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Human biomonitoring reference values derived for persistent organic pollutants in blood plasma from the Canadian Health Measures Survey 2007–2011

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ABSTRACT

Nationally representative human biomonitoring data on persistent organic pollutants (POPs) including organochlorine pesticides (OCs), polychlorinated biphenyls (PCBs) brominated flame retardants (BFRs) and perfluoroalkyl substances (PFASs) are available through the Canadian Health Measures Survey (CHMS). We have used a systematic approach building on the reference interval concept proposed by the International Federation of Clinical Chemistry and Laboratory Medicine and the International Union of Pure and Applied Chemistry to derive human biomonitoring reference values (RV_{95}s) for selected POPs in blood plasma in the general Canadian population. Biomarkers were chosen based on specific selection criteria including their detection in most Canadians (>66% detection rate). Age and sex were evaluated as possible partitioning criteria and separate RV_{95}s were derived for the sub-populations in cases where partitioning was deemed necessary. RV_{95}s for OCs, PCBs, and BFRs were derived both on a whole weight of blood plasma and on a lipid weight adjusted basis whereas they were derived only on a whole weight basis for PFASs. RV_{95}s ranged from 0.018 μg/L (PCB 201) to 21 μg/L (perfluorooctane sulfonate) and from 3.1 μg/kg lipid (PCB 201) to 1400 μg/kg lipid (*p,p′*-DDE). The 22 RV_{95}s reported in this paper represent the first set of reference values for POPs in the Canadian general population against which individual and population human biomonitoring data may be compared.

1. Introduction

Human biomonitoring (HBM) is defined broadly as the measurement of biomarkers (parent chemical and/or its biotransformation products) in human biological fluids or tissues and is used as a tool for estimating human exposure to chemicals in order to inform public health, risk assessment, and risk management decisions (NRC, 2012).

Several countries including Canada, the United States, Germany, Spain, Korea and France have conducted national-level human biomonitoring studies (CDC, 2009; Fréry et al., 2012; Haines et al., 2016; Park et al., 2016; Pérez-Gómez et al., 2013; Schulz et al., 2007). To facilitate the interpretation of clinical chemistry data, the concepts of reference intervals along with the relevant statistical methodologies have been developed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (Solberg, 1987) and the International Union of Pure and Applied Chemistry (IUPAC) (Poulson et al., 1997). The German Human Biomonitoring Commission (HBM Commission) adopted this approach to interpret HBM data using reference values to indicate background exposure to environmental chemicals in a reference population. The HBM Commission defines a reference value (RV_{95}) as "the 95th percentile of the measured pollutant concentration levels in the relevant matrix of the reference population. To derive it, it is rounded off within the 95% confidence interval" (HBM Commission, 2016). The RV_{95} indicates the upper margin of the current background exposure of the general population to a given substance at a given time (Ewers et al., 1999). The IFCC and IUPAC provided recommendations on constructing reference populations, including sample selection, sample size, the use of the most recent data, inclusion and exclusion criteria, partitioning criteria, and quality of analytical methods (Solberg, 1987).

HBM data from representative surveys are considered the most appropriate to derive population-level RV_{95}s for environmental chemicals in human biological materials (Ewers et al., 1999). The Canadian Health Measures Survey (CHMS) has been collecting nationally representative HBM data from the general population

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since 2007 (Haines et al., 2016). Using the CHMS biomonitoring data, we previously derived RV_{95}s for metals and trace elements in blood and urine in the Canadian general population (Saravanabhavan et al., 2016). As a continuation of this effort, the purpose of this paper is to establish RV_{95}s for persistent organic pollutants (POPs) measured in plasma of the Canadian general population using the most recent HBM data available from the CHMS. POPs are a concern for human health primarily due to their persistence in both the environment and the human body.

2. Methods

2.1. Data source

The HBM data on POPs were obtained from the datasets collected from the first (2007–2009) and second (2009–2011) cycles of the CHMS. These represent the most recent POPs datasets available from the CHMS. Detailed descriptions of the CHMS rationale, survey design, sampling strategy, mobile examination centre (MEC) operations and logistics, as well as ethical, legal, and social issues have been published elsewhere (Haines et al., 2016; Day et al., 2007). The CHMS is an ongoing survey designed to provide comprehensive direct health measures at the national level that collects information from the general population. The CHMS sample design covers 96% of the Canadian population (Giroux, 2007). The remaining 4% of the Canadian population not covered by the sample design include full-time members of the Canadian Forces and people living on reserves or in other Aboriginal settlements, in institutions and in some remote regions. CHMS 2007–2009 and 2009–2011 involved an in-person household interview and a subsequent visit to a MEC. The household interview gathered general demographic, labour force activity, and socio-economic data and detailed health, nutrition and lifestyle information. At the MEC visit, scheduled to take place a few days to a few weeks following the household interview, direct physical measurements were taken, including collection of blood and urine samples which were assessed for environmental chemicals including the following classes of POPs: organochlorine pesticides (OCs), polychlorinated biphenyls (PCBs), brominated flame retardants (BFRs), and perfluoroalkyl substances (PFASs). In order to obtain accurate national estimates for some blood measures such as glucose and serum cholesterol, subsamples of respondents were requested to fast prior to the MEC visit. The respondents were considered fasted if they did not eat or drink anything except water for $\geq$10 h prior to the appointment; otherwise, the respondents were categorized as non-fasted. The blood samples for individual measurements of OCs, PCBs and BFRs that were collected in the CHMS 2007–2009 and used in this analysis were all from the fasted subsample of participants aged 20–79 years. The most recent PFAS dpose of this study were collected from fasted and non-fasted 12–79 year old participants from CHMS 2009–2011.

