AMERICAN UNIVERSITY OF BEIRUT

ASSOCIATION BETWEEN THE EXPOSURE TO PERSISTENT ORGANIC POLLUTANTS (POPS) AND BODY WEIGHT STATUS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES

by
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ABSTRACT
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Title: Association Between the Exposure to Persistent Organic Pollutants (POPs) and Body Weight Status: A Systematic Review and Meta-Analysis of Observational Studies

INTRODUCTION: Being a major risk factor of a wide range of Non-Communicable Diseases (NCDs), obesity has been one of the most challenging public health problems today. It is possibly the result of many different factors which include but are not restricted to environmental exposure to Endocrine-Disrupting Chemicals (EDCs), such as Persistent Organic Pollutants (POPs). POPs are a class of highly lipophilic chemical pollutants that reside in lipid-containing tissues for several years before being excreted by the body.
PURPOSE: Because of the possible proposed role of POPs in inducing obesity, this study aims to conduct a Systematic Review (SR) to investigate the association between exposure to POPs and body weight status in all age groups. This thesis will explore specifically the effect of OCPs- a pesticide class of POPs- exposure on birthweight of infants.
METHODS: four databases were searched with all terms and controlled vocabulary relevant to POPs and obesity until 08/10/2020, without any publication date restriction. Starting with 18,367 references, scanning was done by title and abstract followed by full text and then data extraction and meta-analysis.
RESULTS: data of 10 studies (with 25 exposures) analyzed on RevMan suggest a significant correlation between individual exposure to DDE and HCB with regression coefficients of -8.20 g and -2.88 g respectively. The overall pooled primary analysis of all OCPs also suggests a significant inverse correlation with birthweight by -3.815 grams (CI -5.30, -2.33). Upon subgroup analysis, HCH and DDT class showed a correlation as well with regression coefficients of -3.32 g and -6.17 g respectively.
CONCLUSION: exposure of infants to OCPs might be correlated with decreased birthweight.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AhR	Aryl hydrocarbon Receptor
BMF	Biomagnification Factor
BMI	Body Mass Index
c-decBDE	Decabromodiphenyl ether
CINAHL	Cumulative Index of Nursing and Allied Health literature
CV	Controlled Vocabulary
DDE	Dichlorodiphenylethylene
EDCs	Endocrine Disrupting Chemicals
Embase	Excerpta Medica Database
EPA	U.S. Environmental Protection Agency
HCB	Hexachlorobenzene
HCBD	Hexachlorobutadiene
HCH	Hexachlorocyclohexane
KAW	Air-Water partitioning coefficient
KOW	Octanol-Water partitioning coefficient
NCDs	Non-Communicable Diseases
NREs	Nuclear Response Elements
NRs	Nuclear Receptors
NYHA	New York Health Association
OCPs	OrganoChlorine Pesticides
PCBs	PolyChlorinated Biphenyls
PCN	Polychlorinated Naphthalenes
PCP	Pentachlorophenol
PFAS	Polyfluoroalkyl Substances
PFOA	Polyfluorooctanoic Acid
POPs	Persistent Organic Pollutants

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PTDI	Provisional tolerable daily intake
RIS	Research Information System
RoB	Risk of Bias
SCCPs	Short-chained chlorinated paraffins
SR	Systematic Review
TCDD	Tetrachlorodibenzo Dioxin
TDI	Tolerable daily intake
UNEP	United Nations Environment Programme
US	United States
WHO	World Health Organization
XREs	Xenobiotic Response Elements

CHAPTER I

ENDOCRINE DISRUPTING CHEMICALS AS POLLUTION BIOMARKERS AND OBESITY

A. Persistent Organic Pollutants as biomarkers of environmental pollution

The biggest danger the environment and its ecosystems are facing in this century is pollution. Seven million deaths yearly have been estimated to be caused by this silent killer[1]; still, human industrial activities and toxic emissions are not controlled completely, especially in developing countries. Chemical toxic emissions are diverse, depending on their physical and chemical properties. Some are not only causing direct human and environmental harm, but also are persistent to chemical and biological degradation; such chemicals are called Persistent Organic Pollutants (POPs).

1. Introduction to POPs

a. Chemical nature and known health hazards

POPs -pertaining to a class of Endocrine Disrupting Chemicals (EDCs)- are halogenated organic carbon-based chemicals (Figure 1). They are highly lipophilic and bio-accumulative chemicals that reside in lipid-containing tissues for several years before being excreted by the body. These toxicants bio-magnify in the human body and have been associated with different types of cancer[2], metabolic syndrome[3], cardiovascular problems[4, 5], hypertension[2], decrements in cognitive functions[6], immune suppression[7], and other health complications.

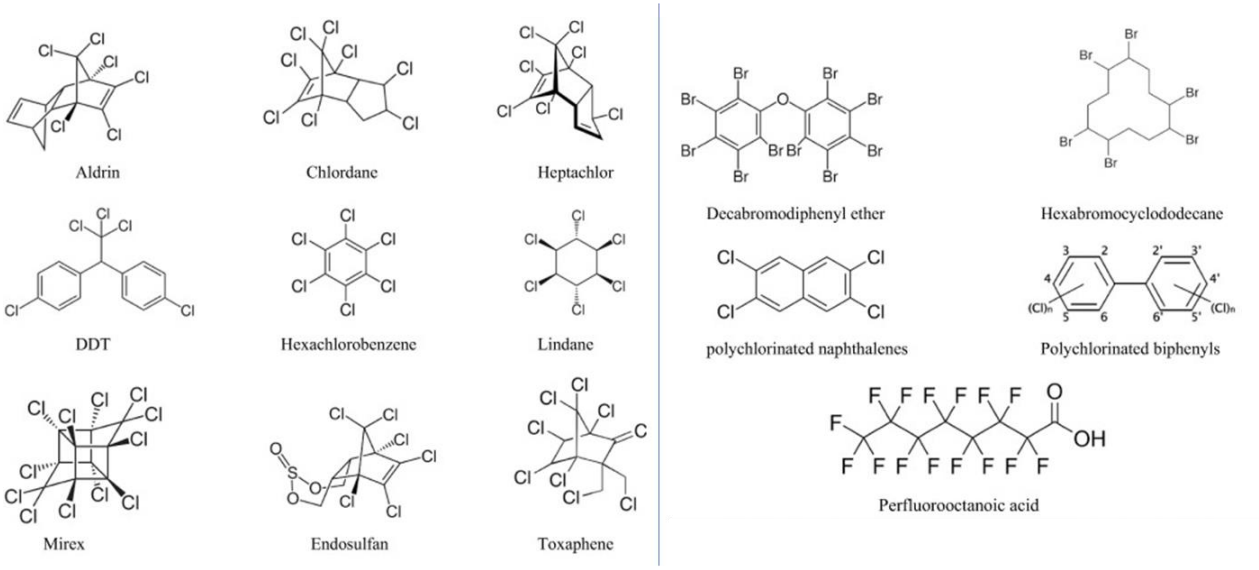


Figure 1: Structure of common OCPs and industrial POPs classified by Stockholm convention

b. Sources of POPs

Several sources are major producers depending on POP chemical class. For example, besides OCPs which were produced as a result of agricultural work, dioxins and furans get produced unintendedly during industrial and non-industrial fuel combustion[8]. As for Polychlorinated biphenyls (PCBs), they are leaked mainly from damaged transformers and capacitors[8]. Other types of POPs are released from different industrial processes depending on the source emission factor for each chemical.

All the sources mentioned above contribute to releasing these toxic chemicals into environmental compartments which can be abiotic, such as air, soil, and different other sediments, or which be biotic matrices and media of humans or other living species[9]. The abiotic environmental compartments themselves become a source of contamination and exposure to humans and other living things.

c. Mode of transportation

Most POPs are semi-volatile and highly soluble in lipids, with few hydrophilic exceptions such as Perfluorooctanoic acid (PFOA). Their vapor pressure ranges between 10^{-4} and 10^{-11} atm at 25°C[2]. This property allows them to associate with aerosols and transport from one place to another[10]. In addition, because of their diverse structures, POPs tend to behave differently in their modes of transport ranging from flyers, to single and multi-hoppers, to swimmers, based on their air-water (k_{AW}) and octanol-water (K_{OW}) partitioning coefficients[11]. The long range-transport of POPs is a repetitive series of a two-step process: liquid/solid phase transformation to vapor (or vice-versa) and atmospheric mixing with the aerosols[12]. Moreover, the reasoning behind POPs migration across the globe can be attributed to the grass-hopper effect, whereby the movement goes from hot areas in the direction of cold areas where the chemicals can deposit and contribute to the global warming issue[2]. Thus, even though POPs are being produced in developing countries, they can be found everywhere, in infant's blood and adipose tissues, and even in remote areas.

2. Migration of POPs inside the body

a. Exposure routes and dosages

POPs enter the human body through many paths including inhalation of air, dietary and nondietary ingestion, and through dermal contact[13]. Ingestion of food and dust via dust-borne POPs is a main source of exposure[14], especially in toddlers who ingest more amounts of dust while playing on the floor[15].

Most food-ingested POPs are found in fat-rich foods, such as fish, meat, meat fat, and dairy products which is due to their lipophilicity. Another food source of POPs -especially OCPs and other pesticides- would be typical daily diet items, such as fruits, vegetables, and peanuts[16]; as a result of agricultural contamination of pesticide residues. This is supported by the Environmental Protection Agency (EPA) which estimates that more than 95% of dioxin intake is achieved through the ingestion of animal fats[17].

Dosages of exposure vary between the general population which receives low background doses of mixtures of POPs through the sources mentioned above, and between the workers or veterans who receive high dosages through short-term exposures of a specific POP during work hours[18]. Therefore, the health hazards at an adult stage would be predicted by the degree of exposure, duration of exposure, and toxicity of the chemical entering the body.

b. Distribution inside the body

Once they surpass the gastrointestinal tract, POPs, such as PCBs, diffuse and enter through the blood circulation towards the lymphatic system[19]. Chemicals with higher lipophilicity tend to accumulate in fat-rich tissues such as liver, brain, breast milk, and skin[19]. Other POPs might be distributed across other types of muscles or even circulate in the serum or plasma of exposed individuals.

The distribution of POPs varies by their lipophilicity degree and by the richness of fat per organ. As a result, some types of POPs can accumulate at certain sites in the body rather than others. For instance, Zong in 2015 performed a cross-sectional study on 2358 adults to determine the distribution of POPs by dual-energy x-ray

absorptiometry[20]. The study observed a strong correlation of circulating lipophilic POPs (β-HCH, PCB-126, hepta and octa dibenzo-p-dioxins) with trunk fat rather than leg fat[20].

c. Metabolism

Once inside the body, POPs rate of metabolism gets based on the number of chlorine atoms attached and on their position; this process is known as preferential metabolism[21]. This means that POPs with lower number of chlorine atoms are metabolized more in comparison to POPs with higher number of chlorines which end up residing in lipid containing tissues in a lipid-soluble form[21].

The liver acts as the primary site of metabolism. PCBs, as a major class of POPs, get metabolized by hydroxylation via a system catalyzed by cytochrome p-450, whereby POPs get conjugated with sulfates and glucuronic acids[21]. Once metabolized, the transformation that the chemical undergoes either leads to bioaccumulation or to excretion.

d. Bioaccumulation, biomagnification, and half-lives

Before entering the final predator body, POPs increase concentrations from one trophic level to a higher trophic level throughout the food web by a certain Biomagnification Factor (BMF)[22]. For instance, PCBs in aquatic organisms, as a result of biomagnification and bioconcentration, might be as one million times higher than levels in the aquatic environment that spread the PCBs in the first place[23].

POPs bioaccumulate for long periods starting with weeks and months for up to decades in the human body and other living species. For instance, Hopf in a study on sera of occupational cohort of workers estimated the half-life for Aroclor 1254 of PCBs by 133.33 years through a linear spline model equation[24].

The bioaccumulation process might be proceeded by structural transitions into metabolites that can bioaccumulate in specific tissues and fluids[19]. But once inside the body, POPs display the ability to bioconcentrate up to 70,000 times higher than their original concentrations[22].

e. Excretion

Depending on the number of chlorine atoms on their phenyl rings, POPs can be excreted out of the body through urine, feces, or breast milk in the case of pregnant women. POPs with lower number of chlorines are metabolized into water soluble substances by connecting to glutathione and glucuronic acid, and then get excreted through feces[19] most of the time due to their lipophilicity.

The ability to excrete and get rid of these chemicals outside the body decreases by age increase[25]. Sometimes, they might reach critical organs before getting excreted and cause severe hazards[25]. Although the rate of excretion in children is higher due to the effect of dilution while growing up, POPs, once inside the body of children - especially fetuses, can cause irreversible damage at many health levels.

3. Banning of POPs and their classifications

Due to all the danger POPs pose on humans and nature upon exposure, a Swedish international environmental treaty was held in 2001 by United Nations Environment Programme (UNEP) to work towards eliminating the production and use of POPs[26]. The chemicals enlisted under POPs were called the 12 dirty dozen and included OrganoChlorine Pesticides (OCPs), PolyChlorinated Biphenyls (PCBs), dioxins, furans, and other chemicals. Later on, the list was extended to include 29 classes of chemicals.

All enlisted POPs fall into one or more of the three categories: Pesticides/insecticides, intentional industrial products such as plasticizers and flame retardants, and unintentional byproducts such as dioxins and furans (Table 1).

Table 1: Persistent Organic Pollutants (POPs) enlisted under Stockholm Convention with their classification, lipophilicty, and estimated biological half-lives.

