo,	497	2010 Spot urine at birth	3-PBA 0.10 (99.1) *Trans*-DCCA 0.10 (99.5); *Cis*-DCCA, 0.10 (95.3)	M (75pct): 3 -PBA 2.24 (3.69) *Trans*-DCCA 3.65 (6.83) *Cis*-DCCA, 1.22 (2.81), µg/g crea	1 y	Cognitive function/mental development. Development Screen Test (DST) scale. Unclear if parent-reported	Maternal education, residence of infants, main carers of infants, infant disease or not	↑ Sum of maternal pyrethroid metabolites negatively associated with child mental development
Horton et al. (2011), CCCEH, prospective cohort	USA, New York City	348 for PBO in air, 272 for permethrin in plasma	1998–2006, maternal and umbilical cord blood at delivery, personal air samples during pregnancy	*cis*- and *trans* permethrin > LOD in maternal plasma: 12.9% and 18.0%, for cord plasma: 7.1% and 5.4%, respectively	Permethrin in plasma and PBO in inhalation air, no urinary 3-PBA or DCCA measurements	3 y	Cognitive function/mental development. BSID (II), Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores.	Child sex. gestational age, ethnicity, maternal education, maternal nonverbal intelligence, quality of the home environment, prenatal exposure to environmental tobacco smoke. Unclear if maternal plasma chlorpyrifos was included.	↑ (↔) PBO in maternal air samples associated with lower MDI scores. No association with plasma permethrin
Studies without HBM data									
von Ehrenstein et al. (2019) Case-control	USA, California, Central Valley	2961 cases and 35,370 controls	1998–2010	GIS based on California state mandated Pesticide Use Reporting, pounds of pesticides applied per acre/ month within 2000 m from maternal residence for 11 high use pesticides		3-15 y	Autism diagnosis vs matched controls	Maternal age, race/ ethnicity and education, pregnancy average NOx as marker of traffic related air pollution.	↑ Risk of autism spectrum disorder was associated with prenatal exposure to permethrin
Gunier et al. (2017),	USA	283	2000			7 y	WISC-IV, FIQ scores	Child age at assessment, sex,	↑ Pyrethroid used

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Table 1 (*continued*)

Study			Exposure			Outcome			Main findings
Reference, Study name and design	**Location**	**Sample size**	**Sampling year and method**	**LOD, µg/L (%>LOD)**	**Urinary conc., unit**	**Child age**	**Outcome and Examination method**	**Covariates included in adjusted analyses**	
CHAMACOS, prospective cohort				kg pyrethroids (a.i.) used within 1 km of maternal residence during pregnancy				language of assessment, maternal education, IQ, country of birth, depression, Home Observation for Measurement of the Environment (HOME) score, household poverty level and prenatal urinary dialkyl phosphates.	within 1 km Associated with reduced Full-scale IQ with strongest effect for perceptual reasoning and verbal comprehension
Shelton et al. (2014), CHARGE, Case-control	USA	970	1997–2008	Pounds of pyrethroids, (a.i.) applied aggregated within 1.25-km, 1.5-km, and 1.75-km buffer distances from the home just before and during pregnancy		2-5 y	full-syndrome ASD or developmental delay (DD) diagnosis vs matched controls	Paternal education, home ownership, maternal place of birth, child race/ethnicity, maternal prenatal vitamin intake	↑ Residence near pyrethroid applications just before conception or during third trimester associated with greater risk for both ASD and DD

↑: statistically significant adverse association; ↔: no significant adverse association; GM: geometric mean; GSD: geometric standard derivation; M: median; 75pct: 75th percentile; 90 pct: 90th percentile; GA: gestational age; GW: gestational week; 3-PBA: 3-phenoxybenzoic acid (common metabolite of most pyrethroids, e.g,: cypermethrin, deltamethrin, permethrin, lambda-cyhalothrin, etofenprox, tau-fluvalinate, esfenvalerate, fenpropathrin, *but not* cyfluthrin or bifenthrin); 4-F-3-PBA: 4-fluoro-3-phenoxybenzoic acid (cyfluthrin); *cis*-DCCA: *cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*cis*-permethrin, *cis*-cypermethrin, *cis*-cyfluthrin);*trans*-DCCA: *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*trans*-permethrin, *trans*-cypermethrin, *trans*-cyfluthrin); *cis*-DBCA: cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (deltamethrin); u-crea: urinary concentration of creatinine; u-specific gravity: specific gravity of the urine, PBO: piperonyl butoxide; HOME: Home Observation for Measurement of the Environment; GIS: geographic information system; ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorders; DD: Delayed development; WISC: Wechsler Intelligence Scale for Children.

suggested widespread exposure to pyrethroids among pregnant women and children with high detection rates of 3-PBA in most of them, especially those performed within the last 10 years because of lower detection limits, and likely, increased use of pyrethroids (Tables 1 and 2). Since exposure and outcome measures, test methods, and the age of the children at examination differed considerably between the studies, meta-analysis of the data was infeasible. Risk of bias assessment of the individual studies is presented in Fig. 1 and Supplementary Table 1.

3.1.1. *Prenatal pyrethroid exposure and neurodevelopment*

Out of the 17 included studies, 15 were based on prospective birth cohorts. Pyrethroid exposure during pregnancy was assessed by analysing pyrethroid metabolites in maternal urine samples in 13 of the studies. 3-PBA was included in all these studies, and nine studies also included metabolites of more specific pyrethroids. One study analysed permethrin in maternal plasma and PBO in air samples. In three studies, exposure was estimated by data on pyrethroid use near maternal residence during pregnancy (Table 1). Regarding assessment of neurodevelopment, Xue et al. (2013) used a Developmental Screen Test but the validation of this test and how it was administered was not clearly described. All other studies used validated assessment tools administered by health professionals or validated caretaker/parent-reported assessment questionnaires (Table 1).

Associations between prenatal pyrethroid exposure and adverse neurodevelopment were reported in 12 of the studies (Table 1). The VHEMBE cohort study among 752 mother-child pairs from a malaria epidemic area in South Africa, with high continuous indoor use of pyrethroids, used the Bayley Scales of Infant Development (BSID) to assess mental (cognition and behaviour) and motor development. Maternal pyrethroid metabolite concentrations in pregnancy (median 3-PBA: 0.7 µg/L) were associated with decrement in social-emotional scores at 1 year of age (adjusted ß = −0.58 (95% CI: −1.11, −0.06), −0.63 (−1.14, −0.12), and −0.48 (−0.92, −0.05) for a10-fold increase in 3-PBA, cis-DCCA, and trans-DCCA concentrations, respectively). Further, at age 2 year, the deltamethrin metabolite, *cis*-DBCA, was associated with lower scores for Language Composite and Expressive Communication (adjusted ß = − 1.74 (−3.34, −0.13) and − 0.40 (−0.77, −0.04)), respectively, for a 10-fold increase) (Eskenazi et al., 2018). Three other studies using the BSID also reported exposure related decrement in mental development index (MDI) scores but none of these studies reported separate subscale scores for neurobehavioral function (Fluegge et al., 2016; Horton et al., 2011; Watkins et al., 2016). The study by Horton et al. (2011) was performed in low-income neighbourhoods in New York City with high residential use of pyrethroids, like in the WHEMBE cohort study. Urinary pyrethroid biomarkers were not included but the concentration of PBO in maternal personal air samples collected during pregnancy was used as a marker of inhalation exposure to pyrethroids. PBO was associated with lower BSID MDI scores (adjusted ß = −1.20 (−0.33, −2.25) per log-unit increase in PBO) at age 3 year. A study from Ohio found higher maternal 3-PBA in third trimester to be associated with lower BSID MDI scores at age 3 months among 118 children while no associations were seen for 3-PBA in second trimester (Fluegge et al., 2016). In this study, the urinary concentrations were presented as ng excreted/kg body weight/day and the decrement in MDI scores was reported to be approximately 0.1 for each one ng/kg/day increase in 3-PBA excretion. A study from Mexico City, also reported an association between higher maternal third trimester 3-PBA and lower BSID MDI scores (Watkins et al., 2016). Participants with detect able 3-PBA was divided into equally sized groups, medium and high (n = 42 each). Lower BSID MDI scores at 24, but not at 36, months of age were observed for the median and high exposure groups (adjusted ß = −3.5 and −3.8, respectively) compared to those with 3-PBA below the limit of detection (LOD) of 0.25 µg/L (n = 103). In a Chinese study, a Development Screen Test was used to assess mental development at age

Table 2
Association between postnatal pyrethroid exposure and child neurodevelopment.

