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A systematic review of human biomonitoring studies of 3-phenoxybenzoic acid, a urinary biomarker pyrethroid insecticide exposure, 1997 to 2019

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Abstract

Pyrethroid insecticides are used, for example, in agriculture, indoor environments, and mosquito control programs, resulting in human exposure. Urinary 3-phenoxybenzoic acid (3-PBA) is a nonspecific biomarker for exposure to many pyrethroids. This systematic review identified human biomonitoring studies with 3-PBA that characterize environmental pyrethroid exposures in children and adolescents, pregnant women, and adults or occupational pyrethroid exposures relative to the National Health and Nutrition Examination Survey (NHANES) populations in the United States (US). PubMed, Embase, and SciFinder were searched for “3-phenoxybenzoic acid ”, CAS No. 3739–38–6, and urine or urinary or urine level. Duplicate studies and studies meeting the exclusion criteria were removed from the search results based on predetermined exclusion criteria. This screening process identified 57 papers. Twenty-one, thirteen, twenty-two, and eleven manuscripts reported urinary 3-PBA levels in children, pregnant women, environmentally exposed adults, and occupationally exposed adults, respectively. Median 3-PBA levels ranged from 0.2 to 4.7 μg/g creatinine in children (1999–2016), 0.23–1.55 μg/g creatinine in pregnant women (1997–2014), and 0.11–3.34 μg/g creatinine in environmentally exposed adults (1999–2017). 3-PBA levels in occupationally exposed adults were significantly higher than in environmentally exposed populations, ranging from 0.43 to 14 μg/g creatinine (2004–2017). 3-PBA levels in children and adults from the general North American population increased significantly with the sampling year.

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A decrease in 3-PBA levels was noted in the adult cohorts from PR China and Japan. 3-PBA levels in most studies appeared to be comparable to levels in the NHANES populations; however, some smaller studies had high pyrethroid exposures. Factors contributing to higher 3-PBA levels in the general population included primarily dietary exposures and residential and agricultural pyrethroid applications. These findings demonstrate that pyrethroid exposures are near-ubiquitous worldwide and, in some regions, appear to increase over time. Thus, exposures to pyrethroid insecticides represent a continuing public health concern.

Keywords

Biological monitoring; Data extraction; Environmental exposure; Human exposure; Occupational exposure; Population research

1. Introduction

Pyrethroids are widely used synthetic insecticides. Their chemical structure is based on pyrethrins isolated from the *Chrysanthemum cineraria folium* flower (Casida and Quistad, 1995). Because pyrethrins are unstable under UV light, chemical modifications were used to develop synthetic pyrethroid, structurally related insecticides with increased stability against UV light. Approximately 40 synthetic pyrethroids are available, with around a dozen pyrethroids on the market. Permethrin is the most widely used pyrethroid (ATSDR, 2003; Spurlock and Lee, 2008). They are used in numerous applications, such as insecticides for agricultural and indoor environments, arthropod repellants in clothing and fabrics, and mosquito control programs. Pyrethroids often replace restricted or banned organophosphate insecticides for their agricultural use. Because of their high insecticidal potency, low environmental persistence, and relatively low mammalian toxicity, pyrethroids account for a significant portion of the global insecticide market (Spurlock and Lee, 2008).

Humans can be exposed to pyrethroids by inhalation, ingestion, and dermal contact. For the general population, ingesting pyrethroids via contaminated food is a principal exposure route. Inhalation and dermal exposure are minor exposure routes for the general population but can be significant routes of exposure for workers in agricultural and other occupational settings. In addition, breast milk can be a source of pyrethroids for infants in areas where pyrethroids have domestic, agricultural, and public health applications (e.g., malaria control programs) (Weldon et al., 2011). Pyrethroids have also been detected at low levels (pg/ml) in the umbilical cords of newborns (Neta et al., 2010). They are rapidly metabolized in humans, and their metabolites are eliminated with urine. In epidemiological studies, these urinary metabolites are frequently used biomarkers of pyrethroid exposure and provide integrated exposure measurements from all sources and routes (Koureas et al., 2012). 3-PBA is commonly used as a nonspecific biomarker for exposure to many pyrethroids, for example, cyhalothrin, cypermethrin, deltamethrin, esfenvalerate, and permethrin, in human biomonitoring studies (Barr, 2008; Schettgen et al., 2016). 3-PBA is also an environmental transformation product that can, for example, be present in residential environments (Starr et al., 2008; Trunnelle et al., 2014b).

Evidence indicates that pyrethroid exposures are near-ubiquitous worldwide, as indicated by human biomonitoring studies using urinary 3-PBA levels. For example, data from NHANES, a survey assessing the health and nutritional status of the general US population, demonstrate that environmental pyrethroid exposure is widespread in US adults and children (Bao et al., 2020; Barr et al., 2010; Lehmler et al., 2020). These findings raise human health concerns. For example, several studies have reported a link between pyrethroid exposure and reduced birth length, weight, head circumference, and gestational weight; however, these findings are inconsistent across studies (Ding et al., 2015; Koureas et al., 2012; Saillenfait et al., 2015). In addition, there is evidence of adverse neuro-behavioral impacts in children following pyrethroid exposure (Horton et al., 2011; Oulhote and Bouchard, 2013; Shelton et al., 2014; van Wendel de Joode et al., 2016; Viel et al., 2015; Wagner-Schuman et al., 2015). Furthermore, pyrethroids appear to have adverse effects on the reproductive function of male children (Imai et al., 2014; Ji et al., 2011; Radwan et al., 2014; Ye et al., 2017a, 2017b) and metabolic and cardiovascular outcomes (Bao et al., 2020; Han et al., 2017; Park et al., 2019; Xue et al., 2021). The Agricultural Health Study, a large-scale prospective study of pesticide applicators in the United States, found no link between pyrethroid exposure and the incidence of different cancers (Rusiecki et al., 2009); however, a study from PR China suggested that urinary levels of pyrethroid metabolites may be associated with an elevated risk of childhood acute lymphocytic leukemia (Ding et al., 2012).

Because the available evidence implicates occupational and environmental exposure to pyrethroid insecticides in adverse health outcomes, the Population, Exposure, Comparator, and Outcomes (PECO) framework (Morgan et al., 2018) was adopted to review published human pyrethroid biomonitoring data. The objective was to determine to which extent human populations worldwide, including children and adolescents, pregnant women, and adults (Population), are exposed environmentally or occupationally to pyrethroid insecticides (Exposure), and how these exposures compare to the NHANES populations (Comparators), using urinary 3-PBA detection frequencies and levels as an outcome measure (Outcomes). In addition, factors associated with elevated pyrethroids exposures are summarized based on the studies identified by this systematic review.

2. Materials and methods

2.1. Search strategy

The systematic literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) best-practice guidelines and is summarized in Fig. 1 (Moher et al., 2009; Smith and Do, 2008). Briefly, three electronic databases (PubMed, Embase, and SciFinder) were systematically searched on January 4, 2019, using the following keywords: 3-phenoxybenzoic acid, urine or urinary or urine level, and CAS No. 3739–38–6 to identify human biomonitoring studies reporting urinary 3-PBA levels (for additional information, see the Supplementary Material). Next, the search results were transferred to an EndNote 20 library (Clarivate, Philadelphia, PA, USA), resulting in a library with 421 distinct references. In addition, one relevant study was identified external to the literature search and included in the subsequent screening and extraction process. Finally, duplicate references were removed, resulting in a library with 222 references.

2.2. Study selection and data extraction

At least two investigators screened the remaining references independently based on pre-established screening criteria and removed irrelevant studies from further consideration (Fig. 1). A third or fourth investigator acted as a tiebreaker. At this stage, studies excluded from further consideration included animal studies, *in vitro* studies, analytical method development studies, and studies reporting no 3-PBA urine analysis. This screening identified 158 potentially relevant studies that were further assessed for eligibility using the exclusion criteria in Fig. 1. After this exclusion step, a total of 57 peer-review manuscripts remained. Subsequently, data were extracted from these 57 papers with a pre-established data abstraction form in Microsoft Excel (see Supplementary Material), followed by a scoping review of factors affecting human pyrethroid exposure reported in these papers, particularly the time of exposure. In addition, 3-PBA data from the NHANES survey performed by the CDC and Health Canada were included in the data summary (Health Canada, 2019; CDC, 2021a, 2021b). The reviewer team classified the study populations as children and adolescents, pregnant women, environmentally exposed adults, and occupationally exposed adults to facilitate the presentation and interpretation of the data. Children (about < 6 years of age) and adolescents (about 11 to 18 years of age) were broadly grouped to match the age classification used by NHANES to the extent possible (i.e., < 6, 6 to 11, and > 11 years of age). 3-PBA detection frequencies and levels are presented in Tables 1 – 4 and discussed below. Within this broad classification, 3-BPA levels of the study populations differed strongly by factors such as gender, diet, age, or child developmental stage. The detection frequency data must be interpreted with caution because of the wide range of detection limits reported and the different analytical procedures used across studies. Moreover, because of the small sample size of most studies, the discussion focuses on the geometric mean (GM) and median 3-PBA levels.

2.3. Statistical analysis

A two-sample *t*-test was used to compare a $\log_{10}$-transformed measurement between populations with occupational or environmental exposures. A Linear Mixed-Effect Model was used to analyze trends in urinary 3-PBA levels with time (year of sample collection); see Table 5. All the statistical analyses were performed in RStudio (version 2021.09.2) with R (version 4.0.5), with $p < 0.05$ being considered significant.

3. Results and discussion

This systematic review identified 57 peer-reviewed studies, out of 422 references identified through the literature search, that meet the inclusion criteria. The following sections discuss the 3-PBA levels reported for these populations and describe the factors affecting urinary 3-PBA levels, as reported in these studies. When interpreting the data summarized below, it is important to keep several limitations in mind. Many studies included small sample sizes and may report exposure pathways that occur by chance. Moreover, study populations were likely selected for investigation because of a known or expected exposure to pyrethroid insecticides and do not reflect exposures of the general population. In addition, sampling year, sampling approach, regional differences, and analytical methods can influence the urinary 3-PBA levels summarized in Tables 1 to 4. Also, when investigated,

different approaches were employed to characterize dietary exposures. Overall, there are considerable uncertainties when analyzing differences in 3-PBA levels with time, location, and population.

3.1. Environmental pyrethroid exposures in children and adolescents

3.1.1. 3-PBA levels in environmentally exposed children and adolescents—

A total of 21 studies were identified that reported urinary 3-PBA levels in children and adolescents (i.e., populations ≤ 18 years) exposed environmentally to pyrethroid insecticides, with samples being collected between 1999 and 2016. When reported, detection frequencies in these studies ranged from 36% to 100% (Table 1).

Urinary 3-PBA levels from these studies and the NHANES 1999–2001 and 2007–2013 cycles are summarized in Table 1 and, where available, are shown in Fig. 2. Median urinary 3-PBA levels ranged from 0.18 ng/ml (N = 284, 2002–2006) in French children (Viel et al., 2015) to 1.5 ng/ml in children from Nicaragua (N = 77, 2008) (Rodriguez et al., 2012). For comparison, NHANES reported median 3-PBA levels ranging from 0.300 ng/ml (N = 580, 2001) to 0.810 ng/ml (N = 408, 2013) in children aged 6–11 and from 0.290 ng/ml (N = 682, 1999) to 0.617 ng/ml (N = 420, 2013) in adolescents aged 12–19.

Creatinine-adjusted median 3-PBA levels ranged from 0.2 μg/g creatinine (N = 406, 2014) in children from a Chinese cohort (Wang et al., 2016) to 4.7 μg/g creatinine (N = 22, 2008) in children from Nicaragua (Rodriguez et al., 2012). For comparison, NHANES reported creatinine adjusted median 3-PBA levels ranging from 0.371 μg/g creatinine (N = 483, 1999) to 1.000 μg/g creatinine (N = 398, 2011) in children aged 6–11 and from 0.205 μg/g creatinine (N = 682, 1999) to 0.523 μg/g creatinine (N = 386, 2011) in adolescents aged 12–19. Comparisons of these creatinine-adjusted data between age groups and adults are challenging because creatinine production depends on the age group (Barr et al., 2005). Because children and adolescents have a smaller lean muscle mass, their creatinine levels are lower than adults, resulting in elevated creatinine-adjusted levels of urinary biomarkers of exposure, such as 3-PBA, in children and adolescents vs. adults.

A significant increase in the GM of volume-adjusted 3-PBA levels was observed in children and adolescents both worldwide (p = 0.0184, N = 26 studies) and in North America (i.e., Canada and the United States, p = 0.0255, N = 20 studies) with time (year of sample collection) (Table 5). This finding is consistent with the analysis of NHANES 2007–2012 data (Lehmler et al., 2020). No significant time trends were observed for the median volume adjusted 3-PBA levels and median and creatinine adjusted 3-PBA levels. Based on the available agricultural uses data, the increase in GM 3-PBA levels in North America is not associated with increased agricultural uses of pyrethroids in the US and Canada. Because organophosphate insecticides (i.e., chlorpyrifos) were phased out for indoor and other uses by both countries in 2000 (Government of Canada, 2020; EPA, n.d.), the increase in pyrethroid exposure may reflect the increased use of pyrethroids for these applications.

3.1.2. Factors affecting pyrethroid exposure of children: residential use—

Several studies investigated how residential use of pyrethroid pesticides affected urinary 3-PBA levels in children. Analogous studies in adolescent populations have not been reported.

Studies from Canada and the US identified residential use of pyrethroids as an important factor contributing to increased 3-PBA residues in children. For example, in children from Canada (N = 85, 2005), the use of head lice treatments, which typically contain pyrethroids (Hansen, 2004), was one factor associated with a significant increase in urinary 3-PBA levels (Fortin et al., 2008). Similarly, studies of volunteers show that the application of pyrethroid-containing formulations increases the excretion of pyrethroid metabolites in the urine (Tomalik-Scharte et al., 2005). Moreover, Canadian children appeared to have a higher exposure to pyrethroids used to exterminate indoor and outdoor pests (and not in agriculture) than adults, as assessed using urinary levels of chrysanthemum dicarboxylic acid (CDCA), a metabolite of certain pyrethroid insecticides (Fortin et al., 2008).

