

Comparison of Developmental Toxicity of Methylmercury In Vitro and In Vivo: Potential Value of the In Vitro-Derived Data for Dose-Response Assessment

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The use of in vitro data in human health risk assessment holds great promise for increasing the rate at which we gain information about potentially hazardous chemicals but it also involves considerable uncertainty. While in vitro studies can provide qualitative (i.e., mechanistic) data on chemical toxicity, the dose-response data derived using a cell culture system are difficult to relate quantitatively to the in vivo situation. Comparisons of in vivo-in vitro toxicological potency are rare in the published literature. In studying the developmental toxicity of methylmercury (MeHg) in the developing rat brain, we have acquired considerable in vitro and in vivo data. In vitro data were collected using rat midbrain cell cultures while in vivo data were collected using the same cell type and same gestational time points. The in vitro data indicate that MeHg inhibits cell cycle progression at concentrations of 1-2 μM (4 to 7 $\mu\text{g Hg/g}$ in the cells). A similar brain cell concentration is required for cell cycle inhibition in our in vivo studies. These results are also consistent with the study of Fuyuta et al (1978) which examined MeHg induced malformations. We have used a toxicokinetic model for MeHg to convert Fuyuta's maternal doses to estimated embryonic brain concentrations. The threshold for effects in the Fuyuta study appears to be within the range of 5 to 9 $\mu\text{g Hg/g}$ brain, consistent with our own findings. Taken together, these data suggest that a carefully chosen in vitro system can provide dose-response data that are quantitatively similar to those observed in vivo. Such an approach provides a framework by which in vitro data can be considered in the process of dose-response assessment.