Study			Exposure			Outcome			Main findings
Reference, Study name and design	**Location**	**Sample size**	**Sampling year and method**	**LOD, μg/L (%>LOD)**	**Urinary concentration, unit**	**Child age**	**Outcome and Examination method**	**Covariates included in adjusted analyses**	
Lee et al. (2020), EDC, cross sectional	Korea	385	2012–13 Child spot urine	3-PBA 0.013	Mean (SD) 3-PBA 1.6 (2.4), μg/L Questionnaire data on residential use	4 y	Behavioural function, the Korean ADHD rating scale (K-ARS), parent-teacher reported, K-ARS scores	Child sex, age and BMI Z-score, maternal age at delivery, education, smoking status, passive smoking, maternal BMI	↑ 3-PBA associated with increased ADHD scores among boys. No associations among girls
Viel et al. (2017), PELAGIE, cross-sectional	France	284	2009–12 Child Spot urine	3PBA 0.008 (63.7) 4F-3PBA 0.003 (15.8) *Trans*-DCCA 0.01 (96.5) *Cis*-DCCA 0.07 (64.5) Cis-DBCA 0.07 (85.2)	M (75pct): 3PBA 0.02 (0.05) *Trans*-DCCA 0.22 (0.58) Cis-DCCA 0.10 (0.19) Cis-DBCA 0.22(0.43), μg/L	6 y	Behavioural function, Strengths and Difficulties Questionnaire (SDQ) parent reported, Subscale scores for prosocial behaviour, internalizing disorders, and externalising disorders	Maternal education, child sex, child U-crea and organophosphate metabolites, other covariates added in separate models for the individual pyrethroid metabolites	↑ 3-PBA associated with higher scores for externalising difficulties and abnormal or borderline social behaviour. *Trans*-DCCA associated with reduced externalising scores.
Wang et al. (2016), cross-sectional	China, Nanjing	406	2014 Child spot morning urine	3-PBA 0.008 (36.0) 4F-3PBA 0.017 (17.7) *Cis*-DBCA 0.8 (0.7)	M (75p): 3-PBA 0.02 (0.16) 4F-3PBA 0.03 (0.07) *Cis*-DBCA 1.27 (1.74), μg/g crea	3-6 y	Cognitive function, Language subscale scores based on Chinese Binet test WISC-subscale scores for arithmetic, picture completion, and maze tests (visual/spatial reasoning), Cancellation test scores (attention, concentration, and comprehension)	Child sex, age, and outside school education expense	↑ 3-PBA > LOD associated with lower language and arithmetic scores. 3-PBA (continuous) associated with lower cancellation test scores.
van Wendel de Joode et al. (2016), families living near plantations, cross-sectional	Costa Rica	140	2007, Child first morning voids	3-PBA 0.1 (94.0)	M (75 pct): 3-PBA 0.8 (1.5), μg/L	6-9 y	Cognitive and behavioural function, WISC-I, index scores for Perceptual Reasoning, Working Memory, and Processing Speed Conner's Parent Rating Scale-Revised Short Version (CPRS-R) (parent reported)	Maternal education, child age at assessment, sex, BMI, number of siblings, repeated a school year, U-crea, and visual acuity impairment	↑ 3-PBA associated with poorer processing speed scores, particularly in girls
Viel et al. (2015), PELAGIE, cross-sectional	France	284	2009–12 Child Spot urine	3PBA 0.008 (63.7) 4F-3PBA 0.003 (15.8) *Trans*-DCCA 0.01 (96.5) *Cis*-DCCA 0.07 (64.5) Cis-DBCA 0.07 (85.2)	M (75pct): 3PBA 0.02 (0.05) *Trans*-DCCA 0.22 (0.58) Cis-DCCA 0.10 (0.19) Cis-DBCA 0.22(0.43), μg/L	6 y	Cognitive function, WISC-IV, Verbal Comprehension index scores and Working Memory index scores	Maternal education and IQ score, Home Observation for Measurement of the Environment score, child U-crea and organophosphate metabolites, other covariates added in separate models for the individual pyrethroid metabolites	↑ 3-PBA and cis-DBCA were associated with lower verbal comprehension scores and working memory scores.
	USA	687	2001–02			8-15 y			

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Table 2 (*continued*)

Study			Exposure			Outcome			Main findings
Reference, Study name and design	**Location**	**Sample size**	**Sampling year and method**	**LOD, µg/L (%>LOD)**	**Urinary concentration, unit**	**Child age**	**Outcome and Examination method**	**Covariates included in adjusted analyses**	
Wagner-Schuman et al. (2015), NHANES, cross-sectional				3-PBA 0.1 (78.8)	M (90p): 3-PBA 0.29 (1.94), µg/L		Behavioural function, caregiver report of prior ADHD diagnosis or meeting Diagnostic criteria on the Diagnostic Interview Schedule for Children (DISC)	Child age, sex, race/ethnicity, income, health insurance status, prenatal tobacco exposure, blood lead level, urinary organophosphate metabolite level, and U-crea.	↑ 3-PBA > LOD associated with higher odds of an ADHD diagnosis, 3-PBA (continuous) associated with higher count ratios for hyperactive-impulsive, strongest associations in boys
Fiedler et al. (2015), Cross sectional	Thailand	N = 53 24 children from a rice farming community, 29 from an aquaculture community	Sampling year not provided, child first morning void collected during two seasons (low and high use of pyrethroids)	No information	GM: 3-PBA Rice farming, low/high use season: 2.24/1.74 Aqua, low/high use season: 2.26/1.80 *Cis/trans*-DCCA, Rice farming low/high use season: 1.11/1.46 Aqua, low/high use season: 1.73/1.28, µg/g crea	6-8 y	Cognitive/ behavioural function, the Behavioural Assessment and Research System (BARS), a computerized neurobehavioral test system	Age and the Home Observation for Measurement of the Environment (HOME) scores,	↔ No adverse associations
Quiros-Alcala et al. (2014), NHANES, cross-sectional	USA	1680	1999–2002	3-PBA 0.1 (77.1) *Trans*-DCCA 0.4 (33.9) *Cis*-DCCA 0.1 (35.6)	M (75pct): 3-PBA 0.31 (0.89) *Trans*-DCCA <LOD (0.68) *Cis*-DCCA <LOD (0.21), µg/L	6-15 y	Parental report based on two Q: 1. Has a representative from a school or a health professional ever told (you) that (the child) had a learning disability (LD)? 2. Has a doctor or health professional ever told (you) that (the child) had attention deficit disorder (ADHD)?	U- crea, child age, sex, race/ethnicity, household education level, low birth weight (≥ vs < 2500 g), maternal age at delivery, neonatal intensive care unit admission, maternal smoking during pregnancy, day care/preschool attendance, health insurance	↔ No significant associations between pyrethroid metabolites and parent reported LD and/or ADHD but all adjusted ORs for 3-PBA and *trans*-DCCA were above 1.
Oulhote and Bouchard (2013), CHMS, cross-sectional	Canada	779	2007–09, Child spot urine	3-PBA 0.01 (99.3) 4F-3PBA 0.008 (41.3) *Trans*-DCCA 0.01 (99.9) *Cis*-DCCA 0.007 (97.3) *Cis*-DBCA 0.006 (48.0)	M (75pct): 3-PBA 0.20 (0.42) 4F-3PBA <LOD (0.01) *Trans*-DCCA 0.15 (0.35) *Cis*-DCCA 0.05 (0.10) *Cis*-DBCA <LOD (0.02), µg/L	6-11 y	Behavioural function, Strengths and Difficulties Questionnaire (SDQ) parent reported, Scores for global/ total difficulties and scores for five-dimension scales: emotional symptoms, conduct problems, hyperactivity/ inattention, peer problems, and prosocial behavior.	Child sex, age, race/ethnicity and U-crea, parental income, education, maternal smoking during pregnancy, birth weight, blood lead concentrations, and for 3-PBA also child BMI and fasting status	↑ cis-DCCA associated with higher scores for total difficulties, strongest association in girls non-significant association between *trans*-DCCA and higher scores for total difficulties and between 3-PBA and conduct problems in girls
Studies without HBM data						<20 y			

