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Variability in PCB Exposure of Adolescent Sexual Maturation in Published Articles

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Variability in PCB Exposure of Adolescent Sexual Maturation in Published Articles

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Abstract

One of the most important aspects of science is replication of research studies between different labs. This capability for scientists to check their work, and that of other scientists, leads to research results of interest being well-accepted and qualified. When research studies cannot be replicated under ideal experimental conditions, people can believe results that are not consistent, and the data is not real. The main objective of this study was to examine the variability on the levels of different PCB congeners from various studies and their effects on sexual maturation in adolescent population. The detectable levels of different PCB congeners were examined from different studies and the data was analyzed to see whether these studies can be replicated. An extensive literature search was performed exclusively in humans using PubMed from 01/01/1994 to 09/12/2019 with more defined search terms on PCB congeners. A total of 98 research papers were initially identified and only 18 relevant articles were selected, and the data was analyzed. There were 50 PCB congeners detected from these publications in adolescent population. The prevalence of these congeners varied from each investigation. Of interest is the observation that a highest score of 16 out of 18 was observed for PCB 138, PCB 153 and PCB 180. A total score of 6 out of 18 was detected for PCB 74, PCB 87, PCB 105 and PCB 149. The variability in different levels of PCB congeners may be due to many factors such as different exposure, duration, doses and methods employed for analysis. Further investigation is needed to generate a database on more relevant and prominent PCB congeners in different gender, age groups, ethnic groups and duration of exposure, etc. This will enable us to create awareness, minimize or completely avoid the exposure to more toxic PCB congeners and help to develop novel drugs to overcome their toxicity in humans.

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Introduction

"You can never step into the same river twice;

for other waters are ever flowing on to you."

This quote from the Greek philosopher Heraclitus means that the world is constantly changing and that no two situations are the same. As the water flows in a river, it is impossible one can touch the exact same water twice when one steps into a river. Just like in research, it is extremely difficult to replicate experiments because there are a number of variables that are hard to keep consistent over time.

Why is Replication Important?

One of the most important aspects of science is replication, which is getting the same results when an experiment is repeated by different researchers from different labs. This ability for scientists to check their work, and that of other scientists, leads to the results of the investigation being well-accepted. When studies cannot be replicated under ideal experimental conditions, people can believe results that are not consistent with reality. For example, in 1998 Andrew Wakefield had a paper published in which he suggested that the common childhood measles, mumps, and rubella vaccine is linked to autism. After this publication, other researchers tried to confirm the findings, however, they were not able to replicate the research results and therefore, there was no link between vaccines and autism. Later, this study was determined to be fraud since it could not be replicated. The effects of this falsely reported research still has lasting impacts today, but if not replicated could have had more detrimental outcomes on the health of the community, especially in the children (CK12, 2019).

What Makes Replication Difficult?

All experiments should be able to be replicated, although they may have varying timetables. It is important to understand sources of variability between labs and experiments. Reproducibility is improved by pinpointing the methods of the original experiment. This can lead to results being updated, revised, or confirmed (Lithgow, Driscoll, and Phillips, 2017).

A large factor that contributes to this crisis is publication bias which lean towards positive results, away from the null hypothesis. This affects replication since negative results tend to not get reported due to authors having grants at stake, journals needing strong stories to generate headlines, or pharmaceutical companies investing large amounts of money and resources toward positive results.

Replication failure in studies is also due to different populations have different levels of exposure which affect the immunological state of the population being studied. Additionally, differences in statistical methods between the original study and the replicator study can lead to differences in results. (Hunter, 2017). Polychlorinated Biphenyls (PCBs) are a good test model for replication studies because there are many congeners.

What are Polychlorinated Biphenyls?

Polychlorinated Biphenyls (PCBs), according to the United States Environmental Protection Agency, are a group of man-made organic chemicals that consist of carbon, hydrogen, and chlorine atoms. PCBs are chemicals formed by attaching one or more chlorine atoms (at the 'X's in Figure 1 below) to a pair of connected benzene rings (ATSDR, 2014). The physical and chemical properties of PCBs are determined by the number of chlorine atoms and their respective location in the molecule. These unique aspects make each compound known as a PCB congener; there are 209 PCB congeners. PCBs are not commercially produced in the United

States anymore but have been used in the past in several industrial products, like electrical and hydraulic equipment, plasticizers in paints and rubber goods, and in some pigments, dyes, and carbonless copy paper. Since PCBs are hydrocarbons, they are not readily broken down when they become released into the environment and can remain in the air, water, and soil for long periods of time (EPA, 2019).

