UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

FROM: Warren Lux
EPA Human Subjects Research Review Official

TO: R. Julian Preston
Associate Director for Health, NHEERL

DATE: March 30, 2010

SUBJECT: Result of HSRRO Review of Research Involving Human Subjects

- **Project Title:** *Cardiopulmonary Responses to Exposure to Ozone and Diesel Exhaust with Moderate Exercise in Healthy Adults*
- **Principal Investigator:** Tina Stevens
- **Engaged Institution:** U.S. Environmental Protection Agency (National Health and Environmental Effects Research Laboratory)
- **FWA #:** FWA00012755
- **UNC IRB Protocol #:** 09-1344
- **HSRRO Project #:** C10-018CS

I have reviewed the project cited above according to the requirements of EPA Order 1000.17 Change A1 (**Policy and Procedures on Protection of Human Research Subjects**) and have determined that it qualifies as intentional exposure research involving human subjects that requires revision in order to qualify for HSRRO approval of the research. There are two significant issues for which revision is mandatory. There is also a suggestion for improvement, which is not in itself disqualifying.

Issue #1: The protocol refers to many, if not most, of the measurements, collections, and specimen analyses as activities that "may" be undertaken. Thus, these are left to investigator discretion, rather than being required by the protocol and reportable as protocol deviations if not undertaken. If *all* the "mays" that currently exist in this protocol are, in fact, undertaken, the research will likely achieve its stated aims. If *none* of them are undertaken, however, it is unlikely that the research will produce useful data. If it is something in between these extremes, it is impossible to know what kind of

outcome will occur without knowing which measurements, collections, and specimen analyses are retained and which are not. It is acknowledged that investigator flexibility confers certain critical advantages at some stages of some research, particularly during the research development phase. Once human subjects are involved in research of the sort contemplated here, however, the protocol needs to include a more definitive commitment to what data will be acquired than is currently present in order for reviewers to evaluate adequately the likelihood that the research aims will be met. Moreover, such review is a critical part of the ethical analysis, since the involvement of human subjects is justified only when there is a reasonable likelihood that the research will produce valid and useful results. If circumstances encountered during the course of conducting the research require deviation from a protocol previously determined to be adequate to generate valid and useful results, then evaluating them *as protocol deviations* is critical to the decision of those monitoring the research as to whether or not the research should be allowed to continue with the involvement of human subjects. The modification required to address this issue is to replace "may" with "will" for a sufficient number of measurements, collections, and specimen analyses that reviewers can be assured that research aims will be met if the protocol is carried out as written.

Issue #2: Both the protocol and the consent form discuss the risks from combined exposure to ozone and diesel exhaust as being additive, not synergistic, although that is, in fact, not known. Indeed, one of the aims of the research is to fill this knowledge gap, as the protocol itself acknowledges. It is one thing to examine the effects of the two exposures using the *hypothesis* that the effects are additive, but it is quite another to apply this to the risk disclosure statement in advance of finding out the definitive answer. In fact, the risks that might be present here are not yet known, and that needs to be disclosed to the potential participants. Reassuring statements about the expectation that risks will be additive are not adequately evidence-based and may mislead persons considering participation in the research. Moreover, it is ethically preferable to discuss this absence of knowledge about risk in the specific context in which it occurs, where possible, rather than rely exclusively on the more general boilerplate language about "previously unrecognized risks" contained in most consent forms, including the one proposed for this study. The current consent form reads: "While this exposure scenario has not been conducted at our facilities before, we anticipate this exposure will include the same risks as diesel exhaust and ozone exposures alone. Therefore, we do not expect the combination of diesel exhaust and ozone to increase the effects of each pollutant individually." The disclosure that more accurately reflects the facts would read: "Because this exposure scenario has not been conducted at our facilities or elsewhere before, we do not yet know whether or not this exposure will include the same risks as diesel exhaust and ozone exposures alone. It is possible that the combination of diesel exhaust and ozone exposures will increase the effects of each pollutant individually, and it is also possible that it will not. We are doing this study in order to find out the answer."

Suggestion: The recruitment materials refer to the minimum age (18) but do not discuss the exclusion of pregnant or nursing women. The exclusions are fully disclosed and discussed in the protocol and consent form, so there is no compliance issue here and no reasonable chance that an excluded subject might be entered into the study. However, it would still not be unreasonable to disclose this exclusion up-front during the recruitment stage and so make this even clearer for anyone looking at this research from the outside. Again, however, this is only a suggestion and not a mandatory change necessary for approval of the research by the HSRRO as compliant with 40 CFR 26.

cc: Robert Truckner