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Table 2 (*continued*)

Study			Exposure			Outcome			Main findings
Reference, Study name and design	**Location**	**Sample size**	**Sampling year and method**	**LOD, µg/L (%>LOD)**	**Urinary concentration, unit**	**Child age**	**Outcome and Examination method**	**Covariates included in adjusted analyses**	
Hicks et al. (2017) Ecological, cross-sectional	USA, New York state	2010–15 19,073 children below 20 y living within 8 zip codes whit aerial pyrethroid applications, 44,697 in 16 control zip codes.		Pesticide exposure in kilograms per km^2 calculated for each zip code, details on timing and volume of aerial pyrethroid application over the zip codes were collected			ICD-9 diagnostic codes for ASD or DD at one of six paediatric outpatient clinics	regional characteristics (poverty, pesticide use, population density, and distance to medical centre), subject characteristics (race and sex), and local birth characteristics (prematurity, low birthweight, and birth rates)	↑ Zip codes with aerial pyrethroid exposure were 37% more likely to have higher rates of ASD/DD

↑: statistically significant adverse association; ↔: no significant adverse association; GM: geometric mean; GSD: geometric standard derivation; M: median; 75pct: 75th percentile; 90 pct: 90th percentile; GA: gestational age; GW: gestational week; 3-PBA: 3-phenoxybenzoic acid (common metabolite of most pyrethroids, e.g,: cypermethrin, deltamethrin, permethrin, lambda-cyhalothrin, etofenprox, tau-fluvalinate, esfenvalerate, fenpropathrin, *but not* cyfluthrin or bifenthrin); 4-F-3-PBA: 4-fluoro-3-phenoxybenzoic acid (cyfluthrin); *cis*-DCCA: *cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*cis*-permethrin, *cis*-cypermethrin, *cis*-cyfluthrin);*trans*-DCCA: *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*trans*-permethrin, *trans*-cypermethrin, *trans*-cyfluthrin); *cis*-DBCA: cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (deltamethrin); U-crea: urinary concentration of creatinine; PBO: piperonyl butoxide; HOME: Home Observation for Measurement of the Environment; GIS: geographic information system; ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorders; DD: Delayed development.

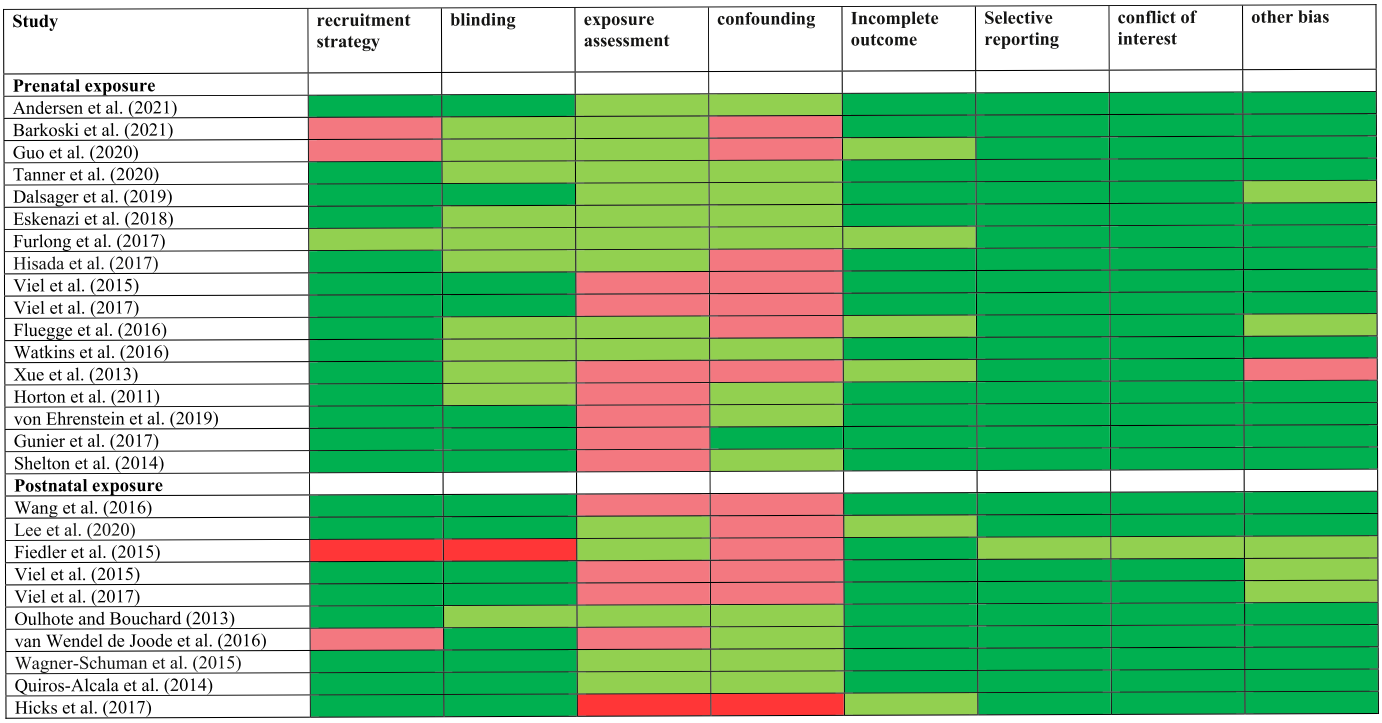

Fig. 1. Summary of the risk of bias judgements (low, probably low, probably high, or high) for each of the included studies. Justifications for the judgements are provided in Supplementary Table 1.

Key: Low | Probably low | Probably high | High

one year among 497 children (Xue et al., 2013). Maternal metabolite concentration at birth (sum of 3-PBA and *cis*-and *trans*-DCCA) was associated with poorer mental development (ß = −0.15). The 3-PBA concentrations were high (median: 2.24 µg/g creatinine) compared to the other included studies. A study from Denmark, with considerably lower maternal 3-PBA concentrations (median 0.24 µg/L), used the parent reported Child Behaviour Checklist (CBCL) to assess ADHD symptoms among 948 children at age 2–4 year (Dalsager et al., 2019). After adjustment each doubling in maternal 3-PBA concentration was associated with a 3% increase in the ADHD score (Ratio: 1.03 (1.00, 1.07)) and higher odds of having an ADHD score ≥ the 90th percentile (OR: 1.13 (1.01,1.25)). Trans-DCCA above the LOD (0.4 µg/L) was also associated with higher OR (1.76 (1.08, 2.86) for scoring above the ≥ the 90th percentile.

