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Physiologically based pharmacokinetic (PBPK) modeling of human lactational transfer of methylmercury in China

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ABSTRACT

Methylmercury can readily cross the human placental barrier and the blood-brain barrier and cause damage to the vulnerable developing brains of the fetus and infants. Most of the previous studies on the maternal transfer of methylmercury to the next generation have focused on the prenatal period. In this study, human physiologically based pharmacokinetic (PBPK) models of methylmercury were established for breastfeeding mothers and suckling infants based on the existing model prototypes of previous studies. Relevant parameters of the models were modified, and the validation was conducted based on measured data in North China. The models could effectively describe the human lactational transfer of methylmercury, including the time-dependent methylmercury levels in different tissues and organs of the breastfeeding mothers and suckling infants. The results indicated that 77.2% and 14.9% of methylmercury were excreted via hair and breast milk, respectively, from breastfeeding mothers during the first year after delivery. Meanwhile, 79.2% was excreted from the suckling infants during the first year after delivery via hair. Lactational transfer of methylmercury was considered an important pathway of methylmercury exposure for the breastfeeding infants, which accounted for approximately 80% of the accumulated adverse impacts at the early stages of human development.

1. Introduction

Methylmercury is well known to the public for being able to accumulate along the food chain. Due to its toxicity to the nervous system and endocrine system, methylmercury could be a significant health threat to vertebrates such as fish, birds, mammals and humans (Grandjean et al., 1999; Burgess, 2005; Crump and Trudeau, 2009). Oral exposure to methylmercury was considered a major pathway for humans, especially in coastal areas, where fish and marine products with elevated methylmercury levels account for a relatively larger proportion of the human diet (NRC, 2000). Approximately 95% of ingested methylmercury could be absorbed by the human gut (Aberg et al., 1969; Miettinen, 1973), with 1%–10% distributed into the blood (USEPA, 2001). Some studies in mining areas in China indicated that rice can also be a primary pathway of methylmercury exposure for the related populations due to its dominance in the dietary structure (Feng et al., 2008; Li et al., 2008; Zhang et al., 2010).

Methylmercury can readily cross the human placental barrier and the blood-brain barrier and cause damage to the vulnerable developing brains of the fetus and infants (NRC, 2000). Evidence of adverse impacts on the nervous system of the fetus caused by methylmercury exposure has been observed in previous studies (Karagas et al., 2012; Ramirez et al., 2003; Suzuki et al., 2010). Potential anthropometric impacts of methylmercury exposure were also observed in other studies (Lee et al., 2010; Ou et al., 2015; Ramón et al., 2009). To protect human health, USEPA established a linear relationship between mercury levels in maternal blood and maternal oral exposure and adopted an oral reference dose (RfD) of 0.1 μg/kg bw/day (USEPA, 2001). Additionally, Stern (2005) established the distribution of RfD by analyzing the impacts of the variation of cord blood to maternal blood ratio (in terms of mercury levels) based on the results of USEPA (2001) via meta-analysis.

Most of the previous studies on the maternal transfer of methylmercury to the next generation focused on the prenatal period due to the effectiveness of placental transfer and the vulnerability of the fetus. However, as the primary pathway of methylmercury exposure during lactation, breastfeeding should also be of concern for the vulnerable suckling infants. Animal studies have shown that both methylmercury and inorganic mercury can be combined with serum albumin and transferred from plasma to breast milk (Sundberg et al., 1999). Approximately 65% of inorganic mercury and 10% of methylmercury in

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whole blood exist in the plasma (Kershaw et al., 1980) and are therefore available for lactational transfer. Even though methylmercury in breast milk can be readily absorbed by the human gut, methylmercury levels in infants can decrease with age due to dilution by growth and change of blood composition (Björnberg et al., 2005). A previous animal study showed that demethylation bacteria in the gut would grow after weaning, while demethylation of methylmercury for infants during lactation is negligible (Rowland et al., 1983). As a quantitative approach of studying the transfer and distribution of methylmercury in the human body, physiologically based pharmacokinetic (PBPK) modeling was developed by Clewell et al. (1999) and Byczkowski and Lipscomb (2001), focusing on the behaviors of methylmercury in the prenatal period.

To quantitatively describe the lactational transfer of methylmercury in humans and the methylmercury levels in the bodies of infants during the lactation period, PBPK models of methylmercury were established for lactating mothers and suckling infants in this study. In addition, the contribution of lactational transfer on methylmercury exposure of suckling infants in China was quantitatively analyzed. Measured methylmercury levels in related bio-indicators from a population in Northern China were used for model validation. Certain parameters were modified to better describe features of the subject population.

