New Study Challenges How Regulators Determine Risk

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A new study of a large U.S. National Cancer Institute database provides the strongest evidence yet that a key portion of the traditional dose-response model used in drug testing and risk assessment for toxins is wrong when it comes to measuring the effects of very low doses, says Edward J. Calabrese, a scientist at the University of Massachusetts Amherst.

The findings, based on a review of more than 56,000 tests in 13 strains of yeast using 2,200 drugs, are published in the journal *Toxicological Sciences* and offer strong backing for the theory of hormesis, Calabrese and his colleagues contend.

Calabrese says the size of the new study and the preponderance of evidence supporting hormesis, a dose-response phenomenon in which low doses have the opposite effect of high doses, is a breakthrough that should help scientists assess and predict risks from new drugs, toxicants and possibly carcinogens. Calabrese says, “This is a fundamental biological principle that has been missed.”

Calabrese says that the field of toxicology got the dose response wrong in the 1930s and this mistake has infiltrated all regulations for low-dose exposures for toxic chemicals and drugs. These low-dose effects can be beneficial or harmful, something that the regulations miss because they are currently based on high-dose testing schemes that differ greatly from the conditions of human exposures.

In this latest study, which uses data from a large and highly standardized National Cancer Institute tumor-drug screening database, Calabrese says the evidence of hormesis is overwhelming. In the study, high doses of anticancer drugs frequently inhibit yeast growth, but at low doses they enhance growth, exactly what the homesis model predicts.

Whether one accepts the hormesis theory is not the critical public policy issue, according to Calabrese. He says that the major issue is that the risk assessments models used by the federal Environmental Protection Agency and the Food and Drug Administration fail to accurately predict responses in the low-dose zone, that is, where people live most of their daily lives.

Calabrese also says challenging the existing dose-response model has profound public policy and health implications. “I believe the hormesis model is the fundamental dose-response and government testing and risk assessment procedures should reflect that,” Calabrese says. For example, in environmental regulations, it has been assumed that most carcinogens possess real or theoretical risks at low levels, and therefore must be nearly completely removed from the environments to assure public safety. Some would contend that if hormesis is the correct model for very low levels, that cleanup standards may have to be significantly changed. Others, however, see the evidence as insufficient for such radical change and worry about other factors that can influence the effects of chemicals in low doses. The new study promises to add fuel to the debate, Calabrese says.

Calabrese also suggests that the findings may have important implications for the pharmaceutical industry and medical practices. He says that hormesis is likely to identify new life-saving drugs that were missed through traditional testing and to markedly improve the accuracy of patient dosing, which will not only improve health outcomes but also reduce adverse side effects.

Source: University of Massachusetts Amherst