PEER Comments on External Review Draft of "Scientific and Ethical Approaches for Observational Exposure Studies"

Docket ID No. EPA-HQ-ORD-2007-0972
November 15, 2007

These comments are submitted by Public Employees for Environmental Responsibility (PEER).

Introductory Comments

1. Lack of Authoritative Guidance Leaves Confusion and Ethical Ambiguity

The authors state that the draft is "not meant to represent an official Agency 'guidance document' and should not be used for that purpose." It is "intended as a resource and reference for …NERL [National Exposure Research Laboratory] scientists as they develop and implement observational studies."

While the document makes reference to the need for the "highest ethical standards," it does not spell out what those standards are or should be.

Consequently, it is not clear what the purpose of the document is or how it adds in any substantive way to published training manuals or other prescriptive advice issued by others. Nor is it clear why this non-guidance "research" document is being circulated for public comment.

Since the document does not purport to offer any guidance, standards or rules, it instead creates more confusion and ambiguity on a matter where some clarity is warranted.

2. Failure to Analyze CHEERS Appears to Be Tacit Endorsement

This document is authored by Dr. Roy Fortmann, the Principal Investigator for the infamous, since-cancelled Children's Environmental Exposure Research Study, known by its anomalous acronym, CHEERS. Yet despite the fact that this draft describes ethical considerations in human observational research, the draft never mentions CHEERS—let alone coherently discusses the issues that led to the controversy surrounding it.

This omission suggests that, in the author's mind, CHEERS exhibited the preferred ethical approaches that Dr. Fortmann is describing. As such, the draft implies that CHEERS-type experiments are precisely the type of "observational" human subject research which the U.S. Environmental Protection Agency (EPA) will continue to conduct and will continue to invite industry to perform for submission to the Agency.

EPA's grudging cancellation of CHEERS (see the statement of EPA Administrator Stephen Johnson at

http://yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/083d681b57e750dd85256fdd00639bc5!OpenDocument) coupled with the Agency's suppression of its own scientists' discussion of the study raises real concerns about EPA's commitment to high ethical standards governing human subject research. The Agency's continued avoidance of an open discussion about CHEERS, if anything, argues for strict guidance on these issues rather than a mushy, amorphous discussion.

To the extent that this draft is meant to facilitate more CHEERS-like studies, EPA should withdraw and rewrite it.

Specific Comments

1. EPA Still Not in Compliance With the Nuremberg Code

In order to comply with the Nuremberg Code, EPA must ensure that pregnant women, fetuses, newborns and children and other sensitive groups are protected against unethical research practices.

The current EPA rule, however, limits its prohibition on testing of pregnant women and children to 1) intentional dosing studies conducted or supported by EPA and 2) third-party studies involving intentional dosing of pesticides.

Thus, EPA now will rely on studies conducted on pregnant women, fetuses, newborns and children submitted by third parties which fall outside its narrow definition of "intentional dosing." Moreover, EPA's Common Rule protections for pregnant women, fetuses, newborns and children in studies involving other than intentional dosing methods do not apply to any third-party research.

Principle #7 of the Nuremberg Code states:

> *"Proper preparations should be made and adequate facilities provided to protect the experimental subject against* ***even remote possibilities of injury, disability or death.****"* [Emphasis added.]

The draft does not discuss the need to ensure that all studies which EPA conducts or relies upon meet the Nuremberg Code.

2. Infants and Children May Be Subjects in Potentially Harmful Experiments.

Under EPA's rule rule, EPA may still conduct or rely upon "observational" studies in which children are subjected to potentially dangerous pesticide exposures, such as CHEERS.

In addition, the current EPA rule prohibiting Agency reliance on research involving intentional dosing of pregnant women, fetuses, newborns or children is limited to "its regulatory decisions-making under [FIFRA] or section 408 of the Federal Food, Drug,

and Cosmetic Act." EPA should adopt ethical guidance prohibiting the use of children from exposure to any potentially dangerous chemicals, regardless of the statutory or regulatory jurisdiction.

More generally, EPA should foreswear placing any human subjects – directly or indirectly – at risk for purely regulatory reasons.

3. Continued Use of Undue Economic Inducements

The draft notes "There is little specific guidance regarding payments or other forms of remuneration in Federal human research regulations" (Page 56). In fact, the EPA rule has no provision to protect potential human research participants from undue economic inducement.

