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By Electronic Submission to www.regulations.gov

Acting Administrator Andrew Wheeler
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Docket ID No. EPA-HQ-OA-2018-0259

Re: COMMENTS ON PROPOSED RULE, STRENGTHENING TRANSPARENCY IN REGULATORY SCIENCE, 83 FED. REG. 18,768 (Apr. 30, 2018)

Dear Acting Administrator Wheeler:

The Emmett Environmental Law & Policy Clinic at Harvard Law School submits this letter on behalf of a distinguished group of experts committed to the advancement of research to improve the health and safety of Americans and people around the world. The signatories include the President of Harvard University, the Presidents and a number of Department Chairs and Chiefs of four of the world's foremost research and teaching hospitals (Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Massachusetts Eye and Ear, and Massachusetts General Hospital), the Deans of Harvard's T.H. Chan School of Public Health and Harvard Medical School, preeminent faculty at the Harvard T.H. Chan School of Public Health, the Harvard Medical School, and the Harvard School of Engineering and Applied Sciences, and numerous esteemed research and clinical doctors affiliated with Harvard and its research hospitals. Work done by the signatories and/or their institutions addresses a broad spectrum of health impacts on infants, children, and adults from exposures to chemicals and activities that are regulated by the U.S. Environmental Protection Agency ("EPA") under various statutes including the Safe Drinking Water Act, the Toxic Substances Control Act, the Comprehensive Environmental Response, Compensation, and Liability Act, the Resource Conservation and Recovery Act, the Clean Water Act, and the Clean Air Act, collectively referred to herein as "the Statutes."

Specifically, signatories of this letter have conducted research to determine whether and how exposures to chemical substances such as lead and mercury in food, water, soil, and air affects the development of fetuses, infant mortality, children's development, and children's educational performance. They have also studied the health effects of indoor and outdoor chemical exposures on adult health and safety, including worker productivity and well-being.

Some of the signatories' research is used to develop vaccines and cures for cancer, improve the medical care of infants, children and adults, improve public and private building design, and plan responses to emergencies. The results are also used to demonstrate the benefits of proposed regulatory actions in accordance with statutory and regulatory requirements.[1]

Their research is routinely relied upon by international, federal, and state agencies—including EPA—when they set standards and establish rules and best practices for the protection of human health, safety, and the environment. As explained below, the proposed rule would—for no rational reason—prevent EPA from relying on much of the research that the signatories, their institutions, and other public health and environmental exposure researchers have conducted and continue to conduct. The rule will cripple EPA's ability to implement the aforementioned Statutes and will jeopardize the health and safety of infants, children, and adults in the United States and beyond.[2]

Without the ability to protect and respect patient/human subject privacy and confidentiality, signatories and other researchers would not be able to conduct the studies that are pivotal to their work and to EPA's ability to fulfill its statutory duty to protect public health. The proposed rule ignores a host of existing methods and best practices already established—and adhered to—by the research community to ensure the transparency, reproducibility, replicability, objectivity, and validity of studies, analyses, models, and reports.[3] The proposed rule thus does not serve its stated purpose to ensure that regulatory decisions are based on "valid" science.[4]

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[1] Signatories' research—which analyzes the human health and environmental impacts of the presence of chemicals in air, soil, drinking water, food, and consumer products—is relevant to EPA's required determinations under the Statutes that its regulations provide societal benefits by reducing harm to human health and the environment. Such research is also critically important to identifying the benefits of EPA regulations when the agency is required by the Statutes or Executive Order to conduct a formal cost-benefit analysis. *See* Exec. Order No. 13783, 82 Fed. Reg. 16,093, §1(e) (Mar. 31, 2017) ("It is also the policy of the United States that necessary and appropriate environmental regulations comply with the law, are of greater benefit than cost, when permissible, achieve environmental improvements for the American people, and are developed through transparent processes that employ the best available peer-reviewed science and economics.").

[2] David Cutler & Francesca Dominici, *A Breath of Bad Air: Cost of the Trump Environmental Agenda May Lead to 80 000 Extra Deaths per Decade*, JAMA NETWORK (June 12, 2018), https://jamanetwork.com/journals/jama/fullarticle/2684596 (copy attached for inclusion in the administrative record, Attachment 1).

[3] *See* Section IV, below, for a discussion of best practices. EPA already has detailed policy and procedural guidance for ensuring and maximizing the quality of information the agency disseminates. *See* EPA, *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by the Environmental Protection Agency* (Oct. 2002), https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf. Note further that the proposed rule incorrectly uses the terms "reproducibility" and "replicability" as though they are interchangeable. In fact, they have different meanings. Typically, in the scientific community, "*reproducibility* refers to the ability of a researcher to duplicate the results of a prior study using the same materials as were used by the original investigator." Steven N. Goodman, et al., *What does research reproducibility mean?*, 8 SCIENCE TRANSLATIONAL MEDICINE 341ps12 (2016). By contrast, "replicability" refers to the ability of a researcher to duplicate the results of a prior study following the same procedures but collecting new data. *Id*.

[4] *See* 83 Fed. Reg. 18,768, 18,773 (Apr. 30, 2018) (stated purpose "to ensure that the regulatory science underlying its actions is publicly available in a manner sufficient for independent validation"); *see also id.* at 18,770 ("It is the charge of regulators to ensure that key findings [of science that informs regulatory actions] are valid and credible.").

Signatories teach graduate and undergraduate students and doctors-in-training about best practices in the conduct of public health, medical, and scientific research. They publish their research results in the most reliable, highest-quality, peer-reviewed medical and scientific journals, including Lancet, Nature, Science, New England Journal of Medicine, Journal of the American Medical Association, Cell, and Environmental Health Perspectives. They conduct peer reviews of the work of other researchers. The approach advocated in the proposed rule is inconsistent with professional best practices in their respective disciplines for conducting, reviewing, and confirming the results/findings of studies, especially those based on confidential personal health data of study participants. As will be shown below, the proposed rule will wreak havoc on public health, medical, and scientific research and undermine the protection of public health and safety.

Accordingly, the signatories strenuously object to the proposed rule and urge EPA to withdraw it.

