People have believed since antiquity that tiny doses of toxicants can be healthful. Now hormesis, a concept once discredited in scientific circles, is making a surprising comeback

Sipping From a Poisoned Chalice

Dioxin and its chemical cousins are among the most deadly compounds on Earth. Spike a rat's water with 10 parts per billion—the equivalent of 7 teaspoons of dioxin dissolved in an Olympic-sized swimming pool—and there's a 50/50 chance that the rat will die of liver cancer. Yet even tinier concentrations of dioxins fed to rats inhibit tumors. The seemingly paradoxical findings have some scientists suggesting what would have been unthinkable not long ago: testing modified dioxins as an anticancer agent in humans.

Dioxin is a poster chemical of a bold campaign: to rehabilitate the old saw that poisons or radioactivity at low doses are good for you. The concept, known as hormesis, has been kicking around for decades but until recently had been considered a marginal effect tainted by an unfortunate association with homeopathy. The improbable return of hormesis from the scientific wilderness, however, has riven the toxicology community.

A flurry of new findings and a reexamination of old ones have thrust hormesis into the limelight. Many drugs, vitamins, and essential minerals exhibit hormesis, as does alcohol: Moderate drinking lowers risk of heart disease, whereas higher levels are associated with higher risks of heart and liver disease. Calorie restriction, the sole indisputable means of extending an animal's life span, may also be a form of hormesis, proponents say: The lack of calories stresses an organism, firing up responses such as DNA repair enzymes and apoptosis, or programmed cell death, which protect the body from environmental insults. And low doses of many chemical toxins, from cadmium to pesticides to dioxin, appear to have paradoxical and possibly beneficial effects on organisms. The heightened scientific scrutiny has generated juicy headlines: "Whatever doesn't kill you might make you stronger," begins an article in the September issue of *Scientific American*. "A little poison can be good for you," declares a recent issue of *Fortune*.

Hormesis is alluring because it challenges the conventional wisdom that toxicants and radiation punish the body at even the smallest of doses. If hormesis is as pervasive as its backers suggest, it could mean that regulations for many chemicals, from arsenic in drinking water to polychlorinated biphenyls at Superfund sites, are too stringent. "It would fundamentally change the whole risk-assessment paradigm," says Edward Calabrese, a toxicologist at the University of Massachusetts, Amherst, who over the past decade has doggedly compiled thousands of studies indicating that infinitesimal amounts of chemicals can help microbes, plants, and animals grow faster and live longer and healthier. "Hormesis is on the verge of being a milestone in the evolution of risk assessment," adds John Doull, professor emeritus at the University of Kansas Medical Center in Kansas City and the co-editor of the premier toxicology textbook.

Crusader. Edward Calabrese has spent 13 years urging toxicologists to recognize that chemicals can have opposite effects at high and low doses.

But others contend that such conclusions reach far beyond the science. Although paradoxical dose responses are "real," the concept of hormesis "has been taken over by rhetoric," says William Farland, risk assessment chief at the U.S. Environmental Protection Agency (EPA). It's too soon, he says, to conclude that the benefits of low-level exposures outweigh the risks. Moreover, a recent wave of studies has found that some hormonelike toxicants known as endocrine disrupters may be *more* harmful at small doses than they are at larger ones. The declaration that low-dose effects are often healthy "is where Ed [Calabrese] falls off the edge of the earth," charges Frederick vom Saal, a reproductive biologist at the University of Missouri, Columbia.

One challenge is to pin down the mechanisms governing low-dose effects. Industry may well see it in their interests to pony up significant funds for such research. But what it will take to get regulators to buy into the concept is another question, says Joseph Rodricks, a risk assessment expert at Environ Corp. in Arlington, Virginia. Hormesis, he says, "is going to be a hard sell."

The dose makes the poison?

Hormesis was first described in 1888 by a German pharmacologist, Hugo Schulz, who observed that small doses of poisons seemed to stimulate the growth of yeast. Schulz also drew on animal studies of drugs at low doses carried out by Rudolph Arndt, a German physician. What became known as the Arndt-Schulz law lost credibility in the 1920s and '30s, however, because Arndt was an adherent of homeopathy, the notion that extremely dilute solutions, often containing a few or no molecules of an active substance, are therapeutic. Hormesis, coined in 1943, involves concentrations at least 10,000 times higher. They "are a direct continuation of the traditional dose response," says Calabrese.