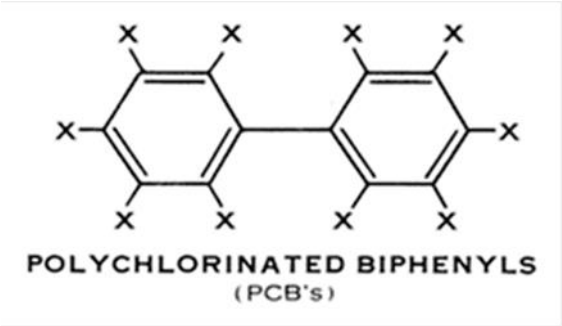

Figure 1: A Backbone Structure of Polychlorinated Biphenyls (PCBs), where X=Chlorine (Cl)

PCBs in the Environment

PCBs are complex molecules, do not readily break down once in the environment. They can remain in the environment for a long period of time in the air, water and soil. They can be carried long distances and have been found in snow and sea water in areas far from where they were released into the environment. In general, the lighter the form of PCB, the further it can be transported from the source of contamination (ATSDR, 2014).

How PCBs Can Enter Humans?

PCBs enter the human body and can be absorbed mainly through the dermal by skin contact, inhalation by breathing in the air, oral by eating and drinking, or transplacental routes. This will result in PCBs getting stored in fatty tissue and not being eliminated, which leads to the accumulation in the body. Depending on the amount of PCB exposure that enters the body, how long exposure lasted, among other factors, affects how PCBs influence health. When mothers

have been exposed, it has been linked to cause birth defects in the developing fetuses when the mother is pregnant and young children are affected after breastfeeding (ATSDR, 2014).

PCBs and Sexual Maturation

The lack of replication or reproducibility extends to include research on human responses to environmental impact, including the effect of PCB congeners on timing of adolescent sexual maturation. Sexual maturation begins at different ages, although roughly around the same age, depending on genetic and environmental factors. In boys, sexual changes include enlargement of the scrotum and testes, lengthening of the penis, and appearances of pubic and facial hair. In girls, sexual maturation is first observed with increasing breast size, start of menstruation, and pubic and axillary hair growth. The Tanner scale is also used as a reference for sexual maturation growth of the penis in boys, breast in girls, and public hair in both (Graber, 2019). Sexual maturation can be delayed due to several factors and this delay is often characterized by absence of sign of gonadal development, including increase of the size of testes or presence of breast budding, before the age of 13 years in girls and 14 years in boys (Sizonenko, 1987).

Objective

The main objective of this study was to examine why different studies, investigating PCB congeners and their effect on sexual maturation in adolescents, obtain different results. A variety of different congeners and the amount of overlap of these congeners were examined to see whether these studies can be replicated. This study focuses on identifying the dose, which is the level of exposure of PCB congeners, that contributes to the challenges in replication.

Methods

In order to test the concept for replication or reproducibility, a thorough search for published articles was conducted for studies regarding PCB congeners and sexual maturation using PubMed exclusively. PubMed was used because it is a free search engine for published papers that contains millions of historical and current articles for free and is maintained by the National Center for Biotechnology Information. It also allows for search terms to be more subject-specific and could limit results to just the title, author and abstract.

Six searches were conducted with terms that were identified to best represent sexual maturation. The search was limited to terms in the Title/Abstract only. These searches included these sets of terms: 1) PCBs, sexual maturation; 2) PCBs, puberty; 3) PCBs, menarche; 4) PCBs, Tanner; 5) PCBs, sexual development; and 6) PCBs, sexual. The searches were conducted with the PubMed Advanced Search Builder function. The search term PCBs was entered in the first search term and the subsequent term representing sexual maturation was entered in the second search term. The searches for all search terms were then further specified to include articles from 01/01/1994 to 09/12/2019, which depicts published articles in this topic from the past 25 years. These searches were then specified again to just include the human species. The search results with these articles were all further considered.

