Biological Effects of Low-level Exposures: A Perspective from U.S. EPA Scientists

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Biological effects of low-level exposures (BELLE) may be very important in characterizing the potential health risks of environmental pollutants. Before some features of BELLE, such as effects that may be modulated by adaptive or defense mechanisms, can be taken into greater consideration in U.S. Environmental Protection Agency risk assessments, however, adequate information on a toxicant's mode of action and answers to other questions are needed. — *Environ Health Perspect* 106(Suppl 1):379–381 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/379-381davis/abstract.html*

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The effects of low-level exposures to environmental pollutants are a matter of particular importance to the U.S. Environmental Protection Agency (U.S. EPA). Extrapolation from experimental high-dose effects to often much lower environmentally relevant concentrations introduces uncertainties in risk assessment. Although the use of conservative default assumptions about the nature of dose–response relationships may be useful for screening purposes and is generally protective of public health, if evidence is available to show that effects at high doses clearly do not occur in the same manner at low doses, then assumptions to the contrary may ultimately prove counterproductive to public health protection, particularly if they result in the expenditure of resources that could more usefully be applied to reduce other pollutants. For these and other reasons, a fuller characterization and understanding of the biological effects of low-level exposures (BELLE) will enable the U.S. EPA to better serve its mission.

When assessing health risks U.S. EPA scientists consider information on the mechanisms of toxicity when such information is available, as illustrated by the role of alpha-2u-microglobulin in producing male rat kidney tumors and by the existence of nongenotoxic carcinogens. However, as the U.S. EPA's 1996 proposed cancer guidelines (*1*) indicate, it is important to think more broadly than the mechanism; that is, one must consider the mode of action, which encompasses all relevant mechanisms as well as other factors that contribute to an agent's influence on the development of tumors or other toxic effects.

Among the questions to be addressed as mode of action is considered are:

- Has a body of data been developed on the agent that fits with a generally accepted mode of action?
- Has a hypothesis on the mode of action been published and has it gained general scientific acceptance through peer-reviewed research, or is it still speculative?
- Is the proposed mode of action consistent with generally agreed-on principles and understanding of carcinogenesis?
- Is the mode of action reasonably anticipated or assumed, in the absence of specific data, to operate in humans? How is this question influenced by information on comparative uptake, metabolism, and excretion patterns across animals and humans?
- On average do humans appear more or less sensitive to the mode of action than animals? Have susceptible subpopulations or individuals been identified or are they likely to exist?
- Does the agent affect DNA either directly or indirectly?
- Are there important determinants in carcinogenicity other than effects on DNA, such as changes in cell proliferation apoptosis, gene expression, immune surveillance, or other influences?

Chronic animal studies may provide important clues to potential modes of action and the relevance of animal tumor findings to humans. In this regard, important factors to consider include tumor types, e.g., those responsive to endocrine influence or those produced by reactive carcinogens; number of tumor sites, sexes, studies, and species showing effects or no effects; influence of route of exposure; the spectrum of tumors (local or systemic sites); and target organ or system toxicity, e.g., urinary chemical changes associated with stone formation or effects on immune surveillance. Other important factors include presence of proliferative lesions, e.g., hepatic foci and/or hyperplasias; progression of lesions from preneoplastic to benign to malignant with dose and time; ratio of malignant to benign tumors as a function of dose and time; time of appearance of tumors after exposure begins; tumors invading locally, metastasizing, and producing death; tumors in laboratory animal sites with high or low spontaneous historical incidence; biomarkers in tumor cells, both induced and spontaneous, e.g., DNA or protein adducts, mutation spectra, chromosome changes, or oncogene activation; and shape of the dose–response curve in the range of tumor observation, e.g., linear versus profound change in slope.

Multisite and multispecies tumor effects are often associated with mutagenic agents or agents (e.g., dioxin) that affect the most basic biological processes, whereas tumors restricted to one sex or species may suggest an influence limited by gender, strain, or species. Late onset of tumors that are primarily benign, that are at sites with a high historical background incidence, or that

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Abbreviations used: BELLE, biological effects of low-level exposures; U.S. EPA, U.S. Environmental Protection Agency.

show reversal of lesions on cessation of exposure may point to a growth-promoting mode of action.

The possibility that an agent may act differently in different tissues or have more than one mode of action in a single tissue must also be kept in mind. This applies equally to carcinogens and noncarcinogens. For example, even essential elements have rather different effects (hence, different modes of action) at different dose ranges (*2*). For example, Se deficiency results in a lowering of glutathione peroxidase but has no effect on succinic dehydrogenase, whereas Se excess affects succinic dehydrogenase as well as other sulfur-containing amino acids. Also, Mn deficiency may result in seizures but excess Mn produces a quite different pattern of neurotoxic effects. Consider too that Mn is possibly protective against lung cancer in smokers but excessive levels of inhaled Mn also raise potential neurotoxicity risks.

