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Mitigating Conflicts of Interest in Chemical Safety Testing

David C. Volz*,† and Kevin C. Elliott‡

†Department of Environmental Health Sciences, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina 29208, United States

‡Department of Philosophy, University of South Carolina, Columbia, South Carolina 29208, United States

While safety testing under the European Union's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) Regulation is a relatively recent development for new and existing industrial chemicals, food/feed additives, and cosmetics, regulatory authorities have long required pharmaceutical and crop protection companies to submit a battery of safety studies for drugs and pesticides prior to approval. Based on a model pioneered by the pharmaceutical industry, crop protection companies now outsource a large majority of safety studies to contract research organizations (CROs) and universities as a strategy to decrease development costs and increase flexibility and productivity. Similar to pesticides, we suspect that this outsourcing model will, in the future, be increasingly utilized for pre- and postmarket testing of other chemicals as REACH-like regulatory oversight programs become more widely adopted around the world.

Previous commentaries have raised concern that industry-funded chemical safety studies—whether performed in-house, or by CROs and universities—may be influenced by well-crafted strategies designed to minimize evidence of harm.[1,2] We suspect that such calculated and egregious strategies are an exception to the norm. Rather, most influences on chemical safety testing, if occurring, are likely mediated via subtle and entirely legal decisions that affect study design, data collection, and selection of statistical models for data analysis. Although regulatory authorities around the world have collaborated with the Organization for Economic Co-operation and Development (OECD) for decades to issue standardized study guidelines that limit the ability to alter design and interpretation of chemical safety studies,[3] a large majority of these standardized test guidelines still provide flexibility in (1) final study design (e.g., selection of test species or strains); (2) extent of data collected throughout the study; and (3) statistical approaches used for data analysis, particularly for regulatory ecotoxicity tests.[4] Moreover, even if financial conflicts of interest do not affect research results, the lack of impartiality surrounding industry-funded studies—whether real or perceived—likely has a negative impact on public trust in the reliability of chemical safety data.[5]

To mitigate these concerns, in our opinion chemical safety studies required for regulatory review should be coordinated through a nonprofit, nongovernmental organization. Specifically, we suggest an approach similar to the one first proposed by Sheldon Krimsky for the pharmaceutical industry.[2] Krimsky suggested that studies conducted for regulatory review should be coordinated through an independent National Institute for Drug Testing (NIDT). Within his proposed scheme, registrants would submit the active ingredient or formulation along with adequate funds for testing to the NIDT and, following issuance of a request for proposals (RFP), qualified CROs or academic laboratories would then bid and compete for contracts. The NIDT would work directly with CROs and universities to negotiate study designs and complete all testing requirements and reports. While the registrant could still voluntarily generate data to support or refute findings from the NIDT, the FDA would only be permitted to use NIDT-derived data to support safety evaluations and risk assessments. Importantly, Krimsky argued that this system would establish a "buffer zone" between registrants and research organizations responsible for conducting safety studies, resulting in mitigation of conflict of interests and study bias during generation of drug safety data.

In our opinion, Krimsky's proposal should be extended to encompass the broader chemical industry. To be consistent with global harmonization of chemical safety testing and registration, one international-level organization—rather than multiple country-level organizations (such as the U.S.-specific NIDT proposed by Krimsky)—should be seriously considered, as this would allow companies to coordinate and streamline testing through one centralized agency. For example, an existing international organization that could naturally assume this role would be the OECD's Environment, Health and Safety (EHS) Program—a program that, among other responsibilities, develops and provides standardized test guidelines used by the chemical industry to conduct toxicology, ecotoxicology, and environmental exposure studies. Using funds allocated from member country contributions, the OECD's EHS Program could potentially sponsor an OECD-affiliated center—for example, an International Center for Chemical Safety Testing

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(ICCST)—that negotiates with registrants to coordinate testing and evaluation of new and existing chemicals for regulatory review. While member countries might incur modest additional expenses associated with establishment of the ICCST, funds provided by registrants would, in large part, cover costs associated with chemical safety testing and study management. Similar to an online database hosted by the European Chemicals Agency for REACH-related data and dossiers (http://echa.europa.eu/), this center could also provide an online, centralized database for regulatory agencies around the world to securely access public or confidential chemical safety data generated by the ICCST.

Creating an organization like the ICCST would have obvious advantages for the public and chemical industry: significant mitigation of conflicts of interest related to CRO− and university−industry partnerships; enhanced data reliability and public trust; enhanced credibility of the chemical industry; and better management of study price inflation via issuance of competitive RFPs. While critics will likely contend that this system introduces additional layers of bureaucracy and study management, we argue that the advantages significantly outweigh the disadvantages, especially considering real opportunities for the chemical industry to further streamline pre- and postregistration units and, as a result, enhance productivity and profitability. Moreover, under this scheme CROs and universities would not lose contracts or the ability to expand operations, as these organizations would simply work with the ICCST rather than directly with registrants. Nevertheless, we fully recognize that implementation of this proposal faces significant political challenges, as it would (1) eliminate registrant oversight or monitoring of safety studies and (2) raise potential confidentiality issues related to new products in development. While the latter problem could be easily addressed by establishing strong confidentiality agreements among all stakeholders, the former issue would likely pose a greater challenge for implementation since manufacturers could no longer have the opportunity to pro-actively address unexpected product-related issues prior to regulatory submission. However, the benefits of enhancing credibility and productivity within the chemical industry would, in the long term, likely outweigh the potential risks of allowing an independent organization to manage and monitor product safety evaluation.

AUTHOR INFORMATION

Corresponding Author

*E-mail: volz@mailbox.sc.edu.

Notes

The authors declare no competing financial interest.

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