The dirty dozen	Class	Classification Under the Stockholm Convention	Estimated Biological half-life	Lipophilicty (log octanol-water partition coefficient log kow)
Aldrin	Organochlorine Pesticide	Elimination	369 days[27]	5.14-7.4[28]
Chlordane	Organochlorine Pesticide	Elimination	Weeks[29]	6[28]
DDT	Organochlorine Pesticide	Restriction (for disease vector control)	7 years[30, 31]	4.89-6.914[28]
Dieldrin	Organochlorine Pesticide	Elimination	300 days[32]	3.692-6.2[28]
Endrin	Organochlorine Pesticide	Elimination	24 hours - week[33]	3.209-5.339[28]
Heptachlor	Organochlorine Pesticide and Industrial Chemical	Elimination	4 weeks[34]	4.40-5.5[28]
Hexachlorobenzene	Organochlorine Pesticide	Elimination	2 years[30, 31, 35]	3.03-6.42[28]
Mirex	Organochlorine Pesticide	Elimination	10 years[28]	6.9[36]
Polychlorinated Biphenyls	Industrial Chemicals	Elimination	0.1-40 years[30, 37]	4.3-8.26[28]
Polychlorinated dibenzo-p-dioxins	Industrial By-products	Reduction	5-10 years[30]	4.75-8.20[28]
Polychlorinated dibenzofurans	Industrial By-products	Reduction	0.2-20 years[37]	5.44-8[28]
Toxaphene	Organochlorine Pesticide	Elimination	Weeks[38]	3.23-5.50[28]
Newly enlisted POPs				
Chlordecone	Organochlorine Pesticide	Elimination	125-165 days[39]	5.41[40]
Endosulfan	Organochlorine Pesticide	Elimination	8-15 hours[41]	3.62-3.83[40]
Polybromodiphenyl ethers	Industrial Chemicals	Elimination	1-12 years[42]	6.265-6.97[43]
Hexabromobiphenyl	Industrial Chemical	Elimination	4-97 years[42]	6.39[44]
Hexachlorocyclohexane	Organochlorine Pesticide and Industrial By-product	Elimination	6 years[30, 31]	3.72-4.14[45]
Pentachlorobenzene	Organochlorine Pesticide and Industrial Chemical and By-product	Elimination	-	5.18[40]
Perfluorooctane sulfonic acid	Industrial Chemical	Restriction	3.3-27 years[46]	4.49[47]
Chemicals proposed for inclusion				
Chlorinated Naphthalenes	Industrial Chemicals	Elimination	1.5-2.4 years[48]	3.93–6.68[49]
Hexabromocyclododecane	Industrial Chemical	Elimination	64 days[42]	5.63[50]
Hexachlorobutadiene	Industrial Chemical	Elimination	-	4.78[40]
Pentachlorophenol	Organochlorine Pesticide and Industrial Chemical	Elimination	1.3-33 hours[51]	5.12[40]
Chlorinated Paraffins	Industrial Chemicals	Elimination	-	4.48-7.38[52]

B. Obesity as a Non-Communicable Disease

1. Health burden

Obesity is defined as the accumulation and storage of excess levels of fat[53]. It is a major cause of type 2 diabetes, cardiovascular diseases, high cholesterol, infertility,

and different types of cancer, thus causing economic and Non-Communicable Diseases (NCDs) health burdens[54].

Being a major risk factor of a wide range of NCDs, obesity has been one of the most challenging public health problems today. Until 2017, it has been estimated that the total number of deaths resulting from obesity is around 9% globally and 20% in Lebanon[55]. These alarming statistics report that more than 40% of adults are obese or overweight with a Body Mass Index (BMI) above 25[56] (Figure 2). Such high numbers of cases are attributed to different factors such as genetic predisposition, overeating, sedentary lifestyle, urbanization, socio-behavioral factors, and environmental exposure to EDCs such as POPs.

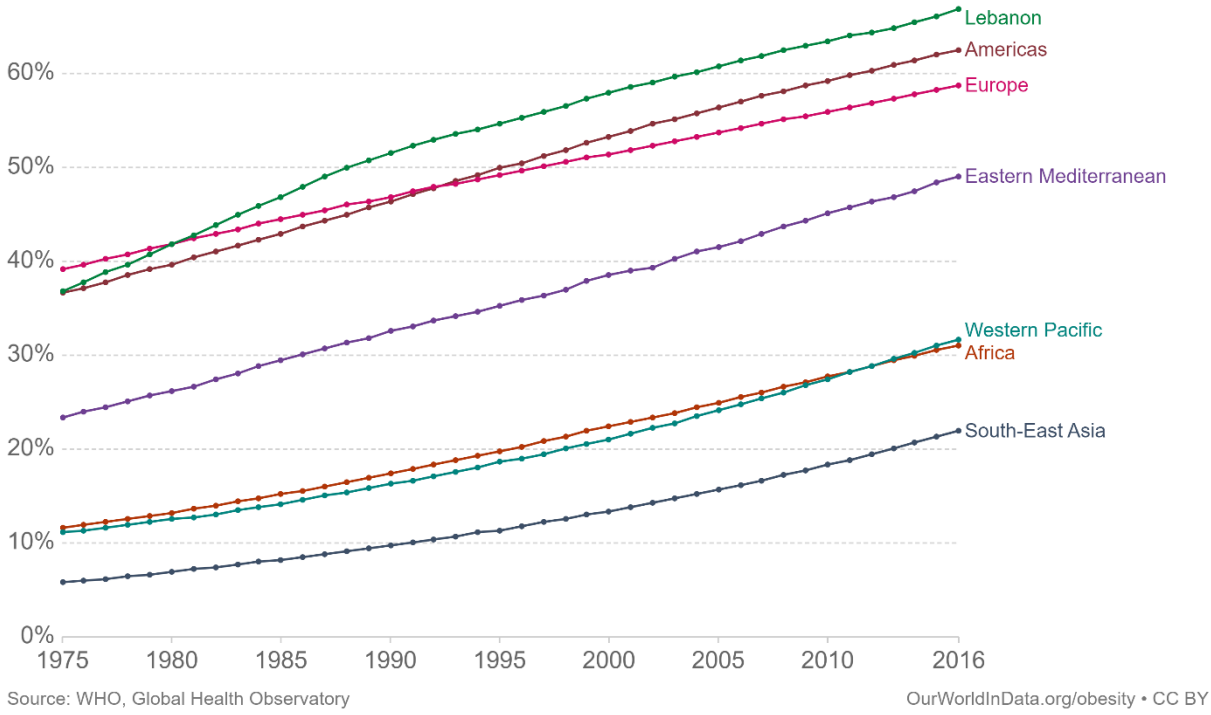


Figure 2[56]: Shares of adults that are overweight or obese, 1975 to 2016

2. Attribution to Endocrine Disrupting Chemicals

POPs are hypothesized to contribute to the development of obesity and metabolic diseases through the elevation of triglyceride levels, glucose intolerance, and cardiovascular diseases[57]. The mechanisms, although complex, are suggested to be mediated by aryl hydrocarbon receptor (AhR) which control cellular response to several pollutants[2, 58].

C. POPs and Obesity

1. Mechanism of POPs/ mode of action in promoting obesity

Till now, the exact mechanism of action of all POPs inside the body is still unknown. However, recently and after the Stockholm convention in 2001, proposed mechanisms along which in vitro and in vivo studies started to compile, providing pieces of evidence towards understanding more the mode of action of these chemicals, how they behave in different matrices, and how they induce gene regulation and thus contribute to the occurrence of NCDs[59].

For instance, Arsenescu in 2008 studied the effect of different POPs when incubated with 3T3-L1 adipocytes[60]. The study concluded that both PCB-77 and TCDD promoted adipocytes differentiation with PCB-77 administration leading to weight gain among mice[60].

Moreover, it has been proposed that POPs as EDCs can induce at early life exposure an epigenetic programming of obesity[59]. This process occurs when POPs bind to Nuclear Receptors (NRs), a transcriptional factors that are able to influence gene expression[59].

In the absence of any POP, and in the cytoplasm, both the Aryl hydrocarbon Receptor (AhR) and the NR are repressed through certain chaperones and/or co-repressors. Some NRs are bound by default to the DNA even when deactivated[61]. Upon exposure to POPs, the AhR and NR get activated by the POP by making a complex, and head towards the nucleus where this complex starts gene transcriptions with the help of coactivators[61]. Whether through direct interaction of with NRs, indirect disturbance of NR signaling, or through changes in hormone production and availability, POPs acts as EDCs and aid in disturbing the metabolism processes[61].

In other studies, DDE pesticide was highly correlated with changes in microbiota composition upon introduction in rats, providing new insight into the mechanism of POP-induced obesity[62].

POPs mechanisms of action as obesogenic chemicals can be diverse, ranging from increasing the number and size of fat cells, altering the regulation of adipose tissue development, affecting microbiome, inducing genetic changes, dysregulating hormone levels, and energy balance, to altering insulin and lipid metabolism[63].

Although some evidence has been explored in this field, further research is needed to elucidate the relationship and demonstrate more clearly the exact mechanisms involved for each POP to refine hazard identification of POPs in promoting obesity[64] or other body-weight changes.

2. Evidence of observational studies

Besides the mechanism described above, many cohorts of people of different ages and health conditions were recruited to collect observational evidence.

Data derived from a Danish cohort of 649 mother-child pairs showed that the in-utero exposure to PFASs is associated with excess adiposity during early childhood[65]. Conversely, a meta-analysis of observational studies of a Flemish infant-mother cohorts (total n=1579) showed that the exposure to PCBs such as PCB 180 during gestation is associated with a lower mean birth weight by 67.11g (-124.96, -9.26)[66], potentially related to disruption of thyroid hormones[67].

The fact that there is conflicting evidence revolving around the idea that POPs induce obesity, and having different possible correlations depending on age, duration of exposure, and other factors, require essentially a way to compile all data and studies done on this matter in a non-biased way and through a constructive statistical analysis; a Systematic Review (SR) and Meta-Analysis (MA).

Therefore, we aim to investigate all evidence and observational studies done through a SR to assess whether any correlation exists between exposure to POPs and body weight status in general and between OCPs and birthweight specifically.

D. Birthweight and Obesity

Birthweight is an indicator of body weight status during adulthood. For instance, low birthweight has been associated with increased rates of obesity[68-70]. It has been also associated with other health burdens such as insulin resistance and type 2 diabetes[68].

Assuming that there is a correlation between exposure to POPs and birthweight, this essentially means that in utero exposure to POPs might not only affect birthweight, but also body weight status later on during adulthood and might lead to other health

consequences[69]. Because of all of the stated above, this thesis focuses on infants as a targeted population rather than any other age group.

E. Systematic Review of the literature

Literature reviews have always been an essential tool to present an overview of the established knowledge on certain public health issues. Although very useful, traditional literature reviews are subjective and rely heavily on the knowledge and expertise of the author[71]. Other than the fact that the regular review's search strategy would lead sometimes to missing essential pieces of evidence and relevant articles, it also provides a very limited presentation of the topic without going into the details of each study separately. Therefore, SRs were conducted to present policymakers with a meticulous synthesis of the best and unbiased evidence that is available.

1. Definition

'A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question'[72]. It aims to provide reliable findings out of which conclusions can be established and policies and decisions can be made[72]. It also constitutes a great tool that can direct research into lessening or producing more evidence on a certain research topic.

2. Aim of this study

This study aims to investigate the association between exposure to POPs and body weight status in all age groups according to the PECO elements: population,

exposure, control, and outcomes. As a part of the SR, this thesis aims specifically to address the association between exposure to OCPs and birthweight in newly born infants according to a subset of specified PECO elements.

In order to answer the general research question and the specific one of this thesis, a Systematic Review (SR) is to be conducted whereby analytical methods are employed systematically to synthesize evidence results.

CHAPTER II

SYSTEMATIC REVIEW METHODOLOGY: SEARCH STRATEGY, DATA SELECTION AND EXTRACTION, AND META-ANALYSIS

A. Formulating the research question

1. Preliminary research and posing the research question

First step in conducting the review was to do a preliminary search on POPs and obesity in several databases, and to check whether other SRs (not regular literature reviews) on this topic have been published. The search revealed that at least a couple of original articles try to assess the relationship between exposure to POPs and obesity, and that no SR or on-going SR with integrated MA have been published before. This led to the development of the review question: Is the exposure to Persistent Organic Pollutants (POPs) associated with bodyweight changes?

2. PECO elements

Using the PECO framework, we divided the research question into the specific components:

a. Population

Given that the effect of POPs on body weight might be different by age categories, this study included healthy individuals of any age, not suffering from chronic advanced diseases that might affect weight or BMI which can be as follows

- New York Health Association (NYHA) classes II, III, and IV
- Active cancer
- liver cirrhosis and end-stage renal disease
- pregnancy complicated by gestational diabetes or hypertension
- growth problems in children: malnutrition, digestive tract diseases, kidney disease, heart disease, lung disease, diabetes mellitus, growth hormone deficiency, Cushing disease, hypothyroidism, turner syndrome, down syndrome, achondroplasia.

For this thesis, which is a section of the SR, we explored only one age category which are healthy infants. Again healthy infants should not suffer from any disease affecting birthweight in agreement with the stated population of interest above.

b. Exposure

Exposure included was to any type of POPs including polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), perfluoroalkyl substances (PFAS), dioxins, and furans…

General list of Persistent Organic Pollutants – to be included in exposure (this list does not include all chemicals in details):

- Aldrin
- Chlordane
- Chlordecone
- DDT

- DDE
- Decabromodiphenyl ether (c-decaBDE)
- Dicofol
- Dieldrin
- Dibenzodioxins
- Dibenzofurans
- Endrin
- Endosulfan
- Heptachlor
- Hexachlorobenzene (HCB)
- Hexachlorobutadiene (HCBD)
- Hexachlorocyclohexane (HCH)
- Lindane (gamma-HCH)
- Mirex
- Polybromodiphenyl ethers
- Pentachlorobenzene
- Pentachlorophenol (PCP)
- Polychlorinated biphenyls (PCBs)
- Polychlorinated Naphthalenes (PCN)
- Perfluorooctane sulfonic acid
- Perfluorooctanoic acid (PFOA)
- Short-chained chlorinated paraffins (SCCPs)
- Toxaphene

However for this thesis, we were interested in assessing the exposure to a pesticide class of POPs, OrganoChlorine Pesticides (OCPs), which mainly enter the body through dietary intake of fruits, vegetables, and fish.

c. Control/comparison

Control groups included were individuals with minimal or no exposure to Persistent Organic Pollutants (POPs). Other control groups were also possibly found in diet-controlled studies whereby the control group would have a restricted POPs free diet.

Minimal exposure means that exposure is within or below acceptable daily intake (ADI) or tolerable daily intake (TDI) or provisional tolerable daily intake (PTDI). Such values are extracted from the individual studies in case it was not provided on the World Health Organization (WHO) website.

d. Outcome

The main outcome was the bodyweight status measured by body mass index (BMI) for adults and elderly, and body weight for infants (birthweight specifically) and children. Studies that did not assess primary and additional outcomes quantitatively were disregarded.

For this thesis, we focused on birthweight as the outcome of interest rather than other outcomes given that the population of interest are newly-born infants.

