

Systematic age, sex, and temporal trends analysis of human exposure to multiple chemicals in Australia and the US

Abstract

Biomonitoring plays an important role in chemical exposure and risk assessment. Pooling several biological specimens from multiple individuals into a single sample enables the identification of exposure trends and susceptible populations in a cost-effective manner, especially for children younger than five with limited extractable serum. Studies analyzing pooled samples have been conducted in Australia for multiple classes of chemicals, but without a data repository that would enable systematic analyses of age and time trends. This study, therefore, aims to conduct a systematical analysis of age, sex, and temporal trends across multiple chemical classes. Based on the regression, we observed evidence that generally, serum brominated flame retardants (BFRs) are negatively associated with age, indicating that children are more susceptible to those exposures. In contrast, most Dioxins (DOX) and polychlorinated biphenyls (PCBs) increase with age suggesting an accumulative effect in older adults. In addition, we conducted a detailed analysis of PFAS, which showed that PFAS levels are decreasing over time, though the declines are not consistent across age groups, sexes, and PFAS substances. Furthermore, we compared the trends in this study with those based on the NHANES data, which did not include data for children younger than 5 years of age. Comparison indicates that temporal trends are similar, but age trends are different.

1. Introduction

Exposures that cause chronic illnesses frequently occur over a long period of time, perhaps decades, before the disease is diagnosed. To characterize an individual's exposure related to health over the life course, we need to understand how chemical biomarker concentrations change over time and by age (Betts, 2012). Currently, substantial research has been done on age and temporal trends of human exposure to chemicals including brominated flame retardants (BFRs), dioxins (DOX), organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and per- and polyfluoroalkyl substances (PFAS) (Arisawa et al., 2018; Iszatt et al., 2015; Toms et.al, 2009), though most of those existing studies tend to focus on individual classes of compounds rather than analyzing their trends in a comprehensive study and contrasting their respective behaviors.

Comprehensive studies would allow us to gather data on vulnerable populations, such as children. Children have been shown to be more vulnerable than adults to toxicant exposures such as BFRs (Malliari, 2017), PFAS (Rappazzo, 2017), due to characteristics such as lower body weight and initial development stage. Also, because of their frequent mouthing behavior, children have higher exposures to chemicals per unit of body weight. Thus, it is critical to conduct a comprehensive trend analysis that includes young ages and identify substances to which children are particularly exposed (Aylward et al., 2014). However, data coverage for children under 5 years old is incomplete due to ethical considerations and the limited amount of blood that can be collected at a younger age, thus younger ages are missing from comprehensive surveys such as NHANES in the US and related age and time-trend studies (Nguyen et al., 2019).

Pooling several biological specimens from multiple individuals into a single sample enables the identification of exposure trends and susceptible populations in a cost-effective manner, especially for children younger than five with limited extractable serum. Studies analyzing pooled

samples have been conducted in Australia for multiple classes of chemicals (Toms et al, 2009, 2018) and on several classes of chemicals. However, the data are spread over multiple chemical class-specific papers and cannot be easily accessed and compared across chemical classes. Therefore, a consistent data repository is needed to systematically analyze age and time trends.

The main objective of this paper is therefore to create a consistent database of Human Biomonitoring Measurements (HBM) in Australia that systematically covers children younger than 5 years and to provide a systematic analysis of age, sex, and time trends across multiple chemical classes to identify chemicals with higher concentrations in young children. More specifically, this study aims to a) Set up a unified database of chemicals analyzed in pooled blood and serum samples from four Australian labs; b) Characterize the coverage and main biomarkers trends; c) Examine the temporal and age trends of all chemicals, identifying chemicals with high exposures in children, particularly in children under the age of five; and d) Provide an in-depth detailed analysis of PFAS trends, comparing Australian trends with US trends from NHANES research (Nguyen et al., 2019).

2. Material and Methods

Data analysis was performed including from raw data collection to data cleaning, then to statistical analysis, and visualization. Details are shown in the following procedure shown in Figure 1. Cross-sectional data on demographic and chemical exposure levels have been collected from 2002-2017 in Australia for an initial number of 330 pooled samples and 244 biomarkers. Because data were analyzed in different labs with inconsistent data formats, we first harmonized code names for each chemical measurement by creating a unique ID with a reference to the QAEHS freezer database for each sample. Then we conducted a statistical analysis on the temporal

and age trends separately for each sex and compared them with previous age-based pattern analysis for the US based on NHANES data (Nguyen et al., 2019).

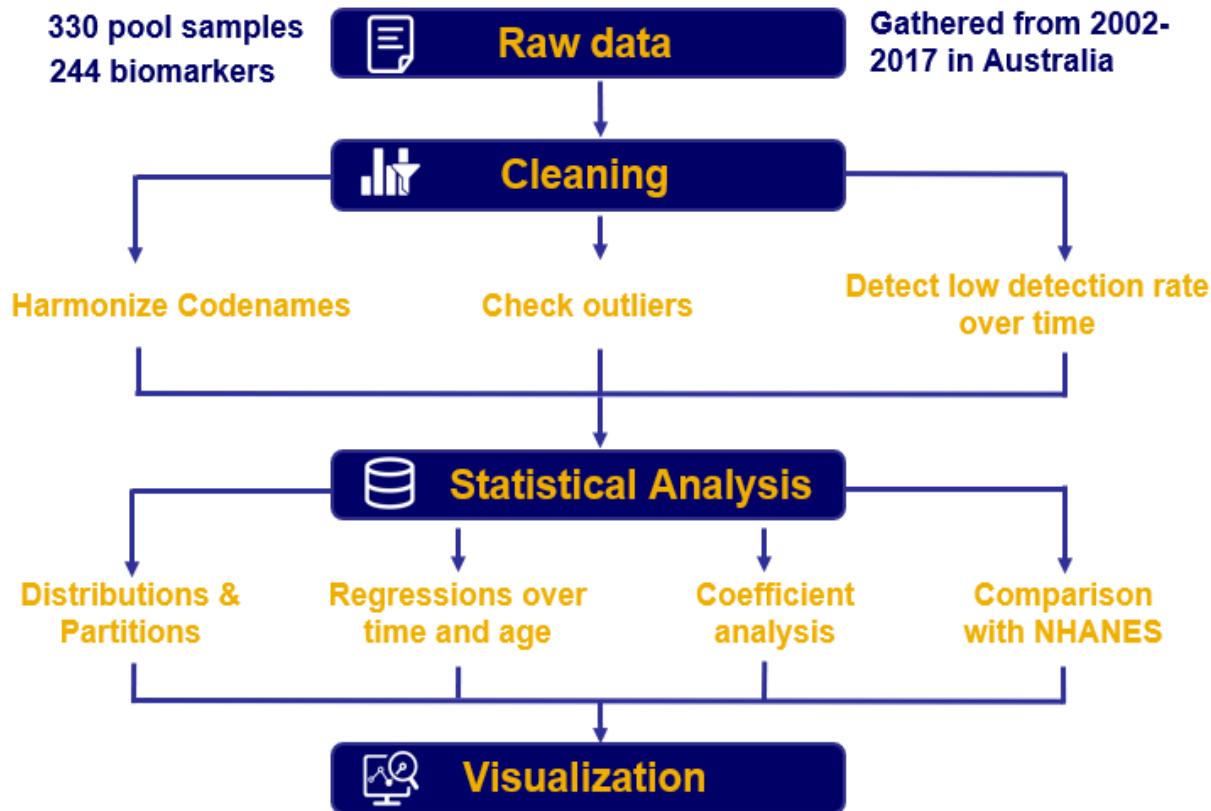


Figure 1 Schematic depiction of the process to perform data analysis from raw data to visualization

2.1. Study population and chemical measurements

Blood serum measurements were gathered for BFRs, DOX, OCPs, PCBs and PFAS from 2002-2017 in Australia for an initial number of 330 pooled samples, and 244 biomarkers. For each pooled sample, participants' age, sex, location, collection year were provided. The mean age of each pool was determined by averaging the ages of all donors included in that pool. We then stratified ages into different age groups in the unit of years old: 0-5, 5-15, 15-30, 30-45, 45-60, >60.

