Late-Breaking ABSTRACT
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Computational and Organotypic Modeling of Microcephaly. Knudsen TB[1], Baker NC[2], Faustman EM[3], Murphy WL[4] and Daly W[4]. [1]USEPA, Research Triangle Park, NC; [2]Lockheed-Martin, RTP NC; [3]University of Washington, Seattle WA; [4]University of Wisconsin, Madison WI.

Microcephaly is associated with reduced cortical surface area and ventricular dilations. Many genetic and environmental factors precipitate this malformation, including prenatal alcohol exposure and maternal Zika infection. This complexity motivates the engineering of computational and experimental models to probe the underlying molecular targets, cellular consequences, and biological processes. We describe an Adverse Outcome Pathway (AOP) framework for microcephaly derived from literature on all gene-, chemical-, or viral- effects and brain development. Overlap with NTDs is likely, although the AOP connections identified here focused on microcephaly as the adverse outcome. A query of the Mammalian Phenotype Browser database for 'microcephaly' (MP:0000433) returned 85 gene associations; several function in microtubule assembly and centrosome cycle regulated by (microcephalin, *MCPH1*), a gene for primary microcephaly in humans. The developing ventricular zone is the likely target. In this zone, neuroprogenitor cells (NPCs) self-replicate during the 1st trimester setting brain size, followed by neural differentiation of the neocortex. Recent studies with human NPCs confirmed infectivity with Zika virions invoking critical cell loss (apoptosis) of precursor NPCs; similar findings have been shown with fetal alcohol or methylmercury exposure in rodent studies, leading to mathematical models of NPC dynamics in size determination of the ventricular zone. A key event in this determination is the plane of mitotic divisions oriented by the centriole. NPCs divide symmetrically before switching to asymmetric (neurogenic) divisions by early 2nd trimester, and a premature switching (or excessive apoptosis) results in a critical reduction in precursor population NPC pool size at the onset of neurogenesis. The putative AOP has broad applicability to the pathogenesis of microcephaly induced by genetic or environmental factors. Search of EPA's ToxRefDB database returned 75 chemicals with relevant, nonsystemic developmental effects on brain development: 40 (51%) invoke reductions in brain size or cellular mass, 39 (52%) invoke dilated ventricles or hydrocephaly, and only 5 (6.3%) invoke both defects. Brain mimicks developed from hNPCs + iPSC-derived endothelia and microglia provide experimental models that can be used to test the key events and their relationships in the proposed AOP for microcephaly in a human system. [This abstract does not reflect US EPA policy].