Redrawing the Dose–Response Curve

Wen he claimed that a little bit of dioxin might be good for people—might even prevent cancer in some cases—risk assessor John Graham brought down a firestorm of indignation during Senate confirmation hearings in 2001. Graham survived the hearings to take his place within the U.S. White House Office of Management and Budget, although his views on dioxin, which first emerged when he was on the U.S. EPA Science Advisory Board, were roundly dismissed by senators and the public (1).

But not by toxicologist Edward Calabrese at the University of Massachusetts, Amherst, who says that Graham was talking about the 1978 Kociba study (2) and that Graham was right. Richard Kociba, a Dow Chemical pathologist, and his colleagues conducted a two-year study of 485 white rats whose food was spiked with dioxin. Kociba’s main finding is clear—dioxin causes cancer. But the paper also shows that dioxin has an anticancer effect at low doses. Despite a multitude of subsequent dioxin studies, the paper remains influential because it describes the largest, longest, and most detailed dioxin experiment.

Toxicologists widely acknowledge that at low doses the Kociba group found reduced tumor incidences of the pituitary, uterus, mammary gland, pancreas, and adrenals, says Joseph Rodricks, health sciences director at ENVIRON environmental consultants in Arlington, Va. They also agree that these findings suggest that dioxin exposure may exert an anticarcinogenic effect, but most toxicologists view this as a curiosity.

But what if it’s not just a curiosity? What if, at low doses, many contaminants elicit an effect opposite to their high-dose effect? That’s just what Calabrese believes. To him, the Kociba study is a manifestation of the widespread phenomenon of hormesis, which is generally characterized by low-dose stimulation and high-dose inhibition. In other words, low doses can have the opposite effect of high doses.

A curious effect
Hormesis seems to be gaining respectability. This winter the U.S. National Academy of Sciences is hosting a meeting to review and evaluate the science of hormesis and is considering whether to sponsor a major study on hormesis and its impact on regulations, according to staffer James Reisa.
The hormesis concept could upset the basis for environmental regulations.
Hormesis occurs in many everyday activities. Fancy an occasional drink? Moderate drinking reduces the risk of heart disease, a hormetic effect that is the opposite of heavy drinking. Take multivitamins? Many vitamins and essential trace minerals like selenium and chromium are beneficial at low doses but harmful at high doses. Exercise regularly? Exercise creates low-level biochemical havoc within cells, which, in turn, results in a beneficial effect. These are just a few examples of hormesis.

Hormesis demands that toxicologists rethink their science to focus on the low doses that generally characterize the real world, says Calabrese (Figure 1). Traditionally, toxicologists study the effects of high-dose exposure to environmental contaminants on laboratory animals. They lower the dose until they find a concentration at which there is no observed adverse effect level (NOAEL). To determine the threshold for noncarcinogenic contaminants, they apply uncertainty factors to the NOAEL to account for differences between lab rats and humans. The result is a reference dose that is usually several hundred times less than the NOAEL. For carcinogenic chemicals, the dose–response curve is extrapolated to zero. The “approved” dose then corresponds to an acceptable level of public risk.

Traditional toxicology assumes that dose–response curves are always monotonic—that is, higher doses have a greater effect than lower doses. So, if no adverse effect is found at high levels, then it is assumed that the contaminant is safe at any lower dose. But if low doses can have the opposite effect of high doses, then toxicologists need to pay attention to the low-dose part of the dose–response curve. The hormesis perspective could challenge the underpinnings of the hazard assessment process that forms the basis for environmental regulations, says Calabrese. The idea that there may be no safe exposure level for many environmental contaminants, especially carcinogens such as radiation and dioxin, could be relegated to history’s dustbin.

Hormesis isn’t the only theory that is critical of toxicology for making assumptions about low dose. Scientists who study endocrine disrupters also believe that many toxicological tests have led to erroneous conclusions about safety. But instead of believing that low doses can have unexpected beneficial effects, they believe that low doses can have unexpectedly adverse effects.

Reproductive biologist Fredrick vom Saal at the University of Missouri, Columbia, brought non-monotonic endocrine-disruptive effects into the spotlight in 1997 when he linked fetal exposure to endocrine disrupters in mice to postnatal impacts (4). vom Saal found that exposure in the womb to the plasticizer bisphenol-A and the synthetic hormone diethylstilbestrol led to adult male mice with heavier prostates. If the mice were exposed to higher doses, there was no enlargement. In fact, the prostates of mice exposed to higher doses were smaller than those of unexposed mice. These results remain controversial, but an independent review organized by the National Toxicology Program also found evidence for non-monotonic low-dose effects (5).

