

Abstract: Thresholds and Their Definition

Characterizing and interpreting the dose response relationship is perhaps the most challenging task in health risk assessment. Toxicologists understand that “the dose makes the poison”, but the types of effects under consideration and the magnitude of their deviation from the “normal” range pose separate and appreciable challenges. In the context of EPA’s Reference Dose paradigm, some effects may not represent adverse changes; for other effects, some deviations, even if statistically significant, have been interpreted to not represent biologically meaningful changes. Application of benchmark dose modeling allows risk assessors to estimate doses associated with predetermined levels of response, often 10% for non-cancer effects, 5% for developmentally toxic effects and 1% for cancer. These values and traditional NOAEL or LOAEL values may be used as point of departure (POD) values for determining risk. Whether defined in animals or humans *in vivo*, the POD is the “jumping off point” from which we depart from the realm of empirical dose response data and begin to extrapolate the identified “point” to human exposure conditions that may differ relative to species, human population subgroup, exposure duration, and/or magnitude of effect. While the POD identified *in vivo* may (might, can) represent a threshold, the further that POD is extrapolated from the conditions under which it is identified, the less certain it becomes as a threshold (in fact, its name changes and its definition often acknowledges a potential range of uncertainty). The decisions surrounding what effect is selected as the critical effect, the acceptability of the study design employed to develop dose response data, the selection of the point of departure and the methods used to extrapolate the POD to the risk value each embody multiple considerations and decisions, carrying with them different levels of bias toward health conservatism – a condition which may not be fully acknowledged or appreciated. This presentation will explore aspects of risk value development focused on identifying and extrapolating the biological threshold for adversity.