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Expanding the RfD Concept to Incorporate and Optimize Beneficial Effects While Preventing Toxic Responses From Non-Essential Toxicants

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Abstract

Increasing evidence that low level exposure to toxic agents induces beneficial effects indicates the need to examine if and how the current EPA Reference Dose (RfD) derivation process could take this phenomenon into account. This paper examines conditions that affect how the RfD process could incorporate chemically-induced beneficial effects while preventing toxic responses. Incorporation of beneficial responses in the RfD process will be affected by:

(1) Size of the dosage range over which the beneficial effects are observed.
(2) Proximity of the optimal beneficial response dosage to the NOAEL.
(3) Size of the intraspecies UF.

Based on data estimating the distance of the median dosage of the optimal beneficial response from the NOAEL (Calabrese, 1994) and the recently described lack of independence of the inter- and intraspecies uncertainty factors (UFs) (Calabrese and Gilbert, 1993), non carcinogenic toxic substances whose RfDs are based on animal model data are predicted to have their toxic effects prevented and possible beneficial effects optimized in the general population by use of an intraspecies UF of 5. In contrast, current EPA practices of employing a 10-fold UF for intraspecies variation in animal model based RfD derivation while also protecting against harmful effects leads to

the general population missing estimated beneficial effects. Such a conclusion has important policy implications since no debate has been directed toward the distribution of population-based pollution-related benefits but only towards the prevention of their harmful effects.

Introduction

Within recent years there has been considerable discussion of the concept and documentation of low dose beneficial responses to radiation and chemical toxicants (Davis and Svendsgaard, 1990; Cook, 1995; Liu, 1994; Sagan, 1987; Sugahara et al., 1992; Calabrese, 1992, 1994, 1995; BELLE Newsletters 1992-1995) as well as exploration of potential underlying mechanisms. Nonetheless, there has been little discussion concerning how the phenomenon of low dose beneficial responses following exposure to toxic substances would affect traditional approaches for human risk assessment by regulatory agencies such as EPA in their reference dose (RfD)/reference concentration (RfC) derivation process for non-carcinogens. The present paper will:

(1) Provide a brief historical foundation and documentation for beneficial effect dose response relationships following exposure to non-essential toxic agents.

(2) Demonstrate how beneficial responses from low dose exposure to non-essential toxic substances relate to the traditional concept of the NOAEL.

(3) Demonstrate how the traditional application of UFs interface with and affects beneficial dose-response relationships.

Beneficial and Toxic Effects and the Dose-Response Continuum

The issue of how chemicals and radiation affect biological systems over wide dose ranges is not the purview of a single discipline but strongly cuts across many fields. In the experience of toxicology this issue has been dominated over the past several decades by debates over the shape of radiation related dose-response relationships and more recently via chemical responses as well.

A general premise inherent in the study of the biological effects of chemicals and radiation is that all toxic responses observed at higher dose rates are the only effects elicited at lower exposure (Boxenbaum et al, 1988). This concept has served in part as the basis for how regulatory and public health agencies begin to deal with the process of deriving acceptable levels of exposures. However, a number of researchers have reported that the dose-response continuum is not simply that of response proportionality with respect to dose. Moreover, data exist that indicate that numerous agents that cause inhibitory effects at high doses stimulate the same response at lower doses. Some of these observations concern biological effects of public health interest such as longevity, and certain diseases (e.g. heart disease, cancer). Consequently, there has emerged considerable interest in whether low doses of generally recognized and possible regulated toxic substances may produce beneficial responses at low doses in contrast to that predicted by the current paradigm of simple dose-response proportionality. This section provides a brief summarization of literature in this area with the intent of addressing the generalizability of such findings to species, agent, and biological endpoint.

