BY OVERNIGHT DELIVERY

May 14, 2012

Arthur A. Elkins, Jr.
Inspector General
U.S. Environmental Protection Agency
Ariel Rios Building (AR), Mail Code 2410T
1200 Pennsylvania Avenue, N.W.
Washington, DC 20004

Re: Request for Investigation of Illegal Human Experimentation by the EPA

Dear Mr. Elkins,

I am writing to request that you investigate whether the U.S. Environmental Protection Agency, ("EPA"), EPA staff and the University of North Carolina at Chapel Hill violated federal law and regulations by intentionally exposing humans in a laboratory setting to potentially lethal and/or disease-producing levels of airborne fine particulate matter ($PM_{2.5}$).

I. Factual Background

Between January 5, 2010 and June 9, 2011, the EPA's National Health and Environmental Effects Research Laboratory in Research Triangle Park, NC conducted experiments on 41 human study subjects.

During these experiments, the study subjects were intentionally exposed to $PM_{2.5}$ at levels ranging from 41.54 micrograms per cubic meter to 750.83 micrograms per cubic meter for periods of up to two hours.

During the 24th experiment , which occurred on October 7, 2010, one study subject (a 58-year old obese woman with a history of heart and health problems and a family history of heart disease) was exposed to a $PM_{2.5}$ level of 111.68 micrograms per cubic meter for approximately 49 minutes, at which time she was removed from the chamber due to the onset of new atrial (or supraventricular) fibrillation. She was then transferred, possibly by ambulance, and admitted to the University of North Carolina Medical Center for overnight observation and telemetry.[1]

[1] The report of the incident states, "During the transfer to the UNC Medical Center approximately 2 hours following the onset of the arrhythmia), she spontaneously reverted back to a normal sinus rhythm." This implies that she was transferred by ambulance.

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The experiments resumed on November 18, 2010. During the 31st experiment, which occurred on February 10, 2011, another study subject was removed from the chamber after 23 minutes of exposure to $PM_{2.5}$ at a level of 66.26 micrograms per cubic meter. The EPA researchers reportedly observed an elevated heart rate during exposure, though the individual denied any symptoms. The individual was provided with copies of the EKG and Holter recording and referred to a physician.

The experiments resumed two weeks later on February 24, 2011. The 41st and final experiment occurred on June 9, 2011. No clinical effects — defined as requiring medical follow-up or referral to a physician — were reported other than for the two cases cited (i.e., the 24th and 31st experiments).

On September 6, 2011, the EPA researchers published in the online edition of the journal *Environmental Health Perspectives* an article entitled, "Case report: Supraventricular Arrhythmia Following Exposure to Concentrated Ambient Air Pollution Particles" ("Case Report").[2] The article reported the supraventricular fibrillation incident and concluded that "Exposure to air pollution including particulate matter may cause supraventricular arrhythmias." The Case Report omitted mention of the 40 other human study subjects had been subjected to the experimental protocol.

On or about September 15, 2011, I sent a request to the EPA pursuant to the Freedom of Information Act ("FOIA") requesting the results of any other similar human experiments conducted by the EPA. On November 21, I received a response listing the exposures and results for all 41 study subjects.[3]

II. Regulation Of Human Experimentation At The EPA

The conduct of the human experiments in question is governed by EPA regulation 40 CFR Part 26 — Protection of Human Subjects ("The Common Rule") — as supplemented by EPA Order 1000.17 Change A1: Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research, which was issued on July 30, 1999 ("EPA Order 1000.17" or the "Order").[4]

A. Basic Protections Under The Common Rule

The Common Rule represents the codification of the "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research," which was mandated by

[2] The original online version of the Case Report is attached to this letter.
[3] A copy of the EPA's response to my FOIA is attached to this letter.
[4] EPA Order 1000.17 was first issued on October 25, 1977 and then modified on July 30, 1999 and, most recently, on July 27, 2011. This analysis employs EPA Order 1000.17 as modified on July 30, 1999 since the human experiments in question began in January 2010 and ended in June 2011.

the 1974 National Research Act which, in turn, was enacted in the wake of the 1972 disclosure of the infamous Tuskegee syphilis experiments.[5]

The Common Rule requires prospective and ongoing reviews of human research by a properly constituted Institutional Review Board ("IRB").[6]

"Research" means,[7]

> a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge…

In order to approve human experiments conducted by the EPA, the IRB must determine that all of the following requirements are satisfied:[8]

> (1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
>
> (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
>
> (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

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[5] In the Tuskegee syphilis experiments, the U.S. Public Health Service studied the natural progression of untreated syphilis in poor, rural African-American males, despite the availability of medical treatment for syphilis. The study subjects were given the impression that they were simply receiving free medical care. The Belmont Report is available at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html.
[6] 40 CFR §§26.103 and 26.109(a).
[7] 40 CFR §26.102(d).
[8] 40 CFR §26.111(a).

> (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by Sec. 26.116.
>
> (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 26.117...

