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Partitioning of hexachlorobenzene between human milk and blood lipid☆

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Abstract

In epidemiological studies on the toxic effects of prenatal exposure to hexachlorobenzene (HCB), researchers report HCB concentrations, either as wet-weight or per lipid weight basis, in matrices like breast milk, and maternal and cord blood. Conversion of exposures across matrices is needed for comparisons of concentrations and dose effect across cohorts. Using data from a birth cohort study in eastern Slovakia, we derived the maternal blood to cord blood HCB concentration ratio utilizing measured concentrations in 1027 paired maternal and cord blood samples, on a per-lipid basis. In addition to data from the Slovak study, the maternal milk to maternal serum ratio was summarized from 23 published studies on partitioning of HCB between human milk lipid and blood lipid. We identified two distinct groups of milk:blood ratios, those ≤0.45 and those ≥0.85. We assumed that using partition ratios ≤0.45 will underestimate HCB exposure estimates. Taking into account this precautionary measure, we suggest a conversion ratio of 1.21, which is the median of the 16 ratios identified in our literature review. We consider our estimate as conservative and providing appropriate safety in risk analysis.

Keywords

Concentration conversion; Hexachlorobenzene; Breast milk; Cord blood; Lipids; Partitioning

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2017.07.087.

1. Introduction

Hexachlorobenzene (HCB) use as a pesticide was banned by the EU in 1981(EFSA, 2006) and its production and uses were phased out by the Stockholm Convention on Persistent Organic Pollutants in 2004 (Stockholm Convention, 2001). Before its ban, HCB was used widely as an agricultural pesticide. As a result of its prevalent use and its slow decay (EFSA, 2006), HCB can remain in the environment for a long time. Indeed, serum specimens from populations worldwide indicate that HCB is ubiquitous (Patayová et al., 2013; Woodruff et al., 2011; Fisher et al., 2016) despite being phased out several decades ago.

The primary targets of toxicity for HCB after occupational or accidental exposure include hepatic, reproductive, and developmental end points. Additionally, HCB exposures have been associated with cancer endpoints (ATSDR, 2015). Presently, investigators focus mainly on prenatal HCB exposures, i.e., on possible associations between levels of HCB in maternal blood or breast milk, cord blood, or children's blood, and developmental end points such as birth size (weight and/or length) or preterm birth, recurrent miscarriage, postnatal growth, postnatal neurodevelopment, maturation, cryptorchidism, hypospadias, and indicators of postnatal thyroid function (ATSDR, 2015). Since the 2015 ATSDR publication, additional studies have documented associations between higher HCB exposure and obesity (Vafeiadi et al., 2015), reduced cognitive development (Kyriklaki et al., 2016), airway obstruction (Hansen et al., 2016), decreased birth length (Lopez-Espinosa et al., 2016), increases in the proportion of optimal birth weight (Callan et al., 2016), small for gestational age (SGA) (Lauritzen et al., 2016), decreased follicle number (Kristensen et al., 2016) and development of metabolic diseases via insulin homeostasis (Tang-Péronard et al., 2015). According to ATSDR (2015), limitations of HCB studies include the lack of quantifiable exposure to HCB, small numbers of subjects, and/or the presence of measureable levels of other organochlorine compounds. The insufficient information on human toxicology of HCB characterizes the statement (ATSDR, 2015) that: “none of the human studies with HCB have provided reliable direct exposure data (dose and duration) and therefore, no evidence of an exposure-response relationship has been possible.” Such insufficient knowledge warrants further investigation of health outcomes of prenatal exposure to HCB. Moreover, the extremely variable elimination half-life of HCB in young adults (Gallo et al., 2015) seems to complicate the developmental health risk analysis of HCB. The assessment of perinatal exposures is based mainly on determination of the toxicant concentration in matrices derived from the body of either mother or infant. Matrices commonly used for this purpose are maternal blood, cord blood, or breast milk. Most relevant to the effect however, are toxicant concentrations in the central compartment represented by circulating blood either of the mother or the fetus. In order to compare exposures using different matrices as maternal serum/plasma, cord serum/plasma or mother milk, it is necessary to convert concentration data across matrices. The present paper summarizes what is known about HCB concentrations in paired matrices, and derives an HCB maternal serum/plasma vs. breast milk ratio based on 23 studies.