Numerous investigators have reported low dose stimulatory and high dose inhibitory and/or toxic responses for a wide variety of biological endpoints in a broad representation of plant and animal species. Such observations have been demonstrated for bacteria, phytoplankton (Gordon and Prouse, 1973), algae (Browne and Davis, 1977; Stromgren, 1980) pollen seed germination and more complex plants (Goldin et al., 1961; Ingram and Fisher, 1973; Williams et al., 1978; Nechay and Saunders, 1978; Nechay et al., 1978; Pauwels, 1961; Calabrese and Howe, 1976; Cathey and Stuart, 1961; Cathey, 1964; Knypl, 1967). Similar observations have been reported for fungi (Branham, 1929; Southam and Ehrlich, 1943). With respect to the animal kingdom, chemically induced low dose stimulation/high dose inhibition has been observed for a wide range of organisms including insects, worms, crabs, clams, oysters, fish, and various mammalian species (e.g. mice, rats, pigs, dogs, and humans). The range of agents employed in such studies has been very diversified including numerous chemicals (e.g. heavy metals, PCBs, pesticides, hydrocarbons from crude oil, chemotherapeutic agents, antibiotics, ethanol, solvents such as a CCl_4 and chloroform, essential trace elements, and numerous other agents) and radiation (Calabrese et al., 1987; Calabrese and Baldwin, 1993; Davis and Svensgaard, 1990, 1994, 1995; Luckey, 1991; Sagan, 1987; Stebbing, 1982; Sugahara et al., 1992; Liu, 1994; Townsend and Luckey, 1960). Some of the biological endpoints measured included weight gain, growth rate, hatching success, tumor inhibition, length of reproductive life, life span, and performance in behavior tests. For example, a lifetime reproductive study in rats revealed that females ingesting low levels of DDT from three weeks of age throughout their lives displayed a markedly longer reproductive life span

(14.5 vs 8.5 months) compared to their litter mates (Ottoboni, 1972). Another example of this low-dose stimulatory phenomena was seen with the work of Roe and colleagues (Roe et al., 1979; Roe and Van Abbe, 1980) with chloroform in which low level exposures enhanced the survival of mice, rats and dogs, while being carcinogenic at high doses. Likewise, considerable data in humans support the hypothesis that consumption of modest quantities of alcohol reduces the risk of myocardial infarction while high consumption rates enhance such risk. Of significance is that underlying biochemical mechanisms are emerging to account for such observations (see Gaziano, 1995). Figure 1 illustrates the relationship of alcohol consumption and various health related endpoints.