2.2. Establishment of human biomarker database (HBD)

Sample characterization and coverage by cycle:

Table 1 presents the number of samples and the chemical coverage for each cycle. 24 pooled samples were created for most periods covering 6 age groups for each of the 2 sexes, with two replicates. A larger number of samples was collected for 2002-2003 to cover Australia's northeastern, southwestern, southern, western, and rural areas. Each sample has unique attributes including age, sex, region, year of collection, sample type and was given a unique ID based on the freezer unique code.

Sampling information				Chemical coverage				
Collection period	# Pooled Samples	Number in pool	Region	BFRs	DOX	OCPs	PCBs	PFAS
2002-03	104	24, 28, 100	NE, SW, S, W, R	48	28	9	37	8
2004-05	24	100	NE	47	29	NA	NA	NA
2006-07	81	Mostly 30; some are 12, 19, 27	NE	13	NA	9	36	8
2008-09	24	100	NE	12	21	9	37	8
2010-11	24	100	NE	12	21	9	37	8
2012-13	51	100	NE	11	21	9	37	8
2014-15	128	20. Some are not provided	NE	NA	NA	NA	NA	28
2016-17	48	NA	NE	NA	NA	NA	NA	28

Table 1. Sample size, collection region and number of chemicals measured in each collection cycle
(NE: Northeast; SW: Southwest; S: South; W: West; R: Rural; NA: Not provided)

Chemical coverage:

The right part of Table 1 summarizes the chemical coverage. The number represents how many chemicals were measured in the collection period. For example, 48 different BFRs were measured in the collection period 2002-03. Based on the table 1, measurements for BFRs, DOX, OCPs, and PCBs are provided for most cycles from 2002 to 2013. For PFAS, on which we will conduct in-depth research, data are available for each collection period from 2002 to 2017 except for the 2004-2005 period, and specific data for young age groups lower than 5 years old are provided.

Chemical family and Variable types:

In each sampling cycle, the value detected, the limit of detection (LOD), whether detected or not are provided for each measurement. Since the data were analyzed by different labs using different formats, we needed to harmonize the code names before analyzing the data. Accordingly, each chemical measurement was given a unique name (details will be provided in the supplementary data).

The first three letters of the harmonized code name represent sample type, type of adjustment, variable type, respectively and the following letters are the chemical abbreviation name. For example, SWVPFOA, the first letter ‘S’ represents the sample is blood serum; the second letter ‘W’ means the type of adjustment is wet weight concentration with the unit of ppt - pg/gwet weight; the third letter ‘V’ indicates the value associated with this code is the value detected; and the following letters ‘PFOA’ show the chemical is Perfluoro-n-octanoic acid.

2.3. Statistical analysis of time, age, and sex trends

R version 4.1.1 is used to perform all the statistical analyses.

To get fairly unbiased averages and standard deviations, we substituted the LOD with $\frac{LOD}{\sqrt{2}}$ for all measurements below LOD. Then we calculated the detection frequencies of each chemical biomarker and only included those with detection frequencies of 50% or above.

Here we used multivariate regression models following log-transformation of the data.

$$\begin{aligned} \log_{10}(X_{chemical concentration}) = & \beta_{age} \times (X_{age} - \overline{X}_{age}) + \beta_{age^2} \times (X_{age} - \overline{X}_{age})^2 \\ & + \beta_{sample year} \times (X_{sample year} - X_{starting year}) + \beta_{sex} \times X_{sex} + \alpha \end{aligned} \quad (1)$$

where $X_{chemical concentrations}$ is the unadjusted chemical biomarker concentration for all participants. X_i , where $i \in \{age, age^2, sample\ year, sex\}$, is the i covariate for all participants, β_i is the linear regression coefficient for the i covariate, and α is the intercept.

\overline{X}_{age} is designated to 28 years old, which is the mean age of all pooled samples, and $X_{sample\ year}$ is 2002, which is the starting year of sampling. For the sex variable, we set X_{sex} to be 1 when the participants are female and 0 when they are male.

For PFOA, PFNA, PFHxS, PFOS, $X_{chemical concentration}$ for the age groups 0 - 5 and 5 - 15 were averaged after log transformation, since the sample size for these two age groups are less than 30, much lower than other pools in which there are typically 100 samples. Smaller pools will have more variation, which may bias the regression.

3. Results and discussion

3.1. Database and data characterization

Figure 2 shows the count of biomarkers for each chemical class, 4 BFRs, 6 PFASs, 5 OCPs, 19 Dioxins, and 10 PCBs biomarkers have been included in the multivariate regression. Figure 3

shows ranges of linear regression coefficient of age, i.e., β_{age} for each chemical class. These values indicate the log-transformed change in biomarker concentration along with one-year age increase. Based on the Figure 3, BFRs show negative association with age, indicating a high concentration in younger population; PFASs show little to no variation with age in general; while other persistent chemicals including OCPs, DOX and PCB are increasing with age, reflecting an accumulative effect in elderly people.

