

December 17, 2008

Michael F. Jacobson, PhD
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Washington, D.C. 20009

Dear Dr. Jacobson:

We are contacting you today in anticipation of establishing a dialog, based on both our organizations' missions to improve public health. A quick perusal of both our Web sites reveals that on matters of food and nutrition policy, PCRM and CSPI have similar overarching goals, and even some similar campaigns. We commend you for your organization's work in areas such as labeling and signage, children's diets, and prevention of food contamination.

However, we are disappointed to see your recent publications regarding the length and scope of the two-year rodent cancer bioassay, and hope that we can reach a more mutual perspective on this issue as well.

In your November 17 news release,¹ Dr. Devra Davis states, "Waiting for proof of human harm before acting to prevent risk is unethical..." We would agree! PCRM has been calling for the reform of the toxicity testing *status quo* almost since our organizations inception. The current paradigm is slow, inaccurate, open to uncertainty and manipulation, and does not protect human health.

Current reliance on high-dose, apical endpoint studies has been recognized as one of the main shortfalls of our hazard assessment strategy. Just this past March, the Society of Toxicology held a "great debate" motion at its annual meeting in Seattle to abandon the Maximum Tolerated Dose due to concerns regarding confounding effects of such high doses.

In its 2007 report, *Toxicity Testing in the 21st Century: A Vision and Strategy*, the National Research Council's Committee on Toxicity Testing and Assessment of Environmental Agents examines and validates this assumption, and moves forward by proposing a shift from this strategy to one of primarily *in vitro*, high-throughput, human-derived cell and tissue assays that assess chemicals' effects on known toxicity pathways. These perturbations prioritize chemicals for further investigation and extrapolation modeling, and all data is directed and assessed in an iterative process, within a framework of chemical characterization, human experience, biomarker assessment, and sensitivity analysis.

The advantages of this approach are many. Such a transformation will "... provide a stronger, mechanistically based approach for environmental decision-making."² This approach will also

save time, making it possible to address the enormous backlog in assessing chemical hazards—and address burgeoning concerns regarding the assessment of mixtures, synergistic effects, low-dose extrapolation and threshold considerations, and the susceptibility of sensitive subpopulations due to disease, stage of development, or genetic makeup. As we have seen, these concerns are not being adequately addressed within the current [i.e., animal testing] paradigm.

Some regulatory scientists have already committed to implementing this new vision.³ Work has begun at the EPA and NIH, through a Memorandum of Understanding announced earlier this year between NIEHS and NTP, the NIH Chemical Genomics Center, and the EPA's Office of Research and Development. This MOU establishes these institutions intentions to work together to implement new toxicity test methods that are "...more scientifically and economically efficient and models for risk assessment that are more biologically based." This will result in the reduced use of animals and "...an increased ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation."

Let me be clear—these assays are not the Ames assay. Sophisticated suites of hundreds of assays running thousands of chemicals can be performed every few hours. Some toxicity pathways have already been established, and the EPA ToxCast program (<http://www.epa.gov/ncct/toxcast/>) is the first such systematic effort so far. I have included a paper recently published in Toxicological Sciences that discusses current and future research, plus an Integrated Toxicology Program, that the authors propose will take advantage of systems biology techniques to address such challenges as defining toxicity pathways and detecting epigenetic effects. We are interested to hear your thoughts after reading it.

While it is true that this technology is still under development, investment into lengthening the rodent bioassay will take us in the other direction. Multiple scientific reviews show that rodents and humans are different enough to be affected very differently by chemicals in the environment; especially for carcinogenesis.^{4,5} The regulatory community is moving a way from two-species bioassay requirements because systematic reviews of historical databases show no contribution, from such efforts, to the determination of human carcinogens or regulatory action.^{6,7,8} The research you cite should be followed up using human-based methods that investigate the mechanism of action at work, and not be used as an excuse to rely more heavily on unreliable tests.

We hope you are interested in speaking further about this topic. If so, please contact Ms. Sullivan using the information below.

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¹ <http://www.cspinet.org/new/200811172.html>; Accessed 10 December 2008

² Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council. 2007. *Toxicity Testing in the 21st Century: A Vision and a Strategy*, pp. 22. National Academies Press, Washington, DC. Available at: http://www.nap.edu/catalog.php?record_id=11970.

³ Collins F et al. 2008. Transforming Environmental Health Protection. *Science* 319:906-7.

⁴ Knight A and Bailey J. 2006. Animal carcinogenicity studies: 1. Poor human predictivity. *Alternatives to Laboratory Animals* 34(1):19-27.

⁵ Knight A and Bailey J. 2006. Animal carcinogenicity studies: 2. obstacles to extrapolation of data to humans. *Alternatives to Laboratory Animals* 34(1):29-38.

⁶ Ennever F and Lave L. 2003. Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Reg. Tox. Pharm.* 38:52-57.

⁷ Jena, G.B., Kaul, C.L., Ramarao, P., 2005. Regulatory requirements and ICH guidelines on carcinogenicity testing of pharmaceuticals: A review on current status. *Indian J. Pharmacol.* 37:209-222.

⁸ Doe JE, Boobis AR, Blacker A, et al. 2006. A Tiered Approach to Systemic Toxicity Testing for Agricultural Chemical Safety Assessment. *Crit. Rev. Tox.* 36:37-68.