

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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