Testimony of Albert Donnay, adonnay@jhu.edu
to National Academy of Sciences Ad Hoc Committee
Assessing Toxicologic Risks to Human Subjects
Used in Controlled Exposure Studies of Environmental Pollutants

Thank you for inviting public comments. My name is Albert Donnay. I am a consulting toxicologist and research associate at the Johns Hopkins Center for Sleep Disorders.

My testimony today is based on research I did into the basis of the EPA's National Ambient Air Quality Standards (NAAQS) for carbon monoxide (CO), the findings of which I shared with EPA's Administrator, Scientific Integrity Officer, and Inspector General (IG) in May 2014 (online here). I also presented a poster summarizing my findings at the annual meeting of Society of Toxicology in 2015 (online here).

Although the EPA has not given your committee any information about the controlled human exposure inhalation (CHIE) studies it conducted on CO from the 1970s to the 1990s, I urge you to consider their history before making your recommendations to the EPA. Unlike the NAAQS for particulates and ozone that Congress, the IG, EPA staff, your committee and today's speakers have all focused on, the CO NAAQS is the only one based exclusively on the results of CHIE studies, and it has been since its adoption in 1971.

In the most recent review of the CO NAAQS concluded in 2011, EPA staff supposedly considered over 15,000 peer-reviewed papers published on CO since the last review, but its Integrated Science Assessment cited fewer than 800, and the Administrator dismissed all of them as inferior to six older CHIE studies of men with angina published from 1973 to 1998.

Table 1. CHIE Studies cited by EPA Administrator in 2011 as basis for CO NAAQS

CO CHIE Studies * authors include ≥ 1 EPA staff	**Study Funding**	**Reported number of completed subjects, all with stable angina** (plus number of dropouts if known)
Adams* 1988	EPA intramural and extramural with UNC	30 men (plus 12 dropouts)
Anderson* 1973	EPA intramural	10 men, 5 of them smokers (no dropouts mentioned)
Allred 1989a,b and 1991	EPA extramural commissioned from Health Effects Institute	63 men (plus 7 dropouts, 6 cut, and 31 not reported)
Kleinman, 1989	CARB extramural and Southern Occupational Health Center intramural	24 men (plus 2 dropouts)
Kleinman, 1998	CARB extramural and Southern Occupational Health Center intramural	17 men, 15 of them ex-smokers (no dropouts mentioned)
Sheps*, 1987	EPA intramural and extramural with UNC	25 men and 5 women (no dropouts mentioned)

All but Kleinman's 1998 study also were cited by EPA as contributing to the basis of the CO NAAQS in the prior review in 1994, and all were conducted and/or funded by either EPA or the California Air Resources Board (CARB). This suggests that the Administrator's decision to keep the 1971 standard unchanged in 2011 was based more on bureaucratic inertia than any serious review of more recent CO literature.

Among other lines of evidence the Administrator dismissed were over 200 epidemiology studies with a combined n of millions (see PubMed collection here). These report dozens of adverse health effects associated with increases in ambient CO exposure of ≤1 ppm above background levels that now average less than 20% of what the CO NAAQS allows. Even other CO CHIE studies were ignored, including two by EPA's Human Studies Lab (Hinderliter 1989 and Sheps 1990).

In contrast, the six CHIE studies that EPA claims provide the best support for the CO NAAQS reported results for only 175 adults, just 5 of them women, and they all used exposures several times higher than the 9 and 35ppm averages that EPA allows for 1 and 8 hours respectively.

Table 2 CO Exposures used in CHIE studies cited by EPA Administrator

CO CHIE Studies * authors include ≥ 1 EPA staff	**CO Exposure Level, Duration and vCOHb Target, if any** Note 1. All exposures exceeded EPA 1-hour NAAQS of 35ppm Note 2. None of the studies that varied individual exposure times to reach COHb targets reported their mean, range or SD
Adams* 1988	Inhaled 100ppm (n=17) or 200ppm (n=13), both for ≥ 1 hour on one day individually timed to reach 6% venous COHb
Anderson* 1973	Inhaled 50 and 100ppm for 4 hours each on two days
Allred 1989a,b and 1991	Inhaled 150ppm for 1 hour on 1st day; 2nd and 3rd days varied from 42 to 357 ppm and from 50-70 minutes, individually timed to reach targets of 2.2% and 4.4% venous COHb
Kleinman 1989	Inhaled 100ppm for 1 hour on one day to reach mean of 3.0% without adjusting individual times
Kleinman 1998	Inhaled 100ppm for ≥ 2 hours each on two days, individually timed to reach 4% venous COHb
Sheps* 1987	Inhaled 100ppm for ≥ 1 hour on one day, individually timed to reach 4% venous COHb^

The largest, Allred et al, which the Administrator said in 2011 was given "primary consideration" in deciding to keep the CO NAAQS unchanged, was commissioned by EPA in 1983 from Health Effects Institute, after doubts were raised about the integrity of several CO CHIE studies done for EPA in the 1970s by a VA cardiologist, Dr. Aronow. (He admitted

fabricating drug safety data he was submitting to FDA on behalf of pharmaceutical companies, and when EPA investigated his CO studies, they found Aronow had discarded all his archives.)