I. THE PROPOSED RULE WOULD PREVENT EPA FROM RELYING ON THE BEST AVAILABLE INFORMATION AND SCIENCE

In the proposed rule, EPA acknowledges that it must use the "best available science" in all of its regulatory actions.[5] The signatories agree that is the correct starting point for EPA. They disagree, however, with EPA's new position in this proposed rule that science is not the "best" unless the associated raw data are released to the public.[6] As an initial matter, releasing raw data will not improve the quality of the resulting report/study/analysis, and therefore will do nothing to render any individual study "better." EPA itself affirmed this point as recently as 2016.[7] Moreover, while it might be helpful in some situations to make raw data publicly available, it is neither practical nor desirable to impose this requirement as a one-size-fits-all approach.

Instead, there are a variety of other best practices that already exist to test and ensure the rigor, quality, and validity of research. These include the peer review process, which evaluates whether the work is based on the best available scientific understanding, and scientists' detailed description of their research methods, code and non-confidential data in their published articles. That detail allows other researchers not only to challenge the study results, but also to reproduce or validate them using the original data, and/or replicate them via other studies using different data sets. The scientific community considers results valid if they are or can be replicated by other researchers conducting studies using new data, but the same method.[8]

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[5] 83 Fed. Reg. at 18,769 (citing Exec. Order No. 13563, 76 Fed. Reg. 8,321 (Jan. 21, 2011)).

[6] *See* 83 Fed. Reg. at 18,772 (rule would require that "dose response data and models underlying pivotal regulatory science are publicly available in a manner sufficient for independent validation.").

[7] EPA, *Plan to Increase Access to Results of EPA-Funded Scientific Research*, at 4-5 (2016), https://www.epa.gov/sites/production/files/2016-12/documents/epascientificresearchtransperancyplan.pdf ("Whether research data are fully available to the public or available to researchers through other means does not affect the validity of the scientific conclusions from peer-reviewed research publications.").

[8] *See, e.g.*, Memorandum from Alison Cullen, Chair, SAB Work Group on EPA Planned Actions for SAB Consideration of the Underlying Science to Members of the Chartered SAB and SAB Liaisons, *Preparations for Chartered Science Advisory Board (SAB) Discussions of Proposed Rule: Strengthening Transparency in Regulatory*

Contrary to EPA's stated goal of improving the basis for its regulatory decisions, requiring the public availability of all raw data will instead undermine EPA's ability to make reasonable decisions. This requirement will effectively prohibit EPA from considering studies that by design are based on data that *cannot* be made publicly available due to laws and contracts designed to protect patient and human subject privacy and ensure willingness of people to participate in research by sharing their private information with researchers. The proposed rule precludes consideration of studies based on confidential data, even when those results have been confirmed by other studies.[9] Hence, the proposal would in many instances *prohibit* EPA from relying on the best available science relevant to many of the regulatory issues that the agency faces.

Moreover, this proposed requirement contravenes five decades of EPA practice. EPA has repeatedly affirmed that its mission requires it to rely on the best available scientific evidence, without ever asserting that it should exclude from consideration studies for which the underlying data were not publicly available. For example, in its 1997 strategic plan, EPA declared one of its seven overall purposes was to ensure that "efforts to reduce environmental risk are based on the best available scientific information."[10] In 2002, EPA issued Information Quality Guidelines in which it took the position that the standard set forth in the Safe Drinking Water Act — "the best available, peer-reviewed science"[11] — should apply to all of the agency's risk assessments.[12]

Science RIN (2080-AA14) 4 (May 12, 2018), https://perma.cc/MM3J-CHEA [hereinafter "SAB Memo"]; Bernard Goldstein, Op-Ed., *This is Why EPA's "Secret Science" Proposal Alarms Public Health Experts*, THE CONVERSATION (May 18, 2018), https://theconversation.com/why-the-epas-secret-science-proposal-alarms-public-health-experts-96000.

[9] One example is the Six Cities Study, Douglas W. Dockery, et al., *An Association between Air Pollution and Mortality in Six U.S. Cities*, 329 NEW ENGLAND J. MED. 1753 (1993), whose results were subsequently confirmed by independent reanalysis, Health Effects Institute, *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality* (2000), https://www.healtheffects.org/system/files/HEI-Reanalysis-2000.pdf. Indeed, both the Six Cities Study and the American Cancer Study of Particulate Air Pollution and Mortality have each been reproduced and replicated. The findings are consistent with the original studies. *See, e.g.*, Qian Di, Francesca Dominici, Joel D. Schwartz, et al., *Air Pollution and Mortality in the Medicare Population*, 376 NEW ENGLAND J. MED. 2513-2522 (2017) (copy attached for inclusion in the administrative record, Attachment 2).

[10] EPA, EPA/190-R-97-002, *EPA Strategic Plan*, at 16 (1997), https://nepis.epa.gov/Exe/ZyPDF.cgi?Dockey=40000 9JX.PDF. Earlier, in a March 1992 report titled *Safeguarding the Future: Credible Science, Credible Decisions*, an independent committee convened by EPA declared that "science is one of the soundest investments the nation can make for the future. Strong science provides the foundation for credible environmental decision making. With a better understanding of environmental risks to people and ecosystems, EPA can target the hazards that pose the greatest risks, anticipate environmental problems before they reach a critical level, and develop strategies that use the nation's, and the world's, environmental protection dollars wisely." EPA, *Safeguarding the Future: Credible Science, Credible Decisions*, at 15 (Mar. 1992), https://nepis.epa.gov/Exe/ZyPDF.cgi/30001ZWJ.PDF?Dockey=30001ZWJ.PDF.

[11] 42 U.S.C. § 300g-1(b)(3)(A)(i).

[12] EPA, *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*, at 21-23 (2005), https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf.

EPA's historic position is consistent with the Statutes. For example, one of EPA's core duties under the Clean Air Act is to set and periodically review the National Ambient Air Quality Standards ("NAAQS") for six common air pollutants. In carrying out this responsibility, Congress commanded EPA to use "the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects [of air pollution] on public health or welfare."[13] Similarly, the Safe Drinking Water Act commands EPA in general to use "the best available, peer-reviewed science" and when deciding whether to regulate a particular contaminant to consider the "best available public health information."[14] The Toxic Substances Control Act requires that regulation of chemical substances be "consistent with the best available science" and that EPA make decisions "based on the weight of the scientific evidence."[15] The water quality criteria that EPA develops under the Clean Water Act must "accurately reflect[] the latest scientific knowledge" on a variety of factors.[16]

Furthermore, because EPA is required under the Statutes to assess the public health benefits of its regulations, it must take into account all relevant science and cannot arbitrarily exclude certain studies demonstrating those benefits. Under the Clean Air Act, EPA must set the NAAQS at a level "requisite to protect the public health."[17] Under the Safe Drinking Water Act, EPA must determine whether a contaminant "may have an adverse effect on the health of persons" before deciding to regulate it.[18]

Many of the fundamental public health studies on which EPA has based key rules and standards under the Statutes are studies for which the raw data were not or could not have been released. Attachment 3 to this letter contains a partial list of studies that likely contain confidential data; these are all studies on which EPA has relied and cited as the basis for its actions under some of the Statutes. Until now, release of the underlying raw data was not an EPA criterion for determining the "best available" reports, studies, analyses, or models. Indeed, none of the Statutes invoked by EPA as support for the proposed rule limits EPA in this fashion; none of the Statutes requires EPA to make raw data publicly available.[19]

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[13] 42 U.S.C. § 7408(a)(2).