Human study subjects must provide informed consent, unless the study involves only "minimal risk," which is defined as follows:[9]

> Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The purpose of the informed consent requirement is for a study subject to be fully aware of the risks and benefits of the study as follows:[10]

> Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.
>
> (a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:
>
> (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
>
> (2) A description of any reasonably foreseeable risks or discomforts to the subject;

[9] 40 CFR §§26.102(i), 26.109(c) and 26.117(c)(2).
[10] 40 CFR §26.116.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research…

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

B. EPA Order 1000.17 Provides Greater Protection of Human Subjects

Section 4.c of EPA Order 1000.17 bars risky and dangerous human experimentation without the submission of "strongly persuasive justification" as follows:

> There is a presumption that studies involving risk of substantial injury to a human subject from the conduct of the study and that studies testing for irreversible health effects in humans will not be approved, even if the studies otherwise meet the requirements of subsection 4.a, unless strongly persuasive additional justification acceptable to the Review Official is submitted. [Emphasis added]

When a study subject is harmed, a designated EPA official must be immediately notified so that the study methods and procedures may be reviewed. According to Section 6(e):

> Any EPA employee who has knowledge that EPA supported or conducted research has been associated with unexpected serious harm to one or more human subjects shall immediately notify the Review Official.

Once notified, the Review Official may suspend or terminate the study, according to section 6.a(4):

> The Review Official has the authority to have any study suspended or terminated (i) if it is found to be in material noncompliance with the assurance or with the IRB approved methods and procedures, or (ii) if HHS withdraws its approval of the institution's MPA, or (iii) if there is good reason to believe that the rights and welfare of the human research subjects are not being adequately protected, or (iv) if there has been unexpected serious harm to one or more human subjects.

III. The EPA Says $PM_{2.5}$ Is Ultrahazardous

A. The EPA Says $PM_{2.5}$ Can be Lethal Within Hours of Exposure

EPA describes $PM_{2.5}$ on its web site as follows:[11]

> "Particulate matter," also known as particle pollution or PM, is a complex mixture of extremely small particles and liquid droplets. Particle pollution is made up of a number of components, including acids (such as nitrates and sulfates), organic chemicals, metals, and soil or dust particles.
>
> The size of particles is directly linked to their potential for causing health problems. EPA is concerned about particles that are 10 micrometers in diameter or smaller because those are the particles that generally pass through the throat and nose and enter the lungs. Once inhaled, these particles can affect the heart and lungs and cause serious health effects. EPA groups particle pollution into two categories:
>
> - "Inhalable coarse particles," such as those found near roadways and dusty industries, are larger than 2.5 micrometers and smaller than 10 micrometers in diameter.
>
> - "Fine particles," such as those found in smoke and haze, are 2.5 micrometers [i.e., $PM_{2.5}$] in diameter and smaller. These particles can be directly emitted from sources such as forest fires, or they can form when gases emitted from power plants, industries and automobiles react in the air. [Emphasis added]

In the agency's most recent (December 2009) scientific assessment of $PM_{2.5}$, the EPA concluded that $PM_{2.5}$ can kill people shortly after exposure. EPA's "Summary of PM2.5 Risk Estimates" states that the risk of death from $PM_{2.5}$ exposure is proportional to the level of $PM_{2.5}$ exposure and that death can occur in hours (i.e., "lag 0-1"): [12]

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[11] *See* http://epa.gov/airquality/particlepollution.

[12] Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139F (December 2009), p. 6-182.

> The risk estimates for all-cause mortality for all ages ranged from 0.29% to 1.21% per 10 [micrograms per cubic meter] increase in $PM_{2.5}$ (Figure 6-26). An examination of cause-specific risk estimates found that $PM_{2.5}$ risk estimates for cardiovascular deaths are similar to those for all-cause deaths (0.30-1.03%), while the effect estimates for respiratory deaths were consistently larger (1.01-2.2%), albeit with larger confidence intervals, than those for all-cause or cardiovascular deaths using the same lag/averaging indices…
>
> An examination of lag structure observed results similar to those reported for PM_{10} with most studies reporting either single day lags or two-day avg [sic] lags with the strongest effects observed on lag 1 or lag 0-1. [Citations omitted]

The EPA further states in its 2009 assessment that everyone is at risk of death and sickness from $PM_{2.5}$, although some populations are "more susceptible":[13]

> Although the level of evidence varies depending on the factor being evaluated collectively, it can be concluded that some populations are more susceptible to PM than the general population.

Not only has the EPA concluded in its scientific assessment that $PM_{2.5}$ kills, it has been regulating ambient air quality on the basis of that conclusion since 1997.[14]

More recently, in the *Federal Register* announcement of its final Cross-State Air Pollution Rule, which was announced in July 2011, the EPA stated:[15]

> A recent EPA analysis estimated that 2005 levels of $PM_{2.5}$ and ozone were responsible for between 130,000 and 320,000 $PM_{2.5}$-related and 4,700 ozone-related premature deaths, or about 6.1 percent of total deaths from all causes in the continental U.S. (using the lower end of the range for premature deaths). In other words, 1 in 20 deaths in the U.S. is attributable to $PM_{2.5}$ and ozone exposure. [Emphasis added. Footnote omitted.]

The "PM-mortality" relationship was also used to justify the vast majority of the benefits of the EPA's Mercury Air Toxics Standard, which was issued in December 2011. Of the total benefits that EPA estimates that will accrue from the MATS rule, virtually all the health benefits (termed "co-benefits") are derived from the EPA's position that $PM_{2.5}$ kills people:[16]

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[13] Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139F (December 2009), p. 8-15.
[14] *See* http://epa.gov/ttn/naaqs/standards/pm/s_pm_history.html.
[15] 76 *FR* 48208, at 48309.
[16] *See* http://www.epa.gov/mats/pdfs/20111216MATSfinal.pdf.

> Our best estimate for the monetized total health and climate co-benefits of this rule in 2016 at a 3 percent discount rate is between $37 billion and $90 billion or between $33 billion and $81 billion (2007$) at a 7 percent discount rate.