Calabrese, a lanky, soft-spoken man with thick glasses and floppy gray hair, says hormesis first caught his attention in 1985, when he received a flyer for a meeting probing the question of whether low-dose radia-

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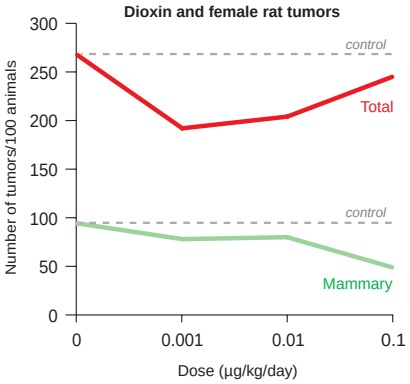
tion is beneficial (see sidebar, p. 378). It rang a bell: As a graduate student, Calabrese had noted that peppermint plants dosed with tiny amounts of phosfon, a herbicide used to stunt growth, grew faster than control plants. Plotting growth on the y-axis against dose on the x-axis, his data formed an inverted U-shaped curve instead of the usual S-shaped or linear plot for a dose-related effect (see diagram).

Calabrese began collecting examples of similar dose responses. He also won funding from various federal agencies, including EPA, for a program of analyses and workshops called Biological Effects of Low Level Exposure (BELLE) and launched a thrice-a-year newsletter with commentaries from invited experts of all stripes on low-dose toxicology. Farland, a member of BELLE's board, says that EPA supports the program because agency scientists too have noticed that many chemicals exhibit U-shaped dose-response curves and want to understand the phenomenon better.

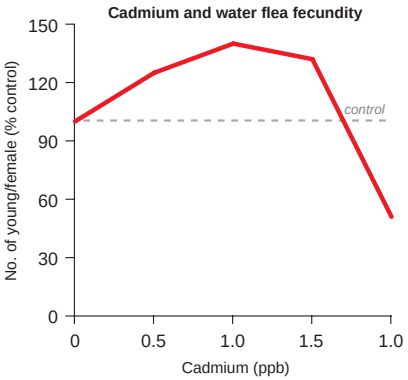


Calabrese suspected that hormesis is commonplace. To find out, he and Amherst colleague Linda Baldwin got about $110,000 from an industry group to comb the literature for studies demonstrating hormesis. They uncovered thousands: plants dosed with herbicides or metals growing lusher; bacteria flourishing in the presence of tiny amounts of antibiotics; immune cells treated with arsenic proliferating faster; insects doused with pesticides or alcohol living longer and producing more eggs; rats fed a little saccharine developing fewer tumors. "We see it across the whole plant and animal kingdom" and at "essentially every endpoint," says Calabrese. The effects, he says, are modest but consistent: typically a 30% to 60% greater response than in controls.

In his latest analysis in the February 2003 issue of *Toxicological Sciences*, Calabrese looked at how frequently hormesis occurs, including all the dose-response curves he could find that featured at least two doses below the established no-effects level and a control. From 195 papers that met this criterion, he reported that hormetic dose-response curves outnumbered curves showing no effect at the lowest doses by 2.5 to 1.

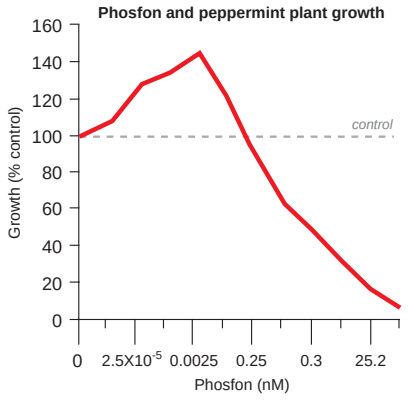
Healthy provocations

The likely explanation for hormesis, Calabrese and others say, is that small doses of most harmful substances stimulate a beneficial response that enhances normal function and girds an organism against subsequent stresses. Potential mechanisms are manifold: enzymes that repair damaged DNA, stimulated immune responses, apoptosis that eliminates damaged cells that would otherwise become cancerous. The universal factor, according to hormesis enthusiasts, is that minute doses prod such responses into a modest overreaction. For example, heavy metals such as mercury spur synthesis of proteins called metallothioneins that remove toxic metals from circulation and likely also protect cells against potentially DNA-damaging free radicals produced through normal metabolism.



