Finding a new 'sweet spot' for improving cancer risk assessment

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Edward Calabrese, the University of Massachusetts Amherst environmental toxicologist who has been an outspoken critic of the current linear no-threshold (LNT) approach to risk assessment for radiation and toxic chemicals, now proposes a new approach integrating LNT with hormetic dose-response models. The new strategy, applied to chronic animal bioassays, would reconcile previously conflicting methods to offer "significant improvements" and maximize public health benefits, he and co-authors say. Details appear in the current issue of *Health Physics*.

Calabrese, of UMass Amherst's School of Public Health and Health Sciences, with Dima Yzaji Samoun of George Mason University and Jaap C. Hanekamp of University College Roosevelt in The Netherlands, point out that over the past 30 years there has been increased attention to hormesis, a dose-response risk assessment model providing evidence that low-dose exposure of some chemicals and ionizing radiation are benign or even helpful.

This interest is driven largely by "the major switch from whole animal to cell culture investigations, which has created the opportunity to efficiently and inexpensively test up to 11 concentrations (plus a control group), replicate it eight times, and evaluate the consistency of responses using a 96-well plate," they write. They submit that adding its strengths to complement the LNT approach offers a superior, more verifiable model than before.

"This could and should be a big deal," Calabrese says, because despite the fact that the LNT model was adopted in the 1950s as the gold standard, that was done "without adequate validation" for making accurate predictions in the low-dose zone. He acknowledges, however, that the LNT "has two attractive features, namely ease of application and likelihood to consistently overestimate risk," that allowed it to become dominant.

Calabrese and colleagues do not propose to replace the LNT with a hormesis dose-response model, but instead to reconcile the two such that they offer "optimal public health protection." To achieve this goal, they say "both models are needed." They show how a "convergence" risk estimate can be reached when integrating the two using a standard benchmark dose method.

The authors apply this to the estimate of risk for a bladder cancer model to illustrate how it works in a specific situation. They add that "a practical example of efficient validation is seen with the research of Sukata et al., who retested the capacity of DDT to produce liver tumors using liver foci in the F344 male rat. This short-term study involved a large number of doses, and it confirmed the cancer-causing effects of DDT at high doses while identifying the hormetic response at low doses."

The ability to validate isn't possible with the LNT model, where low risk levels, less than 1 percent, "cannot be confidently detected and render the LNT model falsifiable," Calabrese and colleagues point out. "The capacity to verify scientific models, even when using a short-term predictive biomarker endpoint as in the case of Sukata et al., is an essential feature of any science. This new proposal brings this important feature back to cancer risk assessment," they add, minimizing model error and providing an objective basis for regulation.

Overall, they say, "This novel approach to cancer risk assessment offers significant improvements over current risk assessment approaches by revealing a regulatory sweet spot that maximizes public health benefits while incorporating practical approaches for model validation."

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