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

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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 apparent improvement in an endpoint occurs at low or intermediate levels of exposure to an otherwise toxic substance. As shown in Fig. 1*a* and *b*, the orientation of the U (upright or inverted) is arbitrary, for it depends merely on how the dependent variable is represented (e.g., latency vis-à-vis speed of response, hematocrit vis-à vis anemia, normal function vis-à-vis dysfunction). The essential feature is that of a relative enhancement of response by comparison to effects at control and high dose levels.

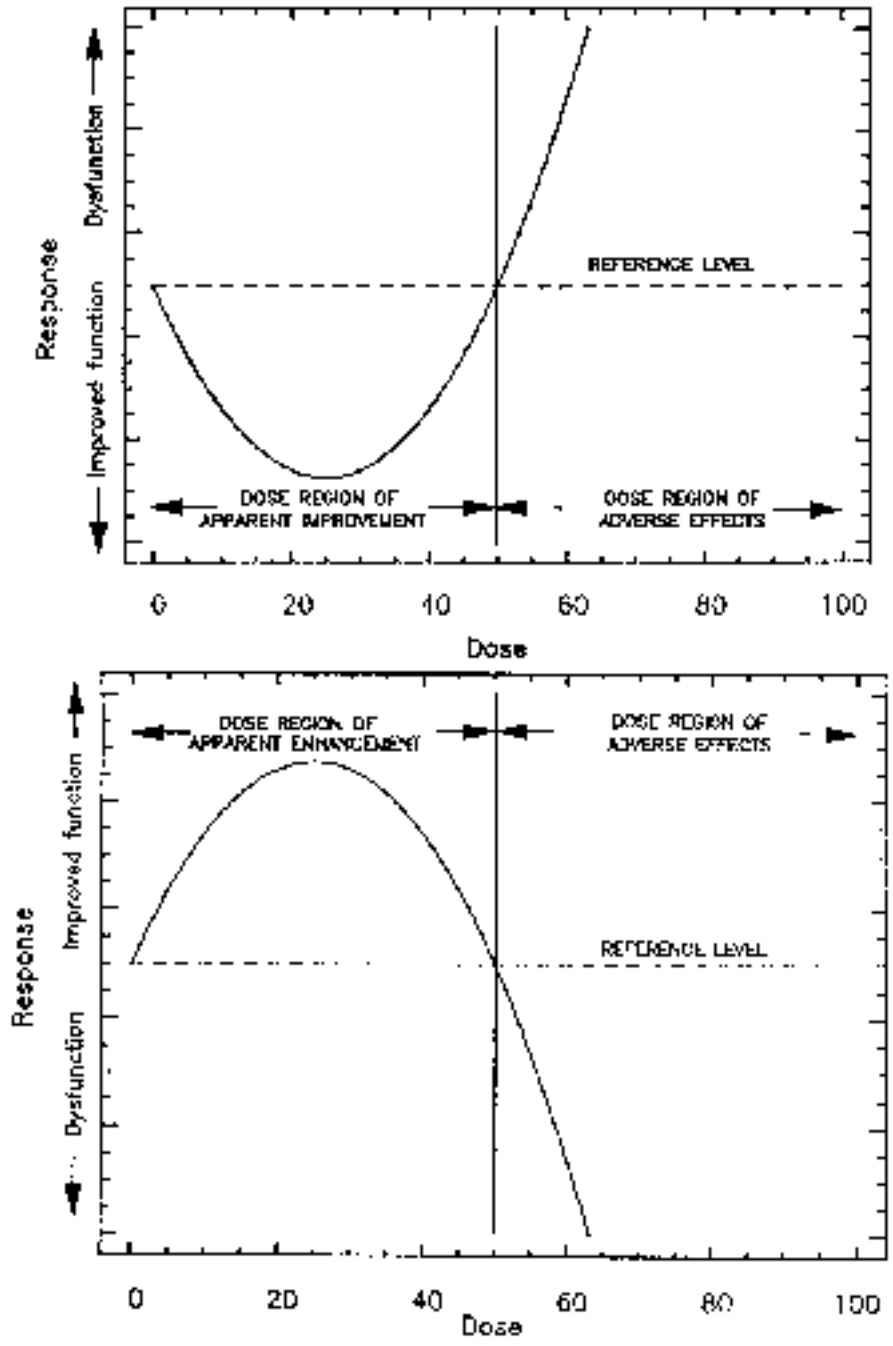

FIGURE 1. (*a*) General form of U-shaped dose-response curve showing response relative to a reference level, with a region of apparent improvement (e.g., reduction in

dysfunction) as well as a region of toxic or adverse effects. (*b*) Reciprocal of the same curve showing a region of apparent enhancement (e.g., increase above normal level of function) as well as a region of toxic or adverse effects.