Floor wipe samples analyzed as part of the Study of Use of Products and Exposure Related Behavior (SUPERB) in Northern California, USA, revealed a positive association between permethrin concentrations in floor wipes and urinary 3-PBA levels in children but not adults (N = 83, 2007–2009) (Trunnelle et al., 2014b). Urinary 3-PBA concentrations of children and adults from the same household in this and another study in California were positively correlated (Trunnelle et al., 2014a), suggesting similar environmental and dietary sources of pyrethroid pesticide exposure within families. In addition, poor housing conditions were positively associated with urinary 3-PBA residue levels in children in the Mexican Immigration to California: Agricultural Safety and Acculturation (MICASA) Study (N = 103, 2009), consistent with higher residential pesticide use under poor housing conditions (Trunnelle et al., 2014a). Other studies from the US also report a link between residential pesticide use and urinary 3-PBA levels (Lu et al., 2006; Naeher et al., 2010).

In a study from PR China, there was no significant association between indoor pesticide use and urinary 3-PBA levels in 9 to 16-year-old boys (N = 463, 2014–2015) from Hangzhou, Zhejiang (Ye et al., 2017a). In contrast, the 3-PBA levels in infants from Jiangsu Province, PR China, were positively associated with residential insecticide and mosquito repellant use, housing quality, ventilation (e.g., use of external exhausts or frequent opening of windows and doors), and an increased hand-to-mouth habit (N = 481, 2010–2011) (Wu et al., 2013). Similarly, urinary 3-PBA residues were positively associated with residential mosquito repellent incense but not insecticide aerosol use in a cohort of 3 to 6-year-old children from Nanjing, PR China (N = 406, 2014) (Wang et al., 2016). This finding suggests that the modality of indoor pesticide use plays a role in pyrethroid exposure in children.

In addition to residential pesticide use, take-home exposure can contribute to pyrethroid exposure in children. For example, occupational pesticide exposure of the parents was associated with higher urinary 3-PBA levels in children from South Australia (N = 340, 2003–2003) (Babina et al., 2012), consistent with US studies of factors increasing pesticide exposure in children (Castorina et al., 2010; Fenske et al., 2002). In contrast, high urinary 3-PBA levels in rural Nicaraguan children were not generally related to parental pesticide applications (N = 77, 2008) (Rodriguez et al., 2012).

3.1.3. Factors affecting pyrethroid exposure of children: diet—Pyrethroid pesticides can be present in foodstuff (Lu et al., 2010; Morgan et al., 2007), and diet is considered an important route of exposure of children to pyrethroid pesticides (Morgan et

al., 2007). Studies investigating how diet influences 3-PBA levels in adolescents were not identified as part of this systematic review. Several US studies have reported dietary factors associated with increased urinary 3-PBA levels. For example, consuming some food items (i.e., cheese, cookies, ground beef, ice cream, tortilla chips, and white bread) was positively associated with urinary 3-PBA concentrations in children (Riederer et al., 2008). In addition, in a small cohort of preschool US children aged 2 to 5 years (N = 69, 2000–2001), mean urinary 3-PBA levels were higher in children who more frequently consumed chicken/turkey meats (Morgan and Jones, 2013). In contrast, dietary factors assessed using questionnaires were not associated with the urinary excretion of 3-PBA in children from Canada in 2003 (N = 85, 2005) (Fortin et al., 2008).

In a longitudinal study from Seattle, Washington, USA, dietary intervention with an organic diet lowered the pyrethroid exposures of children compared to a conventional diet (N = 23, 2003) (Lu et al., 2006). However, the effect of the dietary intervention in this study was modest compared to pyrethroid exposures by other routes, especially exposures resulting from residential pesticide use. A more recent study of 9 to 16-year-old boys (N = 463, 2014–2015) from Hangzhou, Zhejiang, PR China, also reported a negative correlation between organic food intake and pyrethroids exposures (Ye et al., 2017a). In addition, the specific food items and the preparation of fruits and vegetables can alter pyrethroid exposures. For example, a study from Nanjing, PR China (N = 406, 2014) found a negative association between 3-PBA levels and the soaking of fruits and vegetables (Wang et al., 2016).

3.1.4. Factors affecting pyrethroid exposure of children: regional and seasonal differences—

A comparison of regional and seasonal differences between studies is not possible because of the different experimental protocols. However, several studies reported regional and seasonal differences in pyrethroid exposures in children that may be more broadly applicable to other populations. Regional and seasonal differences in pyrethroid exposure were not assessed in the adolescent populations listed in Table 1.

Children aged 3 to 6 years (N = 340, 2003–2004) living in the rural areas of South Australia and from the Adelaide Hills area in South Australia had significantly higher urinary 3-PBA levels than children from metropolitan Adelaide (Babina et al., 2012). Urinary 3-PBA was positively associated with living near agricultural fields in 3 to 6-year-old children from Nanjing, PR China (N = 406, 2014) (Wang et al., 2016). The 3-PBA levels in infants from Jiangsu Province, PR China, were also associated with proximity to agricultural fields (N = 481, 2010–2011) (Wu et al., 2013). In this study, 3-PBA levels showed clear seasonal trends, with the highest levels observed in the summer (i.e., June to August). A survey of school children aged 7–9 years (N = 77, 2008) from rural Nicaragua had the highest environmental pyrethroid exposures reported for all studies summarized in Table 1 (Rodriguez et al., 2012). In this study, median levels of 3-PBA were 2.8 μg/g creatinine in children without parental pesticide application (N = 55) and 4.7 μg/g creatinine in children with parental pesticide application (N = 22). The high environmental pyrethroid exposure in this Nicaraguan cohort is likely due to pesticide drifts from plantations and other cultivated fields.

A more complex picture regarding regional differences in pyrethroid exposures in children emerged in studies from Costa Rica and Thailand. Children (N = 140, 2007) aged 6 to 9

years living near a plantain plantation in Talamanca County, Costa Rica, were exposed to higher levels of pyrethroids than children living near banana and organic plantations (van Wendel de Joode et al., 2016). These regional differences are due to indoor pyrethroid use and vector control and not differences in their agricultural application. In contrast, 3-PBA residues in 6 to 8-year-old children living in rice farming or aquacultural areas of Thailand showed no clear seasonable and regional variability (N = 53, 2011–2012) (Rohitrattana et al., 2014). This study identified several factors associated with higher urinary 3-PBA levels in Thai children, including frequency of pyrethroid use, proximity to rice farms, playing in rice farms, and nonedible object-to-mouth behavior. In addition, a positive correlation was observed between pyrethroid residues on the hands, determined with wipe tests, and urinary 3-PBA levels. These wipe tests also revealed regional differences in pyrethroid use in Thailand. Cypermethrin was detected in hand wipes from children in rice farming and aquacultural areas during the wet season, whereas permethrin was seen only in participants from the aquaculture area. These differences in pyrethroid use were not detected when analyzing the 3-PBA data, thus highlighting an important limitation of 3-PBA as a biomarker of exposure in environmental epidemiology studies.

3.1.5. Factors affecting pyrethroid exposure of children: other factors—

Other factors, such as gender, race/ethnicity, and age, can also be positively associated with pyrethroid exposure in children. For example, a study of 3-year-old Japanese children (N = 223, 2012) reported significantly higher creatinine-adjusted 3-PBA levels in girls than boys (Osaka et al., 2016). This difference was also observed in adult populations from Japan (Ueyama et al., 2009). Higher volume adjusted 3-PBA levels were also reported in girls than in boys (median: 0.49 vs. 0.39 ng/mL, respectively) from the German Environmental Survey on Children 2003–2006 (GerES IV; N = 598) (Schulz et al., 2009). In contrast, a study from Jacksonville, Florida, USA, reported higher mean 3-PBA levels in 4 to 6-year-old boys than girls (N = 201, 2001) (Naeher et al., 2010). This study reported a trend of more elevated mean creatinine but not volume-adjusted 3-PBA levels in Caucasians compared to African Americans and other children. In a study from Costa Rica, younger children 6.5–7.5 years old had higher 3-PBA concentrations than ≥ 7.5 years old children (N = 140, 2007) (van Wendel de Joode et al., 2016). In contrast, a small longitudinal study of children from Seattle, Washington, USA, (N = 23, 2003) reported that the age of children was associated with pyrethroids exposure, with higher 3-PBA levels in older (age 8 to 11) than younger children (age 3 to 7) (Lu et al., 2006). The authors speculate that the age dependence of 3-PBA levels is related to pyrethroid use where older children perform outdoor activities. None of the studies reporting 3-PBA levels in the adolescent populations (Table 1) investigated these or other factors associated with pyrethroid exposure.

3.2. Pyrethroid exposure in pregnant women

3.2.1. 3-PBA levels in pregnant women—

Thirteen studies were identified that reported urinary 3-PBA levels in pregnant women (Table 2). The urine samples for these studies were collected between 1997 and 2014. When reported, detection frequencies in these studies ranged from 30.2 to 100%. When available, median and GM 3-PBA levels in pregnant women are shown in Fig. 3. The 3-PBA levels in non-pregnant women from different NHANES cycles are shown for comparison. Median urinary 3-PBA levels ranged

from < LOD for several studies to 1.01 ng/ml (N = 1149, 2009–2010) in pregnant women from an agricultural area of PR China (Qi et al., 2012). The GM and median levels of 3-PBA were 0.24 and 0.23 ng/ml in pregnant women from NHANES 1999–2002 (N = 205) (Watkins et al., 2016). In comparison, GM and median 3-PBA levels were 0.31 and 0.25 ng/mL in non-pregnant women from NHANES 1999–2002 (CDC, 2021a).

Creatinine-adjusted median 3-PBA levels ranged from 0.23 μg/g creatinine (N = 858, 2010–2012) in pregnant women from Denmark (Dalsager et al., 2018) to 1.55 μg/g creatinine (N = 1149, 2009–2010) in pregnant women from PR China (Qi et al., 2012). A study from 1998 to 2001 was an outlier and reported median urinary 3-PBA levels of 18.3 ng/ml and 19.3 μg/g creatinine in pregnant women from the Children's Environmental Health Study in New York City, New York, USA (N = 307) (Berkowitz et al., 2003). For comparison, GM and median 3-PBA levels in non-pregnant women from NHANES 1999–2014 ranged from 0.32 to 0.84 μg/g and 0.27 to 0.70 μg/g, respectively (CDC, 2021a, 2021b).

No significant changes in 3-PBA levels in pregnant women were observed when analyzing the data shown in Table 1, apart from a downward trend in median creatinine-adjusted 3-PBA levels (p = 0.0129, N = 6 studies) (Table 5). This observation is not surprising because of the small number of 4 to 11 studies reporting urinary 3-PBA levels in this susceptible population.

3.2.2. Factors affecting pyrethroid exposure in pregnant women—Compared to all other cohorts in this systematic review, pregnant women in rural PR China had considerable pyrethroid exposure (Ding et al., 2015; Qi et al., 2012). Higher urinary 3-PBA levels were observed in pregnant women from southern China than in northern China, reflecting regional differences in agricultural uses of pesticides and regional diets. The indoor application of pesticides was associated with higher urinary 3-PBA levels in the cohort from southern China (N = 1149, 2009–2010) (Qi et al., 2012). Similarly, the primary exposure to pyrethroids in metropolitan Tokyo, Japan, was also due to the indoor or outdoor use of insecticides (N = 231, 2009–2011) (Zhang et al., 2013); however, 3-PBA levels were lower in the Japanese than the Chinese populations. Other factors related to increased 3-PBA levels in the Chinese cohort included occupation and season. Higher pyrethroid exposures were also observed in warmer months (i.e., June to October) due to increased agricultural and residential applications in the summer.

The residential use of pyrethroids is more common in tropical environments due to higher year-round pest pressure, thus resulting in higher exposures (Dewailly et al., 2014). Consistent with this general observation, pregnant women from Caribbean countries had higher pyrethroid exposures than women from other developed countries, such as the US and Canada (Dewailly et al., 2014). Out of all Caribbean countries studied from 2008 to 2011, pregnant women from Antigua & Barbuda (N = 22) and Grenada (N = 52) had the highest urinary 3-PBA levels in expecting mothers. This observation is consistent with regional and country-by-country differences in using specific pyrethroid pesticides in Caribbean countries. The authors attribute the higher pyrethroid exposure to higher residential use of pyrethroid-containing pesticides. Pregnant women living in Puerto Rico appeared to have higher pyrethroid exposures (N = 54, 2010–2012) (Lewis et al., 2014) than women

throughout the Caribbean (Dewailly et al., 2014). In contrast, pregnant women living in other tropical locations (e.g., Ecuador, $N = 16$, 2011; Ghana, $N = 17$, 2014; or Mexico, $N = 187$, 1997–2001) (Handal et al., 2016; Watkins et al., 2016; Wylie et al., 2017) had lower urinary concentrations of 3-PBA than pregnant women living in the Caribbean.

Only a few studies were identified in this systematic review that reported factors affecting 3-PBA levels in pregnant women from North America or Europe. In New York City, USA, pyrethroid exposure of pregnant women showed seasonal variability, with higher urinary 3-PBA concentrations during warmer months when pyrethroids are used more often ($N = 307$, 1998–2001) (Berkowitz et al., 2003). In addition, 3-PBA levels were higher in married or cohabiting pregnant women from New York City. Interestingly, urinary 3-PBA concentrations were significantly lower in women living in public housing than those who rented or owned private homes. A study from France observed that, in addition to using pesticides, levels of 3-PBA were positively correlated with smoking during pregnancy, consuming fish and alcohol, and living near crops during pregnancy ($N = 1077$, 2011) (Dereumeaux et al., 2018).