B. Inclusion/exclusion criteria

We determined all criteria before we went any further into the SR to lessens selection bias. Inclusion/exclusion criteria simply determined which studies were included for further scanning and which were excluded. The level of strictness of the inclusion/exclusion criteria determines the levels of heterogeneity and selection

bias[73]; as the criteria is stricter the included articles would be less heterogeneous, but there would be more chances for selection bias.

Below are the Inclusion and exclusion criteria for this thesis:

1. ***Inclusion criteria***

- Studies containing original research data that are peer-reviewed
- Studies that are of observational or interventional designs
- Studies with newly born infants as a population of interest
- Studies assessing the exposure of OrganoChlorine Pesticides (OCPs)
- Studies evaluating birthweight as the outcome of interest

2. ***Exclusion criteria***

- Case reports and case series
- Narrative and systematic reviews
- Qualitative studies
- Studies that do not assess the exposure to OCPs quantitatively
- Studies that do not assess the outcome quantitatively
- Studies written in Chinese, Japanese, or Korean languages.
- Studies with more than 25% of the population suffering from chronic diseases that affect body weight status

C. PROSPERO protocol

Once the research question is framed, it is crucial to draft a transparent plan for a clear unbiased SR. The plan was written in the form of a protocol containing all data that is necessary to be predetermined before starting the actual work.

After all the sections of the protocol were accomplished and reviewed by the team, the protocol was published online in PROSPERO. International Prospective Register of Systematic Reviews (PROSPERO) is an open access online database that allows the registry of SRs with health-related outcomes. PROSPERO lists all published and ongoing registered SRs in order to avoid duplication and reduce the opportunity for reporting bias and thus increase transparency of the review.

D. Search strategy and collection of references

The detailed search strategy in a SR ensures that no published study pertaining to the topic would be missed. The following are all the steps we followed to develop the search strategy:

1. Choice of databases

For this SR, we chose three databases which are the following: Medline, Cochrane, Excerpta Medica Database (Embase), and Cumulative Index of Nursing and Allied Health Literature (CINAHL). These databases were chosen based on the health-related outcome of the research question.

2. Choice of keywords and controlled vocabulary

After looking up several relevant studies in online databases and with the help of a librarian, dictionaries, and experts, all keywords related to the field of ‘persistent organic pollutants’ and ‘weight or adipose tissues’ were listed in excel sheets to be used for database searching.

for each database, we looked up controlled vocabulary (CV). CV are terms and phrases indexed by humans whereby all relevant and synonym words are grouped together, and this technique was used to retrieve all relevant content at once.

We also used truncation mechanism to help broaden the search. Whether external or internal, it allowed searching for all occurrences of a word with a specific root or a predefined number of characters inside this word.

Proximity or adjacency operators were used to force search of two or more words that are directly adjacent, or adjacent within a number of words, and this allowed for a more focused and oriented search towards the research question.

Finally, we used boolean operators AND and OR to combine keywords. OR was used to combine all keywords and CV within the same field i.e. POPs alone/obesity alone, and AND was used to combine keywords and CV of the different fields.

Detailed search results of each database can be found in APPENDIX.

3. Combining results

We modulated all of the above operators to fit differently for each database. Before finalizing the database search, we did multiple checks to ensure that no mistake in vocabulary or in operators was present. Afterward, we conducted the final search on October 8th, 2020.

E. Screening by title and abstract

We collected all references from each database and added them to an EndNote library. We used EndNote X9. Each single reference was scanned by two reviewers (D.Abu Hjeily, Dr. E. Bou Sanayeh, Dr. M.Saade, Dr. N.Youssef, Dr. R.Kwayess) independently and marked with inclusion or exclusion codes according to a predetermined screening by title and abstract sheet.

1. Screening by title and abstract sheet

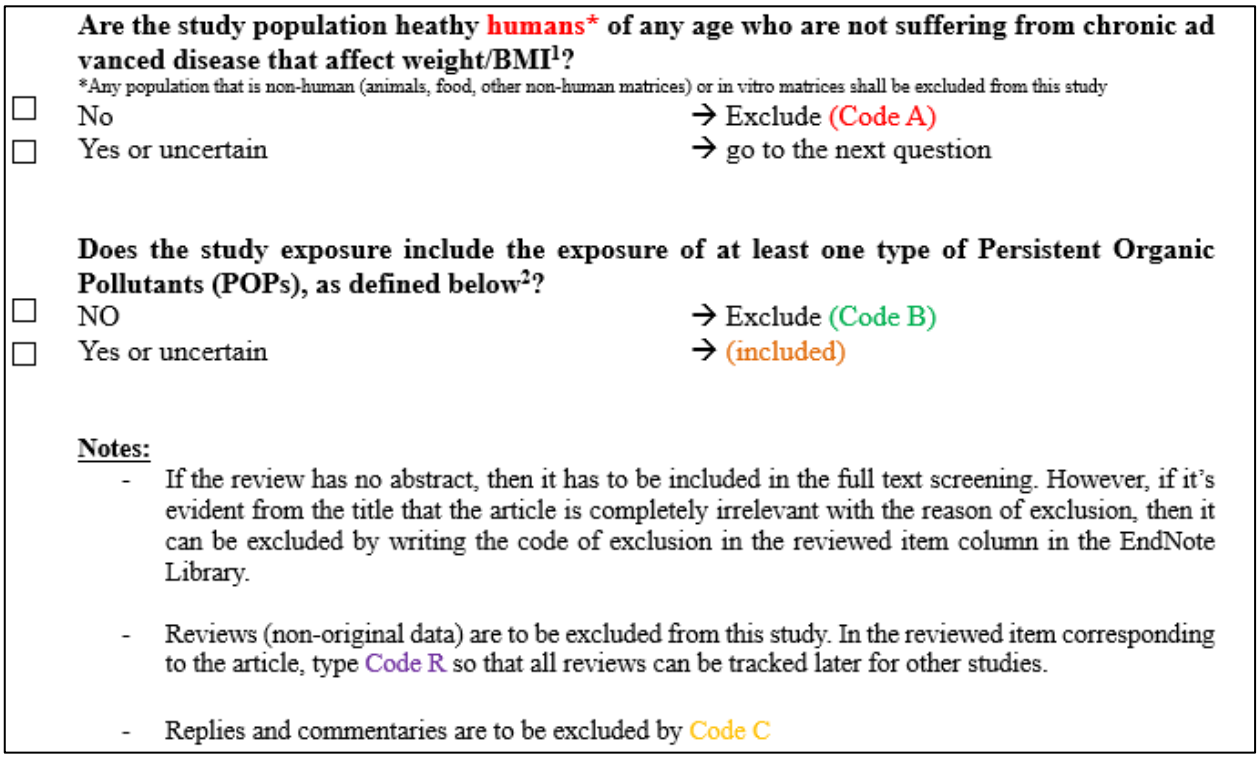
After reading the title and abstract, the reviewer looked at the screening sheet to see if the criteria are met.

The sheet was composed of two questions related to the PECO elements of the research question; if both were met, the reference was included, if not, then the exclusion reason was mentioned according to a list of preset codes as shown in Figure 3 below.

The screening stage team was composed of 5 members. For each reference, two reviewers screened separately and met regularly to identify discrepancies. Discrepancies were resolved by discussion; if not, a third expert reviewer (Dr. N.Saliba, Dr. M.Chakhtoura) intervened.

2. Pilot tests

Before before launching the screening process, we did several screening pilot tests to ensure that the screening sheet is clear to all reviewers. Once the discrepancy rate got low, the official screening process started.



Are the study population heathy humans* of any age who are not suffering from chronic ad vanced disease that affect weight/BMI[1]?

*Any population that is non-human (animals, food, other non-human matrices) or in vitro matrices shall be excluded from this study

☐ No → Exclude (Code A)

☐ Yes or uncertain → go to the next question

Does the study exposure include the exposure of at least one type of Persistent Organic Pollutants (POPs), as defined below[2]?

☐ NO → Exclude (Code B)

☐ Yes or uncertain → (included)

Notes:

- If the review has no abstract, then it has to be included in the full text screening. However, if it's evident from the title that the article is completely irrelevant with the reason of exclusion, then it can be excluded by writing the code of exclusion in the reviewed item column in the EndNote Library.
- Reviews (non-original data) are to be excluded from this study. In the reviewed item corresponding to the article, type Code R so that all reviews can be tracked later for other studies.
- Replies and commentaries are to be excluded by Code C

Figure 3: Screening by title and abstract guide sheet

F. Full-text screening

1. Screening by full-text sheet

After completing the stage of screening by title and abstract, we further screened articles by full text. At least two reviewers screened and labeled each article against a full-text screening sheet. If the study did not meet the criteria in the sheet, it should was excluded with mentioning in detail the exclusion reason in the form of a code as can be seen in (Figure 4). However, if the study met the criteria, then it was

included in the upcoming stages of the SR and thus all relevant data were extracted and collected.

2. Pilot tests

As in the case of screening by title and abstract, pilot tests proceeded the screening process. The reason of exclusion which was pre-specified had to be agreed on between the two reviewers.

1. Is the study design observational or interventional?

☐ No → Exclude
☐ Yes or uncertain → go to the next question

Exclusion Codes:
Code R: reviews and non-original data
Code C: replies and commentaries

2. Are the study population heathy humans* of any age who are not suffering from chronic ad vanced disease that affect weight/BMI[1]?
*Any population that is non-human (animals, food, other non-human matrices) or in vitro matrices shall be excluded from this study

☐ No → Exclude
☐ Yes or uncertain → go to the next question

Exclusion Codes:
Code A: non-human population or in vitro study
Code A1: heart failure condition
Code A2: Cancer
Code A3: liver cirrhosis and end stage renal disease
Code A4: pregnancy complications
Code A5: population not described

3. Does the study exposure include the exposure of at least one type of Persistent Organic Pollutants (POPs), as defined below[2]?

☐ NO → Exclude **Code B**
☐ Yes or uncertain → go to the next question

4. Does the study describe quantitatively one or more of the outcomes of interest[3]?

☐ NO → Exclude
☐ Yes or uncertain → **Include**

Exclusion codes:
Code D1: Outcomes not described
Code D2: Outcomes described qualitatively only

Figure 4: Screening by full-text guide sheet

G. Data extraction

We used an electronic form/data collection form to extract data in an organized manner. All relevant data from the included studies were abstracted in duplicates and independently. In this review, we were interested in collecting the following data from articles that meet the abstract and full-text inclusion criteria:

-Study Characteristics:

Author(s)

Year of publication

Journal/ source

Country of origin

Publication type

Dates of study

Duration of study

Location of study

Study design

Funding source

Conflict of interest

Additional notes

-Baseline Population Characteristics:

Study population

Number of participants

Strategy and setting of recruitment

Age

Sex

Ethnicity

Presence or absence of co-morbidities

Bodyweight measure & BMI

Physical activity

Smoking status

-Exposure Characteristics (exposure to POPs):

Duration

Sources

Location of exposure

Route of exposure

Intensity of intervention: continuous vs. intervals of exposure & occupational vs. regular exposure Methods used to measure exposure
Matrices for POPs measurement (ambient air/indoor air/serum/plasma/adipose tissues/…)
Levels of exposure
Units of exposure

-Outcomes Characteristics:

Achieved parameters, or the change, or the percent change compared to baseline values for the following main and secondary outcomes: Body mass index/Weight/Waist circumference/Waist-hip ratio/Body fat/Visceral fat
Outcome units
Methods used to measure outcome

-Results Characteristics:

Results
Confounders or modifying factors
Sex-specific effects
Age group effects

H. Data synthesis and Meta-analysis

After all relevant data were extracted, we conducted data synthesis according to a pre-specified strategy using RevMan 5.3 software.

We employed studies in this final quantitative analysis whenever we had beta regression coefficient extracted from a linear adjusted model with standards error (SE) or 95% confidence interval (CI). We then converted all units of exposure to µg/L or ppb, and all units of outcome to grams (g).

For each outcome and each comparison, we performed a random-effects meta-analysis when at least two studies were available.

The primary analysis of the SR was split by age category, and studies on pregnant women were analyzed separately. But as this thesis is part of the ongoing SR, we explored here birthweight as a continuous primary outcome instead of BMI, and newly born infants as out targeted population. Therefore, the primary analysis in this case was split by individual chemical exposure.

We expressed continuous outcomes as regression coefficients and their 95% confidence interval.

1. Primary analysis

As stated above, we explored the primary analysis by individual chemicals, and by pooling all OCPs.

We assessed statistical heterogeneity between studies using I^2 with significance at p value = 0.1. The quantitative assessment of heterogeneity was done using I^2. When heterogeneity existed between studies, we explored subgroup analysis.

2. Planned subgrouping

we explored subgroup analysis, based on chemical classes under OCPs:

- DDT/DDE class
- Chlordane class
- HCH class
- HCB class

- Other OCPs

We used random-effects model in case of high heterogeneity, and a fixed-effect model in case of low heterogeneity.

CHAPTER III

SYSTEMATIC REVIEW FINDINGS: ESTABLISHING A CORRELATION BETWEEN OCP EXPOSURE AND BIRTHWEIGHT

A. Results of database searching

1. Number of hits per database

After conducting the search on all databases using the search strategy explained in the methodology section, a total of 18,367 studies were collected which were distributed per database as followed:

Embase: 11956 references

Medline: 5403 references

CINAHL complete: 927

Cochrane Library: 81 references

2. Extraction of data into EndNote X9

We exported collected references to EndNote X9 reference manager as Research Information System (RIS) files. Once in endnote, references were prepared for screening by removing external and internal duplicates.

3. Removal of duplicates

External duplicates were removed automatically by the EndNote system depending on author, year, title, and reference type. Internal duplicates were removed manually moving through the references one by one.

After duplicate removal, the references number dropped down to 13,568 references.

B. Results of the screening process

1. Screening by title and abstract

We screened 13,568 records against the screening guide sheet. 10,763 records did not meet the criteria in the sheet and thus were excluded, leaving 2,805 references for full-text screening.

2. Screening by full text

Only 2,507 references had available full text out of the 2,805 references to be scanned for full text. Therefore, full text was extracted and added to EndNote of these 2,507 which we screened against the guide sheet. 1,602 references did not meet the criteria in the sheet and thus were excluded from the analysis, leaving 905 references.

3. PRISMA Diagram

We continued the screening process to check how many articles actually explored the relationship between types of POPs and body weight status through a quantitative technique. Thus, 96 references were further excluded as they assess the desired correlation qualitatively.