Moreover, there is no safe level of exposure to $PM_{2.5}$. The chairman of the EPA's Clean Air Scientific Advisory Council recently stated in the *New England Journal of Medicine*:[17]

> For ozone and particulate-matter pollution, because no thresholds have been identified below which there is no risk at all, the EPA is using scenarios of risk and exposure to gauge the effects of setting the standards at various concentrations and giving consideration to the burden of avoidable disease. [Emphasis added]

EPA administrator Lisa Jackson has emphasized the lethality of $PM_{2.5}$ in congressional testimony.

During a September 22, 2011 hearing of the Oversight and Investigations Subcommittee of the House Energy and Commerce Committee, Administrator Jackson said:

> Particulate matter causes premature death. It doesn't make you sick. It's directly causal to dying sooner than you should.

At the same hearing, Administrator Lisa Jackson had the following exchange with Rep. Ed Markey (D-Mass.):

> REP. MARKEY: How would you compare it to the fight against cancer, reducing particulate matter?
>
> MS. JACKSON: Yeah, I was briefed not long ago. If we could reduce particulate matter to healthy levels it would have the same impact as finding a cure for cancer in our country.
>
> REP. MARKEY: Could you say that sentence one more time?
>
> MS. JACKSON: Yes, sir. If we could reduce particulate matter to levels that are healthy we would have an identical impact to finding a cure for cancer.

To put these comments in context, consider that cancer kills about 570,000 Americans per year, according to the American Cancer Society, and that the estimated number of deaths in the U.S. during 2010 was about 2.47 million, according to the U.S. Centers for Disease Control.[18] So Administrator Jackson testified to Congress essentially that $PM_{2.5}$ causes almost 25 percent of all deaths in the U.S. annually.

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[17] *See* Samet JM, *N Engl J Med* 2011; 365:198-201 July 21, 2011.
[18] *See* http://www.cancer.org/Cancer/news/News/rates-of-new-cancers-cancer-deaths-dropping and http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf.

Finally, the EPA researchers conducting the humans experiments knew *a priori* that $PM_{2.5}$ is ultrahazardous. In a May 1, 2012 letter to the *Washington Times*, Case Report co-author and director of EPA's Environmental Public Health Division Wayne Cascio admitted:

> … In the case of research into fine-particle pollution, more than 50 clinical studies over the past decade involving human volunteers have been published by scientists from the EPA, many U.S. universities and medical centers. These describe cardiac effects in humans exposed to this harmful pollution... [Emphasis added]

B. The EPA Says $PM_{2.5}$ May Cause Cancer

In *Environmental Defense Fund v. EPA*, a case involving whether certain pesticides were carcinogenic to humans, the U.S. Court of Appeals for the D.C. Circuit noted that it was appropriate to extrapolate the results of animal testing because:[19]

> [T]he ethical problems of conducting cancer experiments on human beings are too obvious to require discussion.

With respect to PM, the EPA stated in its 2009 assessment that,[20]

> Evidence from epidemiologic and animal toxicological studies has been accumulating for more than three decades regarding the mutagenicity and carcinogenicity of PM in the ambient air...
>
> Overall, the evidence is suggestive of a causal relationship between relevant $PM_{2.5}$ exposures and cancer, with the strongest evidence from the epidemiologic studies of lung cancer mortality.

IV. Analysis of the EPA Human Experiments

A. EPA Researchers Violated EPA Order 1000.17 By Intentionally Exposing Human Study Subjects To Lethal Levels Of $PM_{2.5}$

EPA regulates air quality based on its conclusion that $PM_{2.5}$ kills and sickens humans. The agency has concluded that individuals who are exposed to current outdoor levels of $PM_{2.5}$ can die or suffer illness in the hours and days following exposure.

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[19] 510 F.2d 1292 (D.C. Circuit, 1975).
[20] Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139F (December 2009), p. 7-68.

Current outdoor levels of $PM_{2.5}$ average about 10 micrograms per cubic meter on a national basis, according to the EPA.[21] Outdoor air quality violates EPA standards when $PM_{2.5}$ levels exceed 35 micrograms per cubic meter on a 24-hour basis or 15 micrograms per cubic meter on an annual average basis.[22]

Not only did EPA researchers intentionally expose the 41 human study subjects to "killer" $PM_{2.5}$, but the study subjects were exposed to levels of $PM_{2.5}$ that were as high as 750.83 micrograms per cubic meter — i.e., as high as 75 times greater the national average, 50 times greater than the annual regulatory standard and 21 times greater than the 24-hour regulatory standard for $PM_{2.5}$.

EPA Order 1000.17 §4.c. expressly bars "studies involving risk of substantial injury to a human subject from the conduct of a study" and "studies testing for irreversible health effects in humans," unless "strongly persuasive additional justification" is submitted to the IRB.

Death certainly constitutes a "substantial injury" and an "irreversible health effect." In the case of the 58-year old woman, her atrial fibrillation was deemed serious enough that hospitalization was ordered.

The EPA also says that available evidence is suggestive that PM 2.5 causes cancer. Reiterating what the Court of Appeals for the District of Columbia Circuit stated in *Environmental Defense Fund v. EPA*,

> [T]he ethical problems of conducting cancer experiments on human beings are too obvious to require discussion.

Despite a request under the Freedom of Information Act, no evidence has been produced to date by the EPA that any "strongly persuasive additional justification" for intentionally exposing humans to $PM_{2.5}$ was submitted to its IRB, in this case, the University of North Carolina School of Medicine Committee on the Protection of the Rights of Human Subjects.

