Developing predictions of in vivo developmental toxicity of ToxCast chemicals using mouse embryonic stem cells

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Developing predictive models of developmental toxicity is a focus of the virtual embryo project. Our experimental model uses a modified mouse embryonic stem cell (mESC) assay to assess chemical-induced cytotoxicity and altered differentiation. Two time points and differentiation outcomes are currently evaluated: cardiomyogenesis (MYH6/7) and gastrulation (GSC). ToxCast Phase I (TCP-I) compounds were evaluated using both differentiation time points, whereas, ToxCast Phase II (TCP-II) compounds were evaluated using the GSC biomarker alone. NCCT provided chemical stock solutions with 20μM being the highest concentration evaluated due to DMSO solvent toxicity. Forty-six percent (118/257) of TCP-I chemicals affected stem cells at the cardiomyogenic stage. Twenty-eight percent (302/1078) of TCP-I and II compounds affected stem cells at gastrulation. ToxPi tools were used to rank chemical potency. A subset of TCP-I chemicals, were identified as teratogen in rats or rabbits (ToxRefDB); 47% (80/170) of teratogenic chemicals produced effects in mESCs. Of the 118 TCP-1 chemicals that produced effects in mESCs, 80 (68%) are teratogens. Using cytotoxicity burst data, compounds were further classified as specific mESC toxicants if they produced effects at concentrations < cytotoxicity burst. By combining gastrulation-stage cytotoxicity and cardiomyocyte differentiation data, 87% (26/30) of the most potent chemicals classified as specific mESC toxicants were teratogens. This association decreased to 73% as the potency of selective mESC toxicants decreased. Chandler et al., (PLoS One, 2011) developed a putative redox disrupting compound (pRDC) ToxPi based on analysis of TCP-I chemicals that affect cardiomyogenesis. Using this predictive model to evaluate TCP-II compounds, 71% (71/100) of the highest potency pRDCs and 2% (6/323) with no pRDC activity affected mESC at gastrulation. We have used mESCs as a model system to evaluate effects of ToxCast compounds and have shown an association between specific mESC toxicants and teratogens in vivo. Subsequent analysis will evaluate the relationship between constituents of the pRDC ToxPi and chemicals that are teratogenic in vivo. This abstract does not represent US EPA Policy.