The final number of references included in the Systematic Review/Meta-analysis was 809 references. The overall process of screening can be shown in Figure 5 through the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram below.

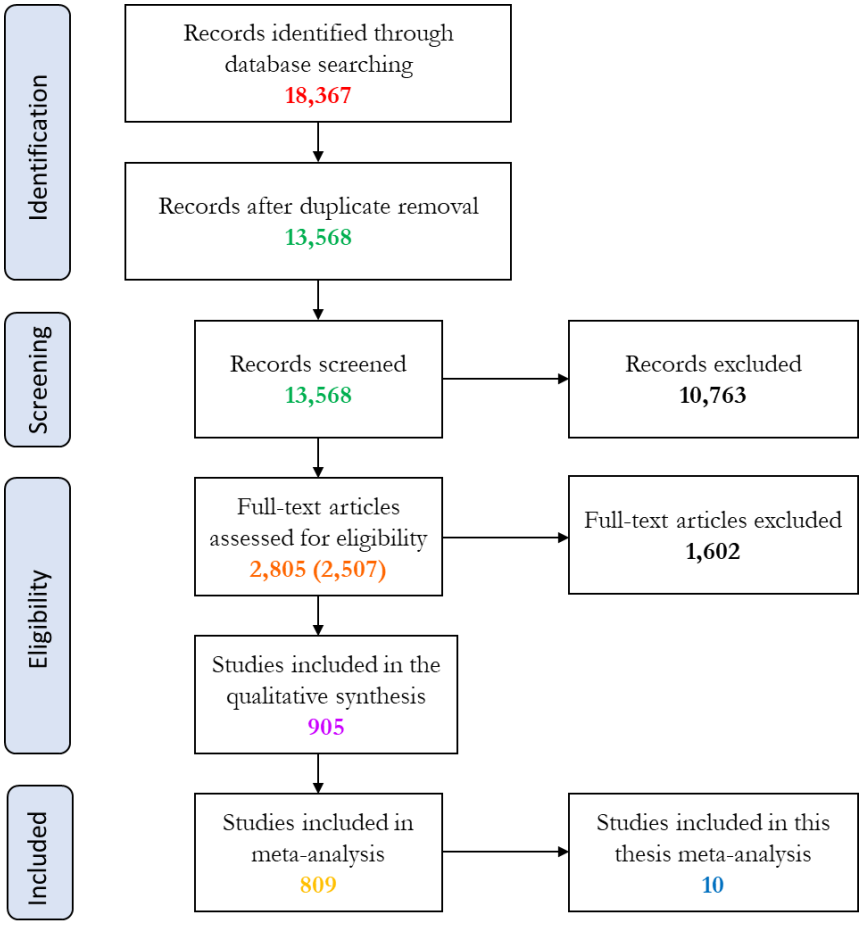


Figure 5: PRISMA flow diagram of the screening process

C. Data extraction results

1. Distribution by birthweight and OCP class

The first meta-analysis we conducted in this SR was the investigation of the possibility of a correlation between OCPs and birthweight. Therefore, the population of the PECO question was narrowed down to one age category which is newly born infants, and the exposure was narrowed down to one class of POPs, OCPs.

Out of the 809 articles that passed the full text screening, only 106 references included chemicals belonging to the class OCPs. To compile data from these studies to be included in RevMan, we made sure to check how the correlation is expressed in each reference, as only linear regression analysis was included in the meta-analysis.

2. Inclusion of data with regression coefficients

35 studies matched the desired criteria of the type of correlation, where beta regression coefficients were used to assess the relationship between the exposure and the outcome. 25 of these studies had either estimated categorical exposure (non-continuous) or exposure with lipid-adjusted concentrations and thus were dropped from the analysis.

The 10 studies left were further classified by the way the regression coefficient is expressed: the change in outcome per 1-Fold OCP change, 2-Fold, 10-Fold, 1-Fold log (OCPs) change, 2-Fold log(OCPs), 8-Fold log (OCPs), and 10-Fold log(OCPs) change.

In order to pool regression coefficients together we transformed all categories into one beta coefficient category as the change of outcome per 1-Fold OCP change. Therefore, betas with log exposure were converted to non-log betas (divided by 2.7), and other betas with several folds exposure were divided by the number of folds.

3. Distribution of references included by several parameters

a. Body matrix analyzed

The 106 studies that were intended to enter the meta-analysis assessed OCP concentrations through several matrices as can be seen in (Figure 6). Cord blood,

maternal blood, and breast milk were the most common matrices used due to their easy collection upon delivery. Other more lipophilic matrices such as adipose tissues were not used quite often due to collection unease.

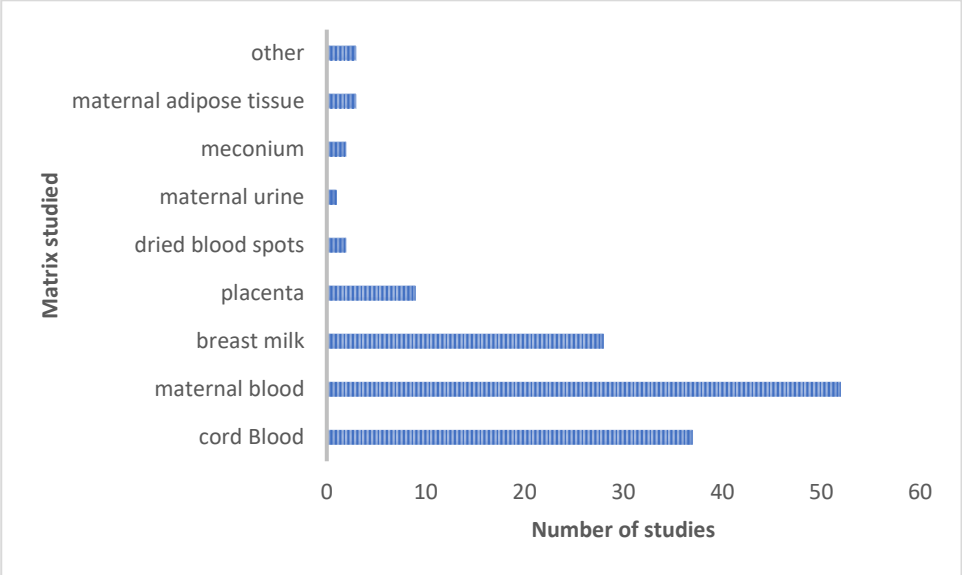


Figure 6: Distribution of studies collected for the birthweight-OCP meta-analysis (106) by body matrix studied used to determine OCP concentrations

b. Geographical locations

Studies assessing the correlation between birthweight and OCPs were mostly located in the United States (US), Spain, Australia, China, India, and Russia. A gap of studies was observed in Africa and the Middle East where only few studies have been conducted as can be seen in Figure 7.

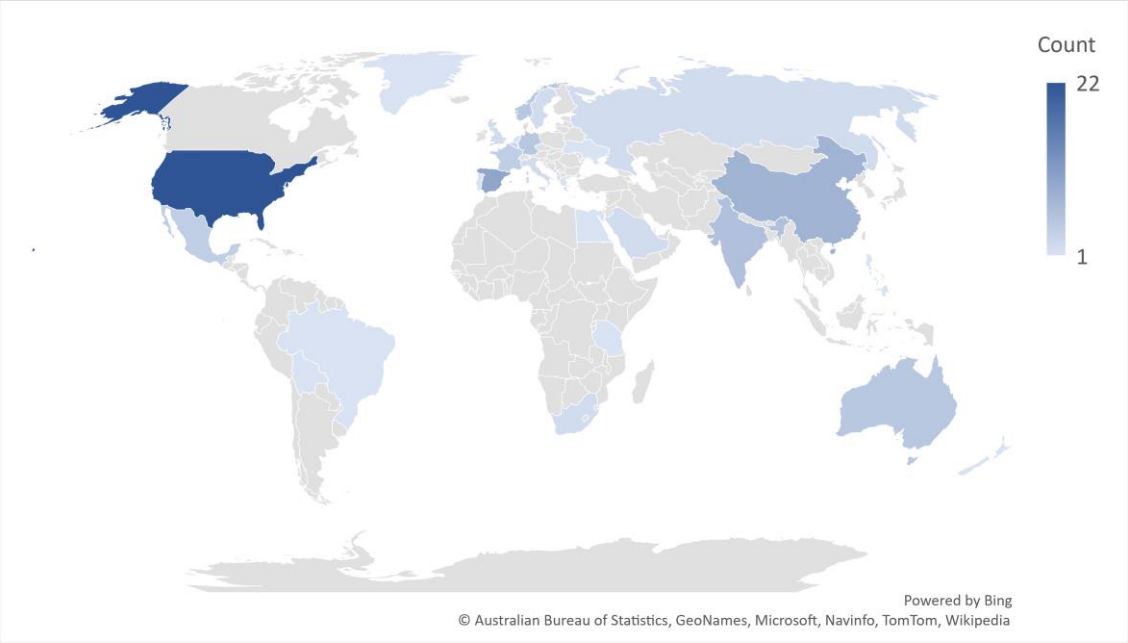


Figure 7: distribution of studies collected for the birthweight-OCP meta-analysis (106) by location of study

c. Year of study

(Figure 8) shows the evolution of the number of studies that aimed to assess the correlation between OCP exposure and birthweight changes between 1981 and 2020. As can be seen below, the number of studies has increased significantly given the risen need to understand these chemicals and their mode of action inside the body whether through observational studies or other types.

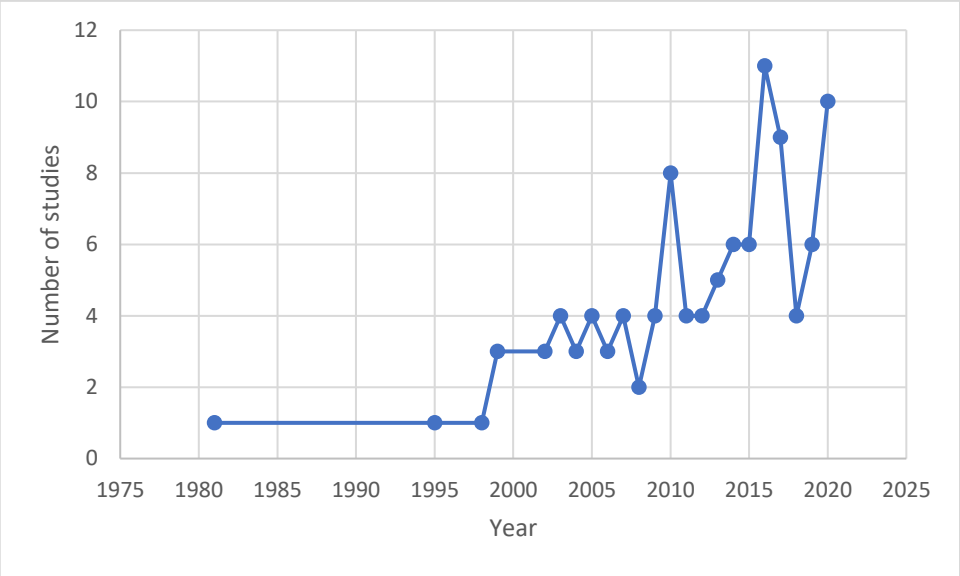


Figure 8: Distribution of studies collected for the birthweight-OCP meta-analysis (106) by year of the study

D. Meta-analysis results

1. Primary analysis

As discussed above, we conducted the primary analysis to generate forest plots after the segregation of studies by individual chemicals.

For each category of studies, units of exposure were expressed differently and therefore all were converted into ug/L (parts per billion)

Therefore, these groups were entered into RevMan:

- OCPs & birthweight (pooled data)
- DDE & birthweight
- DDT & birthweight
- B-HCH & birthweight
- HCB & birthweight

2. Subgroup analysis

After inputting all these five groups for analysis, we further segregated data into subgroups of chemical class (DDT/DDE class, chlordane class, HCH class, HCB class, and other OCPs class) and by matrix used to assess exposure (of maternal origin such as maternal serum or plasma, or of infant origin such as cord blood or placental tissues).

The following are the generated forests plots:

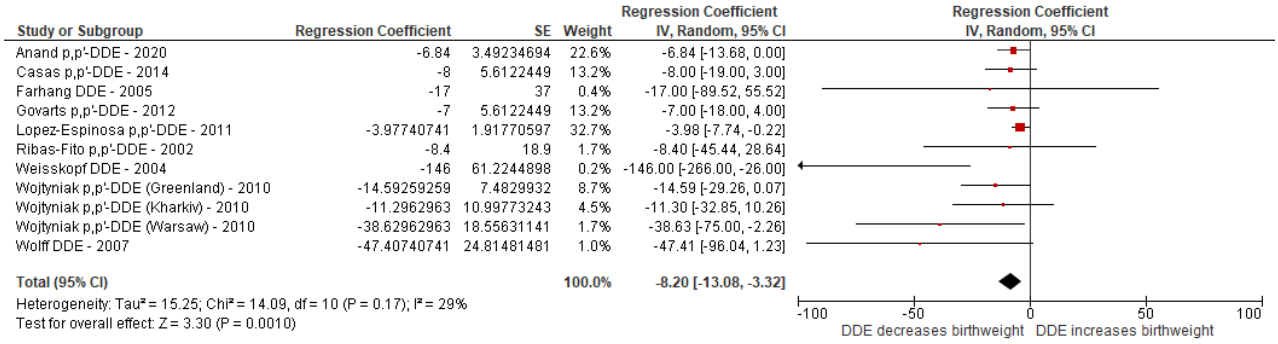


Figure 9: Forest plot displaying the change in birthweight (expressed in grams) per 1 ug/L (part per billion -ppb) change in Dichlorodiphenyldichloroethylene (DDE)

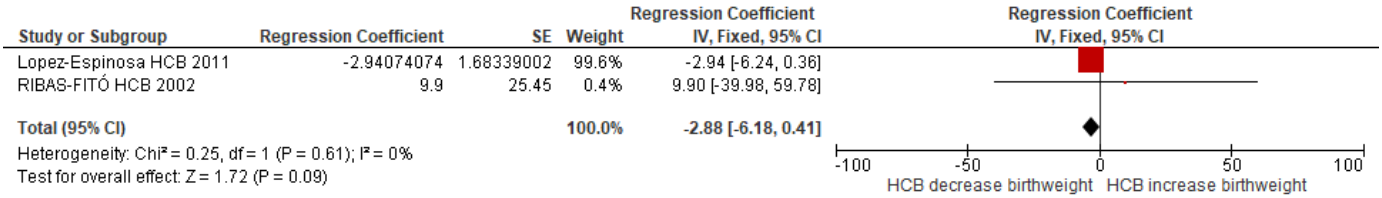


Figure 10: Forest plot displaying the change in birthweight (expressed in grams) per 1 ug/L (ppb) change in Hexachlorobenzene (HCB).