These six searches resulted in the identification of 98 articles. Out of this initial search, 38 articles were duplicate since they were discovered by more than one set of search terms. This left 60 unique articles found in one or more searches. These articles were then grouped (Table 1, see Appendices, p. 16) into four categories: 1) report individual congener level; 2) sum-total of congeners; 3) congeners with no level; and 4) no reported information/ articles that were not relevant to the search. The articles in this category of no information relevant to the search were

further categorized into three categories including articles that did not report levels of any congeners, articles that were not about sexual maturation but a search term used was mentioned in the title and/or abstract, and articles that were not in English.

Reported individual congener level represents articles that give a dose exposure for each congener. There were 3 articles that reported the individual congener level and these articles were considered further. Sum-total of congeners represent articles that give a dose exposure for a group of congeners together without specifying the levels of each congener in the group. There were 9 articles that reported the sum-total of congeners and these articles were also considered further. Congeners with no level represent articles that gave congeners detected, but no reported dose exposure. There were 6 articles that had congeners detected, but with no level and these articles were also considered further. The congeners from each article that was considered further, a total of 18 articles, were put into a spreadsheet (Table 2, see Appendices, p. 17) to determine the frequency and grouping of PCB congener, if any.

No reported information/ articles that were not relevant to the search include articles that did not report of any congeners or articles that were not about sexual maturation and PCBs, it also included articles that were not in English. There were 42 articles that reported no information relevant to the search. These include 14 articles that did not report levels of any congeners, 23 articles that were not about sexual maturation and PCBs but mentioned one of the search terms used in the title and/or abstract, and 5 articles that were not in English. These three subcategories with a total of 42 articles were not considered further

Results

A total of 18 research papers were selected and the results on the detection of various PCB congeners in adolescents have been tabulated (Table 3, see Appendices, p. 18). There were 50 PCB congeners detected from these investigations in adolescent population. The prevalence of these congeners varies from each paper. Of interest is the observation that the highest score of 16 out of 18 was detected for PCB 138, PCB 153 and PCB 180. PCB 118 is the next prominent (with a score of 10 out of 18) form of PCB congeners detected in adolescent population. The concentrations of PCB 52, PCB 99, PCB 101, PCB 170 and PCB 187 all had a score of 7 out of 18, which were reported to be slightly lower compared to PCB 118. The total score of 6 out of 18 was detected for PCB 74, PCB 87, PCB 105 and PCB 149. The contribution of following PCB congeners appear to be minimal as their detection score was 3-5 out of 18: PCB 18, PCB 28, PCB 44, PCB 49, PCB 66, PCB 77, PCB 110, PCB 126, PCB 128, PCB 146, PCB 151, PCB 156, PCB 157, PCB 158, PCB 167, PCB 169, PCB 172, PCB 177, PCB 178, PCB 183, PCB 189, PCB 194, PCB 195, PCB 196, PCB 201, PCB 203, and PCB 206. The detection of following PCB congeners was low (score was ≤ 2 out of 18) compared to rest of the PCB congeners: PCB 70, PCB 81, PCB 84, PCB 90, PCB 95, PCB 123, PCB 163, PCB 164, PCB 199 and PCB 209.

There were three articles that measured individual congener level (Table 4, see Appendices, p. 19). Windham *et al.* (2015) reported the levels, specifically the 50^{th} percentile, of the six most frequently detected PCBs: PCB 99 had a 50^{th} percentile of 2.1 ng/g lipid, PCB 118 had a 50^{th} percentile of 3.4 ng/g lipid, PCB 153 had a 50^{th} percentile of 7.2 ng/g lipid, PCB 170 had a 50^{th} percentile of 1.6 ng/g lipid, PCB 180 had a 50^{th} percentile of 3.6 ng/g lipid, and co-eluted PCBs 138/158 had a 50^{th} percentile of 5.5 ng/g lipid. Su *et al.* (2012) reported the median

level of sample of 56 boys and girls, in ng/g lipid, of the three PCBs detected in their study: PCB 138 was 7.4 ng/g lipid, PCB 153 was 8.8 ng/g lipid, and PCB 180 was 6.2 ng/g lipid. Kristensen *et al.* (2016) also reported the median level of a sample of 341 young Danish women, in ng/g lipid, of the PCBs detected: PCB 118 was 18 ng/g lipid, PCB 138 was 84 ng/g lipid, PCB 153 was 152 ng/g lipid, PCB 156 was 11 ng/g lipid, PCB 170 was 40 ng/g lipid, and PCB 180 was 71 ng/g lipid.