Other terms have also been used to describe such findings. The descriptive term J-shaped may be more accurate in some cases than U-shaped. Mathematically, these relationships are nonmonotonic or curvilinear, and may be approximated by quadratic functions. The term *biphasic* is sometimes applied to such effects. One connotation of the latter term is that of a time course or temporal dimension to the measured response (e.g., an increase in a reaction to a given agent followed later in time by a decrease). In addition, the term *hormesis* has lately been used to refer to paradoxical effects of low-level toxicants (e.g., Sagan, 1987), although it originally referred more specifically to stimulatory effects on growth or body weight (Stebbing, 1982).

Other types of U-shaped functions exist but may be distinguished from the type considered here. Essential trace elements are well known to have a U-shaped relationship to physiological functioning (Mertz, 1981), ranging from impairment at levels of deficient intake, to optimal function at intermediate levels, to toxicity at excessive intake levels. However, only a few elements are known to be nutritionally essential, so the distinction between a toxic or xenobiotic agent and a naturally occurring essential element is usually clear. Nelson (1981) drew attention to "negative" dose-response curves in which "a higher level of a test agent produces less (if any) deviation from control than dose a lower level." The latter type of curvilinear relationship is of less importance to the present discussion because the anomaly occurs at high dose levels, whereas the focus in risk assessment is generally on the lower regions of the dose-response curve.

Although the apparently paradoxical nature of U-shaped relationships is one of their key defining features and a major impetus for this discussion, it is important to avoid drawing the facile conclusion that the inverted part of the curve is necessarily beneficial or that, in more colloquial terms, "a little bit of something bad is good for you." A classical expression of this notion may be found in the often quoted dictum, "Only the dose determines that a thing is not a poison," from Paracelsus's defense of his use of toxic agents as medicaments in the sixteenth century (Deichmann et al., 1986). While this statement, implying a dose-response relationship spanning a therapeutic range

at low doses and a toxic range at high doses, may be appropriate for pharmacologic agents, it provides no specific guidance for toxicological risk assessment and, if applied uncritically a priori, could have unfortunate implications for public health protection. After presenting selected examples of U-shaped relationships and considering some possible explanations, we will discuss some of the complexities involved in interpreting U-shaped relationships and their implications for risk assessment.

EXAMPLES

Graphs of data fitting a U-shaped function are rare in the published toxicology literature. One obvious reason for this fact is that such studies typically are not designed to detect nonadverse effects. Moreover, researchers may dismiss or even overlook U-shaped dose-response relationships in their data because nonlinearities of this sort do not fit the expected pattern of results, perhaps reflecting the "paradigmatic thinking" that has characterized most of the history of science (Kuhn, 1962).

We have found many cases of U-shaped relationships in the toxicology and epidemiology literature, especially in the area of lead neurotoxicology. Otto (1985, 1989) noted some unexpected findings from his studies of the electrophysiological functioning of lead-exposed children, including the curvilinear relationship between blood lead level and a measure of the latency of auditory brainstem evoked potentials shown in Fig. 2. As blood lead levels increased to approximately 25-30 µg/dl, latencies paradoxically decreased; above that level, latencies increased, as would be expected.