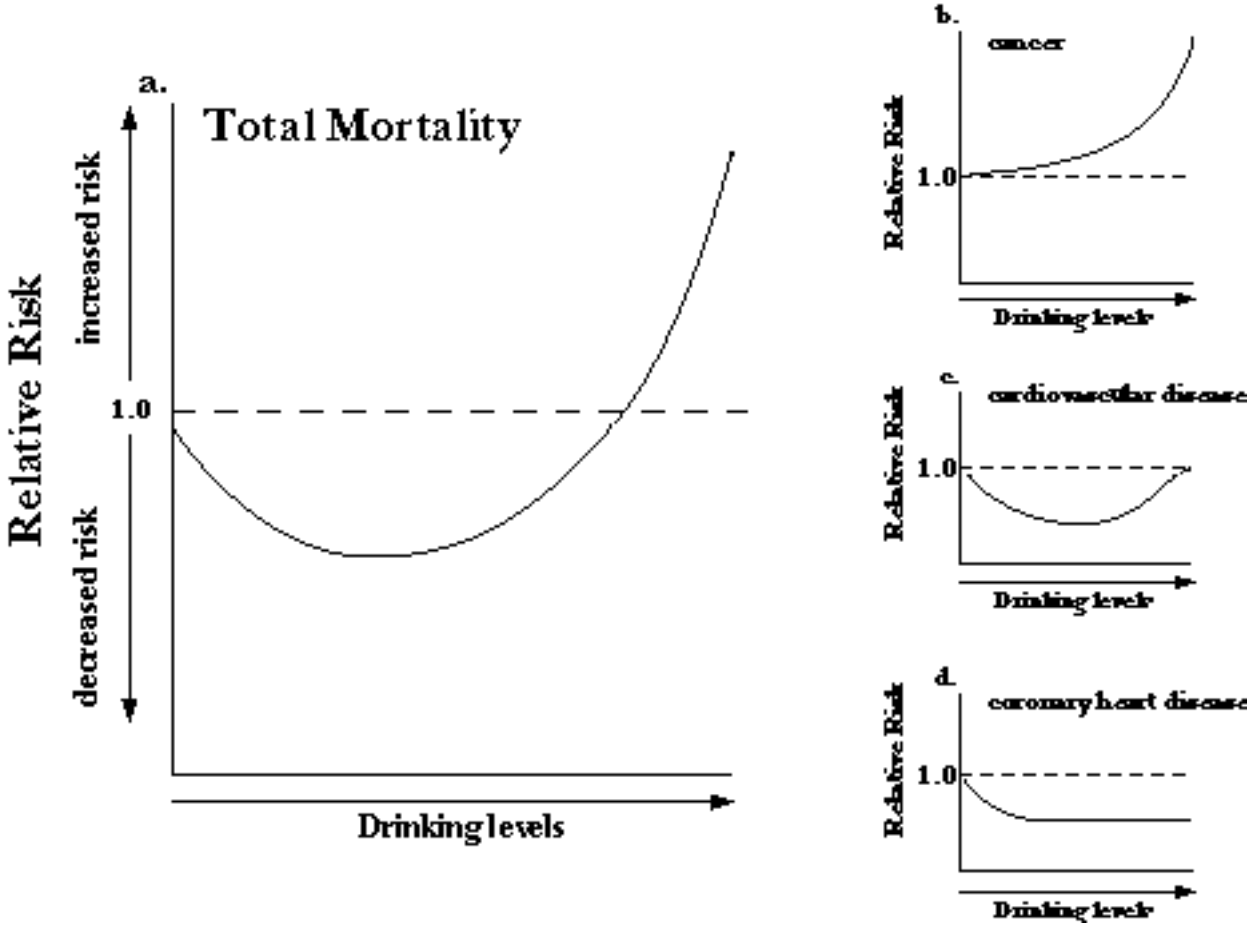

Figure 1. The relationship between alcohol consumption and total

mortality is a J-shaped curve (a); for cancer there is no apparent increase until higher drinking levels (b); for all cardiovascular causes the relationship is U-shaped (c); and for myocardial infarction there appears to be an L-shaped threshold effect (d) (Gaziano, 1995).

Of particular basic research interest has been the related phenomenon of "adaptive response", first reported by Olivieri et al. (1984) in which a prior low dose of radiation protects against a subsequent more massive exposure. Since this initial finding a substantial number of reports have confirmed and extended this original observation. Of relevance is the elucidation of adaptive mechanisms induced by low levels of chemicals or radiation useful in preventing/repairing damage from subsequent elevated exposures to both radiation and chemical agents [see UNSEAR, (1993) for a review of the topic "adaptive response"].

The Dose-Response Continuum and the RfD Process

While Stebbing (1982) presented several types of dose-response relationships that are purported to describe the low dose stimulating response, the most frequently reported response is the so called ß-curve (Figure 2). An analysis of published data of numerous experiments displaying ß curve dose-response relationships involving a wide range of biological models, endpoints, and chemical agents offered critical features of the dose-response continuum (Calabrese, 1994a). First, the maximum stimulatory response (i.e., height of ß-curve) ranged from 15% to several fold above the control with the median increase being approximately 50%.

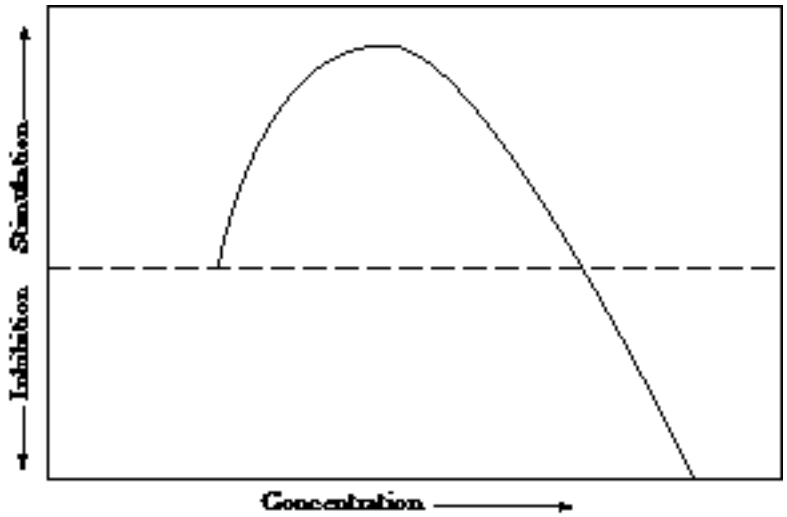

Figure 2. Generalized Example of A ß-Curve Dose-Response Relationship (Adapted from Stebbing, 1982).

Second, the difference between the dose observed to cause the maximum stimulation and the dose estimate where the ß-curve descended through the control value (e.g. the traditional approximate - NOAEL) was 3 - 4-fold. Third, the stimulatory phase range of the dose-response curve varied from several fold to several orders of magnitude with the majority approaching 10 fold. These observations provide a quantitative point of reference for application to the assessment of the RfD-derivation process. These collective findings are in general agreement with the observations reported in the numerous above cited references concerning the quantitative nature of the stimulatory phase of the dose-response continuum.

