Profiling Developmental Toxicity of 387 Environmental Chemicals using EPA's Toxicity Reference Database (ToxRefDB).

Thomas B. Knudsen[1], Matthew T. Martin[1], Robert J. Kavlock[1], Richard S. Judson[1], David J. Dix[1] and Amar V. Singh[2]

[1] National Center for Computational Toxicology (NCCT), Office of Research and Development, U.S. Environmental Protection Agency, and [2] Lockheed Martin, contractor to NCCT, Research Triangle Park, NC

EPA's Toxicity Reference Databases (ToxRefDB) was developed by the National Center for Computational Toxicology in partnership with EPA's Office of Pesticide Programs, to store data derived from in vivo animal toxicity studies [www.epa.gov/ncct/toxrefdb/]. The initial build of ToxRefDB includes source data from guideline prenatal studies on 387 chemicals, mostly pesticides, in rat and rabbit. ToxRefDB data were entered by target-description fields and lowest effect levels (mLEL, maternal parameters and dLEL, developmental parameters). Of 988 standardized endpoints, 293 (29.7%) were recorded across 751 studies. The distribution of developmental effects was analyzed by target organ system (19 aggregated effects by system), chemical count (387 total, 350 in rat and 317 in rabbit), and test species. For 283 chemicals with data in both species, 53 chemicals (18.7%) had critical effects on development that were specific (no maternal toxicity) or sensitive (dLEL < mLEL) to exposure in either species. Rat was the more sensitive species to developmental effects on an administered dose basis. The species differences may reflect biological factors, with complications form study design differences or examination techniques of the fetuses. The primary expressions of developmental toxicity were fetal weight reduction and skeletal defects (rat > rabbit), pregnancy/fetal losses (rabbit > rat), urogenital defects (rat > rabbit), and CNS defects (rabbit > rat). ToxRefDB is a novel data model that provides a structured format for relational assessment of source data from guideline (in vivo) prenatal developmental toxicity studies. It can be applied to large-scale profiling and predictive modeling of developmental toxicity for environmental chemicals. [This work has been reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy].