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Title:

"The challenging use and interpretation of blood biomarkers of exposure related to lipophilic endocrine disrupting chemicals in environmental health studies"

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List of abbreviations

Adipose tissue (AT); body mass index (BMI); dichlorodiphenyldichloroethylene (DDE); dichlorodiphenyltrichloroethane (DDT); high density lipoprotein (HDL); lipophilic endocrine disrupting chemicals (LEDCs); low density lipoprotein (LDL); octanol-water partition coefficients (Kow); polyaromatic hydrocarbons (PAH); persistent organic pollutants (POPs); polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs); polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs); pharmacokinetic (PK); triacylglycerols (TAGs); tetrachlorodibenzo-p-dioxin (TCDD); total serum lipids (TSL); very-low-density lipoproteins (VLDLs)

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Abstract

The use of exposure biomarkers has been growing during the last decades, being considered the 'gold-standard' approach for individual exposure assessment to environmental chemicals. However, lipophilic endocrine disrupting chemicals (LEDC) have specific physicochemical and biological properties implying particular analytical challenges and interpretative caveats. The epidemiological literature is therefore afflicted by methodological inconsistencies and results divergences, in part due to recognised sources of exposure measurement error and misinterpretation of results. The aim of the present review is to identify external and endogenous sources of variability and uncertainty associated with the LEDC blood biomarkers in epidemiological studies. The dynamic nature of blood and an overview of the known mechanisms of transport, storage and partition of LEDCs in the organism are first described. The external sources of variability and uncertainty introduced at pre-analytical and analytical level are subsequently presented. Subsequently, we present some specific cases where the dynamics of lipids and LEDCs may be substantially modified and thus, the interpretation of biomarkers can be particularly challenging. The environmental obesogens as source of biomarkers variability is also discussed in the light of the most recent findings. Finally, different modelling approaches (statistical and pharmacokinetic models) proposed to improve the use and interpretation of biomarkers are appraised.

1. Introduction

The term “biomarkers of exposure” refers to the measurement of exogenous molecules or their metabolites in human tissues or biological specimens such as blood or urine. The use of biomarkers of exposure has been growing during the last decades, mainly for biomonitoring purposes, as well as for implementation in epidemiological studies (Calafat, 2016). Persistent organic pollutants (POPs) encompass a wide range of chemicals characterized by lipophilic and stability properties, being thus accumulated in fatty tissues and amplified through the trophic chains, and posing serious health problem for human health with regard to their toxicological impact (Porta, et al., 2008). Even though POP exposures have been declining since the Stockholm Convention came into force, most populations still present concerning background concentrations due to the biological and toxicological activity of these chemicals at very low doses (Lee et al., 2017). Actually a large number of POPs may interact with nuclear hormone receptors and disrupt the normal hormonal function, which will be referred in this review as lipophilic endocrine disrupting chemicals (LEDCs) (Gore et al., 2015). Relevant families of historical LEDCs include polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), organochlorine pesticides or polycyclic aromatic hydrocarbons (PAH), listed in the Stockholm Convention (Xu et al., 2013).

The fast evolution of analytical methods has allowed the large-scale determination of biomarkers in small volumes of biological fluids at ultra-trace concentrations, with high accuracy and reliability (Salihovic et al., 2013). However, it has not been accompanied by a proportional improvement of our deep understanding of biomarkers behaviour, beyond steady and healthy states. Blood (i.e. serum) is the most extensively used biological matrix in epidemiological studies, followed by breast milk, cord blood and adipose tissue (AT) in very much lesser extent. Whereas, the levels of POPs in AT are considered to be more representative and reliable of long-term exposures, the invasive sample collection appears as a main limiting factor to apply it at epidemiological scale (Jackson et al., 2017; La Merrill et al., 2013). Traditionally, the use and interpretation of blood biomarkers has been constrained to simplistic biological and pharmacokinetic assumptions including stable concentrations

through the time or that individuals are under a steady-state, situation far from many disease scenarios (Phillips et al., 1989; Porta et al., 2009). Remarkably, LEDCs biomarkers are often used as spatial and temporal surrogates, either of local exposures in target tissues and/or proxies of outlying sensitive temporal windows. Hence, the interpretation will be always constrained to a list of assumptions to depict the underlying causal scenarios (O'Brien et al., 2016; Schisterman et al., 2005).

Exposure detection bias or measurement error remains a cornerstone among major sources of bias threatening the internal validity and consistency of epidemiological findings (Edwards and Keil, 2017; Rooney et al., 2016). Whereas some external sources of variability of biomarkers may be easily identified (e.g. analytical) (Salihovic et al., 2013); it is critical to consider the endogenous sources of variability to understand the behaviour of lipophilic biomarkers in both storage (AT) and circulating (blood) compartments, and the impact of lipid metabolism on LEDCs dynamics. The tight relationship between LEDCs and lipids implies that positive associations may be interpreted as a result of the partitioning or a disruption of lipid metabolism (Guo et al., 1987). A number of diseases are known to progressively impair the lipid metabolism and/or adipocyte function resulting in concurrent altered lipid profiles patterns (i.e. pancreatic cancer, type 2 diabetes mellitus), which may prone to disease progression bias (Lopez et al., 2014). In turn, the sequestration of LEDCs in AT has been suggested as a protective mechanism of exposure for more sensitive organs, and a source of deleterious effects during weight loss, explaining inconsistent findings among obese and lean populations (Lee et al., 2018; Jansen et al., 2017). A novel stream of evidence is also supporting that endocrine disrupting chemicals may also target adipose tissue and liver at low-doses, progressively impairing the lipid metabolism and alter the lipid dynamics (i.e. obesogenic chemicals), resulting in unknown impact on LEDCs dynamics (Heindel and Blumberg, 2018; Heindel et al., 2017). Overall, many fundamental questions still remain to be answered for ease thorough interpretations of lipophilic biomarkers of chemicals with metabolic disrupting activity.

The aim of the present review is to discuss external and endogenous sources of variability and uncertainty associated with blood biomarkers of LEDC hampering their use and interpretation in epidemiological studies. In the first sections we highlight the dynamic nature of lipids and LEDCs

providing an overview of known mechanisms of transport, storage and partition of LEDCs in the organism (Section 2, 3 and 4). Throughout Section 5 we summarize external sources of variability introduced at pre-analytical and analytical level. In the subsequent sections (6, 7 and 8) we introduce some specific cases where dynamics of LEDCs may be modified and interpretations can be challenging due to endogenous sources of variability. The sections 9 and 10 introduce some modelling approaches (statistical and pharmacokinetic models) proposed to improve the use and interpretation of biomarkers. Finally, some remaining open questions and research needs are formulated on the basis of the published evidence.