3.3. Environmental pyrethroid exposures in adult populations

3.3.1. 3-PBA levels in environmentally exposed adult populations—

The systematic review found 22 studies describing urinary 3-PBA levels in adults exposed environmentally to pyrethroid insecticides. These studies analyzed urine samples collected between 2004 and 2017. The reported detection frequencies of 3-PBA ranged from 36.8 to 100% (Table 3). When available, median and GM 3-PBA levels in adult populations, relative to NHANES data, are shown in Fig. 4 and summarized in Table 3. Median urinary 3-PBA levels ranged from 0.15 ng/ml ($N = 75$, 2000–2003) to 2.4 ng/ml ($N = 55$, 2012). These values were reported for two small US cohorts (Arcury et al., 2018; Young et al., 2013). For comparison, NHANES reported median volume-adjusted 3-PBA levels ranging from 0.230 ng/ml ($N = 833$) in 1999 to 0.420 ng/ml ($N = 1110$) in 2007 in adults. Creatinine-adjusted median 3-PBA levels ranged from 0.11 μg/g creatinine ($N = 75$, 2000–2003) in a US cohort (Young et al., 2013) to 3.34 μg/g creatinine ($N = 82$, 2009) in women from South Africa (Motsoeneng and Dalvie, 2015). Creatinine-adjusted data in adults reported by the NHANES were 0.595 μg/g creatinine ($N = 1632$) in 2011 and 0.598 μg/g creatinine ($N = 1797$) in 2013.

Creatinine-adjusted urinary 3-PBA levels worldwide increased significantly with the sampling year in the environmentally exposed adult populations (Median, $p = 0.0371$, $N = 34$; GM, $p = 0.0377$, $N = 28$) (Table 5). There appeared to be opposing time trends in the 3-PBA levels in different world regions. For example, both volume and creatinine-adjusted levels of 3-PBA in environmentally exposed adults from North America (i.e., Canada and the United States) significantly increased with time (volume adjusted: median, $p = 0.0005$, $N = 26$ studies; GM, $p = 0.0015$, $N = 20$ studies; creatinine adjusted: median, $p = 0.0189$, $N = 23$ studies; GM, $p = 0.0021$, $N = 20$ studies). This finding is consistent with the earlier observation that urinary 3-PBA levels increased significantly with time in the general adult NHANES 2007–2012 population (Lehmler et al., 2020). In contrast, the volume-adjusted GM levels of 3-PBA in environmentally exposed adults from Japan and PR

China significantly decreased with time ($p = 0.0103$, $N = 5$ studies). Additional studies are needed to confirm that there is indeed a significant decrease in pyrethroid exposures in adult populations from Asia.

3.3.2. Factors affecting pyrethroid exposure in environmentally exposed adult populations: diet—Human biomonitoring studies consistently identified diet as a major source of non-occupational pyrethroids exposure in adults (Becker et al., 2006; Fortes et al., 2013; Han et al., 2008; Kimata et al., 2009b; Park et al., 2016; Radwan et al., 2015; Schettgen et al., 2016, 2002; Trunnelle et al., 2014b; Ueyama et al., 2009; Wielgomas et al., 2013). For example, coffee, fruit juice, and bean consumption were positively correlated with urinary 3-PBA levels. In contrast, bread consumption was negatively associated with urinary 3-PBA levels in a small cohort ($N = 50$, 2009–2011) from North Carolina, USA (Morgan et al., 2016). In an urban population from New York City, USA ($N = 1452$, 2004), consuming more than 7 servings of vegetables per week was also associated with increased 3-PBA levels (McKelvey et al., 2013). An analysis of NHANES 1999–2002 data revealed that the consumption of wine, orange juice, biscuits, rice, bacon, chicken patties, spinach, salsa, lettuce, broccoli, salty snacks, or peanut butter was associated with increased urinary 3-PBA levels (Riederer et al., 2008). In a cohort of young Japanese men ($N = 322$, 1999–2003), 3-PBA levels varied significantly with the season of urine collection (Imai et al., 2014). In this population, the consumption frequency of beef and vegetables was also a significant determinant in 3-PBA levels in the ANOVA; however, no linear relationships between 3-PBA levels and consumption frequencies of either food item were noted. The same study also did not observe increased 3-PBA levels with increasing consumption of fruits and vegetables, suggesting a more predominant role of non-dietary routes of pyrethroid exposure. In contrast, dietary factors assessed using questionnaires were not associated with the urinary excretion of 3-PBA in Canadian adults ($N = 74$, 2005) (Fortin et al., 2008).

3.3.3. Factors affecting pyrethroid exposure in environmentally exposed adult populations: outdoor vs. residential use—Several studies discuss indoor and outdoor pesticide use as important sources of pyrethroid exposure (Han et al., 2017; Li et al., 2018; Trunnelle et al., 2014b; Ueyama et al., 2009). Levels of 3-PBA in men and women in Xin Zhou City, Shanxi Province, PR China, were attributed to urban pesticide application ($N = 208$, 2013–2014) (Han et al., 2017). In women from Zhejiang, PR China, pyrethroid exposures were explained with pyrethroid use for pest control in residential and horticultural settings ($N = 419$, 2015–2017) (Li et al., 2018). In contrast, no association between residential pyrethroid use and urinary 3-PBA levels was observed in the NHANES 1999–2002 population (Riederer et al., 2008). In addition, a study comparing urinary 3-PBA levels in the general population from rural and suburban areas in Japan ($N = 209$, 2005 and 2007) found no significant difference, suggesting that pyrethroid exposures are independent of the sampling location in these cohorts (Kimata et al., 2009b).

Time spent outside the home was positively correlated with increased urinary 3-PBA levels in a small cohort ($N = 50$, 2009–2011) from North Carolina, USA (Morgan et al., 2016). In contrast, no association was observed with other lifestyle factors (i.e., sampling season

and pesticide use) in this cohort. A suggested positive association between the time spent gardening and urinary 3-PBA levels was reported for the NHANES 1999–2002 population (Riederer et al., 2008). In a small cohort of adults (N = 121, 2001) in Ohio, USA, sampling season, pet ownership, and removal of shoes before entering the home were predictive of 3-PBA levels (Morgan, 2015). Interestingly, owning a cat or dog was associated with lower 3-PBA levels, while not removing shoes before entering the home caused an increase in 3-PBA levels. In Japanese men (N = 322, 1999–2003), urinary 3-PBA also showed seasonal variability, with higher levels observed in the summer and autumn (Imai et al., 2014).

3.3.4. Factors affecting pyrethroid exposure in environmentally exposed adult populations: other factors—

In a Canadian cohort, male smokers had significantly lower weight-adjusted 3-PBA levels than male non-smokers (N = 74, 2005) (Fortin et al., 2008). The authors speculate that the lower urinary 3-PBA levels in smokers than in non-smokers are due to a poorer diet. In contrast, an analysis of NHANES 1999–2002 data found that tobacco use was positively associated with urinary 3-PBA levels (Riederer et al., 2008). The authors speculate that this association may be due to altered cytochrome P450 activities in smokers, direct pyrethroid exposures from tobacco, or increased hand-to-mouth behaviors in smokers. No relationship between smoking and 3-PBA levels was observed in the NHANES 2007–2012 population (Lehmler et al., 2020).

The use of prescription or non-prescription drugs was also associated with increased urinary 3-PBA levels in the Canadian cohort (Fortin et al., 2008). Similarly, a suggested positive association between medications that inhibit cytochrome P450 enzymes and urinary 3-PBA levels was observed in the NHANES 1999–2002 population (Riederer et al., 2008). Other studies have also reported a link between factors altering the expression of drug-metabolizing enzymes and 3-PBA levels. For example, higher alcohol intake was associated with higher urinary 3-PBA levels in the Korean National Environmental Health Survey (KNEHS) 2009–2011 (N = 3671) (Yoo et al., 2016). In NHANES 2007–2012, urinary 3-PBA levels in heavy drinkers significantly differed from those in non-drinkers (Lehmler et al., 2020).

3.4. Agricultural and occupational pyrethroid exposures in adult populations

3.4.1. 3-PBA levels in agriculturally and occupationally exposed adult populations—

Eleven studies reported urinary 3-PBA concentrations in adult populations exposed agriculturally or occupationally to pyrethroids (Table 4). These studies include agricultural workers and cohorts investigating workers with non-agricultural occupational pyrethroid exposures. When reported, the detection frequencies ranged from 11.8 to 100%. Median and GM 3-PBA levels in these populations, when available, are shown in Fig. 5. The 3-PBA levels in adult NHANES populations are shown for comparison. The highest volume-adjusted median urinary 3-PBA levels of 16 ng/ml were observed in 2010 in textile workers from PR China (N = 30, 2010) (Lu et al., 2013). Otherwise, volume-adjusted median 3-PBA levels ranged from 0.36 ng/ml in Japanese farmers (N = 87, 2005) (Ueyama et al., 2009) to 5.16 ng/ml in flight attendants (N = 11, 2009) (Wei et al., 2013). Unlike in environmentally exposed adults, changes in urinary 3-PBA levels with sampling time could not be assessed because of the small number of studies (Table 5).

The highest median creatinine adjusted 3-PBA levels of 27 μg/g creatinine were reported in pest control operators from Japan who applied pesticides the week before sample collection (*N* = 14, 2007) (Kimata et al., 2009b). Otherwise, median creatinine-adjusted 3-PBA levels in occupationally exposed cohorts ranged from 0.43 μg/g creatinine in Japanese farmers (*N* = 87, 2005) (Ueyama et al., 2009) to 14 μg/g creatinine in textile workers from PR China (*N* = 30, 2010) (Lu et al., 2013). Across all studies, the levels in these occupationally exposed populations were significantly higher than in the other environmentally exposed population groups (Fig. 6).

3.4.2. Factors affecting pyrethroid exposure in occupationally exposed adult populations—Factors affecting urinary 3-PBA levels were reported by five studies of agriculturally or occupationally exposed populations (Kimata et al., 2009b; López-Gálvez et al., 2018; Panuwet et al., 2008; Ueyama et al., 2009; Wang et al., 2007). In pest control workers (*N* = 44, 2004–2005) from Japan, higher 3-PBA levels were observed in the summer than in winter (GM levels of 12.2 μg/g creatinine vs. 3.9 μg/g creatinine, respectively) (Wang et al., 2007). Similarly, 3-PBA levels were significantly higher during the summer compared to the spring season in this population of migrant grape farm workers in Sonora, Mexico (*N* = 20, 2016) (López-Gálvez et al., 2018). Japanese farmers, irrespective of whether they applied pesticides or not, had significantly higher 3-PBA levels than the general Japanese population (*N* = 30, 2007) (Kimata et al., 2009b). A 2006 study in Thailand found regional differences in 3-PBA levels in farmers in different farming areas, Inthakhin (median of 2.0 ng/mL or 1.1 μg/g creatinine; *N* = 62) and Pong Yaeng (median of 0.88 ng/mL or 0.64 μg/g creatinine; *N* = 52) (Panuwet et al., 2008).

In addition, this systematic review identified two studies investigating pyrethroid exposures in non-agricultural occupational cohorts (Lu et al., 2013; Wei et al., 2012). Both studies had some of the highest 3-PBA levels compared to the other occupationally exposed cohorts identified in the systematic review. In 2009–2010, a study assessed the permethrin exposure of flight attendants due to the use of permethrin on planes before flights to reduce the transport of invasive insect species between countries (Wei et al., 2012). High 3-PBA levels were observed in permethrin-exposed flight attendants (*N* = 11), with median levels of 2.18 ng/mL (4.13 μg/g creatinine), than non-exposed flight attendants (median of 0.7 ng/mL or 0.83 μg/g creatinine; *N* = 17). Inhalation was predicted to make the largest contribution to 3-PBA levels (89.7%), followed by dermal (5.3%) and oral (5.0%) exposure in this cohort (Wei et al., 2013). Moreover, the number of days from aircraft disinsection to flight was identified as the most significant predictor of urinary 3-PBA levels. Textile workers from two plants in Eastern China were also shown to have high levels of 3-PBA in their urine, with median concentrations of 14 and 16 ng/mL (12 and 14 μg/g creatinine) in plant 1 (*N* = 20, 2010) and plant 2 (*N* = 30, 2010), respectively (Lu et al., 2013). The 3-PBA levels in this cohort were comparable to or higher than the 3-PBA levels detected in the flight attendants. The exposure of these workers was predicted to be due to direct contact with insecticides used in the textile production process and appears to depend on specific job responsibilities.

