Association of prenatal exposure to dioxin-like compounds, polychlorinated biphenyl, and methylmercury with event-related brain potentials in school-aged children: the Hokkaido study

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Abstract

Previous studies have indicated that prenatal exposure to dioxin-like compounds (DLC) or polychlorinated biphenyl (PCB) has a negative association with neurodevelopment in school-aged children. Event-related brain potentials (ERP) can reveal subtle and specific differences in the modulation of cognitive processes that are assumed when they are associated with lower levels of prenatal exposure to DLC or PCBs. This prospective birth cohort study was conducted to examine the association between prenatal exposure to relatively low levels of DLC, PCB or methylmercury (MeHg), and ERP. A total of 55 children who were 13 years old participated in a 3-stimulus oddball task to detect P3a and P3b waves. The task required participants to respond to a target among random stimuli at two difficulty levels. The P3a amplitude reflects an automated attention capture process, and P3b reflects a voluntary attention allocation process. We analyzed DLC congeners in blood samples from four groups, including 7 polychlorinated dibenzo-*p*-dioxins (PCDD), 10 polychlorinated dibenzofuranes (PCDF), 4 non-*ortho* PCBs, and 8 mono-*ortho* PCBs. PCB-153 was chosen as an indicator because of its high correlation with the sum of 58 NDL (non-dioxin-like)-PCBs. MeHg exposure level was assessed by the mercury concentration in hair samples (HHg) taken during the perinatal period.

The reaction time to the target stimulus during the oddball task shortened with the increasing MeHg exposure level. Furthermore, P3b latency, which reflect response decision and correlates

with reaction time, was also shortened with increasing MeHg level in the difficult condition. These results are counterintuitive because shorter reaction times or rapid decision making reflected by P3 latency are generally favorable. This might be due to nutritional factors such as fatty acids, which have beneficial effects on brain development. The P3a amplitude decreased with non- and mono-*ortho* PCB and HHg levels, regardless of the difficulty level, and with PCDD, PCDF, and total DLC levels, especially in the difficult condition. P3b latency shortened with HHg, and P3b amplitude decreased with mono-*ortho* PCBs and PCB-153 in both conditions and with PCDD, PCDF, non-*ortho* PCBs, and total DLC in the difficult condition.

In conclusion, we found an association between prenatal exposure to DLC and a decrease in both P3a and P3b amplitude, even when DLC levels were lower than in most previous studies. Additionally, our results suggest that the automated attention capture process reflected by P3a is associated with maternal MeHg exposure and that the voluntary attention allocation process reflected by P3b is associated with PCB-153. However, these results should be interpreted with caution because of the limitations on sample size, population bias, and statistical analyses.

Keywords: dioxin-like compound, polychlorinated biphenyl, child, prenatal exposure, event-related potential, methylmercury

1. Introduction

Human exposure to persistent organic pollutants, including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) from environmental sources and daily food intake is widespread (Todaka et al., 2008). Seventeen PCDDs/PCDFs and 12 PCBs have been categorized as dioxin-like compound (DLC) (Van den Berg et al., 2006). Mercury (Hg) is another environmental contaminant that is converted to methylmercury (MeHg) in the aquatic environment and then bioaccumulated in fish, shellfish, and marine mammals through the food chain. Ingestion of these seafoods is the main route of MeHg exposure. Exposure to higher levels of these environmental contaminants during the prenatal and neonatal periods is known to cause various toxicities, including carcinogenicity, teratogenicity, endocrine, immune, and reproductive disruption, as well as neurobehavioral issues (Clarkson and Magos, 2006; Todaka et al., 2010; Wigle et al., 2008).

There are numerous epidemiological studies regarding prenatal exposure to these contaminants and child neurodevelopment, including dioxins or DLC (Ames et al., 2019; Caspersen et al., 2016; Granillo et al., 2019; Hui et al., 2016; Ikeno et al., 2018; Nakajima et al., 2006, 2017; Neugebauer et al., 2015; Nowack et al., 2015; Sioen et al., 2013; Ten Tusscher et al., 2014; Tran et al., 2016; Winneke et al., 2014), and PCB (Berghuis et al., 2013; Bernardo et al., 2019; Boucher et al., 2012, 2016; Braun et al., 2014; Caspersen et al., 2016; Chu et al., 2019; Dickerson et al., 2019; Ethier

et al., 2015; Gascon et al., 2013; Grandjean et al., 2012; Granillo et al., 2019; Kim et al., 2018; Kyriklaki et al., 2016; Nakajima et al., 2006; Nowack et al., 2015; Sioen et al., 2013; Šovčíková et al., 2015; Stewart et al., 2012; Verner et al., 2015; Winneke et al., 2014). Most of these studies predominantly used questionnaires or face-to-face behavioral examination to assess behavioral problems, cognitive ability, or intelligence (e.g., Strength and Difficulties Questionnaire, Finger tapping test, or Wechsler Intelligence Scale for Children etc.).

Furthermore, several previous studies have investigated the effect of neurotoxic substances on cognition and attentional processing using event-related brain potential (ERP). ERP can reveal subtle and specific differences in brain activity and there is accumulating evidence on variability of ERP waves related to cognitive processes (Rugg & Coles, 1995). One of the most prominent waves of ERP is the P3 observed during an oddball task where participants respond to (or count) a target stimulus during the random presentation of a series of targets and frequent, standard stimuli. The P3 elicited by the target stimuli is called "P3b"; its amplitude is considered to reflect voluntary attention allocation, and its latency is interpreted as the speed of stimulus evaluation in determining whether the current stimulus should be responded to (Polich & Criado, 2006; Riggins & Scott, 2020). P3b has a parietal scalp distribution with a peak latency between 300-600 ms from stimulus onset (Donchin, 1981; Katayama & Polich, 1996a; Sutton et al., 1965). Although P3b is a part of P3, usually the term "P3" is used to mean P3b. Therefore, the term "P3" used in

101 the following previous studies can be interpreted as basically referring to P3b.

102 The association between the dioxin level in breast milk and P3 during a visual oddball task was

103 investigated in a cohort study in Amsterdam (Schellart & Reits, 2008; Ten Tusscher et al., 2014).

104 They reported that the high-exposure group had a longer P3 latency and smaller P3 amplitude

105 than the norm value calculated using a control group.

106 With respect to PCB exposure, previous studies have investigated P3 in children during an

107 oddball task. In Taiwan, Chen and Hsu (1994) reported significantly longer P3 latencies, and

108 significantly reduced amplitude in the Yu-Cheng ("oil disease") group compared to the control

109 group during an auditory oddball task. In The Netherlands, Vreugdenhil et al. (2004) also found

110 that children with high prenatal exposure to PCBs in the maternal plasma had longer P3 latencies

111 than those with low prenatal exposure; however, this did not affect the P3 amplitude. Boucher et

112 al. (2010) showed that prenatal PCB exposure was associated with a decrease in the P3b amplitude

113 in a subgroup of children who had been breastfed < 3 months. In this study, we were interested in

114 whether both PCB and DLCs were associated with P3 latency or amplitude even at low exposure

115 levels.