In deriving RfDs for non-cancer effects it is customary to consider the use of UFs depending on the nature of the available data. The following example will derive an RfD based on a hypothetical study. Assume that a lifetime rodent study was conducted on chemical X using an unexposed control and six dosages (0,2,4,8,16,32, and 64 mg/kg/day). The endpoint represented in the hypothetical study is median life span (Figure 3). The data reflect a dose-response relationship conforming closely to the pattern of the ß-curve of Stebbing (1982) with low doses enhancing survival while high doses are progressively detrimental (i.e. decreased longevity). The treatment of 16 mg/kg/day represents what is referred to as a LOAEL, while the treatment 8 mg/kg/day represents the NOAEL. Under normal circumstances for a lifetime study, the RfD process will utilize at least two UFs, the inter- and intra-

species UFs. The interspecies UF assumes that the average human may be 10-fold more sensitive than the average rodent. Thus, if the NOAEL for the rodent was 8 mg/kg as in the present hypothetical case, the NOAEL for the average human would be assumed to be 0.8 mg/kg based on an interspecies UF of 10. Moreover, the expected shape of the entire dose-response curve (for the toxic response and the low dose stimulation) for humans is similar to the rodent curve just displaced by the interspecies UF. The RfD procedure would normally then apply a 10-fold UF to account for human variation (i.e. an intraspecies UF). Again, even though there is considerable variation in human response, the basic ß-curve is still assumed to be operational just shifted to the left for the so-called high risk subsegment of the population.