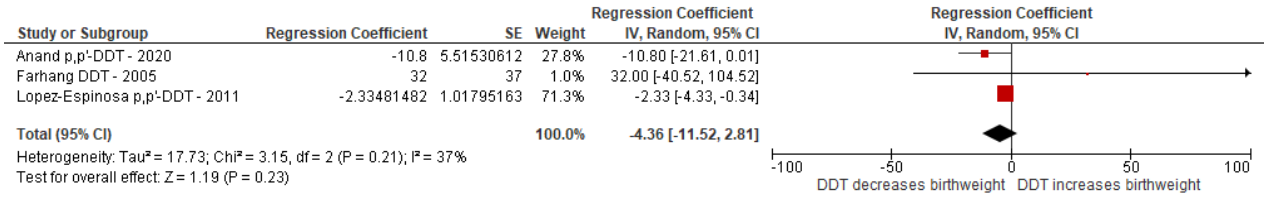


Figure 11: Forest plot displaying the change in birthweight (expressed in grams) per 1 ug/L (ppb) change in dichlorodiphenyltrichloroethane (DDT).

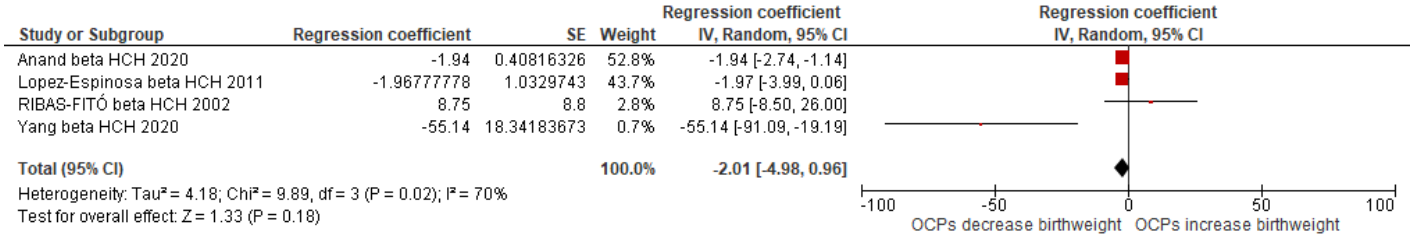


Figure 12: Forest plot displaying the change in birthweight (expressed in grams) per 1 ug/L (ppb) change in beta-hexacyclohexane (B-HCH).

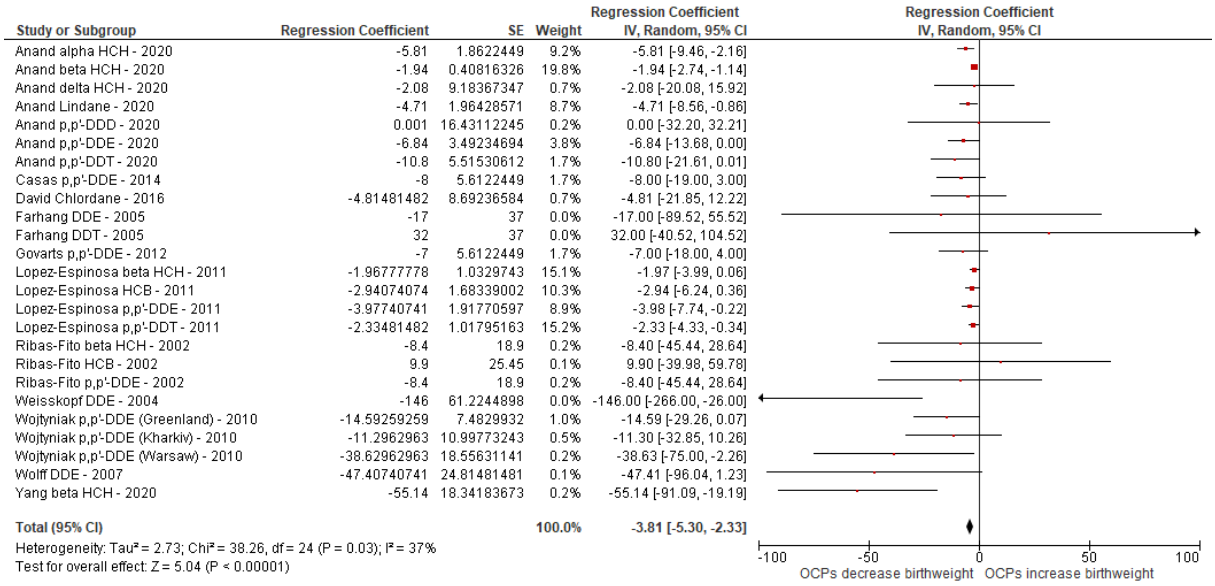


Figure 13: Forest plot displaying the change in birthweight (expressed in grams) per 1 ug/L (ppb) change in OCPs

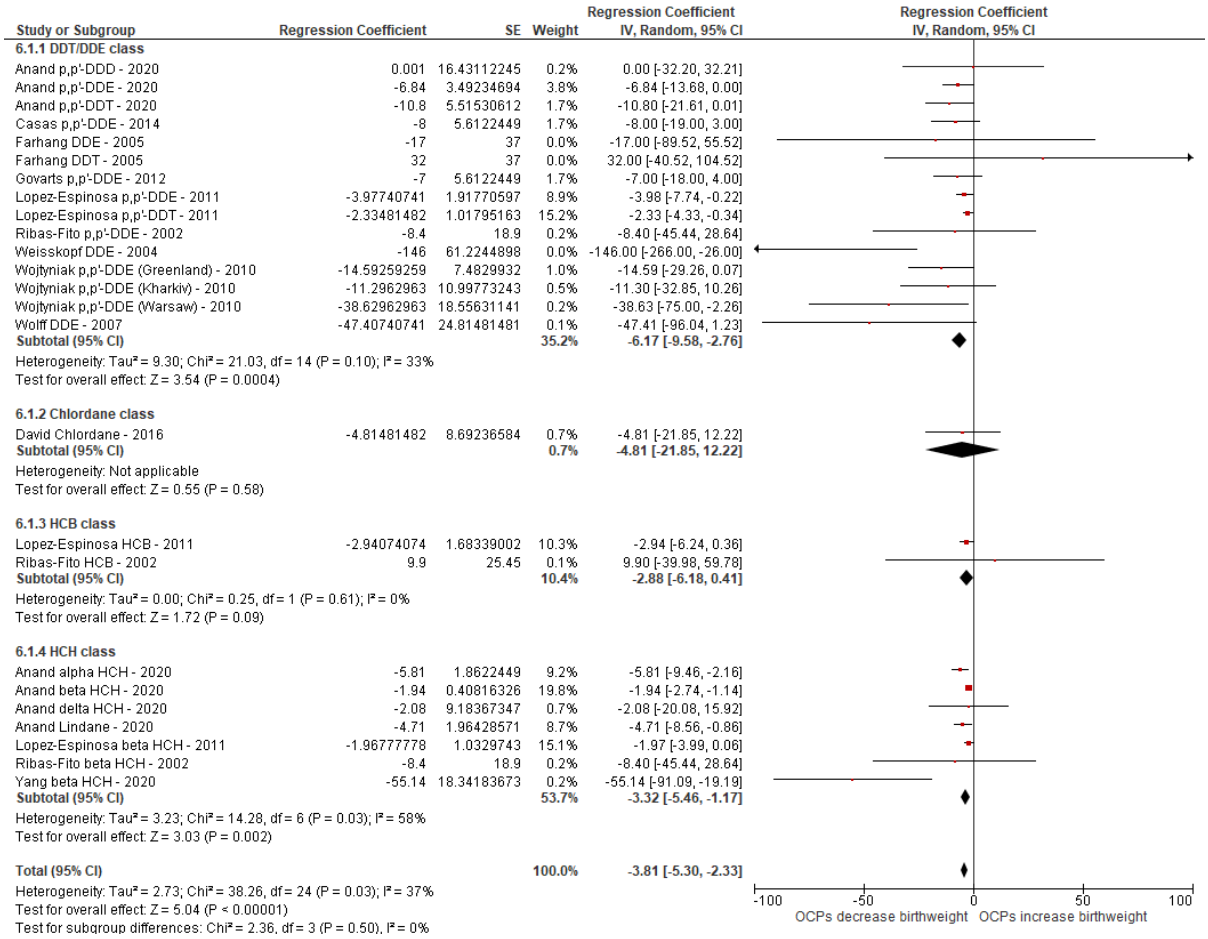


Figure 14: Forest plot displaying the change in birthweight (expressed in grams) per 1 ug/L (ppb) change in OCPs. Data is sub-grouped by OCP class.

3. Discussion of results

Figure 9 represents the change in birthweight (in grams) per 1 ppb increase in DDE. The overall pooled regression coefficient is -8.20 grams (95 CI: -13.08, -3.32). The standard error was calculated from the confidence interval. In the plot, the square represents each study separately whereas the diamond represents the overall pooled analysis or the pooled subgroup analysis. Also, the size of the square or diamond represents the study weight or the subgroup weight with respect to the overall analysis. In this figure, DDE appeared to be significantly inversely proportional to birthweight with a p-value less than 0.0001.

The same significant inverse correlation was established with HCB (-2.88, CI -6.18, 0.41), where the p-value for the overall tests was 0.09 respectively.

On the other hand, beta-HCH and DDT did not exhibit any significant correlation with birthweight (-2.01, CI -4.98, 0.96 and -4.36, CI -11.52, 2.81) with a p-values of 0.18 and 0.23 respectively.

Upon data pooling of all OCPs, data in the forest plot as shown in Figure 13 indicated a significant inverse correlation between exposure to OCPs and birthweight with a regression coefficient of -3.81 grams (CI -5.30, -2.33), where p-value is less than 0.00001. In this case, heterogeneity was assessed by I-squared which was in this case 40 percent which is why we used Random-effects model.

Further subgrouping by chemical class established a correlation with birthweight among the HCH class and DDT class (-3.32 and -6.17 respectively).

This data described above signified that exposure of an infant to 100 ppb DDE for example will result in an estimated decrease in birthweight by more than half a kilogram.

We can conclude that the exposure to different chemicals belonging to OCPs class will result in a decreased birthweight among newly born infants.

It should be noted that we understand the data generated here will require further investigation as this is a work in progress. What we are presenting in this thesis is preliminary analysis of the data; detailed analysis will be presented in the SR results.

CHAPTER IV

CONCLUSION

POPs are considered as extremely dangerous xenobiotics. Because of human activities and uncontrolled emissions, POPs are circulating and transporting among the globe reaching remote areas and entering the human body at various stages and routes. Recent research has established that one of the many consequences of exposure to those chemicals might be weight changes or obesity. We explored this evidence by conducting a systematic review of literature to determine if this correlation is accurate.

While this thesis is part of an ongoing systematic review, it explored infants as a targeted population given the seriousness of this exposure can cause irreversible genetic variations during fetus growth.

This study which was conducted according to a predetermined criterion of methodology and analysis, suggests that exposure to OCPs might be correlated with decreased birthweight. This alarming data calls for more research on this matter and more control over pesticide use and industrial emissions.

APPENDIX

MEDLINE

1. body weight/ or body weight changes/ or weight gain/ or overweight/ or exp obesity/ or Obesity, Abdominal/ or exp Adipose Tissue/ or exp body fat distribution/ or body mass index/ or body size/ or exp body weight/ or sagittal abdominal diameter/ or exp waist circumference/ or waist-hip ratio/ or Adipocytes, White/ or Peritoneum/ or fats/

2. exp Furans/ or Pentachlorophenol/ or Endosulfan/ or exp "dioxins and dioxin-like compounds"/ or halogenated diphenyl ethers/ or polybrominated biphenyls/ or aldrin/ or chlordan/ or chlordecone/ or dicofol/ or hexachlorobenzene/ or ddt/ or dichlorodiphenyl dichloroethylene/ or dichlorodiphenyldichloroethane/ or dieldrin/ or endrin/ or heptachlor/ or hexachlorocyclohexane/ or mirex/ or exp polychlorinated biphenyls/ or toxaphene/ or paraffin/ or dibenzofurans/ or dicofol/ or hexachlorocyclohexane/

3. (((abdom?n* or waist or pad? or tissue* or subcutaneous) adj3 (adipos* or circumferenc* or diameter* or fat* or o-bes* or obes*)) or BMI or ((bodymass or (body adj mass) or quetelet) adj3 (index* or indices)) or (bod* adj3 (fat* or size* or weigh*)) or ((central or white or (intra adj abdom?n*) or intraabdom?n* or mesenter* or periton* or retroperiton* or (retro adj periton*) or viscera*) adj3 (adipos* or fat* or obes* or o-bes* or tissue*)) or ((excess* or under or hyper* or increas* or over or gain* or chang* or los* or decreas*) adj3 (weigh* or fat*)) or o-bes* or obes* or adipos* or

underweigh* or hyperweigh* or overweigh* or thinness or lean* or Cachexia or Emaciation or (Fet* adj3 Macrosomia) or (Lipid* adj3 Product*) or (((waist adj2 hip) or waisthip) adj3 ratio*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