These data should not be altogether surprising, says John Doull, professor emeritus at the University of Kansas Medical Center in Kansas City and the co-author of the leading textbook on toxicology: “Pharmacologists know that drugs produce different effects at different doses—so do contaminants.” He adds that it’s not such a stretch to recognize that “low-dose effects can be beneficial or adverse in comparison to high-dose effects. The challenge for toxicology as a discipline is to figure out how to detect these effects.”

**FIGURE 1**

Three models for the dose–response curve

The (a) linear, (b) threshold, and (c) hormetic models for the dose–response to a toxicant. The linear model assumes no safe dosage, whereas the threshold model marks a no observed adverse effect level (NOAEL) below which the dosage is harmless. Hormesis, on the other hand, postulates that at doses below the NOAEL, there is a positive effect. The hormetic zone is estimated to cover a 10-fold dose region, with a maximum stimulation that averages 130 to 160% of the control. (Adapted with permission from Ref. 3.)
The case for hormesis

The emphasis that hormesis places on dose sounds a bit like the famous remark that “the dose makes the poison” by Paracelsus, the 16th-century father of toxicology. In fact, the concept of hormesis has been around for a long time, but it became discredited through an association with homeopathy—the medical philosophy that believes in the high potency of extremely dilute solutions. By the 1900s, hormesis was marginalized, and an association in the 1930s with radiation as a cure-all appeared to have closed the book.

But Calabrese and his colleague Linda Baldwin, also at the University of Massachusetts, have rehabilitated the concept through a monumental undertaking. Using a rigorous set of a priori defined criteria, they scoured tens of thousands of toxicology papers for evidence of hormetic effects. Of the papers that passed this evaluation, 40% showed evidence of hormesis—in plants, invertebrates, vertebrates, and even microbes (Figure 2). The indefatigable team recently looked for hormesis within the well-designed and comprehensively reviewed dose–range finding studies done by the National Toxicological Program. They found hormetic responses in more than 60% of studies of male mice and more than 40% that involved female mice. On this massive foundation of papers they’ve built what many toxicologists and some regulators agree is a strong case for the widespread presence of hormetic effects.

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To promote this work, Calabrese and other researchers started a newsletter in 1990 called BELLE, for Biological Effects of Low Level Exposures, with an advisory committee of academics, government regulators, and industry researchers (7). A major toxicology reference work published in 2001 suggests that the implications of hormesis for toxicological risk assessment may be profound (8). And to top it off, last

### Figure 2

Some well-known hormesis-like effects

The underlying concept for hormesis is already well established: (a) crude oil extract and cyanobacteria photosynthesis, (b) penicillin and bacterial growth, (c) 2,4-D and oyster growth, and (d) arsenite and human lymphocyte DNA synthesis. (Adapted with permission from Ref. 6.)
year BELLE grew big enough to support a refereed scientific journal, *Nonlinearity in Biology, Toxicology, Medicine*, which is published quarterly.

On the basis of all the data he has amassed, Calabrese is confident that hormesis is a general phenomenon. “I don’t believe that it is wise or fair to attempt to evaluate this on a compound-by-compound basis,” he says. He writes in *Nature*, “The hormetic model is not an exception to the rule—it is the rule” (9). In other words, toxicologists and regulators should make hormesis their default assumption and pay attention to the low-dose part of the dose–response curve.

“*There’s nothing inherent that would prevent us from considering nonlinear relationships,*” says J. Michael Davis.

Critics question how such disparate effects can have the same mechanism. Such criticism is wrong-headed, says Doull. “Different doses can act on different parts of the body through different mechanisms. There is no reason to expect that a range of doses would have a common mechanism,” he says.

Calabrese has identified some common features of hormetic responses. The benefits of the low-dose stimulatory responses are modest, on average about 30 to 60% greater than with no hormetic dose. The greatest effect occurs on average at a dose about 5-fold below the NOAEL (Figure 1c). Here is a hypothetical example: Say that in the general population of dragons, about 10 in every 100 get dropsy. Dragonsbane increases the incidence of dropsy with a NOAEL of 200 parts per billion (ppb). Hormetic effects from dragonsbane at a dose of 40 ppb might be expected to reduce the incidence of dropsy to 5 in every 100. If the general dragon population doesn’t get dropsy, then there would be no hormetic effect to a low dose.