2. Material and methods

We performed a literature search in PubMed, Web of Science, and SCOPUS databases to identify studies that report on simultaneously measured HCB in serum and breast milk. We used the following keywords: “concentration,” “hexachlorobenzene,” “breast milk,” “blood,” “plasma,” “serum,” “lipids,” “partitioning.” We combined the keywords by Boolean operator AND. As the topic of the search was quite specific, the search results with given keywords did not optimally reflect our objective. The final selection of relevant publications was therefore done after a thorough inspection of each result. More papers were identified using literature references included in already identified publications. The literature sources were restricted to human studies and where paired sampling could reasonably be assumed. All studies reporting on HCB concentrations in maternal blood and milk were included, regardless of sample size and other potential exclusion criteria. In such way we obtained a set of 23 data points (item 1).

The following parameters were needed for conversion the lipid adjusted HCB concentration in mother milk to lipid adjusted/wet weight based HCB concentration in cord serum:

1) The ratio of HCB concentration in mother milk lipids to that in mother blood lipids; 2) The ratio of HCB concentration in cord blood plasma/serum to mother blood plasma/serum, using both lipid based and wet weight concentrations; and, 3) The concentration of mother and cord plasma/serum lipids. The ratio under 1) was derived from our literature search. The ratio under 2) was based on our data on partition of HCB between maternal and cord blood lipids (Patayová et al., 2013). Briefly, maternal and cord HCB concentrations were determined in 1027 mother-infant pairs taken part in a birth cohort study in eastern Slovakia (Hertz-Picciotto et al., 2003). Maternal serum was collected during the mother's hospital delivery stay, and cord blood was collected from the infant at birth. Concentrations of HCB were determined using gas chromatography with electron capture detection (GC-ECD). Cord/Maternal serum ratios were calculated for pairs in which data on concentration was available for both mother and her child. Percentage of samples with concentration of HCB ≥ LOD was 96.3%. For switching between wet weight and lipid based data we used our data on lipid concentration in 1065 paired maternal and cord blood serum (Lancz et al., 2015). Lipid concentration was measured using the enzymatic summation method (Akins et al., 1989) (item 3). Specifically, total serum cholesterol (TC) and triglyceride (TG) concentrations were determined at the Department of Clinical Biochemistry of TOP-MED General Hospital Bratislava using a DuPont Automatic Clinical Analyzer III (DuPont, Jonesboro, AR, USA), and cholesterol oxidase without cholesterol esterase was used to detect free cholesterol (FC). The method by Takayama and colleagues was used to determine serum choline-containing phospholipids (PL).45 Total serum lipids were calculated using the formula: $TL = 1.677 \times (TC - FC) + FC + TG + PL$.

3. Results

3.1. The ratios of HCB concentration in maternal milk lipids to that in maternal blood lipids

The 23 lipid-adjusted milk/serum HCB concentration ratios reported in the selected papers are shown in Fig. 1. The summarized information from the individual sources can be found in the Supplement.

Two distinct groups of ratios can be seen in Fig. 1. Those ≤0.45 and those ≥0.848. We assume that using partition ratios ≤0.45 will underestimate HCB exposure estimates and consequently the results of exposure/outcome relationships. We show statistics on the ratios from all 23 values and after deleting values ≤ 0.45 in Table 1. Taking into account this precautionary measure, we suggest for conversion purposes the value of 1.213 which is a median of the 16 ratios ≥0.848.

3.2. The ratio of HCB concentration in maternal plasma/serum lipids to cord plasma/serum lipids and concentration of maternal and cord plasma/serum lipids

We previously reported a median wet weight HCB cord serum/maternal serum concentration ratio of 0.265 based on analyzing 931 samples. For lipid adjusted HCB concentrations, we obtained a median ratio of 1.097 (Patayová et al., 2013).