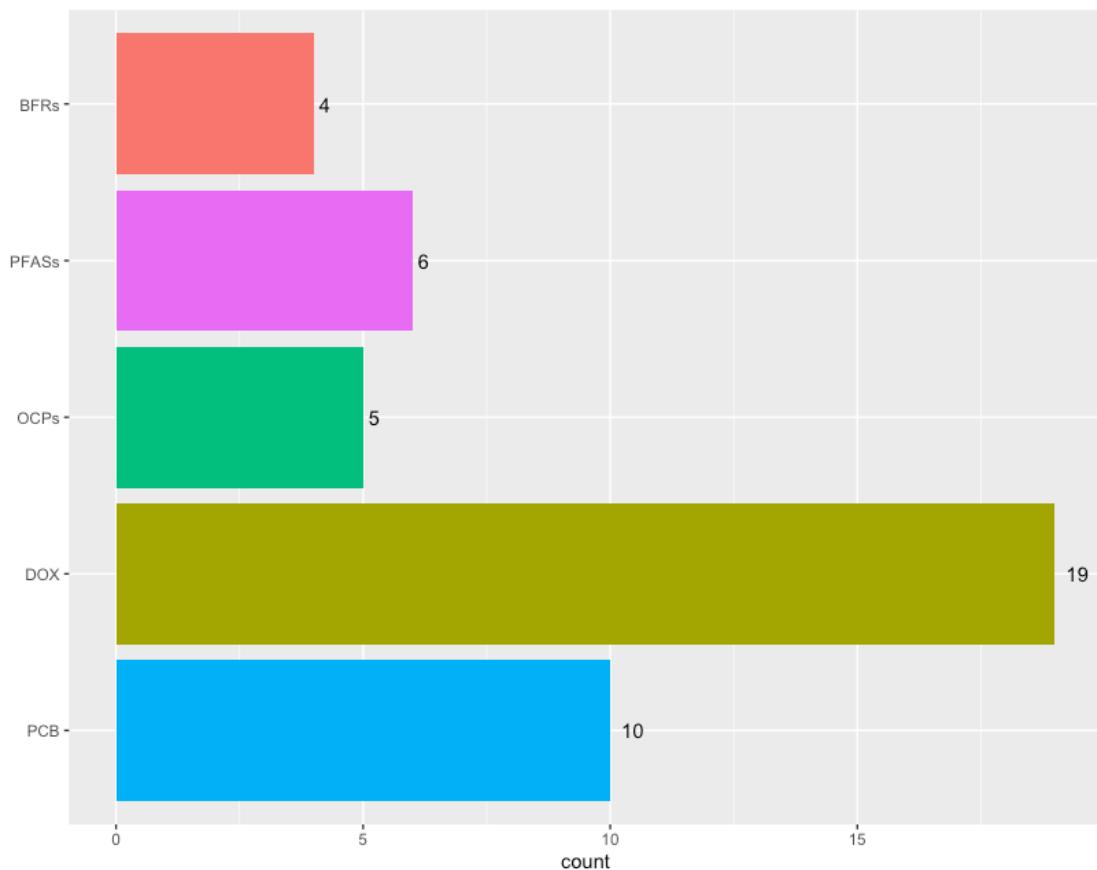


Figure 2 Number of chemical biomarkers included in the regression for each chemical type

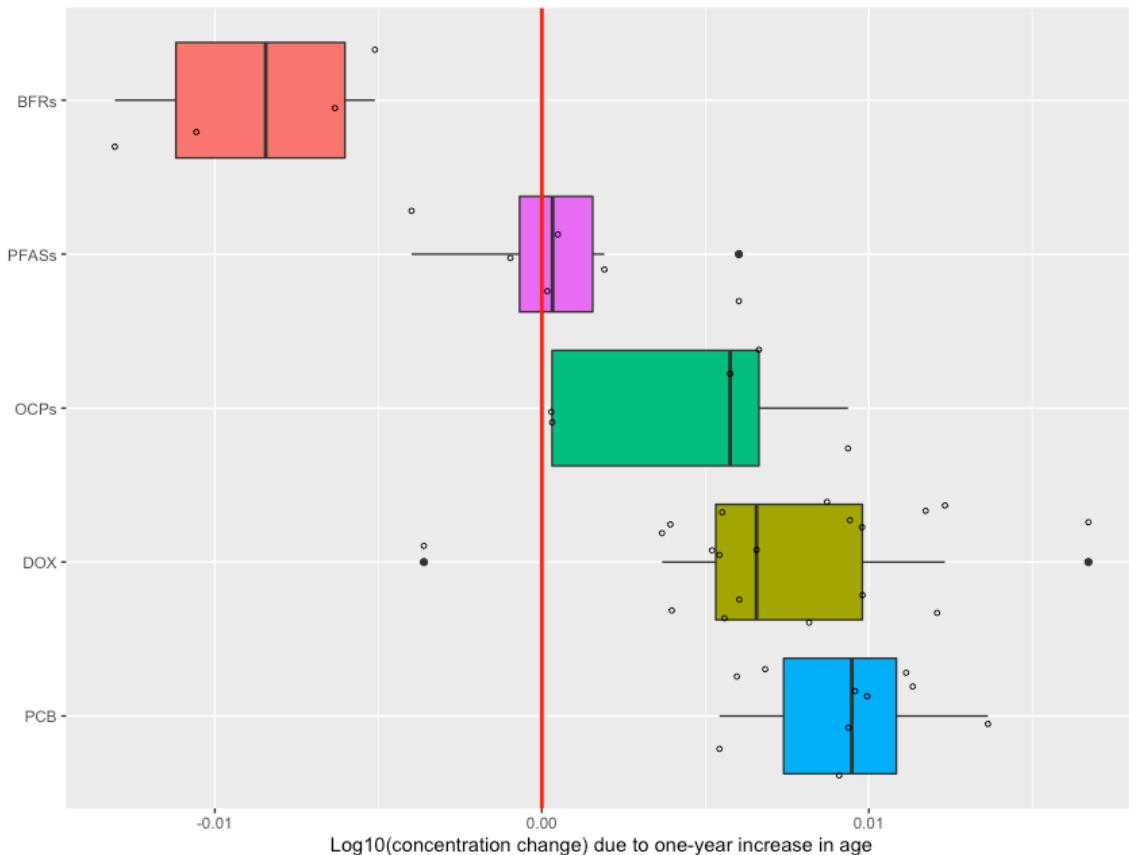


Figure 3 Ranges of log change in chemical concentration due to a one-year increase in age, i.e., linear age coefficients (β_{age})

3.2 Age, time, and sex trends of BFRs, DOX, OCPs, PCBs, PFAS

Given that a linear relationship between age and log-transformed chemical concentrations may not be representative of how biomarkers level change with age, we include centered age square $\overline{X_{age}}^2$ as another predictor in the chemical-specific regression models to better characterize this relationship. β_{age} and β_{age}^2 are the coefficients associated with $\overline{X_{age}}$ and $\overline{X_{age}}^2$. A positive β_{age} shows an increase in biomarker levels along with age, while a negative value indicates that biomarkers degrade with age. A positive β_{age}^2 indicates a convex (or U-shape) association between log-transformed concentration and age while a negative value indicates a concave (or n-shape) relationship.

Figure 4 below summarizes the results for age from the quadratic regression model by presenting the association between β_{age} and β_{age}^2 across all chemicals. The chemical categories are denoted by different shapes, and colors show the different chemicals. The boundary line $\frac{\beta_{age}^2}{\beta_{age}} > \frac{1}{\bar{X}_{age} - X_{age}} = \frac{1}{28 - 5} = \frac{1}{23}$ differentiates chemicals with higher levels in children from those with higher levels in the older population. Based on the equation below, chemicals on the boundary show the equal biomarker level for a child of 5 years old and an adult of 28 years old.

$$\beta_{age} \times (X_{age} - \bar{X}_{age}) + \beta_{age^2} \times (X_{age} - \bar{X}_{age})^2 = 0$$

$$\frac{\beta_{age}^2}{\beta_{age}} = \frac{1}{\bar{X}_{age} - X_{age}} = \frac{1}{23}$$
(2)

Chemicals in the upper-left quadrant tend to be descending and convex across age groups, indicating that the higher levels of biomarkers appear in the young population. All the BFRs denoted in the square appear in this area. Notably, some of the PFAS, including Me-PFOSA-AcOH, PFOA are also found in this area, which indicates that children are more susceptible to these PFASs exposure compared to adults. Most DOX and PCB lie in the upper-right quadrant and below the boundary line, suggesting an accumulative effect in the elderly population.