[14] 42 U.S.C. §§ 300g-1(b)(3)(A)(i), 300g-1(b)(1)(B)(ii)(II).

[15] 15 U.S.C. § 2625(h), (i).

[16] 33 U.S.C. § 1314(a)(1).

[17] 42 U.S.C. § 7409(b).

[18] 42 U.S.C. § 300g-1(b)(1)(A)(i).

[19] When litigants in the past argued that EPA could not rely on studies for which the raw data had not been publicly available, the D.C. Circuit soundly rejected their argument. As the court explained in one case:

> Claiming neither that they were unable to obtain the studies, nor that the studies were improperly published or peer reviewed, Petitioners instead urge us to impose a general requirement that EPA obtain and publicize the data underlying published studies on which the Agency relies. The Clean Air Act imposes no such obligation. . . . More generally, we agree with EPA that requiring agencies to obtain and publicize the data underlying all studies on which they rely "would be impractical and unnecessary."
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> […]

EPA's proposed new approach, which conflicts with the agency's obligations and curtails its authority, is irrational at best and detrimental to public health and safety at worst.

II. THE PROPOSED RULE WOULD EXCLUDE CRITICAL STUDIES FROM CONSIDERATION IN FUTURE EPA RULEMAKING

There are at least two categories of critically-important, health-based studies for which it will be impractical or illegal to make the underlying data publicly available. Within each category are studies that have already formed the basis for decades of EPA regulatory actions producing enormous public health and safety benefits. The proposal would require that EPA stop relying on these studies and prohibit automatic consideration of, or reliance on, others like them in the future for no other reason than that the raw data cannot be released to the public.[20] This result would be extremely harmful to human health, safety, and the environment.

A. THE PROPOSAL WOULD PREVENT EPA FROM RELYING ON STUDIES BASED ON CONFIDENTIAL HUMAN HEALTH DATA

For many studies, disclosure of the raw data would violate researchers' statutory or contractual duties to protect patient or human research participant confidentiality. Many types of crucial health impact studies cannot be conducted without human participants. For any research carried out by healthcare providers that involves the handling of individually identifiable health information, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA")

As EPA persuasively stated in denying Petitioners' original request for information:

> If EPA and other governmental agencies could not rely on published studies without conducting an independent analysis of the enormous volume of raw data underlying them, then much plainly relevant scientific information would become unavailable to EPA for use in setting standards to protect public health and the environment. . . . Such data are often the property of scientific investigators and are often not readily available because of ... proprietary interests ... or because of [confidentiality] arrangements [with study participants].

Am. Trucking Associations, Inc. v. E.P.A., 283 F.3d 355, 372 (D.C. Cir. 2002) (quoting Particulate Matter NAAQS, 62 Fed. Reg. 38,652, 38,689 (July 18, 1997)). The court reiterated this holding six years later in a challenge to the 2008 lead NAAQS. *Coal. of Battery Recyclers Ass'n v. E.P.A.*, 604 F.3d 613, 622 (D.C. Cir. 2010). In that case, the litigants had sought access to the raw data underlying Bruce P. Lanphear, et al., *Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis*, 113 ENVTL. HEALTH PERSP. 894 (2005).

[20] The proposal allows EPA to decide to consider such studies on a case-by-case basis. *See* 83 Fed. Reg. at 18,772. The factors EPA identifies for providing individual exemptions—that such disclosure cannot be done "in a fashion that is consistent with law, protects privacy, confidentiality, confidential business information, and is sensitive to national and homeland security"—merely reiterates the main reasons that data are not currently made publicly available. *Id.* at 18,773. If EPA always allows data to be withheld for those reasons, the rule is meaningless and has no effect. On the other hand, if EPA instead picks and chooses when to allow data to be withheld for those reasons, it will be doing so based on no meaningful standards. *Cf. Pearson v. Shalala*, 164 F.3d 650, 660 (D.C. Cir. 1999) ("It simply will not do for a government agency to declare—without explanation—that a proposed course of private action is not approved. To refuse to define the criteria it is applying is equivalent to simply saying no without explanation.").

Privacy Rule imposes strict confidentiality requirements.[21] Federally-funded research involving human subjects is governed by the Federal Policy for the Protection of Human Subjects, also known as the Common Rule.[22] The Common Rule requires that researchers obtain Institutional Review Board ("IRB") approval and informed consent of research subjects, during which process the researcher will typically need to make promises regarding confidentiality.[23] Most institutions have committed to comply with the Common Rule for all of their research,[24] even when it is not federally-funded.[25]

EPA's suggestion in the proposed rule that "simple data masking, coding, and de-identification," 83 Fed. Reg. at 18,771, will be able to overcome these confidentiality concerns is incorrect. As explained by the EPA's own Science Advisory Board ("SAB"), "[i]n some cases, the data cannot be released simply by redacting portions of it. For example, data may have been collected with an assurance to the participating individuals that their data would be kept confidential."[26] Researchers cannot violate those promises after the fact, particularly if they want to be able to continue to find participants for their studies. In addition, "[i]n the case of clinical trials, there are studies in which removal of all identifying data negates its scientific value."[27]

The understanding of what counts as identifying data is continually expanding: true de-identification of the data may not be possible for some studies, such as those in which the participants come from a small geographical area and/or a specific profession. One study found that the researchers could re-identify approximately one-quarter of the records in a subset of a

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[21] 45 C.F.R. Part 160 and Subparts A and E of Part 164.