In some selected publications, the HCB concentrations are expressed as wet weight, in units of weight HCB/serum volume, and in others as lipid adjusted, in units of weight HCB/weight serum lipid. We have recalculated the wet weight based milk/serum concentration ratios and expressed them on a per-lipid basis. With HCB serum concentration expressed as wet weight, we calculated the concentration of total lipids in serum as 10 mg lipids/ml serum. We observed this value in 1065 subjects (Lancz et al., 2015) (Table 2). The descriptive statistical data on total lipid concentration in mother and cord serum samples are shown in Table 2 (Lancz et al., 2015).

3.3. Application of derived parameters on HCB conversion

We describe the maternal milk to cord plasma/serum conversion procedure for HCB as follows:

The first step is conversion between HCB lipid-adjusted concentrations in milk and maternal serum. We use the currently suggested conversion factor of 1.213. Therefore, we write:

$$Maternal\ milk\ HCB\ level(ng/glipid) = 1.213\ Maternal\ serum\ HCB\ level(ng/glipid) \quad (1)$$

We convert the maternal serum HCB level from ng/g lipid into ng/L serum as follows:

$$10\ Maternal\ serum\ HCB\ level(ng/glipid) = Maternal\ serum\ HCB\ level(ng/Lserum) \quad (2)$$

The coefficient of 10 reflects the average content of fat in serum (g/L) and is based on our data on lipid concentration in 1065 women from samples taken at delivery (Table 2).

The next step is the conversion between mother and cord lipid adjusted or wet-weight based HCB concentration. The respective equations, based on median HCB cord serum/maternal serum concentration ratios of 0.265 for wet weight and 1.097 for lipid adjusted HCB concentrations (Patayová et al., 2013), are as follows:

$$1.097\ Maternal\ serum\ HCB\ level(ng/glipid) = Cord\ serum\ HCB\ level(ng/glipid) \quad (3)$$

$$0.265\ Maternal\ serum\ HCB\ level(ng/Lserum) = Cord\ serum\ HCB\ level(ng/Lserum) \quad (4)$$

Combining the above equations we obtain equations (5) and (6) for direct conversion of maternal milk HCB level (ng/g lipid) to cord serum HCB levels.

$$Cord\ serum\ HCB\ level(ng/Lserum) = 2.18\ Maternal\ milk\ HCB\ level(ng/glipid) \quad (5)$$

or

$$Cord\ serum\ HCB\ level(ng/glipid) = 0.9\ Maternal\ milk\ HCB\ level(ng/glipid) \quad (6)$$

4. Discussion

Maternal milk is the most commonly studied matrix for human biomonitoring of organochlorines (Fång et al., 2015). However the relationship between the concentration of the compounds in milk and the fetus is not straightforward. In our paper, we derive parameters necessary for conversion of breast milk HCB concentrations into cord serum levels, both, wet weighed and lipid adjusted, based on the extant published literature and our own data (Patayová et al., 2013; Lancz et al., 2015).

The ratios of HCB concentration in maternal blood to breast milk observed in the selected literature sources show marked variability. This variability may be explained by the high lipophilicity of HCB {log K_{OW} = 5.7 (Science Dossier, 2014)}, its affinity to triglycerides and cholesterol and changing levels of these main lipid components in maternal blood and milk linked to physiological processes. In the course of normal pregnancy, women show an increase in lipid levels, including levels of triglycerides and total cholesterol, as gestational age progresses (Sattar et al., 1997; Mazurkiewicz et al., 1994; Brizzi et al., 1999; Koletzko et al., 2001; van Stiphout et al., 1987). Moreover diurnal variations in the secretion of milk lipids (Jenness, 1979) and in concentrations of organochlorines in human milk (Pluim et al., 1992) have been described. Thus, heterogeneity in the ratios may reflect different time periods of HCB measurement during pregnancy. Additionally, it should be noted that the reviewed data on milk composition shows large geographic differences (Koletzko et al.,