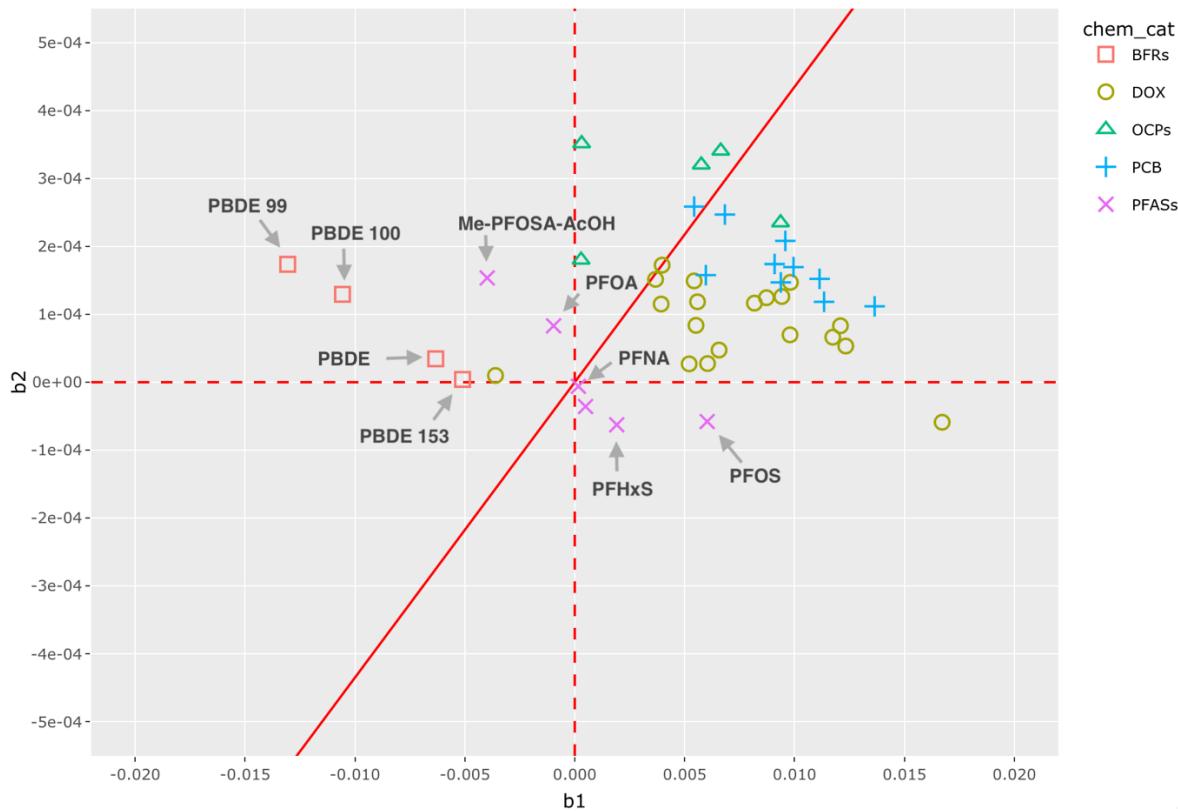


Figure 4 Association between β_{age}^2 and β_{age} for 44 substances for all ages, with shapes indicating chemical classes and colors indicating different chemicals ($b1 = \beta_{age}$, $b2 = \beta_{age}^2$)

To further quantify the factor of biomarker levels between children and adults, two reference lines are calculated and added to the graph 5. The line above the boundary line indicates the concentrations in 5-year-old children are as twice as those in the adults of 28 years old. PBDE 99 and PBDE 100 are above the boundary line, indicating that children under the age of 5 have a concentration more than twice as high as adults ages 28 or older. PBDE 99 and PBDE 100 are above the boundary line, indicating that children under the age of 5 have a concentration more than twice as high as adults ages 28 or older.

$$factor = \frac{X_{chemical\ concentration\ for\ 5\ y/o\ children}}{X_{chemical\ concentration\ for\ 28\ y/o\ adults}}$$

Upper boundary line (factor = 2):

$$\beta_{age} \times (X_{age} - \overline{X_{age}}) + \beta_{age^2} \times (X_{age} - \overline{X_{age}})^2 = \log_{10}(2)$$

$$\beta_{age^2} = \frac{1}{\overline{X_{age}} - X_{age}} \times \beta_{age} + \frac{\log_{10} 2}{(\overline{X_{age}} - X_{age})^2} = \frac{1}{23} \times \beta_{age} + 5.69 \times 10^{-4}$$

(3)

Lower boundary line (factor = 1/2):

$$\beta_{age} \times (X_{age} - \overline{X_{age}}) + \beta_{age^2} \times (X_{age} - \overline{X_{age}})^2 = \log_{10}\left(\frac{1}{2}\right)$$

$$\beta_{age^2} = \frac{1}{\overline{X_{age}} - X_{age}} \times \beta_{age} + \frac{\log_{10} 2}{(\overline{X_{age}} - X_{age})^2} = \frac{1}{23} \times \beta_{age} - 5.69 \times 10^{-4}$$

(4)

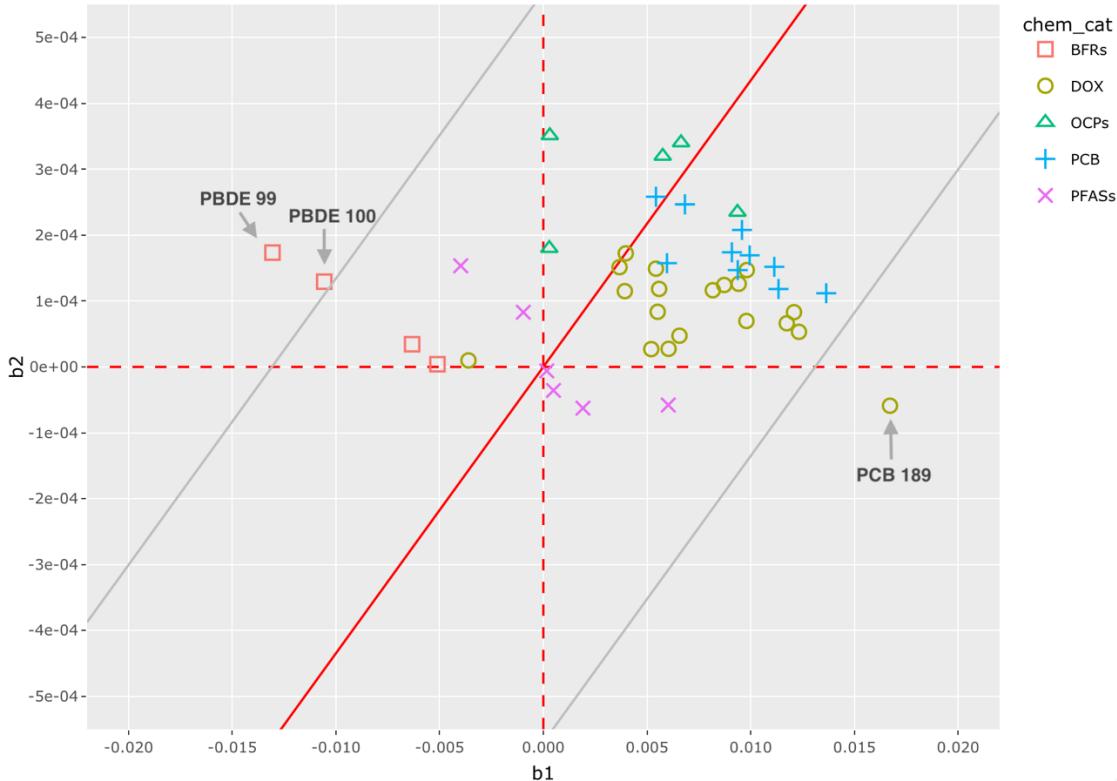


Figure 5 Association between β_{age}^2 and β_{age} for 44 substances for all ages, with shapes indicating chemical classes and colors indicating different chemicals ($b1 = \beta_{age}$, $b2 = \beta_{age}^2$); upper and lower boundary lines indicate biomarker levels in children with 5 y/o are as twice or half as high those in adults ages 28, respectively

3.3 Trend analysis of BFRs

Across all the collection periods, BFRs concentrations in serum are the highest in the youngest group and decrease until 40 or older (Fig. 6). The observed age trends can be explained by the children's frequent hand-to-mouth activities and dermal contact with BFRs treated products including bedding, clothing (Mohamed et al., 2018) and plastic toys (Fatunsin et al., 2020).