In any event, the EPA researchers and the IRB would be most likely be hard-pressed to justify risking the lives of human subjects — i.e., no health benefits from the experiment would accrue to the human study subjects and the EPA had already determined as far back as 1997 that human exposure to $PM_{2.5}$ is ultrahazardous.

B. EPA Researchers May Have Violated The Common Rule By Failing To Obtain Adequate Informed Consent

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[21] *See* http://www.epa.gov/cgi-bin/broker?_service=data&_program=dataprog.aqplot_data_2010.sas&parm=88101&stat=WTDAM&styear=2000&endyear=2010&pre=val.

[22] *See* http://www.epa.gov/air/criteria.html.

The Case Report states that the 58-year old woman who suffered supraventricular fibrillation "provided informed consent."

Taking this assertion at face value and assuming for the sake of argument that similar "informed consent" was obtained from the 40 other human study subjects, such informed consents are most likely materially deficient.

It is highly unlikely that the IRB-approved consent form disclosed to the human study subjects the fact that they were going to be exposed to high levels of an air pollutant that could potentially kill them within hours of exposure.

Requests for copies of the consent forms and documents related to the IRB-approval process have been submitted under FOIA to the EPA and the University of North Carolina School of Medicine.

C. EPA May Have Violated EPA Order 1000.17 By Failing To Review And Terminate The Experiment Following The Serious Injury Sustained In The Case Report

According to EPA Order 1000.17 §6.e, when EPA-conducted research is associated with unexpected serious harm to one or more study subjects, the Review Official (i.e., the director of the National Center for Environmental Research Quality Assurance must be notified.

With respect to the Case Report, the reported supraventricular fibrillation in the 58-year old woman was "unexpected." As the EPA researchers stated in the Case Report,

> To our knowledge, there has been no case report of cardiovascular disease following exposure to elevated concentrations of any air pollutant.

"Serious harm" was described in the Case Report. That is, upon detecting supraventricular fibrillation, the researchers immediately stopped the experiment and transferred the study subject to the hospital for overnight observation and telemetry.

So under §6.e of EPA Order 1000.17, notification of the Review Official was required. Once notified, the Review Official could have suspended or terminated the study under §6.a(4) of EPA Order 1000.17. Grounds for suspension or termination include "unexpected serious harm to one or more human subjects."

To date, the EPA has not produced evidence that such notification and review occurred. All that is known, to date, is that the human experiments continued.

D. EPA Researchers May Have Violated The Common Rule And EPA Order 1000.17 By Failing To Amend The IRB-Approved Consent Forms

Although the EPA researchers disclaimed *a priori* knowledge that intentional exposure to $PM_{2.5}$ might cause the sort of injury described in the Case Report (see Section C, above), they were certainly aware of the possibility following the incident. The researchers acknowledged this awareness of the risk of serious injury in the Case Report — e.g., the Case Report's abstract describes its relevance to clinical practice as follows:

> Exposure to air pollution including particulate matter may cause supraventricular arrhythmias.

The researchers cannot claim that they arrived at this conclusion after the experimentation had terminated since the Case Report was submitted for publication in *Environmental Health Perspectives* on April 29, 2011, whereas the study did not end until June 5, 2011. Five study subjects were experimented upon after submission of the Case Report for publication.

No evidence has been yet produced by EPA indicating that the original IRB-approved consent forms (which were likely initially materially deficient as discussed in Section B, above) were subsequently modified to inform the 25th through 41st human study subjects that they may experience supraventricular fibrillation requiring hospitalization as a result of their experimental exposures to $PM_{2.5}$.

So the final 17 human study subjects might not have provided informed consent with respect to the risk of supraventricular fibrillation, which is a serious injury as it requires hospitalization.

E. The University of North Carolina Violated The Common Rule By Approving The Experiment.

Section 26.111(a)(1) of The Common Rule requires that risks to human study subjects be minimized. But given that a study subject could have been killed in mere hours after exposure to PM 2.5, it's hard to see how this risk was minimized.

Section 26.111(a)(2) requires that risks to subjects be "reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result." But the experiments conveyed no benefits (other than, perhaps, monetary) on the study subjects. The knowledge gained from the experiments can only be considered as minimal given that the EPA has already decided that $PM_{2.5}$ can kill

people in a matter of hours and that the agency already regulates air quality on that basis. This section also proscribes conducting human research for the purpose of setting public policy.

Section 26.111(a)(3) states that the researchers should be "particularly cognizant of the special problems of research involving vulnerable populations…" But the protocol approved by the IRB and used by the EPA researchers permitted experimentation on an obese 58-year old woman with personal medical problems, including heart disease, and a family history of heart disease (i.e., her father died from heart disease at age 57).

Under Section 26.102(d) research approved by the IRB must be "systematic" and "designed to develop or contribute to generalizable knowledge." But the EPA experiment does not appear to have been systematic in design or conduct.

There do not appear to have been any non-exposed or "control" subjects and the study subjects were exposed to apparently random levels of $PM_{2.5}$. As is evidenced by the list of experimental results provided by the EPA in response to the FOIA request, each study subject was exposed to a different level of $PM_{2.5}$, ranging from 41.54 micrograms per cubic meter to 750.83 micrograms per cubic meter. [23]

It is not apparent how this most unsystematic experiment could possibly contribute to "generalizable" knowledge justifying the risks of human experimentation.

V. Conclusion

In *Ethyl Corporation v. Environmental Protection Agency*, a case involving the toxicity of leaded gasoline, the U.S. Court of Appeals for the District of Columbia Circuit noted:[24]

> [S]ignificant exposure to lead is toxic, so that considerations of decency and morality limit the flexibility of experiments on humans that would otherwise accelerate lead exposure from years to months, and measure those results.