Among studies on children at or above 4 years of age, one from New York City found maternal concentrations of 3-PBA and *cis*-DCCA above the LOD of 0.25 and 0.20 μg/L, respectively, to be significantly associated with a variety of behavioural functioning deficits among 118 children measured repeatedly at 4, 6, and 7–9 years of age (Furlong et al., 2017). Neurobehavioral function was assessed by two parent reported assessment tools, The Behaviour Assessment System for Children (BASC) and The Behaviour Rating Inventory of Executive Functioning (BRIEF), and t-scores from all visits were used in the data analyses (longitudinal mixed models). Adjusted effect estimates were strongest for internalizing (ß = −4.50 (−8.05, −0.95) and monitoring (ß = −4.08 (−7.07, −1.08) scales in relation to 3-PBA, and for inhibitory control (ß = −7.20 (−12.0, −2.39) and behavioural regulation (ß = −6.42 (−11.39, −1.45) scales in relation to *cis*-DCCA. Another study, based on the French PELAGIE cohort, also found maternal *cis*-DCCA to be associated with internalizing difficulties (p = 0.05 across tertiles) at 6 years of age assessed by the parent reported Strengths and Difficulties Questionnaire (Viel et al., 2017). No significant associations were seen in relation to 3-PBA, but the reported 3-PBA concentrations were very low (only 30% of the samples above the LOD of 0.008 μg/L) compared to other studies from France (Dereumeaux et al., 2018) and other European countries (Dalsager et al., 2019; Tanner et al., 2020). Since no deconjugation steps were reported in the PELAGIE study, we suspect that the 3-PBA concentration might have been broadly underestimated. Two studies reported associations between prenatal pyrethroid exposure and decrement in intelligence scores (IQ) at age 7 years assessed by the Wechsler Intelligence Scale for Children (WISC) (Gunier et al., 2017; Tanner et al., 2020). Tanner et al. (2020) investigated the impact of mixtures of potential neurotoxicants analysed in maternal serum and urine, including 3-PBA. They used Weighted Quantile (WQS) regression and found that Full scale IQ (FIQ) scores were 1.9 points (CI: −3.6, −0.20) lower in boys for an inter-quartile-range change in the WQS index. No separate effect estimate for 3-PBA was presented but the contribution to the index was 9% for 3-PBA, only exceeded by one other compound, bisphenol F, with a contribution of 14%. Gunier et al. (2017) estimated pyrethroid exposure as amount active ingredients (kg) used within 1 km of maternal residence during pregnancy. Decrements of 2.0 points (−3.7, −0.3) in FIQ, 2.1 points (−4.0, −0.2) in perceptual reasoning, and 1.8 points (−3.4, −0.3) in verbal comprehension were observed among the children for each standard deviation increase in pyrethroid use. Further, two case-control studies from the US reported increased risk of ASD diagnosis related to maternal residential proximity to agricultural pyrethroid use in third trimester (OR = 1.83 (1.04, 3.23) (Shelton et al., 2014) or to permethrin use during pregnancy (OR = 1.10 (1.01, 2.20)) (von Ehrenstein et al., 2019).

Five studies did not find significant associations between prenatal pyrethroid exposure and adverse neurodevelopment. A study from California, based on a cohort enrolling pregnant women with a family history of ASD (MARBLES), did not find association between maternal 3-PBA concentration (median 2.06 μg/L) and worse scores for non-typically development (non-TD) at age 3 years assessed by The Mullen Scales of Early Learning (MSEL) (Barkoski et al., 2021). ASD was evaluated by expert clinicians using the Autism Diagnostic Observation Scale (ADOS) and a non-significant elevated risk of ASD (RRR: 1.34 (0.89, 2.03) per natural-log unit of 3-PB, approximately a 2.7-fold increase) was observed. A likely explanation why this association did not reach significance at the 0.05 level, is the relatively small sample size (n = 201) implying rather few children affected by ASD (n = 45) or non-TD (n = 54) outcomes. The selection of covariates in the final model was guided by 10% or more change in the beta coefficient, which may not be an appropriate method (VanderWeele, 2019). One of the included covariates was maternal urinary concentration of TCPy (metabolite of chlorpyrifos) but if TCPy and 3-PBA was correlated, adjusting for TCPy would weaken the association. Another explanation suggested by the authors, is the selected population with an assumed increased genetic susceptibility for ASD. In a population with a high genetic load, it is difficult to predict whether environmental contributions to ASD will be amplified (e.g., due to gene-by-environment interactions) or reduced because strong genetic susceptibility will confer higher background risk for ASD. Another study reported a positive association between maternal 3-PBA (median 0.39 μg/L) and a higher Development Quotient (DQ) score, assessed by the caretaker-reported Kinder Infants Development Scale (KIDS), at 18 months of age (Hisada et al., 2017). Also, this study, had a limited sample size of only 102 mother child dyads and adjusted for a high number of covariates some of which were potential mediators (e.g., birth weight and gestational age) or occurred after the exposure of interest (breast feeding and infant blood TSH). The positive association between 3-PBA and higher DQ score disappeared when fish consumption was included in the model. A larger cohort study of 755 mother-child pairs, investigated the potential impact of maternal 3-PBA (median 0.24 μg/g creatinine) on language development at 20–36 months of age using the Vocabulary and Complexity scores of the MacArthur-Bates Communicative Development Inventories (Andersen et al., 2021). This study also reported a beneficial association with 3-PBA as a reduced probability for scoring below the 15th percentile Vocabulary score was seen in boys for the highest tertile of 3-PBA. The authors suggest that this finding may be due to residual and unmeasured confounding from socioeconomic factors and dietary habits. The lack of an adverse effect might be explained by the low, mainly dietary, exposure level in this cohort. However, a higher ADHD score related to maternal 3-PBA was reported from this cohort (Dalsager et al., 2019) which may indicate that neurobehavioral outcomes are more sensitive to pyrethroid exposure. This notion is supported by the results from the PELGIE cohort, in which maternal *cis*-DCCA was associated with internalizing difficulties at age 6 years (Viel et al., 2017), while none of the maternal pyrethroid metabolites were significantly associated with lower WISC IQ scores (Viel et al., 2015). A tendency to lower scores for working memory was reported for higher *cis*- and *trans*-DCCA. The potential underestimated 3-PBA measurements (discussed above) and "overadjustment" for child urinary metabolite concentrations might contribute to the null findings in this study. A study from China also found no association between maternal 3-PBA and WISC FIQ scores among 326 children at age 7 years (Guo et al., 2020) despite rather high maternal 3-PBA concentrations (median 1.11 μg/L). A contributing cause for the null finding might be overadjustment from the relatively high number of covariates included in the regression models. Some of these variables did not meet the confounding criteria and were not associated with the outcome in binary analyses (e.g., marital status at assessment, passive smoking, and breast-feeding duration).

The initial rating of the quality across the studies was "moderate" as explained in the Methods section, and we did not find reasons to down- or upgrade this rating (Table 3).The overall risk of bias across the studies was rated as low to moderate (Fig. 1). Exposure assessment and improper adjustment for confounding variables were the most common source of bias. Three studies without HBM measurements of individual exposure were by default rated as "probably high risk of bias" regarding exposure assessment (Gunier et al., 2017; Shelton et al., 2014; von Ehrenstein et al., 2019). The study by Horton et al. (2011) was rated as "probably high risk of bias" because exposure was assessed by an indirect measure (PBO in inhalation air) and plasma concentrations of one pyrethroid, permethrin, with a short half-life in blood (Cote et al., 2014). Three studies quantified 3-PBA in urine but did not mention or refer to a deconjugation step in the description of the analytical method used to analyse urinary 3-PBA (Viel et al., 2015, 2017; Xue et al., 2013). The 3-PBA concentrations in these studies may be imprecise and markedly underestimated. Therefore, exposure assessment was also rated as "probably high risk of bias" for these studies. However, an underestimation of 3-PBA would most likely have diminished the possibility to find an association with the outcome.

Seven studies were rated as "probably high risk of bias" for confounding (Fig. 1). Three of these studies did not control for SES and/or parental education or intelligence (Barkoski et al., 2021; Derakhshan

Table 3
Evaluation of the quality and strength of the body of human evidence for pyrethroids and developmental neurotoxicity.