The puzzle of hormesis. Low doses of phosfon, a herbicide, caused plants to grow better (*below*); small amounts of dioxin, a carcinogen, reduced tumors in rats (*left*); and a little cadmium, a toxic metal, caused water fleas to produce more young (*above*). The effects were reversed at higher doses.

To date, however, molecular studies on hormesis-like, biphasic dose responses have largely been carried out only on drugs, Calabrese says. Detailed studies have focused on a few dozen drugs known to act on receptors for neurotransmitters or other cell messengers. The receptor for a specific compound tends to come in two flavors: stimulatory or inhibitory. When the concentration of the drug is low, the stimulatory type of receptor is more likely to be activated; at higher levels, inhibition takes over. Opiates work this way, for example. "It probably occurs more than we're willing to admit," says Richard Bond, a pharmacologist at the University of Houston, Texas. Such effects are often thought to be spurious or uninformative, Bond says: "We draw a line to make it go away."



Although many scientists applaud Calabrese's tenacity for bringing hormesis into the scientific mainstream, they point out that not all hormetic effects are beneficial. For example, vom Saal stunned his colleagues with a 1997 report linking extremely low levels of the plastics ingredient bisphenol-A fed to pregnant mice and enlarged prostate glands in their male offspring—the reverse of what is observed at higher doses. The study, which industry quickly attacked, led to a U.S. National Toxicology Program review that found that although vom Saal's result had not been reproduced, other experiments support the idea that hormonelike environmental pollutants can trigger effects at far below the levels usually tested (*Science*, 27 October 2000, p. 695).

More such studies have come along since, including two high-profile papers last year from University of California, Berkeley, toxicologist Tyrone Hayes linking tiny concentrations of atrazine with reproductive deformities in frogs (*Science*, 1 November 2002, p. 938). Echoing Calabrese, vom Saal says that "if there are exceptions to linearity, you have to revise the system."

A regulatory revolution?

Scientists are deeply divided, however, over just how the risk-assessment paradigm ought to be revised. The Texas Institute for Advancement of Chemical Technology Inc., which initially sponsored Calabrese's database, put out a flyer in 1998 citing examples of hormesis such as dioxin, mercury, and the pesticide lindane; the brochure declared sunnily that hormesis could allow "society to enjoy the benefits of many chemicals that have been banned." Calabrese says he doesn't think it's that black and white. "There will be circumstances where the response appears to be beneficial, and cases where any change [in a standard] might not be advisable," he says. Nevertheless, Calabrese argues that chemical carcinogens are being overregulated:

SOURCES: (TOP TO BOTTOM) ADAPTED FROM ORIGINAL DATA FROM BODAR *ET AL.*, *AQUATIC TOXICOL.* **12**, 301 (1988); KOCIBA *ET AL.*, *TOXICOL. APPL. PHARMACOL.* **46**, 297 (1978); CALABRESE AND HOWE, *PHYSIOL. PLANT.* **37**, 163 (1976)

Hormesis "emphasizes that there are thresholds for carcinogens," and "the economic implications … are substantial," he wrote in a commentary in *Nature* earlier this year.

But vom Saal says that hormesis suggests exactly the opposite. He says that regulators are missing a whole suite of harmful effects of chemicals that haven't been adequately tested at low levels. Even if the effect appears beneficial—faster growth, larger offspring—that's not necessarily a good thing, he points out. Obesity, for example, is associated with other diseases later in life. "Anything but what would normally be there shouldn't be happening," argues vom Saal.

Hormesis proponents also err by focusing on single endpoints—such as cancer—while ignoring other endpoints, Rodricks and other skeptics argue. Christopher Portier of the National Toxicology Program cites an example from a study his group published in 1993 on cyclophosphamide, a cancer drug that stops cell division. At low doses, the drug seemed to protect rats from flu virus; all survived, unlike controls. But when injected with tumor cells, these animals were more likely to develop cancer. The apparent reason, Portier says, is that the drug skewed the animals' immune cell population, revving up T helper cells, which fight viruses, but reducing natural killer cells, which guard against foreign cancer cells. The end result was both beneficial and harmful. "What would you do with that finding if it were an environmental compound?" Portier asks. The case for the dioxins is murky as well. Tiny amounts of these chemicals suppress breast tumors in animals but can promote liver tumors. Only when all tumors are combined do the dioxins exhibit a U-shaped curve.