116 Additionally, there are nine studies regarding the association between prenatal exposure to

117 MeHg and basic perceptual processes using evoked brain potentials (Boucher et al., 2012, Ethier

118 et al., 2012, Grandjean et al., 1997, 2001a, 2001b, 2004; Murata et al., 2002, 2004b; Yorifuji et

al., 2013), and seven studies found some modulation in visual evoked potential or auditory brainstem responses (Ethier et al., 2012, Grandjean et al., 1997, 2001a, 2004; Murata et al., 2002, 2004b; Yorifuji et al., 2013). Boucher et al. (2010) also reported that cord blood Hg was associated with the N1 wave during oddball tasks, but not with the P3, and suggested that prenatal MeHg exposure alters the attentional mechanisms modulating the early processing of sensory information as reflected by N1. It is worthwhile to investigate MeHg in addition to DLC and PCB exposure because ERP wave related to attentional capture process might associate with MeHg, and because the exposure sources were mainly fish/seafood intake in the Japanese population (Miyashita et al., 2015).

Although these previous studies investigated association between chemical exposure and children's cognitive process using mainly P3b, the term "P3" is used to mean P3b and not included P3a. To examine additional cognitive processes, we focused on another P3 elicited by non-target stimuli during the 3-stimulus oddball task, which is called "P3a," and thought to reflect attentional capture by the distractor stimuli (Escera et al., 1998; Friedman et al., 2001; Rushby et al., 2005; Sawaki & Katayama, 2008). P3a shows a wider frontal scalp distribution, with a shorter peak latency compared to P3b (Courchesne et al., 1975; Squires et al., 1975). P3a is not easily detectable in the 2-stimulus oddball task but is detectable when using the 3-stimulus oddball task in which non-target stimuli are presented with low probability in addition to target and standard

stimuli presented as in typical 2-stimulus oddball tasks (Courchesne et al., 1975; Katayama & Polich, 1996b). There is a developmental difference between P3a and P3b (Fuchigami et al., 1995) wherein the automatic processes indexed by P3a seem to mature earlier than the controlled processes reflected by P3b (Stige et al., 2007). If P3a and P3b could be separated, it might be possible to examine whether DLC and/or PCB affects the automated attention capture process reflected by P3a, or the voluntary attention allocation process reflected by P3b. Therefore, we aimed to explore the association between exposure to prenatal DLC, PCB, and HHg at low levels and the cognitive processes indicated by P3a and P3b using a 3-stimulus oddball task which is suitable for detecting P3a (Comerchero & Polich, 1999; Katayama & Polich, 1998).

2. Methods

2.1 Study population

This study was conducted using data from a prospective study, the Sapporo Cohort of the Hokkaido Study on Environment and Children's Health (Kishi et al., 2011, 2013, 2017, 2021). In brief, we recruited 514 pregnant women from the Sapporo Toho Hospital in Hokkaido, Japan, between July 2002 and July 2005. All participants were native Japanese women, residing in Sapporo and surrounding areas. The participants completed a self-administered questionnaire after the second trimester of their pregnancy, with baseline information such as educational level,

155 family income, tobacco/smoking history, and alcohol consumption. Clinical perinatal data of
156 mothers and infants were collected from the participants' medical records. To obtain information
157 on maternal fish intake throughout pregnancy, participants were contacted within 5 days of
158 delivery. Participants also provided a hair sample for mercury measurements and information on
159 their history of having their hair permed.

160 Invitation letters were sent to 293 children who could be followed up and were living close to
161 Sapporo city at the time of ERP recording (11-14 years old) among the initial 514 participants.
162 Ninety-three pairs of mothers and children agreed to participate in ERP recordings. Thirteen
163 participants who participated in preliminary test recordings, seven who had a developmental
164 disorder diagnosis (3 with pervasive developmental disorder, 1 with Asperger syndrome, 1 with
165 attention deficit hyperactivity disorder, 2 with unidentifiable disorder), and two lacking DLC or
166 PCB data were excluded. Of the remaining 71, ERP data from 16 participants who had excessive
167 eye blinking or noise in either experimental condition were not included (Luck, 2014). Finally,
168 data from 55 participants with complete ERP, DLC, and PCB data were included in the analysis.
169 The flowchart of participant recruitment and data selection is shown in Figure 1.

170 The protocol for this study was approved by the Ethics Review Board for Epidemiological
171 Studies at the Hokkaido University Graduate School of Medicine and the Hokkaido University
172 Center for Environmental and Health Sciences (14-10-1) and was conducted in accordance with

173 the principles of the Declaration of Helsinki. All mothers and children who participated in the

174 ERP recording provided written informed consent.

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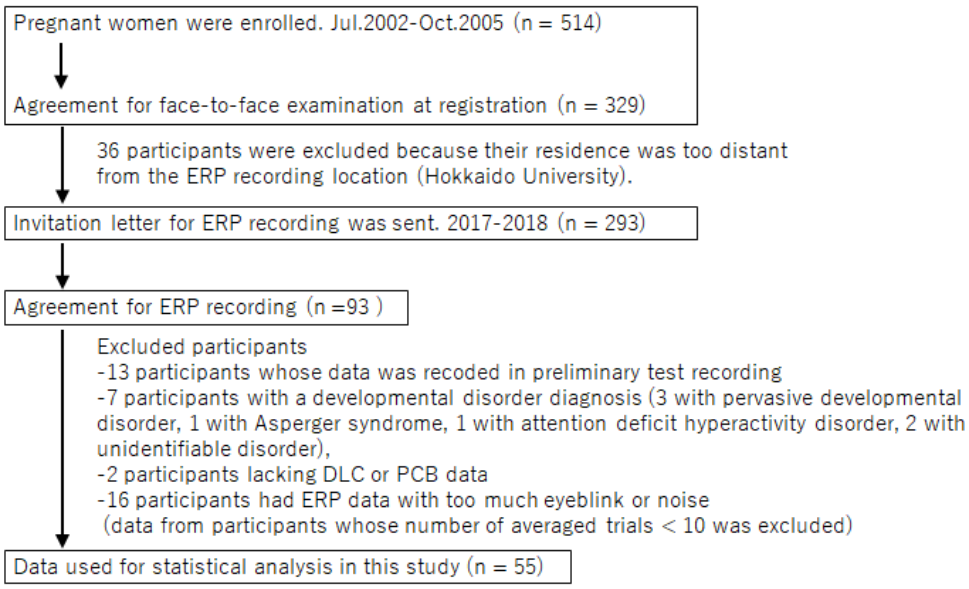

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183 Figure 1. Flowchart of participant recruitment and data selection.