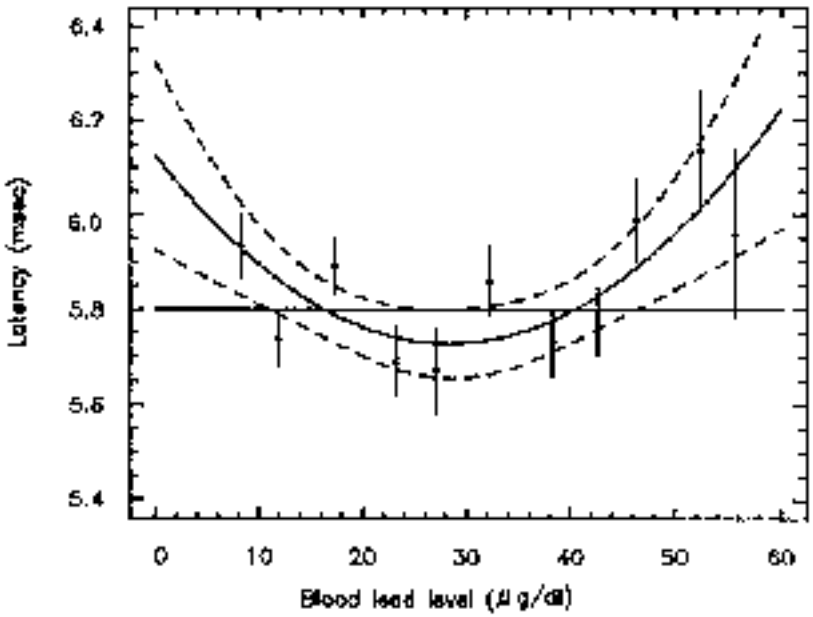

FIGURE 2. Relationship between evoked potential latencies and blood lead levels. The upper and lower curves show the 95% confidence intervals for the middle curve as taken from Otto (1989). The points and standard errors (based on pooled error) shown in this figure represent mean averages of individual data points for blood lead groupings of 5 µg/dl. The horizontal line demonstrates the lack of overlap between the upper confidence interval at the lowest point of the regression line (approximately 25-30 µg/dl) and the lower confidence interval at zero blood lead level, thus indicating a significant decrease in latencies at the lowest point in the curve.

Remarkably similar results in lead-exposed children were independently obtained by Ewert et al. (1986), who found

that visual evoked potential latencies decreased as blood lead levels increased from 4 to 23 µg/dl. Since none of these subjects had blood lead levels exceeding 23 µg/dl-, no upturn in latencies was evident. However, other work with occupationally exposed adults has confirmed that visual evoked potential latencies are longer at higher blood lead levels (Sborgia et al., 1983). The children in the study by Ewert et al. (1986) also showed a paradoxical relationship between blood lead and peripheral nerve conduction velocity: at relatively low levels of exposure, velocity increased as blood lead level increased. Feeney et al. (1979) found similar effects on visual evoked potentials in lead exposed rats.

The neurotoxicology of lead provides other illustrations of U-shaped dose-response functions. For example, several animal studies (reviewed by Cory-Slechta, 1984) have shown that at comparatively low blood lead concentrations, conditioned operant response rates are higher than those of controls; as lead levels increase, response rates decline to control or below control rates of response. It should be noted that these results were not unique to one species or to one particular set of experimental conditions. Other forms of behavior have at times also suggested a U-shaped relationship to lead exposure: based on the many studies of the relationship between lead exposure and hyper- and/or hypoactivity (U.S. EPA, 1986a), it seems clear that lead can cause some degree of elevated locomotor activity at low to moderate exposure levels and can cause reduced activity at relatively high levels of exposure (at an extreme, the total absence of activity in death!).

It is impossible to summarize here all the evidence suggesting the existence of U-shaped dose-response functions. Table 1 lists several studies containing data that fit a U-shaped function (regardless of whether the investigators described their results as such). In addition, several papers from a conference on radiation hormesis were recently published in *Health Physics* (vol. 52, no. 5, May 1987), including an overview of chemically induced hormesis by Calabrese et al. (1987).

POSSIBLE EXPLANATIONS

Having established that U-shaped dose-response curves exist in toxicological and epidemiological data, we must emphasize that we do not view these functions as evidence of a unitary phenomenon. It is quite likely that different explnations account for different instances of U-shaped relationships. For example, some cases could simply be statistical artifacts. In a computer simulation study, Tachibana (1982) found that "statistically significant" nonlinear dose-response results could be obtained in approximately 5% of the samples taken from a population in which a

linear dose-response relationship actually existed.