Discussion

A significant difference in the levels of various PCB congeners were observed between different investigators in adolescent population. Of interest is the observation that the concentrations of PCB congeners, PCB 138, PCB 153 and PCB 180 are more frequently detected in adolescent population from all the data collected from 18 different studies. From the three articles that reported the individual levels of PCB congeners, there were differences in the exposures measured, but they all detected congeners PCB 138, PCB 153, and PCB 180. For PCB 138, Kristensen *et al.* (2016) had reported the level that was more than 11 times more than the level reported by Su *et al.* (2012) and more than 15 times more than the level reported by Windham *et al.* (2015). For PCB 153, Kristensen *et al.* (2016) reported 17 times more exposure than Su *et al.* (2012) and 21 times more exposure than the level reported by Windham *et al.* (2015). Likewise, for PCB 180, Kristensen *et al.* (2016) reported more than 11 times the exposure than Su *et al.* (2012) and about 20 times more exposure reported by Windham *et al.* (2015). These results imply the notable variability in the levels of PCB congeners between articles.

These results also suggest that replication is difficult because each sample tested has a different exposure and dose. This can also suggest a weakness in the field because, even though studies had common reported congeners, these experiments were hard to replicate because the large amount of variability among the study group and research methods used.

Strengths and Weaknesses

A strength of this study was that many search terms were used to describe sexual maturation and PCBs, which allowed a wide range of articles within the past 25 years. All articles were reviewed and only articles that were deemed relevant were examined further. This

allowed for articles with reported congeners to be considered. An additional strength was that most articles that were considered further had the same three congeners reported. A weakness in this study is that the search results were limited to just the PubMed database. Articles that were not written in English were not included for further investigation. In addition, the articles were limited to the reported PCB congeners and not articles that referenced studies that may have individual congener levels.

Future Research

A significant amount of various PCB congeners are widely distributed in the environment we live in such as the air we breathe, water we drink, places we live near, fish or vegetables we eat, exposure to paints, oils and soaps around the house we live in, to name a few. One can quantitatively analyze and replicate the concentrations of the detectable levels of PCB congeners in human blood or serum samples to identify relevant toxic PCB congeners in humans. This will allow us to generate a database and correlate the data on the exposure to type of source material and relevant PCB congeners being detected in blood samples. These results can also be further investigated for different gender, ethnic, and age groups and duration of exposure, etc. This will enable us to derive to a conclusion to create awareness, minimize or completely avoid the exposure to more toxic PCB congeners and help to develop novel drugs to overcome the toxicity in humans.

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Appendices

Table 1: Number of articles from search results

				Articles That Reported No Information Related to the Search			
	Individual Level	**Sum Total**	**No Level**	**No Reported Levels of any Congeners**	**Not About Sexual Maturation**	**Not in English**	**Total**
PCBs; Sexual Maturation	0	3	2	1	2	0	8
PCBs; Puberty	1	4	4	5	7	3	24
PCBs; Tanner	1	0	0	0	0	0	1
PCBs; Menarche	1	0	0	2	4	1	8
PCBs; Sexual Development	0	1	0	1	3	1	6
PCBs; Sexual	0	1	0	5	7	0	13
	3	9	6	14	23	5	60

Table 2: Congeners detected from each article and respective categories, if applicable