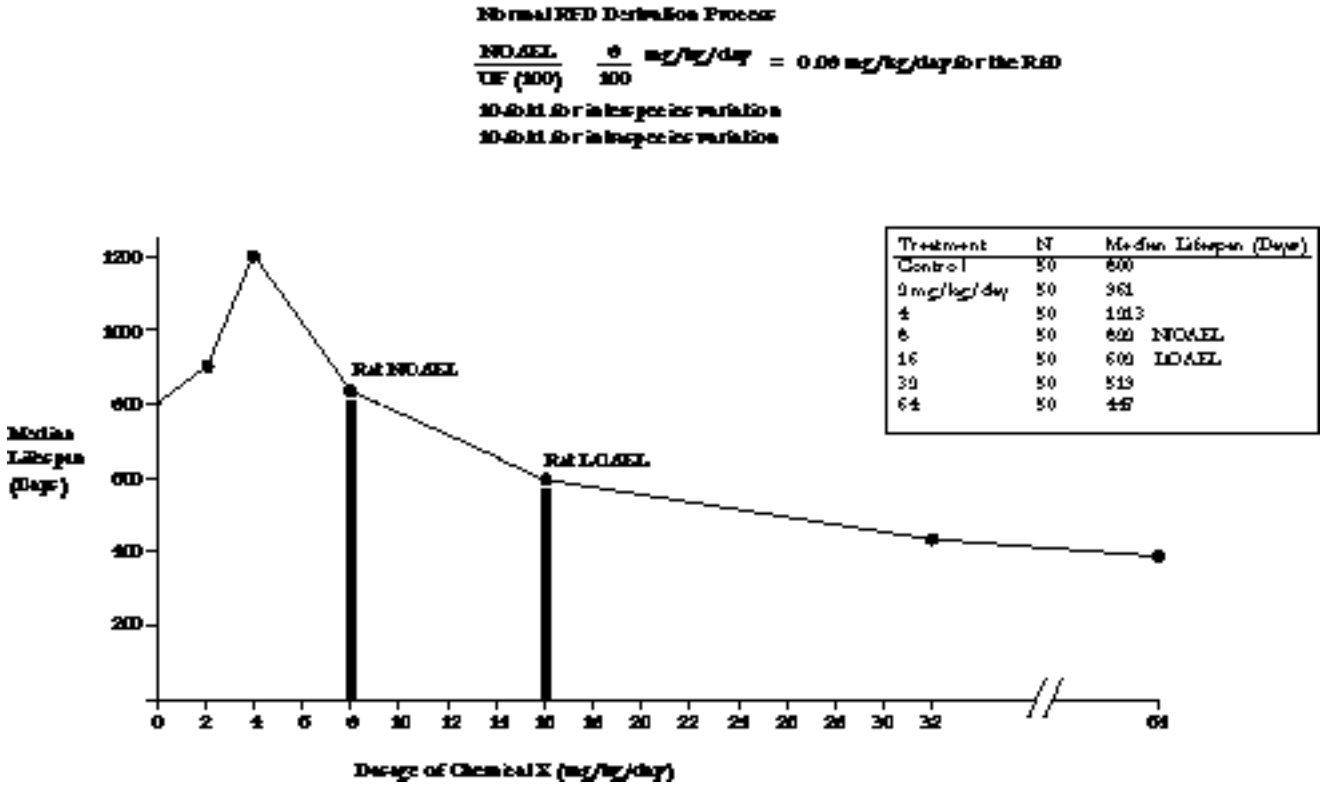

Figure 3. The Effect of Chemical X on the Median Lifespan of a Rodent Strain

Figure 4, which represents the spectrum of adverse and beneficial effects in the traditional UF RfD approach, indicates that the average human will experience beneficial effects when exposed in the range of ~0.08 to ~0.8 mg/kg/day while above the NOAEL of 0.8 mg/kg/day adverse effects would be expected. However, when one considers that subsegment of the population that is considered at high risk, the RfD of 0.08 mg/kg/day will provide assurances that this sub-group and all less susceptible individuals will not experience adverse health effects. Beneficial effects in the high risk subsegment from chemical X would be predicted to occur with an exposure of ~0.008 to ~0.08 mg/kg/day, assuming the same distribution as non-high risk (i.e. average) humans.

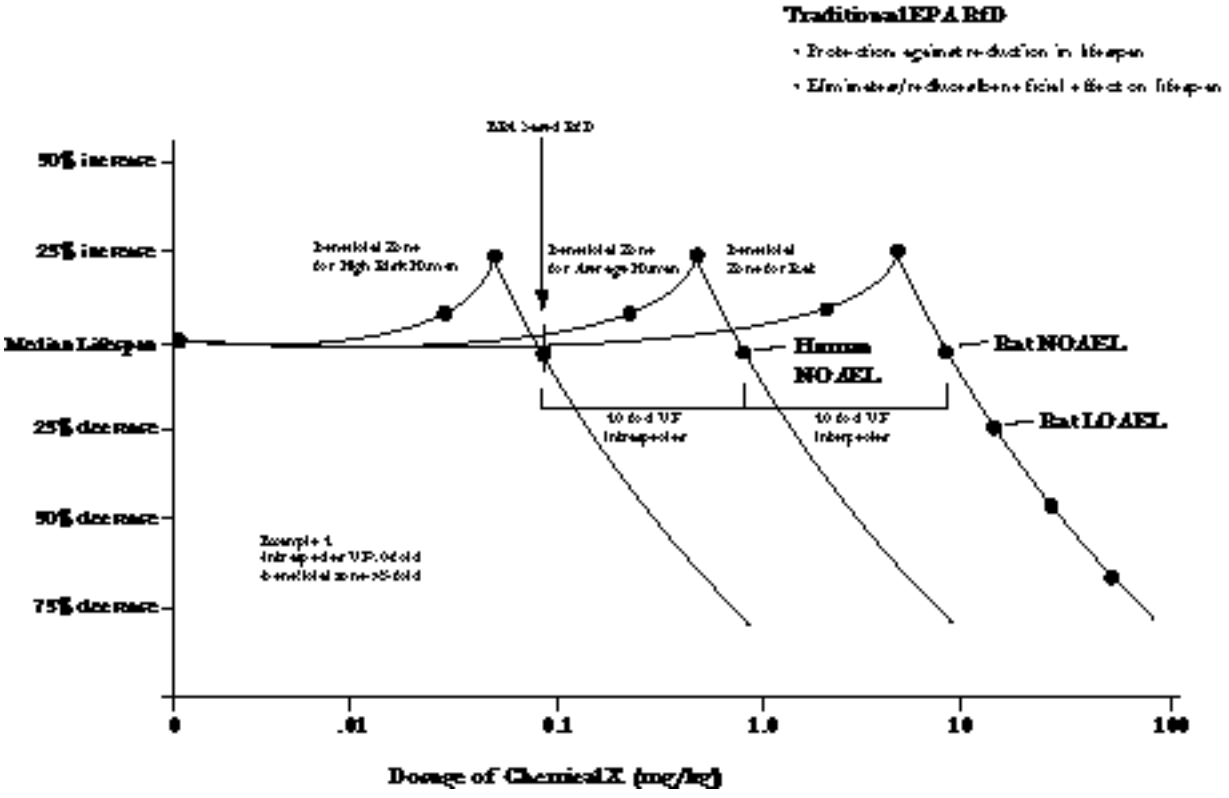

Figure 4. EPA RfD Derivation Process Affects Beneficial Effect Depending on the Size of the Beneficial Zone and the Size of the Intraspecies UF

This assessment illustrates that if the exposure is limited to a maximum of 0.08 mg/kg/day (i.e. the standard derived RfD) both normal and high risk segments of the population will be protected from possible adverse effects. However, the vast majority of the population including both average and high risk groups will not be able to take advantage of the beneficial effect (i.e. increased longevity).