Another cautionary tale is cadmium. Animal studies suggest that low doses of this element could help prevent some cancers, Calabrese notes. But in the August issue of *Nature Medicine*, researchers reported that at these low doses—even below those recommended as safe in the diet—cadmium acts as an endocrine disrupter in female rats, causing growth in uterine and breast tissues that could lead to cancer.

To take a possibly beneficial effect into account in risk assessment, an agency would have to know "how all the pieces fit together," including mechanisms, says Farland. EPA's latest cancer risk assessment guidelines encourage researchers to use that kind of data; the agency is also making an effort to integrate cancer and noncancer endpoints. "We are certainly interested in complex dose response function," but "we're really trying to get at the biology that underlies the phenomenon," Farland says.

That won't come cheap, however. Because spontaneous cancers are rare in rodents, a statistically robust study showing that a toxicant cuts cancer risk would require lots of animals. "I'd have to have pretty convincing evidence before killing 5000 animals to prove the existence of a suppression effect," Portier says. Toxicologist David Eaton of the University of Washington, Seattle, agrees. For carcinogens, he says, "I don't think the idea of hormesis is going to greatly influence the way bioassays are done. It's just too expensive … you'll never be able to characterize [a hormetic effect] to the point where people think it's real."

But the spotlight on hormesis is unlikely to fade anytime soon. The U.S. National Academy of Sciences is mulling whether to sponsor a study of "the science of hormesis," says staffer James Reisa. Calabrese will lead a roundtable on hormesis at the Society of Toxicology's annual meeting in Baltimore next March, and he has been organizing international conferences on hormesis thanks to a hefty grant from the U.S. Air Force, which is interested in the phenomenon because of issues such as cleaning up jet fuel spills and safety in space flight. And a journal that debuted this year, *Nonlinearity in Biology, Toxicology, and Medicine*, brings together on its editorial board scientists on both sides of the hormesis debate.

Calabrese and likeminded scientists are bullish on the prospect of their colleagues coming around to the importance of hormesis, which they are convinced will transform medicine, toxicology, and pharmacology. Many skeptics, however, are neither fomenting such a revolution nor rooting for it to begin. **–JOCELYN KAISER**

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Nuclear Physics

Proton Guns Set Their Sights on Taming Radioactive Wastes

Once mooted as energy sources, nuclear reactors that substitute particle accelerators for chain reactions are taking long-range aim at a new mission

KUMATORI, JAPAN—On the grounds of Kyoto University's Research Reactor Institute, workers have dug into a hillside to give a 30-year-old experimental nuclear reactor an unusual companion: a proton synchrotron. When it starts up in fall 2005, the synchrotron will fire protons into the heart of the reactor, straight down the axis of a cylinder of heavy metal wrapped in a core of nuclear fuel. Neutrons dislodged from the target will hurtle into the fuel, shattering atoms as they go.

It may seem a roundabout way to generate a nuclear reaction, and it is. But this type of accelerator-driven system (ADS), as it's called, isn't primarily designed to generate power. Instead, its aim is to transform some of the nastier ingredients of spent reactor fuel into less troublesome elements. The technology "has a unique role to play in treating nuclear wastes," says Stefano Monti, a nuclear physicist at the Italian National Agency for New Technologies, Energy, and the Environment (ENEA) in Rome.

Kyoto University, with its $10 million Kumatori Accelerator-driven Reactor Test Facility (KART), is not alone. By the end of this year, the Joint Institute for Nuclear Research (JINR) in Dubna, Russia, expects to start building a $1.75 million experiment chamber for nuclear reactions at an existing proton accelerator. And ENEA, the French Atomic Energy Commission (CEA), and Germany's Forschungszentrum Karlsruhe are joining forces for the $22 million TRIGA Accelerator-Driven Experiment (TRADE), which will add a proton accelerator to an experimental reactor at ENEA's Casaccia Research Center in Rome. The three partners expect to commit to funding the project within this year and hope to

Getting real. In Kyoto, Kaichiro Mishima and colleagues are building the first complete accelerator-driven system.