4. (Aldrin? or isoaldrin? or chlordan? or chlordane? or octachlor? or chlorindan? or chlordecone? or kepone? or merex or dichlorodiphenyldichloroethylene? or DDE? or "p,p'-Dichlorodiphenyldichloroethylene?" or "p,p'-DDE?" or "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene?" or DDX? or DDMU? or Dichloroethylene? or Dichlorodiphenyl? or (dichlorodiphenyl adj dichloroethylene?) or dichlorodiphenyltrichloroethane? or (di adj (chlorodiphenyldichloroethylene? or chlorodiphenyltrichloroethane?)) or DDT? or "4,4'-DDT?" or "p,p'-DDT?" or Chlorophenothane? or "1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane" or "4,4'-Dichlorodiphenyltrichloroethane" or (TbisC adj ethane?) or Benzochloryl? or Chlorophenothan? or dioxin? or dicofol? or Kelthane? or Keltane? or (decabromodiphenyl adj3 (ether? or oxide?)) or (c adj decaBDE?) or ("Bis(pentabromophenyl)" adj3 ether?) or "1,1'-oxybis(pentabromobenzene)" or "1,2,3,4,5-pentabromo-6-(2,3,4,5,6-pentabromophenoxy)benzene" or "2,3,4,5,6-Pentabromo-1-(2,3,4,5,6-pentabromophenoxy)benzene" or (deca adj (bromodiphenyl adj3 ether?)) or cdecaDBE? or dieldrin? or (Alvit adj "55") or Alvit55 or Alvit or endosulfan? or ((beta or alpha) adj endosulfan?) or Thiodan? or Thiodon? or Thiotox or endrin? or Hexadrin? or (Isodrin adj2 Epoxide?) or Endrex or NEndrin or MEndrin or

furan? or heptachlor? or hexachlorobenzene? or HCB? or (hexa adj (chlorobenzene? or bromobiphenyl? or bromocyclododecane? or (bromodiphenyl adj3 ether?) or chlorobutadiene? or chlorocyclohexane?)) or hexabromobiphenyl? or HBB? or hexabromocyclododecane? or HBCD? or (hexabromodiphenyl adj3 ether?) or (heptabromodiphenyl adj3 ether?) or (hepta adj (bromodiphenyl adj3 ether?)) or hexachlorobutadiene? or HCBD? or hexachlorocyclohexane? or HCH? or (gamma adj Benzene adj Hexachloride) or (gamma adj BenzeneHexachloride) or (PMS adj lindane) or (gamma adj "666") or (gamma adj HCH) or (Zeta adj hexachlorocyclohexane) or (Eta adj hexachlorocyclohexane) or (Epsilon adj hexachlorocyclohexane) or (Benzene adj Hexachloride) or lindane? or Gammexane? or Jacutin? or Kwell? or Scabecid? or Scabisan? or Delitex? or Hexachlorane? or Tetocid? or Scabene? or mirex? or (polychlorinated adj3 (biphenyl? or naphthalene? or (dibenzo adj p adj dioxin?) or dibenzodioxin? or (di adj benzodioxin?) or dibenzofuran? or (di adj benzofuran?))) or tetrachlorodibenzodioxin? or (tetra adj (chlorodibenzo adj p adj dioxin?)) or polychlorodibenzopdioxin? or (polychloro adj (dibenzo adj p adj dioxin?)) or (chlorinated adj (dibenzopdioxin? or dibenzodioxin? or (dipenzo adj p adj dioxin?))) or TCDD? or PCDD? or (Chlorinated adj (Dibenzofuran? or (di adj benzofuran?))) or Chlorodibenzofuran? or PCDF? or PCN? or (Polychlorobiphenyl adj3 Compound?) or PCB? or aroclor? or pentachlorobenzene? or PeCB? or (penta adj (chlorobenzene? or chlorophenol? or (bromodiphenyl adj3 ether?))) or pentachlorophenol? or (Sodium adj2 Pentachlorophenate?) or (perfluorooctanoic adj3 acid?) or PFOA? or (pentabromodiphenyl adj3 ether?) or pentabromodiphenylether? or (perfluorooctane adj3 sulfonic adj3 acid?) or PFOS? or (perflurooctane adj3 sulfonyl adj3 fluoride?) or POSF? or (persistent adj2 bioaccumulative adj2 toxic) or PBT? or (persistent adj toxic)

or (polybrominated adj biphenyl?) or PBB? or (Polybromobiphenyl adj3 Compound?) or (polybrominated adj (diphenyl adj3 ether?)) or PBDE? or (brominated adj (diphenyl adj3 ether?)) or POP or POPS or (persistent adj2 organic?) or (stockholm adj2 convention?) or (short adj chain adj3 (chlorinated adj3 paraffin?)) or SCCP? or toxaphene? or Polychlorocamphene? or (tetrabromodiphenyl adj3 ether?) or campheclor?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. 1 or 3

6. 2 or 4

7. 5 and 6

8. 7 not (Animals/ not (Animals/ and Humans/))

EMBASE

#1 'aldrin'/de OR 'chlordane'/de OR 'chlordecone'/de OR 'dieldrin'/de OR 'chlorphenotane'/de OR '1,1 dichloro 2,2 bis(4 chlorophenyl)ethylene'/de OR 'dioxin'/de OR 'decabromodiphenyl ether'/de OR 'endrin'/de OR 'furan'/de OR 'heptachlor'/de OR 'hexachlorobenzene'/de OR 'hexabromobiphenyl'/de OR '2,2`,4,4`,5,5` hexabromodiphenyl ether'/de OR 'hexachlorobutadiene'/de OR 'lindane'/de OR 'mirex'/de OR 'polychlorinated biphenyl'/de OR 'pentachlorobenzene'/de OR 'pentachlorophenol'/de OR 'polychlorinated naphthalene'/de OR 'perfluorooctanoic acid'/de OR 'pentabromodiphenyl ether'/de OR 'perfluorooctanesulfonic acid'/de OR 'polychlorinated dibenzodioxin'/de OR 'polychlorinated dibenzofuran'/de OR

'polybrominated biphenyl'/de OR 'polybrominated diphenyl ether'/exp OR 'persistent organic pollutant'/de OR 'short chain chlorinated paraffin'/de OR 'campheclor'/de OR 'endosulfan'/de OR '2,2`,4,4` tetrabromodiphenyl ether'/de OR 'dibenzofurans'/de OR 'dicofol'/de OR 'hexachlorocyclohexane'/de OR 'paraffin'/de

#2 'abdominal obesity'/de OR 'abdominal circumference'/de OR 'abdominal fat'/exp OR 'adipose tissue'/de OR 'body mass'/de OR 'body fat'/de OR 'body size'/de OR 'body weight'/exp OR 'central adiposity'/de OR 'central obesity'/de OR 'fat pad'/de OR 'mesenteric fat'/de OR 'obesity'/exp OR 'intraperitoneal fat'/de OR 'peritoneal tissue'/de OR 'sagittal abdominal diameter'/de OR 'visceral adiposity'/de OR 'visceral obesity'/de OR 'waist circumference'/de OR 'waist hip ratio'/de OR 'body weight change'/exp OR 'body fat distribution'/de OR 'white adipose tissue'/de OR 'white adipocyte'/de OR 'fat'/de OR 'intra-abdominal fat'/exp OR 'peritoneum'/de

#3 ((abdom$n* OR waist OR pad$ OR tissue* OR subcutaneous) NEAR/2 (adipos* OR circumferenc* OR diameter* OR fat* OR 'o-bes*' OR obes*)) OR bmi OR ((bodymass OR 'body mass' OR quetelet) NEAR/2 (index* OR indices)) OR (bod* NEAR/2 (fat* OR size* OR weigh*)) OR ((central OR white OR 'intra abdom$n*' OR intraabdom?n* OR mesenter* OR periton* OR retroperiton* OR 'retro periton*' OR viscera*) NEAR/2 (adipos* OR fat* OR obes* OR 'o-bes*' OR tissue*)) OR ((excess* OR hyper* OR increas* OR over OR gain* OR chang* OR los* OR under OR decreas*) NEAR/2 (weigh* OR fat*)) OR 'o-bes*' OR obes* OR adipos* OR hyperweigh* OR underweigh* OR overweigh* OR thinness OR lean* OR cachexia OR

emaciation OR (fet* NEAR/3 macrosomia) OR (lipid* NEAR/2 product*) OR (('waist hip' OR waisthip) NEAR/2 ratio*)

#4 aldrin$ OR isoaldrin$ OR chlordan$ OR chlordane$ OR octachlor$ OR chlorindan$ OR chlordecone$ OR kepone$ OR merex OR dichlorodiphenyldichloroethylene$ OR dde$ OR "p p dichlorodiphenyldichloroethylene$" OR "p p dde$" OR "1 1 dichloro 2 2 bis(p chlorophenyl)ethylene$" OR ddx$ OR ddmu$ OR dichloroethylene$ OR dichlorodiphenyl$ OR (dichlorodiphenyl NEXT/1 dichloroethylene$) OR dichlorodiphenyltrichloroethane$ OR (di NEXT/1 (chlorodiphenyldichloroethylene$ OR chlorodiphenyltrichloroethane$)) OR ddt$ OR "4 4 ddt$" OR "p p ddt$" OR chlorophenothane$ OR '1 1 1 trichloro 2 2 bis(p chlorophenyl)ethane' OR '4 4 dichlorodiphenyltrichloroethane' OR (tbisc NEXT/1 ethane$) OR benzochloryl$ OR chlorophenothan$ OR dioxin$ OR dicofol$ OR kelthane$ OR keltane$ OR (decabromodiphenyl NEAR/2 (ether$ OR oxide$)) OR (c NEXT/1 decabde$) OR ('bis(pentabromophenyl)' NEAR/2 ether$) OR '1 1 oxybis(pentabromobenzene)' OR '1 2 3 4 5 pentabromo 6 (2 3 4 5 6 pentabromophenoxy)benzene' OR '2 3 4 5 6 pentabromo 1 (2 3 4 5 6 pentabromophenoxy)benzene' OR (deca NEXT/1 bromodiphenyl NEAR/2 ether$) OR cdecadbe$ OR dieldrin$ OR (alvit NEXT/1 55) OR alvit55 OR alvit OR endosulfan$ OR ((beta OR alpha) NEXT/1 endosulfan$) OR thiodan$ OR thiodon$ OR thiotox OR endrin$ OR hexadrin$ OR (isodrin NEAR/1 epoxide$) OR endrex OR nendrin OR mendrin OR furan$ OR heptachlor$ OR hexachlorobenzene$ OR hcb$ OR (hexa NEXT/1 (chlorobenzene$ OR bromobiphenyl$ OR bromocyclododecane$ OR chlorobutadiene$ OR chlorocyclohexane$)) OR (hexa NEXT/1 bromodiphenyl

NEAR/2 ether$) OR hexabromobiphenyl$ OR hbb$ OR hexabromocyclododecane$ OR hbcd$ OR (hexabromodiphenyl NEAR/2 ether$) OR (heptabromodiphenyl NEAR/2 ether$) OR (hepta NEXT/1 bromodiphenyl NEAR/2 ether$) OR hexachlorobutadiene$ OR hcbd$ OR hexachlorocyclohexane$ OR hch$ OR (gamma NEXT/1 benzene NEXT/1 hexachloride$) OR (gamma NEXT/1 benzenehexachloride$) OR (pms NEXT/1 lindane) OR (gamma NEXT/1 666) OR (gamma NEXT/1 hch$) OR (zeta NEXT/1 hexachlorocyclohexane$) OR (eta NEXT/1 hexachlorocyclohexane$) OR (epsilon NEXT/1 hexachlorocyclohexane$) OR (benzene NEXT/1 hexachloride$) OR lindane$ OR gammexane$ OR jacutin$ OR kwell$ OR scabecid$ OR scabisan$ OR delitex$ OR hexachlorane$ OR tetocid$ OR scabene$ OR mirex$ OR (polychlorinated NEAR/2 (biphenyl$ OR naphthalene$ OR "dibenzo p next/1 dioxin$" OR dibenzodioxin$ OR "di benzodioxin$" OR dibenzofuran$ OR "di benzofuran$")) OR tetrachlorodibenzodioxin$ OR (tetra NEXT/1 ("chlorodibenzo p dioxin$" OR polychlorodibenzopdioxin$ OR "polychloro dibenzo p dioxin$")) OR (chlorinated NEXT/1 (dibenzopdioxin$ OR dibenzodioxin$ OR "dibenzo p dioxin$")) OR tcdd$ OR pcdd$ OR (chlorinated NEXT/1 (dibenzofuran$ OR 'di benzofuran$')) OR chlorodibenzofuran$ OR pcdf$ OR pcn$ OR (polychlorobiphenyl NEAR/2 compound$) OR pcb$ OR aroclor$ OR pentachlorobenzene$ OR pecb$ OR (penta NEXT/1 (chlorobenzene$ OR chlorophenol$)) OR (penta NEXT/1 bromodiphenyl NEAR/2 ether$) OR pentachlorophenol$ OR (sodium NEAR/1 pentachlorophenate$) OR (perfluorooctanoic NEAR/2 acid$) OR pfoa$ OR (pentabromodiphenyl NEAR/2 ether$) OR pentabromodiphenylether$ OR (perfluorooctane NEAR/2 sulfonic NEAR/2 acid$) OR pfos$ OR (perflurooctane NEAR/2 sulfonyl NEAR/2 fluoride$) OR posf$ OR (persistent NEAR/1 bioaccumulative NEAR/1 toxic) OR pbt$ OR (persistent

NEXT/1 toxic) OR (polybrominated NEXT/1 biphenyl$) OR pbb$ OR (polybromobiphenyl NEAR/2 compound$) OR (polybrominated NEXT/1 diphenyl NEAR/2 ether$) OR pbde$ OR (brominated NEXT/1 diphenyl NEAR/2 ether$) OR pop OR pops OR (persistent NEAR/2 organic$) OR (stockholm NEAR/2 convention$) OR ('short chain' NEAR/2 ‘chlorinated paraffin$’) OR sccp$ OR toxaphene$ OR polychlorocamphene$ OR (tetrabromodiphenyl NEAR/2 ether$) OR campheclor$

#5 #1 OR #4

#6 #2 OR #3

#7 #5 AND #6 NOT ([animals]/lim NOT [humans]/lim)

CINAHL

S1 (MH "Adipocytes") OR (MH "Adipose Tissue+") OR (MH "Adipose Tissue Distribution") OR (MH "Body Mass Index") OR (MH "Body Size") OR (MH "Body Weight+") OR (MH "Body Weight Changes+") OR (MH "Fats") OR (MH "Obesity+") OR (MH "Peritoneum") OR (MH "Waist Circumference") OR (MH "Waist-Hip Ratio")

S2 (MH "Dibenzofurans") OR (MH "Dioxins") OR (MH "Paraffin") OR (MH "Polychlorinated Biphenyls")