2. Mechanism of transport, storage and dynamics of LEDCs within the organism

Nowadays, diet remains a main source of exposure to historical LEDCs for humans originated from developed countries. However, the mechanisms of intestinal absorption, packing and internal transport have not been detailed for many chemicals yet. It is believed that the mechanisms of absorption and transport of many lipophilic chemicals are shared with dietary lipids, undergoing the lymphatic pathway and/or the portal vein to liver. This entry mechanism is determined by the octanol-water partition coefficients (K_{ow}) of chemicals. For instance, LEDCs with a log K_{ow} of 3.5 are transported predominantly by the portal vein (Jandacek, Rider, Yang et al., 2009), shifting towards the direct transport via lymphatic system at log K_{ow} of at least 5, whereas highly lipophilic chemicals can bypass liver and diffuse directly into AT. For instance, the pesticide dichlorodiphenyltrichloroethane (DDT) is a highly lipophilic chemical (log K_{ow} = 6.91) with a very long half live (26 years) whose transport to the peripheral tissues undergoes mainly via lymph packed in the core of chylomicrons, entering to the systemic blood through the subclavian vein. Before the transport to the liver, there is a partial transfer of DDT from chylomicrons to the peripheral tissues (mainly AT) that has been reported to be faster than that of triacylglycerols (TAGs) or cholesterol esters and independent of lipoprotein lipase action (Kohan et al., 2013; Trevaskis et al., 2006). For PCBs, the influence of the number and position of chlorine substituents on the uptake and accumulation in adipocytes has been demonstrated: highly halogenated PCBs (i.e. 153 and 118) therefore gets an equilibrium appear to diffuse more slowly into the intracellular, hydrophobic cytoplasm of *in vitro* adipocytes in comparison

to less halogenated congeners (i.e. 28) (Bourez et al., 2012; Bourez et al., 2013). The stage of adipocyte differentiation and TAG levels were important determinants of *in vitro* PCB-126 uptake, which was shown to be incorporated to the droplets by passive diffusion at high concentrations (Bourez et al., 2012).

The major storage of LEDCs, as for TAGs, is white adipose tissue, although these chemicals have been found at lower concentrations in other tissues such as liver, brain, kidney or ovary (Jackson et al., 2017). The partitioning of LEDCs through different AT locations has been assumed to be comparable under steady-state conditions. Nonetheless, whereas several studies have shown high correlation of LEDCs concentrations in visceral adipose tissue and sub-cutaneous adipose tissue (Malarvannan et al., 2013; Ploteau et al., 2016), others have found low correlation or substantial differences on their concentrations (Pestana et al., 2014; Kim et al., 2014; Yu et al., 2011). Metabolic perturbations and variations on the cytochrome P450 activity were suggested as potential factors responsible for the differential patterns of distributions of LEDCs in the fat pads (Kim et al., 2014; Yu et al., 2011).

Adipose tissue represents the main reserve of energy in the organism and TAGs are mobilized during those times of energy deprivation orchestrated by the lipolytic machinery. During lipolysis, a relevant amount of free fatty acids and glycerol is released to the circulation, being important to supply substrate for hepatic synthesis of very-low-density lipoproteins (VLDLs) (Duncan, Ahmadian, Jaworski et al., 2007). LEDCs stored in the adipocyte droplets are mobilized with TAGs during lipolysis, but at lower rates (Louis et al., 2014). The mobilization of LEDCs is determined by the fat mass, being mobilised at slower rates in large fat pads and individuals with larger adiposity.

LEDCs are poorly metabolized and slowly excreted mainly via bile, faeces and breastmilk, and marginally via urine or perspiration, determined by age, body fat and smoking (Jandacek and Tso, 2001). It is suspected that the fraction of LEDCs that undergoes enterohepatic circulation is a function of the fraction of the LEDCs that is carried in the blood to the liver and enterocytes (Jandacek and Genuis, 2013). The changes in concentrations of LEDCs over time is known as the apparent half-live; the result of the net balance between elimination, changes in body composition and intake (Milbrath

et al., 2009). For instance, the half-life of the pesticide dichlorodiphenyldichloroethylene (DDE) was estimated to be about 5 years in lean subjects and 10 years for obese individuals (Wolff et al., 2007).

3. Partition of POPs between adipose tissue and blood

The coefficient of concentrations of chemicals in AT and serum in steady-states (i.e. AT:Serum partition coefficient or ratio) determines the degree at which a chemical accumulates in fat pads (Petreas et al., 2004). On the basis that LEDCs in blood reaches equilibrium with adipose tissue throughout the body, the correction of serum levels of LEDCs in weight basis by the lipid levels (e.g. lipid-normalized) has been extensively embraced in biomonitoring and environmental epidemiology to increase the comparability between compartments and account for gender and fasting variability (Phillips et al., 1989). In a steady-state, partitioning of highly lipophilic compounds between tissue and blood is agreed to be roughly equal to the tissue:blood lipid concentration ratio (Brown and Lawton, 1984). Accordingly, Haddad et al., (2000) explored the (theoretical) determinants of the adipose tissue:blood partition ratios ($PC_{at:b}$) of organic chemicals (equation 1), concluding that independently of the K_{ow}, the $PC_{at:b}$ can be predicted from the lipid composition of tissue and blood (Haddad, Poulin and Krishnan, 2000). Specifically, for organic chemicals with log $K_{ow} \geq 4$, the $PC_{at:b}$ equals the ratio between the fraction of neutral lipid equivalents in adipose and blood. The higher K_{ow} also determines the higher uptake rates of chemicals in adipose tissue, commonly described by the "diffusion-limited" model (Levitt, 2010). In parallel, the mobilisation of chemicals into the blood stream has been shown to be selective and strongly dependent on the log K_{ow}, less lipophilic PCBs being more efficiently released (Louis et al., 2014). Recently, it has been shown that some biological factors may also affect the bioaccumulation potential of lipophilic chemicals, including the different types of lipids or the composition of non-lipid molecules (Endo, Brown and Goss, 2013), probably explaining the large variability of partitioning attributed to inter- and intra-individual pharmacokinetic differences (Mussalo-Rauhamaa, 1991). For instance, serum cholesterol was found to be a major factor influencing the partitioning of PCBs between serum and adipose tissue (Guo et al., 1987).

