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Considerations for Deriving a Safe Intake of Propylene Glycol

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The use of propylene glycol (PG) in food and other applications is widespread, and some estimates of dietary exposure to PG approach or exceed the current acceptable daily intake (ADI). An ADI is defined as an amount of an additive in food or drinking water that can be safely consumed daily over a lifetime without adverse health effects. In 1974, JECFA established an ADI of up to 25 mg/kg bw-day, which was reaffirmed by EFSA in 2018. The ADI of 25 mg PG/kg bw-day is based on a no observed adverse effect level (NOAEL) of 2,500 mg PG/kg bw-day from a 2-year dietary study in rats. The development of the ADI also considered a study in dogs that reported non-adverse hematological changes indicative of a hemolytic effect at 5,000 mg PG/kg bw-day. An uncertainty factor of 100 (*i.e.*, 10 for interspecies differences, 10 for intraspecies variability) was applied. However, the available toxicology studies and human data indicate that reliable quantitative information on toxicokinetics and/or a plausible mode of action (MoA) could support reducing the total uncertainty factor. We conducted literature searches for PG toxicology information, including toxicokinetic and toxicodynamic studies in humans, animals, and *in vitro*, as well as human clinical studies. PubMed and Scopus were utilized to identify clinical and laboratory studies published through October 2022. For animal data, we focused our search on studies of oral exposure. To identify existing comprehensive assessments, we utilized ToxPlanet, an online database that compiles all safety assessment documents for chemicals from national and international regulatory and research agencies. In particular, our analysis focused on intra- and interspecies differences in toxicodynamics and toxicokinetics, and whether the data supported the use of chemical-specific adjustment factors (CSAFs) for these areas of uncertainties. The available toxicology studies and human data indicate a plausible MoA involving an increase in serum PG concentrations after metabolic saturation, leading to serum hyperosmolarity and hemolytic changes. The human clinical data are not appropriate to serve as a point of departure (POD) due to numerous limitations, including pre-existing conditions, co-exposures, and short-term, intravenous dosing. The available data, however, indicate that the toxicodynamics of the hemolytic response is expected to be similar in humans compared to relevant test species (*i.e.*, rats and dogs). Thus, the data support a CSAF of 1 for interspecies toxicodynamic differences, reducing the total uncertainty factor from 100 to 40. Information on toxicokinetics was not sufficient to derive a quantitative CSAF for this area of uncertainty. Based on scientific support for a plausible MoA, we derived a revised ADI for PG of 62.5 mg PG/kg bw-day. Based on the species similarities in toxicodynamic response for this critical effect, the data support increasing the ADI from 25 to 62.5 mg PG/kg bw-day. The human clinical data provide evidence to support that this health-based toxicity value is protective for both children and adults. The reduction of the toxicodynamic portion of the interspecies adjustment factor to 1.0 is consistent with agency assessments, in which an uncertainty factor of 1.0 was applied when a plausible MoA exists and the toxicological data indicate similar potency across test species.