S3 ((abdom?n* or waist or pad# or tissue* or subcutaneous) N2 (adipos* or circumferenc* or diameter* or fat* or o-bes* or obes*)) or BMI or ((bodymass or "body mass" or quetelet) N2 (index* or indices)) or (bod* N2 (fat* or size* or weigh*)) or ((central or white or intra-abdom?n* or intraabdom?n* or mesenter* or periton* or retroperiton* or retro-periton* or viscera*) N2 (adipos* or fat* or obes* or o-bes* or

tissue*)) or ((excess* or under or hyper* or increas* or over or gain* or chang* or los* or decreas*) N2 (weigh* or fat*)) or o-bes* or obes* or adipos* or underweigh* or hyperweigh* or overweigh* or thinness or lean* or Cachexia or Emaciation or (Fet* N2 Macrosomia) or (Lipid* N2 Product*) or ((waist-hip or waisthip) N2 ratio*)

S4 (Aldrin# or isoaldrin# or chlordan# or chlordane# or octachlor# or chlorindan# or chlordecone# or kepone# or merex or dichlorodiphenyldichloroethylene# or DDE# or "p,p'-Dichlorodiphenyldichloroethylene#" or "p,p'-DDE#" or "1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene#" or DDX# or DDMU# or Dichloroethylene# or Dichlorodiphenyl# or (dichlorodiphenyl adj dichloroethylene#) or dichlorodiphenyltrichloroethane# or (di adj (chlorodiphenyldichloroethylene# or chlorodiphenyltrichloroethane#)) or DDT# or "4,4'-DDT#" or "p,p'-DDT#" or Chlorophenothane# or "1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane" or "4,4'-Dichlorodiphenyltrichloroethane" or (TbisC-ethane#) or Benzochloryl# or Chlorophenothan# or dioxin# or dicofol# or Kelthane# or Keltane# or (decabromodiphenyl N2 (ether# or oxide#)) or (c-decaBDE#) or ("Bis(pentabromophenyl)" N2 ether#) or "1,1'-oxybis(pentabromobenzene)" or "1,2,3,4,5-pentabromo-6-(2,3,4,5,6-pentabromophenoxy)benzene" or "2,3,4,5,6-Pentabromo-1-(2,3,4,5,6-pentabromophenoxy)benzene" or (deca W1 (bromodiphenyl N2 ether#)) or cdecaDBE# or dieldrin# or (Alvit W1 55) or Alvit55 or Alvit or endosulfan# or ((beta or alpha) W1 endosulfan#) or Thiodan# or Thiodon# or Thiotox or endrin# or Hexadrin# or (Isodrin N1 Epoxide#) or Endrex or NEndrin or MEndrin or furan# or heptachlor# or hexachlorobenzene# or HCB# or (hexa W1 (chlorobenzene# or bromobiphenyl# or bromocyclododecane# or (bromodiphenyl N2 ether#) or

chlorobutadiene# or chlorocyclohexane#)) or hexabromobiphenyl# or HBB# or hexabromocyclododecane# or HBCD# or (hexabromodiphenyl N2 ether#) or (heptabromodiphenyl N2 ether#) or (hepta W1 (bromodiphenyl N2 ether#)) or hexachlorobutadiene# or HCBD# or hexachlorocyclohexane# or HCH# or (gamma W1 Benzene W1 Hexachloride) or (gamma W1 BenzeneHexachloride) or (PMS W1 lindane) or (gamma W1 666) or (gamma W1 HCH) or (Zeta W1 hexachlorocyclohexane) or (Eta W1 hexachlorocyclohexane) or (Epsilon W1 hexachlorocyclohexane) or (Benzene W1 Hexachloride) or lindane# or Gammexane# or Jacutin# or Kwell# or Scabecid# or Scabisan# or Delitex# or Hexachlorane# or Tetocid# or Scabene# or mirex# or (polychlorinated N2 (biphenyl# or naphthalene# or (dibenzo-p-dioxin#) or dibenzodioxin# or (di W1 benzodioxin#) or dibenzofuran# or (di W1 benzofuran#))) or tetrachlorodibenzodioxin# or (tetra W1 (chlorodibenzo-p-dioxin#)) or polychlorodibenzopdioxin# or (polychloro W1 (dibenzo-p-dioxin#)) or (chlorinated W1 (dibenzopdioxin# or dibenzodioxin# or (dipenzo-p-dioxin#))) or TCDD# or PCDD# or (Chlorinated W1 (Dibenzofuran# or (di W1 benzofuran#))) or Chlorodibenzofuran# or PCDF# or PCN# or (Polychlorobiphenyl N2 Compound#) or PCB# or aroclor# or pentachlorobenzene# or PeCB# or (penta W1 (chlorobenzene# or chlorophenol# or (bromodiphenyl N2 ether#))) or pentachlorophenol# or (Sodium N1 Pentachlorophenate#) or (perfluorooctanoic N2 acid#) or PFOA# or (pentabromodiphenyl N2 ether#) or (pentabromodiphenylether#) or (perfluorooctane N2 sulfonic N2 acid#) or PFOS# or (perflurooctane N2 sulfonyl N2 fluoride#) or POSF# or (persistent N1 bioaccumulative N1 toxic) or PBT# or (persistent W1 toxic) or (polybrominated W1 biphenyl#) or PBB# or (Polybromobiphenyl N2 Compound#) or (polybrominated W1 (diphenyl N2 ether#)) or PBDE# or (brominated W1 (diphenyl N2

ether#)) or POP or POPS or (persistent N1 organic#) or (stockholm N1 convention#) or (short-chain N2 (chlorinated N2 paraffin#)) or SCCP# or toxaphene# or Polychlorocamphene# or (tetrabromodiphenyl N2 ether#) or campheclor#)

S5 S1 OR S3

S6 S2 OR S4

S7 S5 AND S6

S8 S7 NOT (((MH "Animals+") OR (MH "Animal Studies") OR (TI "animal model*")) NOT (MH "human"))

COCHRANE

#1 MeSH descriptor: [Abdominal Fat] explode all trees

#2 MeSH descriptor: [Waist Circumference] explode all trees

#3 MeSH descriptor: [Obesity, Abdominal] explode all trees

#4 MeSH descriptor: [Intra-Abdominal Fat] explode all trees

#5 MeSH descriptor: [Adiposity] explode all trees

#6 MeSH descriptor: [Adipose Tissue] this term only

#7 MeSH descriptor: [Body Mass Index] explode all trees

#8 MeSH descriptor: [Body Size] this term only

#9 MeSH descriptor: [Body Weight] this term only

#10 MeSH descriptor: [Weight Gain] this term only

#11 MeSH descriptor: [Obesity] this term only

#12 MeSH descriptor: [Overweight] this term only

#13 MeSH descriptor: [Sagittal Abdominal Diameter] explode all trees

#14 MeSH descriptor: [Waist-Hip Ratio] explode all trees

#15 MeSH descriptor: [Body Weight Changes] this term only

#16 MeSH descriptor: [Adipose Tissue, White] explode all trees

#17 MeSH descriptor: [Adipocytes, White] explode all trees

#18 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19 MeSH descriptor: [Aldrin] this term only

#20 MeSH descriptor: [Chlordan] this term only

#21 MeSH descriptor: [Chlordecone] this term only

#22 MeSH descriptor: [Dichlorodiphenyl Dichloroethylene] this term only

#23 MeSH descriptor: [Dicofol] this term only

#24 MeSH descriptor: [Dieldrin] this term only

#25 MeSH descriptor: [Dioxins] explode all trees

#26 MeSH descriptor: [Endosulfan] this term only

#27 MeSH descriptor: [Endrin] this term only

#28 MeSH descriptor: [Furans] explode all trees

#29 MeSH descriptor: [Heptachlor] explode all trees

#30 MeSH descriptor: [Hexachlorobenzene] this term only

#31 MeSH descriptor: [Hexachlorocyclohexane] this term only

#32 MeSH descriptor: [Pentachlorophenol] this term only

#33 MeSH descriptor: [Pesticides] explode all trees

#34 MeSH descriptor: [Polybrominated Biphenyls] this term only

#35 MeSH descriptor: [Halogenated Diphenyl Ethers] this term only

#36 MeSH descriptor: [Polychlorinated Biphenyls] explode all trees

#37 MeSH descriptor: [Dibenzofurans, Polychlorinated] this term only

#38 MeSH descriptor: [Toxaphene] this term only

#39 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38

#40 (Aldrin? or chlordane? or chlordecone? or dieldrin? or dichlorodiphenyltrichloroethane? or (di NEXT (chlorodiphenyldichloroethylene? or chlorodiphenyltrichloroethane?)) or DDT? or dichlorodiphenyldichloroethylene? or DDE? or dioxin? or dicofol? or (decabromodiphenyl NEAR/2 ether?) or (deca NEXT (bromodiphenyl NEAR/2 ether?)) or cdecaDBE? or (c NEXT decaBDE?) or endrin? or furan? or heptachlor? or hexachlorobenzene? or (hexa NEXT (chlorobenzene? or bromobiphenyl? or bromocyclodecane? or bromocyclodecane? or (bromodiphenyl NEAR/2 ether?) or chlorobutadiene? or chlorocyclohexane?)) or HCB? or hexabromobiphenyl? or hexabromocyclodecane? or (hexabromodiphenyl NEAR/2 ether?) or (heptabromodiphenyl NEAR/2 ether?) or (hepta NEXT (bromodiphenyl NEAR/2 ether?)) or hexachlorobutadiene? or HCBD? or hexachlorocyclohexane? or HCH? or lindane? or mirex? or (polychlorinated NEAR/2 (biphenyl? or naphthalene? or (dibenzo NEXT p NEXT dioxin?) or dibenzofuran? or (di NEXT benzofuran?))) or PCB? or pentachlorobenzene? or (penta NEXT (chlorobenzene? or chlorophenol? or (bromodiphenyl NEAR/2 ether?))) or PeCB? or pentachlorophenol? or (perfluorooctanoic NEAR/2 acid?) or PFOA? or (pentabromodiphenyl NEAR/2 ether?) or PBDE? or (perfluorooctane NEAR/2 sulfonic NEAR/2 acid?) or PFOS? or (perflurooctane NEAR/2 sulfonyl NEAR/2 fluoride?) or PCDD? or PCDF? or (polybrominated NEXT biphenyl?) or PBB? or (polybrominated NEXT (diphenyl

NEAR/2 ether?)) or POP or POPS or (persistent NEAR/2 organic?) or (stockholm NEAR/2 convention?) or (short NEXT chain NEAR/2 (chlorinated NEAR/2 paraffin?)) or SCCP? or toxaphene? or endosulfan? or (tetrabromodiphenyl NEAR/2 ether?) or campheclor?)

#41 #39 or #40

#42 ((((abdom?n* or waist or pad? or tissue*) NEAR/2 (adipos* or circumferenc* or diameter* or fat* or o-bes* or obes*)) or BMI or ((bodymass or (body NEXT mass) or quetelet) NEAR/2 (index* or indices)) or (bod* NEAR/2 (fat* or size* or weigh*)) or ((central or white or (intra NEXT abdom?n*) or intraabdom?n* or mesenter* or periton* or retroperiton* or (retro NEXT periton*) or viscera*) NEAR/2 (adipos* or fat* or obes* or o-bes* or tissue*)) or ((excess* or under or hyper* or increas* or over or gain* or chang* or los* or decreas*) NEAR/2 (weigh* or fat*)) or o-bes* or obes* or adipos* or underweigh* or hyperweigh* or overweigh* or thinness or lean* or Cachexia or Emaciation or (Fet* NEAR/2 Macrosomia) or (Subcutaneous NEXT Fat*) or (Lipid* NEAR/2 Product*) or (((waist NEXT hip) or waisthip) NEAR/2 ratio*)))

#43 #18 OR #42

#44 #41 AND #43

REFERENCES

1. WHO, *Air Pollution.*
2. Alharbi, O.M.L., et al., *Health and environmental effects of persistent organic pollutants.* Journal of molecular liquids, 2018. **263**: p. 442-453.
3. Dusanov, S., et al., *Associations between persistent organic pollutants and metabolic syndrome in morbidly obese individuals.* Nutrition, metabolism, and cardiovascular diseases, 2018. **28**(7): p. 735-742.
4. Ljunggren, S.A., et al., *Persistent organic pollutants distribution in lipoprotein fractions in relation to cardiovascular disease and cancer.* Environment international, 2014. **65**: p. 93-99.
5. Lind, L. and P.M. Lind, *Can persistent organic pollutants and plastic-associated chemicals cause cardiovascular disease?* Journal of internal medicine, 2012. **271**(6): p. 537-553.
6. Jacobson, J.L., S.W. Jacobson, and H.E.B. Humphrey, *Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children.* The Journal of Pediatrics, 1990. **116**(1): p. 38-45.
7. Schwacke, L.H., et al., *Anaemia, hypothyroidism and immune suppression associated with polychlorinated biphenyl exposure in bottlenose dolphins (Tursiops truncatus).* Proceedings of the Royal Society. B, Biological sciences, 2012. **279**(1726): p. 48-57.
8. Kakareka, S.V., *Sources of persistent organic pollutants emission on the territory of Belarus.* Atmospheric Environment, 2002. **36**(8): p. 1407-1419.
9. de Boer, J., et al., *Organic contaminants and trace metals in flounder liver and sediment from the Amsterdam and Rotterdam harbours and off the Dutch coast.* Journal of Environmental Monitoring, 2001. **3**(4): p. 386-393.
10. Kaupp, H. and M.S. McLachlan, *Distribution of polychlorinated dibenzo-P-dioxins and dibenzofurans (PCDD/Fs) and polycyclic aromatic hydrocarbons (PAHs) within the full size range of atmospheric particles.* Atmospheric Environment, 2000. **34**(1): p. 73-83.
11. Wania, F., *Potential of Degradable Organic Chemicals for Absolute and Relative Enrichment in the Arctic.* Environmental science & technology, 2006. **40**(2): p. 569-577.
12. Beyer, A., et al., *Assessing Long-Range Transport Potential of Persistent Organic Pollutants.* Environmental Science & Technology, 2000. **34**(4): p. 699-703.
13. Wilson, N.K., et al., *Aggregate exposures of nine preschool children to persistent organic pollutants at day care and at home.* Journal of Exposure Science & Environmental Epidemiology, 2003. **13**(3): p. 187-202.
14. Sohail, M., et al., *Persistent organic pollutant emission via dust deposition throughout Pakistan: Spatial patterns, regional cycling and their implication for human health risks.* Science of The Total Environment, 2018. **618**: p. 829-837.
15. Grova, N., et al., *Epigenetic and Neurological Impairments Associated with Early Life Exposure to Persistent Organic Pollutants.* International Journal of Genomics, 2019. **2019**: p. 2085496.

