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Human biomonitoring reference values for metals and trace elements in blood and urine derived from the Canadian Health Measures Survey 2007–2013

Gurusankar Saravanabhavan*, Kate Werry, Mike Walker, Douglas Haines, Morie Malowany, Cheryl Khoury

Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario, Canada

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ABSTRACT

Human biomonitoring reference values are statistical estimates that indicate the upper margin of background exposure to a given chemical at a given time. Nationally representative human biomonitoring data on 176 chemicals, including several metals and trace elements, are available in Canada from 2007 to 2013 through the Canadian Health Measures Survey (CHMS). In this work, we used a systematic approach based 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 reference values (RV_{95}s) for metals and trace elements. These RV_{95}s were derived for blood and urine matrices in the general Canadian population based on the latest biomonitoring data from the CHMS. Biomarkers were chosen based on specific selection criteria, including widespread detection in Canadians (≥66% detection rate). Reference populations were created for each biomarker by applying appropriate exclusion criteria. Age and sex were evaluated as possible partitioning criteria and separate RV_{95}s were derived for the subpopulations in cases where partitioning was deemed necessary. The RV_{95}s for metals and trace elements in blood ranged from 0.18 μg/L for cadmium in young children aged 3–5 years to 7900 μg/L for zinc in males aged 20–79 years. In the case of urinary biomarkers, the RV_{95}s ranged from 0.17 μg/L for antimony in the total population aged 3–79 years to 1400 mg/L for fluoride in adults aged 20–79 years. These RV_{95}s represent the first set of reference values for metals and trace elements in the general Canadian population. We compare the RV_{95}s from other countries where available and discuss factors that could influence such comparisons.

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. Human biomonitoring measures the internal dose of a chemical resulting from integrated exposures from all exposure routes. It has been used increasingly as a tool for quantifying human exposure to chemicals in order to inform public health, risk assessment, and risk management decisions (NRC, 2012).

National-level biomonitoring studies have been conducted in several countries including Canada, the United States, Germany, France and the Republic of Korea (CDC, 2015a; Fréry et al., 2012; Haines et al., 2017; Lee et al., 2012; Schulz et al., 2007). Interpretation of HBM data can be performed at varying levels of complexity. Preliminary interpretation involves statistical review of the data to obtain descriptive statistical parameters regarding the concentration of biomarkers, for example, arithmetic means, geometric means, and percentiles. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (Dybkoer, 1987; PetitClerc and Solberg, 1987; Solberg, 2004; Solberg, 1987a,b; Solberg and PetitClerc, 1988) and the International Union of Pure and Applied Chemistry (IUPAC) (Poulson et al., 1997) developed the concept of reference intervals along with the relevant statistical methodologies to indicate background exposure to chemical substances in a reference population. In addition, forward and reverse dosimetry based approaches have also been used to interpret HBM data in a health-risk based context. Biomonitoring equivalents, derived based on forward dosimetry, have been developed for an

* Corresponding author at: 269, Laurier Avenue West, Ottawa, Ontario K1A0K9, Canada.
E-mail address: gurusankar.saravanabhavan@hc-sc.gc.ca (G. Saravanabhavan).

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increasing number of substances using pharmacokinetics to relate external reference doses to concentrations in blood or urine (Hays et al., 2008). Intake estimates for chemicals have been derived using reverse dosimetry taking into consideration factors such as pharmacokinetics (CHAP, 2014; Koch et al., 2003; Saravanabhavan et al., 2014). Finally, based on extensive epidemiological studies for chemicals such as mercury and lead, tissue based guidance values have been developed that relate HBM data directly to health outcomes (Legrand et al., 2010; NRC, 2006).

As an indicator of background exposures in the general population, reference values (RV_{95}s) for environmental chemicals have been derived based upon the IFCC and IUPAC reference interval concept. Biomonitoring data from nationally representative surveys are considered appropriate to derive population-level RV_{95}s for chemicals (Ewers et al., 1999). The IFCC and IUPAC provided recommendations on constructing reference populations including the ones listed below.

- Sample selection: When a priori selection is not possible, a posteriori selection may be used by applying a set of exclusion and partitioning criteria. Exclusion and partitioning criteria for each biomarker are derived based on the knowledge of confounding factors.
- Sample size: The sample size of the reference population should be large enough to include different age groups, race, ethnicity and sex. The IFCC recommends a sample size of at least 120 people.
- Time period: As exposure to environmental chemicals in the general population can vary over time, use of the most recent biomonitoring data is preferred for developing RV_{95}s.
- Exclusion criteria: These are specific factors that are not categorised as the general characteristics of the reference population. Examples of such factors include smoking habits and fasting.
- Partitioning criteria: If there is a significant difference in RV_{95}s among different population segments, it is recommended to derive separate RV_{95}s for the subgroups.
- Quality of the analytical methods: It is essential to assess the overall quality of the biomonitoring data in terms of the specificity and the sensitivity (limit of detection) of the analytical methods used, and the quality assurance/quality control procedures followed during sampling, sample pre-treatment and instrumental analysis.

