Comments on Supplementary Notice of Proposed Rulemaking on Science Transparency
Docket # EPA–HQ–OA–2018–0259

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I am Bernard D. Goldstein, MD. My comments are based on my background as a physician, including taking care of patients with lung disease, heart disease and infectious disease as a board certified internist. I have been involved in environmental health science and policy since 1966 when I served two years as a Commissioned Officer in the USPHS Division of Air Pollution. I was a member of two CASAC subcommittees and chaired CASAC in the early 1980s under Administrator Gorsuch. I served as President Reagan's appointee as Asst. Administrator of EPA for Research and Development under Administrators Ruckelshaus and Thomas. I am an elected member of the American Society for Clinical Investigation and of the National Academy of Medicine, have chaired a dozen committees for the NAS and served on or chaired committees for various US governmental agencies, the World Health Organization, and the United Nations Environmental Program. I am also past president of the Society for Risk Analysis.

My written comments will focus on three aspects of the SNPRM.

1) The SNPRM deceives the American public by repetitively and inappropriately citing a National Academies of Science workshop as a major basis for its decisions.
2) The SNPRM fails to appropriately consider the web of science, and particularly the role of biological plausibility, which is an essential part of the weight of evidence approach to interpreting scientific evidence relevant to EPA's decision processes.
3) EPA has not considered the potential impact of the globalization of environmental health science on the ability to obtain data relevant to the important role of biological plausibility in its decision processes.

1) Deceiving the American Public

EPA's Supplemental Notice of Proposed Rulemaking is required to contain information about how the public can provide comments to which EPA is required to respond. The obvious implication is that the Federal Register Notice contains a fair and accurate representation of the basis for the proposed rulemaking. But in this case, it does not. Of the 15 references cited, clearly the most authoritative is to a National Academies of Science Workshop on Principles and Obstacles for Sharing Data from Environmental Health Research.[1] This Workshop is cited 9 times, all within the

[1] National Academies of Science, 2016. Principles and Obstacles for Sharing Data from Environmental Health Research: Workshop Summary. National Academies Press, Washington, DC

Federal Register section on Definitions, which addresses the central issues raised by the proposal. None of the other 9 references within this section is cited more than once.

The US National Academies of Science is perhaps the most respected source of unbiased scientific opinion in the world, so citation to the NAS would seem to provide authoritative backing for EPA's proposal. But not if it is for a workshop. Speakers are chosen by the NAS to accurately and fairly represent divergent points of view rather than to present a recommendation obtained through the consensus of an expert scientific committee. In this case, industry representatives were involved in the planning committee for this Workshop, and three were speakers, including the industry consultant who controversially heads EPA's Clean Air Scientific Advisory Committee. The NAS report has a very strong disclaimer that EPA chose to ignore.

> **"The statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the [NAS] and they should not be construed as reflecting any group consensus."**

Individual opinions summarized by rapporteurs in the Workshop report, as well as specific quotations, are citable, but only to the individual who made the comments.

In pointing out this inappropriate NAS citation, I am not just playing "gotcha." On a particularly important point, the definition of the science subject to EPA's new requirement, EPA has a lengthy paragraph in their Federal Register notice that is almost word-for-word from the Workshop report's account of what was said by Dr Lynn Goldman who chaired the workshop. But no citation is given to the speaker. Immediately below is the wording in the workshop report to which I have added track changes to demonstrate how EPA has edited these remarks to remove any language that would make it seem other than an NAS consensus report. I follow that with EPA's language from the Federal Register.

> There are various approaches to testing and validating previous scientific work, she said. "A *reanalysis* is when you conduct a further analysis of data." A person doing a reanalysis of data may use the same programs and statistical methodologies that were originally used to analyze the data or may use alternative methodologies, but the point is to analyze exactly the same data and see if the same result emerges from the analysis.
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> "*Replication* means that you actually repeat a scientific experiment or a trial to obtain a consistent result," she continued. The second experiment uses exactly the same protocols and statistical programs but with data from a different population. The goal is to see if the same

results hold with data from a different population.

"And then, finally, when you *reproduce*, you are producing something that is very similar to that research, but it is in a different medium or context," she said. In other words, a researcher who is reproducing an experiment addresses the same research question but from a different angle than the original researcher did. "Most of us, when we are doing systematic reviews, are more convinced that something is going on when we see reproducibility as well as replicability[2]

[3]

Further, by removing the quotation marks and "she said" language from the Workshop statement, EPA hides the fact that this was the opinion of an individual speaker rather than the consensus of an NAS Committee. Also highly misleading is EPA's omission of the last sentence from the Workshop paragraph, which clearly is at odds with EPA's goals. Stated in that summary sentence is that environmental health science inherently moves forward by "reproducibility as well as replicability," which is contrary to EPA's focus on reanalysis of existing data by industry consultants. Had it been known to the readers of the Federal Register announcement that it was Dr. Goldman who was being directly quoted, they could have looked up her views on EPA's transparency proposal. They would have found that she is in fact strongly opposed to this action.