16. Schafer, K.S. and S.E. Kegley, *Persistent toxic chemicals in the US food supply**. Journal of Epidemiology and Community Health, 2002. **56**(11): p. 813.
17. Everett, C.J., et al., *Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999–2002 National Health and Nutrition Examination Survey.* Environmental Research, 2007. **103**(3): p. 413-418.
18. Lee, D.-H., et al., *Chlorinated Persistent Organic Pollutants, Obesity, and Type 2 Diabetes.* Endocrine reviews, 2014. **35**(4): p. 557-601.
19. GreenFacts, *What happens to PCBs when they enter the body?*
20. Zong, G., et al., *Circulating persistent organic pollutants and body fat distribution: Evidence from NHANES 1999-2004.* Obesity, 2015. **23**(9): p. 1903-1910.
21. CDC, A., *CASE STUDIES IN ENVIRONMENTAL MEDICINE*

Polychlorinated Biphenyls (PCBs) Toxicity. 2014.
22. Rathore, H.S. and L.M.L. Nollet, *Pesticides: evaluation of environmental pollution*, ed. H.S. Rathore and L.M.L. Nollet. 2012, Boca Raton, Fla: CRC Press.
23. ATSDR, *TOXICOLOGICAL PROFILE FOR*

POLYCHLORINATED BIPHENYLS (PCBs). 2000.
24. Hopf, N.B., et al., *Concentration-dependent half-lives of polychlorinated biphenyl in sera from an occupational cohort.* Chemosphere, 2013. **91**(2): p. 172-178.
25. Lee, Y.M., et al., *Persistent organic pollutants in adipose tissue should be considered in obesity research.* Obesity reviews, 2017. **18**(2): p. 129-139.
26. Pollutants, S.o.t.S.C.o.P.O., *STOCKHOLM CONVENTION ON PERSISTENT ORGANIC POLLUTANTS (POPs)* 2009.
27. Hunter, C.G., J. Robinson, and M. Roberts, *Pharmacodynamics of Dieldrin (HEOD): Ingestion by Human Subjects for 18 to 24 Months, and Postexposure for Eight Months.* Archives of environmental health, 1969. **18**(1): p. 12-21.
28. L. Ritter, K.R.S., J. Forget, *A REVIEW OF SELECTED PERSISTENT ORGANIC POLLUTANTS*

DDT-Aldrin-Dieldrin-Endrin-Chlordane-Heptachlor-Hexachlorobenzene-Mïrex-Toxaphene-Polychlorinated biphenyls-Dioxins and Furans 1995.
29. *Chlordane*. 1984, Geneva: WHO.
30. Woodruff, T., et al., *Organochlorine Exposure Estimation in the Study of Cancer Etiology.* Environmental research, 1994. **65**(1): p. 132-144.
31. Kutz, F.W., et al., *SELECTED PESTICIDE-RESIDUES AND METABOLITES IN URINE FROM A SURVEY OF THE UNITED-STATES GENERAL-POPULATION.* Journal of toxicology and environmental health, 1992. **37**(2): p. 277-291.
32. Kanthasamy, A.G., et al., *Dieldrin-Induced Neurotoxicity: Relevance to Parkinson's Disease Pathogenesis.* NeuroToxicology, 2005. **26**(4): p. 701-719.
33. ORGANIZATION, U.N.E.P.-I.L.O.-W.H., *ENDRIN HEALTH AND SAFETY GUIDE.* IPCS INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY Health and Safety Guide No. 60, 1991.

34. Wagstaff, D.J., J.R. McDowell, and H.J. Paulin, *Heptachlor residue accumulation and depletion in broiler chickens.* American journal of veterinary research, 1980. **41**(5): p. 765-768.
35. Currier, M.F., C.D. McClimans, and G. Barna-Lloyd, *Hexachlorobenzene blood levels and the health status of men employed in the manufacture of chlorinated solvents.* Journal of toxicology and environmental health, 1980. **6**(2): p. 367-377.
36. Oliver, B.G., *Biouptake of chlorinated hydrocarbons from laboratory-spiked and field sediments by oligochaete worms.* Environmental science & technology, 1987. **21**(8): p. 785-790.
37. Milbrath, M.O.G., et al., *Apparent Half-Lives of Dioxins, Furans, and Polychlorinated Biphenyls as a Function of Age, Body Fat, Smoking Status, and Breast-Feeding.* Environmental health perspectives, 2009. **117**(3): p. 417-425.
38. (HSDB), N.L.o.M.-H.S.D.B., *Annotation Record for TOXAPHENE.* 2021.
39. Mehendale, H.M. and Z. Cai, *Chlordecone*, in *Encyclopedia of Toxicology (Second Edition)*, P. Wexler, Editor. 2005, Elsevier: New York. p. 542-544.
40. Hansch, C., A. Leo, and D.H. Hoekman, *Exploring QSAR*. 1995, Washington, D.C: American Chemical Society.
41. Service, U.S.D.O.H.A.H.S.-P.H. and A.f.T.S.a.D. Registry, *TOXICOLOGICAL PROFILE FOR ENDOSULFAN* 2015.
42. Geyer, H.J., et al. *Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans*. 2004. Germany.
43. ATSDR, *Technical Fact Sheet –Polybrominated Diphenyl Ethers (PBDEs).* 2017.
44. Information, N.C.f.B., *PubChem Compound Summary for CID 42948, 2,2',4,4',5,5'-Hexabromobiphenyl.*
45. services, N.T.P.-U.d.o.h.a.a.h., *14th Report on Carcinogens- Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers.* 2016.
46. (ATSDR), A.f.t.s.a.d.r., *Toxicological Profile for Perfluoroalkyls.* 2021.
47. EPA, U., *Predictive Models and Tools for Assessing Chemicals under the Toxic Substances Control Act (TSCA).* 2012.
48. (WHO), W.H.O., *Concise International Chemical Assessment Document 34 - CHLORINATED NAPHTHALENES.* 2001.
49. Puzyn, T. and J. Falandysz, *QSPR Modeling of Partition Coefficients and Henry's Law Constants for 75 Chloronaphthalene Congeners by Means of Six Chemometric Approaches—A Comparative Study.* Journal of physical and chemical reference data, 2007. **36**(1): p. 203-214.
50. Agency, E.E.C., *SHVC Support Document. Substance name: Hexabromocyclododecane (HBCDD) and all major diastereoisomers identified.* 2015.
51. (WHO), W.H.O., *Environmental Health Criteria 71 - PENTACHLOROPHENOL.* 1987.
52. services, N.T.P.-U.d.o.h.a.a.h., *14th report on carcinogens-Chlorinated Paraffins.* 2016.
53. Ogden, C.L. and K.M. Flegal, *Changes in terminology for childhood overweight and obesity.* National health statistics reports, 2010(25): p. 1-5.

54. Monsey, M.S. and D.M. Gerhard, *Obesity. Introduction.* The Yale journal of biology & medicine U6 - ctx_ver=Z39.88-2004&ctx_enc=info%3Aofi%2Fenc%3AUTF-8&rfr_id=info%3Asid%2Fsummon.serialssolutions.com&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Ajournal&rft.genre=article&rft.atitle=Obesity.+Introduction&rft.jtitle=The+Yale+journal+of+biology+%26+medicine&rft.au=Monsey%2C+Melissa+S&rft.au=Gerhard%2C+Danielle+M&rft.date=2014-06-01&rft.eissn=1551-4056&rft.volume=87&rft.issue=2&rft.spage=97&rft_id=info%3Apmid%2F24910555&rft.externalDocID=24910555&paramdict=en-US U7 - Journal Article, 2014. **87**(2): p. 97-98.
55. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, U.S.I.f.H.M.a.E.I., 2018., *Share of premature deaths attributed to high body mass index.* 1990 – 2017.
56. World Health Organization (WHO), G.H.O., *Prevalence of overweight adults aged 18 and above. A person is defined as overweight if they have a body-mass index (BMI) equal to or greater than 25. BMI is a person's weight in kilograms divided by his or her height in metres squared.* 1975 – 2016.
57. Barrett, J.R., *Another Piece of the Obesity-Environment Puzzle: Potential Link between Inflammation and POP-Associated Metabolic Diseases.* Environmental health perspectives, 2012. **120**(4): p. A164-A164.
58. Myre, M. and P. Imbeault, *Persistent organic pollutants meet adipose tissue hypoxia: does cross-talk contribute to inflammation during obesity?* Obesity reviews, 2014. **15**(1): p. 19-28.
59. Stel, J. and J. Legler, *The Role of Epigenetics in the Latent Effects of Early Life Exposure to Obesogenic Endocrine Disrupting Chemicals.* Endocrinology, 2015. **156**(10): p. 3466-3472.
60. Arsenescu, V., et al., *Polychlorinated Biphenyl-77 Induces Adipocyte Differentiation and Proinflammatory Adipokines and Promotes Obesity and Atherosclerosis.* Environmental Health Perspectives, 2008. **116**(6): p. 761-768.
61. Swedenborg, E., et al., *Endocrine disruptive chemicals: mechanisms of action and involvement in metabolic disorders.* Journal of Molecular Endocrinology, 2009. **43**(1): p. 1-10.
62. Liang, Y., et al., *New insight into the mechanism of POP-induced obesity: Evidence from DDE-altered microbiota.* Chemosphere (Oxford), 2020. **244**: p. 125123-125123.
63. Darbre, P.D., *Endocrine Disruptors and Obesity.* Current obesity reports, 2017. **6**(1): p. 18-27.
64. Latini, G., F. Gallo, and L. Iughetti, *Toxic environment and obesity pandemia: Is there a relationship?* Italian Journal of Pediatrics, 2010. **36**(1): p. 8.
65. Jensen, R.C., et al., *Prenatal exposures to perfluoroalkyl acids and associations with markers of adiposity and plasma lipids in infancy: An odense child cohort study.* Environmental Health Perspectives, 2020. **128**(7): p. 1-11.
66. Govarts, E., et al., *Early-life exposure to multiple persistent organic pollutants and metals and birth weight: Pooled analysis in four Flemish birth cohorts.* Environmental International, 2020. **145**.
67. Vafeiadi, M., et al., *Persistent organic pollutants exposure during pregnancy, maternal gestational weight gain, and birth outcomes in the mother-child cohort*

in Crete, Greece (RHEA study). Environment International, 2014. **64**: p. 116-123.
68. Barker, D.J.P., *The developmental origins of chronic adult disease.* Acta Pædiatrica, 2004. **93**(s446): p. 26-33.
69. Jornayvaz, F.R., et al., *Low birth weight leads to obesity, diabetes and increased leptin levels in adults: The CoLaus study.* Cardiovascular diabetology, 2016. **15**(1): p. 73-73.
70. Desai, M., T. Li, and M.G. Ross, *Hypothalamic neurosphere progenitor cells in low birth-weight rat newborns: Neurotrophic effects of leptin and insulin.* Brain research, 2011. **1378**: p. 29-42.
71. Aromataris, E. and A. Pearson, *The Systematic Review: An Overview.* The American journal of nursing, 2014. **114**(3): p. 53-58.
72. Higgins, J.P.T. and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*. 2008.
73. Davis, D., *A practical overview of how to conduct a systematic review.* Nursing standard, 2016. **31**(12): p. 60-71.
74. Farhang, L., et al., *Association of DDT and DDE with birth weight and length of gestation in the child health and development studies, 1959-1967.* American Journal of Epidemiology, 2005. **162**(8): p. 717-725.
75. Casas, M., et al., *Prenatal exposure to PCB-153, p,p'-DDE and birth outcomes in 9000 mother-child pairs: Exposure-response relationship and effect modifiers.* Environment International, 2015. **74**: p. 23-31.
76. Guo, H., et al., *Prenatal exposure to organochlorine pesticides and infant birth weight in China.* Chemosphere, 2014. **110**: p. 1-7.
77. Fang, J., et al., *Association of prenatal exposure to organochlorine pesticides and birth size.* Science of the Total Environment, 2019. **654**: p. 678-683.
78. Anand, M. and A. Taneja, *Organochlorine pesticides residue in placenta and their influence on anthropometric measures of infants.* Environmental Research, 2020. **182**.
79. Yang, X., et al., *Metabolomics study and meta-analysis on the association between maternal pesticide exposome and birth outcomes.* Environmental Research, 2020. **182**.
80. Weisskopf, M.G., et al., *Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight.* Environmental research, 2005. **97**(2): p. 149-62.
81. Hjermitslev, M.H., et al., *Persistent organic pollutants in Greenlandic pregnant women and indices of foetal growth: The ACCEPT study.* Science of the Total Environment, 2020. **698**.
82. Lauritzen, H.B., et al., *Maternal serum levels of perfluoroalkyl substances and organochlorines and indices of fetal growth: A Scandinavian case-cohort study.* Pediatric Research, 2017. **81**(1): p. 33-42.
83. Callan, A.C., et al., *Sex specific influence on the relationship between maternal exposures to persistent chemicals and birth outcomes.* International journal of hygiene and environmental health, 2016. **219**(8): p. 734-741.
84. Guo, J., et al., *Associations of prenatal exposure to five chlorophenols with adverse birth outcomes.* Environmental Pollution, 2016. **214**: p. 478-484.

85. Wojtyniak, B.J., et al., *Association of maternal serum concentrations of 2,2', 4,4'5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE) levels with birth weight, gestational age and preterm births in Inuit and European populations.* Environmental Health: A Global Access Science Source, 2010. **9**(1).
86. Wolff, M.S., et al., *Prenatal pesticide and PCB exposures and birth outcomes.* Pediatric Research, 2007. **61**(2): p. 243-250.
87. Fenster, L., et al., *Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population.* Environmental Health Perspectives, 2006. **114**(4): p. 597-602.
88. Schade, G. and B. Heinzow, *Organochlorine pesticides and polychlorinated biphenyls in human milk of mothers living in northern Germany: Current extent of contamination, time trend from 1986 to 1997 and factors that influence the levels of contamination.* Science of the Total Environment, 1998. **215**(1-2): p. 31-39.
89. Basterrechea, M., et al., *Prenatal exposure to hexachlorobenzene (HCB) and reproductive effects in a multicentre birth cohort in Spain.* The Science of the total environment, 2014. **466-467**: p. 770-6.
90. Neta, G., et al., *Fetal exposure to chlordane and permethrin mixtures in relation to inflammatory cytokines and birth outcomes.* Environmental Science and Technology, 2011. **45**(4): p. 1680-1687.