Temporal trends of BFRs concentrations are depicted in the Figure 7. The levels of PBDE 47, PBDE 99 and PBDE 100 decrease across all the age groups while the most rapid decrease has been observed in the children. The decreasing trends are consistent with the previous studies that observed a significant reduction in PBDEs concentrations since the commercial Penta- and Octa-PBDE mixtures was banned in Australia in 2005 (Drage et al., 2019).

PBDE 153 concentrations also decrease rapidly in children while for people aged between 5 – 30 years, PBDE 153 concentrations in blood serum show a peak around 2006 and followed by a decrease in 2011 and 2013. And for participants older than 30, PBDE 153 even increases with time. The inconsistent trends for PBDE 153 across the ages are likely related to the long half-life of PBDE 153 that can be up to 12.4 years (Geyer et al., 2004).

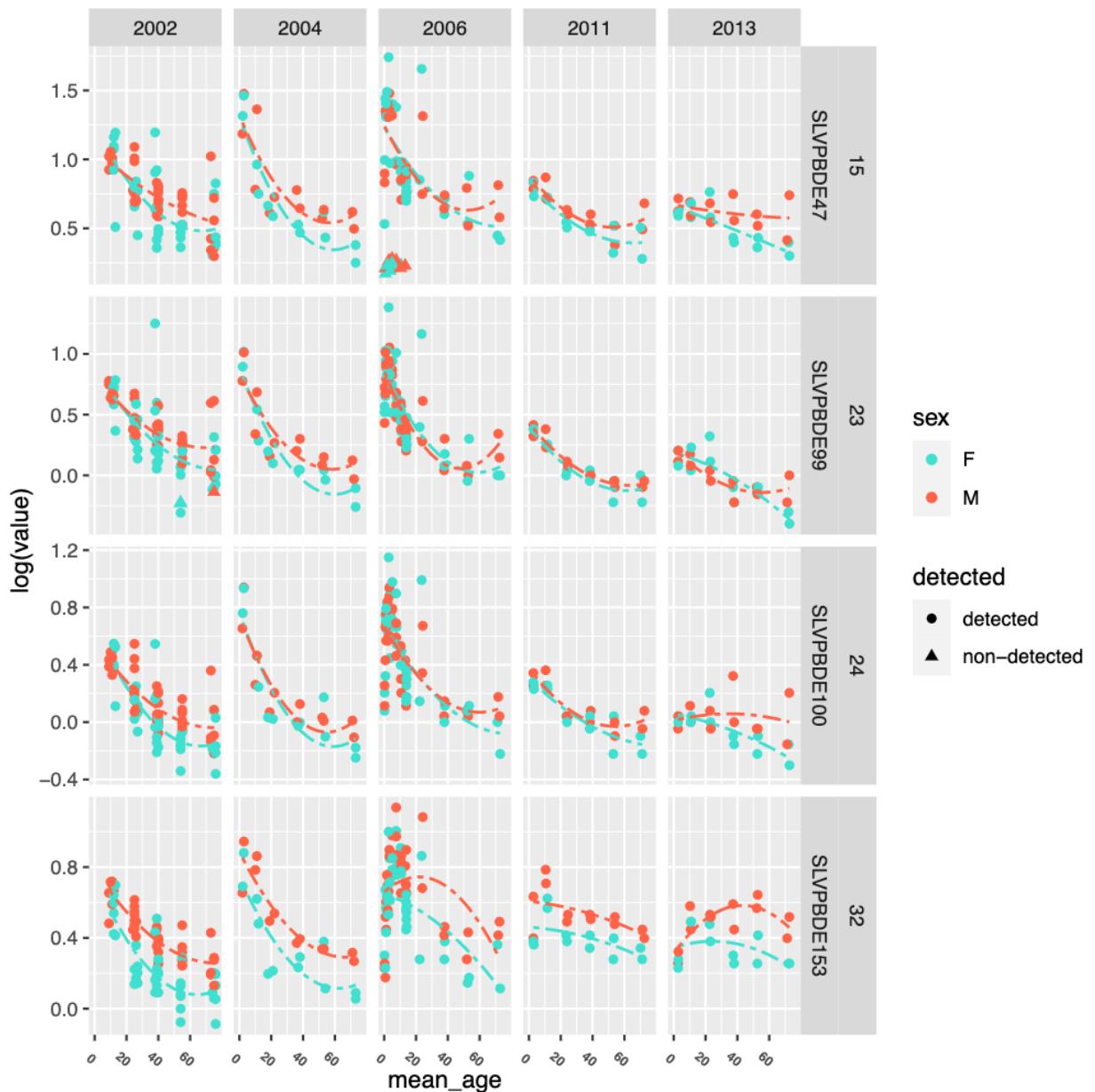


Figure 6 Age trends of PBDE 47, PBDE 99, PBDE 100, PBDE 153 across all the sampling years (y axis: \log (detected value) or LOD/ if not detected; unit: ppb - ng/glipid)

