

Figure: Cumulative risk ratios of congenital malformations between valproate and non-valproate groups for combined major congenital malformations;

reproduced with permission: Tanoshima M, Kobayashi T, Tanoshima R, *et al.* Risks of congenital malformations in offspring exposed to valproic acid in utero: a systematic review and cumulative meta-analysis. *Clin Pharmacol Ther* 2015; 98: 417–41.



← 1983: Koch's study shows no significant effect of valproate on congenital malformations

← 1990: The cumulative risk ratio reaches statistical significance after eight studies have been combined

← 2004: The cumulative risk ratio shows double the risk (P<0.0001)

← 2005: The lower bound of the 95% confidence interval shows that the risk is more than doubled

← 2014: The latest estimate in more than 20,000 individuals confirms that the risk is more than doubled