The partition ratios may be affected by the normalization of blood biomarkers (i.e. biomarker concentration on lipid basis), for instance, values close to 1 were found when the lipid correction were

used, but ranging from 0.5 to 2.9 without normalization were reported for DDE (Arrebola et al., 2012; Lopez-Carrillo et al., 1999). Age and body composition also contribute to this variability, with higher ratios reported for instance for older women. Similar variations of the partition ratios have been observed more recently in a study where the adipose tissue/serum ratio of PCBs and PBDEs have been reported from population living around a Chinese E-waste plan area (Lv et al., 2015). The Log K_{ow} appeared to be linearly correlated with the lipid-based adipose-serum ratio for PCBs and PBDEs, with some exceptions (e.g. PCB-180). The authors suggested the transfer of more lipophilic chemicals to AT could also be affected by the larger volumes or molecular weights, that may explain a lower adipose-serum ratio (Lv et al., 2015). An applied example, comparing serum:AT ratios of LEDCs under disease conditions, found substantial differences between cases of endometriosis and controls (Ploteau et al., 2016). The authors hypothesized that using the ratio of lipophilic chemicals could be a novel integrated biomarker, informing about the equilibrium states of chemicals between these complementary compartments.

Even though the AT/blood partition coefficient is one of the most relevant parameters in pharmacokinetic models with major implications for predicting the toxicological effect of chemicals, little empirical evidence from humans is currently available (Papadaki, Karakitsios and Sarigiannis, 2017). Thus, further research on factors affecting the partitioning of LEDCs under specific physiological conditions is required to improve the interpretation of biomarkers and the application of more integrative approaches.

4. Vascular transport of LEDCs and distribution in blood lipoprotein subfractions

Blood is an extremely complex fluid, and the detailed distribution of LEDCs in the different blood subfractions and its relationships with health has been scarcely explored to date. Circulating biomarkers are commonly determined in the lipid fraction of serum, that represent about 0.5 % of the total volume. This fraction includes different lipoproteins, with different functions on lipid transport, homogenized during the sample preparation procedure preceding the analysis of LEDCs. For instance, chylomicrons contain TAG and LEDCs primarily of dietary origin from recent intakes.

To date, few studies have considered the analysis of LEDCs in lipoproteins subfractions but the results are suggestive. For example, one study found that high POP concentrations in high density lipoprotein (HDL) were more associated with cardiovascular disease while high POP concentrations in low density lipoprotein (LDL) and VLDL were more associated with cancer (Ljunggren et al., 2014). The authors suggested that HDL and LDL are relevant distribution routes of POPs that merits further attention in environmental health studies. In a cross-sectional analysis National Health and Nutrition Examination Survey (NHANES) 1999-2006, PCBs and organochlorine pesticides have been associated with higher levels of TAGs, specially PCB-74, PCB-170, oxychlordane and trans-nonachlor. In turn, heptachlor epoxide was associated with lower levels of cholesterol-HDL (Patel et al., 2012). Some studies have shown that LEDCs may interplay actively with the different lipoprotein fractions and exhibit specific patterns of distribution among the different blood compartments. For instance, organochlorine compounds were more associated with the lipoprotein depleted fractions, containing primarily albumin, than other plasma lipoproteins (Noren et al., 1999). On the other hand, the lipoprotein transport may also impact on cellular uptake of certain chemicals. For instance, the transport of radiolabelled benzo[a]pyrene in LDL favoured the uptake into fibroblast whereas HDL impeded the cellular uptake, and opposite results were observed in hepatocytes (Busbee et al., 1990).

The vascular transport within lipoproteins raise additional questions related the potential interactive effects between bioactive lipids and LEDCs. Actually, a growing list of lipids has been found to be highly bioactive and capable of modulating cell signalling pathways and molecular functions directly involved in many pathogenic pathways (Lopategi et al., 2016; Juarez-Hernandez et al., 2016). Thus, the comprehensive profiling of lipids may help the identification of bioactive mixtures interacting on the pathogenic pathways at study, moving forward beyond the assumption that lipids are inactive transporters.

The understanding of vascular distribution and transport of LEDCs has major implications in the interpretation of circulating biomarkers. Refinement of blood biomarkers could account for the determination of LEDCs in specific lipoprotein subfractions that target critical organs (e.g. LDL) instead of considering the total pool lipids as the same fraction.

5. Analytical sources of variability: collection, storage and determination

A number of external sources of variability and uncertainty, associated with the laboratory methods and protocols used for sample collection and analysis of LEDCs, should be also considered. External (procedural) contamination of biological samples, upstream to their analysis (i.e. during sample collection), appears as a first source of variability, specially by using clinical materials and collection tubes affected by the presence of residues of ubiquitous LEDCs or by conducting the analysis in laboratories with substantial indoor background levels. For example, brominated flame retardants (including BDE-209, BDE-47 and other major representative markers from this wide family) can be extensively found widespread in indoor air and dust, including from laboratories (Wong et al., 2018). In many cases, epidemiological studies have used biological samples from historical and consolidated biobanks for which the storage conditions and overall collection quality standards have been questioned compared to more recent protocols. There is also still limited information regarding the stability of LEDCs during their long-term storage, but one may suspect little variations due to their chemical stability and persistence in the environment and organisms. That is not the case of lipids, a critical fraction required to report and interpret LEDCs, highly sensitive to freeze-thaw cycles, extraction and storage temperatures. For instance, loss of 14-46% of lipid fractions have been shown after 3 years of storage at -20°C. Whereas long-term storage (i.e. 10 years) at -80°C has been shown to exhibit minor impact on lipid stability, no studies have explored longer periods (Matthan et al., 2010).