4. Conclusions

This systematic review of human biomonitoring studies of 3-PBA, a urinary biomarker of pyrethroid exposure, identified 57 studies investigating pyrethroid exposure in children and adolescents, pregnant women, environmentally exposed adults, and occupationally exposed adults. Most studies, including large human biomonitoring surveys from the US and Canada, reported high detection frequencies of 3-PBA in the general population. This observation underscores that the general population worldwide is continuously exposed to pyrethroid pesticides. Based on the scoping review of the biomonitoring studies, the pyrethroid exposures of the general population appear to be similar and occur primarily from food sources and residential and agricultural pyrethroid applications. However, the available information about exposure pathways is limited and has considerable uncertainties, making it challenging to identify which exposure routes are globally most relevant for the general population. It is also noteworthy that factors associated with pyrethroid exposures in adolescents were not reported in any study included in this review, pointing to an important knowledge gap. Occupationally exposed populations and populations living near agricultural sites with heavy pyrethroid insecticide had higher detection frequencies and significantly higher GM and median 3-PBA levels than environmentally exposed children and adolescents, pregnant women, and adults. In addition, 3-PBA levels in the general population in North America increased significantly with the sampling year, possibly as an indirect consequence of the phase-out of organophosphate insecticides for indoor and other uses in the US and Canada (Government of Canada, 2020; EPA, n.d.). A decrease in 3-PBA levels was noted in the adult cohorts from PR China and Japan. This downward trend needs to be interpreted with caution due to the small sample size, and more data are required to confirm this trend. Although some smaller studies had relatively high pyrethroid exposures, 3-PBA levels across most studies were comparable to levels in the NHANES populations. These findings demonstrate that pyrethroid exposures are near-ubiquitous worldwide and, in some countries, appear to increase over time. Because of the growing body of evidence implicating pyrethroid exposure in adverse health effects in humans, these exposures represent a continuing public health concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

3-PBA	3-phenoxybenzoic acid

GM	geometric mean
NHANES	National Health and Nutrition Examination Survey
PECO	Population, Exposure, Comparator, and Outcomes
US	United States

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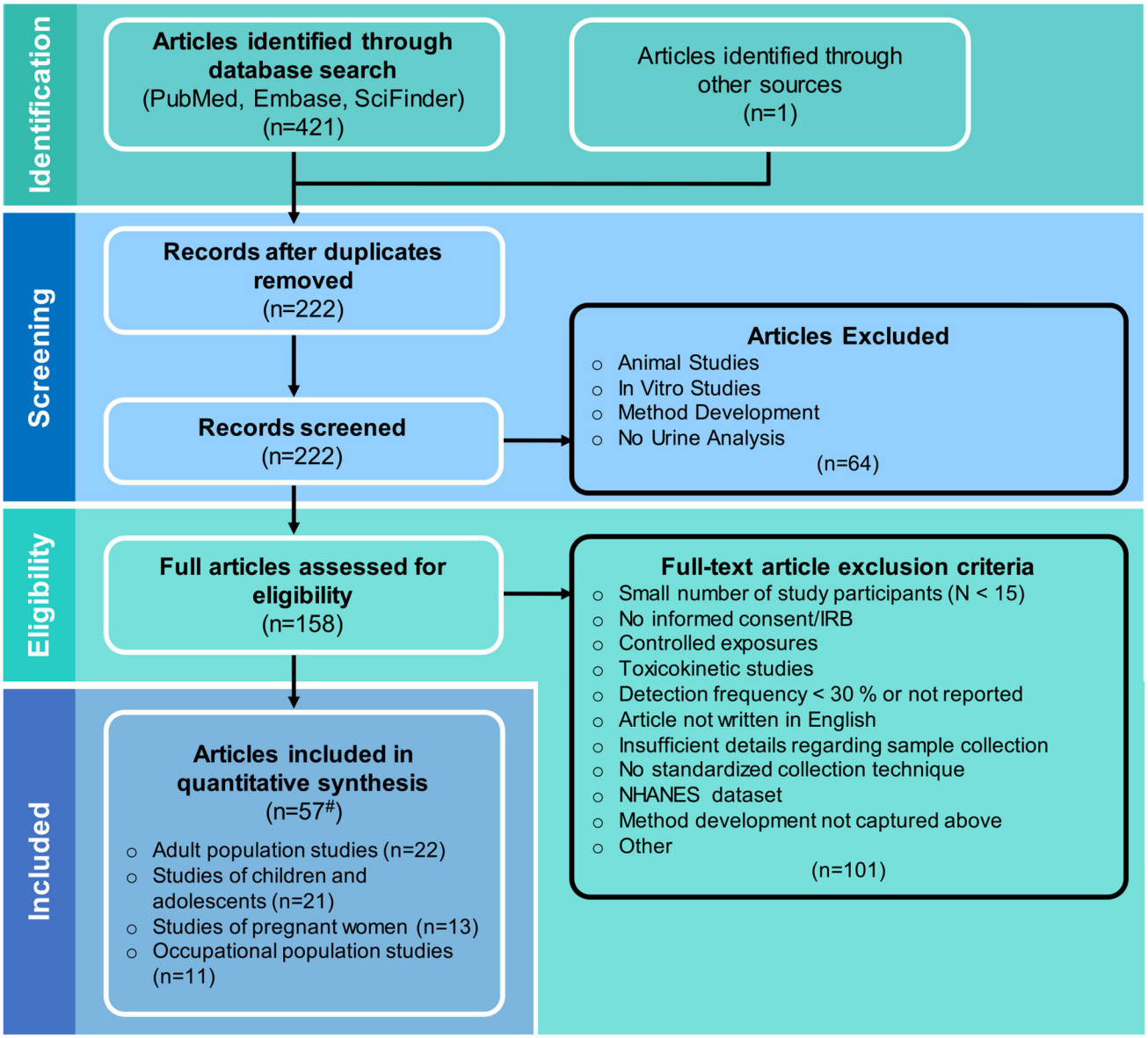

Fig. 1.

Systematic search process flowchart adapted from the PRISMA outline (Moher et al., 2009) details the search process, exclusion criteria, and studies included in the final analysis. # Several studies reported data for different populations. Therefore, the number of studies of different populations is larger than the number of studies included in the systematic review; for detailed information, see Tables 1 to 4.

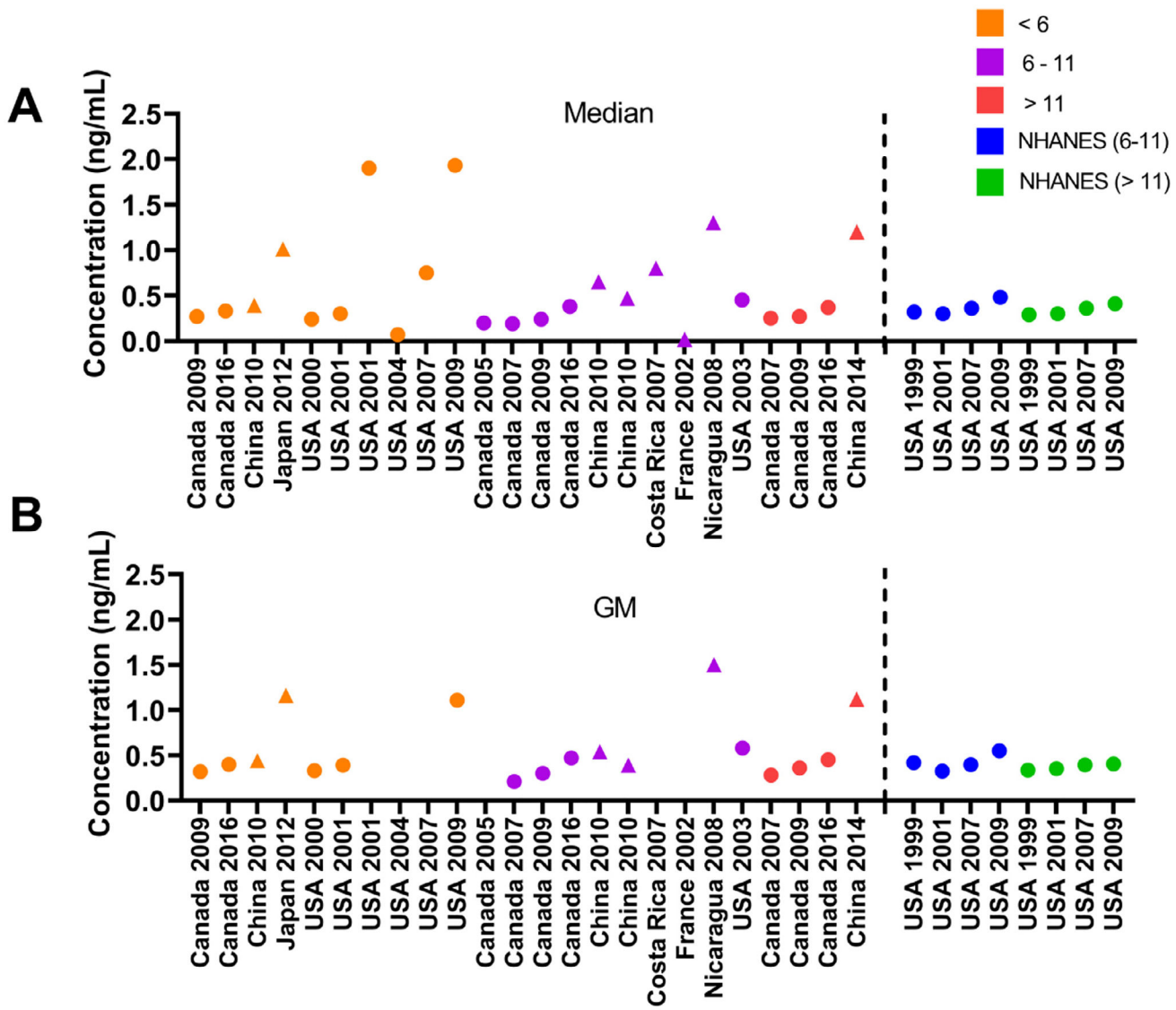

Fig. 2.

Comparison of published (A) median and (B) geometric mean (GM) urinary 3-PBA levels (adjusted by volume, ng/mL) in children and adolescents from different countries with NHANES data. Cohorts were grouped by age (i.e., approximately ⟨ 6, 6 to 11, and > 11 years of age) to approximate the age groups used by NHANES. Circles represent cohorts from North America, while triangles indicate cohorts from other countries. Studies without a symbol did not report data in the respective unit. The data are summarized in Table 1.

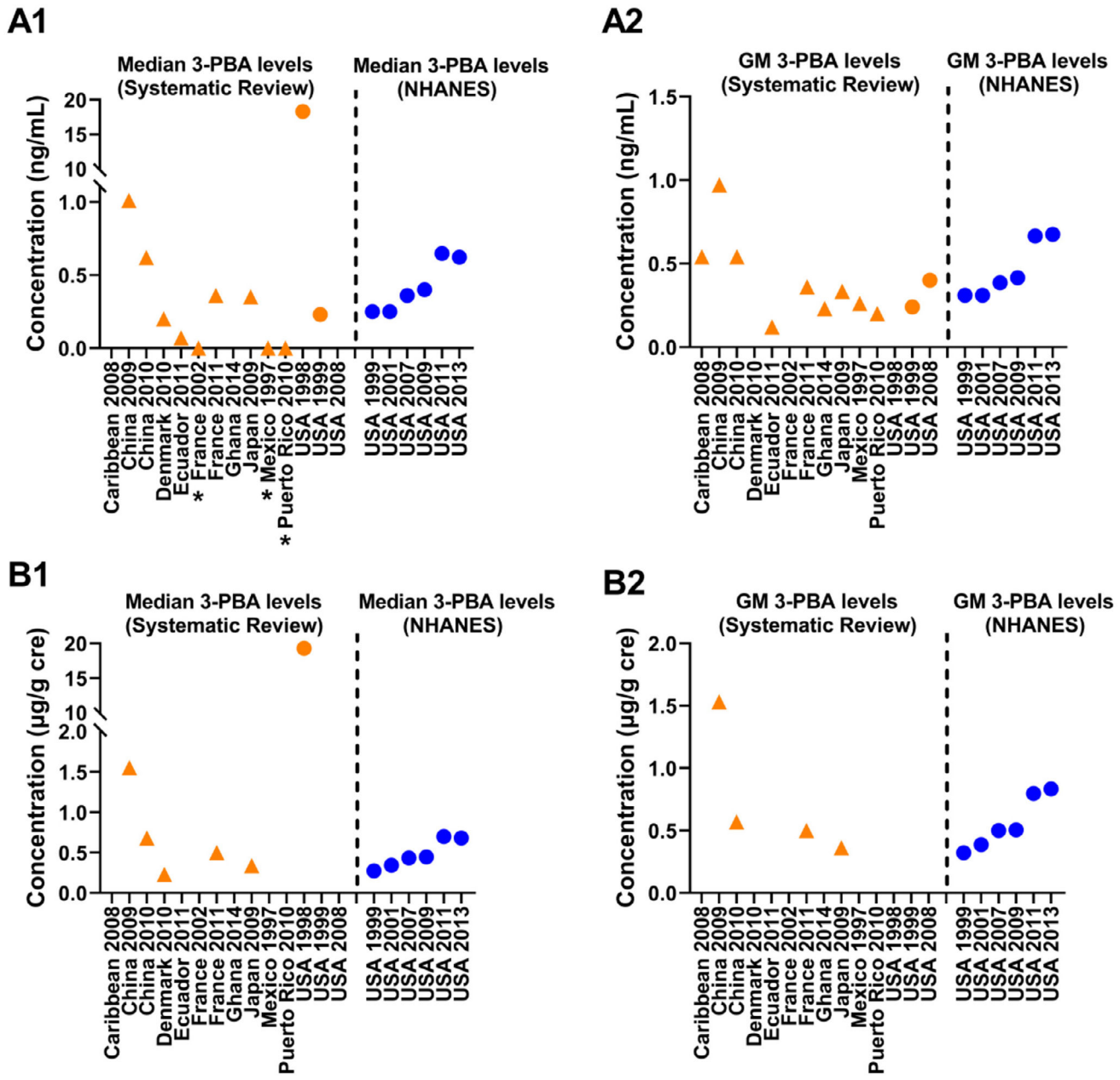

Fig. 3.

Summary of the median and geometric mean (GM) urinary 3-PBA levels in pregnant women adjusted by volume (A1-A2) and creatinine (B1-B2). Data from non-pregnant women from different NHANES populations are shown for comparison. Circles represent cohorts from North America, while triangles indicate cohorts from other countries. Studies without a symbol did not report data in the respective unit. The data are summarized in Table 2. * values below the detection limit.

