

Joint Modeling of Multiple Developmental Toxicity Endpoints: a Causal Inference Approach

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Abstract:

In a typical Segment II developmental toxicity study, pregnant dams are randomized into groups for treatment with a toxin during organogenesis, the major period of organ development in the growing fetuses. The pregnant dams are sacrificed near term and the fetuses are examined for a variety of developmental endpoints including signs of malformations and fetal body weight. To assess the risk of the toxin on fetal development, it is of great interest to estimate the effect of the toxin on the various developmental endpoints jointly.

Current approaches to analyzing data from these Segment II studies take the observed outcome differences in live fetuses between dose groups as the effect of toxin. The estimates from these practices usually lack causal interpretations for two reasons. First, fetuses that survive to birth at a high dose level of the toxin might be more robust on average than those at a low dose level. As such, the set of fetuses that would survive to term in a high dose group is likely not identical to the set of those who would survive to birth under a low dose group. Second, litter size (the number of fetuses that develop and survive until birth) plays a mediating role in data from Segment II studies, since it is affected by the toxin on one hand and affects the developmental endpoints on the other. As a result, failing to control litter size likely produces bias.

In this paper, we use the potential outcome framework to estimate the causal effect of a toxic agent on multiple developmental endpoints. As in a recently finished paper of ours on developmental toxicity studies with a single continuous outcome (Elliott et al., 2004), we define the causal toxic effect as the difference between what the outcomes would have been for a fetus had the dam in which the fetus develops been exposed to dose level $Z = z$ rather than dose level $Z = z^*$. In particular, we employ the Frangakis and Rubin (2002) principal stratification approach and construct principal strata that are a function of survival status of the fetuses. We propose various estimands of the effect and consider their identifications and interpretations. We also accommodate correlations within a dam of fetuses for both the outcomes and principal strata by using random effects. Bayesian procedures are developed to estimate the model and to make inference.

We illustrate the proposed methodology through application to data from a developmental toxicity study of ethylene glycol in mice conducted by the National Toxicology Program. In particular, we conduct causal inference on the toxic effect of ethylene glycol on fetal malformation (a binary variable) and fetal body weight (a continuous variable) jointly and discuss the results in relation to previous analyses of these data.

References

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