Payment for participation in human research was discussed by the National Academies of Science in its 2004 report. NAS Recommendation 5-3 states:

> "[Institutional Review Boards], all relevant review boards, investigators, and research sponsors should ensure that payments to participants in intentional human dosing studies are neither so high as to constitute undue inducement nor so low as to be attractive only to individuals who are socio-economically disadvantaged. Proposed levels of and purposes for remuneration (e.g., time, inconvenience, and risk) should be scrutinized in light of the principles of justice and respect for persons.
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> Moreover, EPA, in conjunction with other federal agencies, should consider developing further guidance on remuneration for participation in intentional human dosing studies, including guidance regarding whether remuneration should reflect the level of risk as well as the time and inconvenience involved."

Despite that invitation from NAS, this draft provides no coherent advice about payment to participants (or to parents of children who would become experimental subjects, as in CHEERS). The draft should attempt to very specifically inform the Agency and the Human Subjects Review Board how to protect all persons from the lure of undue economic inducement.

At the very least, the Agency should adopt the NAS recommendation by setting requirements that payments to participants be duly considered by all reviewing officials and people involved with the study.

Moreover, the Agency should go beyond the NAS recommendation by protecting participants of other than intentional dosing studies from undue economic inducement. EPA must recognize that even research which could legitimately be considered passive observation, such as skin tests or urinalysis, can itself change

behavior, especially in impressionable, socio-economically disadvantaged and trusting subjects.

CHEERS, as described above, is an excellent example of why such safeguards are needed. The EPA should acknowledge the public outcry over that study, which was largely centered on the cash and gift inducements, including over $900 and a camcorder, offered to participants who were intentionally recruited in socio-economically disadvantaged communities. Perhaps the most insidious incentive was that participants could keep the camcorder (and thus the home movies of their infant) only if they continued applying pesticides in the room primarily occupied by their infant for the entire two-year period of the study.

In CHEERS, EPA disregarded the high potential for poorly informed low-income families to change household pesticide use in order to qualify for a camcorder they might otherwise never have the resources to purchase. Disturbingly, the only discussion in the EPA records about CHEERS is whether the payment level was high enough.

4. "Minimal Risk" May Include Dangerous Behaviors in Observational Studies

The draft states (Page 23) that "EPA is permitted to conduct or support *only* those observational studies that meet the regulatory definition of 'minimal risk'…" The draft concedes that additional issues are raised by "background" risks, like poor housing but does not resolve these additional issues.

When presented with the opportunity to participate in a study for payment, people may continue behavior or exposure which they have been informed is potentially harmful. Potential participants may decide to adopt new behaviors to please researchers and qualify for the study's remuneration, falsely certifying that they already prescribed to the behaviors to be studied. The burden should therefore be on the Agency to make sure that its research does not allow for these unethical scenarios.

Finally, the draft ignores situations where the scientist but not the subject knows the true dangers to the "daily life" activities, especially when those activities involve exposure to potentially harmful chemicals, like pesticides.

5. Conflicts of Interest Still Permitted

The draft implies that conflicts of interest (no matter how large) will be permitted, so long as they are disclosed. The draft states (Page 25) "It is recommended that potential conflicts of interest among researchers or study participants be identified…" and "It is highly recommended that researchers disclose all potential or apparent conflicts of interest on their part to the IRB."

Apart from the lack of directive language, the draft implies that it is no bar for a scientist or reviewer to continue with a study having a direct conflict of interest, so long as it is reported.

In CHEERS, the American Chemistry Council, representing pesticide manufacturers, contributed funding to this study – a study that could have affected whether certain pesticides would be banned from home use.

6. Only Passing Reference to Need for Protecting Prisoners and Other Captive Populations

The draft spends less than a paragraph discussing the absence of any EPA protections for prisoners, wards of the state or other involuntarily confined groups used in human subject experiments.

EPA's silence on this topic actually creates an incentive for third parties to use prisoner populations in research, as that research would be subject to fewer regulatory constraints. The Agency's current posture sends the unmistakable message that certain human subjects are not worthy of safeguards.

7. Subjects of Special Vulnerability Given Short Shrift

The draft defines (Page 34) vulnerable persons as those incapable of protecting their own interests "owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care, or being a junior or subordinate of a hierarchal group. Vulnerable persons may have insufficient power, intelligence, resources, strength or needed attributes to protect their own interests."

Following this definition, the draft does not explain how EPA should protect these vulnerable subjects from experimental abuse. Moreover, it ignores altogether the extra obligation that EPA scientists bear in that these government specialists occupy a position of special trust, particularly in the eyes of gullible or less knowledgeable subjects.