As "toxic" as the Court and EPA may have considered lead to be, that level of toxicity pales in comparison to the EPA-claimed toxicity of $PM_{2.5}$ — as no one has ever contended that ambient levels of lead in the air could cause death in the hours following exposure. Yet the EPA does just that.

In *Glastetter v. Novartis*, a medical products liability case involving the medication Parlodel, the Eight Circuit Court of Appeals noted,[25]

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[23] A copy of the EPA's response to my FOIA is attached to this letter.
[24] 541 F.2d 1. Certiorari Denied June 14, 1976.See 96 S.Ct. 2662, 2663.
[25] 252 F.3d 986 (2001), at 992.

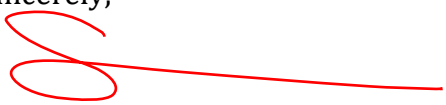
> [Scientists] cannot perform controlled experiments because it would be unconscionable to induce strokes in postpartum women simply to advance the medical community's understanding of Parlodel.

In the 41 human experiments conducted by EPA researchers — experiments in which study subjects risked their lives and health — the EPA conducted them merely to increase, by a small increment, the EPA's understanding of $PM_{2.5}$. The EPA's experiments provided no chance of health benefits to the human study subjects and, in fact, only involved risk of serious harm — thereby violating, at the very least, a basic ethical principle of acceptable human experimentation.

So as discussed herein, substantial evidence has been developed that the EPA and its Institutional Review Board at the University of North Carolina permitted EPA researchers to conduct illegal experiments on human subjects.

I am requesting that you conduct a bona fide and thorough investigation of this experimentation and make a detailed report of your findings to the public as soon as possible. EPA should immediately suspend such research until the completion of your investigation.

Sincerely,



Steve Milloy
Publisher

Attachments

Cc: Sen. Barbara Boxer, Chairman, Senate Environment and Public Works Committee
Sen. James Inhofe, Ranking Minority Member, Senate Environment and Public Works Committee
Rep. Fred Upton, Chairman, House Energy and Commerce Committee
Rep. Henry Waxman, Ranking Minority Member, House Energy and Commerce Committee
Rep. Joe Barton, House Energy and Commerce Committee
Rep. John Dingell, House Energy and Commerce Committee
Rep. Darrell Issa, Chairman, House Oversight and Government Reform Committee
Rep. Elijah Cummings, Ranking Minority Member, House Oversight and Government Reform Committee
Lisa Jackson, Administrator, U.S. EPA

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Case report: Supraventricular Arrhythmia Following Exposure to Concentrated Ambient Air Pollution Particles

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NIEHS
National Institute of Environmental Health Sciences

National Institutes of Health
U.S. Department of Health and Human Services

Case report: Supraventricular Arrhythmia Following Exposure to Concentrated Ambient Air Pollution Particles

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Running Title: Arrhythmia after air pollution particles

Disclaimer: This report has been reviewed by the National Health and Environmental Effects Research Laboratory, United States Environmental Protection Agency and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agency nor does mention of trade names or commercial products constitute endorsement or recommendation for use. None of the authors has any actual or potential competing financial interests.

Abbreviations: concentrated ambient particles (CAPs), implantable cardioverter defibrillator (ICD), particulate matter (PM); University of North Carolina (UNC)

Key words: Air pollution; arrhythmias; atrial fibrillation; atrial flutter; heart diseases; particulate matter

Abstract

CONTEXT: Exposure to air pollution can result in the onset of arrhythmias.

CASE PRESENTATION: We present a case of a 58 year old woman who volunteered to participate in a controlled exposure to concentrated ambient particles (CAPs). Twenty minutes into the exposure, telemetry revealed new onset of atrial fibrillation. The exposure was discontinued and she reverted to normal sinus rhythm approximately two hours later. No abnormality was evident on the volunteer's laboratory examination or echocardiography which could explain an increased risk for supraventricular arrhythmia.

DISCUSSION: Epidemiologic evidence strongly supports a relationship between exposure to air pollutants and cardiovascular disease, but population-level data are not directly relevant to the clinical presentation of individual cases. To our knowledge, this is the only case report of an individual suffering an episode of atrial fibrillation following exposure to an air pollutant. The resolution of the arrhythmia with termination of the particle exposure further supports a causal relationship between the two.

RELEVANCE TO CLINICAL PRACTICE: Exposure to air pollution including particulate matter may cause supraventricular arrhythmias.

Introduction

Epidemiologic investigation supports a positive relationship between exposure to air pollution and cardiovascular disease (Rich et al. 2006) with the number of deaths from such illness estimated to exceed that for respiratory disease following elevated levels of pollutants (Dockery 2001). Air pollutants have been associated with acute cardiac events including myocardial infarctions and cardiac arrests (Forastiere et al. 2005; Rosenthal et al. 2008; Zanobetti and Schwartz 2005). In addition, air pollution has been associated with the incidence of cardiac arrhythmias (Link and Dockery 2010; Peters et al. 2000; Routledge and Ayres 2005). Studies have demonstrated that discharges by implantable cardioverter defibrillators (ICDs) for ventricular arrhythmias increase with higher levels of black carbon, fine particles, coarse particles, nitric oxide, ozone, NO_2, nitric oxide, carbon monoxide, and SO_2 (Rich et al. 2006; Peters et al. 2000; Metzger et al. 2007; Rich et al. 2005; Santos et al. 2008). Evidence also supports an association between measures of air pollution and the incidence of supraventricular arrhythmias. In one ICD study, there was a statistically significant relationship between the incidence of supraventricular arrhythmias and increased O_3 concentrations in the hour preceding the arrhythmia (Rich et al. 2005). Holter examinations revealed an increased risk of supraventricular arrhythmias in association with 5-day moving averages of $PM_{2.5}$, ozone, and sulfate in non-smoking adults (Sarnat et al. 2006). In yet another holter study, both supraventricular and ventricular arrhythmias were increased in association with PM and NO_2 exposures (in the previous 24 to 72 hours and with 5 day moving averages) among men with coronary artery disease (Berger et al. 2006). These arrhythmias developed within a few hours of increased levels of air pollution (Ljungman et al. 2008).