Rating category		Rating[a] and rationale	
Downgrading factors	**Summary of criteria for downgrading**	**Prenatal pyrethroid exposure**	**Postnatal pyrethroid exposure**
Risk of bias	Rate down if most evidence came from studies with high risk of bias, i.e., substantial risk of bias across the available body of evidence	0 Moderate across the studies with rating between "low" and "probably high". Confounding and exposure assessment were the domains most frequently judged to be "probably high". However, we agreed that the limitations within these studies were not strong enough to downgrade the overall risk of bias across the studies.	0 Moderate across the studies although the risk of bias was assessed to be "high" for some domains for a few studies,
Indirectness	Rate down if substantial differences exist between the study population, exposure, comparator, or outcome measured compared to the PECO-statement	0 Included studies measured neurodevelopmental outcomes in human populations and were relevant to the research question and PECO statement	0 All the included studies investigated neurodevelopment in human populations and were relevant to the study question outlined in the PECO statement.
Inconsistency	Rate down if studies conducted in similar populations had widely different effect estimates (unexplained heterogeneity/ variability in the results)	0 Most included studies reported associations between prenatal pyrethroid exposure and adverse neurodevelopment, with strongest consistency for studies investigating neurobehavioral outcomes	0 Consistent adverse associations between postnatal pyrethroid exposure and neurodevelopment. The associations were statistically significant in 80% of the studies.
Imprecision	Rate down if most studies had small sample sizes leading to wide confidence intervals (95% CIs)	0 We judged that the width of the CIs of the association estimates was sufficiently narrow given the sample size of the individual studies.	0 We judged that the width of the CIs of the association estimates was sufficiently narrow given the sample size of the individual studies.
Publication bias	Rate down if an over- or underestimation of the true exposure effects is suspected because unpublished studies are missing	0 Publication bias cannot be excluded but some included studies showed null findings or results that indicated beneficial associations between pyrethroids and neurodevelopment. Any larger well-designed study would be expected to be published.	0 The possibility of publication bias cannot be eliminated but we did not find the evidence strong enough to warrant downgrading.
Upgrading factors	**Summary of criteria for upgrading**		
Large magnitude of effects	Rate up if large effect estimates (e.g., relative risk >2) that cannot be explained by confounding alone	0 The effect estimates were generally small to moderate	0 The effect estimates were generally small to moderate
Dose-Response	Rate up if consistent dose-response gradients within one or multiple studies and/or across studies	0 A dose-response gradient for neurodevelopmental outcomes was reported in several studies but dose-response relationship across the studies could not be evaluated due to the heterogeneity in reporting of effect estimates	0 Dose-response relationship was seen within some well-conducted studies but dose-response relationship across the studies could not be evaluated due to the heterogeneity in reporting of effect estimates
Confounding minimizes the effect	Rate up if consideration of all plausible residual confounding or biases would underestimate the effect	0 Some biases related to exposure assessment (lack of conjugation step) or confounding (e.g., no adjustment for child age at examination or adjustment for potential mediators) might have underestimated the effect in some studies, but we did not find the evidence strong enough to upgrade the overall body of evidence	0 Some biases related to exposure assessment (lack of conjugation step) or confounding (e.g., no adjustment for child age at examination) might have underestimated the effect in some studies, but we did not find the evidence strong enough to upgrade the overall body of evidence
Overall quality of evidence	(Initial rating was not changed)	Moderate	Low (cross-sectional studies)
Overall strength of evidence		Sufficient. Moderate quality of evidence cross studies, a relationship between prenatal pyrethroid exposure and adverse neurodevelopment was observed. The association was consistent for neurobehavioral outcomes. Evidence for decrement in cognitive function with increasing pyrethroid exposure was also observed in most studies. The available evidence included results from several well-designed, well-conducted studies. We assess that chance, bias, and confounding could be ruled out with reasonable confidence, and find it unlikely that the conclusion will be strongly affected by the results of future studies.	Limited This rating was based on the low quality of evidence across studies because of the cross-sectional study design of all included studies combined with consistent adverse associations between childhood exposure to pyrethroids and neurodevelopment, and reasonable confidence in the association from several well-conducted studies.

[a] Ratings of quality and strengths of evidence were performed according to the Navigation Guide methodology. Criteria and definitions are described in Johnson et al. (2014). Possible ratings: 0 (no change from initial quality rating), −1 (one level downgrade), −2 (two level downgrade), +1 (one level upgrade), +2 (two level upgrade).

et al., 2020; Hisada et al., 2017) considered to be the most important potential confounders. Some of the studies included covariates that might be on the causal pathway between exposure and outcome, e.g., birth weight and gestational age (Fluegge et al., 2016; Hisada et al., 2017; Horton et al., 2011) and adjusting for such mediating variables might have weakened the association. Two studies from the French PELAGIE cohort (Viel et al., 2015, 2017) adjusted for child's own urinary pyrethroid metabolite concentrations at examination. Since this exposure occurs after the exposure of interest it cannot confound the association and if child and maternal concentrations were correlated

such adjustment would diminish the association. In one study, the statistical methods were inadequately described including the selection of covariates (Xue et al., 2013). Many of the studies did not control for the exact age of the child at the examination (Barkoski et al., 2021; Furlong et al., 2017; Guo et al., 2020; Horton et al., 2011; Tanner et al., 2020; Viel et al., 2015, 2017; Watkins et al., 2016; Xue et al., 2013). Depending on the age span in the individual studies, this might have caused larger variation in the outcome measurement leading to broader confidence intervals and reduced ability to obtain statistically significant associations. Overall, we agreed that these limitations within some studies were not strong enough to downgrade the overall risk of bias across the studies (Table 3). All the included studies measured neurodevelopment in human populations and were relevant to the study question outlined in the PECO statement. Therefore, downgrading for indirectness was not considered relevant. Most (71%) of the studies found significant associations between prenatal pyrethroid exposure and adverse neurodevelopment. Among six studies using specific measures of neurobehavioral outcomes, five showed significant association with worse behavioural scores (Dalsager et al., 2019; Furlong et al., 2017; Viel et al., 2017) or increased risk of ASD diagnosis (Shelton et al., 2014; von Ehrenstein et al., 2019). The last study (Barkoski et al., 2021) found a modest but non-significant association with higher ASD risk based on a rather small sample size (n = 201). The picture was less consistent for measures of cognitive function and overall mental development where 7 out of 12 studies found significant adverse associations (Eskenazi et al., 2018; Fluegge et al., 2016; Gunier et al., 2017; Horton et al., 2011; Tanner et al., 2020; Watkins et al., 2016; Xue et al., 2013) while 5 studies did not (Andersen et al., 2021; Barkoski et al., 2021; Guo et al., 2020; Hisada et al., 2017; Viel et al., 2015). Most of these studies (8 out of 12) assessed children below 4 years of age among whom the ability to detect subtle effects on cognitive function might be limited although effects might manifest later in childhood after cascading developmental processes (Rice and Barone, 2000) and better possibility for examination of complex cognitive functions e.g., by using IQ-tests. The last four studies assessed cognitive function using the WISC-IQ test among 6–7 years old children (Gunier et al., 2017; Guo et al., 2020; Tanner et al., 2020; Viel et al., 2015). The results seem diverging but were not directly comparable because one study did not present FIQ scores specific for pyrethroid exposure (Tanner et al., 2020), one did not use HBM but an indirect exposure estimate (Gunier et al., 2017) and the study by Viel et al. (2015) did not report FIQ scores but only subscale scores and the 3-PBA concentration was likely underestimated as explained above. We judged that the number of studies using the same assessments tool at the same age and reporting similar outcome measures for cognitive function was small and did not provide enough evidence to downgrade for inconsistency. The sample sizes varied between 118 and 948 in the prospective cohort studies and 10 out of 14 included more than 200 mother-child pairs. In general, the 95%CIs were sufficiently narrow given the sample size in the individual studies and downgrading for impression was not warranted. We cannot exclude the possibility of publication bias but some of the included studies showed null findings, and we would expect that any well-designed larger study within this topic would be published despite null findings. Thus, downgrading for publication bias was not warranted. Regarding criteria that could upgrade the quality of evidence across the studies, the effect estimates of adverse associations were generally small. Although a dose-response gradient for neurodevelopmental outcomes was reported in well-designed studies (Dalsager et al., 2019; Eskenazi et al., 2018) dose-response relationship across the studies could not be evaluated due to the heterogeneity in reporting of effect estimates. Biases related to exposure assessment or confounding within some of the studies might have underestimated the effect, but we did not find the evidence strong enough to upgrade the overall body of evidence. Thus, the initial moderate quality rating across the studies was not changed (Table 3).

Overall, we concluded that the strength of evidence for an association between prenatal pyrethroid exposure and adverse neurodevelopment was sufficient. This rating was based on an overall moderate quality of evidence across the studies, consistent adverse associations between pyrethroid exposure and neurobehavioral outcomes including evidence from large, well-conducted studies, and some evidence for decrement in cognitive function with increasing prenatal pyrethroid exposure although not consistent over all studies. We assess the confidence to be reasonable and find it unlikely that the conclusion will be strongly affected by the results of future studies.

