CORRECTING FOR MODEL UNCERTAINTY WHEN USING FRACTIONAL POLYNOMIALS TO ESTIMATE A SAFE LEVEL OF EXPOSURE

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An important issue in developmental toxicity is the estimation of a safe level of exposure. The benchmark dose (BMD) is defined as the dose corresponding to a small increase in risk over background, and is estimated from the estimated dose-response model. Although the BMD has attractive features, the reliability of the BMD is often questioned since this low-dose extrapolation is highly dependent on the model choice. It is clear that a flexible model should be used when estimating the dose-response curve. Fractional polynomials (Royston and Altman, 1994), basically being a set of (generalized) linear models, are a nice alternative approach to classical polynomials, providing the necessary flexibility. Typically, one selects the best fitting fractional polynomial and ignores the model-selection uncertainty in the inference. However, simulation studies show the large model uncertainty coming from this model selection procedure. We show that model averaging using the set of fractional polynomials reduces bias and has better precision in estimating the BMD, compared to an estimator from the selected best model. To estimate a lower limit of this BMD, an approximation of the variance of the model-averaged estimator, as proposed by Burnham and Anderson (2002), can be used. However, this is a conservative method, often resulting in unrealistically low safe doses. Therefore, a bootstrap based method to more accurately estimate the variance of the model averaged parameter is proposed.