Mode of action is also relevant to the selection of a dose–response extrapolation procedure. For example, a default assumption of linearity is appropriate when the mode of action involves gene mutation because of DNA reactivity. If carcinogenicity is secondary to toxic effects that have a threshold, however, an assumption of nonlinearity may be more appropriate. Both linear and nonlinear processes may be involved if, for example, an agent is both DNA reactive and is highly active as a promoter at high doses.

The role of adaptive or defensive mechanisms may also be considered in risk assessment. Again, however, sufficient information is needed to instill confidence that the mode or modes of action are adequately understood. Dioxin and polycyclic aromatic hydrocarbons illustrate the possibility of inducible enzyme pathways that can yield either toxic metabolites or detoxification. Thus, isolating adaptive aspects alone or assuming that such mechanisms are always operative (i.e., in all individuals or at all dose/concentration levels) may not be warranted. Nevertheless, it is important to consider the extent to which such adaptive or defensive effects may occur.

When the effects induced by an agent are not just adaptive but even apparently beneficial, as may be described by a U-shaped dose–response relationship, assessing the health risks posed by such an agent becomes somewhat more complicated (*3,4*). Such complications have arisen in deriving oral reference doses for nutritionally essential trace substances such as Se and Zn (*5,6*). The U.S. EPA has no formal policy or guidance on how to address these situations generally. Each case must be evaluated individually, with care taken to avoid deriving reference values that might overlap with deficient levels of intake. After all, nutritionally essential environmental pollutants are the exception rather than the rule. However, in evaluating agents showing U-shaped dose–response relationships, some questions should be considered:

- Beneficial compared to what? There may be a tendency to presume that different types of effects are arrayed across a dose continuum such that a toxic effect occurs at a high dose and a beneficial effect occurs at a low dose. In fact, multiple effects may occur at any given dose level and some such effects may be judged beneficial whereas others may be judged adverse. For example, caloric restriction may enhance longevity in laboratory animals but it may also affect their reproductive function (*7*). Similarly, moderate ethanol consumption may be associated with lower risk of cardiovascular morbidity but it may also be associated with increased risk of other diseases (e.g., breast cancer) and injury due to accidents (*3*). Although it is worthwhile to bring attention to the possibility of beneficial effects at low levels of exposure, the converse is clearly even more important: risk assessors must be careful to avoid focusing only on apparent benefits and ignoring concurrent adverse effects. A certain relativity of values may also come into play. Consider the human dilemma of quantity versus quality of life in the example of caloric restriction. For some persons a substantial reduction of caloric intake for a potentially longer lifespan may not be an acceptable trade off for the perceived diminished quality of life.
- Beneficial to whom? Even if it is accepted that a beneficial effect is associated with a certain level of exposure to a substance or agent on average, the U.S. EPA is typically required to formulate public health policy and set standards in a manner to protect not just the average person but susceptible subpopulations as well (e.g., the young, the elderly, those who suffer from diseases such as asthma). The question that arises is whether enough information exists on the apparently beneficial effects of an otherwise toxic agent to justify confidence that these effects would be generally experienced across an entire population. There might be some percentage of the population who, possibly because of polymorphisms or other factors, would experience only the adverse aspects of an agent and not the beneficial effects that the average person would receive.
- Beneficial at what exposure level? Although controlled experimental exposures may be suggestive of a U-shaped dose–response relationship with apparently beneficial effects at low levels, can we necessarily relate low in the experimental context to exposures in the actual environment? To illustrate, some experimental evidence from animals on controlled diets suggests that ultra-trace levels of lead may be nutritionally essential (*8*). Regardless of whether the animal evidence is adequate to support this conclusion, perhaps the ultimate question is whether such findings have any practical relevance to anyone on earth, given the global pervasiveness of lead and widespread exposure to it. Dose–response information is not enough to judge risk. An adequate exposure assessment is also needed and it may be that an exposure assessment would show that humans are already in the toxic range of the dose continuum.

As U.S. EPA scientists, our position on BELLE must be guided by scientific data. Cogent data and arguments need to be compiled and presented to support greater awareness of BELLE in the U.S. EPA's risk assessment methods. At present it is not clear that general principles pertaining to BELLE exist for U.S. EPA scientists to consider. Thus, those who wish to advance the consideration of BELLE in public health regulatory contexts bear a certain burden of proof to show enough evidence to support a conclusion that a benefit actually results from low-level exposure to an environmental pollutant.

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