[22] 45 C.F.R. 46 subpart A is the U.S. Department of Health and Human Services ("HHS") citation for the Common Rule. A total of 18 federal agencies have adopted it; each agency has its own separate entry in the Code of Federal Regulations. This federal rule governs ethical constraints that federally funded studies must follow, including academic research, responding to earlier concerns of ethical lapses in medical research. *See, e.g.*, Jerry Menikoff, *Could Tuskegee Happen Today?*, 1 ST. LOUIS U. J. HEALTH L. & POL'Y 311, 312-16 (2008) (describing the Congressional response to public outcry when the details of the Tuskegee experiment were brought to light). The thrust of the Common Rule is to address such matters of research ethics as informed consent, informational risk, and institutional oversight when research involves human subjects. *See* 82 Fed. Reg. 7,149-7,274.

[23] For example, under its "Basic elements of informed consent" provisions, the Common Rule provides that "in seeking informed consent the following information shall be provided to each subject: . . . A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained." 45 C.F.R. § 46.116(b)(5). The Common Rule also requires that the IRB ensure that the researchers make "adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data." 45 C.F.R. § 46.111(a)(7).

[24] *See Federalwide Assurance (FWA) for the Protection of Human Subjects*, HHS, https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/fwas/fwa-protection-of-human-subjecct/index.html (describing Common Rule policy for institutions performing government-funded human subject research) (last visited August 3, 2018).

[25] Harvard University, for example, has established policies for all university research that go beyond the requirements of the Common Rule. *Statement of Policies and Procedures Governing the Use of Human Subjects in Research at Harvard University*, HARVARD UNIVERSITY, https://provost.harvard.edu/use-human-subjects-research (last visited August 3, 2018).

[26] SAB Memo, *supra* note 8, at 4.

[27] Lynn R. Goldman & Ellen K. Silbergeld, *Assuring Access to Data for Chemical Evaluations*, 121 ENVTL. HEALTH PERSPECTIVES 149, 150 (2013).

HIPAA-compliant environmental health data set.[28] For some studies, it may not be possible to de-identify the data set while still protecting patient or research subject confidentiality.

The proposed rule would prohibit the continued and future use of these studies by EPA thereby obstructing EPA's statutory duty to consider the "best," "reasonably" available information in its decision-making processes. The resulting information vacuum would occur for no other reason than that the underlying human subject data is private and cannot be publicly disseminated.[29]

The proposed rule would also impede EPA's ability to address new and emerging public health risks in future rulemakings. For example, former Administrator Pruitt announced on May 22, 2018, that EPA will begin to develop maximum contaminant levels under the Safe Drinking Water Act for two fluorochemicals, perfluorooctanoic acid ("PFOA") and perfluorooctane sulfonate ("PFOS").[30] EPA also plans to designate PFOA and PFOS as hazardous chemicals, potentially under the Comprehensive Environmental Response, Compensation, and Liability Act.[31] If finalized, however, the proposed rule would prevent these EPA actions.[32]

When EPA issued health advisories for these two chemicals in 2016, the Health Effects Support Documents relied extensively on epidemiological studies generated by the C8 Health Project.[33] A key component of the evidence for the harmfulness of these chemicals consists of epidemiological studies based on data that are not publicly available. Researchers published more than three dozen papers based on these data, identifying probable links between PFOA

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[28] Latanya Sweeney, et al., *Re-identification Risks in HIPAA Safe Harbor Data: A Study of Data from One Environmental Health Study*, TECH. SCI., 2017082801 (Aug. 28, 2017), https://techscience.org/a/2017082801.

[29] Note that some of the Statutes require EPA to use the "best" available information and others have a lower standard. For example, the Toxic Substances Control Act compels EPA to take "reasonably" available information into account. 15 U.S.C. § 2625(k).

[30] Amena H. Saiyid, *Pruitt Plans to Declare Two Fluorochemicals Hazardous*, BLOOMBERG BNA (May 22, 2018), https://news.bloombergenvironment.com/environment-and-energy/pruitt-plans-to-declare-two-fluorochemicals-hazardous.

[31] Press Release, EPA, *Administrator Pruitt Kicks Off National Leadership Summit on PFAS* (May 22, 2018), https://www.epa.gov/newsreleases/administrator-pruitt-kicks-national-leadership-summit-pfas.

[32] Epidemiological studies, which were essential to discovering the immunotoxicity of perfluorinated alkylate substances, including PFOA and PFOS, were based on confidential human health data. *See* Philippe Grandjean, *Delayed discovery, dissemination, and decisions on intervention in environmental health: a case study on immunotoxicity of perfluorinated alkylate substances*, 17:62 ENVTL. HEALTH 1 (2018) (copy attached for inclusion in the administrative record, Attachment 4).

[33] EPA, EPA 822-R-16-003, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, at 3-1 to 3-60 (May 2016), https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final-plain.pdf; EPA, EPA 822-R-16-002, *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)*, at 3-1 to 3-49 (May 2016), https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf. The C8 Health Project was funded through the settlement agreement in a lawsuit brought over drinking water contaminated by PFOA from the DuPont Washington Works facility near Parkersburg, West Virginia. The study involved close to 70,000 participants, for each of whom "demographic data, medical diagnoses (both self-report and medical records review), clinical laboratory testing, and determination of serum concentrations of 10 perfluorocarbons (PFCs)" were collected. Stephanie J. Frisbee et al., *The C8 Health Project: Design, Methods, and Participants*, 117 ENVTL. HEALTH PERSP. 1873, 1876 (2009) ("To protect participant privacy, the presiding judge subsequently sealed the data set.").

(also known as C8) exposure and "diagnosed high cholesterol, ulcerative colitis, thyroid disease, testicular cancer, kidney cancer, and pregnancy-induced hypertension."[34]

This situation underlines the arbitrariness and irrationality of the proposed rule. On the one hand, EPA is proposing to take regulatory action to protect the American people from emerging health threats. On the other—through the proposed rule—it is simultaneously undermining its own ability to follow through on those proposals.

