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GRADIENT

Adaptation of a Physiologically Based Pharmacokinetic (PBPK) Model to Evaluate Intermittent or Variable Cadmium Exposure

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Background and Purpose: Several agencies have specified exposure limits for the consumption of cadmium (Cd) from food. For example, the United States Food and Drug Administration (US FDA) toxicological reference value (TRV) is 0.21-0.36 µg/kg-day. The TRV is a daily dose range from birth to age 50 years that would not exceed a urine Cd concentration of about 0.50 µg/g creatinine (0.21 µg/kg-day) or a mean renal cortex concentration of 50 µg/g (0.36 µg/kg-day). Similarly, the US Environmental Protection Agency (US EPA) oral reference dose (RfD) for Cd in food is 1 µg/kg-day. The RfD is a lifetime daily dose that would not exceed a renal cortex concentration of 200 µg/g. Further, the European Food Safety Authority (EFSA) set a tolerable weekly intake (TWI) for Cd of 2.5 µg/kg-week (0.36 µg/kg-day). The TWI is a weekly dose from birth to age 50 years that would not exceed a urine Cd concentration of 1 µg/g creatinine. In the case of intermittent or variable exposures, where a single exposure is greater than a regulatory limit, additional analysis is necessary to determine if such exposures would exceed the internal dose of Cd (*e.g.*, urine or renal cortex concentrations) associated with the regulatory limit. Such an analysis may be performed using an adapted version of the Kjellström and Nordberg (KN) model, a physiologically based pharmacokinetic (PBPK) model, to estimate Cd concentrations in renal cortex and creatinine-adjusted urine associated with consumption of Cd-containing products relative to regulatory limits. Here, we describe an adapted version of the KN model that allows for the simulation of Cd exposures varying in frequency, duration, and magnitude over the lifespan. We applied this approach to two case studies to determine whether intermittent exposure to Cd in food products would exceed regulatory limits for Cd as set by US FDA, US EPA, and EFSA.

Methods: To investigate the potential impacts of various intermittent Cd exposures on renal cortex and creatinine-adjusted urine concentrations, we used an adapted version of the KN model (as described in Pouillot *et al*., 2022). The adapted KN model used by Pouillot *et al*. (2022) included updated parameter inputs for the movement of Cd throughout the body (*i.e.*, *C5*, *C7*, *C8*, *C16*, *C17*, *C19*, *C20*, and *C21*), as well as National Health and Nutrition Examination Survey (NHANES) data to model body weight and creatinine excretion. Additionally, we modified the model's dietary intake function (*G*) to allow for the simulation of Cd intakes (or doses) that varied in frequency, duration, and magnitude.

In the first case study, we modeled intermittent Cd exposures from a green vegetable-based smoothie used for a "juice cleanse" in a female adult aged 20-30 years. Based on the US FDA Total Diet Study, which reported Cd concentrations for various foods, we assumed a hypothetical high-end concentration of 25 µg of Cd per serving and a consumption frequency of three servings per day (*i.e.*, 75 µg/day) for 7 days every month. In the second case study, we modeled the impact of Cd exposures from one year of intermittent consumption of nuts and seeds in a female adult aged 25 years. Based on the US FDA Total Diet Study, we assumed a concentration of 30 µg of Cd per serving and a consumption frequency of one serving every 5 days. We also incorporated a background exposure to Cd into our modeling scenarios using Centers for Disease Control and Prevention (CDC) biomonitoring data from the most recent NHANES. According to the CDC, the median Cd urine concentration for the total US population is 0.13 µg/g creatinine, which is associated with a modeled daily Cd exposure in women of about 0.07 µg/kg-day. We modeled Cd concentrations in renal cortex and creatinine-adjusted urine

associated with the US FDA TRV of 0.21-0.36 µg/kg-day, EFSA TWI of 2.5 µg/kg-week, and US EPA RfD of 1 µg/kg-day starting at birth to age 50-70 years, and compared the modeled Cd concentrations in renal cortex and creatinine-adjusted urine with those associated with the hypothetical case studies.

Results: In the first case study, the daily Cd dose associated with consumption of the green vegetable-based smoothie was about 1.08 µg/kg-day (including background exposure). Based on the specified exposure assumptions, the pattern of Cd consumption resulted in a modeled urine concentration of 0.16 µg/g creatinine at age 30 years and 0.21-0.28 µg/g creatinine at age 50-70 years. Further, the pattern of Cd consumption resulted in a modeled renal cortex concentration of about 16 µg/g at age 30 years and 18 µg/g at age 50-70 years.

In the second case study, the daily Cd dose associated with consumption of nuts and seeds was about 0.47 µg/kg-day (including background exposure). Based on the specified exposure assumptions, the pattern of Cd consumption resulted in a modeled creatinine-adjusted urine concentration of 0.058 µg/g at age 26 years and 0.13-0.22 µg/g at age 50-70 years. Further, the pattern of Cd consumption resulted in a modeled renal cortex concentration of about 5.3 µg/g at age 26 years and 10-12 µg/g at age 50-70 years.

The modeled kidney cortex and creatinine-adjusted Cd concentrations resulting from Cd exposure as specified in the two case studies were generally lower than those associated with daily intake of Cd at the US FDA TRV, EFSA TWI, and US EPA RfD. For example, under the lowest Cd exposure limit examined (*i.e.*, 0.21 µg/kg-day), modeled kidney cortex Cd concentrations were about 18 µg/g at age 30 years and 30-36 µg/g at age 50-70 years, while modeled urine Cd concentrations were about 0.16 µg/g creatinine at age 30 years and 0.39-0.64 µg/g creatinine at age 50-70 years.

Conclusions: An adapted version of the KN model can be used to simulate realistic Cd exposures that vary in frequency, duration, and magnitude over the lifespan. The results from these two case studies demonstrate how Cd PBPK modeling can help determine whether a Cd intake exceeds biomarkers of Cd exposure (*e.g.*, creatinine-adjusted urine and kidney cortex) associated with a regulatory limit, particularly in situations involving intermittent or variable Cd exposure where a single exposure is greater than the regulatory limit. Using our exposure assumptions, we showed that in two hypothetical cases of intermittent or variable Cd exposures in which a single exposure was greater than a regulatory limit, such exposures did not exceed Cd biomarkers associated with the regulatory limit. This analysis demonstrates the utility of Cd PBPK modeling in the context of regulatory compliance and human health risk assessment.