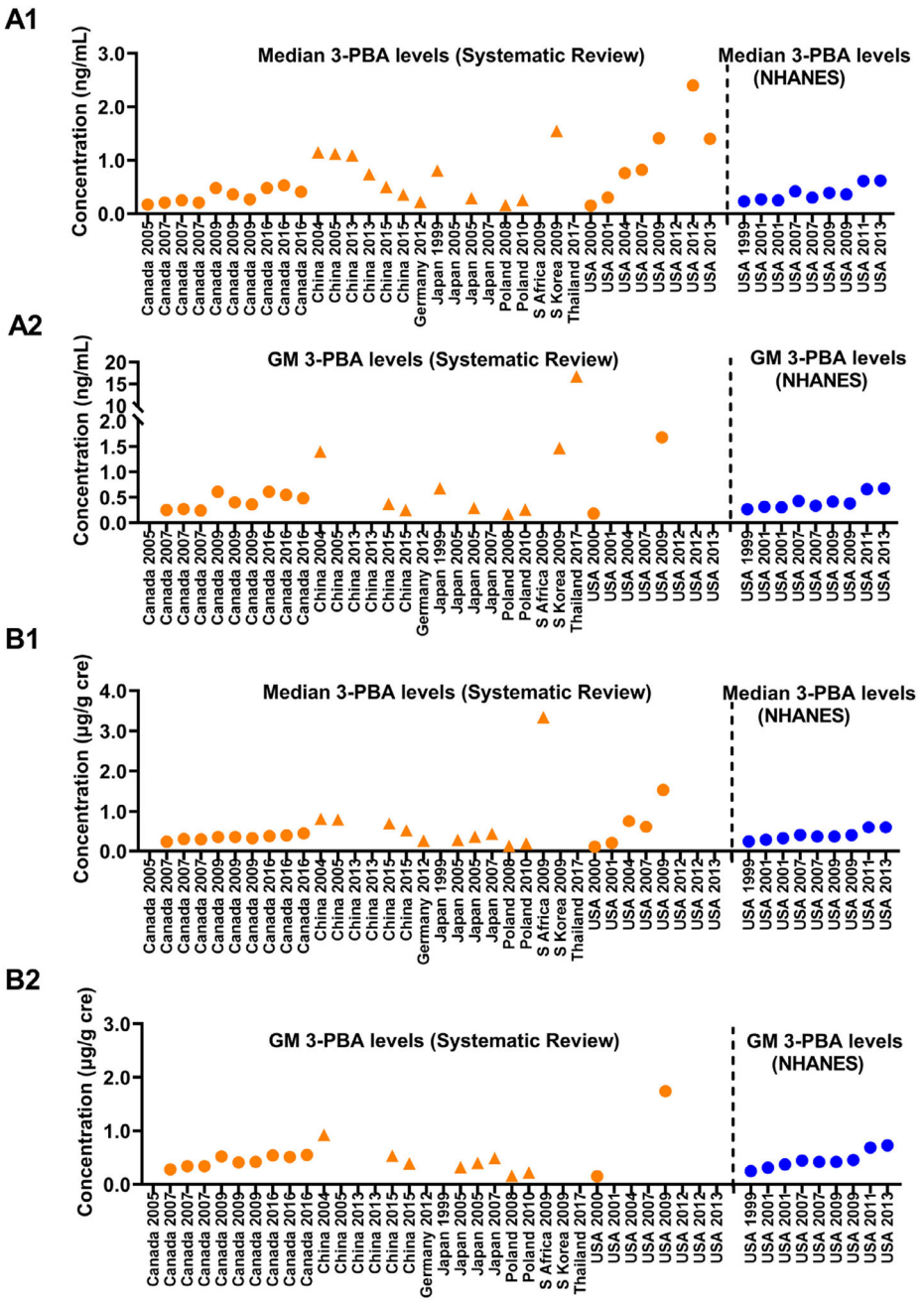

Fig. 4.

Comparison of published median and geometric mean (GM) urinary 3-PBA levels adjusted by volume (A1-A2) and creatinine (B1-B2) in environmentally exposed adults from different countries with NHANES data. Circles represent cohorts from North America, while triangles indicate cohorts from other countries. Studies without a symbol did not report data in the respective unit. The data are summarized in Table 3.

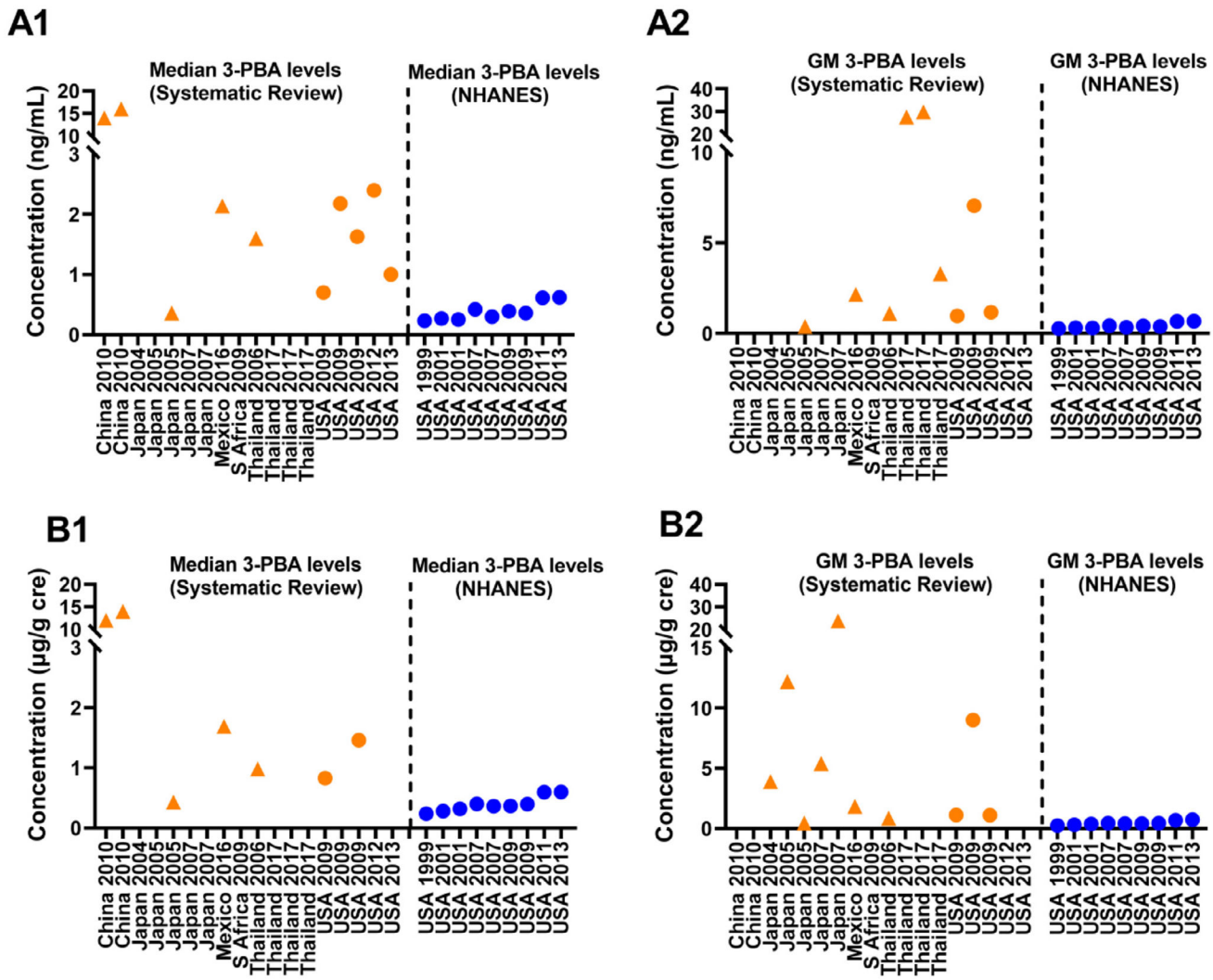

Fig. 5.

Summary of the median and geometric mean (GM) urinary 3-PBA levels in occupationally exposed populations adjusted by volume (A1-A2) and creatinine (B1-B2). Circles represent cohorts from North America, while triangles indicate cohorts from other countries. Studies without a symbol did not report data in the respective unit. The data are summarized in Table 4.

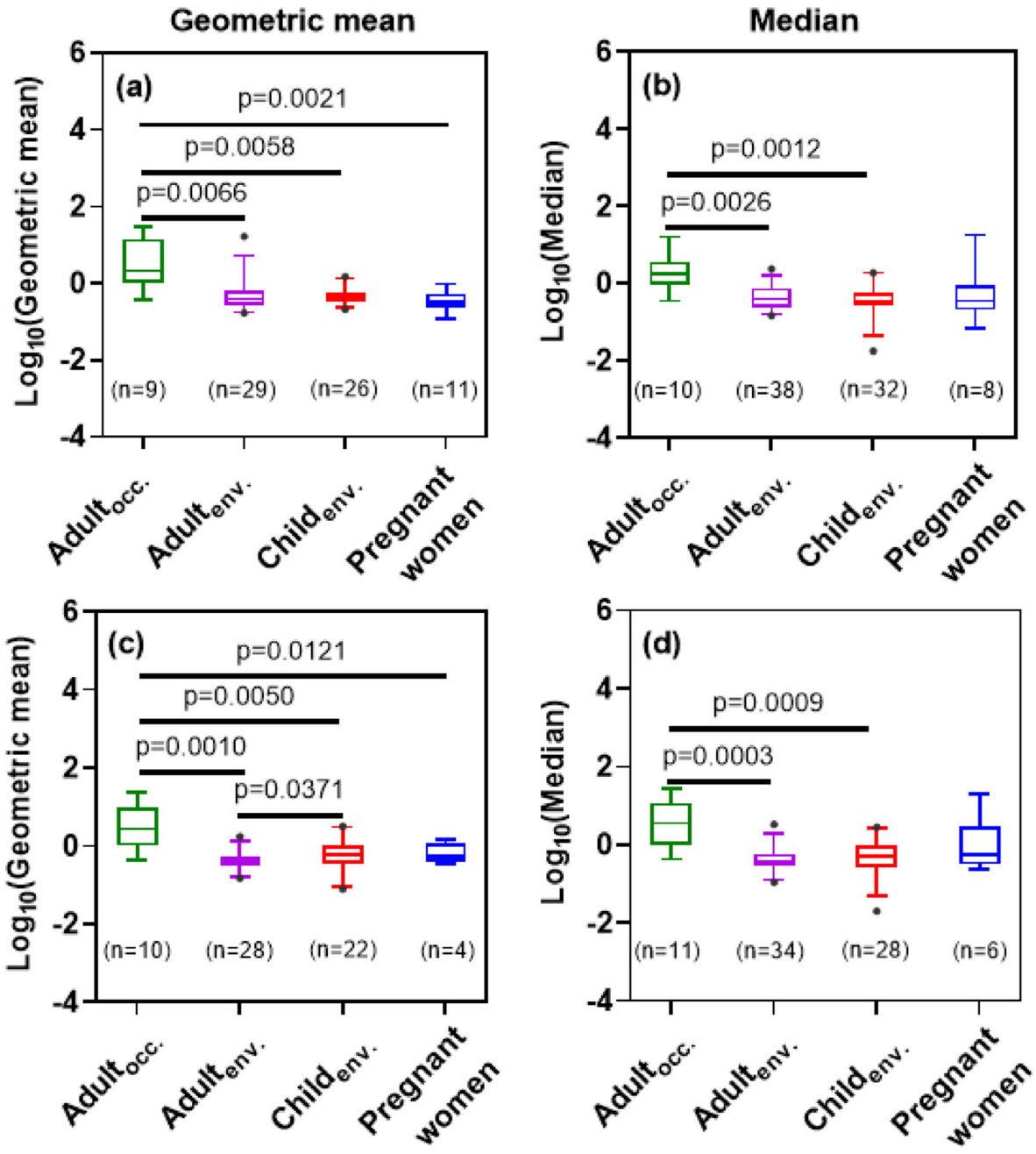

Fig. 6.

Comparison of (a) geometric mean and (b) median volume adjusted pyrethroid levels in ng/mL and (c) geometric mean and (d) median pyrethroid levels expressed in μg/g creatinine in adults, children, and pregnant women exposed occupationally (adults only) or environmentally to pyrethroid insecticides. Numbers in parenthesis indicate the numbers of studies from across the world reporting pyrethroid levels (see Tables 1 to 4). The whiskers show the 5th and 95th percentile. The two-sample *t*-test was used to compare

log_{10}-transformed values between population groups, with $p < 0.05$ considered significantly different.

Table 1

Summary of volume and creatinine adjusted 3-PBA levels in children reported in 21 publications meeting the inclusion criteria of the systematic review. The data are ordered by the country of origin and the year[2] of sample collection. In addition, the population characteristics, detection limit, detection frequency, and analytical methods are reported to facilitate the comparison between studies. Data of the entire study population (bold text) and selected subpopulations (normal text) are included in this Table).

Country	N[3]	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels[mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
Australia[4]	**115**	**2003**	**0.10**				**1.2**		**0.5**	**80.9**	**3–6**	**M/F**	(Babina et al., 2012)
Australia[5]	**111**	**2003**	**0.10**				**1.4**		**0.8**	**86.5**	**3–6**	**M/F**	(Babina et al., 2012)
Australia[6]	**114**	**2003**	**0.10**				**1.6**		**1.1**	**84.2**	**3–6**	**M/F**	(Babina et al., 2012)
Canada	**85**	**2005**	**0.043**			**0.2**				**94.1**	**6–12**	**M/F**	(Fortin et al., 2008)
Canada[7]	**1025**	**2007**	**0.01**		**0.21**	**0.19**		**0.32**	**0.27**	**99.3**	**6–11**	**M/F**	(Health Canada, 2019)
Canada[8]	**977**	**2007**	**0.01**		**0.28**	**0.25**		**0.25**	**0.19**	**99.8**	**12–19**	**M/F**	(Health Canada, 2019)
Canada[9]	**522**	**2009**	**0.01**		**0.32**	**0.27**		**0.56**	**0.15**	**99.9**	**3–5**	**M/F**	(Health Canada, 2019)
Canada[10]	**515**	**2009**	**0.01**		**0.30**	**0.24**		**0.34**	**0.26**	**100**	**6–11**	**M/F**	(Health Canada, 2019)
Canada[11]	**509**	**2009**	**0.01**		**0.36**	**0.27**		**0.27**	**0.21**	**100**	**12–19**	**M/F**	(Health Canada, 2019)
Canada[12]	**551**	**2016**	**0.012**		**0.40**	**0.33**		**0.70**	**0.16**[13]	**100**	**3–5**	**M/F**	(Health Canada, 2019)
Canada[14]	**534**	**2016**	**0.012**		**0.47**	**0.38**		**0.56**	**0.41**	**100**	**6–11**	**M/F**	(Health Canada, 2019)
Canada[15]	**533**	**2016**	**0.012**		**0.45**	**0.37**		**0.35**	**0.28**	**100**	**12–19**	**M/F**	(Health Canada, 2019)
China[16]	**176**	**2010**	**0.1**		**0.54**	**0.65**		**0.81**	**0.93**	**88.1**	**0–14**	**M/F**	(Ding et al., 2012)
China[17]	**180**	**2010**	**0.1**		**0.39**	**0.47**		**0.60**	**0.68**	**81.7**	**0–14**	**M/F**	(Ding et al., 2012)
China	**481**	**2010**	**0.1**		**0.44**	**0.39**				**83.8**	**~1**	**M/F**	(Wu et al., 2013)
China[18]	265	2010	0.1		0.47	0.40				84.5	~1	M	(Wu et al., 2013)
China[19]	216	2010	0.1		0.41	0.39				82.8	~1	F	(Wu et al., 2013)
China[20]	**463**	**2014**	**0.005**		**1.12**	**1.20**		**0.97**	**0.90**	**98.7**	**9–16**	**M**	(Ye et al., 2017a)
China	**305**	**2014**	**0.005**					**1.42**	**1.42**	**89**	**9–15**	**F**	(Ye et al., 2017b)

