

Legal Lookout: Proposed Rule on Human Studies

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On Sept. 12, 2005, EPA issued its human studies proposed rule, and led a stakeholder briefing on the proposal on Sept. 7. The proposed rule focuses on third-party intentional dosing studies involving pesticides, although EPA seeks comment on alternative approaches with a broader scope. The rule, as proposed, would prohibit new third-party intentional dosing studies for pesticides involving pregnant women or children as subjects, as well as all first- and second-party intentional dosing studies of any substance involving pregnant women or children as subjects. More information on the proposed rule and stakeholder briefing is below. This Legal Lookout column describes this important proposed rule and outlines its implications.

The proposed rule

EPA's proposed rule lists two actions with respect to human research conducted by the agency (first-party research) or by others with EPA's support (second-party research). The proposal categorically prohibits any intentional dosing studies involving pregnant women or children as subjects, and adopts the Department of Health and Human Services regulations that provide additional protections to pregnant women and children as subjects of other than intentional dosing studies.

EPA lists four actions applicable to human research conducted by third parties (i.e., by others without any support from EPA or other federal government agencies). The proposal would categorically prohibit any third-party intentional dosing studies for pesticides involving pregnant women or children as subjects; extend the provisions of the Federal Policy for the Protection of Human Subjects of Research (known as the Common Rule) to all other third-party intentional dosing human studies intended for submission to EPA under the pesticide laws; require, before testing is initiated, submission to EPA of protocols and related information for proposed research covered by this extension of the Common Rule; and require information about the ethical conduct of covered human studies when the results of the research are submitted to the agency.

The proposed rule would also establish an independent Human Studies Review Board to review proposals for covered intentional dosing human research and reports of completed research. EPA also proposes to address non-compliance with the provisions of a final rule and define the ethical standards the agency would apply in deciding whether to rely on relevant, scientifically sound data derived from intentional dosing human studies for pesticides. Importantly, the proposed rule would forbid EPA to rely in its decision-making under the pesticide laws on human research involving intentional exposure of pregnant women or children, with one potential exception noted below.

In the proposed rule, EPA discusses the ethical standards that it believes should apply to determine whether to rely on scientifically sound human studies with ethical deficiencies completed before promulgation of the final rule. For covered types of research conducted after the effective date of the rule, EPA would refuse to rely on data from scientifically sound and relevant human research "unless EPA has adequate information demonstrating that the research complied with the Common Rule." For covered types of research conducted before the effective date of the rule, EPA would rely on data "from scientifically sound and relevant

human research unless there is clear evidence to show the conduct of the research was fundamentally unethical or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted." Throughout the text of the rule and repeatedly in its description of the rule during the stakeholder briefing, EPA cited the results of the 2004 National Academy of Sciences (NAS) report on intentional human dosing studies as a basis for its proposal.

The proposed rule includes a formal process that EPA could use to make an exception to these standards when "scientifically sound but ethically deficient research" would provide "crucial support to a regulatory action more protective of public health than could be justified without relying on the ethically deficient research." The "extraordinary procedure" would also apply if a scientifically sound study involving the intentional dosing of pregnant women or children as subjects "were found to be crucial to the protection of public health." EPA will make decisions on a case-by-case basis, "taking into account the particular circumstances of the study and the way it could affect the regulatory action, and seeking the best possible advice." EPA states that it "agrees such decisions should consider the importance of the research to a potential regulatory decision, and particularly whether it would support a regulatory position more protective of public health than would be justified without reliance on the data." Under EPA's proposed rule, EPA would consult the Human Studies Review Board and public comment before deciding whether to rely on such data.

Stakeholder briefing

During the Sept. 7 stakeholder briefing, EPA stated that it believes its proposed rule is consistent with the 2004 NAS report and that in some respects, its proposal is more protective than NAS recommends. EPA said that until it promulgates a final rule, in accordance with its understanding of Congress's intent, as expressed in the fiscal year 2006 appropriations bill for EPA (Pub. L. No. 109-54), it is discontinuing its reliance on human data. EPA expects to issue a final rule in late January 2006, as directed by Congress.

Stakeholders asked questions such as how many people will serve on the Human Studies Review Board and whether members will be chosen in a manner similar to that for EPA's Science Advisory Board or Scientific Advisory Panel. EPA responded that the review board will be an independent entity and members will be subject to conflict of interest rules. Because the agency has only begun to look at the composition and procedures for the board, it welcomes public comments on these issues. EPA intends to have the first board in place when it issues its final rule.

When asked when EPA will issue guidance documents addressing issues such as the definition of a scientifically unsound document, the agency said that it does not have a schedule for when guidance documents will be available. According to the agency, in the absence of guidelines, the purpose of the protocol review is to ensure studies are conducted in an ethical and scientifically sound manner.

In response to a question regarding EPA's proposed catch-all exception, and whether they would consider relevant "scientifically sound but ethically deficient" data supporting a less protective standard, EPA said that if the data tend to show that the compound is safer than would otherwise be expected by looking only at animal data or other ethical human studies, the intent of the proposed provision is that the agency would not be able to avail itself of this exception.

Implications

EPA's actions will have an important impact on testing initiatives involving industrial and agricultural chemicals, especially the latter. In the short term, the limitations on EPA's consideration of human studies arising under the 2006 appropriations bill could slow down or otherwise significantly impact EPA's ongoing review of pesticides in any context where EPA review of data is required. These include, for example, EPA review of data in pesticide registration, re-registration, inert assessment and related pesticide actions.

In theory, review of any human data under any EPA program, for example, the Toxic Substances Control Act, Clean Air Act, Clean Water Act, etc., will be impacted by the agency's interpretation of the 2006 appropriations provision noted above. Plainly, however, EPA's review of data in connection with its pesticides program will be the most profoundly impacted, and work on pesticide reviews including these data will be slowed. In the absence of human data, EPA can be expected typically to apply additional safety factors to account for animal to human extrapolations. Application of these safety factors could have a significant impact on any risk assessment involving the chemical, and thus impact applications, formulations and use sites.

Until the final rule is issued, which is expected to be early next year, there will be considerable uncertainty regarding the outcome of EPA's review of chemicals, especially pesticides. Readers with such data should stay tuned, and expect a bumpy road ahead.

ADDITIONAL INFORMATION

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