Another analytical issue is related to the method used to determine this lipid content in biological matrices. Determination of total lipids in food and human tissues is historically performed by gravimetry, widely employed in the regulatory context of chemical food safety. This approach is also the reference for biomonitoring studies using adipose tissue or other solid human matrices for which the lipid content is relatively high, presenting some advantages for international harmonization. However, the value determined with this method do not permit a more refined analysis related to the different subclasses of lipids present in the sample and susceptible to more specifically interact with the POP biomarkers. For liquid matrices with low lipid content, blood in particular, the

implementation of enzymatic methods has been developed that permit to obtain a more detailed lipid composition including TAGs, cholesterol and phospholipids determination. From these values, the total lipid content is thus calculated using mathematical equations. Although some of these existing equations appears as a reference in the field (Akins et al., 1989; Phillips et al., 1989), these cannot be considered as universal and definitive options because the approximations made for a number of biological parameters induce de facto an error on the final generated value. Thus the choice of such predictive formula for total lipid content reconstitution from enzymatic measurement may substantially impact the final lipid normalized results. For example, it was demonstrated a variation of 16-17% of the estimates in case of DDE (Covaci et al., 2006). This type of analytical error can be also related to the nature and quality of the biological sample, that may present substantial variability associated to the haemolytic status due some blood components (e.g. haemoglobin, bilirubin glucose…) or the type of enzymatic test use in the procedure. Further sources of error related to the lipid determination include the analytical uncertainty originated from matrix interferences, inadequate quality control, or restricted sample amounts for which the representativeness of the determined value may be questioned (Cooper et al., 2002).

During the last four decades and empowered by Stockholm Convention on POPs enforcement in 2004, there has been a substantial improvement of analytical methods of LEDCs, towards ultra-trace and multi-residue methods, requiring low sample volumes and shorter processing times (Xu et al., 2013). The determination of LEDCs-related biomarkers then requires firstly the extraction of the lipid fraction (extracted either by high-pressure extraction or liquid/liquid extraction). Clean-up is commonly performed by liquid-liquid washing of the organic layer with sodium hydroxide, followed by sulphuric acid or Florisil® purification. Gel permeation chromatography is another possible option for some compounds (i.e. organochlorine pesticides). Determination of LEDCs in extracts are finally conducted by gas chromatography coupled to high-resolution mass spectrometry (GC-HRMS) after electron impact ionization (PCDD/Fs, PCB, PBDE, pesticides) or liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) after electrospray ionization (Hexabromocyclododecane, perfluorinated compounds). Despite this typical analytical workflow globally appears well established

and consolidated, some particular modifications in these steps may introduce substantial variability. For instance, the introduction of a preliminary freeze-drying stage may both contribute to a procedural contamination for some compounds, as well as, leading to a loss of some more volatile compounds. The application of multi-residue analytical protocols involves less specific extraction and separation procedures, resulting in substantial impacts on accuracy and sensitivity of estimates (i.e. higher limits of detection, LOD). The loss of accuracy and reliability is specially concerning for those molecules commonly found close to the LOD. The presence of non-detected samples will further introduce uncertainty on the exposure estimation, even if advanced statistical methods to handle the left-censorship are applied (Schisterman et al., 2006). Regardless the method, the implementation of well-established quality assessment/quality control protocols for the analytical procedures becomes a major determinant of quality of biomarkers determination (Salihovic et al., 2013).

6. Dyslipidemia may alter LEDC dynamics

In normal conditions intra-individual factors (i.e. physiological variation, lifestyle or clinical factors) may account for about 18 and 22% of variation of TAGs levels in blood during a follow-up of 5-6 months, substantially higher than the 2.7-5% accounted by analytical factors that would account for fasting status (Evans and Laker, 1995). Abnormal regulation of lipid metabolism may result in increased or decreased levels of lipids or lipoproteins in blood, known as dyslipidemia, which may be inherited or caused by some pathological condition (i.e. obesity, diabetes or renal disease) (Ramasamy, 2016). For instance, according the Endocrine Society normal levels of TAGs should stand below 150 mg/dL but it may go up to 2000 mg/dL in severe hypertriglyceridemia (Brahm and Hegele, 2013). That fluctuation may have major implications for ultra-trace substances such as PCDD/Fs, commonly found in the range of pg/g lipid.

The distribution of lipophilic chemicals in blood may be altered in hypertriglyceridemia as demonstrated with mitotane (o,p'-DDD), parent chemical of the insecticide DDT used for the treatment of adrenal cortical carcinoma. In such condition, most of mitotane was found in the TAG-rich fraction (chylomicrons + VLDL), while normolipidemic conditions showed that mitotane bound to HDL and albumin (Gebhardt et al., 1992). Similarly, mitotane-induced dyslipidemia was

demonstrated in a case-report study to cause overestimation of plasma mitotane by a matrix effect. The matrix effect lead to a gradual increase of o,p'-DDE and a gradual decrease of p,p'-DDE (used as internal standard), as the levels of hypercholesterolemia and/or hypertriglyceridemia increased (Paci et al., 2016).

Dyslipidemia and lipolysis can also increase the adipocyte turnover, the normal capacity of an adipocyte to store and replace TAGs during the entire cell life-span of 10 years, estimated to be about 6 times (Arner et al., 2011). Considering that TAG mobilize LEDCs during lipolysis, it should be expected that higher adipose tissue turnover will result in a higher LEDC turnover, increasing the daily exposure of sensitive organs. In other words, at same stable concentrations of LEDCs in adipose tissue (or blood), increased adipocyte turnover will result in increased internal exposures of sensitive organs.

Whereas cross-sectional epidemiological studies have shown significant associations between LEDCs and serum lipids (Patel et al., 2012; Arrebola et al., 2014), the direction of the associations have not been established and the extent of the impact of dyslipidemia on LEDCs dynamics remains fairly unexplored.

7. Intentional weight loss and LEDCs dynamics

Adaptive mechanisms allow the maintenance of fat mass throughout life, even with daily energy fluctuations. Only if alterations of energy balance are persistent over time, the fat mass will be proportionally modified. The major consequences of weight loss on LEDCs dynamics have been described in the literature, as: 1) increase of the blood concentrations of LEDCs, 2) mobilisation of LEDCs to more sensitive or ectopic depots and 3) increase of adverse effects resulting from the transitory high exposure.

