A comprehensive data survey of the relative value of rat versus rabbit developmental toxicity data in the risk assessment for pharmaceuticals

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The impact of testing in a second species for embryofetal developmental toxicity was discussed during a 2010 ICH Workshop in Tallinn, Estonia. It was proposed to review the frequency with which the results from studies in the rat versus rabbit have driven the lowest observed adverse effects level (LOAEL) and exposure margins in risk assessment for pharmaceuticals. The goal of this retrospective analysis is to better understand the implications of either postponing the testing in one of the two required species or waiving the need for one of the two embryofetal toxicity testing in specific circumstances. The ILSI Health and Environmental Sciences Institute’s Developmental and Reproductive Toxicology Technical Committee (HESIDART) organized a cross-industry data survey in which anonymized embryofetal development and toxicokinetic study data from marketed and unmarketed drugs were submitted for analysis. Additionally, compounds for which rat and rabbit data were derived from the files of the Medicines Evaluation Board. The two sources have accumulated data from more than 800 studies spanning more than 400 compounds which have been entered in US EPA’s ToxRefDB database. Fetal and maternal effect levels are being determined to address species sensitivity based on dose and internal exposure. In addition, the nature and severity of embryofetal findings in the rat and rabbit is being reviewed to establish which differences of embryofetal effects between species are driving risk assessment. Results will be discussed in the presentation. This comprehensive data survey will support integrated testing strategy for developmental toxicity testing of pharmaceuticals.