1992; Kumar et al., 2016). For instance, the ratios 0.9 and 0.07 (Skaare et al., 1988), while both derived from women in Norway, the 0.07 ratio was estimated based on concentrations from immigrants to Norway from developing countries. Moreover the value of 0.4 from the same author (Skaare et al., 1988) is for Norwegian mothers and their infants delivered by Caesarean operation. Furthermore, most studies indicate that HCB binds to blood lipoproteins (Mussalo-Rauhamaa, 1991; Gómez-Catalán et al., 1991; Norén et al., 1999) which by themselves, demonstrate variable levels (Mjøs et al., 1979). HCB vectors, triglycerides and cholesterol, being nonpolar lipid substances (insoluble in water), need to be transported in the plasma associated with various lipoprotein particles (Cox and García-Palmieri, 1990). Similarly, chlorinated hydrocarbon pesticides in milk are preferentially concentrated in the surface layers of the fat globule. Although many milk components were associated with pesticides, most of the pesticide on a total concentration basis was associated with triglycerides in the interior of the fat globule (Hugunin and Bradley, 1971). It was shown that because of the differences in these chlorinated hydrocarbon concentrations observed with different sample collection regimens, meaningful comparison of analytical results requires correction by total serum lipid levels (Phillips et al., 1989; Pluim et al., 1994) which has not been sufficiently documented in all literature sources reviewed in the present study.

We did not weigh the published values relative to their study size. Neither we used any QA/QC measures to select the studies from the literature (e.g., sample size). Thus, a mean ratio derived from a few paired samples was given equal weight as a study with a greater number of paired samples. When the concentration was expressed as wet weight, we had to impute lipid concentrations in serum with regard to comments on adjustment of concentration of lipophilic compounds on serum lipids (Schisterman et al., 2005; O'Brien et al., 2016). As already mentioned, the data on concentrations of serum lipids show great variability. For the conversion between maternal wet weight and lipid weight HCB serum concentrations, we used the coefficient of 10 reflecting the average content of fat in serum (g/L) based on our data from 1065 women (Table 2). Other sources give lower, however variable values (Dayton et al., 1966; The Serum Lipids and Lipoproteins, 1958; Cheek and Wease, 1969). Our value is close to mean maternal lipid concentration of 8.9 g/l reported by Needham et al. (2011). In secondary analyses using this value, we derived a ratio of 1.94, which was not meaningfully different from our ratio of 2.18 (data not shown). Here and in our study (Lancz et al., 2015), the lipid level might have been influenced by labor. Furthermore, in some of the reviewed papers the authors reported that blood and milk samples from the same individual were not collected at the same time. This also may contribute to variability in the data.

We conclude, after acknowledging all these sources of uncertainty, that it is possible to derive a valid milk/cord serum conversion factor for HCB from the published data when adopting a certain measure. The median of 0.925 obtained as a result of consideration of all 23 papers reviewed (Table 1) is markedly influenced by the ratios ≤0.45. For precautionary reasons we have suggested a cut-off limit of 0.848. For the milk/serum ratios ≥0.848 the calculated median value of 1.213 (Table 1) seems to warrant safety in risk analysis. We are aware that such proceeding may raise some concern, however our choice of the value of 1.213 is close to the value of 1.48 (Needham et al., 2011) which was derived from a large

number of observations. However the best way to eliminate all uncertainties would be to conduct a study under controlled conditions in which HCB will be determined in human serum and in milk at the same time, in many subjects, at multiple time points.

In the course of searching for relevant original data, we found a review article on partitioning of persistent organic pollutants, HCB included, between human serum and breast milk (Mannetje et al., 2012). The 11 literature sources considered in this review were limited to studies that were conducted in humans and those reporting on paired samples including at least five individuals. In the 11 studies resulting from that literature search, 4 were excluded because the serum and breast milk concentrations were not reported on a lipid weight basis. Another 2 publications were excluded because the serum samples were not fully paired with the breast milk samples. We consider using the suggested estimate of the serum/milk ratio of 0.633 (range 0.33−1.25), based on 5 publications, in risk assessment, problematic.