1) Increase of circulating levels of LEDCs

The increase of LEDCs levels in the blood stream due to an imbalance between weight loss-induced lipolysis and excretion is known as the phenomenon of "bioamplification" (Li and Wania, 2017). A substantial number of studies has evaluated the impact of intentional weight loss on POPs dynamics, comprehensively reviewed by Jansen et al., 2017. Dietary caloric restriction commonly led to a moderate weight loss (10%) compared to bariatric surgery, that results in about 30-40 % of weight

loss. In both cases the levels of POPs were raised proportionally during a follow-up period of 1 year, with an estimated increase of 2-4% per kilogram of weight loss for many POPs (Jansen et al., 2017). This effect becomes dramatic for severe weight loss where the circulating levels of POPs may increase by 150-400%. Conversely, the total body burden of POPs following the weight loss has been shown to moderately decrease (Kim et al., 2011). Interestingly, one study suggested that visceral adipose tissue was the dominant contributor of increasing PCB serum levels during weight loss, supporting that dynamics of LEDCs may be differentially determined by the fat compartments (Dirinck et al., 2015).

2) Metabolism and mobilisation of LEDCs to more sensitive or ectopic depots

The increased levels of LEDCs during weight loss have been shown to redistribute the chemicals in sensitive tissues, but also the increased blood levels of cholesterol may modify the excretion patterns by induction of phase II enzymes and conjugation reactions (Dirtu et al., 2013). For instance, weight loss of rodents dosed with LEDCs lead to redistribution of hexachlorobenzene to brain and kidneys (Jandacek et al., 2005) or DDT to liver, heart or brain (Ohmiya and Nakai, 1977; Dale et al., 1962).

3) Adverse effects resulting from the higher exposure

The raised exposure in sensitive organs resulting from weight loss has been linked to different health effects. For instance in humans, the serum levels of POPs one year after bariatric surgery were positively correlated with liver toxicity markers and lipid parameters, adjusting for age and body mass index (BMI) (Kim et al., 2011).

Furthermore, the changes of circulating concentrations of POPs following weight loss were the main explanatory variables of decreased resting metabolic rate, potentially interfering the thyroid regulatory system (Pelletier et al., 2002; Tremblay et al., 2004). On that basis, a negative feedback loop has been suggested after weight loss, where the "obesogenic" LEDCs raised during caloric restriction or bariatric surgery could counteract or mitigate weight loss or favour the weight rebound (Li and Wania, 2017). Whereas these studies were performed with individuals with obesity and severe obesity, little is known about the impact of moderate weight loss induced by certain sub-clinical pathological conditions among overweight or normal-weight individuals.

8. Metabolic disrupting chemicals may alter LEDCs trajectories

A growing body of work has shown that industrial chemicals, either lipophilic and hydrophilic (i.e. bisphenol A), may alter the lipid metabolism and energy balance, resulting in the alteration of blood lipids (Heindel and Blumberg, 2018; Heindel et al., 2017; Janesick and Blumberg 2016; Veiga-Lopez et al., 2018). Metabolic disruptors mainly target AT and liver, which may have direct effects on LEDCs trajectories, releasing or sequestrating them with TAGs through lipolysis and lipogenesis.

The perturbation of lipid metabolism may lead to conflicting situations where the biomarkers may either be causes or consequences of such physiological condition. For instance, an experimental study with Rhesus monkeys fed with tetrachlorodibenzo-p-dioxin (TCDD) for about 4 years and followed-up 7-11 years resulted in higher TAG levels in serum but also increased concentrations of other lipophilic chemicals such as PCBs accidentally ingested through the laboratory diet (Rier et al., 2001). The results suggested that TCDD and/or endometriosis, that spontaneously appeared within the treated group, were responsible for the differential pattern of bioaccumulation. The study illustrates how a primary causative exposure may result in the perturbation of pharmacokinetics patterns of LEDCs, resulting in confusing secondary exposure trends. This fact is reflected in the overall body of epidemiological research on endometriosis-TCDD research harmed by substantial inconsistencies, in large measure due to the methodological constraints related to the use of exposure biomarkers (Cano-Sancho et al., 2019). An overview of chemicals and endpoints affected by lipophilic metabolic disruptors are presented in Figure 1.

[Note to the editor. Figure 1 may be placed here. Figure Legend:

***Figure 1**. Schematic representation of LEDCs distribution system, with adipose tissues as main storage depot and blood as main vehicle, all orchestrated by liver to satisfy the energy demands. In gray boxes appears the main metabolic endpoints directly linked to LEDC distribution and that has been reported to be impaired by LEDCs (examples of obesogenic LEDCs in red).]*

8.1. Obesogenic effects of LEDCs in adipose tissue

During the last decade, an emerging field of research has been consolidating the basis of knowledge linking environmental pollutants and obesity (Janesick and Blumberg, 2016). Animal and *in vitro* studies have shown that the exposure to environmental chemicals may result in increased fat pads, body weight as well as increased adipocyte size and number (Heindel and Blumberg, 2018). Furthermore, dosing adipocytes to environmental chemicals may produce other local molecular effects such as insulin insensitivity, production of pro-inflammatory cytokines or dysregulation of adipokines, overall known as a dysfunctional adipocyte phenotype (Pestana et al., 2017; Howell et al., 2015; Ruzzin et al., 2010). Other endogenous toxins such as ceramides and other lipids may also cause or contribute to the adipocyte dysfunction along with genetic factors (Kloting and Bluher, 2014). Also, in many metabolic pathological processes such as obesity or diabetes, adipose tissue function appears impaired (Bluher, 2009). Some chemicals such as the dioxin TCDD have shown an anti-lipogenic action on adipocytes, reducing the lipid accumulation and promoting its mobilization, mainly due to the inhibition of lipoprotein lipase (Jackson et al., 2017).

The impact of adipocyte dysfunction on dynamics of stored LEDCs remains unexplored, yet many studies on metabolic disruption have shown high levels of circulating lipids also associated with LEDCs and dysmetabolism. For instance, many epidemiological studies on diabetes have reported the concurrency of high levels of LEDCs in serum and high levels of TSL which can lead to misleading conclusions due to the role of serum lipids in the progression of the disease (Lee et al., 2014; Lee et al., 2010; Lee et al., 2011; Gasull et al., 2012; Airaksinen et al., 2011). That is a major issue in observational studies, even in well-designed observational prospective studies, because the intrinsic high correlation between LEDCs and serum lipids.