2. Methods

2.1. Model structure

The PBPK model in this study consists of three sub-models, i.e., the Pregnancy Model, the Lactation Model (for lactating mothers), and the Infant Model (for suckling infants). Human PBPK models of methylmercury established by Clewell et al. (1999) and Byczkowski and Lipscomb (2001) were referenced as prototypes of the model structures in this study, which mainly consist of the compartments of red cells, plasma, brain, slowly perfused tissue, hair, liver, gut, gut lumen, kidney and richly perfused tissue. Structures of the sub-models are described in Fig. 1. PBPK modeling in this study mainly includes the following steps: 1) run the Pregnancy Model with the measured methylmercury levels as bio-indicators for the prenatal period (i.e., maternal hair and venous blood) (Supplementary Material, Table S1) to obtain the maternal oral dose of methylmercury of the subject population and the initial inputs for the Lactation Model and the Infant Model (i.e., methylmercury levels in relevant compartments); 2) obtain the amount of methylmercury transferred via breastfeeding using the Lactation Model; 3) characterize the varying methylmercury levels in suckling infants using the Infant Model (assuming breast milk to be the only pathway of methylmercury exposure of suckling infants); and 4) quantitatively describe the contribution of lactational transfer to methylmercury exposure of suckling infants by comparing the model results of different breastfeeding scenarios.

2.2. Model parameters

Parameters of the PBPK models in this study include human physiological parameters, distribution coefficients of methylmercury in human tissues and organs and kinetic parameters of methylmercury. Parameters of the PBPK models in this study were primarily adopted from the studies of Clewell et al. (1999) and Byczkowski and Lipscomb (2001), except for the physiological parameters of the suckling infants. According to Clewell et al. (1999) and Byczkowski and Lipscomb (2001), maternal and fetal cardiac output and placenta plasma flow were described as proportional to the 3/4 power of the body weight, but the proportionality coefficients were different. Plasma flow of individual organs or tissues was in proportion to cardiac output. Similarly, the volume of an individual organ or tissue was in proportion to the body weight. Partition coefficients of methylmercury in maternal and fetal organs/tissues were assumed to be the same except for red cells since red cells of the fetus appear to have a larger methylmercury partition coefficient than do those of the mother (Clewell et al., 1999). Kinetic parameters of demethylation, enterohepatic recirculation, brain absorption, gut absorption and excretion of methylmercury in the human body were also described as proportional to the 3/4 power of the body weight. In the Pregnancy Model, kinetic parameters of the fetuses were assumed to be the same as those of the pregnant mothers after adjustment for body weight. Kinetic parameters and partition coefficients of the Lactation Model and the Infant Model were treated consistently with those of the Pregnancy Model (mother part) and Pregnancy Model (fetus part), respectively. In the Pregnancy Model, the variation of physiological parameters was not considered, and the relevant parameters (i.e., values at delivery) were treated as constants, given that the aim of this study was not to characterize the kinetics of methylmercury during pregnancy.

In this study, the body weight of an infant was described as a function of time (i.e., growth curve), and therefore, plasma flow and the volume of organs and tissues were described as functions of time accordingly. Partition coefficients (if related to body weight) were also described similarly. Additionally, the weight ratio of hair and the methylmercury excretion rate for fetus and infants were both treated as one-third of those of the mothers (Byczkowski and Lipscomb, 2001). Considering the significant gender difference in body weight development of human infants, the Infant Model was established for girls and boys separately.

Data from 18,848 Chinese infants (Ministry of Health of PRC, 2008) were adopted to yield the growth curves used in the PBPK modeling of this study. To better reflect physiological characteristics of the subject population in this study, measured weights of neonates were adopted as the initial values of the growth curves. Measured body weights (mean ± SD) of mothers, neonatal girls and neonatal boys were 68.11 ± 10.95 kg, 3.45 ± 0.44 kg and 3.55 ± 0.41 kg, respectively.

According to a previous study (Björkman, 2004), the ratios of organ weight/body weight for brain and kidney varied significantly with body weight at different ages, while the ratios of other organs and tissues remain relatively consistent. In addition, the ratios of plasma/cardiac output for brain, kidney and liver also varied significantly with body weight at different ages, while the ratios of other organs and tissues remained relatively consistent. Quantitative descriptions of the aforementioned time-dependent and time-independent ratios were established in this study using the data of the previous study (Björkman, 2004).

Based on the measured data of methylmercury levels in maternal venous blood (at delivery) and breast milk (at the 30th day of the lactation) (Supplementary Material, Table S1) and the ratios of methylmercury in red cells and plasma from a previous study (i.e., 12:1) (Clewell et al., 1999), the partition coefficient of methylmercury (mature breast milk/maternal venous plasma) at the 30th day of the lactation was calculated to be 2.0. According to a previous study (Kunz and Lonnerdal, 1992), the protein concentration in breast milk varies significantly with time during lactation. Additionally, considering methylmercury occurs in breast milk primarily as a form bonded to protein, the partition coefficient of methylmercury between breast milk and plasma is expected to vary accordingly with time during lactation. Therefore, a quantitative time-dependent partition coefficient of methylmercury in breast milk was established by adjusting the calculated coefficient at the 30th day of lactation (i.e., 2.0) by the quantitative variation of protein levels during lactation, obtained using data from the previous study (Kunz and Lonnerdal, 1992).

According to Arcus-Arth et al. (2005), the intake rate of breast milk by infants can be described as a function of infant age (intake rate = −0.312*age + 157.7, where the unit of intake rate is g/kg infant body weight/day, and the unit of age is days). According to data provided by Nommsen et al. (1991), the ratio of yield rate over intake rate of breast milk was calculated to be 1.085, which indicates the relationship between the oral exposure of methylmercury by suckling