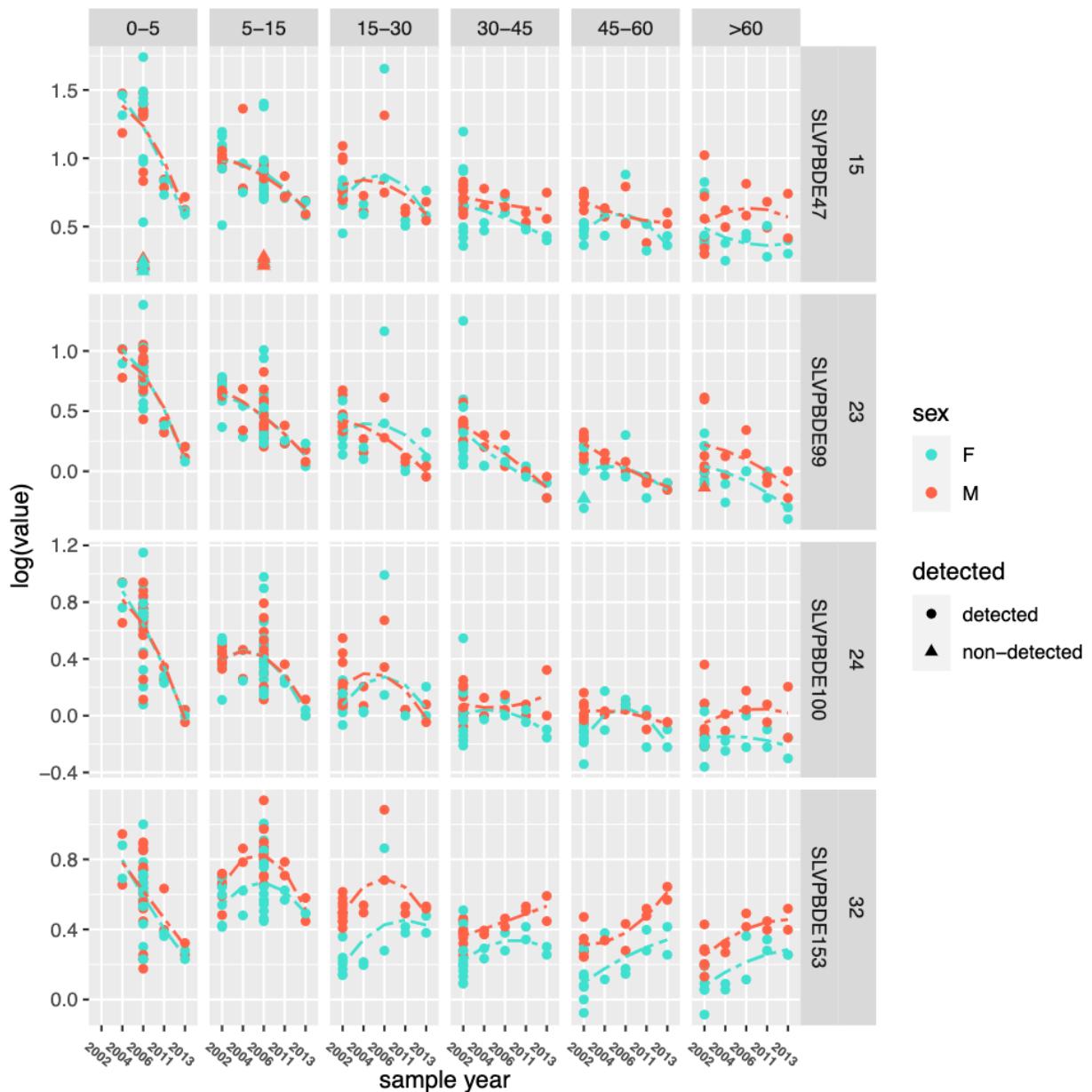


Figure 7 Temporal trends of PBDE 47, PBDE 99, PBDE 100, PBDE 153 from 2002 to 2017 across all the age groups (y axix: $\log(\text{detected value})$ or $\text{LOD}/\sqrt{2}$ if not detected; unit: ppb - ng/glipid)

3.4 In-depth trend analysis of PFAS

As shown in Figure 8, patterns of PFAS concentration by age vary in Australia. PFOS concentrations appear to increase from birth across all years for both females and males. Concentrations in women, however, show less growth with age, especially when for those between

20 and 60 years of age. Females and males exhibit more distinct trends in PFHxS. Males' concentrations peak around the age of 40, while concentrations are the lowest for women at the same age.

PFOA concentrations decrease before the age of 30 - 40 but then rise. This pattern suggests that children and the elderly experience higher exposures. The high concentration in children is most likely explained by the exposure to PFOA via intake from breast milk and more frequent contact with house dust (Winkens et al., 2017). Intermediate age groups have lower concentrations because of dilution caused by growth. A few factors could contribute to the high concentration in the elderly, including a potentially lower elimination rate due to degraded renal function (Gekle, 2017).

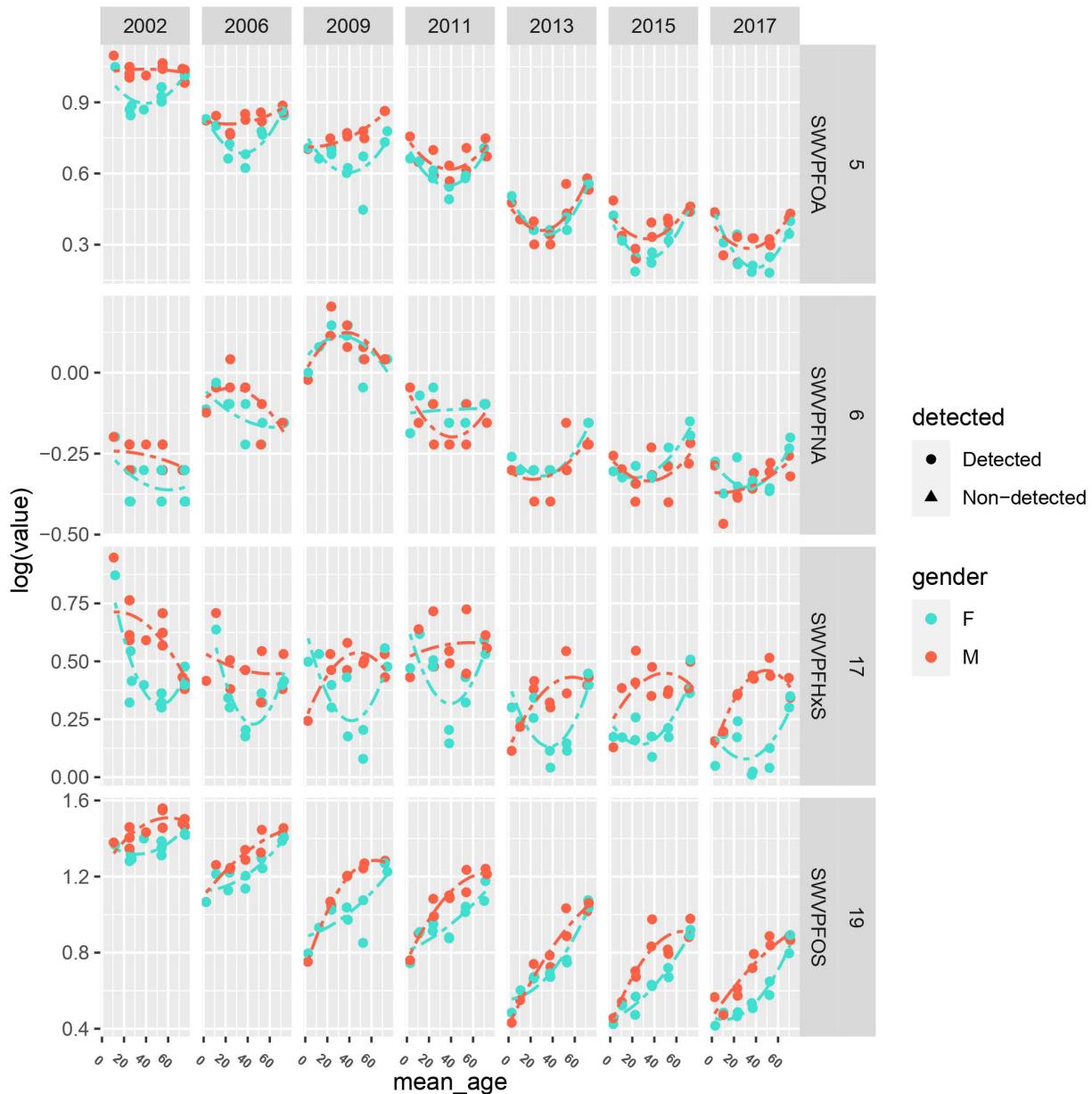


Figure 8 Age trends of PFOA, PFNA, PFHxS, PFOS across all the sampling years (y axis: $\log(\text{detected value})$ or $\text{LOD}/\sqrt{2}$ if not detected; unit: ppt - pg/g wet weight)

Figure 9 shows the quadratic temporal trend of PFAS concentration across all age groups. Over the 15 years from 2002 to 2007, PFAS concentrations have been decreasing by a factor of 3 for PFOA and PFOS, by a factor 2 for PFHxS. PFNA concentrations exhibit a downward U-shape, peaking in 2009 and decreasing in the following decade.