B. THE PROPOSAL WOULD PREVENT EPA FROM RELYING ON STUDIES CONDUCTED MANY YEARS AGO FOR WHICH DATA ARE NO LONGER AVAILABLE

Many key EPA regulatory decisions in effect today were based on studies conducted decades ago. Due to the passage of time, the raw data from these studies may no longer be available. Records may have been lost; researchers may have retired or passed away. Or, the data may have been stored in electronic media such as tapes that are no longer compatible with existing systems or otherwise difficult to access.[35] As noted by John Ioannidis, who is a strong advocate of data transparency,[36] "we should recognize that most of the raw data from past studies are not publicly available. . . . If the proposed rule is approved, science will be practically eliminated from all decision-making processes. Regulation would then depend uniquely on opinion and whim."[37]

C. STUDIES THAT EPA WILL BE PROHIBITED FROM CONSIDERING UNDER THE PROPOSAL HAVE SERVED AS THE BASIS FOR MULTIPLE RULEMAKINGS BY EPA AND OTHER AGENCIES

Studies that would be excluded from EPA consideration under the proposal form the basis for multiple regulatory actions that EPA and other agencies have taken over the course of many years. Consider, for example, early studies on the neurological effects of low-dose exposure to lead such as Herbert Needleman's 1979 paper finding a negative relationship between the level of lead in children's teeth and IQ scores.[38] EPA relied on this study in its 1986 Air Quality

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[34] *The Science Panel Website*, C8 SCIENCE PANEL, http://www.c8sciencepanel.org/index.html (last updated Jan. 4, 2017). Even the scientists selected to lead the research were provided with access only to de-identified data from the participants, except in the case of some participants who consented to provide additional data for follow-up studies.

[35] Goldman & Silbergeld, *supra* note 27, at 150.

[36] Ioannidis was one of the authors of Marcus R. Munafò et al., *A Manifesto for Reproducible Science*, 1 NATURE HUMAN BEHAVIOUR 1 (2017), DOI: 10.1038/s41562-016-0021, http://www.nature.com/articles/s41562-016-0021.pdf.

[37] John P.A. Ioannidis, *All Science Should Inform Policy and Regulation*, 15(5) PLOS MEDICINE 1, 1-2 (May 3, 2018), https://doi.org/10.1371/journal.pmed.1002576.

[38] Herbert L. Needleman, et al., *Deficits in Psychologic and Classroom Performance of Children with Elevated Dentine Lead Levels*, 300 NEW ENGLAND J. MEDICINE 689 (1979).

Criteria document for lead.[39] EPA's Lead and Copper Rule, which established the federal regulations for lead under the Safe Drinking Water Act, in turn relied on that Air Quality Criteria document to identify blood lead levels of concern.[40] EPA relied on both the 1986 Air Quality Criteria and on Needleman's research directly in establishing standards for lead-based paint hazards under the Toxic Substances Control Act.[41] Needleman's work, and subsequent studies building upon it, also supported EPA's decision to revise the NAAQS for lead in 2008.[42] The D.C. Circuit specifically ruled that the underlying data from one of the studies on which EPA relied in this rulemaking did not need to be publicly available for EPA to rely on the study.[43]

After 40 years, and with the principal investigator no longer alive, it is not clear that the raw data from the Needleman study is available. Even if the data were, they could not be made publicly available without invading the privacy of the study participants. Importantly, it would not be possible to conduct that same study at this time, because children no longer have blood or dental lead levels as high as they did in the 1970s as a result of EPA's implementation of the Statutes.

EPA's drinking water standard for arsenic under the Safe Drinking Water Act is similarly dependent on studies that the agency would now be compelled to ignore under the proposed rule. EPA established a drinking water standard of 10 ppb for arsenic in 2001.[44] The Food and Drug Administration ("FDA") then relied on EPA's determination.[45] In setting this standard, EPA relied on a National Research Council review of the scientific evidence, which "concluded that [certain epidemiological] studies from Taiwan provided the current best available data for the risk assessment of inorganic arsenic-induced cancer."[46] The Taiwanese papers looked at rates of skin cancer and blackfoot disease in villagers from southwestern Taiwan who were exposed to

[39] EPA, AIR QUALITY CRITERIA FOR LEAD, VOL. IV, 12-86 to 12-88, 12-95 (1986), https://nepis.epa.gov/Exe/ZyPDF.cgi/9101HLA1.PDF?Dockey=9101HLA1.PDF.

[40] Maximum Contaminant Level Goals and National Primary Drinking Water Regulations for Lead and Copper, 56 Fed. Reg. 26,460, 26,468–26,469 (June 7, 1991).

[41] Lead; Identification of Dangerous Levels of Lead, 63 Fed. Reg. 30,302, 30,316–30,317 (proposed June 3, 1998). The final rule was published at 66 Fed. Reg. 1,206 (Jan. 5, 2001).

[42] National Ambient Air Quality Standards for Lead, 73 Fed. Reg. 66,964 (Nov. 12, 2008).

[43] *Coal. of Battery Recyclers Ass'n v. E.P.A.*, 604 F.3d 613, 622-624 (D.C. Cir. 2010) (rejecting need to make raw data publicly available from Bruce P. Lanphear, et al., *Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis*, 113 ENVTL. HEALTH PERSPECTIVES 894 (2005)).

[44] National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring, 66 Fed. Reg. 6,976, 7,036 (Jan. 22, 2001).

[45] The FDA subsequently relied on EPA's drinking water standard, as well as the research underlying it, when it proposed an action level for arsenic for apple juice in 2013. *See* Draft Guidance for Industry on Arsenic in Apple Juice: Action Level; Supporting Document for Action Level for Arsenic in Apple Juice; A Quantitative Assessment of Inorganic Arsenic in Apple Juice; Availability, 78 Fed. Reg. 42,086 (July 15, 2013); *see also* Clark D. Carrington et al., FDA, *A Quantitative Assessment of Inorganic Arsenic in Apple Juice* (2013), https://www.fda.gov/downloads/Food/FoodScienceResearch/RiskSafetyAssessment/UCM360016.pdf.

[46] National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring, 65 Fed. Reg. 38,888, 38,902 (proposed June 22, 2000).

high levels of arsenic in their drinking water.[47] These studies were based on data from clinical examinations of the research subjects and therefore included confidential patient data that likely cannot be released to the public. In addition, given that the first data were collected more than 50 years ago, the studies are based on data that may no longer be available.

Even though the proposed rule "is intended to apply prospectively," it will also have a retroactive impact. Some of the Statutes require EPA to periodically review its prior regulatory decisions. For example, EPA must reconsider the lead NAAQS every five years.[48] EPA is also in the process of reconsidering the Lead and Copper Rule under the Safe Drinking Water Act.[49] The proposed rule would prohibit EPA from continuing to rely on Needleman's critically-important study in future reconsiderations of the lead NAAQS and revisions to the Lead and Copper Rule.

