Hypothesis: A tiny dose of a chemical causes a greater biological response than a small or moderate dose. Sound ridiculous? Sure does. But that idea, known as hormesis, sounds just as wacky as when Einstein outlined quantum mechanics and Wegener proposed continental drift (and we know how those turned out).

When presented with quantum entanglement, Albert Einstein derided it as spooky action at a distance. When meteorologist Alfred Wegener proposed his theory of continental drift, he was mocked [1]. And when internist Barry Marshall’s suggestion that ulcers were caused by a bacterium was dismissed by the biomedical community, he swallowed a flask-full [2] of the stuff to prove his point.

What these three completely unrelated topics quantum entanglement, continental drift, and ulcers as an infectious disease have in common are two striking features: (1) they sounded completely nuts at the time; and (2) they are demonstrably and undeniably true.

It is within this intellectual milieu that we approach the concept known as hormesis [3] i.e., that tiny doses of a particular chemical can cause a greater biological response than small or moderate doses. Sound ridiculous? Sure does. But, crazier things have happened.

One of the cornerstones of any epidemiological investigation into causation is a concept known as dose-response. It is relatively straightforward: The bigger the dose, the bigger the response. If a person drinks one cup of coffee, he will wake up; if he drinks 10 cups, he will bounce off the walls. At some point, the dose becomes so large that it no longer increases the response, which is why the dose-response curve is S-shaped.
Chemicals that are thought to have a hormetic effect, on the other hand, do not have S-shaped dose-response curves. Instead, their curves are J-shaped or U-shaped. Under the hormetic model, low doses of a chemical cause a greater response than high doses. In fact, large doses inhibit a biological response altogether.

Though hormesis sounds like something a homeopath would invent, there is actually plenty of evidence that this effect exists. Perhaps the most infamous involves so-called endocrine disruptors, chemicals that interfere with the effect of hormones in the body. Bisphenol A (BPA), one such chemical that has (rather implausibly) been linked to everything from obesity to male infertility, is thought to act through a hormetric mechanism.

Setting aside the specific debate over BPA, a much larger mystery lurks behind hormesis: How exactly does such a bizarre phenomenon work at the molecular level? A paper in Critical Reviews in Toxicology by Edward Calabrese at the University of Massachusetts tries to answer this perplexing question by examining data on more than 100 agents.

Dr. Calabrese discusses three mechanisms:

1. A single cellular receptor, which interacts with the chemical agent, is responsible for both stimulating and inhibiting the biological response when the chemical is at a low dose and a high dose, respectively. Corticosterone and estradiol, both hormones, have been shown to act via this mechanism.

2. One cellular receptor responds to low doses of an agent by stimulating a biological response, while a different cellular receptor responds to high doses of an agent by inhibiting a biological response. Histamine, an inflammatory mediator, has been shown to act via this mechanism.
(3) A cellular receptor stimulates a low-dose response, but the cause of the high-dose inhibition is unknown. Nitric oxide exemplifies this mechanism.

Suppose you have a high-affinity receptor that is present in small quantities on the surface of a cell. It might be responsible for activating in the presence of a chemical. Then, suppose you have a low-affinity receptor that is present in high quantities on the surface of a cell. It might be responsible for deactivating in the presence of the same chemical. In that way, a cell can respond to both low/high concentrations in different ways.

The fact that the hormetric effect has been widely observed in different kinds of cells using different kinds of receptors strongly suggests that the phenomenon is quite real. Detection of hormesis in whole organisms further underlines that this is not simply an artifact of in vitro research.

Obviously, hormesis has wide biomedical implications. Dosing studies for medication must account for this effect. Furthermore, pollutants once thought to be harmless due to being present at a low concentration in the environment may not be as innocuous as we thought.


Edit: the third paragraph from the bottom was missing in the first published version.