The decreasing trends, however, are not consistent across all age groups. Children under 5 years old experience a slower decline in PFOA, whereas PFHxS declines at all ages but increases before decreasing in the elderly over age 60. Notably, PFHxS levels in females are much lower than in males for middle-aged people, which is consistent with our finding in age trends across all sampling years.

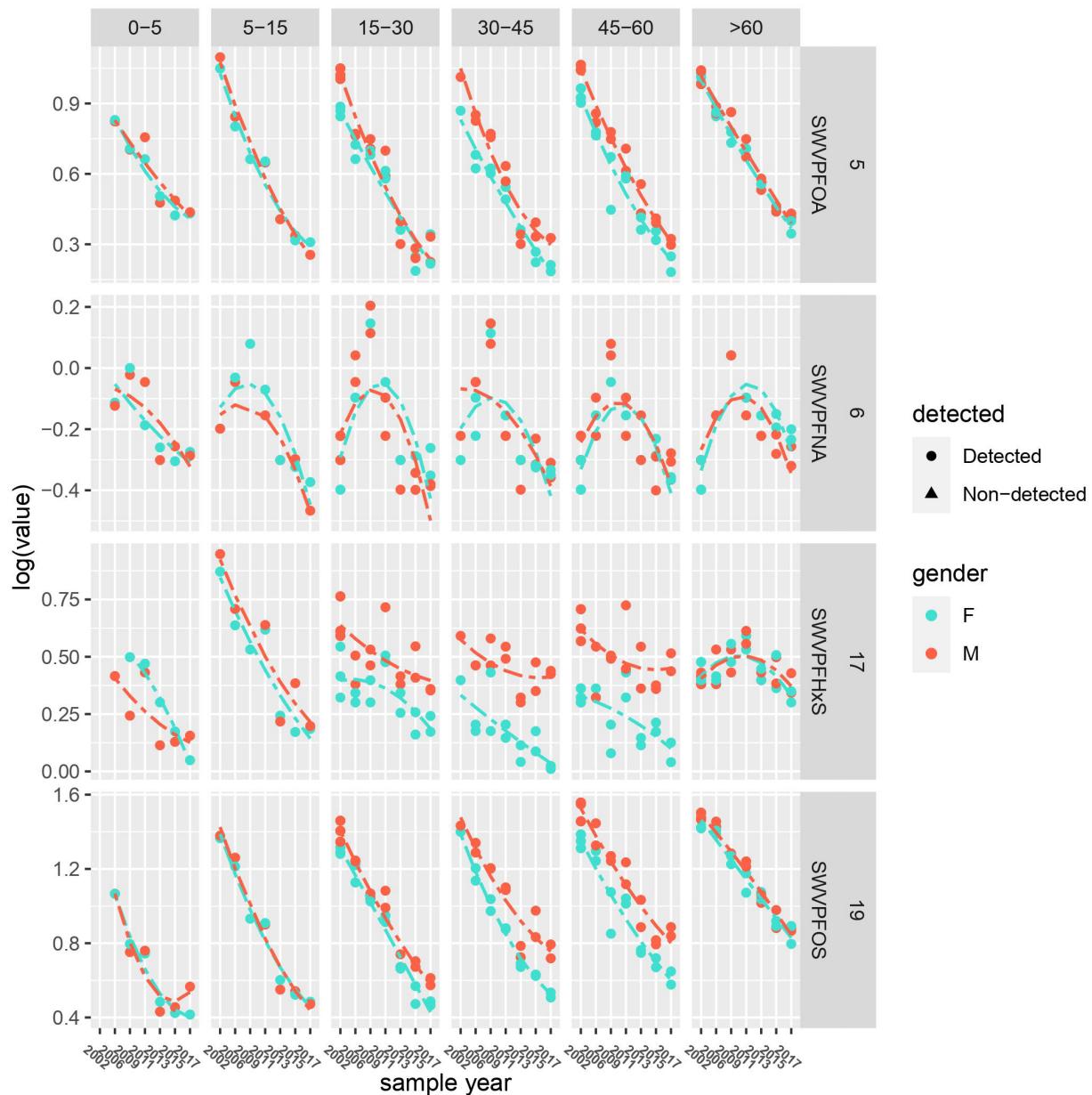


Figure 9 Temporal trends of PFOA, PFNA, PFHxS, PFOS from 2002 to 2017 across all the age groups (y axis: $\log(\text{detected value})$ or LOD $\sqrt{2}$ if not detected; unit: ppt - pg/gwet weight)

3.4 Comparison with NHANES data

The NHANES data show very similar temporal trends to Australian data. In all age groups, the levels of PFOA, PFHxS and PFOS decrease with time. The PFNA shows an n-shape relationship with time, peaked in 2009 then declined in subsequent years (Fig.10). Similar variations with sex have also been observed in NHANES data – PFHxS and PFOS concentrations are lower in females than in males due to the menstrual blood loss.

However, different patterns in age trends have been observed in NHANES data. As shown in the Figure 11, PFOA, PFNA concentrations in male samples in Australia decrease with age before the age of 30, whereas NHANES data indicate a downward U shape - a concentration increase with age followed by a small decrease. As children under five years old tend to have relatively high concentrations of PFOA and PFNA (Fig. 8), not including them from the NHANES research could explain the reversed age trends for males.

