Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency

Developmental and Reproductive Toxicant Identification Committee (DARTIC) Meeting
October 18, 2022

Potential Discussion Questions for the Agenda Item: Use of Zebrafish Data in Developmental and Reproductive Toxicity (DART) Health Hazard Assessment

These questions are provided to suggest possible areas of discussion by the DARTIC related to the use of DART data generated in zebrafish for human health hazard assessment; they are not meant to limit the areas of discussion. The DARTIC may choose to use these or other questions in discussion with the invited speakers.

Part I. Zebrafish biology and suitability for toxicity screening

In setting up an experiment using zebrafish, how many adult fish of each sex would you typically start with as a source of ova and sperm?

- Is potential parental contribution considered in study design or data analysis? For example:
    - Is potential parental contribution considered in test-group assignment, or are all embryos considered equivalent prior to distribution among test groups?
    - In analyzing results for offspring, what are statistical considerations, if any, for parental identity (as is done for rodents or lagomorphs)?
- Studies included in OEHHA's recent hazard identification documents provide examples of similar biological systems or pathways being affected in both zebrafish and mammals by a given chemical, but with different directionality of response or with a different downstream outcome. How do we consider the differences as well as similarities between species in evaluations?

Part II. Beyond screening: Zebrafish as a model for developmental mechanisms at the cellular and molecular levels

- In the absence of mammalian and mechanistic data on the effects of chemicals such as domoic acid or BPA, could zebrafish screening studies (for general and/or neurological effects) alone have indicated the need for additional studies to fully characterize toxicity and mechanisms of action?

- To design appropriate zebrafish studies, what other types of evidence could help define appropriate lines of experimentation? For example, both domoic acid and BPA have documented adverse effects on wildlife that correspond to those observed in humans and test animals, and could suggest detailed laboratory examination of adverse effects and mechanisms.
- Should zebrafish data generated for the purpose of acute fish toxicity testing, conducted for environmental hazard assessment, be more generally incorporated in consideration of likely adverse harm to humans?

Part III. Use of zebrafish data in DART health hazard assessment

- Given that biological differences between zebrafish and mammals (e.g., lack of internal fertilization and pregnancy), what are the issues that should be discussed in considering zebrafish data in human hazard assessment?
- How might considerations of life stage and windows of susceptibility be used in evaluating data from zebrafish?
- What are some of the ways route of exposure and toxicokinetics could be considered in interpreting the results from zebrafish assays (e.g., the lack of a placenta, or exposure from maternal circulation or metabolism) in the context of human exposures?
- Many applications of the zebrafish model focus on upstream essential processes in reproduction and development, rather than final, apical outcomes.
    - How would you suggest this be considered in addressing coherence among data streams from human, animal, and other experimental models?
- Given the diversity of zebrafish study types and outcomes measured, how might these studies be best evaluated for study quality for the purposes of hazard/risk assessment?