

EMBARGOED TO 3/24/2015 Why Donnay believes the HEI's Multicenter Study of Carbon Monoxide should NOT have been:

A. Commissioned

1. The EPA commissioned this study from the HEI in 1983 to “replicate and extend” the results of a similar study it commissioned in 1979 from Dr. Wilbert Aronow. The EPA did so only after Aronow admitted falsifying human drug studies he had submitted to the FDA, and after four researchers sent by the EPA to investigate his CO studies discovered he'd discarded his records. But all of Aronow's CO results had already been discredited in detailed re-analyses submitted to EPA in 1982 by the Spokane Air Pollution Control Authority and General Motors. The EPA rejected their critiques at the time but in 1985 based the NAAQS on a different study, making replication of Aronow moot.

B. Conducted

1. The HEI CO Oversight Committee that designed the study should have known it was unethical to expose men with heart disease to CO at levels above the EPA's 1-hour NAAQS for no medical benefit and at significant risk, especially given that no animal or human CO studies except Aronow's supported the primary hypotheses. Many others had published results to the contrary, including some of members of the CO Oversight Committee.

2. IRB approval was obtained from JHU, SLU and USC but not the Harvard School of Public Health despite the involvement of at least 10 faculty, staff and students who worked there at the study's “Statistical and Data Management Center” from 1984-89.

C. Published

1. The HEI, *The NEJM*, and *EHP* should have rejected the authors' papers based on a fatal design error noted in 1988 by HEI's Health Review Committee: The authors' primary independent variable--the %COHb in venous blood--was in fact a dependent variable that decreased significantly as minute ventilation increased during exercise after exposure.

2. Statistical reviewers including the late Drs. John Tukey and Paul Meier (both hired by the HEI) should have noted that the 2ⁿ permutation method of calculating P-values reported by the authors for their n=63 results was impossible given the computing power and run-times then available to departments of biostatistics.

D. Cited by EPA in 2011 as primary basis for CO NAAQS

1. The study used overlapping low and high ranges of CO exposure from 1.2 to over 10 times higher than allowed by EPA's 1-hour NAAQS of 35ppm. Yet no adverse effects were reported as COHb rose at rest, only after when subjects exercised in fresh air and their COHb fell.

2. Primary results--exercise times until angina and an ST change >1mm--did not correlate with individual CO levels or venous %COHb at the end of exercise.

3. The study's 3 clinical sites could not consistently replicate even the direction of their results, Aronow's, or anyone else's--so there was no reason for EPA to base the CO NAAQS on their combined means.

Why the Health Effects Institute, *The NEJM* and *EHP* refused to retract Allred *et al* as Donnay requested on 5/19/14

A. *NEJM* to Donnay, 5/21/14

“You provide no solid evidence of scientific or ethical misconduct; we therefore conclude that retraction is not warranted. If you have concerns about the validity of the article's conclusions, we suggest that you repeat the experiments, to the extent to which you believe this can be done ethically, and report your findings in a scientific journal for others to read and critique. We now consider this matter closed.”

*Dr. Jeffrey Drazen, Editor-in-Chief,
The New England Journal of Medicine*

B. HEI to Donnay, 6/2/14

“We have consulted with HEI staff about both your earlier questions and your May 19 letter. Given the extraordinary care with which this study was conducted and independently reviewed, they have recommended, and we agree, that there is no reason to retract this study. Therefore, we do not intend to do so. I should add that HEI has long been pleased with not only the quality of the work, oversight and review that went into the CO Multi-Center Study, but also its long-lasting benefit for public health.”

Governor Richard Celeste, HEI President

C. HEI to *EHP*, 6/30/14

“We have had the opportunity to further consider Mr. Donnay's assertions in his most recent letter, dated May 19, 2014. We have found no evidence that there was research misconduct.

... We reviewed these findings also with our Board of Directors and informed the Board that we do not see any reason that HEI should retract Research Report 25. The HEI Board has concurred with our findings and has informed Mr. Donnay that we will not be retracting the report.”

Daniel Greenbaum, HEI Exec. Director

D. *EHP* to Donnay, 7/14/14

“Since journals such as *EHP* are not in a position to investigate such claims directly, I contacted the [HEI] who funded the Multicenter CO Study.

... On 30 June 2014 I received a letter from Dr. [sic] Greenbaum stating that HEI had considered your allegations and found no evidence that there was research misconduct.

... We believe that your allegations have been thoroughly investigated and we consider the matter closed.”

*Dr. Hugh Tilson, Editor-in-Chief,
Environmental Health Perspectives*

Comments on AD's Poster by Dr. Roger McClellan, HEI CO Oversight Comm (1983-1991) and Chair of EPA CASAC (1987-1992)

Re: AD's Reanalysis

“In my opinion, you have done an admirable job of reconstructing the core data for the HEI CO Multi-Center Study.”
Dr. Roger McClellan (all quotes are from a 4-page review he sent Donnay on 2/23/14)

Re: AD's Conclusions

“I am sufficiently confident in your reconstruction of the data and re-analysis that I will accept your conclusions at the end of the Poster.” *Note RM also sent his review to officials at SOT, HEI and EPA.*

Re: AD's Language

“I would not have used the same language to describe your findings and conclusions. ... in retrospect the HEI CO Multi-Center study did have some ‘warts and blemishes.’”

Re: HEI's Recordkeeping

“The only serious finding you reported that is disappointing to me is my learning that the original study records were destroyed by the HEI in 2008.”
[all refs available from adonnay@jhu.edu]