Other future rulemakings would also be undermined by the proposed rule. In 2011, EPA decided to regulate perchlorate as a contaminant under the Safe Drinking Water Act.[50] "Perchlorate is commonly used as an oxidizer in rocket propellants, munitions, fireworks, airbag initiators for vehicles, matches, and signal flares" and is also present in some fertilizers.[51] It is known to disrupt thyroid function by competitively inhibiting the uptake of iodide by the thyroid, and EPA in 2011 concluded "that there is a substantial likelihood that perchlorate will occur in public water systems with a frequency and at levels of public health concern."[52] Late in 2017, EPA issued a draft report identifying potential approaches to deriving a maximum contaminant level goal for perchlorate.[53] To develop these approaches, EPA focused on five epidemiological studies.[54] All five studies relied on confidential patient data. In addition, all five studies were

[47] The original papers were W.P. Tseng et al., *Prevalence of Skin Cancer in an Endemic Area of Chronic Arsenicism in Taiwan*, 40 J. NAT'L CANCER INST. 453 (1968) and Wen-Ping Tseng, *Effects and Dose Response Relationships of Skin Cancer and Blackfoot Disease with Arsenic*, 19 ENVTL. HEALTH PERSP. 109 (1978). Subsequent articles discussed longer-term health effects among the study cohort.

[48] 42 U.S.C. § 7409(d)(1).

[49] *See Lead and Copper Rule Long-Term Revisions*, EPA, https://perma.cc/U5GV-B93M.

[50] Drinking Water: Regulatory Determination on Perchlorate, 76 Fed. Reg. 7,762 (Feb. 11, 2011).

[51] *Perchlorate in Drinking Water*, EPA, https://www.epa.gov/dwstandardsregulations/perchlorate-drinking-water (last visited August 3, 2018).

[52] 76 Fed. Reg. at 7,763.

[53] EPA, *Draft Report: Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water* (2017), https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0438-0019.

[54] *Id.* at 6-1 to 6-19 (citing Tim I. M. Korevaar et al., *Association of Maternal Thyroid Function during Early Pregnancy with Offspring IQ and Brain Morphology in Childhood: A Population-based Prospective Cohort Study*, 4 THE LANCET DIABETES & ENDOCRINOLOGY 35 (2016); Martijn J. J. Finken et al. *Maternal Hypothyroxinemia in Early Pregnancy Predicts Reduced Performance in Reaction Time Tests in 5- to 6-Year-Old Offspring*, 98 J. CLINICAL ENDOCRINOLOGY & METABOLISM 1417 (2013); F. Vermiglio et al., *Attention Deficit and Hyperactivity Disorders in the Offspring of Mothers Exposed to Mild-Moderate Iodine Deficiency: A Possible Novel Iodine Deficiency Disorder in Developed Countries*, 89 J. CLINICAL ENDOCRINOLOGY & METABOLISM 6054 (2004); Victor J. Pop et al., *Maternal Hypothyroxinemia during Early Pregnancy and Subsequent Child Development: A 3-year Follow-up Study*, 59 CLINICAL ENDOCRINOLOGY 282 (2003); Victor J. Pop et al., *Low Maternal Free Thyroxine Concentrations during Early Pregnancy Are Associated with Impaired Psychomotor Development in Infancy*, 50 CLINICAL ENDOCRINOLOGY 149 (1999)).

carried out in Europe, where scientists may be subject to different data confidentiality requirements than in the United States. As a result, the proposed rule risks undermining the scientific basis for this EPA action as well.

Many other EPA rulemakings and decisions have relied on studies that cannot be replicated and whose data likely could not be made publicly available. For example:

- **PCBs**: EPA's regulations establishing water quality standards for polychlorinated biphenyls ("PCBs") under the Clean Water Act were based in part on long-term epidemiological studies of cancer rates in workers exposed to PCBs.[55]

- **Radionuclides**: EPA's Safe Drinking Water Act regulation for radionuclides relied on epidemiological studies of survivors from the Hiroshima and Nagasaki atomic bomb attacks.[56]

- **Particulate matter**: EPA's 1997, 2006, and 2012 NAAQS for fine particulate matter all relied on studies using confidential data, such as the Six Cities Study.[57]

- **Methylmercury**: EPA's reference dose for methylmercury in fish that will be consumed by humans relied on data from human exposures in the Faroe Islands.[58]

Precluding reliance on these and other studies for the sole reason that the underlying raw data has not been or cannot be released to the public is arbitrary, capricious, contrary to professional best practices, and antithetical to protection of public health and safety as required by the Statutes. The proposed rule will prevent EPA from relying on the "best available science."

III. "TRANSPARENCY" IN SCIENCE DOES NOT REQUIRE RELEASE OF PRIVATE INFORMATION; IT REQUIRES A CLEAR STATEMENT AND DETAILED DESCRIPTION OF THE METHODOLOGY USED BY THE RESEARCHER

Transparency is valuable and important. As used in the draft rule, however, transparency is a guise for excluding large bodies of valid—and best available—science. The concept of

[55] Thomas Sinks et al., *Mortality among Workers Exposed to Polychlorinated Biphenyls*, 136 AM. J. EPIDEMIOLOGY 389 (1992); Pier Alberto Bertazzi et al., *Cancer Mortality of Capacitor Manufacturing Workers*, 11 AM. J. INDUS. MED. 165 (1987).

[56] *See* Environmental Data and Governance Initiative ("EDGI"), *Public Protections Under Threat at the EPA: Examining Safeguards and Programs That Would Have Been Blocked by H.R. 1430* 9-10 (2017), https://perma.cc/3NUU-MDHM.

[57] Douglas W. Dockery, et al., *An Association between Air Pollution and Mortality in Six U.S. Cities*, 329 NEW ENGLAND J. MED. 1753 (1993).

[58] P. Grandjean, et al., *Cognitive Deficit in 7-Year-Old Children with Prenatal Exposure to Methylmercury*, 19(6) NEUROTOXICOL TERATOL 417 (1997).

transparency promoted by the draft rule is harmful to good decision-making, to implementation of the Statutes, and, most of all, to protection of public health and safety.

In the professional scientific and medical research community, "transparency" means clear and detailed disclosure of all methods, data, assumptions, and uncertainties. Studies are considered "transparent" when the study design and methodology are clear enough to allow other scientists to challenge assumptions, test hypotheses, and either reproduce or replicate the study to determine whether the results obtained are consistent with the original study. Having the raw data associated with the original study is not usually necessary to validate a study.[59]

Transparency does *not* mean violating the confidentiality of study participants or making all raw data publicly available. The proposed rule does not comport with the fundamental approach to conducting scientific and medical research that is the standard practice for experienced, advanced scholars and researchers.