The IFCC defines reference intervals for a clinical biomarker based on the 2.5th and 97.5th percentile estimates of its concentration in a reference population. While evaluating the CHMS datasets, we observed that the 2.5th percentile concentration of the biomarkers of environmental contaminants were often below their respective limits of detection. Even in cases where the 2.5th and 97.5th percentiles were estimated, the coefficient of variation was often too high to be published according to Statistics Canada's publication policies (Statistics Canada, 2015, 2013, 2010). Moreover, in terms of human exposure to environmental chemicals, people at the upper end of the exposure distribution are considered more vulnerable than those at the lower end and hence reference values based on the upper end of the distribution are more valuable in exposure assessments.

Based on the recommendations of IFCC and IUPAC, the German Human Biomonitoring Commission (HBM Commission) defined 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). By using the 95th percentile rather than the geometric mean or other measures of central tendency, RV_{95}s thus 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 term "background exposure" indicates exposure to chemicals through environmental sources as experienced by the general population (CDC, 2001). The HBM Commission has developed RV_{95}s for a number of environmental chemicals including metals, persistent organic pollutants and emerging contaminants in the German population (Schulz et al., 2011). Other countries such as Brazil (Freire et al., 2015), Italy (Alimonti et al., 2011), the Czech Republic (Batáriová et al., 2006) and the Republic of Korea (Lee et al., 2012) have developed RV_{95}s for selected environmental chemicals in their respective general population or population sub-groups. However, in several instances we observed that the definition of "reference value" is not well-articulated or details on the methodology used for deriving RV_{95} lack clarity (Ewers et al., 1999).

There are several uses for RV_{95}s in public health. The RV_{95}s provide a basis for identifying individuals or sub-populations with an increased level of exposure compared with the background general population level (Ewers et al., 1999; NRC, 2006). The RV_{95} is not a bright line for exposure classification (i.e. high exposure vs low exposure). Rather, exceedance of RV_{95}s in individuals/subpopulations indicates the requirement for follow-up to understand key exposure sources and factors that are responsible for the increased exposure in those populations compared to the background. It will also help to develop statistical associations between increased exposure and health outcome in sub-populations. In addition, RV_{95}s could be used to assess temporal changes in exposure to chemicals, patterns of use and the effectiveness of actions to reduce exposure (Bevan et al., 2013). Since an RV_{95} by definition represents the upper margin of background exposure, it could also be used in developing extreme exposure cases based on worst-case scenarios in a human health risk assessment. It should be emphasised that RV_{95}s are statistical estimates of biomarkers in relevant biological matrices derived to reflect the level of background exposure to a given environmental chemical. Unlike health based guidance values, RV_{95}s do not take into account toxicological information on biomarkers and, as such, they can neither be used to assess health risks nor as a threshold for clinical action on either at an individual or population level. In addition, RV_{95}s are defined at a given time point and may need periodic revisions when new data become available.

Beginning in 2007, HBM data have been collected in Canada through the Canadian Health Measures Survey (CHMS) (Haines et al., 2017). The CHMS is a comprehensive, nationally-representative direct health-measures survey implemented by Statistics Canada in partnership with Health Canada and the Public Health Agency of Canada, aimed at assessing the general health of Canadians through household questionnaires, direct physical measures and biochemical analysis. This biennial survey covers about 96% of the general Canadian population (Tremblay et al., 2007). Full-time members of the Canadian Forces and residents of the three territories, reserves and other Aboriginal settlements in the provinces, institutions and certain remote regions are excluded (Giroux, 2007). The data collected to date in the CHMS make it possible to establish population-based HBM RV_{95}s for a broad range of environmental chemicals.

The purpose of this paper is to derive RV_{95}s for metals and trace elements in blood and urine in the Canadian population based on the latest HBM data available from the CHMS using the reference interval concept recommended by IFCC and IUPAC. Using an a posteriori selection approach and by applying the appropriate exclusion criteria, reference populations are created for each biomarker. Statistical criteria are used to assess whether age and sex partitioning of the reference population are required. Separate RV_{95}s are derived for the sub-populations in cases where partitioning was deemed necessary.