Spurious U-shaped relationships could also result from confounding factors or other problems with a study's design. For example, the seemingly beneficial effects of low to moderate intake of alcohol (see Marmot, 1984, and several examples in Table 1) could be due in part to a tendency for some persons with health problems to avoid alcohol or to the grouping of former drinkers (some of whom may have been problem drinkers) with lifelong abstainers (Eward, 1986). Such confounding could contribute to an increase in various dysfunctions at zero consumption levels and thus a specious relative reduction in morbidity at low to moderate consumption levels. Shaper et al. (1987) found that in their large-scale prospective study of the relation between alcohol intake and ischemic heart disease, light drinkers not only had less disease but as a group smoked less, had the lowest blood pressure, had the lowest body mass index, and were less likely to be manual workers. These factors were considered more plausible explanations for an apparent protective effect of light drinking against heart disease than a direct effect of alcohol itself. Other possible explanations for a U-shaped alcohol-morbidity relationship have been noted by Hennekens (1983).

TABLE 1. Examples of Studies with Data Fitting a U-Shaped Curve

Reference	Subjects	Agent or Factor	Effect
Alfano and Petit (1985)	Rats	Lead /anticholinergics	Locomotor activity
Ashton et al. (1978)	Humans	Nicotine	Brain electrical activity
Bengtsson (1979)	Minnows	PCBs	Growth rate
Bjorklund et al. (1980)	Rats	Lead	Cerbral cortex growth
Brenn (1986)	Humans	Alcohol	Serum lipids; blood pressure

Bulpitt et al. (1987)	Humans	Alcohol	Hypertension
Cory-Slechta et al. (1983)	Rats	Lead	Operant behavior
Friedman and Kimball (1986)	Humans	Alcohol	Mortality due to coronary heart disease (CHD)
Geist et al. (1985)	Rats	Lead	Maze performance
Gill et al. (1986)	Men	Alcohol	Stroke
Glowa and Dews (1987)	Mice	Volatile organic solvents	Operant behavior
Gordon and Doyle (1987)	Men	Alcohol	Mortality (all causes; CHD and non-CHD causes)
Grant et al. (1980)	Rats	Lead	Age at vaginal opening
Gross-Selbeck and Gross-Selbeck (1980)	Rats	Lead	Operant behavior
Jackson et al. (1985)	Humans	Alcohol	Blood pressure
Jacobs and Gottenborg (1981)	Humans	Smoking	Body weight
Kittner et al. (1983)	Men	Alcohol	Total mortality; CHD
Laughlin et al. (1981)	Crabs	Jet fuel	Growth rate

Lilienthal et al. (1983)	Monkeys	Lead	Discrimination learning task
Marmot et al. (1981)	Men	Alcohol	Cardiovascular and total mortality
Nelson et al. (1986)	Rats	Ethanol	Body temperature
Pocock et al. (1984)	Men	Lead	Serum urea and urate
Ponecorvo et al. (1985)	Pigeons	Toluene	Operant behavior choice reaction time
Schwartz et al. (1986)	Children	Lead	Body weight and height
Sobotka et al. (1974)	Rats	Methyl mercury	Body weight of dams; clinging ability of pups
Stampfer et al. (1988)	Women	Alcohol	CHD; ischemic stroke
Tilson et al. (1982)	Rats	Triethyl lead	Locomotor activity
Toews et al. (1986)	Rats	Trimethyl tin	Neuronal synthesis of macromolecules
Yaari et. Al (1981)	Men	Cholesterol	Total mortality (all causes)

Valid U-shaped dose-response relationships can be understood in terms of various possible underlying mechanisms. Interactive effects are often responsible for nonmonotonic functions. Epidemiological evidence suggests that exposure to different metals may interact to inhibit carcinogenesis (Nordberg and Andersen, 1981). The apparent protective action of optimal selenium levels against the induction of tumors (Fishbein, 1986) is one example of such interactive effects. Hildebrandt (1987) has speculated on how "composite" actions of agents such as TCDD could yield protective effects as well as toxic outcomes. In a mathematical treatment of drug interactions, Ashford and Cobby (1975) have modeled how alcohol, either alone or in combination with another drug, could produce curvilinear effects on blood pressure and neurobehavioral performance.