5. Conclusions

In epidemiological studies on toxic effects of prenatal exposure to HCB, researchers report assessment of HCB concentration, either wet weight or lipid adjusted, in matrices like breast milk, maternal blood and cord blood. Conversion of exposures across matrices is needed for comparison of health outcomes between cohorts. From three parameters needed for conversion between breast milk and cord blood, we derived two, maternal blood to cord blood HCB concentration ratio and the concentration of mother and cord serum lipids, from our previously published data. We assessed the value of the maternal milk to maternal serum ratio from 23 published data on partitioning of HCB between human milk lipid and blood lipid. We consider our estimate as conservative and as providing appropriate safety in risk analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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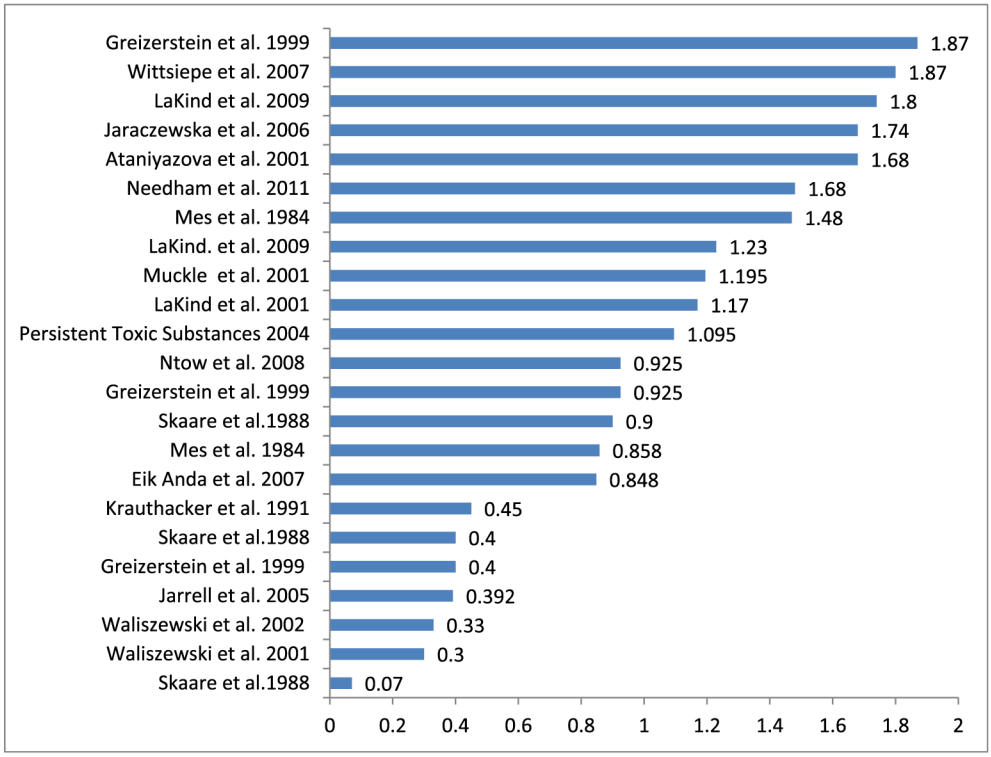

Fig. 1.

The plot of the 23 lipid adjusted ratios identified in the literature of HCB concentration in maternal milk lipids to that in maternal blood lipids (Ataniyazova et al., 2001; EikAnda et al., 2007; Greizerstein et al., 1999; Jaraczewska et al., 2006; Jarrell et al., 2005; Krauthacker, 1991; LaKind et al., 2001; LaKind et al., 2009; Mes et al., 1984; Muckle et al., 2001; Ntow et al., 2008; Persistent Toxic Substances, 2004; Waliszewski et al., 2001; Waliszewski et al., 2002; Wittsiepe et al., 2007).

Table 1

Descriptive statistics on the lipid adjusted milk/serum HCB concentration ratio calculated from all 23 values and after omitting values of ratios ≤0.45.

	Values of ratios	
Statistic	**All**	**≥0.848**
Number of observations	**23**	**16**
Minimum	0.070	0.848
Maximum	1.870	1.870
1st Quartile	0.4	0.925
Median	0.925	1.213
3rd Quartile	1.48	1.680
Mean	1.009	1.304
Variance (n-1)	0.305	0.135
Standard deviation (n-1)	0.552	0.368

Table 2

Descriptive statistics of total lipids in maternal and cord blood serum samples (N = 1065).

Total lipids mg/mL	Mean	Std. Deviation	Median	Minimum	Maximum	Geometric Mean
Mother	10.23	1.98	10.17	1.75	20.17	10.03
Cord	2.52	0.52	2.46	0.13	5.34	2.47