184 ERP, event-related brain potential; DLC, dioxin-like compound; PCB, polychlorinated biphenyl

185

186 *2.2 Exposure assessment*

187 A 40 mL blood sample was collected from the maternal peripheral vein in the last trimester, except

188 in those subjects with pregnancy-related anemia, from whom blood samples were collected

189 immediately after delivery (16 among 55 included participants). All blood samples were stored at

190 -80°C. Non-dioxin-like (NDL)-PCB, PCDD/PCDF, and DL-PCB levels in the maternal blood

191 were assessed with high-resolution gas chromatography/high-resolution mass spectrometry

192 equipped with a solvent-cut large-volume injection system at the Fukuoka Institute of Health and
193 Environmental Sciences, as previously described (Iida and Todaka, 2003; Todaka et al., 2003,
194 2008). NDL-PCB, PCDD/PCDF, and DL-PCB levels have been described in our previous study
195 (Miyashita et al., 2015) and were adjusted by total lipid content (pg/g lipid) (Todaka et al., 2003).
196 Toxic equivalent (TEQ) values were calculated by multiplying the concentration of the individual
197 congener of PCDDs/PCDFs and DL-PCBs by its specific toxic equivalency factor value (Van den
198 Berg et al., 2006). Values below the detection limit were assigned as 50% of the detection limit.
199 Finally, 58 NDL-PCBs, 12 DL-PCBs, and 17 PCDD/PCDF congeners were analyzed in 426 blood
200 samples. DLC congeners were categorized into four DLC groups, including 7 PCDDs, 10 PCDFs,
201 4 non-*ortho* PCBs, and 8 mono-*ortho* PCBs. PCB-153 was chosen as an indicator because it had
202 a high correlation with the sum of 58 NDL-PCBs (Pearson's correlation coefficient = 0.97, $p <$
203 0.01). MeHg exposure in utero was estimated from total HHg concentration in the maternal hair
204 (Joint FAO/WHO Expert Committee on Food Additives (2003: Rome, Italy), World Health
205 Organization & Food and Agriculture Organization of the United Nations, 2004). Total mercury
206 concentrations were determined in 1 cm hair segments closest to the scalp (0.7–1.2 mg) using the
207 oxygen combustion-gold amalgamation method using a MD-1 atomic absorption detector
208 (Nippon Institute, Co., Ltd., Osaka, Japan) at the National Institute for Minamata Disease, as
209 previously described (Yasutake et al., 2003).

2.3 ERP procedure

ERPs were recorded during the 3-stimulus visual oddball task. Two conditions, which manipulated the difficulty of target/standard identification were implemented because P3a is larger and easier to detect when for difficult tasks compared to the waveform during easy conditions (Comerchero & Polich, 1999; Katayama & Polich, 1998). During the experiment, the child sat at a viewing distance of 1 m from a computer screen. The standard (70% presentation probability), target (15%), and non-target (15%) stimuli were visually presented in a random series, once every 2 s for a 300 ms duration on a gray background using E-Prime (E-Prime 2.0, Psychology Software Tools Inc., Pittsburgh, PA, USA). Figure 2 summarizes the stimuli used in this study. The standard stimulus was a blue circle (0.23° × 0.23°, 40 mm in diameter) in both conditions. The target stimulus was a small blue circle (0.16° × 0.16°, 28 mm in diameter) for easy tasks and a blue circle (0.21° × 0.21°, 36 mm in diameter) slightly smaller than the standard blue circle for difficult tasks. The non-target stimulus was a square (0.23° × 0.23°, 40 mm on each side). The child was asked to respond to the target stimuli by pushing a button with the right thumb as quickly as possible, and to ignore standard or non-target stimuli. The target stimulus elicits larger P3b compared to the ERP triggered by the standard stimulus, and the non-target stimulus elicits larger P3a especially in the difficult condition according to previous studies

(Comerchero & Polich, 1999; Katayama & Polich, 1998). In each condition, there were four blocks consisting of 100 trials each, as well as one practice block at the beginning. The participants could rest between blocks to minimize the influence of motivation and fatigue.

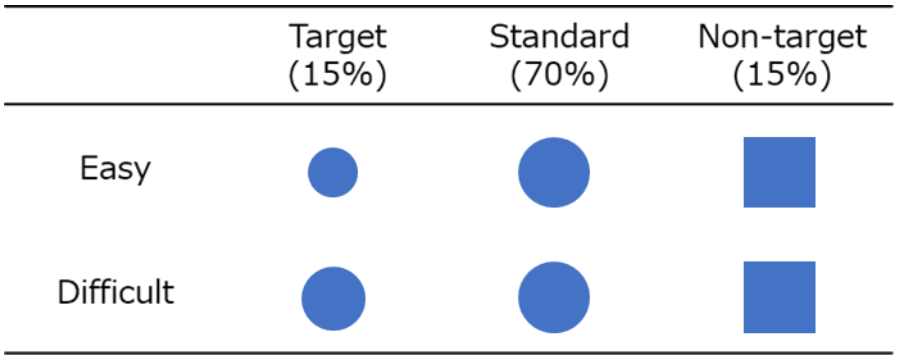

Figure 2. Stimuli used in the oddball task

2.4 ERP Recording and Analysis

Electroencephalograms (EEGs) were recorded from four midline scalp sites (Fz: frontal, Cz: central, Pz: parietal, and Oz: occipital) according to the 10-20 system and from the earlobes by referring to the nose tip, with the forehead as ground and impedance at ≤10 kΩ using the MaP2260 system (NIHON SANTEKU Co., Ltd, Osaka, Japan). Additional electrodes were placed at approximately 1 cm from the upper right eye and below the left eye to monitor electrooculogram (EOG) activity with bipolar recording. The signals were digitized online at a rate of 1000 Hz with a low-pass filter at 100 Hz and high-pass filter at 0.053 Hz. A 30 Hz low-pass filter was applied for all data offline, and the EEGs were re-referenced by averaged earlobes. Waveforms were averaged offline for 800 ms with a 200-ms pre-stimulus baseline, such that trials with a response

error or those where the EEG or EOG >±75 μV were rejected automatically. Data from participants who had <10 trials within the rejection criteria for any condition were not included. Eventually, 55 participants who had complete ERP data were included in the analysis.

The P3 component was defined as the largest positive peak occurring within the 300–600 ms latency window. To calculate the mean amplitudes, P3a peak at Cz were identified as 369 ms in the easy condition and 396 ms in the difficult condition on grand-averaged ERP waveforms, and P3b peaks at Pz were as 435 ms and 514 ms, respectively. These electrode sites were chosen for analyses a priori, with reference to previous studies (Katayama & Polich, 1996a, b; 1998; Polich & Criado, 2006; Sawaki & Katayama, 2008). Subsequently, the mean amplitudes within the ± 50 ms range of peak latencies were calculated for P3a (319 -419 ms in the easy condition, 346-446 ms in the difficult condition) and P3b (385-485 ms in the easy condition, 464-564 ms in the difficult condition) at Fz, Cz, Pz, and Oz on each participant's individual ERP waveforms automatically. For regression analysis, the mean amplitude and peak latency at Cz when the non-target stimulus was presented were designated as P3a, and the mean amplitude and peak latency at Pz when the target stimulus was presented were designated as P3b. ERP analysis was implemented using EEGLAB version 14 (http://www.sccn.ucsd.edu/eeglab, Delorme and Makeig, 2004) running under MATLAB 9.5.0 (The MathWorks, Natick, MA, USA).