The standard way of deciding what influences a decision in both science and law is to look at the references cited. These clearly have influence, or they would not have been cited. Another reasonable inference is that "pivotal" findings should certainly be among these references, and would likely be among the most highly referenced. Further, in both science and law, the references chosen to be cited are crucial determinants of the probity and validity of the argument advanced. So it is highly ironic that EPA has misled the public in this disgraceful way.

Also ironic is EPA's heavy reliance on the NAS in that the current EPA leadership has steadfastly refused to consult the Academies on any of the issues related to its attempts to change the scientific processes at EPA. Similarly, in violation of congressional mandates, it has not involved its external scientific committees in considering the rationale for any of its major proposed changes in EPA's scientific processes.

It is unclear as to whether this deception is unintentional or intentional. If unintentional, it is one more piece of evidence as to how out of touch EPA's policy leadership is with its own scientists, let

[2] Ibid. page 6

[3] Strengthening Transparency in Regulatory Science. EPA-HQ-QA-2018-0259-9322 Regulations.gov, March 18, 2020. Page 6

alone the scientific community.[4] Supporting the likelihood that the intention was to deceive is the presence of appropriate quotation marks in a footnote in the Federal Register notice describing an OMB directive.

2) The Web of Science

Most perplexing and disconcerting about this proposal is its lack of clarity about how the EPA will decide which studies fit into the category of influential scientific information. The definitions are unclear.

There is a frequently used term in research called "The Web of Science." The strength of a spider's web includes the redundancy among its linkages such that a minor flaw in one link does not cause the whole web to fail. But suppose EPA or one of its stakeholders wants to wrongly assign weakness to the entire web by analyzing only the weakest link in an otherwise redundant support loop? This would give a false picture of the strength of the entire web. Accordingly, without a clear understanding of what constitutes influential scientific information, one is left with significant doubt about whether to trust EPA and its stakeholders to choose appropriately among the web components. Those with significant financial advantages can test each scientific link in advance and pick the weakest or strongest, depending upon their self-interest. Accordingly, this Supplemental just exacerbates the inherent environmental justice issues caused by the original "transparency" proposal.

A central facet of considering cause and effect relations in environmental health science is the issue of biomedical plausibility. In essence, does the purported relationship conform to our understanding of science? Biomedical plausibility has continued to be a very important part of the scientific basis of regulatory decisions. The most recent EPA Integrated Science Assessment, that for particulate matter, states:

> Biological plausibility can strengthen the basis for causal inference (U.S. EPA, 2015). In this ISA, biological plausibility is part of the weight-of-evidence analysis that considers the totality of the health effects evidence, including consistency and coherence of effects described in experimental and observational studies.[5]

Indicating its importance is that for each of the particulate health endpoints there is a separate discussion of biological plausibility. Each of these has multiple literature references.

An example of coherence and biological plausibility is the finding of narrowed airways in rats experimentally exposed to particulates and epidemiological evidence of asthma attacks in children. Coherence is furthered by studies showing that the mechanism of action of particulates includes inflammation, which is known to be causally related to asthma attacks in humans. In contrast, carbon monoxide has no direct pulmonary effects in laboratory animals, nor would such direct

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[4] Bernard D. Goldstein. How EPA Administrator Wheeler Completely Misinterprets Science. The Hill, 6/20/19. https://thehill.com/opinion/energy-environment/449465-how-epa-administrator-wheeler-completely-misinterprets-science

[5] Integrated Science Assessment (ISA) for Particulate Matter, EPA/600/R-19/188, December 2019. www.epa.gov/isa

effects be consistent with our understanding of the biochemical mechanism of carbon monoxide toxicity. Accordingly, an epidemiological study associating carbon monoxide inhalation with asthma would not pass the biological plausibility test. Such an unexpected finding would be grounds for discarding the association as unlikely to be causally related.

Development of the fine particulate standard provides an excellent example of the web of science. For fine particulates, a pivotal, scientifically influential study was performed in the 1940s when scientists funded by the Atomic Energy Commission showed that fine particles penetrate deeply into the lung and were more toxic than coarse particles, which were scrubbed out in the upper airways. So why didn't EPA set a fine particle standard under the 1970 Clean Air Act? A major reason was that there was no robust way to measure fine particles outside of specialized laboratories. In addition, while I can point historically to these studies, there needed to be years of confirmatory approaches in laboratory animals and in lung inhalation models. Not all were fully supportive, mainly because of limitations in scientific techniques that are now apparent in retrospect. Until there were the pivotal and influential studies leading to an appropriate measurement technique, and the confirmatory evidence of the high likelihood that fine particulates were important to human health, we could not have had either the Harvard Six City study nor the American Cancer Society study—the poster children for the alleged need for transparency. Most importantly, the acceptance of these two studies depends upon not only the work that preceded their publication, but also the literally hundreds of studies that have since confirmed these findings to the satisfaction of the overwhelming majority of the scientific community. Again, not unanimously.