How would this concept of risk/benefit be employed by regulatory agencies to establish optimal risk management actions? In the case of this hypothetical example, a range of goals could be identified:

- € Prevent compound-induced decreased longevity in the vast majority of individuals, including sensitive individuals (i.e. the traditional RfD).
- € Select the RfD that maximizes the number of days lived by the entire population.
- € Select dosage that optimizes risks and benefits for the high risk groups.

Since its inception EPA has been concerned with preventing the harmful effects of contaminants. This is reflected in the use of multiple UFs for non-cancer toxicity depending on available data, the use of the critical toxic effect (often the most sensitive endpoint in the most sensitive study) as well as with encouraging studies that define the full spectrum of the toxicity dose-response continuum, while often ignoring possible beneficial effects at lower doses. These collective and mutually reinforcing actions have lead to the type of RfD which theoretically prevents the harmful effects of chemical exposure to all members of the population, while excluding dosages beneficial to the general population. Nonetheless, regulatory agencies have had to modify standard RfD derivation procedures to account for essential and/or beneficial effects of toxic agents by taking into account the entire dose-response continuum. For example, the regulation of fluoride in drinking water recognizes beneficial dental effects at low doses and a variety of adverse effects at higher doses (Calabrese, 1978). Likewise, the beneficial and harmful effects seen for essential but yet toxic elements such as copper, selenium, and sodium has been addressed by EPA in an RfD derivation process designed to assure benefits while preventing adverse effects.

Regulatory agencies have followed procedures (e.g. RfD derivation process) that tend to avoid making health trade offs amongst different segments of the population. For example, EPA could regulate under the assumption that most people, even those at recognized increased risk, may be protected from adverse effects. While this situation would still be the case, the question raised in this paper is how should estimated beneficial effects be distributed. For the scheme developed here, however, it is not possible in a regulatory sense to optimize benefits for both the average and high risk segments of the population.

Under the traditional EPA RfD-derivation methodology in which the intraspecies UF of 10 is employed, any beneficial effect on the general public would either be missed or minimal. However, if the intraspecies UF were 5-fold as has recently been recommended by Calabrese and Gilbert (1993) based, in part, on the presumed lack of independence of the intra- and interindividual UFs, the idealized RfD derivation process would be able to approach goals of prevention of toxicity with an adequate margin of safety, as well as optimize the likelihood of obtaining a beneficial response in the general population. In contrast, the use of the current intraspecies UF of 10 is likely to both prevent toxicity in average and high risk groups while usually missing the optimized likelihood of a beneficial response in so-called high risk groups and the average individual. Note that one could use other values than 5 for the optimum beneficial fold distance below the NOAEL in order to optimize the beneficial response for specific cases where data are available in critical studies. The value of 5 was used in order to offer the most generalizable condition based on the information above (Stebbing, 1982; Luckey, 1991).

At this point it is necessary to reexamine the use of the intraspecies UF especially with respect to its possible interdependence with the interspecies UF. For UFs to be properly applied it is expected that they are independent of each other and consequently have a multiplicative interaction. However, despite this rather long-held operative assumption by US regulatory agencies there is a rather high degree of interdependence between these two UFs (Calabrese and Gilbert, 1993). The interspecies UF in human risk assessment is generally recognized as providing an extrapolation from the average animal to the average human, assuming that humans are 10-fold more sensitive. The intraspecies UF assumes that most human responses [i.e. spanning the more (but not most) sensitive to the more (but not most) resistant subjects) to an agent fall within approximately a 10-fold range (Calabrese, 1994a). Given this assumption the application of the intraspecies UF should begin with the average person and extend to cover the higher risk subsegments of the population. Consequently, an intraspecies UF of 5 would be expected to protect most humans including the majority of those considered at high risk (Figure 5).

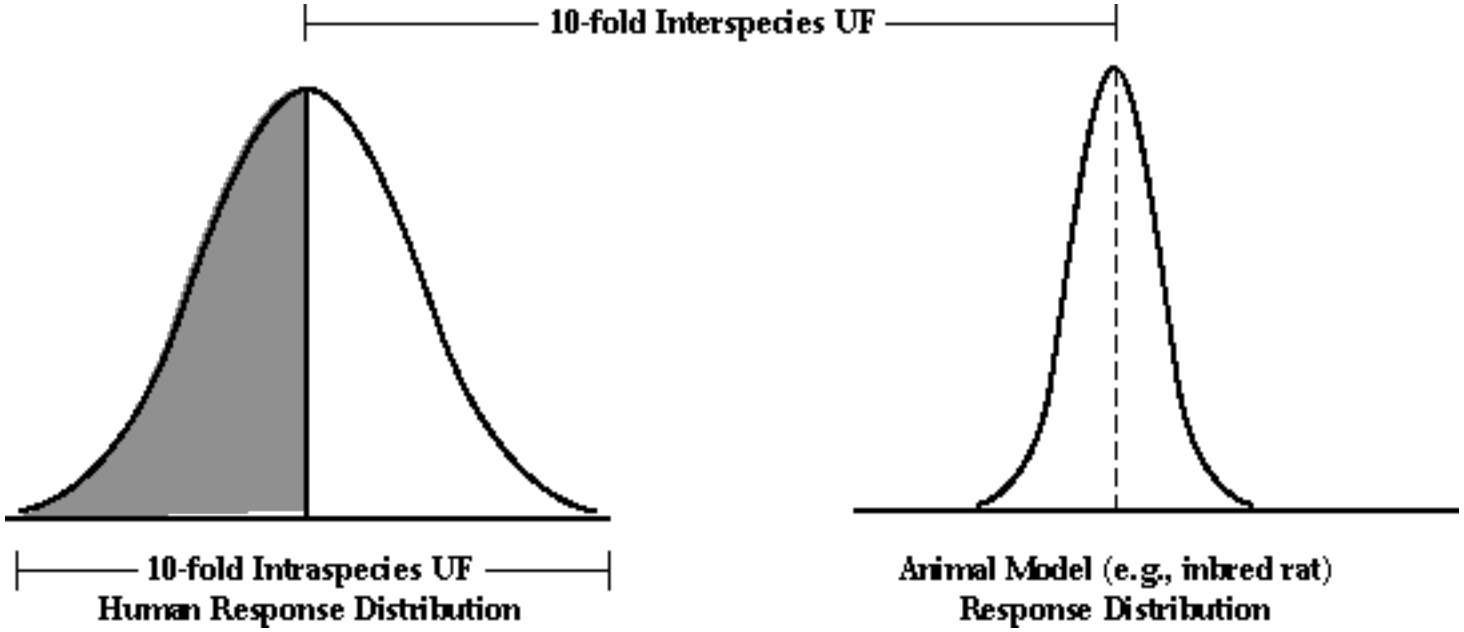

Figure 5. Interdependence of Uncertainty Factors (UF)

The use of a 10-fold UF for intraspecies variation would be more (but probably not fully) justified if it were based on occupational epidemiological study data. These data do not consider the most sensitive humans and are likely to involve principally healthy workers and a self-selection component that consists of the less sensitive members of the population (Figure 6).

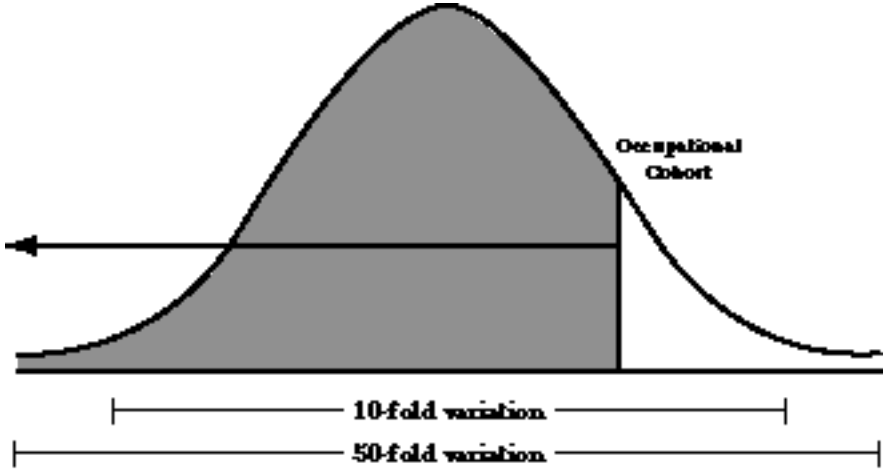

Figure 6. Intraspecies Uncertainty Factors (UF) Based on Occupational Cohort

Therefore, it is concluded that the current use of a 10-fold factor for interindividual variation, as typically applied to animal toxicological studies used in risk assessment, represents an important deviation from the original intention of uncertainty factor use. This consideration of interindividual variation is more satisfied with an UF of 5 when based on animal studies, but with a factor of nearly 10 when based on occupational epidemiological studies. This argument applies to the basic relationship (i.e. lack of independence) between the interspecies and intraspecies UF. The UF values of 10 and 5 are used here because of their relationship to current EPA practice and for illustrative purposes. This concept would be applicable whether the size of the UFs were larger or smaller than 10. Consequently, if the recommended intraspecies UF of 5 were adopted this is predicted to result in a nearly optimized effect for the general population including prevention of harmful effects and maximizing of beneficial responses. However, high risk groups would only receive protection against adverse effects.