EPA nevertheless asked HEI to attempt to replicate Aronow's CHIE methods in the hope of replicating his CO results. HEI tried to do this at three cardiology clinics simultaneously (at Johns Hopkins, St. Louis University and USC), each of which was supposed to test 25 men. But although the authors enrolled a total of 107 men in 6 years, they only reported complete results for 69, 6 of whom they later cut, and 7 more who dropped out, leaving 31 unaccounted for.

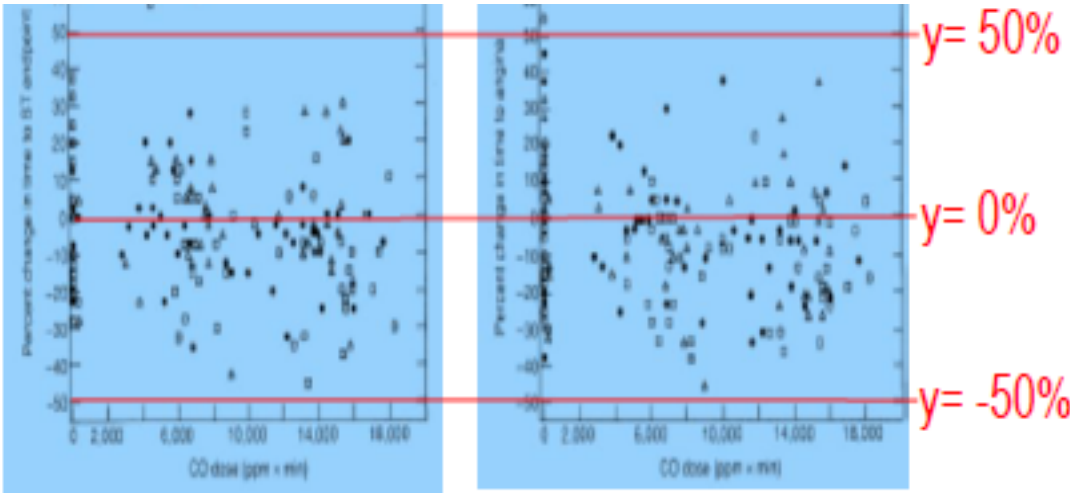
This is an improvement over one tiny study of n=10 from EPA's Human Studies Laboratory (Anderson et al 1973) that EPA cited as the sole basis for the CO NAAQS in its 1985 review, but it is still inadequate to serve as the basis for a national standard. (Anderson et al also reported EPA's first CO CHIE study with an n of 37 in a 1971 abstract but this was never published in a peer-reviewed journal or cited by EPA in any NAAQS reviews.)

All six of these CHIE studies share several other shortcomings that should disqualify them from being given any weight in future CO NAAQS reviews:

1. They mistakenly assumed that brief high-level exposures could be evaluated as substitute for chronic low-level exposures. This is never true of CO, not even when minute ventilation and the number of ppm*hours involved (the product of exposure and time) are the same.

2. All mistakenly assumed that men with heart disease were at high risk from CO exposure and therefore an appropriate group on which to base the NAAQS, even though this was not supported by any epi or animal studies. Results contrary to their hypotheses that showed inconsistent effects, such as the figures below from Appendix C of the Allred study published in 1989 by the Health Effects Institute (here), were not included or even mentioned in the authors' journal articles (one published simultaneously in The New England Journal of Medicine here and one published two years later in Environmental Health Perspectives here).

Allred Figures C1 and C2 from Appendix C of HEI Research Report #25, 1989, p56
*Showing the same range of "CO doses" in ppm*minutes on the x-axis and on the y-axis, in Fig. C1 at left, the % change in time to ST segment change during post-exposure exercise in Fig. C2 at right, the % change in time to angina during same post-exposure exercise*