262 *2.5 Data analysis*

263 The characteristics of the participant group and the other participants of the cohort (defined as
264 non-participant group) were initially analyzed using the chi-square test and Student's t-test. The
265 DLC (Sub-total PCDD, Sub-total PCDD, Sub-total non-ortho PCBs, Sub-total mono-ortho PCBs),
266 PCB (PCB-153), and mercury concentration in hair samples (HHg) were compared between
267 participants and non-participants using the Mann–Whitney U test. DLC, PCB and HHg values
268 were log10 transformed since the exposure level of these contaminants shows log-normal
269 distributions. For the oddball task performance, omission errors, false alarms, and reaction times
270 across conditions were compared using paired-sample t-tests. The omission error rate indicates
271 the prevalence of missing to press the button to the target stimulus, false alarm rate indicates the
272 prevalence of button press to the standard stimulus. The hit reaction time is the mean of time from
273 stimulus presentation to the button press to the target stimulus. These behavioral measures can
274 confirm whether subjects performed the task properly and whether the task difficulty condition
275 worked as intended.

276 P3a and P3b latency and mean amplitude were assessed using repeated measures analysis of
277 variance (ANOVA). Greenhouse–Geisser correction was applied to the degrees of freedom in
278 ANOVA, when appropriate. Post-hoc comparisons were performed using the Bonferroni
279 procedure when a significant main effect of the electrode or any interaction was obtained.

Multiple regression analysis was performed to examine the association of DLC, PCB, or HHg concentrations with behavior or P3a/b during the oddball task. Potential confounders were selected based on previous studies (Boucher et al., 2010; Miyashita et al., 2015; Schellart & Reits, 2008; Vreugdenhil et al., 2004). Subsequently, directed acyclic graphs (DAGs) were used to determine the adjustment factors (Supplemental Figure 1). The set of variables selected for adjustment were maternal age, smoking during pregnancy, and being first-born or not. However, the smoking status during pregnancy could not be considered because there were only three smoking mothers among our participants. The breastfeeding period (Boucher et al., 2010; Vreugdenhil et al., 2004) and age at the time of ERP examination (Schellart & Reits, D., 2008) were included a priori because both were crucial for ERP. The blood sampling period was also included for the DLC, PCB models. To facilitate interpretation of the study results, post hoc power analysis was conducted using G* Power3 software (Faul et al., 2007). In the multi-regression analysis with six predictors for the DLC, PCB models (exposure, maternal age, smoking during pregnancy, being first-born, breastfeeding duration, age at examination, and blood sampling period), the detectable effect size f 2 was 0.28 ($n = 55$, $\alpha = 0.05$, $\beta = 0.2$); in the analysis with five predictors for the HHg model, where the predictors were the same as in the s model except for the blood sampling period, the detectable effect size f 2 was 0.26 $n = 55$, $\alpha = 0.05$, $\beta = 0.2$). According to Cohen's guidelines (1988), f 2 ≥ 0.02, f 2 ≥ 0.15, and f 2 ≥ 0.35 represent small,

298 medium, and large effect sizes, respectively. Therefore, our analysis could detect a medium to
299 large effect size. The significance level was set at $p < 0.05$. All statistical analyses were performed
300 using SPSS version 22.0. (SPSS, Chicago, IL, USA).
301
302 **3. Results**
303 *3.1 Descriptive statistics*
304 The basic characteristics of the study population are summarized in Table 1. The average
305 maternal age at delivery was 32.9 ± 4.2 years (mean ± standard deviation [SD]) and paternal age
306 was 35.0 ± 5.8 years. Most of the mothers had an education > 13 years (72.7%) and did not smoke
307 during pregnancy (94.5%). Among the infants, 47.3% were male, 49.1% were first-born, and
308 14.5% had breastfeeding for > 3 months. Comparing the characteristics of participant included in
309 the analysis and non-participant groups who were the other participants of the cohort, participants
310 had higher maternal and paternal ages, higher education level, and lower smoking rate.
311 Additionally, the prevalence of children who were breastfed for > 3 months was lower.
312 Maternal serum DLC, PCB, and HHg concentrations are shown in Table 2. PCDD, non-*ortho*
313 PCBs, mono-*ortho* PCBs, total DLC, and PCB-153 were significantly higher, and PCDF was
314 marginally higher but significant in the participant than in the non-participant group. HHg levels
315 did not differ between groups.

Table 1. Characteristics of parents and infants

Characteristic		ALL (n = 497)			Participants (n = 55)		Non-participants (n = 442)		p-value
		Mean (± SD) or No.	(%)	Range	Mean (± SD) or No.	(%)	Mean (± SD) or No.	(%)	
Mother									
Age at delivery (years)		30.7	(± 4.9)	(17 –48)	32.9	(± 4.2)	30.5	(± 4.9)	<0.01
Education Level (years)	< 13	221	(44.5)		15	(27.3)	206	(46.6)	0.01
	≥ 13	276	(55.5)		40	(72.7)	236	(53.4)	
Smoked during pregnancy	No	413	(83.1)		52	(94.5)	361	(81.7)	0.01
Alcohol intake during pregnancy	No	344	(69.2)		38	(69.1)	306	(69.2)	1.00
Blood sampling	during pregnancy	351	(70.6)		39	(70.9)	312	(70.6)	1.00
	after delivery	141	(28.4)		16	(29.1)	125	(28.3)	
Father									
Age at delivery (years)		32.3	(± 5.6)	(18 –50)	35.0	(± 5.8)	32.0	(± 5.5)	< 0.01
Education Level (years)	< 13	216	(43.5)		19	(34.5)	197	(44.6)	0.19
	≥ 13	280	(56.3)		36	(65.5)	244	(55.2)	
Smoked during pregnancy	No	152	(30.6)		17	(30.9)	135	(30.5)	1.00
Family									
Annual income (million yen)	< 5	340	(68.4)		35	(63.6)	305	(69.0)	0.75

	≥ 5	147	(29.6)		17	(30.9)	130	(29.4)	
Children									
Sex	Male	238	(47.9)		26	(47.3)	212	(48.0)	1.00
	Female	259	(52.1)		29	(52.7)	230	(52.0)	
Gestational age (days)		275.2	(± 10.0)	(217 –292)	274.9	(± 8.5)	275.3	(± 10.2)	0.80
Birth weight (g)		3050.9	(± 394.5)	(794 –4292)	3128.8	(± 342.5)	3041.2	(± 399.8)	0.12
First-born	Yes	239	(48.1)		27	(49.1)	212	(48.0)	0.89
Breastfeeding (> 3 months)	Yes	169	(34.0)		8	(14.5)	161	(36.4)	< 0.01
Age at examination					12.45	(± 0.6)			

SD, standard deviation; HHg; mercury concentration in hair samples.

Table 2. DLC and PCB concentrations in maternal blood, and mercury in maternal hair samples

	Participants (n=55)					Non-participants (n = 442)						p-value
	min	25th	median	75th	max	n	min	25th	median	75th	max	
DLCs												
Sub-total PCDD (TEQ pg/g lipid)	1.87	6.21	8.03	10.16	17.32	371	1.65	4.95	6.67	8.82	29.32	0.00
Sub-total PCDF (TEQ pg/g lipid)	0.80	1.94	2.58	3.41	7.77	371	0.64	1.76	2.35	3.01	12.11	0.06
Sub-total non-ortho PCBs (TEQ pg/g lipid)	0.90	3.12	4.85	6.58	16.75	371	0.65	2.60	4.13	5.66	23.17	0.03
Sub-total mono-ortho PCBs (TEQ pg/g lipid)	0.12	0.25	0.40	0.53	1.09	371	0.05	0.22	0.33	0.46	1.49	0.03
Total DLC (TEQ pg/g lipid)	4.39	12.70	17.24	20.58	42.93	371	3.17	9.73	13.82	17.87	43.35	0.01
PCB-153 (pg/g lipid)	2821	14494	20773	30232	120172	371	2821	14494	20773	30232	120172	0.02
HHg (μg/g)	0.32	1.04	1.39	2.04	3.90	405	0.24	0.96	1.42	1.89	7.55	0.57

TEQs were calculated using toxic equivalency factor values (Van den Berg et al., 2006). IQR, interquartile range; DLCs, dioxin-like compounds; TEQ, toxic equivalent; PCDD, polychlorinated dibenzo-p-dioxins; PCDF, polychlorinated-dibenzofuran; PCB, polychlorinated biphenyl.

p-values were calculated using the Mann–Whitney U test.