3.1.2. Postnatal pyrethroid exposure and neurodevelopment

Ten studies investigated neurodevelopment in relation to pyrethroid exposure during childhood. All these studies were cross-sectional and nine assessed pyrethroid exposure by analysing pyrethroid metabolites in child urine collected when the child was examined (Table 2). One of the studies had an ecological cross-sectional design using zip codes for areas with yearly aerial pyrethroid applications (Hicks et al., 2017). One study used parent-response to two interview questions included in the National Health and Nutrition Examination Survey NHANES as outcome variables for Learning Disability (LD) and ADHD (Quiros-Alcala et al., 2014). The remaining studies assessed neurodevelopmental outcomes using validated assessment tools or caretaker/parent-reported assessment questionnaires.

Eight of the ten studies showed significant associations between childhood pyrethroid exposure and adverse neurodevelopment (Table 2). A study from the US, based on 8–15 years old participants in the NHANES (2001–2002), found 3-PBA above the LOD (0.1 μg/L) to be associated with higher odds (adjusted OR 2.42 (1.06, 5.57)) for meeting ADHD-diagnosis criteria. Hyperactive-impulse symptoms increased by 50% per 10-fold increase in 3-PBA (median 0.29 μg/L). The associations were stronger in boys than in girls (Wagner-Schuman et al., 2015).This finding was supported by a study from Korea, in which a high urinary 3-PBA concentration above 3.80 μg/g creatinine was associated with a 58% increase in ADHD scores among 4 years old boys compared to those with 3-PBA below 0.5 μg/g creatinine while no association was seen among girls (Lee et al., 2020). A study from Canada found *cis*-DCCA, but not 3-PBA, to be associated with high scores for total difficulties at the SDQ-scale (adjusted OR 2.0 (1.1, 3.6) for a 10-fold increase) among 6–11 years old children with the strongest association among girls (Oulhote and Bouchard, 2013). A study from the French PELAGIE-cohort reported higher SDQ subscale scores for externalising difficulties associated with child 3-PBA concentrations at age 6 years (cox p value of 0.04) and higher odds for abnormal or borderline social behavior for the intermediate and highest 3-PBA categories (adjusted OR 2.93 (1.27, 6.78) and OR 1.91 (0.80, 4.57), respectively) compared to those below the LOD (Viel et al., 2017). Another study from the same cohort found 3-PBA and *cis*-DBCA to be associated with lower WISC-scores for verbal comprehension (p-trend across three exposure categories: 0.04 and 0.01, respectively) and working memory (p-trend: = 0.05 and 0.01, respectively) (Viel et al., 2015). The child 3-PBA concentrations reported in these two last-mentioned studies were low (median 0.02 μg/L) and likely underestimated because no deconjugation step was applied (as discussed above). These two studies did also investigate maternal exposure in pregnancy and were therefore included in Table 1 as prospective cohort studies for prenatal exposure. Interestingly, maternal pyrethroid metabolite concentrations were not related to impaired neurodevelopment, except for *cis*-DCCA being marginally associated with internalizing difficulties (Viel et al., 2017). This finding may indicate higher risk associated with pyrethroid exposure in childhood, which is biological plausible, since the children are exposed directly to the neurotoxic parent pyrethroids.

A study among 140 children aged 6–9 years living close to banana plantations and plantain farms in Costa Rica found 3-PBA (median 0.8 μg/L) to be associated with poorer WISC scores for processing speed (adjusted ß: 5.3 (−10.3, −2.0) for a 10-fold increase), especially among girls, while no significant associations were seen for other cognitive function subscales or behavioural problems (van Wendel de Joode et al.,

2016). A study from China among 406 children aged 3–6 years, reported lower scores in the Cancellation test to be associated with 3-PBA (adjusted ß: 3.96 (−7.06, −0.86) for a 10-fold increase) indicating decrement related to attention, concentration, and comprehension. Besides, lower scores in the Binet language test (adjusted ß −3.47 (−5.82, −1.12)) and the WISC arithmetic test (−1.09 (−1.78, −0.41)) were seen for children with 3-PBA above LOD compared to those below (Wang et al., 2016). The 3-PBA concentrations reported in this study were low (median 0.02 μg/g creatinine) and since no deconjugation step was mentioned in the analytical methodology (Supplementary Table 2), we suspect an underestimation of 3-PBA like in the studies from the PELAGIE-cohort. Finally, an ecological study, without individual exposure assessment, found higher rates of ASD and developmental delay (DD) diagnosis among children from zip code areas with aerial pyrethroid applications compared to zip code areas without (adjusted RR 1.37 (1.06, 1.78) using information from the New York State Department of Environmental Conservation Database with quality assured data linking zip codes to pesticide use by commercial applicators (Hicks et al., 2017).

Only two of the included studies on postnatal pyrethroid exposure did not find significant associations with neurodevelopmental outcomes (Table 2). One of these studies was very small (53 children) (Fiedler et al., 2015) with several methodical limitations (Fig. 1). The other study was based on NHANES, and used parental report of LD and ADHD (yes/no) based on evaluation by a school representative or health professional as outcome among 6–15 years old children (Quiros-Alcala et al., 2014). Thus, "milder" symptoms not reported by teachers or health professionals were not included. Although the study did not find significantly increased risk for LD or ADHD, almost all odd ratios (ORs) were above one.

Regarding the quality across the studies, we decided beforehand to assign an initial rating of "low" because of the cross-sectional study design. We did not find reason to downgrade this rating further (Table 3). The risk of bias across the studies was low to moderate although the risk of bias was assessed to be "high" for some domains for a few studies, and one study had a very small sample size (Table 2 and Fig. 1). All the included studies investigated neurodevelopment in human populations and were relevant to the study question outlined in the PECO statement. Most (80%) of the studies found significant associations between childhood pyrethroid exposure and adverse neurodevelopment (Table 2). The possibility of publication bias cannot be eliminated but we did not find the evidence strong enough to warrant downgrading. The effect estimates of adverse associations between child pyrethroid exposure and neurodevelopment were generally small to moderate. Dose-response relationship was seen within larger well-conducted studies (Oulhote and Bouchard, 2013; Wagner-Schuman et al., 2015), but, like for the prenatal exposure studies, the lack of standardized analytical methods for the urinary metabolites combined with the variety in outcome measurements, and age of the children at examination hampered the assessment of exposure-response relationships across the studies. Thus, we judged that upgrading the quality of evidence across the studies was not justified and the quality of the overall body of evidence was kept as "low". Combined with a consistent direction of the effect in the included studies, and confidence in the effect from several well-conducted studies, we assessed the overall strength of evidence to be limited for an association between childhood pyrethroid exposure and impaired neurodevelopment.

3.2. Mechanistic evidence

The KEs suggested in the existing AOPs for DNT were related to three overall modes of action: 1) disturbance of thyroid hormone function, 2) altered levels of BDNF, and 3) neuroinflammation.

3.2.1. Disturbance of thyroid hormone function

THs are essential for normal brain development and influence neurogenesis, neuronal migration, neuronal and glial cell differentiation, myelination, and synaptogenesis. These TH-dependent processes are crucial for both pre- and postnatal brain development. During the first 10–12 weeks of gestation, the foetus relies entirely on maternal TH and maternal TH deficiency adversely affects offspring neurodevelopment (Mughal et al., 2018; Zoeller and Crofton, 2005).

Reduced TH synthesis (KE 277), decreased T4 in serum (KE 281), and decreased T4 in neuronal tissue (KE 280) are shared KEs by AOPs 42 and 54. The overall concept of AOPs assumes that the essential step in triggering the chain of events is the Molecular Initiating Event (MIE). Some literature discussed below and data from US EPA ToxCast support the hypothesis that pyrethroids might directly inhibit the Na+/I- symporter (NIS) which is a MIE for AOP54. Five out of eight tested pyrethroids (allethrin, cyfluthrin, cypermethrin, prallethrin and tetramethrin) inhibited NIS ("NIS_RAIU_inhibition" assay from ToxCast) with 50% active concentrations (AC50) ranging 10.9–44.1 μM. Inactive in the ToxCast assay were fenpropathrin, resmethrin and tefluthrin. The ToxCast results partially correspond to the findings reported by Hallinger et al. (2017) who showed that cypermethrin and deltamethrin were among weak to moderate RAIU inhibitors while permethrin was inactive. A follow-up study by Dong et al. (2019) showed that the effects might be cell specific as deltamethrin had variable effects in different cell lines. Some pyrethroids were also found to inhibit thyroperoxidase (TPO), which is the MIE for AOP 42. All three pyrethroids that were tested for TPO inhibition in ToxCast (allethrin, prallethrin and resmethrin) were active in a specific assay (NCCT_TPO_AUR_dn) with AC50 ranging 40–54 μM.