POPs were measured in plasma at the Centre de toxicologie du Québec (CTQ) of l'Institut national de santé publique du Québec (INSPQ) using validated analytical methods (Health Canada, 2013, 2010). The laboratory carried out quality control protocols during the batch processing of the samples and tested standard reference materials or certified reference materials when available. In addition, the laboratory analysed field blanks, replicate samples, and blind quality control samples over the course of each two year cycle to demonstrate the method performance. Moreover, CTQ leads the Arctic Monitoring and Assessment Program Ring Test for Persistent Organic Pollutants in Human Serum which is an external quality assessment scheme for PCB congeners, OCs, BFRs, and PFASs (INSPQ, 2016).

Triglycerides (TG) and total cholesterol (TC) in serum were measured by enzymatic methods (Health Canada, 2009a, 2009b). Triglycerides were measured using the VITROS TRIG Slide method based on the procedure described by Spayd et al. (1978) and TC was measured using the VITROS CHOL Slide method based on the procedure by Allain et al. (1974). Total lipids (TL) were estimated using the formula: $TL\,(g/L) = 2.27 \times TC\,(g/L) + TG\,(g/L) + 0.623$ (Phillips et al., 1989; Bernert et al., 2007; Bergonzi et al., 2009).

OCs, PCBs and BFRs were reported as weight of chemical per volume of plasma (whole weight, μg chemical/L plasma) and as weight of chemical per kilogram of total lipid (lipid weight, μg chemical/kg lipid). PFASs were reported as whole weight only. If a respondent's TL and/or TG value was missing or below the limit of detection (LOD) then the estimate of that respondent's lipid adjusted chemical was also set as missing.

2.2. Statistical analysis

Statistical analysis was conducted using R (R Core Team, 2015) and SUDAAN 10.0.1 software (RTI International, USA). Biomarker concentrations that were below LOD were assigned a value of LOD/2. Unlike RV_{95}s derived previously for metals and trace elements from CHMS data, no exclusion criteria were examined for any of the POPs in this analysis as no confounders were considered to sufficiently influence biomarker concentrations due to their ubiquitous presence and persistence in the environment and in humans. Reference populations were constructed for each biomarker based only on the partitioning criteria of age group (12–19, 20–39, 40–59, and 60–79 years) and sex. Information on age and sex were taken from the household and clinic questionnaire databases.

Partition testing and extreme value removal followed the approach outlined in Saravanabhavan et al. (2016). Briefly, candidate partitions were tested by comparing the weighted percentage of each partition's population that is above the overall population's 95th percentile, declaring partitioning necessary if any such percentage was larger than 7.8% or smaller than 2.2%. These cutoff values are based on the approach described by Lahti et al. (2002), but adapted to the present one-sided context of the upper limit (defined at the 95th percentile), instead of the original two-sided context of the reference interval (defined by the 2.5th and 97.5th percentiles.) Within each such required partition, extreme values were then removed to ensure the resulting RV_{95}s are indicative of background levels of exposure. Extreme values were removed by applying either Tukey's approach (Tukey, 1977) or Tukey's adjusted approach (Hubert and Van der Veeken, 2008) to the natural log-transformed data, with the adjusted approach being applied if the data remained skewed after log-transformation. For the POPs analysed, less than 4% of the samples in any given partition were removed as extreme values except for the 60–79 years age group partition for perfluorodecanoic acid (PFDA)which had 8.4% removed.

After extreme value removal, weighted 95th percentiles and associated confidence intervals were computed for each partition and reported as RV_{95}s. Variance estimation for all tests, models and percentile estimates used the Balanced Repeated Replicates (BRR) approach required by CHMS, using the supplied bootstrap weights. All results were rounded to two significant figures and assessed for publication quality based on the coefficient of variation (CV) as per the CHMS release guidelines (Statistics Canada, 2013). An estimate with a CV greater than 33.3% was deemed too high to publish, and an estimate with a CV between 16.6% and 33.3% must be interpreted with caution. RV_{95}s derived from estimates with CVs between 16.6% and 33.3% are considered provisional. These procedures of partition testing, extreme value removal, and RV_{95} calculation were carried out separately for whole-weight (μg/L plasma) and lipid-adjusted (μg/kg lipid) data for each of the POPs.