3.2 Oddball task results

Task performance during ERP recordings is shown in Table 3. The omission error rate, which is the rate of failure to press the button for the target stimulus was higher in the difficult condition than in the easy condition, $t(54) = 16.93$, $p < 0.01$, $r = 0.92$. The false alarm rate, defined as the rate of button presses in response to the non-target or standard stimulus, was higher in the difficult condition than in the easy condition, $t(54) = 6.03$, $p < 0.01$, $r = 0.63$. The reaction time to the target stimulus was shorter in the easy condition than in the difficult condition, $t(54) = 12.52$, $p < 0.01$, $r = 0.86$. These behavioral results indicate successful manipulation of the task difficulty.

Table 3 Summary of behavior during oddball task (n = 55)

	Easy		Difficult	
	Mean ± SD	Range	Mean ± SD	Range
Omission errors rate (%)	1.7 ± 2.6	(0.0–11.7)	28.8 ± 12.5	(8.3–60.0)
False alarm rate (%)	0.6 ± 0.9	(0.0–5.6)	5.2 ± 6.2	(0.0–36.2)
Mean hit reaction time (ms)	436 ± 77	(213–750)	543 ± 86	(235–784)

SD, standard deviation

Figure 3 illustrates the grand-averaged ERP waveform from three electrodes (Fz, Cz, Pz) in response to the standard, target, and non-target stimuli. We observed P3a around 400 ms after the non-target stimulus presentation in the Cz region in both conditions. P3b was clearly observed when the target stimulus was presented from 400 to 600 ms over the Pz region.

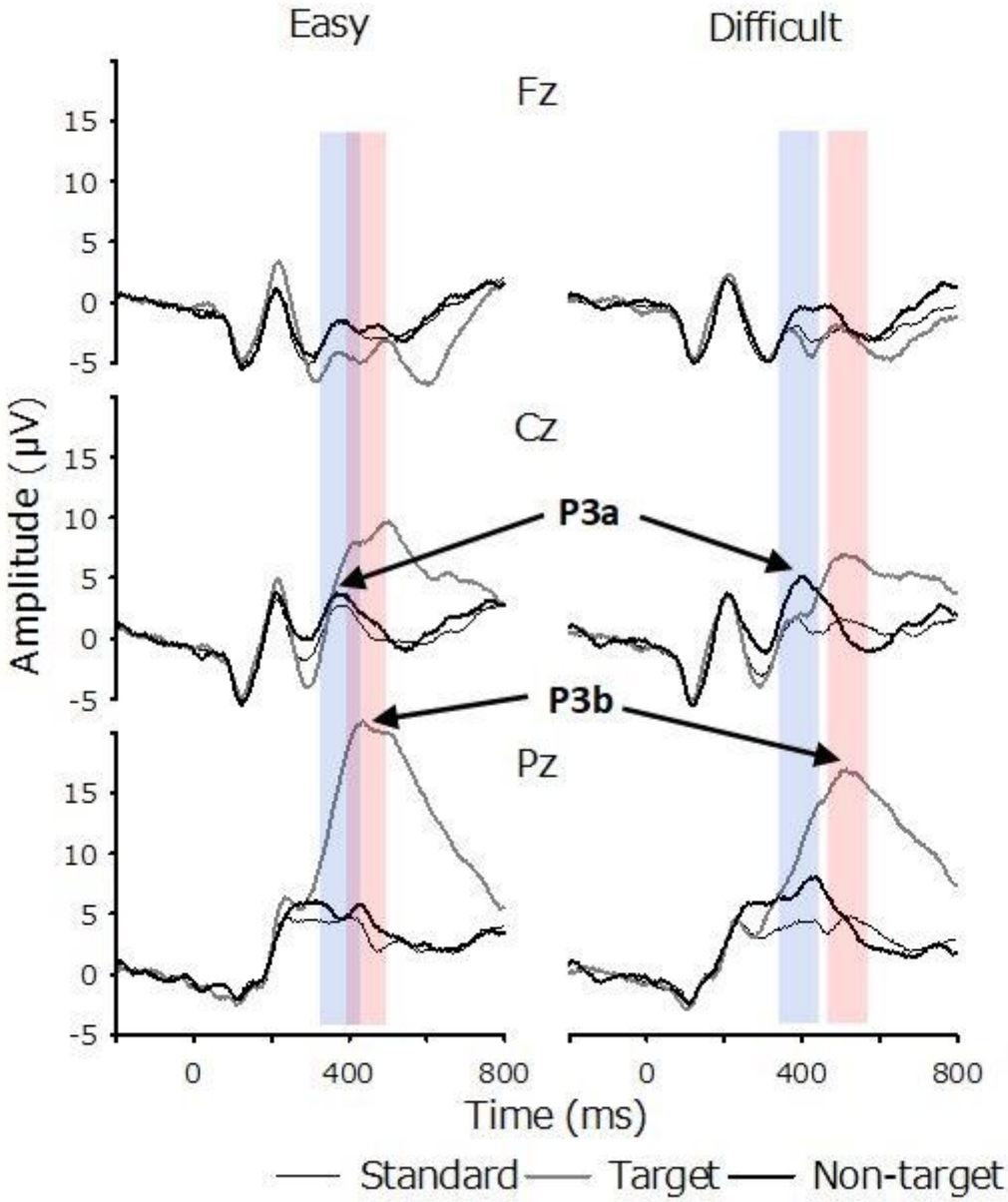

Figure 3. Grand averaged waveform from all participants in each condition from three electrode sites (Fz, Cz, and Pz). Shaded areas indicate latency windows of the P3a (blue) and P3b (red). Fz, frontal; Cz, central; Pz, parietal

Figure 4 summarizes the peak latency and mean amplitude of P3a and P3b under the easy and difficult condition. For P3a latency, one-factor ANOVA [2 Difficulty level (easy vs. difficult)] revealed no significant difference between conditions, $F(1, 54) = 1.75$, $p = 0.19$, $\eta_p^2 = 0.03$. For

P3a mean amplitude, two-factor ANOVA [2 Difficulty level (easy vs. difficult) × 3 Electrode (Fz, Cz, vs. Pz)] revealed a significant main effect of difficulty, $F(1, 54) = 8.63$, $p = 0.005$, $\eta_p^2 = 0.14$, and electrode, $F(2, 108) = 153.71$, $p < 0.001$, $\varepsilon = 0.76$, $\eta_p^2 = 0.74$. Post hoc comparison for the main effect of electrode showed that P3a amplitudes were significantly different among all electrodes, $p < 0.001$. These results indicate that P3a latency was not modulated by task difficulty; furthermore, the amplitude was larger in the difficult condition than in the easy condition and had a dominant distribution from the central to the parietal scalp region.