Country	N[3]	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels[mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
China[21]	33	2014	0.005				0.99			89	9–15	F	(Ye et al., 2017b)
China[22]	83	2014	0.005				2.00			89	9–15	F	(Ye et al., 2017b)
China[23]	95	2014	0.005				3.10			89	9–15	F	(Ye et al., 2017b)
China[24]	64	2014	0.005				1.88			89	9–15	F	(Ye et al., 2017b)
China[25]	7	2014	0.005				2.57			89	9–15	F	(Ye et al., 2017b)
China[26]	91	2014	0.005				1.27			89	9–15	F	(Ye et al., 2017b)
China[27]	79	2014	0.005				1.95			89	9–15	F	(Ye et al., 2017b)
China[28]	93	2014	0.005				3.03			89	9–15	F	(Ye et al., 2017b)
China[29]	26	2014	0.005				1.79			89	9–15	F	(Ye et al., 2017b)
China[30]	2	2014	0.005				1.36			89	9–15	F	(Ye et al., 2017b)
China	**406**	**2014**	**0.008**				**0.17**	**0.08**	**0.02**	**36**	**3–6**	**M/F**	(Wang et al., 2016)
Costa Rica	**140**	**2007**	**0.1**			**0.8**				**94**	**6–9**	**M/F**	(van Wendel de Joode et al., 2016)
Costa Rica	69	2007	0.1		0.8						6–9	M	(van Wendel de Joode et al., 2016)
Costa Rica	71	2007	0.1		0.9						6–9	F	(van Wendel de Joode et al., 2016)
Costa Rica	43	2007	0.1		1.2						6.5–7.5	M/F	(van Wendel de Joode et al., 2016)
Costa Rica	47	2007	0.1		0.8						≥7.5–8.5	M/F	(van Wendel de Joode et al., 2016)
Costa Rica	50	2007	0.1		0.7						≥8.5–9.3	M/F	(van Wendel de Joode et al., 2016)
France	**284**	**2002**	**0.008**			**0.018**				**63.7**	**6**	**M/F**	(Viel et al., 2015)
Germany	**598**	**2003**	**0.1**						**0.43**	**98**	**7–14**	**M/F**	(Schulz et al., 2009)
Germany	288	2003	0.1						0.49	98	7–14	F	(Schulz et al., 2009)
Germany	310	2003	0.1						0.39	97	7–14	M	(Schulz et al., 2009)
Japan[31]	**223**	**2012**	**0.02**		**1.16**	**1.01**		**1.71**	**1.40**	**100**	**3**	**M/F**	(Osaka et al., 2016)
Nicaragua	**77**	**2008**	**0.2**		**1.5**	**1.3**		**3.2**	**2.8**	**96.7**	**7–9**	**M/F**	(Rodriguez et al., 2012)
Nicaragua[32]	55	2008	0.2		1.7	1.3		3.7	2.8	96.0	7–9	M/F	(Rodriguez et al., 2012)
Nicaragua[33]	22	2008	0.2		2.4	2.1		5.0	4.7	97.0	7–9	M/F	(Rodriguez et al., 2012)
Thailand	**53**	**2011**						**1**			**6–8**	**M/F**	(Rohitrattana et al., 2014)

Country	N[3]	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels[mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
Thailand[34]	24	2011	0.01		1.33	1.24		1.74	1.65	88	6–8	M/F	(Rohitrattana et al., 2014)
Thailand[35]	23	2011	0.01		1.97	2.23		2.24	2.57	96	6–8	M/F	(Rohitrattana et al., 2014)
Thailand[36]	29	2011			1.16	1.37		1.94	1.63	86	6–8	M/F	(Rohitrattana et al., 2014)
Thailand[37]	29	2011			2.06	1.86		2.4	1.94	86	6–8	M/F	(Rohitrattana et al., 2014)
USA	**483**	**1999**			**0.417**	**0.320**		**0.450**	**0.371**		**6–11**	**M/F**	(CDC, 2021a)
USA	**682**	**1999**			**0.336**	**0.290**		**0.227**	**0.205**		**12–19**	**M/F**	(CDC, 2021a)
USA[38]	**69**	**2000**	**0.2**	**0.5**	**0.33**	**0.24**				**64**	**2–5**	**M/F**	(Morgan and Jones, 2013)
USA[39]	**127**	**2001**	**0.2**	**0.9**	**0.39**	**0.3**	**1.5**	**0.5**	**0.4**	**67**	**1–5**	**M/F**	(Morgan et al., 2007)
USA	**201**	**2001**	**0.19**	**5**		**1.9**	**6.5**		**2.5**	**99.5**	**4–6**	**M/F**	(Naeher et al., 2010)
USA	**580**	**2001**			**0.325**	**0.300**		**0.423**	**0.383**		**6–11**	**M/F**	CDC, 2021a
USA[40]	**831**	**2001**			**0.353**	**0.300**		**0.274**	**0.236**		**12–19**	**M/F**	CDC, 2021a
USA[41]	**23**	**2003**	**0.1**	**1.22**	**0.58**	**0.45**				**82**	**4–11**	**M/F**	(Lu et al., 2006)
USA[42]	**60**	**2004**	**0.1**			**0.07**			**0.15**	**40**	**1–6**	**M/F**	(Arcury et al., 2007)
USA	**83**	**2007**	**0.58–0.75**			**0.75**			**0.8**	**60**	**2–8**	**M/F**	(Trunnelle et al., 2014b)
USA	**371**	**2007**			**0.397**	**0.360**		**0.511**	**0.448**		**6–11**	**M/F**	(CDC, 2021a)
USA[43]	**361**	**2007**			**0.393**	**0.360**		**0.316**	**0.281**		**12–19**	**M/F**	(CDC, 2021a)
USA[44]	**103**	**2009**	**0.1**	**2.4**	**1.11**	**1.93**	**3.83**	**1.97**	**2.56**	**77.7**	**1.6–8.4**	**M/F**	(Trunnelle et al., 2014a)
USA	**383**	**2009**			**0.549**	**0.480**		**0.744**	**0.667**		**6–11**	**M/F**	(CDC, 2021a)
USA	**398**	**2009**			**0.403**	**0.410**		**0.347**	**0.301**		**12–19**	**M/F**	(CDC, 2021a)
USA	**398**	**2011**			**0.785**	**0.715**		**1.09**	**1.00**		**6–11**	**M/F**	(CDC, 2021b)
USA	**386**	**2011**			**0.648**	**0.598**		**0.587**	**0.523**		**12–19**	**M/F**	(CDC, 2021b)
USA	**408**	**2013**			**0.726**	**0.810**		**0.939**	**0.974**		**6–11**	**M/F**	(CDC, 2021b)
USA	**420**	**2013**			**0.637**	**0.617**		**0.544**	**0.500**		**12–19**	**M/F**	(CDC, 2021b)

3-PBA, 3-phenoxybenzoic acid; cre, creatinine; DF, Detection Frequency; DL, detection limit (i.e., the limit of detection or limit of quantification, as reported); F, female; GM, Geometric Mean; M, male; N, number of samples.

[2]The earliest year is reported in the Table for studies where samples were collected over two or more years.

[3] N is the number of study participants. If applicable, footnotes indicate if data include results from repeated sample analyses from the same individuals.

[4] Urban cohort of children from metropolitan Adelaide in South Australia.

[5] Peri-urban cohort of children from the Adelaide Hills area in South Australia.

[6] Rural cohort of children from agricultural areas in South Australia.

[7] *N* = 1022 for creatinine adjusted values.

[8] *N* = 975 for creatinine adjusted values.

[9] *N* = 521 for creatinine adjusted values.

[10] *N* = 513 for creatinine adjusted values.

[11] *N* = 507 for creatinine adjusted values.

[12] N = 542 for creatinine adjusted values.

[13] Data are marked as “Use data with caution”.

[14] N = 526 for creatinine adjusted values.

[15] N = 526 for creatinine adjusted values.

[16] Children newly diagnosed with childhood acute lymphocytic leukemia.

[17] Children who served as age-matched controls in a study investigating a possible link between pyrethroid exposure and childhood acute lymphocytic leukemia.

[18] Male infants from Jiangsu province, China.

[19] Female infants from Jiangsu province, China.

[20] Cohort of boys exposed, at least in part, to pyrethroids at home, with 75.7% of households sometimes and 18.2% of households always using pesticides.

[21] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 1 of breast development.

[22] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 2 of breast development.

[23] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 3 of breast development.

[24] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 4 of breast development.

[25] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 5 of breast development.

[26] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 1 of pubic hair development.

[27] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 2 of pubic hair development.

[28] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 3 of pubic hair development.

[29] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 4 of pubic hair development.

[30] Chinese girls 9–15 years of age with pubertal maturation in the Tanner Stage 5 of pubic hair development.

[31] A method development study also reported 3-PBA levels in 3-year-old children from Aichi, Japan (Ueda et al., 2018). This study was excluded here.

[32] A total of 112 urine samples from 55 children without parental pesticide application were analyzed for 3-PBA.

[33] A total of 99 urine samples from 22 children with parental pesticide application were analyzed for 3-PBA.

[34] Children in a rice farming area in the Khlong Luang district, Pathum Thani province, Thailand, an area where insecticides are heavily used in agriculture. Urine samples were collected during the wet season.

[35] Children in a rice farming area in the Khlong Luang district, Pathum Thani province, Thailand, an area where insecticides are heavily used in agriculture. Urine samples were collected during the dry season.

[36] Children in a rice farming area in the Lum Luk Ka district, Pathum Thani province, Thailand, an area with fish and shrimp farms. Insecticides are not heavily used in this area. Urine samples were collected during the wet season.

[37] Children in a rice farming area in the Lum Luk Ka district, Pathum Thani province, Thailand, an area with fish and shrimp farms. Insecticides are not heavily used in this area. Urine samples were collected during the dry season.

[38] Preschool children from Ohio, USA.

[39] N = 112 for creatinine adjusted values.

[40] N = 380 for creatinine adjusted values.

[41] Volume-adjusted 3-PBA levels for 724 urine samples collected from 23 children over a 15-day period.

[42] Latino farmworker children.

[43] N = 359 for creatinine adjusted values.

[44] Children from the Mexican Immigration to California: Agricultural Safety and Acculturation (MICASA) study in Mendota, California, USA (for data of their mothers from the same study, see Table 4).

Table 2

Summary of volume and creatinine adjusted 3-PBA levels in pregnant women reported in 13 publications meeting the inclusion criteria of the systematic review. The data are ordered by the country of origin and the year[45] of sample collection. In addition, the population characteristics, detection limit, detection frequency, and analytical methods are reported to facilitate the comparison between studies. Data of the entire study population (bold text) and selected subpopulations (normal text) are included in this Table).

Country	N	Year	DL [ng/mL]	Volume-adjusted 3-PBA levels [ng/mL]			Creatinine-adjusted 3-PBA levels [mg/g cre]			DF [%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
Caribbean Countries	**297**	**2008**	**0.01**		**0.54**					**100**	**27#**	**F**	(Dewailly et al., 2014)
Antigua and Barbuda	22	2008	0.01		1.77					100		F	(Dewailly et al., 2014)
Belize	15	2008	0.01		0.21					100		F	(Dewailly et al., 2014)
Bermuda	15	2008	0.01		0.56					100		F	(Dewailly et al., 2014)
Dominica	48	2008	0.01		0.45					100		F	(Dewailly et al., 2014)
Grenada	52	2008	0.01		0.81					100		F	(Dewailly et al., 2014)
Jamaica	45	2008	0.01		0.32					100		F	(Dewailly et al., 2014)
Montserrat	15	2008	0.01		0.36					100		F	(Dewailly et al., 2014)
St. Lucia	20	2008	0.01		0.58					100		F	(Dewailly et al., 2014)
St. Kitts and Nevis	15	2008	0.01		0.64					100		F	(Dewailly et al., 2014)
St. Vincent and the Grenadines	50	2008	0.01		0.54					100		F	(Dewailly et al., 2014)
China[46]	**1149**	**2009**	**0.1**	**1.68**	**0.97**	**1.01**	**2.79**	**1.53**	**1.55**	**98.8**	**17–45**	**F**	(Qi et al., 2012)
China[47]	**454**	**2010**	**0.1**		**0.54**	**0.62**		**0.57**	**0.68**	**82**	**>18**	**F**	(Ding et al., 2015)
Denmark[48]	**858**	**2010**	**0.3**			**0.2**		**0.23**		**94.3**	**30.3**[#]	**F**	(Dalsager et al., 2018)
Ecuador[49]	**16**	**2011**	**0.1**		**0.12**	**0.07**				**35**	**28.4**[#]	**F**	(Handal et al., 2016)
France	**205**	**2002**	**0.008**			**<LOD**				**30.2**	**_**[50]	**F**	(Viel et al., 2015)
France	**1077**	**2011**	**0.014**		**0.36**	**0.36**		**0.5**	**0.5**	**99.7**	**> 18**	**F**	(Dereumeaux et al., 2018)
Ghana	**17**	**2014**	**0.1**		**0.23**					**75.5**	**26**	**F**	(Wylie et al., 2017)
Japan[51]	**231**	**2009**	**0.02**	**0.611**	**0.334**	**0.351**	**0.652**	**0.363**	**0.338**	**97.8**	**20–50**	**F**	(Zhang et al., 2013)
Mexico[52]	**187**	**1997**	**0.25**		**0.26**	**<LOD**				**44.9**	**26**[$]	**F**	(Watkins et al., 2016)