8.2. Obesogenic effects of LEDCs in liver

The liver plays a central role in the homeostasis of lipids, but also in the metabolism of LEDCs and their transport in blood through the mobilization of TAGs and cholesterol. Excessive fat accumulation in the liver can occur as a result of increased fat delivery, increased fat synthesis, reduced fat oxidation and/or reduced fat export in the form of VLDL (Postic and Girard 2008). Liver is a common target organ of many industrial chemicals, resulting in the so-called toxicant-associated fatty liver

disease (Wahlang et al., 2013). Liver disease is a major determinant of dyslipidemia and lipid metabolism dysfunction and thus, having potentially direct consequences on LEDCs dynamics. For instance, the pesticide DDT may impair the liver lipid metabolism inducing the accumulation of total fat, TAGs and cholesterol and is linked to an increase of circulating lipids in rodents (Cano-Sancho et al., 2017). Mitochondrial dysfunction of hepatocytes was identified as critical target of DDE and β-HCH, impairing fatty acid β-oxidation and associated disorders of fatty acid metabolism in adult male C57BL/6 mice (Liu et al. 2017). Dioxins may also cause hepatic steatosis in rodents, throughout AhR activation that interferes with peripheral fat mobilization and increases fatty acid uptake in the liver (Lee et al., 2010). The concentrations of PCBs have been associated with increased circulating lipids in different epidemiological cross-sectional studies (Ha et al., 2007; Goncharov et al., 2008) and supported by experimental studies. Low concentrations of PCB-126 (i.e. 1.05-2.5 μM/kg body weight) increased both, hepatic and circulating TAGs and non-esterified fatty acids; and upregulated master regulators of lipid metabolism such as SREBP1C, DGAT2, FABP and PPARα of female rats (Boucher et al., 2015; Chapados and Boucher, 2017). Benzo[a]pyrene has been shown to interfere with the ability of lipoproteins to bind receptors in liver required for their clearance, such as LSR and LDL-R for VLDLs and LDL, respectively, without modification of the structure (Irigaray et al., 2006; Layeghkhavidaki et al., 2014). Some organochlorines have been shown to modulate the liver drug transporter activity and increase the biliary flux of pesticides (Bucher et al., 2014).

Despite the growing evidence supporting the metabolic disruption triggered by industrial chemicals, many questions remain unresolved concerning their impact on LEDC's dynamics and the interpretation of related biomarkers, urging for specific experimental studies. For instance, a simple in vitro model has been shown to be very efficient to study the dynamics of mobilization of PCB-153 from rat adipocytes during isoproterenol-induced lipolysis (Louis et al., 2014b).

9. Model specification and statistical approaches for blood biomarkers

The normalization of wet concentrations of blood biomarkers by the lipid content (i.e. division of serum concentrations of POPs by serum total lipids) has become the default approach for lipophilic biomarkers (Phillips et al., 1989). The landmark study conducted by Phillips and collaborators revealed that normalization of biomarkers favours the comparability of fasting and non-fasting

samples. The authors also noticed that corrections for serum lipids based on the short formula to reconstruct TSL from TAGs and CHO may underestimate the global lipid changes as subsequently reported in a comparative study of equations (Covaci et al., 2006). Even though the Phillips approach has been embraced by many epidemiological studies, some researchers have advertised that, in some cases, this approach may produce biased estimates, especially when lipids may fall in the pathway between the exposure and the outcome (O'Brien et al., 2016; Schisterman et al., 2005). Alternative models have been proposed for the application of circulating LEDCs and TSLs to better describe their underlying associations with diseases and other associated covariates. Some of the most reported models are known as: a) the unadjusted model (biomarkers in wet weight); b) the lipid standardized model (ratio of biomarker in wet weight divided by TSL, so-called as lipid weight or normalized); c) covariate adjustment (TSL as confounding variable); d) standardization plus covariate adjustment (combination of b and d), or e) 2-stage model (covariate adjustment for the residuals of TSL-biomarker regression) (O'Brien et al., 2016; Schisterman et al., 2005). Other methods such as the application of Box-Cox transformation followed by a Bayesian hierarchical model or the covariate standardization (i.e. dividing biomarkers by confounding variables) have also been proposed as alternatives, but have not been embraced in applied analysis (O'Brien et al., 2016; Li et al., 2013). Some simulation studies have evaluated the performance of most common modelling approaches to depict different causal scenarios. For instance, Schisterman et al., (2005) concluded that the lipid standardized model may result in highly biased results, especially when TSL has large measurement error associated. Subsequently, O'Brien et al., (2016) reported that the lipid standardized model could be improved if TSL is also included as covariate in the regression model. In both studies, the authors acknowledged the limitations of current statistical approaches and stated that improved methods for standardization are required. In applied epidemiological studies there is growing interest to further compare and report the risk estimates considering lipid-normalized biomarkers and TSL-covariate adjusted models. In the framework of endometriosis research, we explored the impact of different statistical approaches on risk estimates and elucidated the lack of concordance between blood and AT models (Cano-Sancho et al., 2018).

Overall, the underlying associations between blood biomarkers, circulating lipids, adiposity and the health outcomes are often not sufficiently appreciated and therefore underreported. Improved models should account for the dynamic nature of LEDCs as function of time and fat fluctuations, as well as, the underlying individual metabolic status.

10. Improving the use and interpretation of biomarkers using pharmacokinetic models

The behaviour and trajectories of background concentrations of LEDCs in the general population may be easily described using single-compartment pharmacokinetic (PK) models, requiring the volume of distribution and clearance half-life as parameters (Clewell et al., 2008). Wolff et al., (2007) highlighted the relevance of considering the pharmacokinetic variability in epidemiological studies, illustrating the impact of declining trends of internal DDT levels, cohort age and varying BMI. Overall, the authors predicted differential trajectories of internal DDT after the ban was enforced determined by the BMI and cohort year that could help to explain inconsistent results in published literature (Wolff et al., 2007). The authors also stressed the need to consider the individual trajectories of BMI and body weight changes to minimize the measurement errors of exposure biomarkers. Inspired by that study, mechanistic human exposure models have been subsequently used to confirm the Wolff's predictions on PCBs trajectories in relation to BMI and population age (Wood et al., 2016). The authors confirmed the large impact of sampling year, the range of sample age classes and the range of BMI classes on the cross-sectional body burden of PCBs versus BMI trends. Dilution effects exerted by large BMI and elimination rates of PCBs (determined also by BMI) interplays through the entire life determining the body burden. A shift in the association between PCB-153 and BMI was predicted, being negative for birth cohorts before 90s and positive or negative after that depending on the age.