Besides affecting TH biosynthesis by inhibiting NIS or TPO, TH function can be disturbed in several other ways, including interference with TH receptors and transport proteins (Hernández et al., 2020). Pyrethroids have a structural resemblance to THs and a number of pyrethroids (cycloprothrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, etofenprox, fenvalerate, permethrin, and tetramethrin) and their common metabolite, 3-PBA, were reported to show antagonistic effects *in vitro* using a TH receptor mediated reporter gene assay (Du et al., 2010). Accordingly, cypermethrin and tau-fluvalinate were reported to antagonize T3-induced proliferation in a rat pituitary tumor cell line, GH3 (Ghisari et al., 2015). An AOP suggesting TR antagonism as MIE for adverse neurodevelopment is currently under development (https://aopwiki.org/aops/300).

The transport protein transthyretin (TTR) is synthesized in the liver and the choroid plexus in the brain and carries T4 in serum and cerebrospinal fluid. TRR is essential for the function of THs including the transport into the developing brain (Richardson et al., 2015b). Interaction of permethrin with TTR was investigated in a model using embryonic zebrafish. In that study, permethrin was found to interact with the binding pocket at TTR and to increase the gene expression of TSH, deiodinases, TH receptors and the concentrations of T4 and T3 (Tu et al., 2016a). Binding to TTR is an important molecular initiating event for TH disruptive effects for several environmental chemicals (Ouyang et al., 2017; Weiss et al., 2015). Among the pyrethroids, only permethrin has, to our knowledge, been investigated as described above. Thus, more studies are needed to clarify if pyrethroid exposure in pregnancy can disturb the transport of THs from the maternal circulation to the foetal brain by binding to TTR. An AOP with TTR interference as MIE for adverse neurodevelopment is under development (https://aopwiki.org/aops/152).

In adolescent mice, an oral dose of deltamethrin of 6 mg/kg bw for 28 days caused an increase in TSH, and a decrease in thyrotropin releasing hormone (TRH), T3 and T4. Further, mRNA levels of hypothalamic–pituitary–thyroid (HPT) axis-related genes were affected (Zhang et al., 2020) as previously seen for permethrin (Tu et al., 2016a) bifenthrin and λ-cyhalothrin (Tu et al., 2016b) in a zebrafish embryo model. Besides, a study in adult mice have shown that fenvalerate, at rather high doses (40, 80, and 120 mg/kg bw), inhibited the hepatic activity of 5′-monodeiodinase, resulting in reduced concentrations of T4

in serum (Maiti et al., 1995).

3.2.2. Altered levels of BDNF

BDNF belongs to the neurotrophin family of growth factors and is widely expressed in the developing and mature central nervous system (CNS). BDNF plays an important role in pre- and postnatal brain development by supporting survival of existing neurons and promoting growth and differentiation of new neurons and synapses (Binder and Scharfman, 2004; Park and Poo, 2013). At both pre- and postsynaptic sites, BDNF facilitates the release of neurotransmitters, and promotes the function of ion-transmitters and N-methyl-D-aspartate receptors (NMDARs) (Saghazadeh and Rezaei, 2017). Overall, BDNF seems to strengthen excitatory (glutamatergic) synapses and weaken inhibitory (GABAergic) synapses (Binder and Scharfman, 2004).

Reduced CNS level of BDNF (KE 381) is a common KE for AOP 13 and 54. In AOP 54, reduced BDNF is a mediator of TH-dependent brain development. As described above some pyrethroids were identified in ToxCast as NIS inhibitors (MIE for AOP 54). Regarding AOP13, where MIE is chronic binding to NMDARs, we did not find any evidence in ToxCast. However, ToxCast contains only data for an agonist assay (NVS_LGIC_rGluNMDA_Agonist) and the only pyrethroid tested – cypermethrin – was inactive.

In rats, exposure to deltamethrin (oral, 9 mg/kg bw/day) during pregnancy, caused impaired cognitive abilities and decreased expression levels of NMDAR subunits (GluN1, GluN2A, GluN2B) and BDNF in the hippocampus of offspring, while no effects were seen at lower dose-levels (0.05–2.7 mg/kg bw) (Zhang et al., 2018). In AOP 13, inhibition of NMDAR is followed by reduced calcium influx (KE 52) leading to reduced BDNF level. Accordingly, *cis*- and *trans*-permethrin, caused reduction of BDNF mRNA expression in parallel with reduced calcium influx in mouse cerebellar granule cells (Imamura et al., 2000) and an inhibitory effect on calcium influx was also reported for allethrin by Hildebrand et al. (2004). By contrast, deltamethrin was found to trigger a prolonged increase in intracellular calcium concentrations and to elevate BDNF expression in primary cultures of adult rat cortical neurons (Ihara et al., 2017). Similar findings were reported in another study in which deltamethrin induced higher BDNF mRNA expression in rat cortical cells *in vitro* and in cerebral cortex and hippocampus in adult rat brains *in vivo* (Imamura et al., 2006). In accordance with this, nine structurally diverse pyrethroids (tefluthrin, deltamethrin, lambda-cyhalothrin, beta-cyfluthrin, esfenvalerate, S-bioallethrin, fenpropathrin, cypermethrin, and bifenthrin) were reported to evoke elevated Ca^{2+} influx in primary cultures of mouse neocortical neurons in a concentration-dependent manner (Cao et al., 2011). The elevation in calcium influx was blocked by the VGSC blocker tetrodotoxin for all nine pyrethroids, indicating that the effects depended on VGSC activation. In mice, oral deltamethrin exposure of 3 mg/kg bw every three days throughout gestation and lactation caused lower expression of VGSCs mRNA in the striatum and frontal cortex of the offspring at 10–11 months of age. The reduction in VGSC expression was followed by down-regulation of BDNF in the striatum by 66%, but not in the cortex (Magby and Richardson, 2017). Further, low doses of cypermethrin or deltamethrin to mice during gestation caused a reduction in neuronal proliferation, cell maturation and differentiation, and increased apoptosis in the cerebral cortex of offspring when measured at the end of embryonic development (Guo et al., 2018), but BDNF was not measured in that study.

3.2.3. Neuroinflammation

Neuroinflammation is characterised by activation of microglia and astrocytes. Both cell types are CNS-resident glial cells that have important roles in neurogenesis, gliogenesis, angiogenesis, axonal outgrowth, synaptogenesis, synaptic pruning, and receptor expression (Pierre et al., 2017; Reemst et al., 2016). Depending on the context and stimuli, microglia and astrocytes adopt a broad spectrum of activation types from pro-inflammatory, associated with neurotoxicity, to anti-inflammatory linked to neuroprotection, and in response to neuronal injury or toxic stimuli, they can become mediators of neurodegenerative processes (Pierre et al., 2017; Wheeler et al., 2019). Thus, neuroinflammation is a key event (KE 188) for development of neurodegenerative disease related to neurotoxicants (cf. AOP 3, AOP 12 and AOP 48). Besides, pro-inflammatory activation during brain development may contribute to cognitive dysfunction and neurobehavioral disorders such as ADHD and ASD (Dunn et al., 2019; Petrelli et al., 2016). Accordingly, neuroinflammation (KE 188) is also a key event for impaired neurodevelopment in AOP 17.

Microglia express several ion channels, including VGSC. Deltamethrin and permethrin (1–5 μM) caused a rapid Na^+ influx and increased accumulation of intracellular Na^+ and an increased release of the pro-inflammatory cytokine TNF-α in microglia (isolated from 1-2-day old mice) in a dose- and time-dependent manner. The effect was significantly reduced by tetrodotoxin (Hossain et al., 2017). Further, several pyrethroids (permethrin, deltamethrin, allethrin, and bifenthrin) were shown to induce production of inflammatory mediators and markers of oxidative stress in primary microglia cells (Gargouri et al., 2018). Higher concentrations of oxidative and inflammatory markers were also seen in the frontal cortex and striatum of adult rats exposed to bifenthrin (oral, 0.6 and 2.2 mg/kg bw for 60 days) in association with enhanced anxiety-like behaviour (Gargouri et al., 2018).