Nor is it necessary to reproduce[60] a study to validate it. The proposal provides that "[i]nformation is considered 'publicly available in a manner sufficient for independent validation' when it includes the information necessary for the public to understand, assess, and *replicate* [sic] findings."[61] Neither reproducing nor replicating studies is always possible. Indeed in some circumstances it would be inhumane, immoral, or physically impossible to do so. Some studies involve natural disasters, other one-time events, or exposures and conditions that no longer exist and cannot be reproduced or replicated. Those studies are valid but would be excluded by the proposed rule. Examples include:

- Studies of Hiroshima and Nagasaki survivors that underlie Safe Drinking Water Act radionuclides regulation;

- Studies of the effects of lead from 1970s, when blood lead levels were higher than they are now;

- Studies of worker exposure to polychlorinated biphenyls before PCBs were banned; these studies formed the basis of water quality standards for PCBs under the Clean Water Act;

- Long-term cohort studies of benzene exposure in workers which formed the basis of EPA's 2007 Clean Air Act regulation for emissions of hazardous air pollutants from mobile sources; and

[59] *See supra* notes 3, 7, 8. In the rare instance when the raw data is needed to validate a study, EPA already has the ability to request it. This should be the exception, not the default as it has become in the proposed rule. If, ultimately, EPA is unable to obtain the raw data to verify the study results, it is within the agency's discretion to categorize such data as "qualitative," and taking into consideration inherent uncertainties, weigh the study relative to other evidence. *See* EPA, *Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessments* 9 (Aug. 28, 2012), https://www.epa.gov/sites/production/files/2015-07/documents/lit-studies.pdf.

[60] In the proposed rule, EPA incorrectly uses the term "replicate." *See* note 3, above.

[61] 83 Fed. Reg. at 18,773–18,774.

- Studies based on the massive oil leak at Deepwater Horizon.

IV. THE PROPOSED RULE IGNORES MECHANISMS THAT ALREADY EXIST TO DEAL WITH CONCERNS ABOUT ACCESS TO RAW DATA

The proposed rule fails to acknowledge numerous federal laws, regulations, and guidance that regulate the quality of and access to raw data. These include: the Information Quality Act, Office of Management and Budget ("OMB") Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards ("OMB Uniform Guidance"),[62] and EPA's own Information Quality Guidelines. These already address the data access concerns that EPA raises in the proposed rule. Moreover, the proposed rule is inconsistent with some aspects of these other requirements. For example, OMB Uniform Guidance exempts from its definition of "research data" subject to disclosure any "medical information and similar information the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, such as information that could be used to identify a particular person in a research study."[63] In contrast, the proposed rule would generally prohibit EPA from relying on studies based on data not disclosed to the public, even when disclosure would be a clearly unwarranted invasion of personal privacy. Any decision to consider the study while allowing the data to remain confidential is left to the whim of the EPA Administrator. This standardless, case-by-case approach is inconsistent with OMB's uniform privacy protections.

In the proposed rule, EPA ignores a variety of commonly-used mechanisms for assessing and ensuring the validity of studies without requiring public disclosure of the raw data. These mechanisms include peer reviews, pre-registration of study methodology, corroboration of results by subsequent studies, and in some instances special agreements that enable an independent third party, such as the Health Effects Institute ("HEI"), to re-analyze the raw data. As explained by the Science Advisory Board, the HEI's reanalysis of the Six Cities Study, through "an unusually rigorous form of peer review and independent reanalysis, coupled with many follow-up studies, has accomplished a measure of confidence in findings without public access to data and analytic methods."[64]

For these reasons, the public health, medical, and scientific research community does not regard the public disclosure of all raw data as necessary. For example, the Committee on Publication Ethics ("COPE"), which has over 12,100 member journals and editors covering all areas of scholarly inquiry, has established 10 core practices. COPE's core practice #5 on data and reproducibility provides that "[j]ournals should include policies on data availability and encourage the use of reporting guidelines and registration of clinical trials and other study

[62] *See* OMB, *Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards*, 78 Fed. Reg. 78,590, at 78,631, 2 C.F.R. § 200.315(e)(3) (Dec. 26, 2013) (guidance incorporated from OMB, *OMB Circular A–110, Uniform Administrative Requirements for Grants and Agreements With Institutions of Higher Education, Hospitals, and Other Non-Profit Organizations* § 36(d) (as amended Sept. 30,1999)) [hereinafter "OMB, *Uniform Guidance*"].

[63] OMB, *Uniform Guidance*, 2 C.F.R. § 200.315(e)(3)(ii).

[64] SAB Memo, *supra* note 8, at 4.

designs according to standard practice in their discipline."[65] The simplicity and generality of this core practice statement signals that the question of standards for data transparency, data access, data sharing, data peer review, and replication and reproducibility practices are far from settled. There is no one-size-fits-all approach to the critical questions of data transparency, data sharing, and reproducibility.

The proposed rule was announced by EPA without any meaningful consultation with the broad research community despite the fact that it addresses a complex and contentious issue that is not yet ripe for regulatory action. There are ample and adequate safeguards in place at the leading journals to ensure "transparency" – the ability of other researchers to question, challenge, and validate the results of published studies. This would include the journals' policies on treatment of data from research published years and even decades ago. It is contrary to good scientific study and practice and the advancement of knowledge for EPA to arrogate to itself the determination of what constitutes useable research and data, and to grant sweeping discretion to the Administrator—who may not even be a scientist—to make those determinations.

In a rare joint statement, the editors of the journals *Science*, *Nature*, *PLOS One*, *Proceedings of the National Academy of Sciences*, and *Cell* explained:

> It does not strengthen policies based on scientific evidence to limit the scientific evidence that can inform them; rather, it is paramount that the full suite of relevant science vetted through peer review, which includes ever more rigorous features, inform the landscape of decision making. Excluding relevant studies simply because they do not meet rigid transparency standards will adversely affect decision-making processes.[66]

As has long been recognized by the professional public health, medical, and scientific research community—and by EPA itself until now[67] —whether or not the raw data underlying a study is released does not determine the quality of the study. Rather, it is the scientific method that is determinative. The proposed rule fails to take into account the fact that studies are reliable and constitute the best available science when they comply with professionally-established best practices for describing the methodology, sampling size, sampling procedure and assumptions utilized and the results are consistent with those of other studies.

[65] *Core Practices*, COPE, https://publicationethics.org/core-practices (last visited August 3, 2018) (copy attached for inclusion in the administrative record, Attachment 5).