Articles	Grouping	18	28	44	49	52	66	70	74	77	81	84	87	90	95	99	101	105	110	118	123	126	128	138	146	149	151	153	156	157	158	163	164	167	169	170	172	177	178	180	183	187	189	194	195	196	199	201	203	206	209
Schell et al. (2014)	Σ16PCBs					X		X	X			X	X		X	X	X	X	X	X				X		X		X										X		X											
Schell et al. (2014)	Σ8PerPCBs								X							X		X		X				X				X										X		X											
Schell et al. (2014)	Σ6NonPerPCBs					X						X			X		X		X							X																									
Schell et al. (2014)	Σ7EstrogenicPCBs					X		X							X	X	X		X									X																							
Schell et al. (2014)	AntiestrogenicPCBs																	X																																	
Schell et al. (2014)	Σ4Mono-OrthoPCBs							X	X									X		X																															
Schell et al. (2014)	Σ8Di-OrthoPCBs					X							X	X		X			X					X					X											x											
Schell et al. (2014)	Σ3Tri-and Tetra-OrthoPCBs											X			X																																					
Eskenazi et al. (2017)		X	X	X	X	X	X		X				X			X	X	X	X	X			X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X			X	X
Eskenazi et al. (2017)	dioxin-like																			X									X							X																
Eskenazi et al. (2017)	non-dioxin-like	X	X	X	X	X	X		X							X	X							X	X			X																X		X		X	X				
Korrick et al. (2011)		X	X	X	X	X	X		X				X			X	X	X	X	X			X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Den Hond et al. (2011)																								X				X													X											
Schell, Gallo (2010)																				X				X				X							X						X	X	X								
Denham et al. (2005)						X		X	X			X	X	co	X	X	X	X	X	X	co			X		X		X				co	co							X		X									
Denham et al. (2005)	estrogenic/neurotoxic					X		X									X																										X									
Denham et al. (2005)	antiestrogenic								X									X		X				X																												
Denham et al. (2005)	enzyme-inducing															X												X													X											
Staessen et al (2001)																								X				X													X											
Leijs et al (2017)									X													X													X																	
Sergeyev et al. (2017)	co-planar PCB								X	X												X													X																	
Sergeyev et al. (2017)	non-coplanar PCB	X	X	X	X	X	X		X				X			X	X	X		X			X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Burns et al. (2016)	dioxin-like PCBs								X	X												X													X																	
Burns et al. (2016)	non-dioxin like PCBs	X	X	X	X	X	X		X				X			X	X	X	X	X			X	X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Windham et al. (2015)																X				X				X				X			co					X					X										
Grandjean et al. (2012)																								X				X													X										
Wolff et al. (2008)																				X				X				X													X										
Mol et al. (2002)																								X				X													X										
Su et al. (2012)																								X				X													X										
Kristensen et al. (2016)																				X				X				X	X							X					X										
Croes et al. (2014)																								X				X													X										
Winneke et al. (2014)			X			X											X						X				X											X													
	TOTAL	4	5	4	4	7	4	2	6	3	2	2	6	1	2	7	7	6	5	10	1	3	5	16	4	6	5	16	5	4	3	1	1	4	3	7	4	5	4	16	5	7	4	4	4	4	2	3	3	4	2

Table 3: Distribution of various PCB congeners in adolescent population congregated from 18 different research articles

PCB Congeners	Number of Papers	PCB Congeners	Number of Papers
138	16	**157**	4
153	16	**167**	4
180	16	**172**	4
118	10	**178**	4
52	7	**189**	4
99	7	**194**	4
101	7	**195**	4
170	7	**196**	4
187	7	**206**	4
74	6	**77**	3
87	6	**126**	3
105	6	**158**	3
149	6	**169**	3
28	5	**201**	3
110	5	**203**	3
128	5	**70**	2
151	5	**81**	2
156	5	**84**	2
177	5	**95**	2
183	5	**199**	2
18	4	**209**	2
44	4	**90**	1
49	4	**123**	1
66	4	**163**	1
146	4	**164**	1

Table 4: Three articles that reported individual congener level for the median in ng/g lipid

PCB	Windham et al. (2015)	Su et al. (2012)	Kristensen et al. (2016)
99	2.1		
118	3.4		18
138	5.5 (co-eluted with PCB 158)	7.4	84
153	7.2	8.8	152
156			11
170	1.6		40
180	3.6	6.2	71