These characteristics have huge implications for the design of experiments aimed at studying hormesis. Such experiments need to have many more low doses. In addition, the experiments may have to run longer because what starts out as a low-dose inhibition often turns into stimulation as an organism...
There are sound mathematical reasons for doing an operating in a high-dose world, says Thomas McKone, "effect," he says. See studies that have a sufficient number of doses considering hormesis in regulatory toxicology. "We don’t see instances. But there's not enough evidence to while high doses are harmful.

Metals, which recognize that low doses are beneficial between beneficial and harmful doses is currently em-

For Toxic Substances and Disease Registry. "There’s a currently don’t foresee any revolutionary changes, says Christopher De Rosa. "There’s nothing inherent that would prevent us from understanding, says Doull. "Low-dose effects present regulators with a huge difficulty. Where there are benef-

Regulators are keeping an eye on hormesis but currently don’t foresee any revolutionary changes, says Christopher De Rosa.

Davis hastens to add that even if hormesis were proven, its impact on environmental regulations is unclear and would raise a host of difficult questions. For example, a low dose that has a beneficial effect on a healthy adult might have a different effect on children or elderly people. There’s also the question of background exposure. Take lead, for example; thanks to the industrial revolution, we all carry much higher lead levels in our bodies than did preindustrial populations, says Davis. Even if ultratrace amounts of lead might have a beneficial effect on people living in a pristine environment, we already carry too much.

Regulators’ reluctance to embrace hormesis is understandable, says Doull. “Low-dose effects present regulators with a huge difficulty. Where there are beneficial low-dose effects, the regulators need to act to avoid the bad effects, but not the good ones. It’s not enough to just ban something or insist that the lowest possible exposure is always the best,” he says.

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Regulators remain reluctant

But to do these experiments, hormesis supporters will have to convince the regulators who inadvertently constrain the universe of data that interests toxicologists, Calabrese said at a conference in May 2003. Currently, the toxicity studies funded by regulators follow two paradigms: the threshold model for noncarcinogens and the linear low-dose model for carcinogens (Figure 1). For the threshold model, toxicologists start lab animals at a high dose and work downward until they find a NOAEL. The recommended safe dose or reference dose is often 2 to 3 orders of magnitude lower than the NOAEL.

For cancer risk assessments, toxicologists currently assume that there is no safe exposure—an increment of exposure results in an increment of risk, so that the relationship between dose and response is linear at low dose. Thus, the only safe dose is no dose. But cancer assessments are changing. EPAs most recent guidance doesn’t insist on a linear low dose (11). “There's nothing inherent that would prevent us from considering nonlinear relationships,” says J. Michael Davis at EPAs National Center for Environmental Assessment in Research Triangle Park, N.C.

Regulators are keeping an eye on hormesis but currently don’t foresee any revolutionary changes, says Christopher De Rosa, director of the toxicology division at the Centers for Disease Control’s Agency for Toxic Substances and Disease Registry. “There’s a growing body of evidence across a range of different disciplines showing dose-dependent transitions in effects,” he says. He also notes that the switch between beneficial and harmful doses is currently embodied in the U.S. Food and Drug Administration’s recommendations for chromium(III) and other trace metals, which recognize that low doses are beneficial while high doses are harmful.

EPA’s Davis agrees that hormesis, when narrowly defined as a stimulatory effect, appears to occur in some instances. But there’s not enough evidence to consider hormesis in regulatory toxicology. “We don’t see studies that have a sufficient number of doses and the statistical power to demonstrate a strong effect,” he says.

Government toxicologists shouldn’t apologize for operating in a high-dose world, says Thomas McKone, a risk assessor at the University of California, Berkeley. There are sound mathematical reasons for doing animal experiments with high doses. High doses generate relatively big effects that are relatively easy to study with confidence. A statistically reliable low-dose study would require a ridiculously large number of animals, he says.

Toxicologist Michael Dourson says that regulators ignore evidence for hormesis because the rationale of the public policy that guides them is to protect public health. “This is not a willful disregard of hormesis or other low-dose effects,” says the former EPA risk assessor, who now directs Toxicology Excellence for Risk Assessment, a nonprofit corporation based in Cincinnati, Ohio.

References

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