Country	N	Year	DL [ng/mL]	Volume-adjusted 3-PBA levels [ng/mL]			Creatinine-adjusted 3-PBA levels [mg/g cre]			DF [%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
Mexico[53]	21	1997	0.25		0.27	0.25				52.4		F	(Watkins et al., 2016)
Mexico[54]	21	1997	0.25		0.26	0.25				57.1		F	(Watkins et al., 2016)
Mexico[55]	21	1997	0.25		0.23	<LOD				42.9		F	(Watkins et al., 2016)
Puerto Rico [56]	**54**	**2010**	**0.1**		**0.2**	**<LOD**				**46.1**	**18–40**	**F**	(Lewis et al., 2014)
USA	**307**	**1998**	**16**			**18.3**			**19.3**	**65**	**>18**	**F**	(Berkowitz et al., 2003)
USA	137	1998	16						13.3		< 20	F	(Berkowitz et al., 2003)
USA	127	1998	16						19.3		20–24	F	(Berkowitz et al., 2003)
USA	43	1998	16						16.8		25–29	F	(Berkowitz et al., 2003)
USA	57	1998	16						22.7		30–34	F	(Berkowitz et al., 2003)
USA	22	1998	16						80.1		≥35	F	(Berkowitz et al., 2003)
USA[57]	78	1998	16						25.3			F	(Berkowitz et al., 2003)
USA[58]	104	1998	16						13.4			F	(Berkowitz et al., 2003)
USA[59]	198	1998	16						16.8			F	(Berkowitz et al., 2003)
USA[60]	6	1998	16						235.5			F	(Berkowitz et al., 2003)
USA	**205**	**1999**			**0.24**	**0.23**				**68.3**	**>18**	**F**	(Watkins et al., 2016)
USA	**388**	**2008**	**0.06**		**0.4**						**>18**	**F**	(Kalloo et al., 2018)

3-PBA, 3-phenoxybenzoic acid; cre, creatinine; DF, Detection Frequency; DL, detection limit (i.e., the limit of detection or limit of quantification, as reported); F, female; GM, Geometric Mean; M, male; N, number of samples.

mean age.

$ median age at delivery.

45 The earliest year is reported in the Table for studies where samples were collected over two or more years.

46 Study investigates pyrethroid pesticide exposures in pregnant women in an agricultural area of the Province of Jiangsu, China.

47 Samples were collected during hospital admission for delivery (within 3 days before delivery) from women who worked in agriculture and likely had physical contact with pyrethroids (permethrin or cypermethrin) used on crops and/or dietary exposure to pyrethroids.

48 N = 857 for creatinine adjusted values.

[49] Urine samples (n = 66) were collected repeatedly throughout pregnancy from 16 pregnant rose workers. The study also reported 3-PBA levels in urine samples (n = 50) that were collected repeatedly throughout pregnancy from 10 pregnant non-rose workers. The GM and mean 3-PBA levels in this population were 0.12 ng/mL and 0.07 ng/mL, respectively. These data are not reported in the Table based on the exclusion criteria.

[50] This study investigates several age groups ranging from < 27 to > 32 years old.

[51] Data from this cohort are also reported in a second reference.

[52] Urinary 3-PBA level samples of the total amount of pregnant women exposed only during the third trimester in Mexico City.

[53] Urinary 3-PBA level samples of pregnant women in their first trimester in Mexico City.

[54] Urinary 3-PBA level samples of pregnant women in their second trimester in Mexico City.

[55] Urinary 3-PBA level samples of pregnant women in their third trimester in Mexico City.

[56] A total of 114 samples from 54 pregnant women were analyzed at three time points of gestation: 20 ± 2 weeks, 24 ± 2 weeks, and 28 ± 2 weeks.

[57] Pregnant women from the Children's Environmental Health Study in New York City, New York, USA identifying as White.

[58] Pregnant women from the Children's Environmental Health Study in New York City, New York, USA identifying as African American.

[59] Pregnant women from the Children's Environmental Health Study in New York City, New York, USA identifying as Hispanic.

[60] Pregnant women from the Children's Environmental Health Study in New York City, New York, USA identifying as "other" race/ethnicity.

Table 3

Summary of volume and creatinine adjusted 3-PBA levels in adults environmentally exposed to pyrethroid pesticides reported in 22 publications meeting the inclusion criteria of the systematic review. The data are ordered by the country of origin and the year[61] of sample collection. In addition, the population characteristics, detection limit, detection frequency, and analytical methods are reported to facilitate the comparison between studies. Data of the entire study population (bold text) and selected subpopulations (normal text) are included in this Table).

Country	N	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels [mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
Canada	**74**	**2005**	**0.043**			**0.17**				**98.7**	**18–64**	**M/F**	(Fortin et al., 2008)
Canada [62]	**1159**	**2007**	**0.01**		**0.25**	**0.21**		**0.28**	**0.23**	**99.6**	**20–39**	**M/F**	(Health Canada, 2019)
Canada [63]	**1216**	**2007**	**0.01**		**0.27**	**0.25**		**0.34**	**0.30**	**99.2**	**40–59**	**M/F**	(Health Canada, 2019)
Canada [64]	**1073**	**2007**	**0.01**		**0.24**	**0.21**		**0.34**	**0.29**	**99.3**	**60–79**	**M/F**	(Health Canada, 2019)
Canada [65]	**345**	**2009**	**0.01**		**0.61** [&]	**0.48** [&]		**0.52**	**0.35** [&]	**100**	**20–39**	**M/F**	(Health Canada, 2019)
Canada [66]	**346**	**2009**	**0.01**		**0.40**	**0.36**		**0.41**	**0.35**	**100**	**40–59**	**M/F**	(Health Canada, 2019)
Canada [67]	**279**	**2009**	**0.01**		**0.36** [&]	**0.27** [&]		**0.42** [&]	**0.32**	**100**	**60–79**	**M/F**	(Health Canada, 2019)
Canada [68]	**375**	**2016**	**0.012**		**0.61** [&]	**0.48** [&]		**0.54**	**0.37** [&]	**100**	**20–39**	**M/F**	(Health Canada, 2019)
Canada [69]	**359**	**2016**	**0.012**		**0.55**	**0.53**		**0.51**	**0.39**	**99.9**	**40–59**	**M/F**	(Health Canada, 2019)
Canada [70]	**354**	**2016**	**0.012**		**0.48** [&]	**0.41**		**0.55**	**0.44**	**100**	**60–79**	**M/F**	(Health Canada, 2019)
China	**199**	**2004**	**<0.05**		**1.398**	**1.149**		**0.925**	**0.815**	**100**	**20–40**	**M**	(Han et al., 2008)
China	**240**	**2005**				**1.12**			**0.79**	**100**	**28.5** [#]	**M**	(Ji et al., 2011)
China [71]	**72**	**2013**	**0.1**			**1.09**				**94.40**	**62.5** [#]	**M/F**	(Han et al., 2017)
China [72]	**136**	**2013**	**0.1**			**0.74**				**88.97**	**60.0** [#]	**M/F**	(Han et al., 2017)
China [73]	**172**	**2015**	**0.013**	**0.999**	**0.372**	**0.501**	**1.423**	**0.535**	**0.688**	**89.0**	**16–45**	**F**	(Li et al., 2018)
China [74]	**247**	**2015**	**0.013**	**0.657**	**0.251**	**0.354**	**0.878**	**0.39**	**0.514**	**88.3**	**16–45**	**F**	(Li et al., 2018)
Germany	**38**	**2012**	**0.01**			**0.22**			**0.26**	**100**	**25–58**	**M/F**	(Schettgen et al., 2016)
Japan [75]	**322**	**1999**	**0.08**	**1.22**	**0.679**	**0.808**				**91.3**	**18–24**	**M**	(Imai et al., 2014)
Japan [76]	**143**	**2005**	**0.02**					**0.32**	**0.28**		**63.9** [#]	**M**	(Kimata et al., 2009b)

Country	N	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels [mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
Japan [77]	**448**	**2005**	**0.02**	**0.63**	**0.29**	**0.29**	**0.73**	**0.40**	**0.36**	**98**	**39–85**	**M/F**	(Ueyama et al., 2009)
Japan [78]	143	2005	0.02	0.6	0.32	0.31	0.59	0.32	0.28		39–85	M	(Ueyama et al., 2009)
Japan [79]	305	2005	0.02	0.65	0.28	0.28	0.80	0.45	0.44		39–85	F	(Ueyama et al., 2009)
Japan [80]	52	2005	0.02	0.48	0.26	0.25	0.54	0.39	0.41		39–41	M/F	(Ueyama et al., 2009)
Japan [81]	304	2005	0.02	0.67	0.31	0.30	0.80	0.42	0.36		50–69	M/F	(Ueyama et al., 2009)
Japan [82]	92	2005	0.02	0.58	0.26	0.27	0.61	0.36	0.31		70–85	M/F	(Ueyama et al., 2009)
Japan [83]	**66**	**2007**	**0.02**					**0.49**	**0.43**		**49.3** [#]	**M**	(Kimata et al., 2009b)
Poland [84]	**334**	**2008**	**0.1**	**0.32**	**0.17**	**0.16**	**0.3**	**0.16**	**0.13**	**71.59**	**22–44**	**M**	(Radwan et al., 2015)
Poland	**132**	**2010**	**0.1**	**0.393**	**0.26**	**0.255**	**0.327**	**0.22**	**0.19**	**80.00**	**5–77**	**M/F**	(Wielgomas et al., 2013)
South Africa [85]	**82**	**2009**	**0.05**						**3.34**		**31–49**	**F**	(Motsoeneng and Dalvie, 2015)
South Korea [86]	**6232**	**2009**			**1.47**	**1.55**				**99.78**	**> 19**	**M/F**	(Park et al., 2016)
South Korea	2893	2009			1.47	1.54				99.76	> 19	M	(Park et al., 2016)
South Korea	3339	2009			1.48	1.56				99.79	> 19	F	(Park et al., 2016)
Thailand [87]	**38**	**2017**	**1**	**20.3**	**16.7**					**36.8**	**18–65**	**M/F**	(Wongta et al., 2018)
USA	**833**	**1999**			**0.267**	**0.230**		**0.246**	**0.239**		**20–59**	**M/F**	(CDC, 2021a)
USA	**75**	**2000**	**0.1**	**0.57**	**0.18**	**0.15**	**0.5**	**0.15**	**0.11**	**56**	**20–54**	**M**	(Young et al., 2013)
USA [88]	**121**	**2001**	**0.2**	**0.6**		**0.3**	**0.5**		**0.2**	**66**	**20–49**	**M/F**	(Morgan, 2015)
USA	**1128**	**2001**			**0.314**	**0.270**		**0.311**	**0.282**		**20–59**	**M/F**	(CDC, 2021a)
USA [89]	**509**	**2001**			**0.303**	**0.250**		**0.372**	**0.319**		**≥ 60**	**M/F**	(CDC, 2021a)
USA	**1452**	**2004**	**0.64**			**0.76**			**0.75**	**58.50**	> 20	**M/F**	(McKelvey et al., 2013)
USA	602	2004	0.64			0.76			0.61	58.50	> 20	M/F	(McKelvey et al., 2013)
USA	850	2004	0.64			0.76			0.89	58.50	> 20	F	(McKelvey et al., 2013)
USA	708	2004	0.64			0.78			0.69	58.50	20–39	M/F	(McKelvey et al., 2013)
USA	554	2004	0.64			0.75			0.83	58.50	40–59	M/F	(McKelvey et al., 2013)
USA	190	2004	0.64			0.78			0.76	58.50	≥ 60	M/F	(McKelvey et al., 2013)

Country	N	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels [mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
USA[90]	411	2004	0.64			0.76			0.83	58.50	> 20	M/F	(McKelvey et al., 2013)
USA[91]	315	2004	0.64			0.87			0.63	58.50	> 20	M/F	(McKelvey et al., 2013)
USA[92]	180	2004	0.64			0.88			1.12	58.50	> 20	M/F	(McKelvey et al., 2013)
USA[93]	519	2004	0.64			0.67			0.63	58.50	> 20	M/F	(McKelvey et al., 2013)
USA[94]	**90**	**2007**	**0.58–0.75**			**0.82**			**0.61**	**64**	**18–27**	**M/F**	(Trunnelle et al., 2014b)
USA	**1110**	**2007**			**0.427**	**0.420**		**0.443**	**0.401**		**20–59**	**M/F**	(CDC, 2021a)
USA	**612**	**2007**			**0.335**	**0.300**		**0.418**	**0.363**		**≥ 60**	**M/F**	(CDC, 2021a)
USA	**50**	**2009**	**0.25**	**2.43**	**1.68**	**1.41**	**2.85**	**1.74**	**1.53**	**98**	**19–50**	**M/F**[95]	(Morgan et al., 2016)
USA	20	2009	0.25		1.73						19–50	F	(Morgan et al., 2016)
USA	30	2009	0.25		1.60						19–50	M	(Morgan et al., 2016)
USA	27	2009	0.25		1.59						≤ 30	M/F	(Morgan et al., 2016)
USA	23	2009	0.25		1.78						> 30	M/F	(Morgan et al., 2016)
USA	**1296**	**2009**			**0.416**	**0.390**		**0.419**	**0.365**		**20–59**	**M/F**	(CDC, 2021a)
USA	**646**	**2009**			**0.382**	**0.360**		**0.455**	**0.397**		**≥ 60**	**M/F**	(CDC, 2021a)
USA	**1632**	**2011**			**0.661**	**0.613**		**0.687**	**0.595**		**≥ 20**	**M/F**	(CDC, 2021b)
USA	**55**	**2012**	**0.03**	**1.52**						**52.70**	**> 18**	**M/F**	(Davis et al., 2013)
USA[96]	**55**	**2012**	**0.5**			**2.4**				**60**	**18–55**	**F**	(Arcury et al., 2018)
USA[97]	**28**	**2013**	**0.4**			**1.4**				**89.3**	**18–55**	**F**	(Arcury et al., 2018)
USA[98]	**1799**	**2013**			**0.674**	**0.620**		**0.728**	**0.598**		**≥ 20**	**M/F**	(CDC, 2021b)

3-PBA, 3-phenoxybenzoic acid; cre, creatinine; DF, Detection Frequency; DL, detection limit (i.e., the limit of detection or limit of quantification, as reported); F, female; GM, Geometric Mean; M, male; N, number of samples.

