Controversy on toxicological dose–response relationships and extrapolation of an incidence to low dose can be the consequence of misleading data presentation, diverging mechanistic understanding, or lack of differentiation between a continuous response variable, such as any concentration of a biomarker, and an incidence derived from a binary response (yes or no?) in individuals (dichotomous variable). In this chapter, we address respective issues and illustrate them with examples for genotoxicity, mutagenicity, and cancer incidence. The rate of any interaction of a toxicant with a biological target molecule at low dose is proportional to its concentration. Linear extrapolation is therefore a reasonable default for rates of first-line interaction in the low-dose range. In toxicity testing however, (i) we do not measure rates of interactions but concentrations of biomarkers, and (ii) we deal with a dose range that usually expands to overt toxicity. Deviation from linearity is observed with increasing dose whenever saturation, inhibition, or induction of a process involved comes into play. A nonmonotonic shape of the dose–response curve may be observed as a special case of nonlinearity, if a background measure in untreated controls is decreased at low dose but increased at high dose. A dose response can appear as a threshold if two processes that affect the background level in opposite directions cancel each other out. A mathematical threshold, where there is no effect at all up to a defined breakpoint of the dose–response "curve," cannot be advocated for any continuous response measure. We use computational modeling to characterize how competing influences that are dominant over different dose ranges combine to generate different shapes. The situation is different for an incidence of a defined effect, e.g., a diagnosis of cancer. On an individual level, the response is given by a binary "yes or no." For dose response, each individual has its own "threshold dose" to switch from "no cancer" to "cancer"; the dose–incidence "curve" represents a staircase of individual threshold doses and reflects the tolerance distribution in the examined population. Extrapolation to low dose therefore follows differences in individual susceptibility and cannot be predicted by the mode of interaction between toxicant and biological target. For complex endpoints of toxicity such as cancer, individual susceptibility is determined by numerous genetic and in-life factors, such as enzymatic activation and detoxification of endogenous and exogenous carcinogens, DNA repair, or cell cycle control. Multiplicative combination of the individual activity of these factors and

application of the central limit theorem of statistics suggests that the tolerance distribution – and with this the dose–incidence relationship – is approximated by a cumulative normal curve against log (dose). Using this model for a dose–incidence extrapolation, the cancer risk drops faster than by linear extrapolation, the more we approach dose zero. In the last section, we combine a mechanistically supported nonmonotonic dose response with individual differences for the rate of the underlying counteracting processes. Monte Carlo simulations indicate that a nonmonotonic shape of a dose response for a biomarker, determined as an average of a dose group, does not exclude a monotonic shape for some individuals. An observation of a nonmonotonicity in animals cannot be carried over by default to a dose–incidence response in a human population.