ETHICS

Human Health Research Ethics

E. Silbergeld, S. Lerman,* L. Hushka

The issue of ethics surrounding studies for regulatory decision–making has been the subject of recent discussions at the Environmental Protection Agency (EPA) that could have broad implications for human subject research. In 2000, a report from a joint meeting of the Agency's Science Advisory Board (SAB) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel (SAP) recommended that the Agency require "active and aggressive" review of human studies conducted by external groups (*1*). EPA announced a moratorium indicating it would not consider "third-party" generated data (i.e., from academia, industry, or public interest groups) in its regulatory process until ethical issues were resolved (*2*). This ban centered on several clinical studies submitted by pesticide manufacturers since 1998. However, EPA's policy appeared to have implications for other toxicology and epidemiology studies. In 2001, EPA requested that the National Research Council (NRC) "furnish recommendations regarding the particular factors and criteria EPA should consider to determine the potential acceptability of third-party studies." EPA also asked the NRC to provide advice on a series of questions, including "recommendations on whether internationally accepted protocols for the protection of human subjects (the 'Common Rule') could be used to develop scientific and ethical criteria for EPA" (*3*).

In May 2003, EPA issued an Advanced Notice of Proposed Rulemaking (ANPRM), the first formal step toward developing a regulatory standard and solicited public comment (*4*). The ANPRM noted that third-party research is not legally subject to the Common Rule. The Common Rule, which is administered by the Department of Health and Human Services (DHHS), details accepted ethical standards for the protection of human subjects in research conducted or sponsored by all federal agencies (*5*). In its ANPRM, EPA raised questions regarding policy options being considered, including applicability of the Common Rule and whether the standard of acceptability should vary depending on research design, provenance, impact on regulatory standard, or EPA's assessment of the risks and benefits of the research. In addition, they requested input on a prospective and retroactive study review process.

We do not find a compelling reason for EPA to propose alternate and complex criteria. We believe that the best approach is the application of the Common Rule or equivalent international standards (*6*, *7*). The Common Rule codifies existing ethical guidance, is built on decades of experience and practice, and thus is both necessary and sufficient to ensure protection of human research subjects. There should be no difference in the standards based on the study design, source of funding, or, most disturbingly, the impact of the study on a regulatory standard. Otherwise, data that were obtained in studies deemed ethically acceptable under the Common Rule could be excluded, or (perhaps worse) data from studies that do not meet these norms could be included.

We find troubling the notion that the ethical standard for a human toxicity test or a clinical trial would be different when conducted by a nonprofit organization or an industry. Whether or not studies with human subjects to test pesticides and industrial chemicals will be judged ethically acceptable is not the point. We are also concerned that different ethical norms might be applied on the basis of whether the study's conclusions strengthen or relax an EPA regulatory position. Biasing the process in either direction is bad science and public policy.

In February 2004, the NRC recommended (*8*) that studies be conducted and used for regulatory purposes if they are adequately designed, societal benefits of the study outweigh any anticipated risks, and recognized ethical standards and procedures are observed. It also stated that EPA should ensure that all research it uses is reviewed by an appropriately constituted Institutional Review Board (IRB) before initiation, regardless of the source of funding. These conclusions are consistent with other counsel that all research proposals involving human subjects be submitted for scientific and ethical review (*9*).

Although we agree with these recommendations, we strongly disagree with NRC's call for creation of an EPA review process and review board for human studies proposed for use in formulating regulations. Private entities would submit research plans before beginning a study, and again before submitting the study results. It is unclear how post-study review can contribute to protection of research subjects. Introduction of such a parallel review process will create confusion regarding which set of rules applies to a particular study. It is also likely to create resource and logistical problems. We suggest that EPA require that private entities obtain review under the Common Rule or its foreign equivalent before undertaking a study and provide documentation of this review in order to submit their data for regulatory purposes. By requiring studies to follow the Common Rule or a foreign equivalent, EPA can strongly discourage the practice of conducting human-subjects research and clinical trials outside the United States, to avoid federal scrutiny.

By a strong endorsement and legally binding adoption of the Common Rule and equivalent international standards, EPA can ensure that ethical concerns are fully considered. By joining the community of biomedical ethics, rather than establishing a separate path, EPA will strengthen all of our efforts.

E. K. Silbergeld is with the Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD 21205, USA. S. E. Lerman is with ExxonMobil Biomedical Sciences Inc., Annandale, NJ 08801, USA. L. J. Hushka is with Exxon Mobil Corporation, Houston TX 77079, USA.

*Author for correspondence. E-mail: steven.e.lerman@exxonmobil.com

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