[#] mean age.

[&] data are marked as “use data with caution.”

[61] The earliest year is reported in the Table for studies where samples were collected over two or more years.

[62] N = 1155 for creatinine adjusted values.

[63] N = 1211 for creatinine adjusted values.

[64] N = 1073 for creatinine adjusted values.

[65] N = 343 for creatinine adjusted values.

[66] N = 344 for creatinine adjusted values.

[67] N = 278 for creatinine adjusted values.

[68] N = 371 for creatinine adjusted values.

[69] N = 358 for creatinine adjusted values.

[70] N = 353 for creatinine adjusted values.

[71] Cases diagnosed with coronary heart disease from Shanxi province, PR China.

[72] Age-matched healthy control group for cases diagnosed with coronary heart disease.

[73] Cases diagnosed with primary ovarian insufficiency.

[74] Age-matched health control group for women diagnosed with primary ovarian insufficiency.

[75] Japanese males were recruited from May 1999-May 2000 and April 2002-May 2003. The chemical analysis and the data are reported in (Yoshinaga et al., 2014).

[76] Rural residents from Hokkaido, Japan.

[77] Study of a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[78] Men from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[79] Women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[80] 39–49-year-old men and women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[81] 50–69-year-old men and women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[82] 70–85-year-old men and women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[83] Suburban residents from Aichi Prefecture, Japan.

[84] Data from this cohort are also reported in (Jurewicz et al., 2016, 2015; Radwan et al., 2014).

[85] Women living in towns near farming areas in the Western Cape region of South Africa.

[86] Data from the Korean National Environmental Health Survey.

[87] Nonfarm workers living for at least one year in San Pa Tong District, Chiang Mai Province, Thailand.

[88] N = 106 for creatinine adjusted values. The study population was mostly female (111 females and 10 male).

[89] N = 508 for creatinine adjusted values.

[90] Adults from the New York City, New York, USA, Health and Nutrition Examination Survey identifying as White, non-Hispanic.

[91] Adults from the New York City, New York, USA, Health and Nutrition Examination Survey identifying as Black, non-Hispanic.

[92] Adults from the New York City, New York, USA, Health and Nutrition Examination Survey identifying as Asian, non-Hispanic.

[93] Adults from the New York City, New York, USA, Health and Nutrition Examination Survey identifying as Hispanic.

[94] Study investigated residential pyrethroid exposures in adults.

[95] Population included whites, non-Hispanic and blacks, non-Hispanic. Hispanics, Asians, and Native Americans were excluded from the analysis due to the small sample size (<7) by group.

[96] Latina immigrants from Forsyth County, North Carolina, USA.

[97] Latina immigrants from Forsyth County, North Carolina, USA. Samples collected in 2012 were also analyzed from the same women.

[98] N = 1797 for creatinine adjusted values.

Table 4

Summary of volume and creatinine adjusted 3-PBA levels in agriculturally and other occupationally exposed workers reported in 11 publications meeting the inclusion criteria of the systematic review. The data are ordered by the country of origin and the year[99] of sample collection. In addition, the population characteristics, detection limit, detection frequency, and analytical methods are reported to facilitate the comparison between studies. Data of the entire study population (bold text) and selected subpopulations (normal text) are included in this Table).

Country	N	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels [mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
China[100]	**20**	**2010**	**0.1**	**16**		**14**	**12**		**12**	**100**	**20–52**	**M/F**	(Lu et al., 2013)
China[101]	**30**	**2010**	**0.1**	**26**		**16**	**31**		**14**	**100**	**18–44**	**M/F**	(Lu et al., 2013)
Japan[102]	**44**	**2004**	**0.04**					**3.9**		**97.7**	**22–59**	**M**	(Wang et al., 2007)
Japan[103]	**44**	**2005**	**0.04**					**12.2**		**95.5**	**22–53**	**M**	(Wang et al., 2007)
Japan[104]	**87**	**2005**	**0.02**	**0.76**	**0.38**	**0.36**	**0.81**	**0.45**	**0.43**	**98**	**39–85**	**M/F**	(Ueyama et al., 2009)
Japan[105]	41	2005	0.02	0.94	0.46	0.41	0.63	0.40	0.33		39–85	M	(Ueyama et al., 2009)
Japan[106]	46	2005	0.02	0.6	0.31	0.33	0.97	0.50	0.50		39–85	F	(Ueyama et al., 2009)
Japan[107]	11	2005	0.02	0.92	0.43	0.49	0.80	0.53	0.51		40–49	M/F	(Ueyama et al., 2009)
Japan[108]	56	2005	0.02	0.79	0.40	0.35	0.88	0.46	0.45		50–69	M/F	(Ueyama et al., 2009)
Japan[109]	20	2005	0.02	0.57	0.32	0.33	0.61	0.38	0.36		70–85	M/F	(Ueyama et al., 2009)
Japan[110]	**16**	**2007**	**0.02**					**5.4**	**5.5**	**100**	**38.2**[#]	**M**	(Kimata et al., 2009b)
Japan[111]	**14**	**2007**	**0.02**					**23.8**	**27**	**100**	**38.5**[#]	**M**	(Kimata et al., 2009b)
Mexico[112]	**20**	**2016**	**0.1**		**2.14**	**2.14**		**1.83**	**1.69**	**100**	**19–49**	**M**	(López-Gálvez et al., 2018)
South Africa[113]	**101**	**2009**	**0.05**						**3.61**		**27–40**	**F**	(Motsoeneng and Dalvie, 2015)
Thailand[114]	**136**	**2006**	**0.1**		**1.1**	**1.6**		**0.86**	**0.98**	**86.8**	**20–65**	**M**	(Panuwet et al., 2008)
Thailand[115]	67	2006	0.1		0.93	0.88		0.73	0.64	77.6	20–65	M	(Panuwet et al., 2008)
Thailand[116]	69	2006	0.1		1.4	2.0		1.0	1.1	89.9	20–65	M	(Panuwet et al., 2008)
Thailand[117]	**38**	**2017**	**1**	**40.9**	**27.52**					**44.7**	**18–65**	**M/F**	(Wongta et al., 2018)

Country	N	Year	DL[ng/mL]	Volume-adjusted3-PBA levels[ng/mL]			Creatinine-adjusted3-PBA levels [mg/g cre]			DF[%]	Age	Gender	Ref.
				Mean	GM	Median	Mean	GM	Median				
Thailand [118]	**31**	**2017**	**1**	**43.8**	**29.80**					**30.0**	**18–65**	**M/F**	(Wongta et al., 2018)
Thailand [119]	**17**	**2017**	**1**	**4.03**	**3.29**					**11.8**	**18–65**	**M/F**	(Wongta et al., 2018)
USA [120]	**17**	**2009**	**0.08**		**0.96**	**0.7**		**1.12**	**0.83**	**100**	**18–65**	**M/F**	(Wei et al., 2012)
USA [121]	17	2009	0.08		0.86	0.54		1.09	0.73	100	18–65	M/F	(Wei et al., 2012)
USA [122]	17	2009	0.08		1.01	0.84		1.17	0.92	100	18–65	M/F	(Wei et al., 2012)
USA [123]	17	2009	0.08		1.06	0.48		1.36	0.87	100	18–65	M/F	(Wei et al., 2012)
USA [124]	**11**	**2009**	**0.08**		**7.06**	**2.18**		**9.01**	**4.13**	**100**	**18–65**	**M/F**	(Wei et al., 2012)
USA [125]	11	2009	0.08		1.36	1.07		2.26	1.74	100	18–65	M/F	(Wei et al., 2012)
USA [126]	11	2009	0.08		14.4	5.16		17.6	6.88	100	18–65	M/F	(Wei et al., 2012)
USA [127]	11	2009	0.08		4.53	2.39		5.45	3.29	100	18–65	M/F	(Wei et al., 2012)
USA [128]	**105**	**2009**	**0.1**	**2.62**	**1.17**	**1.63**	**3.15**	**1.1**	**1.46**	**81.9**	**23–52**	**F**	(Trunnelle et al., 2014a)
USA [129]	**31**	**2012**	**0.1**			**2.4**				**74.2**	**18–55**	**F**	(Arcury et al., 2018)
USA [130]	**12**	**2013**	**0.4**			**1.0**				**91.7**	**18–55**	**F**	(Arcury et al., 2018)

3-PBA, 3-phenoxybenzoic acid; cre, creatinine; DF, Detection Frequency; DL, detection limit (i.e., the limit of detection or limit of quantification, as reported); F, female; GM, Geometric Mean; M, male; N, number of samples.

[#]mean age.

[99]The earliest year is reported in the Table for studies where samples were collected over two or more years.

[100]Textile worker from Eastern China (plant 1). 3-PBA levels are reported only for the second urine collection. Workers were actively working in the plant during the sampling period.

[101]Textile worker from Eastern China (plant 2). 3-PBA levels are reported only for the second urine collection. Workers were actively working in the plant during the sampling period.

[102]Urinary 3-PBA levels among 44 pest control operators who sprayed during winter (off-season) in Japan. Age range represents the entire study population (n = 78).

[103]Urinary 3-PBA levels among 44 pest control operators who sprayed during summer (high-season) in Japan. Age range represents the entire study population (n = 66).

[104]Study of a middle-aged and elderly population of farmers from a rural area of Hokkaido, Japan. Individuals were involved in the spraying of pesticides based on a self-administered questionnaire. The data are also reported in (Kimata et al., 2009a).

[105] Men from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[106] Women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[107] 39–49 year old men and women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[108] 50–69 year old men and women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[109] 70–85 year old men and women from a middle-aged and elderly general population from a rural area of Hokkaido, Japan. The data are also reported in (Kimata et al., 2009a).

[110] Pest control operators who did not spray pesticides during the week prior to sample collection.

[111] Pest control operators who sprayed pesticides during the week prior to sample collection.

[112] Study included only migrant farmworkers from the central region of Sonora, Mexico, who did not apply pesticides.

[113] Women living on farms in the Western Cape region of South Africa. This cohort includes women mostly farm workers plus several farm residents who are not working on the farm.

[114] Samples from the Pong Yaeng and Inthakhin subdistricts in Chiang Mai Province, Thailand.

[115] Samples from the Pong Yaeng subdistricts in Chiang Mai Province, Thailand.

[116] Samples from the Inthakhin subdistricts in Chiang Mai Province, Thailand.

[117] Urine sample from rice grower workers ages 18 to 6 who had lived for at least one year in San Pa Tong District, Chiang Mai Province, Thailand.

[118] Urine sample from longan grower workers who had lived for at least one year in San Pa Tong District, Chiang Mai Province, Thailand.

[119] Urine samples from vegetable grower workers who had lived for at least one year in San Pa Tong District, Chiang Mai Province, Thailand.

[120] Total urine samples were collected from flight attendants in a non-disinsection aircraft.

[121] Total samples were collected preflight from flight attendants in a non-disinsection aircraft.

[122] Total samples were collected postflight from flight attendants in a non-disinsection aircraft.

[123] Total samples were collected 24 h post-flight from flight attendants in a non-disinsection aircraft.

[124] Total samples were collected from flight attendants in a disinsection aircraft.

[125] Total samples were collected from flight attendants in a pre-flight disinsection.

[126] Total samples were collected from flight attendants in post-flight disinsection.

[127] Total samples were collected from flight attendants with a 24 h post-flight disinsection.

[128] Women from the Mexican Immigration to California: Agricultural Safety and Acculturation (MICASA) study in Mendota, California, USA (for data of children from the same study, see Table 1). N = 102 for creatinine adjusted values.

[129] Latina farmworkers from Harnett, Johnston, and Sampson Counties, North Carolina, USA.

[130] Latina farmworkers from Harnett, Johnston, and Sampson Counties, North Carolina, USA. Samples collected in 2012 were also analyzed from the same women, see footnote 129.

Table 5

The statistical analysis of the 3-PBA levels summarized in Tables 1 to 4 using a Linear Mixed-Effect Model reveals significant changes in urinary 3-PBA levels with time (i.e., sampling year) in populations worldwide, in North America, and Asia. See Figs. 1–4 for graphical representations of the underlying data by country and sampling year.

Region	Population	Volume-adjusted						Creatinine-adjusted					
		Median			GM			Median			GM		
		Direction	p-value	N	Direction	p-value	N	Direction	p-value	N	Direction	p-value	N
Worldwide	Children	up	0.0659	32	up	0.0184	26	up	0.7162	28	up	0.262	22
	Pregnant Women	down	0.1221	8	up	0.7403	11	down	0.0129	6	down	0.6341	4
	Adults	up	0.0697	38	up	0.1709	29	up	0.0371	34	up	0.0377	28
	Occupational	up	0.6623	10	na	na	9	up	0.7028	11	up	0.6909	10
North America	Children	up	0.4913	24	up	0.0255	20	up	0.8057	17	up	0.3056	14
	Pregnant Women	up	0.2022	2	up	0.2022	3	up	0.2022	1	na	na	0
	Adults	up	0.0005	26	up	0.0015	20	up	0.0189	23	up	0.0021	20
	Occupational	na	na	5	na	na	3	na	na	3	na	na	3
Asia	Children	up	0.9995	5	up	0.9926	5	down	0.9695	6	na	na	7
	Pregnant Women	down	0.9999	3	down	0.9983	3	down	0.3861	3	down	0.9873	3
	Adults	down	0.0828	8	down	0.0103	5	down	0.3845	7	down	0.4064	6
	Occupational	na	na	3	na	na	1	up	0.9998	5	na	na	5

N, number of studies, see Tables 1–4; na, not enough data for a 3-PBA vs. time analysis.