The PK models have been also shown to be promising to back-extrapolate prenatal levels using concentrations of biomarkers during childhood. A two-compartment model was used to simulate mother's lifetime environmental exposure and child exposure through transplacental diffusion, breastfeeding and environmental exposure to DDT/E and PBDEs. The results showed that the method

successfully predicted pre-natal exposure levels, which may be implemented to increase the sample size of prospective birth cohorts with new enrolments (Verner et al., 2015).

The impact of intentional weight loss on body burdens of LEDCs has also been evaluated using a mechanistic one-compartment PK model, simulating the bioamplification phenomena that succeed the intentional weight interventions (Li and Wania, 2017). Such simulations have large potential to improve understanding of cross-sectional biomarkers that may be a result or involved in a pathological process where modifications of BMI are experienced. Considering the high cost of longitudinal sample points and multiple analysis of LEDCs, PK models intended to capture full trajectories of exposures become a cost-effective way to expand the interpretation of 'raw' single-point biomarkers. Whereas a PK model cannot substitute multiple sample analysis and longitudinal modelling, their application may help formulate new hypothesis and interpret inconsistent findings.

11. Concluding remarks and future perspectives

In the present review we have attempted to identify some major sources of variability and uncertainty associated with the determination, modelling and interpretation of LEDC biomarkers that may help to explain divergent and non-reproducible results in environmental epidemiology. Considering that LEDCs are suspected to exert biological effects at low concentrations, minimal measurement error and reduced variability (unrelated to the disease of interest) becomes critical for the identification of subtle associations. Even though LEDC biomarkers, both in blood and AT, are commonly acknowledged to reflect stable and long term exposures, a list of external and internal factors may substantially influence their estimates and interpretation (Summarized in Figure 2).

[Note to the editor. Figure 2 may be placed here. Figure Legend:

***Figure 2**. Endogenous and external sources of variability and uncertainty related to the use and interpretation of biomarkers of lipophilic endocrine disrupting chemicals in exposome-health studies. The plot about burden of polychlorinated biphenyls vs sampling year and body mass index was adapted from Wood et al., 2017. Abbreviations: AT:Blood, adipose tissue:blood partition ratio; $LEDC_{AT}$, lipophilic*

endocrine disrupting chemicals in adipose tissue; $LEDC_{BLOOD}$, lipophilic endocrine disrupting chemicals in blood; O, health outcome; TSL, total serum lipids.]

The improvement of our understanding of biomarkers goes in parallel with the search for novel biospecimens, more directly related with target organs or tissues. Actually, the particularities of blood in terms of sample accessibility and molecular richness endow the red fluid with invaluable attributes for environmental health research. Thus, the comprehension of mechanisms of packing, transport and storage of LEDCs, will be critical to encompass the new generation of exposome biomarkers in blood from large scale environment-health studies.

As a matter of fact, single spot biomarkers will never reflect the trajectories of LEDCs exposure through time and should be interpreted with caution. The longitudinal collection of confounding variables (i.e. BMI) may help to reconstruct the pharmacokinetic behaviour of LEDCs through the time. In this sense, the application of chemical-specific and generic PK models will support the prediction of internal exposures through the time and in target organs and tissues. The novel generation of sensors and smartphone applications may help the longitudinal collection of valuable individual data (i.e. body fat trajectories) to incorporate in longitudinal exposure models and compute more realistic internal exposure estimates.

A growing list of lipophilic chemicals may activate signalling pathways related with lipid metabolism, liver lipid regulation and/or adipocyte function, and consequently impact internal exposure trajectories. Whereas experimental studies will be necessary to better understand the pharmacokinetic impact of metabolic disruptors, epidemiological studies should not dismiss these potential underlying associations. Last but not least, circulating lipids are commonly considered as mere carriers of biomarkers but the literature supports their active role in many molecular pathways and cell signalling involved in most pathogenic processes (e.g. oxidative stress, inflammation). Thus, the risk models should consider the potential joint or interactive effects of toxicant-lipid complexes.

In addition to lipophilic chemicals we would like also draw attention to those environmental chemicals with lower lipid affinity (i.e. Kow < 4), including bisphenols, parabens or perfluoroalkyl substances. This vast family of chemicals has major relevance in terms of industrial production and human exposure, presenting particular physicochemical and biological properties and specific analytical challenges (Weaver et al., 2016). Despite their fast metabolism and excretion resulting in short half-lives, some recent studies have demonstrated that these chemicals may also be partially stored in adipose tissue and slowly released to serum (Artacho-Cordón et al., 2017, 2018). These findings suggest that the lipid compartment may be chemically much more complex and rich than commonly agreed, with potential implications on AT function and the internal release of complex mixtures of contaminants.

Overall, many opportunities are emerging during this OMIC era for exposure biomarkers research. For instance, the application of cutting-edge mass-spectrometry technologies (i.e. lipidomics) coupled with advanced statistics will vastly extend our current knowledge of blood composition and its determinants of variability. Large-spectra chemical agnostic approaches are believed to favour the identification of mixtures of endogenous and exogenous molecules that may help to better explain complex exposome-health associations.

Conflict of interest

The authors declare no conflict of interest. No specific grants has been attributed to this study.

