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Simulating Limb Formation in the U.S. EPA Virtual Embryo - Risk Assessment Project.

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The U.S. EPA's Virtual Embryo project (v-Embryo™) is a computer model simulation of morphogenesis that integrates cell and molecular level data from mechanistic and in vitro assays with knowledge about normal development processes to assess in silico the effects of chemicals on development. One of the initial modules is early limb-bud outgrowth, a well-studied developmental process with signaling networks broadly representative of a number of other subsystems. A previous, relatively simple model developed by Glazier and co-workers using the CC3D modeling environment simulated emergence of the paddle shape of the growing chick limb bud based on diffusion of primary morphogens (FGF8, FGF4) from the apical ectodermal ridge (AER) into the underlying mesenchyme, and the resulting effect on differential growth and division [Poplawski et al., 2007]. The present study has expanded this computational model to represent more complex morphogen interactions and cell behaviors during early limb-bud outgrowth, including apoptosis and multiple signaling pathways (e.g., SHH, FGF10, BMP, Gli3, dHAND). In addition to representation of biological rules for cellular signals and responses, the expanded model can assess the potential impact of chemical perturbation of target pathways on system-level behaviors such as the AER-mesenchymal interactions and cell growth. This model is being used to integrate high throughput screening (HTS) and high content screening (HCS) assay data on the chemical disruption of key pathways in order to predict complex cellular changes in the context of realistic in vivo dynamics leading to dysmorphogenesis. [This abstract does not necessarily reflect EPA policy.]

KeyWords: virtual embryo, biological models, developmental toxicity, high throughput assays, morphogenesis, embryotoxicity, in silico,

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