HORMESIS: Implications for Public Policy Regarding Toxicants*

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■ Abstract Protecting workers and the public from toxic chemicals, particularly carcinogens, has been a principal goal of public policy. In the absence of knowing by what mechanism of action a toxicant harms people, regulatory toxicology assumes that even tiny doses can cause harm. Risk aversion has led to legislation and regulation that seek to ban toxic chemicals or lower exposure to trivial levels. Contradicting this policy, many studies show health benefits from low-level exposure to toxicants, including some carcinogens. This is known as hormesis. Thus, hormesis could lead to a fundamental change in the policy for regulating toxic substances. In particular, all toxicants that benefit health at low-level exposures should face similar change in regulations for low-dose exposure. The result would be the dissolving of the source of differences in policy for carcinogens and noncarcinogens at low doses. Two questions must be answered before hormesis can be incorporated into regulatory policy. (a) Are there sensitive individuals who would be harmed at doses that would help most people? (b) Is the hormetic effect toxicant specific or would exposure to just a few toxicants achieve the full benefit from hormesis?

INTRODUCTION: Regulation of Toxicants

Federal legislation such as the Toxic Substances Control Act and Federal Insecticide, Fungicide, and Rodenticide Act commit federal regulatory agencies to reducing harm from exposure to toxicants through a preventive approach. Rather than identifying toxicants by observing increased morbidity and mortality in a population and then inferring its cause, the legislation commits agencies to protect people before there is evidence of harm.

This preventive approach spawned the field of regulatory toxicology. Government toxicologists are asked to identify substances that would harm humans and then determine a safe dose. In the absence of knowing by what mechanism of

*See related article on page 15: “U-Shaped Dose-Responses in Biology, Toxicology, and Public Health” by EJ Calabrese and LA Baldwin.
action a toxicant harms people, toxicologists assume, for example, that rodent carcinogens are human carcinogens and that even tiny doses can cause cancer (1).

Even when human data are available, as with leukemia caused by benzene, it is impossible to establish whether cancer incidence is raised at low levels of exposure. For example, it would be all but impossible to design a study that could isolate a 1% increase in cancer incidence. Thus, because the data cannot establish the dose relationship at low doses, regulators assume that cancer incidence is proportional to dose for even extremely low doses.

However, hundreds of studies show benefits, not harm, from low-level exposure to toxicants (3). Hormesis, the notion that low doses of toxicants can enhance health, contradicts two basic assumptions of risk analysis: The incidence of harm is not proportional to dose at low doses; and a toxicant could improve health, not cause harm, at low doses. Thus, regulatory toxicology might be completely wrong in assuming harm at low doses. The legislation and regulations designed to protect people might be wasting billions of dollars each year and actually harming public health by preventing low-level exposures.

For example, benzene was first shown to cause cancer in Turkish shoe workers at exposure levels at or exceeding hundreds of parts per million (5). Background levels of benzene in the United States are a few parts per billion. What are the public health implications of actions that lower benzene exposure from 5 ppb to 3 ppb? The usual risk assessment model would assume that the incidence of leukemia is proportional to dose. Thus, if 260 million Americans experienced a 2-ppb decrease in benzene exposure, risk analysis implies that there would be dozens fewer cases of leukemia each year. In contrast, hormesis suggests that this lower exposure is likely to worsen health or, at best, to have no beneficial effect.

Hormesis squarely challenges the standard risk analysis model and thus the basis for regulation of toxicants at low concentrations. Rather than protecting people from low-level exposure to toxicants, hormesis suggests that public health officials should be encouraging or even mandating some toxicant discharges.

Another implication of hormesis is to dissolve the distinction between carcinogenesis and other adverse response at low doses. Past studies find that, for some substances tested, carcinogens are similar to other toxicants in improving health at low doses. If so, the current regulatory distinctions are inappropriate.

THE IMPLICATIONS OF HORMESIS FOR REGULATING TOXICANTS: Qualifications

The above interpretation of hormesis may be simplistic. Calabrese & Baldwin (3) suggest that the hormetic response may be due to activating the immune system. If so, people with undeveloped or compromised immune systems would not display the beneficial effect at low exposures. For example, babies, people weakened by severe malnutrition or disease, or those with aplastic anemia or AIDS would be less likely to display a hormetic response. If so, more than 95% of the population
could benefit from being exposed to an additional 2 ppb of benzene, but the 5% with compromised or nonworking immune systems could be hurt.

