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 (AC_{50}) 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 (EC_{50}). Toxicity potency rankings derived from AC_{50} and EC_{50} calculations were compared. Some chemicals (for example, thiram, rotenone, butafenacil) were highly toxic regardless of how toxicity was expressed. In contrast, assessing potency by EC_{50} substantially affected the ranking for a number of chemicals. Daminozide had a high AC_{50} (66.5 μM) but due to its low LogP, limited uptake was predicted with a very low EC_{50} (0.04 μM). In contrast, the pyrethroids (n=12) were among the most toxic chemicals with a mean AC_{50} of 4.01 μM. Due to their high LogP (mean = 5.78), however, the mean EC_{50} 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 EC_{50}, chemical class, and known *in vivo* effects.

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