While epidemiologic data strongly support a relationship between exposure to air pollutants and cardiovascular disease, this methodology does not permit a description of the clinical presentation in an individual case. To our knowledge, there has been no case report of cardiovascular disease following exposure to elevated concentrations of any air pollutant.

Case Presentation

A 58 year old, Caucasian female presented to the Environmental Protection Agency's Human Studies Facility in Chapel Hill, North Carolina for participation in a study requiring sequential exposures to filtered air and concentrated ambient particles (CAPs). Protocols and consent forms were approved by the University of North Carolina (UNC) School of Medicine Committee on the Protection of the Rights of Human Subjects and the subject provided informed consent. Two years previously, she had participated in an identical exposure protocol without any complication. At that time, two 24 hour holter examinations obtained during the exposures to filtered air and CAPs demonstrated 29 and 54 episodes of supraventricular ectopy respectively.

On the day of exposure to CAPs, the volunteer had no symptoms. There was a history of osteoarthritis and hypertension treated with an angiotensin-converting enzyme inhibitor and a diuretic (lisinopril 10 mg and hydrochlorothiazide 12.5 mg). Previous surgeries included a hernia repair, a cholecystectomy, and a total left knee arthroplasty. The family history was significant for her father dying at 57 years of age with a myocardial infarction. The volunteer was a lifetime non-smoker. On physical examination, she was 173 cm tall and weighed 104.4 kg (the body mass index was 34.9 and her waist was 45 inches). Her pulse was regular at 66 per minute and her blood pressure was 144/61. The baseline electrocardiogram showed normal sinus

rhythm (Figure 1A). A holter monitor was placed and this demonstrated evidence of increased supraventricular ectopy with 157 ± 34 premature atrial contractions per hour during the 3 hours immediately preceding the exposure to CAPs.

Twenty three minutes into the exposure to CAPs (with a filter weight revealing 112 $\mu g/m^3$ and the particle number being 563912/cc), the telemetry monitor revealed that the subject had non-sustained atrial fibrillation that quickly organized into atrial flutter. She was immediately removed from the exposure chamber. The volunteer reported no symptoms and there was no change in the physical examination. The twelve lead EKG verified that she remained in atrial flutter (Figure 1B). Her serum electrolytes, blood urea nitrogen, creatinine, glucose, and complete blood count were all normal. Creatine kinase and the MB fraction were also normal. During the transfer to the UNC Medical Center (approximately 2 hours following the onset of the arrhythmia), she spontaneously reverted back to a normal sinus rhythm.

The patient was admitted to the hospital overnight for observation and telemetry. The following morning, the EKG documented normal sinus rhythm. Her serum electrolytes, blood urea nitrogen, creatinine, glucose, creatine kinase, and the MB fraction were again normal, and her complete blood count was normal except for a hematocrit of 35.7% (with a lower limit of normal being 36.0%). Resting transthoracic echocardiography demonstrated normal right ventricular contraction with an ejection fraction of 55 to 60%, aortic sclerosis, and diastolic left ventricular dysfunction. The left atrium was considered mildly dilated; all other chambers of the heart were normal in size. She was discharged on no new medication. Approximately 6 weeks later, she underwent electrophysiology study, which did not provoke atrial fibrillation or significant atrial ectopy. The study did indicate a reentrant circuit of the cavotricuspid isthmus which was ablated to prevent potential future episodes of atrial flutter.

Discussion

The volunteer demonstrated evidence of increased supraventricular ectopy immediately preceding her exposure to CAPs but there was no evidence of atrial arrhythmias. She then suffered the onset of atrial fibrillation within a very short time after exposure to CAPs was initiated. Within 2 to 3 hours after the cessation of exposure, the arrhythmia resolved and she returned to normal sinus rhythm. Atrial fibrillation is the most common supraventricular arrhythmia affecting 1 to 2% of the general population (Falk 2001). This arrhythmia is uncommon before 60 years of age but it afflicts about 10% of the population by 80 years of age.. Risk factors for atrial fibrillation include hypertension (especially uncontrolled), coronary artery disease, heart failure, cerebrovascular disease, diabetes, thyroid conditions, sleep apnea, obesity, a past history of rheumatic heart disease and/or congenital heart defects, pericarditis, sick sinus syndrome, a family history of atrial fibrillation, and echocardiographic abnormalities (Kannel and Benjamin 2008, 2009). In addition, cigarette smoking, alcohol use, caffeine consumption, and stimulant drugs can help trigger atrial fibrillation. Of these defined risk factors, the volunteer had a history of well controlled hypertension and her body mass index was consistent with obesity. Her history of premature atrial contractions may also have increased her risk for atrial fibrillation (Binici et al. 2010). In a similar manner, pre-existing cardiovascular disease, diabetes and impaired glucose tolerance, chronic obstructive pulmonary disease, and current cigarette smoking all increase susceptibility for cardiovascular disease associated with air pollution (Chen et al. 2006; Liao et al. 2009; Mills et al. 2007; Wheeler et al. 2006; Whitsel et al. 2009; Zareba et al. 2009). There was no obvious explanation for her onset of a supraventricular arrhythmia during the exposure. While coincident atrial fibrillation cannot be excluded, the

onset of her arrhythmia was associated with her exposure to ambient air pollution particles. The correlation between the resolution of the arrhythmia and the termination of the CAPs exposure further supports a causal relationship between the two.