3.2.4. Biological plausibility

As reviewed above, there is evidence that pyrethroids can interfere with neurodevelopmental key events included in established AOPs for adverse neurodevelopmental health outcomes. The strongest evidence was seen for interference with TH function, but more studies are warranted, especially for binding to TTR, so far only investigated for permethrin. Regarding alterations of BDNF levels, the findings suggest that pyrethroids have the potential to interfere with BDNF expression probably by interference with calcium channels. However, only two pyrethroids (deltamethrin and permethrin) have been investigated for effects on BDNF levels and only one (cypermethrin) has been tested for binding to NMDARs in ToxCast. Mechanistic studies on pyrethroids and neuroinflammation are scarce but indicate a direct pro-inflammatory activation of microglia via VGSCs, the primary target of pyrethroids.

Our understanding of brain development is still limited and many other molecular targets and cellular events than those captured in the established AOPs might be involved. Thus, a range of mechanisms related to DNT effects of pyrethroids in experimental studies have been presented in recent reviews (Abreu-Villaca and Levin, 2017; Pitzer et al., 2021; Soderlund, 2020). The principal target for pyrethroids is binding to VGSCs causing slower opening and closing but they also binds to voltage gated calcium channels (VGCCs), chloride channels (VGClCs), and the lambda-aminobutyric acid (GABA) receptor-chloride ionophore (Soderlund, 2020). While the effects of pyrethroids on these channels are documented in adult rat and mouse brain (Soderlund, 2020), their effects during development are not yet known (Pitzer et al., 2021), but might mediate neuroinflammation and alterations in BDNF-levels as described above. Another common effect reported from several experimental studies is altered dopamine dynamics and dopamine transporter (DAT) expression related to pyrethroid exposure during neurodevelopment (Abreu-Villaca and Levin, 2017; Pitzer et al., 2021). These effects may be particularly important to understand a potential link between pyrethroid exposure and ADHD development, since ADHD pathophysiology is suggested to be related to disturbance of dopaminergic and noradrenergic neurotransmission (Russell, 2011; Thapar and Cooper, 2016).

Overall, we find the mechanistic evidence for pyrethroids to be developmental neurotoxicants sufficient to conclude that impaired neurodevelopment related to pyrethroid exposure during brain development is biological plausible.

4. Discussion

This review found sufficient evidence for an association between pyrethroid exposure during pregnancy and adverse neurodevelopment. All studies addressing neurobehavioral outcomes reported worse scores or higher risk of ASD diagnosis with increasing pyrethroid exposure. Diminished cognitive function was also associated with increased pyrethroid exposure but not consistently over all studies. The evidence for an adverse effect of pyrethroid exposure during childhood was limited because of the cross-sectional design of the included studies. However, the majority of studies strongly suggested an adverse effect on neurodevelopment, even though reverse causation cannot be ruled out. Combined with biological plausibility based on the mechanistic evidence, we conclude that pyrethroids are probably human developmental neurotoxicants.

To our knowledge, no previous reviews have systematically evaluated the overall quality and strength of evidence for adverse impacts on child neurodevelopment related to both prenatal and postnatal exposure to pyrethroids. A challenge to this review was that the included epidemiological studies used a variety of different assessment methods, evaluated the health outcome in different age groups of children, and reported the association estimates on different scales and/or based on different exposure categories. This fact made it difficult to compare the results directly and a meta-analysis was not feasible. The potential underestimation of 3-PBA in some studies, further hampered the possibility to assess exposure-response relationships across the studies. Furthermore, differences in main exposure routes between the studies may affect the results because maternal hepatic first-pass metabolism is avoided after inhalation and dermal exposures causing potential higher foetal exposure to the parent compounds. However, dose-response relationship was seen both within studies reporting high 3-PBA concentrations after high residential use (Eskenazi et al., 2018) and studies in the lower range of 3-PBA with mainly dietary exposure (Dalsager et al., 2019). Another limitation was that all the included studies on postnatal exposure were cross-sectional without possibility to assess the temporal relationship between exposure and neurodevelopment. Although we find a reverse causation rather unlikely, we cannot exclude that e.g., children with behavioural problems are more active and e.g., eat more food with pesticide residues.

Further, the epidemiological evidence assessed is this review was mainly based on associations between urinary concentrations of 3-PBA and neurodevelopmental outcomes. Most of the studies used single spot urine samples and, due to within-subject variability, some exposure misclassification is likely. This misclassification will most often be non-differential (i.e., independent of the health outcome) and tend to bias the findings toward the null and thereby reduce the possibility to detect a true association with the outcome. Because 3-PBA is a common metabolite of most pyrethroids, it is not possible to pinpoint specific ones, but some associations were also seen for *cis*- and *trans*-DCCA suggesting that exposure to permethrin and cypermethrin contributed to the effects. Anyway, 3-PBA represents real-life exposure to multiple pyrethroids and associations with adverse neurodevelopment illustrate the need for taking mixture effects into account in risk assessment.

We assessed the link between pyrethroids and DNT to be biological plausible, but the exact mechanisms are not yet fully understood. One approach would be to focus further investigations on effect biomarkers related to AOPs for DNT. It would also be highly relevant to develop specific AOPs for neurobehavioral disorders like ADHD and ASD, associated with pyrethroid exposure in both epidemiological and rodent studies. In addition, most of the mechanistic evidence comes from studies on rather few pyrethroids, especially deltamethrin, permethrin, and cypermethrin. Although these are among the most widely used, more studies on others would be relevant to elucidate potential differences.

To further strengthen the evidence for a causal association in humans, more longitudinal HBM studies on pre- and especially postnatal pyrethroid exposure in large populations based on quality-assured analytical methods, preferably repeated urinary samples, and validated test methods of neurodevelopmental outcomes are strongly encouraged. Specifically for cognitive effects related to prenatal exposure, more studies among children above 4 years of age are needed to increase the confidence. For childhood exposure, longitudinal studies with exposure assessment during the first 1–2 years of life would be highly relevant. All the available studies on childhood exposure were performed among children aged 3 years or older implying that the most vulnerable exposure windows during early postnatal brain development was not included and therefore exposure related effects might be underestimated. Another research gap is the potential sex-specific vulnerability. Some of the included studies found stronger associations in males than females (Lee et al., 2020; Tanner et al., 2020; Wagner-Schuman et al., 2015) as also seen in some experimental studies (Laugeray et al., 2017; Pitzer et al., 2019; Richardson et al., 2015a). However, other included studies reported females to be more affected (van Wendel de Joode et al., 2016; Viel et al., 2017; Watkins et al., 2016) but most studies did not investigate sex-exposure interaction in the statistical analyses.

The topic for this review is of large public importance, as an increasing number of children experience mental problems affecting their daily life with large societal, personal, and economic implications. Exposure to neurotoxic and endocrine disrupting chemicals at vulnerable time windows during pregnancy and childhood are suggested to contribute to the rise in neurobehavioral and cognitive deficits (Grandjean and Landrigan, 2014). Within HBM4EU, pyrethroids were prioritised as a substance group of high concern by the EU authorities and partner countries, because of rising exposure levels and limited knowledge on potential long-term health impacts. Currently, the Acceptable Daily Intake (ADI) values for individual pyrethroids in the EU are often established based on neurotoxicity in adult experimental animals (https://ec.europa.eu/food/plants/pesticides/eu-pesticides-database_en) without taking DNT into account. Based on the findings in this review, we suggest including DNT in future risk assessment of pyrethroids and also to take mixture effects of pyrethroids into consideration.

5. Conclusion

Based on this review, we conclude that pyrethroids are probably developmental neurotoxicants and adverse impacts of pyrethroid exposure on neurodevelopment are likely at exposure levels occurring in the general population. Therefore, implementation of preventive measures to protect vulnerable population groups such as pregnant women and children are warrated.

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Declaration of competing interest

The authors declare the following financial interests/personal

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Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113935.

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