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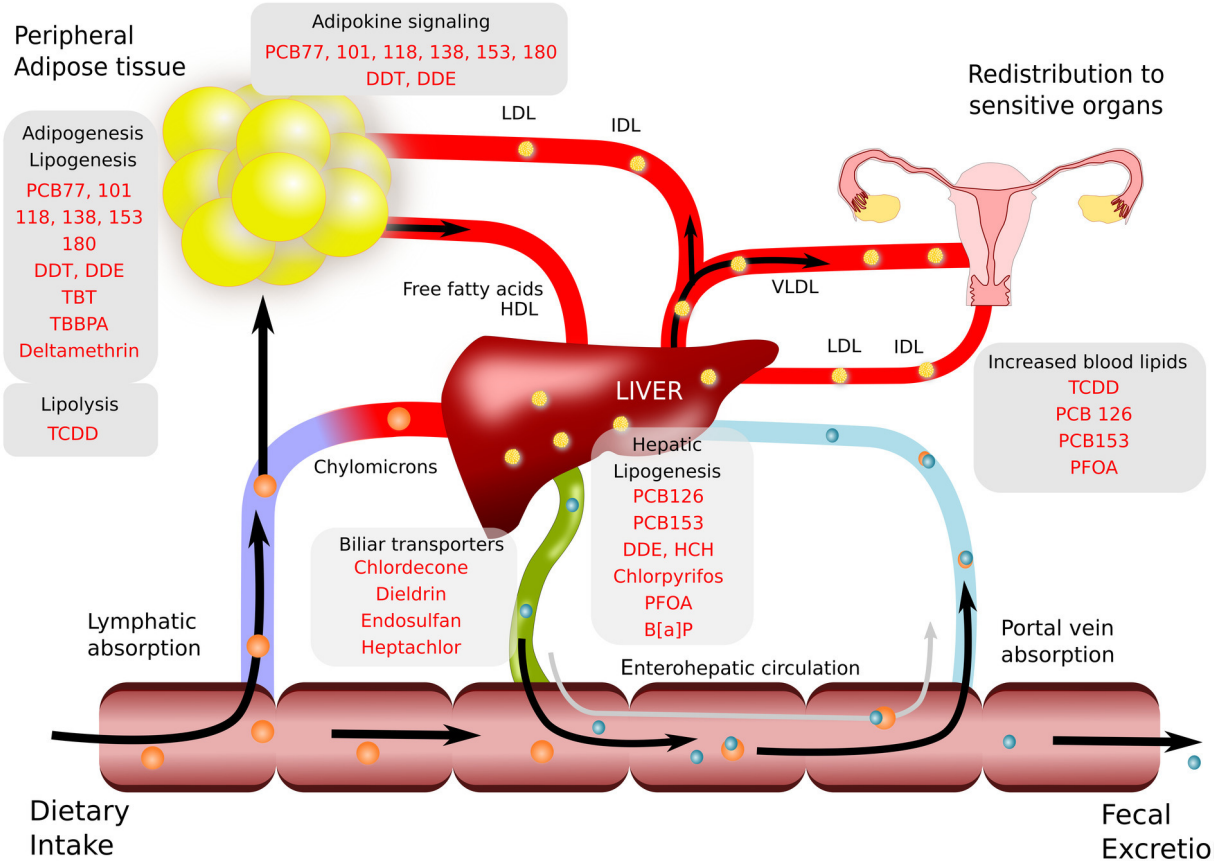
Table 2: Outcomes per FET according to endometrial preparation

Outcomes per cycle with embryo transfer	Mild ovarian stimulation (OS) N (%)	Artificial cycle (AC) N (%)	p value	adjusted[a] p value
Number of cycles with FET	N = 357	N = 664		
Implantation rate (%)	18.90 %	16.30 %	.247	.145
Positive pregnancy test	100 (28%)	156 (23.5%)	.113	.075
Clinical pregnancy	87 (24.4%)	138 (20.8%)	.188	.105
Early pregnancy loss	21 (5.9%)	60 (9.0%)	.078	.097
Ectopic pregnancy	2 (0.56%)	5 (0.75%)	.723	.672
Ongoing pregnancy after 12 WG (OP)	64 (17.9%)	73 (11.0%)	**.002**	**.001**
Medical interruption of pregnancy (after 12 WG)	2 (0.56%)	5 (0.75%)	.723	.637
Late pregnancy loss (after 12 WG)	0	3 (0.45%)	na	Na
In Utero fetal death	1 (0.28%)	0	na	na
Live birth	61 (17.1%)	65 (9.8%)	**<.001**	**<.0001**
Multiple pregnancy (% of OP)	9 (14.1%)	9 (12.2%)	.741	.896

[a]Adjusted on age at freezing, woman smoking status, PCOS, endometriosis, previous history of recurrent pregnancy loss, and rank of transfer

FET: frozen-thawed embryo transfer; WG: weeks of gestation; PCOS: Polycystic Ovarian Syndrome;


Peripheral
Adipose tissue
Adipokine signaling
PCB77, 101, 118, 138, 153, 180
DDT, DDE
Adipogenesis
Lipogenesis
PCB77, 101
118, 138, 153
180
DDT, DDE
TBT
TBBPA
Deltamethrin
Lipolysis
TCDD
LDL
IDL
Free fatty acids
HDL
VLDL
LDL
IDL
Redistribution to
sensitive organs
Increased blood lipids
TCDD
PCB 126
PCB153
PFOA
LIVER
Chylomicrons
Hepatic
Lipogenesis
PCB126
PCB153
DDE, HCH
Chlorpyrifos
PFOA
B[a]P
Biliar transporters
Chlordecone
Dieldrin
Endosulfan
Heptachlor
Lymphatic
absorption
Enterohepatic circulation
Portal vein
absorption
Dietary
Intake
Fecal
Excretion

Physicochemical properties LEDCs

Biological activity

Mixture characteristics

Individual characteristics

Metabolic status/ disease progression

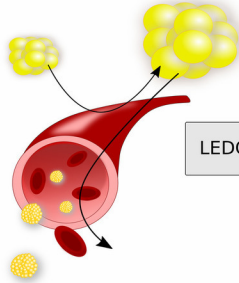
Sampling, storage and analytical measurements

Cross-sectional measurements

$Lipids_{AT}$

$Lipids_{AT:Blood}$

$Lipids_{Blood}$



$LEDC_{AT}$

$LEDC_{AT:Blood}$

$LEDC_{Blood}$

Individual history

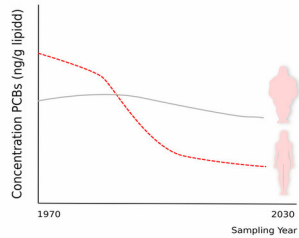
Metabolic status/ disease progression

Multiple measurements

Collection year

PBPK models

Longitudinal trajectories



Biological knowledge

Metabolic status/ disease progression

Causal structures

Measurement error

Identification of confounders

Statistical models

$p(y) = \alpha + \beta\,(E_{blood}) + \varepsilon$

$p(y) = \alpha + \beta\,(E_{blood}) + \lambda(TSL) + \varepsilon$

$p(y) = \alpha + \beta\,(E_{blood/TSL}) + \varepsilon$

$p(y) = \alpha + \beta\,(E_{blood}) + \lambda(TSL) + \omega(C) + \varepsilon$

Interpretation of lipophilic exposome-outcome associations