OTHER ISSUES

Assessing Low Dose Beneficial Response

Numerous questions remain about the nature of the dose-response continuum for chemicals of concern and the wide range of biological endpoints measured. Unfortunately, the vast majority of toxicological studies emphasize high doses and toxic responses, and their mechanistic underpinnings. It is only more recently that major research emphasis has focused on elucidating adaptive mechanisms. In addition, the available data, as noted earlier,

suggest that low-dose beneficial responses are of a relatively modest magnitude (up to 50%) (Calabrese , 1994a) and more difficult to detect in a statistical sense (Gaylor, 1994) than the many fold increases in damage as is often seen in the measurement of toxic endpoints (e.g. increase in serum enzymes, DNA damage). This basic reality makes studying the effects of low level responses more formidable since the likelihood of describing a beneficial response is more difficult than a toxic response. The investigation of low dose beneficial effects has also built in disincentives:

- € *Ideological Bias* - against finding that harmful substances may cause beneficial responses.
- € *Larger Sample Sizes* - In order to have adequate statistical power larger sample sizes are required resulting in higher costs to conduct meaningful low dose research.
- € *Maintaining Tradition* - Toxicological education and training is principally designed to assess hypotheses relating to specific toxic endpoints. Assessing beneficial effects is not part of the normal toxicological methodological repertoire.
- € *Grants from Federal Agencies* - Unless there is a commitment by funding agencies to explore the low dose end of the dose-response continuum, progress will be slow in this area. Writing unsolicited proposals in this area may be professionally risky since it diverts time away from one's higher funding likelihood areas.

Despite this brief listing of the above researcher disincentives, enough data have emerged which (1) challenge the current paradigm, (2) suggest ways to incorporate such information into improved methods for deriving acceptable exposures, and (3) provide a basis for our current institutional frameworks to address some of the types of disincentives (e.g. ideological bias, traditional toxicological paradigms, and grants programs) that affect progress in this area.

It may be objected that the term beneficial has been used throughout this paper to characterize the enhanced longevity response. It is recognized that instead of the term "beneficial" a non value laden term such as stimulation or pharmacological inversion (Furst, 1987) may have been substituted. However, the intent of this manuscript is to provide a vehicle by which EPA may modify the RfD derivation process in a generic manner that is conceptually consistent with previous actions on essential but toxic elements.

The RfD in Ecological Context

While the principal focus of this paper deals with how the EPA-RfD derivation process could incorporate the concept of beneficial effects of toxic substances, it is necessary to consider this proposal in light of broader ecological and evolutionary considerations. Assuming that low dose exposure to toxic substances induce "beneficial" responses (e.g. enhanced survival in the example described here), are there physiological costs incurred as a result of defending against toxic substances even within the context of beneficial responses? The range of strategies employed to resist such chemical challenges include avoidance responses, (e.g. aquatic animals display enhanced mucous secretion on exposed surfaces), removal (absorbed pollutants can be detoxified and excreted), neutralized (by complexation with protective proteins such as metallothionein), and repair of damage caused by the toxic substance.

According to Calow (1991) these strategies for combating the harmful effects of toxic substances are likely to be metabolically costly. Calow argued that metabolic costs are increased following exposure to toxic substances, and if energy income remains the same, production must be diminished. In ecological terms, there should be a trade-off between the capacity to survive the chemical insult, growth rate and reproductive output and that such trade-offs are likely to have been selected for. That is, trade-offs between individual growth rate and survival rates for a variety of species could relate to differential strategies in which some species invest more in survival at the expense of growth and/or reproduction. Thus, even though a "beneficial" response (e.g. survival) may be observed at low doses it does not come without some metabolic costs which may affect growth and/or reproductive production. While the views of Calow are intended to be broadly ecological in nature, they are relevant to the present discussion and suggest the need for a more detailed ecologically-based critique of the present proposal. Such comments are also equally relevant to the evolving field of ecological risk assessment, and may provide the type of theoretical foundation needed in deriving acceptable levels of contamination in ecological settings.

Should all toxic substances be expected to cause beneficial effects at low doses? This would appear to be an important question of both theoretical and practical interest since its answer affects how/when the concept of incorporating beneficial effects in the RfD derivation process is implemented. Should the incorporation of beneficial effects be considered on a case-by-case basis or should beneficial effects be generally assumed to occur at low doses such that the RfD process incorporates this consideration as standard practice in the above recommended procedure? However, this is a non-issue because the proposed methodology is designed to assure protection for average and high risk groups whether beneficial effects occur or not.

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