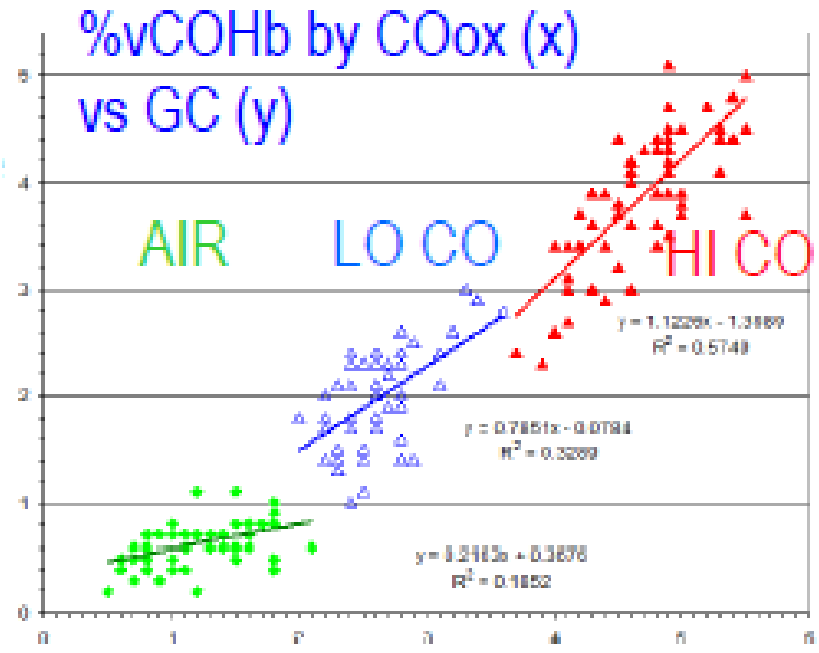
These null results also were not mentioned by either of the EPA's Clean Air Scientific Advisory Committees on CO that recommended the study to the Administrator in the early 1990s and again in 2010, even though both were chaired by members of the "ad hoc" HEI committee that designed and oversaw the multi-center CO study (Dr. Roger McClellan in the early 1990s and Dr. Joseph Brain in the late 2000s).

3. All only reported variables measured after CO exposure stopped, when their subjects were breathing room air and their blood CO levels were declining. None reported experiencing angina or any other adverse outcomes during exposures at rest when blood CO levels were rising and the subjects were presumably at greatest risk. This suggests the adverse cardiac outcomes studied in these CHIE studies were not triggered by inhaling CO but by the graduated exercise that followed, which subjects were told to continue until they experienced angina.

4. All misinterpreted venous COHb as an independent measure of each subject's CO exposure or absorbed dose. It is instead a measure of CO excretion that is highly dependent on minute ventilation, a variable that was not controlled for or even measured in most of these studies.

5. All used CO-oximeters made by Instrumentation Laboratories to measure COHb in blood despite knowing their results could not be accurately calibrated or replicated by any means. Even the supposedly more accurate GC methods used in the Allred study for quality control could not be replicated. Allred et al also could not consistently correlate their IL and GC measures across the 0-6% range of CO they reported, as shown in this figure assembled from individual data they published only in Appendix B of their HEI report.

Donnay Figure 1.
Correlation of Allred venous COHb results from IL CO-oximeter (x) and Gas Chromatography (y)



Although some of the authors had published other studies using more accurate and non-invasive breath CO analyzers to estimate COHb, none of the 6 CHIE papers selected by EPA mention this option or why it was not used to reduce the number of times subjects had to give blood (22 over 4 visits in the Allred study).

6. Most critically, none were able to replicate each other's primary results, and the three sites in the Allred multi-center study could not consistently agree even on the direction of the mean effects they reported. Allred et al also published at least three different versions of their results without explanation, two of them in the same HEI report (compare Tables 8, 9a, and 9b with Table M1 in which the rows and columns are transposed).

Even if these CHIE studies had been done--or could be redone now--without these many flaws, they are still an inappropriate design to rely upon for either setting ambient air quality standards or evaluating how well they protect sensitive subpopulations.

There are at least three reasons for this that apply to all the NAAQS, not just CO:

1) CHIE studies are by their nature small and so lack the statistical power needed to study the relatively rare but significant adverse effects detected in large epidemiology studies.

2) Asking volunteers to inhale toxic exposures at levels far above what EPA standards allow for no possible health benefit is contrary to the Common Rule and many other ethical standards, especially if only testing hypotheses that are not yet supported by any animal model.

3) Even with informed consent, CHIE studies can only test the effects of relatively brief air pollution exposures indoors. They cannot replicate the chronically waxing and waning outdoor exposures to complex mixtures of NAAQS and other air pollutants that EPA is responsible for regulating.

In conclusion, I urge your committee to advise EPA to stop conducting, funding and citing CHIE studies in support of NAAQS rulemakings.

If EPA wants to learn more about the effects of exposure to air pollutants on human health, it need only recruit volunteers already living in more or less polluted regions of the US to participate in personal monitoring studies. Many researchers have already demonstrated that both children and adults can carry a portable device to measure NAAQS pollutants in their breathing zone while also wearing biomedical sensors such as EKG patches to record their physiological responses in real time.

Thank you for your consideration. I welcome any questions.

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