

## U-SHAPED DOSE-RESPONSE CURVES: THEIR OCCURRENCE AND IMPLICATIONS FOR RISK ASSESSMENT

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*A class of curvilinear dose-response relationships in toxicological and epidemiological studies may be roughly described by "U-shaped" curves. Such curves reflect an apparent reversal or inversion in the effect of an otherwise toxic agent at a low or intermediate region of the dose continuum. Several examples of U-shaped dose-response functions are presented to illustrate the variety of agents and end points that can follow this form. Such findings are not thought to represent a unitary phenomenon, but may be explained through numerous possible principles or mechanisms, some of which are illustrated and discussed in general terms. U-shaped dose-response curves raise important issues for toxicological and environmental health risk assessments, particularly in the identification of no-observed-effect levels and in the evaluation of multiple outcomes and the tradeoffs between potential risks and benefits of a given agent. It is especially important to avoid focusing exclusively on an apparent improvement in one end point and failing to consider other, possibly deleterious effects of the same agent.*

### INTRODUCTION

Of the various forms that dose-response (or exposure-effect) relationships may take, certain types of curvilinearities are particularly noteworthy because they describe seemingly paradoxical effects of known toxicants. We refer to U-shaped dose-response relationships, in which an

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