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Short SAB Consultation on Updating EPA Guidelines for Carcinogen and Non-Cancer Risk Assessment.

Comments from Barbara Morrissey, liaison member, Chair of Children's Health Protection Advisory Committee

I support the Agency effort to update its risk assessment guidance for cancer and non-cancer endpoints. Given the short turnaround of the consult (3 weeks) and my role as liaison member from the CHPAC, I focused my comments on a few areas of importance to children's health. First, a few general comments.

It is critical that the Agency **allows for robust scientific and public review of updates** to these critical guidance documents. EPA should allow sufficient time and follow an open and transparent process. The Agency should seek a full SAB review of proposed revisions to ensure changes reflect the best available science. The process must also respect the large community of risk assessment practitioners in state and local governments and in business that follow EPA guidance. EPA should engage this wider community of practice through informal webinars early in the process and allow for debate and comment on drafts. Sufficient time must be allocated for public and practitioner review and comment.

Consider combining cancer and non-cancer endpoints into a single risk assessment guidance document. Our growing understanding of the many biological mechanisms that contribute to cancer development has made clear that regulatory emphasis on complete carcinogens (single chemicals that produce cancer when administered in laboratory animals) and on mutagenic and genotoxic mechanisms of action is overly narrow. Cancer assessment should consider other contributing mechanisms such as: oxidative stress, inflammation, endocrine disruption, altered epigenetic regulation of gene expression, and suppression of immune defenses. A number of these mechanisms contributing to cancer development also contribute to non-cancer endpoints such as organ damage, immune suppression, metabolic dysregulation and obesity, and neurodevelopmental disorders. Combining cancer and non-cancer endpoints in a single guidance document would allow fuller integration of mechanistic evidence across endpoints.

Q1. Areas of existing guidance for cancer risk assessment that need updating/revision

Early life exposure to carcinogens. Exposure to a carcinogen early in life may result in a greater lifetime risk of cancer for several reasons: childhood exposure increases the number of years that long-latency cancers can progress and present clinically, exposure to agents that act on DNA or the epigenome will impact a larger number of cell divisions and a larger population of somatic cells, and developmental of the central nervous system and many organs is under hormonal control and thus more sensitive to hormonal carcinogens during critical developmental periods. Early life stages may also be at higher risk because of differences in intestinal absorption, excretion, distribution, and expression of enzyme systems that activate or detoxify carcinogens.

Accordingly, EPA should reconsider **age-dependent adjustment factors for early life exposure to carcinogens for non- mutagenic modes of action** (in EPA 2005). A number of examples of early life susceptibility to non-mutagenic carcinogens have been described (OEHHA 2009). For example, maternal use of the estrogenic compound diethylstilbestrol (DES) during pregnancy resulted in a variety of morphological changes to the genital tract and a 40-fold increase in the risk of vaginal or cervical clear-

cell adenocarcinoma in daughters (Reeda and Fenton 2013). EPA should revisit it's guidance for early life exposure to carcinogens and develop guidance for a default approach that includes carcinogens with non-mutagenic or unknown modes of action. The Agency may want to consider the age-dependent adjustment factors and default approach adopted by California EPA, Office of Environmental Health Hazard Assessment, Air Toxicology and Epidemiology Branch (OEHHA 2009).

Adopting age-dependent defaults into risk assessment guidelines is also likely to incentivize collection of data to fill important data gaps on early life exposures. As EPA recognized in its 2005 guidelines, cancer potency in laboratory animals is typically derived from experiments in adult-aged animals with exposure beginning after puberty. Occupational studies are similarly focused on adult exposures. Reliance on adult datasets potentially underestimates cancer risk for lifetime exposures that start in early life.