So which of these studies are "pivotal" or "scientifically influential"? We can only know this in retrospect, i.e., these terms are more suitable to the history of science. If the original Atomic Energy funded studies of radioactive particles had not been confirmed in many ways, we would not have had such an interest in fine particles. So aren't these confirmatory studies scientifically influential? The definitions given in the SNPRM are little more than handwaving.

Such definitions can be used by historians long after the fact. They can be used by advertising agencies. They could be used by a dean of a school of public health to claim that her or his school provides more pivotal or scientifically influential research than my school of public health.

Actually, I could respond to the other dean by simply comparing the number of times published research from my school has been cited by other scientists. Citation of research within an EPA document on which a regulatory decision is based could also be used to define pivotal or influential science. While imperfect, it is still far more understandable and accountable than any of the definitions in the SNPRM.

So let me use it to look at the biological plausibility of the science that EPA used to underpin regulation. Biological plausibility is almost uniformly referred to as a factor in EPA's description of the scientific analysis underlying regulation. As much of the studies related to biological plausibility that are cited by EPA are not dose response models, they will clearly be affected by the new approach otherwise vaguely described in the Supplemental proposal.

Biological plausibility is an important part of the weight of evidence underlying scientific determinations relevant to EPA decisions. For example, the December 2019 Particulate ISA states: "In this ISA, biological plausibility is part of the weight-of-evidence analysis that considers the totality of the health effects evidence, including consistency and coherence of effects described in experimental and observational studies." Each of the six health effects chapters contains a section on biological plausibility. In addition to its own newly added references, the sections on biological plausibility referenced the previous ISA in 2011, so one could even add those references as being influential. Not surprisingly, as noted in the ISA, there was not always complete agreement among the studies.

Another example of the problems caused by the Supplement's inherent lack of understanding of EPA's scientific processes, let alone standard scientific reasoning, is to consider what this poorly defined expansion means to studies reported by the Health Effects Institute. I can think of no other more influential or pivotal source of research related to air pollution than the body of work chosen to be funded by Health Effects Institute. HEI is funded equally by EPA and by the American automobile industry, and it responds to the need for science underlying strategic regulatory decisions. A particularly influential aspect of HEI's activities is the funding of an external Review Committee, which independently reviews the study. Both the study itself and the Review Committee's analysis are bound together as an HEI document. The review is aimed both at considering the scientific value of the study as well as its implications. A quick look at the recent HEI Review Committee reports shows a median of over 20 references that are cited by the reviewers (https://www.healtheffects.org/publications). Such a citation inherently implies that the study was influential in the Review Committee's influential decisions about the validity and pertinence of the study they are reviewing. These reviewers do not ask for, or look at, the raw or completed data set for the papers that they are citing to write their influential analysis. Further, it is inconceivable that all of the references cited by the Review Committee will have such data available. Does EPA plan to tell the HEI not to allow its Review Committee to consider any literature for which the committee members have not personally evaluated the completed data, or at least are certain that the completed data are available?

Similarly, EPA's own analyses, such as the ISA's reviewed by CASAC, often simply cite previous EPA documents, or other reviews such as those performed by the National Academy of Science, as foundations on which they then overlay the more recent scientific studies. Does EPA now plan to destroy these foundations, or to subject the literally thousands of papers that went into the weight of evidence for previous EPA analyses to considerations as to which are pivotal or influential? Or has EPA even given a serious thought to the issue?

Biological plausibility is not a one-way street leading to regulation. For example, ascribing causality to the epidemiologically observed linkage between sulfur dioxide and respiratory health effects needed to be reconsidered when it was found that sulfur dioxide was usually absorbed in the upper airways rather than penetrating to the lung.

3) <u>Globalization of Environmental Health Research</u>

The United States was among the first to develop a sustained environmental research enterprise. When the EPA was formed 50 years ago from components of different existing federal agencies, it incorporated laboratory activities and facilities from the Public Health Service Divisions of Air Pollution and of Water Pollution, as well as components of the US Departments of Agriculture and of Interior. The National Institute of Environmental Health Sciences traces its origins to 1966. Funding from both EPA and NIEHS, as well as from interested donors, led to a rapid growth of university-based research programs. These research programs were integral to the initial burst of environmental laws and regulations. They were themselves spurred by the development of US environmental laws, almost all of which contained provisions requiring that regulatory actions be based on the best available science.