At a physiological level, another possible basis for U-shaped effects derives from the principle of homeostasis, which states that the body attempts to maintain a stable physiological milieu in the face of perturbations. For example, Smyth (1967) proposed that chronic low-level exposure to a toxic substance may constitute a "sufficient but not overwhelming challenge" to which an organism may adapt. In such cases, better-than-normal performance might be evident in comparison to non-adapted individuals. The idea of homeostatic adjustments also suggests the possibility that enhancement of function could result from transient "overcorrections" in the operation of feedback mechanisms (Stebbing, 1979). A related notion was proposed by Cragg and Rees (1984) to account for the hormetic effects of organic lead on body growth. These authors speculated that the "extra metabolism required for detoxification acts as a stimulus to body growth."

Various compensatory and/or protective mechanisms are well known in toxicology (MacNider, 1935; Ishikawa et al., 1986). Zenick (1983) commented on the difficulties in detecting neurotoxic effects, particularly at circa-threshold dose levels, because of the compensatory capacity of the central nervous system. Metallothionein and intracellular nuclear inclusion bodies have been noted as possible protective mechanisms against renal injury from metals such as cadmium and lead (Goyer, 1986). Glutathione levels in the intestine appear to increase upon exposure to arsenic and may help serve a protective function (Pisciotto and Graziano, 1980). In the respiratory system, various antioxidants (e.g., vitamin E, sulfhydryls, glutathione, glucose-6-phosphate dehydrogenase, superoxide dismutase) help defend the lung against oxidant toxicity from air pollutants such as ozone (U.S. EPA, 1986b). In all of these examples, however, any protection afforded by such mechanisms is limited to relatively brief and/or low exposure levels; with increasing exposure, toxic effects can be expected eventually to prevail over protective effects.

IMPLICATIONS

One of the most important implications of U-shaped dose-response relationships for risk assessment concerns the identification of thresholds and "no-observed-effect levels" (NOELs). Nonlinearities are always a potential complication that warrant caution in risk assessment when estimating allowable levels of exposure. In the particular case of U-shaped nonlinear functions, a study may appear to have used both supra- and infrathreshold dose levels when, in fact, responses to an agent might have occurred at even lower dose levels, if they had been administered. The hypothetical data depicted in Fig. 3 illustrate how a limited selection of dose levels in a toxicology study could generate a misleading dose-response function. Responses to dose levels 3-5 appear to fit a monotonic function, with dose level 3 constituting a NOEL equivalent to the control. If, however, dose levels 1 and 2 had been included, it would have been evident (assuming sufficient statistical power) that an alteration in function occurred at levels below the apparent NOEL and that the dose-response curvature actually extended to even lower dose levels.

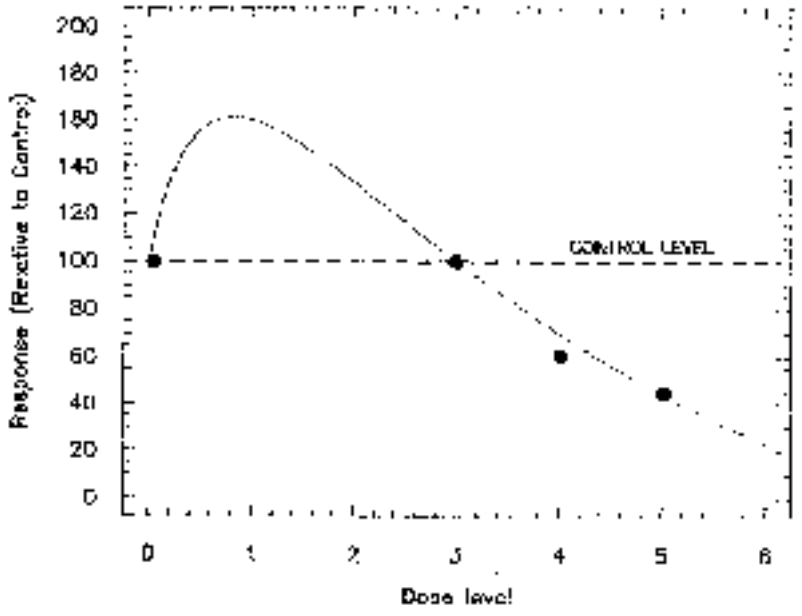

FIGURE 3. Hypothetical data for response to dose levels 0 (control), 3, 4, and 5. In the absence of data for dose levels 1 and 2, the no-observed-effect level would appear to occur at dose level 3.