With respect to P3b latency, one-factor ANOVA revealed shorter latency in the easy condition than in the difficult condition, $F(1, 54) = 1.75$, $p < 0.001$, $\eta_p^2 = 0.52$. Two-factor ANOVA revealed a significant interaction for P3b amplitude, $F(2, 108) = 33.00$, $p < 0.001$, $\varepsilon = 0.66$, $\eta_p^2 = 0.38$. Post hoc comparison for the interaction showed significant differences in P3b amplitude between the easy and difficult conditions at Fz and Pz. These results indicate that the amplitude was larger in the easy condition than in the difficult condition at the Pz scalp region and vice-versa in the Fz region.

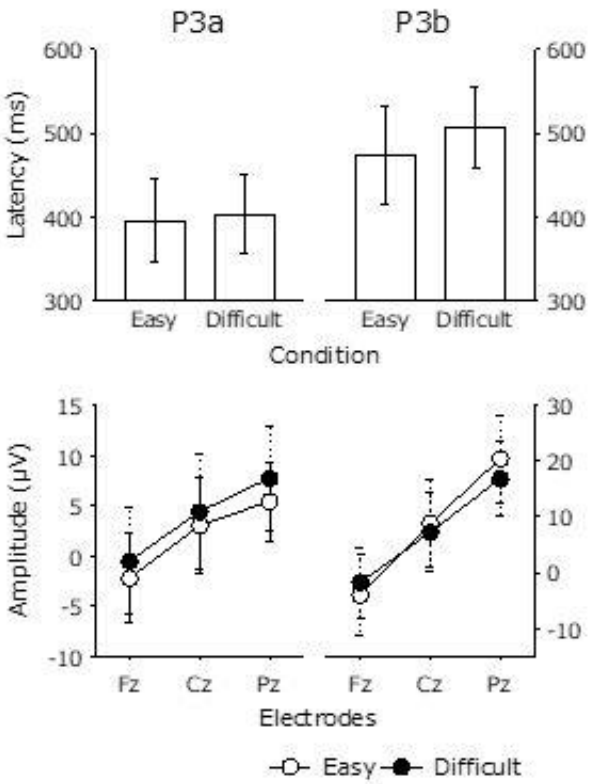

Figure 4. Averaged P3a and P3b latency and amplitude (n =55).

3.3 Association between contaminants, behavioral performance, and P3

The association between maternal DLC, PCB, or HHg concentration, and behavioral performance during the oddball task is shown in Table 4. There was no significant association between the omission error rate and false alarm rate. Reaction time was significantly and negatively associated with PCDF in the difficult condition (β = -132; 95% confidence interval [CI]: -251, -14), and HHg in both conditions (β = -97; 95% CI: -175, -19 for easy, and β = -99; 95% CI: -192, -6 for difficult level, respectively).

Table 4. Association between behavioral performance and maternal DLC, PCB-153, or HHg concentration (n =55).

	Omission error rate (%)						**False alarm rate (%)**						**Mean hit reaction time (ms)**					
	Easy			Difficult			Easy			Difficult			Easy			Difficult		
	β	95%CI		β	95%CI		β	95%CI		β	95%CI		β	95%CI		β	95%CI	
DLC																		
Sub-total PCDD	-0.9	(-5.3,	3.5)	2.5	(-15.5,	20.5)	-1.0	(-2.2,	0.2) †	-9.4	(-19.7,	1.0) †	-74	(-179,	30)	-96	(-220,	28)
Sub-total PCDF	-0.7	(-5.0,	3.6)	2.7	(-14.7,	20.2)	-1.1	(-2.3,	0.0) †	-5.9	(-16.1,	4.3)	-56	(-158,	46)	-132	(-251,	-14) *
Sub-total non *ortho* PCBs	-0.3	(-3.3,	2.7)	-1.4	(-13.6,	10.8)	-0.5	(-1.3,	0.4)	2.2	(-5.0,	9.3)	-31	(-103,	41)	-67	(-152,	17)
Sub-total mono- *ortho* PCBs	-0.8	(-4.3,	2.7)	-1.4	(-15.8,	13.0)	-0.7	(-1.7,	0.2)	-0.5	(-9.0,	7.9)	-46	(-130,	38)	-63	(-163,	36)
Total DLC	-0.4	(-4.7,	3.9)	0.5	(-17.1,	18.0)	-0.9	(-2.1,	0.3)	-3.9	(-14.2,	6.4)	-64	(-166,	38)	-109	(-230,	11) †
PCB-153	-1.3	(-4.8,	2.3)	-2.2	(-16.9,	12.4)	-0.8	(-1.8,	0.2)	-1.5	(-10.2,	7.1)	-49	(-135,	36)	-42	(-144,	61)
HHg	-0.6	(-3.9,	2.7)	2.7	(-10.9,	16.4)	0.1	(-0.8,	1.0)	-0.5	(-3.3,	2.2)	-97	(-175,	-19) *	-99	(-192,	-6) *

CI, confidence interval; DLC, dioxin-like compound; TEQ, toxic equivalent; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated-dibenzofuran; PCB, polychlorinated biphenyl; HHg, mercury concentration in hair samples.

Models were adjusted by maternal age, parity, breastfeeding period, and age at examination. The blood sampling period was added to the models for DLC and PCB-153.

The omission error rate indicates the prevalence of missing to press the button to the target stimulus, false alarm rate indicates the prevalence of button press to the standard stimulus. The hit reaction time is the mean f time from stimulus presentation to the button press to the target stimulus $^{*}p < 0.05$, $^{\dagger}p < 0.1$

Table 5 shows the association between maternal DLC, PCB, or HHg concentration, and P3 latency or amplitude. While P3b latency was negatively associated with HHg in the difficult condition (β = -71; 95% CI: -132, -11), no other association was observed regarding P3a and P3b latency. Regarding P3a amplitude, non-*ortho* PCBs (β = -4.7; 95% CI: -9.2, -0.2), mono-*ortho* PCBs (β = -6.1; 95% CI: -11.3, -0.8), and HHg (β = -5.5; 95% CI: -10.4, -0.6) had a negative association in the easy condition, and PCDD (β = -8.6; 95% CI: -16.3, -0.9), PCDF (β = -11.3; 95% CI: -18.5, -4.0), non-*ortho* PCBs (β = -7.6; 95% CI: -12.7, -2.5), mono-*ortho* PCBs (β = -7.4; 95% CI: -13.5, -1.3), total DLC (β = -10.4; 95% CI: -17.8, -3.1), and HHg (β = -7.2; 95% CI: -13.1, -1.3) had a negative association in the difficult condition. Regarding P3b amplitude, mono-*ortho* PCBs (β = -9.7; 95% CI: -18.5, -0.9) and PCB-153 (β = -9.2; 95% CI: -18.2, -0.2) had a negative association in the easy condition, and PCDD (β = –11.6; 95% CI: –22.1, –1.1), PCDF (β = –16.2; 95% CI: –26.0, –6.3), non-*ortho* PCBs (β = –10.1; 95% CI: –17.1, –3.1), mono-*ortho* PCBs (β = –9.4; 95% CI: –17.8, –1.0), total DLC (β = –14.4; 95% CI: –24.4, –4.4), and PCB-153 (β = –9.0; 95% CI: –17.6, –0.4) had a negative association in the difficult condition.