Systemic inflammation and underlying oxidative stress may increase the risk of atrial fibrillation (Kumagai et al. 2004). Patients with atrial fibrillation demonstrate evidence of inflammation with elevated levels of inflammatory markers including C reactive protein, interleukin-6, and tumor necrosis factor-α (Chung et al. 2001; Gaudino et al. 2003). There is some evidence that statin treatment may potentially alter the risk for this arrhythmia by modifying oxidative stress (Siu et al. 2003). The specific association between increased arrhythmia induction and air pollution may reflect oxidant generation and inflammation following exposure, consistent with mechanisms involved in the initiation and maintenance of some other forms of atrial fibrillation (Mazzoli-Rocha et al. 2010). The oxidative stress and inflammation associated with the pollutant have been postulated to affect coronary perfusion and consequently enhance the propensity for such arrhythmias through tissue ischemia. However, the rapid onset of the onset of this volunteer's atrial fibrillation following CAPs exposure suggests that the basis for the arrhythmia may be a disruption of the normal cardiac autonomic control rather than a systemic inflammation as the latter would require greater durations of time to develop (Routledge and Ayres 2005). In an animal model, diesel exhaust increased the sensitivity of the heart to triggered arrhythmias via an activation of airway sensory receptors (e.g. TRPA1) (Hazari et al. 2011). It has been suggested that this leads to autonomic imbalance and a predisposition for arrhythmia development. A comparable mechanism has been proposed to explain the cardiac response to ozone and cigarette smoke (Joad et al. 1998; Mutoh et al. 2000).

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Figure legend

Figure 1. The volunteer's electrocardiogram (12 lead and rhythm strip) before (A) and immediately following (B) exposure to concentrated ambient particles. The electrocardiogram before the exposure (A) reveals a regular sinus rhythm with defined P waves (arrows) while that following the exposure (B) is irregular with "flutter" waves (arrows).

Figure 1

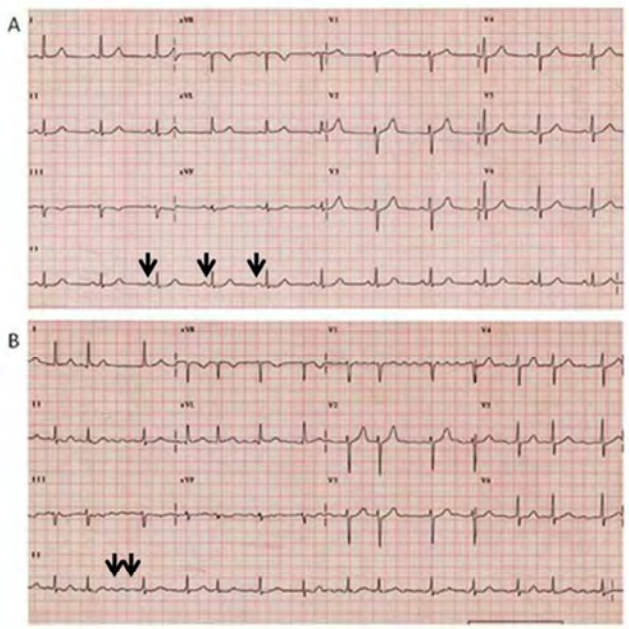

Figure 1. The volunteer's electrocardiogram (12 lead and rhythm strip) before (A) and immediately following (B) exposure to concentrated ambient particles. The electrocardiogram before the exposure (A) reveals a regular sinus rhythm with defined P waves (arrows) while that following the exposure (B) is irregular with "flutter" waves (arrows).
76x57mm (300 x 300 DPI)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
National Health and Environmental Effects Research Laboratory
Research Triangle Park, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

November 21, 2011

Steven Milloy
12309 Briarbush Lane
Potomac, MD 20854

SUBJECT: Freedom of Information Act Request No: HQ-FOI-02235-11

Dear Mr. Milloy:

This is in response to your Freedom of Information Act request, cited above, dated September 15, 2011 requesting the results of all research conducted at EPA's Human Studies Facility relating to human volunteers exposed to concentrated ambient particles (CAPs). Based on your email response to Karis Boerner on 11/8/11, you further clarified your request for data to include a timeframe frame "starting 2010" focusing on "clinical effects" of all subjects.

Your request was assigned to the Office of Research and Development (ORD), National Health & Environmental Effects Research Laboratory (NHEERL). NHEERL has completed its work on your request. Included with this letter is one (1) enclosed document that we have determined to be relevant to your request. This concludes ORD's response to your request. There is no cost to you for this information.