A related issue is estimating the dose at which the greatest beneficial (hormetic) response occurs. This dose is likely to vary from substance to substance and even from person to person. For healthy people, toxicant A might have a beneficial effect in the parts per hundred range whereas toxicant B might be harmful above a few parts per billion. Similarly, a newborn baby or person with AIDS might be harmed by toxicant A at a few parts per billion. To find a safe exposure level, regulators would have to know the hormetic range for each toxicant for each population group. Answering this question is impossible because it would require experimenting with both healthy and compromised individuals to find the dose levels at which benefits and harm occur. Would a human subjects committee permit highly compromised individuals to be exposed to any level of a toxicant?

MECHANISM OF ACTION

Although there is ample laboratory data demonstrating a hormetic dose-response relationship, scientists are more likely to incorporate the notion into their thinking when they understand the mechanism of action. Similarly, whether a chemical is likely to display a hormetic effect at low dose depends on the mechanism of action that causes harm. In 1996, the Environmental Protection Agency (EPA) formally announced that the agency would rely on a mechanism-of-action approach in regulating carcinogens, when science established the mechanisms (9). In other words, the EPA would set aside the default assumptions when mechanisms of action had been established. These mechanisms of action could demonstrate that there is a threshold in chemical carcinogenicity.

For chemicals causing kidney cancer in male rats due to an alpha-2u globulin mechanism, the EPA agrees that the burden has been met (6). For formaldehyde, some elegant science (which I find convincing) has so far failed to convince the EPA that there is a threshold for nasal cancer due to formaldehyde (7).

The point is that hormesis is a (or a set of) mechanism(s) of action for carcinogenesis at low-level exposures. Because the EPA's policy is to accept mechanism-of-action explanations, it should judge hormesis in the same way it judges other proposed mechanisms. No change in EPA policy is required.

The practical importance of the EPA's 1996 policy on mechanisms of action is unclear. If the EPA demands a high standard of proof, such as scientific consensus, few mechanisms of action will be accepted and hormesis cannot become important for regulatory policy. Whether the EPA accepts a proposed mechanism of action depends on public attitudes as well as scientific data. The public abhorrence of cancer and other toxic effects leads EPA officials and scientists to demand a high level of proof before deciding that a substance that harms rodents is safe for humans.
RISK ANALYSIS UNDER HORMESIS

Assuming that the mechanism of action involves immune system stimulation, does hormesis stimulate the immune system generally or is the response toxicant specific? If there is a general stimulation, almost all of us are exposed to enough toxicants; more stimulation is not needed. For a laboratory rodent reared in an environment devoid of toxicants, low-level exposure to a toxicant could have a large stimulatory benefit; little or no benefit would be expected for humans or rodents who live in a “sea of toxicants.” Thus, if the effect of hormesis is a general stimulatory response, there might be little or no benefit to additional low-level exposure to toxicants. At the opposite extreme, the immune system stimulation might be toxicant specific. In this case, exposure to low levels of each toxicant would be beneficial to most people.

If the vast majority of the population manifests a hormetic response, risk analysis must be revised. A risk analysis might find that a 2-ppb increase of benzene in the air helps 95% of people while harming 5% of people. If so, the estimated cancer increase due to additional benzene exposure would be relevant only for the 5%, reducing harm by a factor of 20, with possibly some offsetting benefit to the other 95%. The Food and Drug Administration often faces this sort of problem with food additives. Nonnutritive sweeteners in soft drinks might help most people control their weight while posing risks to others. Enriching flour with folic acid could help many people, but it potentially harms others. The Food and Drug Administration seeks to manage the adverse effects by educational campaigns to alert those at risk to the possible harm and by labeling the foods. Although avoiding the additional 2 ppb of benzene would not be easy, public health officials could take other steps to identify and help protect the 5% at greater risk.

CONCLUSION

Calabese & Baldwin (3) make an important contribution by pointing to the contradiction between the standard assumptions of regulatory toxicology and the data showing health benefits at low levels of exposure. Current regulation of toxicants at low exposures might be wasting billions of dollars and harming the health of the groups they are designed to protect. However, before public policy can be refashioned to incorporate this fundamental change, we need to understand (a) the effects of low doses on the most sensitive individuals and (b) whether the hormetic effect is general for all or for wide classes of toxicants or whether it is toxicant specific. If the stimulatory effect already takes place because of current low-level exposures to toxicants, or if there are many sensitive individuals who would be harmed by low doses, hormesis might have no effect on the policy for regulating toxic substances.

Public policy toward potentially toxic chemicals is driven by public concern. This concern can reach hysterical levels, as with silicone breast implants,
precluding scientific input (2). Proposed changes in policy are unlikely to be adopted unless they are compatible with public perceptions and desires. Fortunately, a scientific literature has been exploring public risk perception (4, 8).

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