Use of the Zebrafish Developmental Screen and Estimation of Internal Concentration to Assess Toxicity

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Traditional toxicology tests required by U.S. regulatory agencies are expensive and time-consuming especially in light of the many chemicals that require such testing. An alternative vertebrate model for developmental toxicity is the zebrafish embryo (Danio rerio). In this study, 309 environmental chemicals were screened, mainly pesticides and antimicrobials from the ToxCast™ Phase I chemical library. Embryos were immersed in media containing chemical concentrations from 0.001 to 80 μM and the half-maximal activity concentration (AC₅₀) for toxicity (lethality, non-hatching, or dysmorphology) determined. To extrapolate to mammalian toxicity, the demonstrated relationship between lipophilicity (LogP) and bioconcentration was used to estimate a body burden associated with developmental toxicity (EC₅₀). Toxicity potency rankings derived from AC₅₀ and EC₅₀ calculations were compared. Some chemicals (for example, thiram, rotenone, butafenacil) were highly toxic regardless of how toxicity was expressed. In contrast, assessing potency by EC₅₀ substantially affected the ranking for a number of chemicals. Daminozide had a high AC₅₀ (66.5 μM) but due to its low LogP, limited uptake was predicted with a very low EC₅₀ (0.04 μM). In contrast, the pyrethroids (n=12) were among the most toxic chemicals with a mean AC₅₀ of 4.01 μM. Due to their high LogP (mean = 5.78), however, the mean EC₅₀ for the class was estimated at 843.25 μM. To further assess extrapolation to mammalian systems, oral equivalent doses from reverse toxicokinetic studies were used to correlate in vitro concentrations with potential in vivo effects. The ability of the zebrafish developmental screen to predict mammalian toxicity was then assessed by examining the correlation between chemical potencies based on EC₅₀, chemical class, and known in vivo effects.

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