You may appeal this response to the National Freedom of Information Officer, U.S. EPA, FOIA and Privacy Branch, 1200 Pennsylvania Avenue, N.W. (2822T), Washington, DC 20460 (U.S. Postal Service Only), FAX: (202) 566-2147, email: hq.foia@epa.gov. Only items mailed through the United States Postal Service may be delivered to 1200 Pennsylvania Avenue N.W. If you are submitting your appeal via hand delivery, courier service or overnight delivery, you must address your correspondence to 1301 Constitution Avenue, NW, Room 6416J, Washington, DC 20004. Your appeal must be in writing, and it must be submitted no later than 30 calendar days from the date of this letter. The Agency will not consider appeals received after the 30 calendar day limit. The appeal letter should include the case number stated above (HQ-FOI-02235-11). For quickest possible handling, the appeal letter and its envelope should be marked "Freedom of Information Act Appeal."

If you have questions regarding this response, please contact Karis A. Boerner, FOIA Coordinator, NHEERL/ORD, (218) 529-5035.

Sincerely,

H. Zenick

Harold Zenick, Ph.D.
Director
National Health & Environmental Effects
Research Laboratory

Enclosure(s)

Exposure Date	SUBJECT	Entered Chamber	Exited Chamber	Filter	Conc (ug/m3)	Clinical Effects*
1/5/2010	OMC019	11:02	13:02		205.27	No clinical effects requiring follow-up observed
1/6/2010	KCN112	9:34	11:34		153.58	No clinical effects requiring follow-up observed
2/9/2010	OMC021	10:52	12:52		442.49	No clinical effects requiring follow-up observed
3/9/2010	OMC023	10:45	11:08		750.83	No clinical effects requiring follow-up observed
3/23/2010	OMC024	10:49	12:49		147.42	No clinical effects requiring follow-up observed
4/13/2010	OMC025	10:43	12:43		431.06	No clinical effects requiring follow-up observed
4/20/2010	OMC026	11:19	13:19		336.56	No clinical effects requiring follow-up observed
4/27/2010	OMC027	11:00	13:00		257.18	No clinical effects requiring follow-up observed
4/28/2010	KCN111	9:13	11:13		154.36	No clinical effects requiring follow-up observed
5/4/2010	OMC028	10:54	12:54		326.78	No clinical effects requiring follow-up observed
5/5/2010	KCN113	9:26	11:26		578.95	No clinical effects requiring follow-up observed
5/11/2010	OMC022	10:51	12:51		247.77	No clinical effects requiring follow-up observed
6/8/2010	OMC030	10:48	12:48		257.12	No clinical effects requiring follow-up observed
6/15/2010	OMC031	11:28	13:28		468.96	No clinical effects requiring follow-up observed
6/29/2010	OMC033	11:04	13:04		321.36	No clinical effects requiring follow-up observed
7/13/2010	OMC034	10:49	12:49		177.02	No clinical effects requiring follow-up observed
7/15/2010	XCE224	11:10	13:10		137.19	No clinical effects requiring follow-up observed
8/10/2010	OMC035	11:00	13:00		411.98	No clinical effects requiring follow-up observed
8/12/2010	XCE225	10:59	12:59		157.63	No clinical effects requiring follow-up observed
8/25/2010	KCN114	9:55	11:55		232.91	No clinical effects requiring follow-up observed
9/9/2010	XCE226	10:55	12:55		87.36	No clinical effects requiring follow-up observed
9/23/2010	XCE228	11:05	13:05		174.61	No clinical effects requiring follow-up observed
10/6/2010	KCN115	9:31	11:31		131.50	No clinical effects requiring follow-up observed
10/7/2010	XCE227	11:21	12:10		111.68	Removed from chamber due to new onset of atrial fibrillation. Individual reverted to normal sinus rhythm approximately two hours later. Individual was admitted to the hospital overnight for observation and telemetry. Detailed in Ghio et al., 2011 Case Report, Environ Health Perspect doi:10.1289/ehp.1103877
11/18/2010	XCE229	11:14	13:14		59.09	No clinical effects requiring follow-up observed
12/2/2010	XCE231	10:55	12:55		35.60	No clinical effects requiring follow-up observed
1/6/2011	XCE233	11:05	13:05		43.65	No clinical effects requiring follow-up observed
1/24/2011	XCE232	10:47	12:47		150.63	No clinical effects requiring follow-up observed
1/31/2011	XCE234	11:03	13:03		90.95	No clinical effects requiring follow-up observed
2/3/2011	XCE236	11:12	13:12		57.91	No clinical effects requiring follow-up observed
2/10/2011	XCE235	11:12	11:35		66.26	Removed from chamber due to a short episode of an elevated heart rate during exposure. The individual denied any symptoms. This individual was provided with copies of the EKG and holter recording and referred to MD.
2/24/2011	XCE238	10:57	12:57		103.51	No clinical effects requiring follow-up observed
3/28/2011	XCE239	10:52	12:52		80.06	No clinical effects requiring follow-up observed
4/14/2011	XCE237	10:48	12:48		93.24	No clinical effects requiring follow-up observed
4/18/2011	XCE242	11:09	13:09		72.89	No clinical effects requiring follow-up observed
4/25/2011	XCE240	11:05	13:05		41.54	No clinical effects requiring follow-up observed
5/2/2011	XCE244	11:13	13:13		85.31	No clinical effects requiring follow-up observed
5/16/2011	XCE243	11:00	13:00		142.50	No clinical effects requiring follow-up observed
5/23/2011	XCE245	10:57	12:57		266.92	No clinical effects requiring follow-up observed
6/2/2011	XCE247	11:00	13:00		179.58	No clinical effects requiring follow-up observed
6/9/2011	XCE246	10:55	12:55		359.52	No clinical effects requiring follow-up observed

* Note : Clinical Effects is defined as requiring medical follow-up or referral to physician