Q1. Areas of existing guidance for non-cancer risk assessment that need updating/revision

Update Life-stage assessment tools and guidance for non-cancer endpoints. A lifestage approach incorporates key age-related characteristics into risk assessment including children's unique and evolving anatomy, physiology, toxicokinetics, diet, environment, and behaviors. The unique characteristics of key developmental stages are important to address because these characteristics can influence exposure estimates, levels of concern, and the dose-response relationship used in a risk assessment. Because impacts to a child's health carry forward into adulthood, protecting early life stages benefits health across the entire population. I encourage the Agency to update and integrate their guidance on early lifestages. Also update information on other lifestages marked by pronounced growth and development such as puberty and pregnancy (see Varshavsky et al. 2019).

Consider extending guidance for age-appropriate safety factors for children for non-cancer endpoints such as the framework used under the Food Quality Protection Act (FQPA). While a full ten-fold additional margin may not be needed in all cases, an age-specific safety factor should be the "default" approach where uncertainties and data gaps in children's exposure or vulnerabilities exist.

Q2. New topic areas for cancer and non-cancer risk assessment.

Add guidance for recommended use of high through-put testing results. Guidance should be updated to include integration of new streams of evidence from Toxcast and Tox21 high-throughput testing. EPA should follow recommendations of the National Research Council in 2007 (NRC, 2007) and the National Academies of Sciences, Engineering, and Medicine in 2017 to incorporate, where appropriate, new technologies and approaches to screening for toxicity. These include in vitro, in silico, non-mammalian models such as zebrafish, and genomics and other "-omics" technologies. These can enhance traditional screening approaches such as structural alerts and "read-across" from chemical analogs. These new tools also have potential to broaden understanding about mode of action and human relevance of toxicity observed in laboratory animals.

Q3 iii Highest priority to update

The **Guidelines for Developmental Toxicity Risk Assessment** (EPA/600/FR-91/001, Dec 1991) is nearly 30 years old. It should be updated to reflect the considerable advancement in our understanding and assessment of developmental toxicity including neurobehavioral assessment and the

importance of evaluating sex-linked outcomes. A number of published reviews may be helpful (Felter et al. 2015,Makris et al. 2011, Knudsen et al. 2011, Foster 2017).

Additional suggestions for ongoing Agency work to update Human Health Exposure Assessment guidance.

Additional work is needed to guide assessment of **toddler exposure to indoor dust.** This is an area in need of cumulative risk assessment as household and daycare dust can accumulate multiple contaminants (Mitro et al. 2016, Bradman et al. 2012). In addition, EPA's current guidance uses soil ingestion rates as a proxy for house dust ingestion. The rates of intake may in fact be quite different. Children spend much more time indoors than outdoors. Their inadvertent ingestion of soil while digging and playing outside is unlikely to be similar to dust intake while crawling indoors and engaging in hand-to-mouth behavior. Children's natural behaviors may cause more dust to become inhaled or ingested (e.g., jumping on the couch or making forts with cushions). Direct mouthing of furniture, other textiles, electronics, and other consumer products may lead to intake of dust with higher concentrations of contaminants than on floor or settled indoor dust. For example, surface wipes of dust on electronics was found to have higher levels of flame retardants (Brandsma et al. 2014, Yang et al. 2019).

Infant exposure modelling. Enhanced guidance and methods are needed to estimate aggregate exposure to infants from transplacental and lacational pathways. Neither the 2006 EPA lifestages framework nor the 2016 EPA draft Guidelines for Human Exposure Assessment Risk Assessment adequately address the challenge of estimating transplacental or lactational transfer of contaminants to breast-fed infants. Recent progress should be incorporated into guidance (e.g., Kapraun et al 2019). This is especially critical for biopersistent chemicals and other chemicals that are widely detected in maternal serum, cord blood and/or breastmilk (OEHHA 2012). If a chemical is expected/known to be present in cord blood or expected/known to be present in breastmilk, these pathways should be explicitly included in Agency estimates of infant aggregate exposure. Estimation tools based on the known partitioning and other properties of the chemical would be helpful as would guidance for default assumptions to address data gaps in this area. A recent illustration of the importance of these exposure pathways to infant exposure is a model developed by Minnesota Department of Health for PFOA exposure (Goeden et al. 2019)

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