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Evaluating the Potential for Reproductive Effects from Intermittent Lead Exposures Using Blood Lead Modeling Under Proposition 65

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Proposition 65 requires that a warning be provided on products containing a chemical listed by California as a reproductive toxicant, unless the exposure for a typical consumer is determined to be less than a "safe harbor" level. The safe harbor level for lead (Pb), or maximum allowable dose level (MADL), is 0.5 microgram (µg) per day, which was derived from the Occupational Safety and Health Administration's permissible exposure limit (PEL) of 50 µg per cubic meter of air. In the case of intermittent exposures where a single exposure is greater than 0.5 µg, compliance with the MADL under Proposition 65 requires additional analysis to determine if such exposures would exceed the blood lead level (BLL) associated with the MADL. Such an analysis may be performed through the use of the All-Ages Lead Model (AALM), a physiologically-based pharmacokinetic model, to estimate BLLs associated with consumption of Pb-containing products relative to the MADL. We applied this approach to two case studies to determine whether exposure to Pb in food products would present a risk for reproductive effects later in life. We first reviewed studies conducted in animals and humans to determine an estimated Pb exposure threshold for reproductive effects and to evaluate the reproductive toxicity criterion used as the basis of the MADL. We evaluated studies with respect to their study design, consistency, coherence, and other factors. Then, to investigate the potential impacts of various intermittent Pb exposures on BLLs, we used the AALM in two hypothetical case studies. In the first case study, we modeled intermittent Pb exposures from snack foods in children aged 2-5 years. We assumed hypothetical concentrations of 1.0 µg of Pb per serving and a consumption frequency of one serving every 2-3 days. In the second case study, we modeled the impact of Pb exposures from one year of intermittent chocolate consumption in adults aged 25 years. We assumed a high-end concentration of 1.3 µg of Pb per ounce of chocolate, based on a 2023 *Consumer Reports* publication on the content of Pb and cadmium in dark chocolate, and a consumption of 1-2 ounces once every 5-7 days. We modeled BLLs associated with daily intake at the MADL of 0.5 µg/day starting at birth, and compared the BLLs at age 25 years (relevant to reproductive endpoints) from both scenarios to the MADL at age 25 years. As summarized by US EPA and ATSDR, the epidemiology and toxicology evidence of female reproductive effects (*e.g.*, hormone levels, fertility, spontaneous abortion, preterm birth, age of menopause onset) was generally limited and inconsistent. The human and animal studies of male reproductive effects generally indicated a threshold BLL of 35-45 µg/dL. For the case studies, consumption of Pb from the food products based on the specified assumptions resulted in a modeled BLL of about 0.001 µg/dL at age 25 years from early childhood consumption of snack foods, and modeled BLLs ranging from 0.02-0.03 µg/dL from intermittent chocolate consumption at age 25 years. These estimated BLLs were well below the BLL of 0.045 µg/dL at age 25 years associated with lifetime Pb intake at the MADL level (*i.e.*, 0.5 µg/day)._Based on our review of the toxicology and epidemiology literature, the MADL of 0.5 µg/day remains protective of male and female reproductive effects. The results from these two case studies demonstrate how blood Pb modeling with the AALM can help determine whether a Pb intake is likely to exceed the BLL associated with the MADL in situations involving intermittent exposure where a single exposure is greater than 0.5 µg. Using our assumptions of food frequency, intake, and Pb concentration, we showed that in these two specific cases of intermittent exposures where a single exposure was greater than 0.5 µg, such exposures did not exceed the BLL associated with the MADL. This analysis demonstrates the utility of blood Pb modeling in the context of regulatory compliance under California's Proposition 65.