Having obtained such data, one must conduct statistical analyses to determine whether the results are significantly different from chance occurrences. However, many statistical tests assume monotonicity and thereby sacrifice power to detect effects in the unexpected direction. The one-sided *t*-test illustrates this tradeoff. The one-sided *t* has better power than the two-sided test to detect change in a predicted direction but is ineffective for dealing with unpredicted effects. Williams's test (1972) extends the one sided approach to the comparison of two or more treatment means with a control mean. Similarly, Jonckheere's (1954) test for ordered alternatives extends the nonparametric one-sided Mann-Whitney test to comparisons involving several dose levels or populations. Both of these techniques explicitly assume monotonicity. In addition, the fitting of probit, logistic, and straight lines to dose-response curves tends to emphasize the monotonic features of such data. However, as illustrated above, a paucity of dose levels or a large deviation from monotonicity could lead to a lack of significance or a poor estimate of threshold.

Tests to detect U-shaped dose-response relationships have not received much consideration in the statistical or risk assessment literature, with only a few authors even touching upon statistical aspects of such data (Bray et al., 1967; Brisbin et al., 1987; Crump, 1984; Glowa and Dews, 1987; Tukey et al., 1985; Williams, 1972). The problem does not appear to be a trivial one, and more attention should be given to statistical techniques for dealing with U-shaped functions and for determining when the assumption of monotonicity is inappropriate.

From the standpoint of risk assessment, it is particularly important in characterizing the potential health risks of an agent that one *not* focus exclusively on an apparent improvement in one endpoint and ignore other, possibly deleterious effects of the same agent. For example, until the early 1900s arsenic compounds were commonly used for the medicinal treatment of anemia and other disorders (Squibb and Fowler, 1983). The regenerative hematopoietic response that occurs to low-level arsine exposure suggests a possible basis for arsenic's therapeutic use in treating anemia, but the increase in the number of red blood cells at low therapeutic doses does not reflect the various pathologtic alterations in the resulting immature erythrocytes (Blair et al, 1987), nor the other sequelae of medicinal arsenic use, including certain forms of cancer (Cuzick et al., 1982) and other effects (Kerr and Saryan, 1986).

Although the balance between risks and benefits is relatively clear in the case of arsenic, other agents may be less easily judged. Alcohol provides a classic example of such tradeoffs. Even if one assumes that low to moderate alcohol intake provides some degree of protection against coronary heart disease, it may also exact a cost in terms of increased risk of cancer (Schatzkin et al., 1987; Willett et al., 1987), hemorrhagic stroke (Donahue et al., 1986; Stampfer et al., 1988), accidents (Kozararevic et al., 1980), and potential abuse and its incidental effects (Blume et al., 1986). Thus, apparent benefits or low-level exposure to an agent may not be as beneficial as they seem or, even if real, may not compensate for other, unmeasured risks or impairments.

Also, it is important to distinguish between different individual circumstances, population characteristics, or other variables in evaluating such tradeoffs. For many adult males an aspirin taken every other day may reduce the likelihood of myocardial infarction, but for some men such a regimen may also increase the risk of hemorrhgic stroke (Steering Committee of the Physicians' Health Study Research Group, 1988). It is important, therefore, to consider not only negative as well as positive consequences of an agent but the fact that the balance between the two may not be the same for different individuals or populations.

Investigators should recognize the possibility of curvilinearities in their data and not simply dismiss such results as inexplicable anomalies. It is especially important to be alert to indications of U-shaped functions when dealing with relatively low doses in the threshold region. Risk assessors also need to be aware of U-shaped relationships in evaluating the results of any given study or group of studies. In addition, risk assessors should consider the uncertainty that such curvilinearities may contribute to estimates of thresholds or NOELs from studies using a limited number of range of dose levels. Finally, while it is always important to avoid narrowly focusing on only one of multiple outcomes of an agent, it is particularly important where a U-shaped relationship is concerned, for the superficial appearance of improved function (or reduced dysfunction) in one end point may not accurately characterize the overall risks posed by exposure to a substance.

We solicit other investigators' comments and their examples of U-shaped dose-response relationships not already cited here.

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