Table 5. Association between ERP P3 and maternal DLC, PCB-153, or HHg concentration (n = 55).

	Latency							Amplitude							
	Easy				Difficult			Easy				Difficult			
	β	95%CI			β	95%CI		β	95%CI			β	95%CI		
P3a															
Dioxin-like compound															
Sub-total PCDD	-31	(-111,	49)		-64	(-133,	6)	†	-3.2	(-10.0,	3.6)		-8.6	(-16.3,	-0.9)	*
Sub-total PCDF	-33	(-110,	45)		-33	(-102,	35)		-4.8	(-11.3,	1.7)		-11.3	(-18.5,	-4.0)	**
Sub-total non-*ortho* PCBs	-1	(-55,	54)		-14	(-63,	34)		-4.7	(-9.2,	-0.2)	*	-7.6	(-12.7,	-2.5)	**
Sub-total mono-*ortho* PCBs	-10	(-74,	54)		-16	(-73,	40)		-6.1	(-11.3,	-0.8)	*	-7.4	(-13.5,	-1.3)	*
Total DLC	-20	(-98,	58)		-47	(-116,	21)		-5.3	(-11.8,	1.2)		-10.4	(-17.8,	-3.1)	**
PCB-153	-31	(-96,	34)		-13	(-71,	45)		-5.3	(-10.7,	0.1)	†	-5.2	(-11.5,	1.2)	
HHg	-42	(-101,	17)		-26	(-79,	27)		-5.5	(-10.4,	-0.6)	*	-7.2	(-13.1,	-1.3)	*
P3b															
Dioxin-like compound															
Sub-total PCDD	-25	(-100,	50)		-77	(-158,	4)	†	-7.9	(-19.2,	3.3)		-11.6	(-22.1,	-1.1)	*
Sub-total PCDF	-7	(-79,	66)		-58	(-137,	22)		-10.7	(-21.5,	0.0)	†	-16.2	(-26.0,	-6.3)	**
Sub-total non-*ortho* PCBs	7	(-44,	58)		-18	(-74,	38)		-7.2	(-14.7,	0.3)	†	-10.1	(-17.1,	-3.1)	**
Sub-total mono-*ortho* PCBs	6	(-54,	66)		-35	(-101,	30)		-9.7	(-18.5,	-0.9)	*	-9.4	(-17.8,	-1.0)	*
Total DLC	-9	(-82,	64)		-58	(-137,	22)		-10.2	(-21.0,	0.7)	†	-14.4	(-24.4,	-4.4)	**
PCB-153	0	(-61,	61)		-53	(-120,	13)		-9.2	(-18.2,	-0.2)	*	-9.0	(-17.6,	-0.4)	*

HHg	-17	(-72,	39)	-71	(-132,	-11)	*	-2.3	(-10.8,	6.2)	-3.07	(-11.5,	5.4)

CI, confidence interval; ERP, event-related brain potential; DLC, dioxin-like compound; TEQ, toxic equivalent; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated-dibenzofuran; PCB, polychlorinated biphenyl; HHg, mercury concentration in hair samples.

Models were adjusted by maternal age, parity, breastfeeding period, and age at examination. The blood sampling period was added to the models for DLC and PCB-153.

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{\dagger}p < 0.1$

417

418 **4. Discussion**

419 In this study, we examined the association between prenatal exposure to DLC, PCB, or MeHg
420 and the cognitive processing of children during a 3-stimulus oddball task using P3a and P3b.
421 Regarding the behavioral performance, there was a negative association between the reaction time
422 to target stimulus and PCDF level in difficult conditions, and MeHg exposure level in both easy
423 and difficult conditions. P3a amplitude decreased with non- and mono-*ortho* PCB and MeHg
424 levels regardless of task difficulty, and with PCDD, PCDF, and total DLC levels alone in the
425 difficult condition. P3b latency shortened with MeHg in the difficult condition, and P3b amplitude
426 decreased with mono-*ortho* PCBs and PCB-153 in both conditions, and PCDD, PCDF, non-*ortho*
427 PCBs, and total DLC in the difficult condition.

428 Regarding the DLC concentration, the median total TEQ level in this study was 17.24 TEQ pg/g
429 lipid, which was lower than that reported by other studies; more specifically, 22.1 TEQ pg/g lipid
430 in Japan (Masuda et al., 2005), 35.8 TEQ pg/lipid in Holland (Weisglas-Kuperus et al., 2000),
431 28.4 TEQ pg/lipid in Germany (Wittsiepe et al., 2007), and 39.1 TEQ pg/lipid in America
432 (Schecter et al., 2005). The PCB concentration in this study is also considered lower than in
433 previous studies. Chen and Hsu (1994) reported that children were accidentally exposed to
434 extremely high PCBs levels. Vreugdenhil et al. (2004) reported that the sum of four PCB
435 congeners (International Union of Pure and Applied Chemistry [IUPAC] numbers 118, 138, 153,

436 and 180) in the high exposure group was 2.54 μg/l median; in the present study the median sum
437 of the same four congeners was 0.20 ng/g in whole blood (which is approximately the same as
438 0.20 μg/Kg). Boucher et al. (2010) reported that the PCB-153 cord blood level was 103.0 ng/g fat
439 median, higher than the PCB-153 level in the present study (25.6 ng/g lipid as shown in Table 2).
440 With respect to the behavioral performance during the oddball task, there was a negative
441 association between the reaction time to target stimulus and PCDF level in difficult conditions,
442 and MeHg exposure level in both easy and difficult conditions. In other words, the reaction time
443 became shorter with increasing exposure to MeHg. Furthermore, P3b latency, which reflects
444 response decision and correlate with reaction time, was also shortened in association with MeHg
445 levels under the difficult condition. The results are counterintuitive because shorter reaction time
446 or rapid decision making reflected by P3 latency are generally favorable. This might be due to
447 nutritional factors such as fatty acids, which have beneficial effects on brain development (Choi
448 et al, 2014, Saint-Amour et al., 2006). On the other hand, P3a and P3b amplitudes were
449 significantly associated with various exposures. Boucher (2010) also found a significant
450 association of PCB exposure with P3b amplitude for breast feeding < 3months, but not with
451 behavioral performance. Taken together, it might indicate higher ERP sensitivity for specific
452 aspects of cognitive processes, as attentional resources etc., which are difficult to detect in
453 behavioral performance.