While far from being the only player, quite clearly US environmental health science had a leadership role in the 1970s and is still a significant component of global environmental health research. But to what extent has that changed, and how could that possibly affect the SNPRM under consideration, particularly as peer-reviewed studies have substantially increased our knowledge of the biological mechanisms involved thereby adding to the weight of evidence supporting a causal association between environmental pollutants and adverse health effects?

I chose to review the country of origin of the research listed in the National Library of Medicine's PubMed under the heading "fine particles health effects" for which there were 1,288 entries. My rationale for the choice of PubMed includes the comprehensive approach to the world's literature taken by the National Library of Medicine and its restriction against literature that has not been peer reviewed or is not in established journals. It is highly unlikely that any original reference cited by EPA related to human health effects will not have been listed in PubMed. Undoubtedly, any non-EPA study considered by EPA to be pivotal or scientifically influential will have been included in the NLM's comprehensive approach. My recent quick sampling demonstrates the extent to which this has become a global effort. Of 1,288 total listed, the first 40, up to year 1995, show 28 US, 11 non-US, one collaborative US/non-US; the middle 40, 2012-2013, show 12 US, 25 non-US, and 3 collaborative; and the most recent 40 show 7 US, 27 non-US, and 6 collaborative. For those that I consider to be other than directly related to dose response, i.e., relevant to the current SNPRM, the following is found. Of the 20 such papers in the earliest period, 16 (80%) are solely from US scientists and 4 (20%) from elsewhere; of the 18 papers in the second period, 4 (22%) are solely from US scientists 12 (67%) solely from other countries, and 2, (11%) are collaborations between US and foreign institutions; and of the 12 in the most recent period, 2 (17%) are solely from the US and 10 (83%) are from elsewhere. I rejected 11% of the reviewed studies based upon considering them not relevant (e.g., related to moon dust or to cows or parrots) and replaced the study by the next on the NLM list. (A quick look at other topics suggests a similar picture of movement toward predominance of scientific sources other than the US.)

The obvious question pertinent to this Supplement is whether the non-US scientists would be willing to subject themselves to nitpicking attacks by paid industry consultants who are hired to find a minor blemish, which then are falsely magnified into flaws—something that has happened far too often and is well known to the global scientific community. Why not ask?

Another question is related to the increasing number of co-authors in each published study. In the snapshot I described above, the first group of studies of fine particulate listed in PubMed had an average of 3.6 authors per paper; while for the most recent group it was 6.5 authors per paper. Would each author have to agree to share the data so that any one author would have veto power over sharing? EPA could find out by sampling the scientific community represented in cited publications underlying its regulatory decisions. But like so many other aspects of the initial transparency rule and this Supplement, it has not bothered to do any preliminary analyses or to have such analyses done by the NAS or the SAB. A not unreasonable conclusion is that current EPA leadership would prefer not to have science interfere with its preconceived judgments.

Let me take this one step further. Imagine a series of peer-reviewed animal and in vitro studies from non-US institutions suggesting an existing chemical was harmful. None of the authors agreed to turn over their data sets to EPA. Let's further suppose that based on these studies much of the world decided to ban the chemical. What would EPA do? Further, let's suppose that the manufacturers of this chemical in other countries, without their home market, sought to export the chemical to the US? Would that be OK? Are we about to become the third-world country in which toxic chemicals are dumped?

This snapshot I provided is not a definitive study of the world's research on environmental health. But this is only one of the numerous studies that could be done by EPA if it really wanted to evaluate the feasibility and impact of its new rule. It has steadfastly avoided doing so.

Before potentially excluding from consideration this very large percent of relevant scientific literature, EPA could have surveyed these non-US scientists to find out whether they would have cooperated with their new rule or its extension in the SNPRM. They could have done a far more intensive analysis of the sources of the studies that they cite in existing regulations, or have responded to my and others previously expressed concerns. For example, the International Society of Environmental Epidemiology[6] has made this point very strongly. EPA's failure to do any such analysis, or to submit consideration of this new rule to the National Academies of Science or even their own Science Advisory Board, is a dereliction of their duty to the American public and to Congressional mandates for basing environmental regulations on the best available science.

Thank you for your consideration of the issues raised above.

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[6] Comments of the International Society for Environmental Epidemiology on EPA's proposed rule on Strengthening Transparency in Regulatory Science (EPA-HQ-OA-2018-0259-0001) May 2019. https://www.iseepi.org/Public/About_Us/Advocacy/Public/About_Us/Advocacy.aspx?hkey=ba9675be-a51b-4b9d-bc7c-2683e1af3c9b.

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