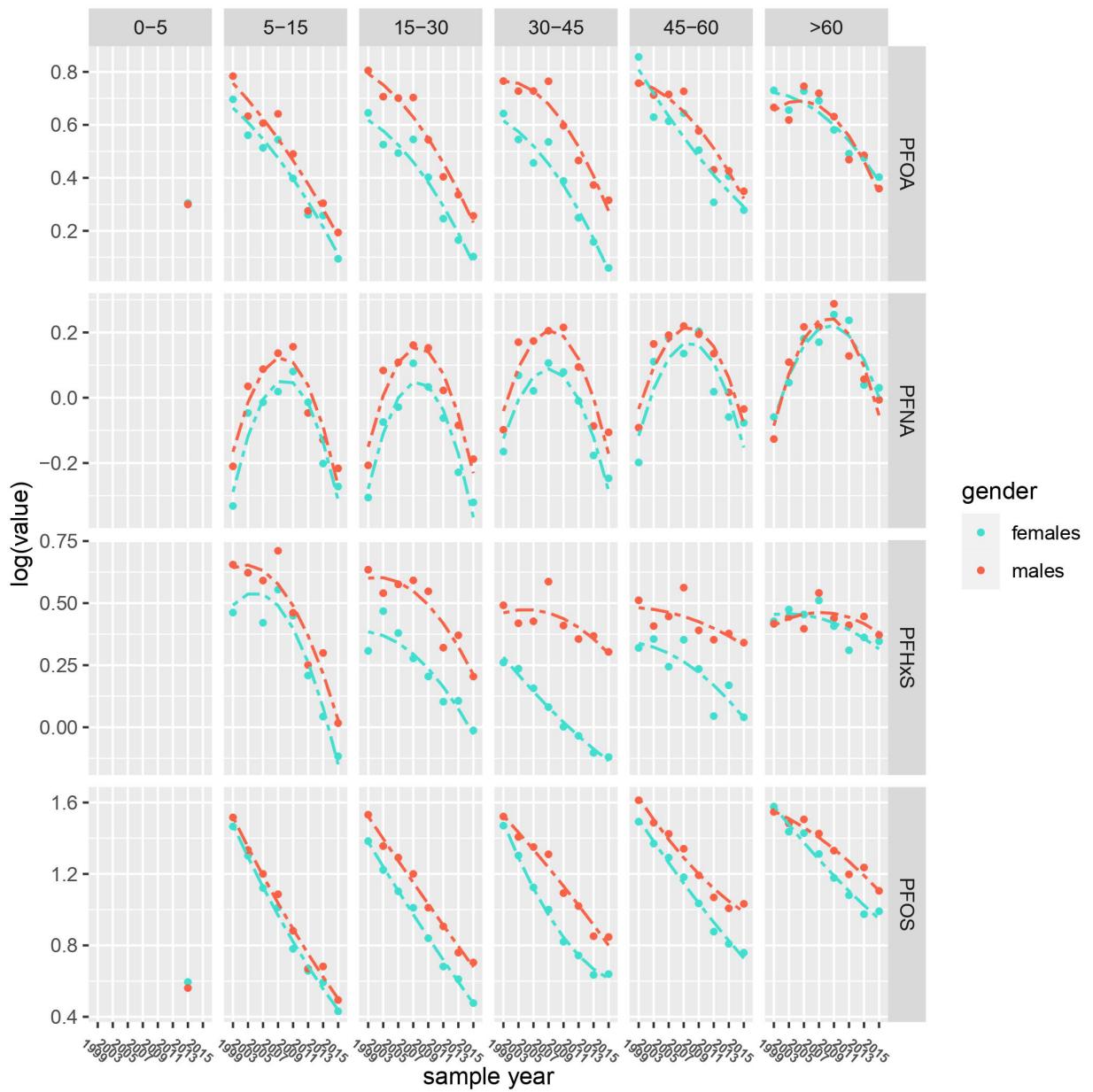


Figure 10 Age trends of PFOA, PFNA, PFHxS, PFOS across all the sampling years based on NHANES data (y axis: log(detected value) or LOD/ $\sqrt{2}$ if not detected; unit: ppt - pg/g wet weight)

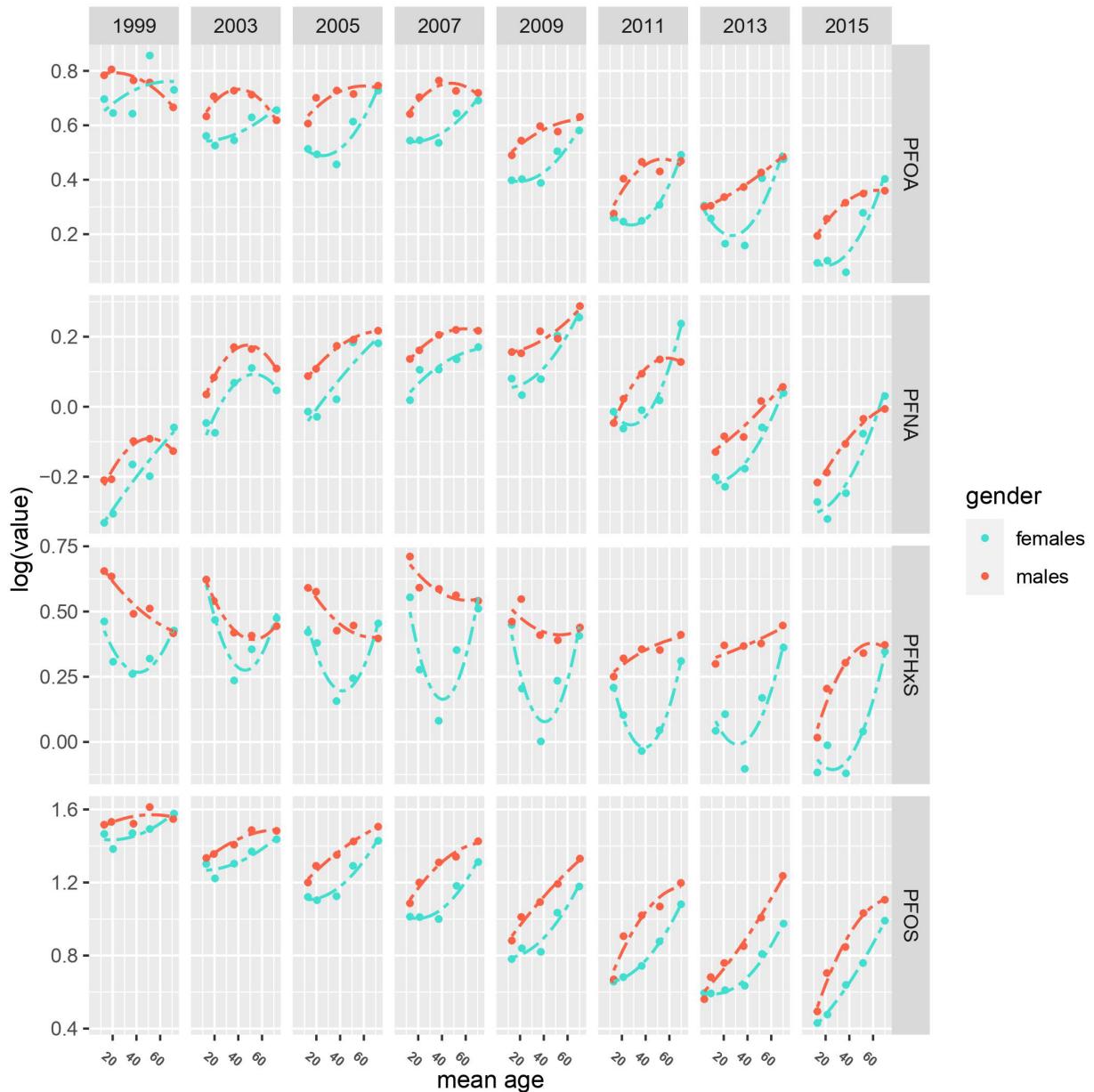


Figure 11 Temporal trends of PFOA, PFNA, PFHxS, PFOS from 2002 to 2017 across all the age groups based on the NHANES data (y axis: log(detected value) or LOD/ $\sqrt{2}$ if not detected; unit: ppt - pg/g wet weight)

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Supplementary data

Chemical unique code explanation:

The first letter: Sample types

Code	Matrix
S	Blood Serum
U	Urine
F	Feces
I	Wastewater Influence
E	Wastewater Effluent
V	Bovine
C	Cord blood
M	Breast Milk
W	Water
A	Air
L	Soil
P	Passive samples
H	Hair
D	Dust
O	Biosolids
F	Landfill leachate

The second letter: Type of Adjustment

Code	Type of adjustment	Default unit (unless specified)
W	Wet weight concentration	ppt - pg/g _{wet weight}
L	Lipid adjusted concentration	ppb - ng/g _{lipid}
V	Volume adjusted concentration	ng/ml
C	Creatinine corrected concentration	µg/g _{creatinine}
G	Specific Gravity corrected concentration	/
M	Mass load	mg/p-d
D	Dose (drug dose)	# doses

The third letter: Variable Type

Code	Value
V	Value (concentration or load), or ND for non detected or NA Non available = blank
D	Limit of detection
Q	Limit of quantification
N	Non detect or non quantified code - Above or below the limit of detection/quantification
S	Standard Deviation
I	Confidence interval
C	Corrected - value replaced by LOD/sqrt(2)
H	Corrected - value replaced by LOD/2
L	Labcode