454 Regarding the association between DLC and P3b during the oddball task, Schellart & Reits
455 (2008) reported that the latencies increased and that the amplitudes decreased in response to the
456 oddball task in the higher exposure group to dioxin, but not to P3a (their P3a data were not shown).
457 Although it is difficult to compare the results directly because they calculated the latencies and
458 amplitude using original methods, a decrease in amplitude as a response to oddball task in the
459 higher dioxin level group seems consistent with the present results. However, we observed an
460 association between DLC levels and P3a amplitude. This may be due to the 3-stimulus oddball
461 task with two difficulty levels in our study, which elicited larger P3a waves, and enabled the
462 detection of the association between P3a and DLC.
463 With consideration to PCB, we found an association between the increase in PCB-153 and the
464 decrease in P3b amplitude, both in the easy and difficult conditions. Chen and Hsu (1994) reported
465 an increase in P3b latency and decrease in amplitude, and Vreugdenhil et al. (2004) reported an
466 increase in P3b latency without amplitude modulation in the PCB higher exposure group.
467 However, Boucher et al. (2010) found an association between PCB exposure and a decrease in
468 P3b amplitude only in a subgroup of children who had been breastfed for < 3 months; no
469 association was found regarding latency. The exposure levels of PCBs are reportedly higher in
470 the abovementioned studies than in the present study results; the concentration level does not
471 sufficiently explain the inconsistency of the results. The inconsistency may be due to differences

472 in the study design, the type of oddball task, and sensory modalities.

473 Interestingly, we found different patterns of association between P3a or P3b amplitudes and HHg
474 and PCB-153 levels. Nieuwenhuis et al. (2005) suggested that P3a and P3b reflect the response
475 of the locus coeruleus–norepinephrine system, and that one region surrounding the
476 temporoparietal region (TPJ) was critical for the generation of both the P3a and the P3b. Another
477 region, in the lateral prefrontal cortex, is critically involved in the generation of the P3a by novel
478 stimuli. The fact that the amplitude of P3a decreased as the HHg levels increased, but P3b did not
479 change indicates that MeHg might tap the attentional capture process reflected by P3a (Escera et
480 al., 1998; Friedman et al., 2001; Rushby et al., 2005; Sawaki & Katayama, 2008) and the source
481 of P3a located at lateral prefrontal cortex (Nieuwenhuis et al., 2005). On the other hand, only P3b
482 amplitude was negatively associated with the PCB-153 level. PCB exposure might be associated
483 with voluntary attentional allocation and evaluation reflected by P3b (e.g., (Donchin, 1981;
484 Katayama & Polich, 1996a; Sutton et al., 1965).

485 The present results that both P3a and P3b amplitudes are associated with DLC levels might be
486 explained by the fact that excitatory postsynaptic potentials (EPSPs), a cause of scalp-recorded
487 P3a and P3b (Frodl-Bauch et al., 1999), could be altered by DLC exposure directly in an animal
488 experiment (Hong et al., 1998). Additionally, the glutamatergic metabolic system might be a
489 MeHg exposure mechanism because the glutamine/glutamate ratio in the anterior cingulate cortex

490 has a positive correlation with P3a amplitudes but not with P3b amplitude (Hall et al., 2015), as
491 shown in the present study. It is difficult to interpret the association between PCB and P3b
492 amplitude because P3b is influenced by multiple sources (Nieuwenhuis et al. 2005). One possible
493 mechanism is the influence of thyroid hormones, which act on the migration and differentiation
494 of nerve cells, synapse formation, and myelination in various parts of the brain during pregnancy
495 and the early postnatal period (Bernal, 2007). Although a previous study reported the absence of
496 an association between maternal PCB levels and maternal and neonatal thyroid hormones (Baba
497 et al., 2018), another suggested that hydroxylated PCBs, the predominant metabolites of PCBs,
498 had effects on fetal thyroid functions (Itoh et al., 2018). From a different perspective, one might
499 consider that these associations come from children's fatigue and motivation, not from alterations
500 of the cognitive process itself. However, we did not observe a negative association between
501 exposure and behavioral results, which is thought to be related to these factors. Additionally,
502 different cognitive processes reflected by P3a and P3b show different modulations. Therefore, the
503 children's fatigue and motivation could not explain these present results.
504 A major strength of our study was that the outcome of cognitive function in children was
505 measured by ERP without examiner bias, which is often problematic with psychological testing.
506 Additionally, we adopted a 3-stimulus oddball paradigm with two difficulty levels, which enabled
507 the discrimination between P3a and P3b and the individual cognitive processes they reflect.

508 Although previous studies have analyzed either PCBs or dioxins (Chen & Hsu, Vreugdenhil 2004,
509 Shellart 2008), or PCBs and MeHg (Boucher 2010), we found different patterns of association
510 between P3a/b and DLC, PCB, or HHg by analyzing these compounds.

511 One limitation of our study was that only a small number of participants agreed to participate in
512 the ERP experiment. In addition, the data was limited in the ERP analysis where noisy data had
513 to be excluded (n=55). According to Cohen's guidelines, our analysis could detect a medium to
514 large effect size but might miss small associations. Additionally, the comparison of baseline
515 characteristics showed older maternal age, higher educational levels, and lower smoking
516 prevalence in participants in the study, in whom DLC or PCB concentration was also higher than
517 in non-participants. These differences mean that participants in the present study might conform
518 a slightly biased population. To generalize the results of this study, a bigger sample should be
519 analyzed. Another limitation is the long time-window from prenatal exposure to the ERP outcome
520 in school age. Although Chu et al. (2019) demonstrated using structural and functional magnetic
521 resonance imaging (MRI) that prenatal exposure to a high level of PCBs was associated with
522 brain structure and function in men aged approximately 30 years, the limitation remains that we
523 could not analyze postnatal exposure to DLC, PCB, and MeHg and other chemicals. It is primarily
524 needed to examine multiple exposures because fish and seafood consumption would be the main
525 dietary sources of these chemicals and might include other common toxicants. Although the

526 association between P3a/b and exposures seems consistent, these results should be carefully
527 considered because of the multiple regression analyses. Despite these limitations, the results of
528 the analysis showed an association between fetal exposure to the studied substances and P3, which
529 is considered a valuable finding in line with previous studies. Further research is needed to
530 investigate the relevant mechanisms observed in the current study and whether they continue until
531 adulthood.
532

533 **5. Conclusions**

534 The reaction time to the target stimulus during oddball task became shorter as the exposure level
535 to MeHg increased. Furthermore, P3b latency, which reflects response decision and correlates
536 with reaction time, was also shortened in association with MeHg levels under the difficult
537 condition. It might be due to nutritional factors such as fatty acids, which have beneficial effects
538 on brain development. An association between prenatal exposure to DLC and a decrease in both
539 P3a and P3b amplitudes was found, even when DLC levels were lower than reported in most
540 previous studies. Additionally, our results suggest that the automated attention capture process
541 reflected by P3a was associated with maternal HHg, and the voluntary attention allocation process
542 reflected by P3b was associated with PCB-153 in maternal blood. However, these results should
543 be considered carefully because of the limitations on sample size, population bias, and statistical

analyses.

Author contributions

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Atsuko Ikeda-Araki: Writing - review & editing,

Chihiro Miyashita: Data curation, Writing - review & editing,

Tsuguhide Hori: Resources of chemical data, Investigation, Writing - review & editing,

Noriyuki Hachiyac: Resources of chemical data, Investigation, Writing - review & editing,

Reiko Kishi: Writing - review & editing, Supervision, Project administration, Funding acquisition.

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