[66] Jeremy Berg et al., *Joint Statement on EPA Proposed Rule and Public Availability of Data*, SCIENCE (Apr. 30, 2018), http://science.sciencemag.org/content/early/2018/04/30/science.aau0116 (copy attached for inclusion in the administrative record, Attachment 6).

[67] *See supra* note 7.

V. THE PROPOSAL WOULD IMPOSE AN IMMENSE AND UNNECESSARY COST AND PAPERWORK BURDEN ON EPA, OTHER FEDERAL AGENCIES, AND THE RESEARCH COMMUNITY

EPA has not established a legitimate need for the proposed rule. EPA has made thousands of regulatory decisions over the last 50 years. The Congressional Budget Office estimates that EPA "relies on about 50,000 scientific studies annually to perform its mission."[68] The proposed rule fails to identify a single regulatory action based on faulty science.[69] The rule is not needed or warranted. It will do far more harm than good.

Although OMB did not have a meaningful opportunity to review the proposed rule before former Administrator Pruitt signed and released it (OMB had a mere five days) and presumably did not intend to allow EPA's new definitions to modify OMB's Uniform Guidance, one might argue that that is an effect of the proposed rule. If so, its radical and erroneous "transparency" requirements would extend to all federal agencies, wreaking chaos.

The CBO estimates that it will cost between $10,000 and $30,000 per study to make the raw data available.[70] If EPA continues to rely on roughly the same number of studies, it could cost hundreds of millions of dollars a year to implement the proposal. Imposing these costs on all federal agencies would be a staggering burden. Given the cost and the impracticality of releasing all raw data to the public, EPA will have effectively but wrongly undermined public health and safety.[71]

Even if EPA or the researchers do spend this money and considerable time to de-identify data to comply with the proposed rule, that effort will not necessarily protect patient or research subject confidentiality. As mentioned above, it is frequently possible to re-identify individuals from supposedly de-identified datasets. For example, one study found that the researchers could re-

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[68] Congressional Budget Office ("CBO"), *Cost Estimate: H.R. 1030, Secret Science Reform Act of 2015* 2 (Mar. 11, 2015), https://www.cbo.gov/sites/default/files/114th-congress-2015-2016/costestimate/hr1030.pdf.

[69] Importantly, this proposed rule shifts the presumption of validity away from non-biased, peer-reviewed studies conducted by professional and academic researchers to non-peer reviewed studies conducted by the interested, regulated enterprises. In fact, if there is a problem anywhere in the science on which EPA relies, it is in the industry studies submitted for licensing and permitting—yet these actions are excluded from the coverage of the rule by the definition of "regulatory decisions." *See* Thomas O. McGarity, *Beyond Buckman: Wrongful Manipulation of the Regulatory Process in the Law of Torts*, 41 WASHBURN L.J. 549, 559-63 (2002) (detailing incidents in which data required to be submitted by manufacturers or their contractors under the Federal Fungicide, Insecticide, and Rodenticide Act ("FIFRA") and the Food, Drug, and Cosmetic Act ("FDCA") were either withheld or were misleading or fraudulent); *cf.* SHELDON KRIMSKY, SCIENCE IN THE PRIVATE INTEREST: HAS THE LURE OF PROFITS CORRUPTED THE VIRTURE OF BIOMEDICAL RESEARCH? (2003) (discussing this problem throughout the book and providing considerable support).

[70] CBO, *supra* note 68, at 2.

[71] In the proposal, EPA cites a paper prepared by Randall Lutter and David Zorn for the Mercatus Center, which arrives at a lower cost estimate than the CBO, to support its conclusion that "the benefits of this proposed rule justify the costs." 83 Fed. Reg. at 18,772 & n.24. EPA cannot abdicate its responsibility to conduct its own analysis of the costs and benefits of this regulation by relying on this paper.

identify approximately one-quarter of the records in a subset of a HIPAA-compliant environmental health dataset.[72]

Relatedly, for some studies (e.g. prospective cohort studies that include extensive personal data; environmental health effects studies), it is impossible to de-identify the data without negating its scientific value. To protect against re-identification, it would be necessary to remove so much demographic information from the dataset that other scientists would not be able to perform meaningful re-analyses of the data.

VI. THE PROPOSED RULE WOULD CREATE CONFUSION AND CHAOS DETRIMENTAL TO THE PROTECTION OF PUBLIC HEALTH

The proposal, as drafted, contains significant ambiguities. As a result, it is entirely unclear what the effect of the proposed rule will be on studies that have already formed the basis of existing rules but as to which the underlying raw data has not been and cannot be made available for various reasons. These studies are considered by professionals to be the "best" available science.

The following crucial questions are not addressed by the proposed rule:

1. Will EPA continue to rely on those studies or will they now arbitrarily be excluded from consideration?

2. Will EPA implement the new rule by ensuring that raw data are made available (very costly) or simply by ignoring existing, valid studies as to which the data cannot be made available or would be extremely expensive to de-identify?

3. How will EPA implement its exemption authority? What are the governing standards for when the Administrator will exercise this authority?

4. Will the proposed rule apply to old studies or only new ones and to past regulatory decisions or only new ones? The latter point is especially a concern under statutes that require EPA to revise standards periodically. Will previously-established standards be abandoned because the data from the studies underlying those decisions (in many cases decades old) is no longer available?

5. How will the proposal affect the actions of other agencies that rely on EPA's findings or decisions or that provide information to EPA? For example, what will the effect be on Agency for Toxic Substances and Disease Registry ("ATSDR") analyses that EPA is required to consider pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act?

6. How will EPA's re-interpretation of OMB's Uniform Guidance and other rules that apply uniformly to the entire federal government be administered? For example, how will the Food and Drug Administration's review of applications for new drugs be affected?

[72] Sweeney, et al., *supra* note 28.

In addition, EPA has not included any analysis of the impact of the proposed rule on its existing or future regulations.

Many of the signatories conduct studies, reports, analyses, and models that are used to support the work of numerous state and federal agencies. The proposed rule will interfere with the ability of these agencies to work together as required by some statutes to develop joint approaches to protection of public health and safety due to the restrictions in the proposed rule. Specifically, the rule will impede EPA's ability to work effectively with the Food and Drug Administration, ATSDR, the Department of Agriculture, and other agencies whose mission is to protect public health.

VII. THE PROPOSED NEW APPROACH TO DOSE-RESPONSE MODELING IS ANTITHETICAL TO PROPER SCIENTIFIC METHODOLOGY AND CONTRAVENES THE ADVICE OF EXPERTS IN THE FIELD, INCLUDING THE NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE

EPA proposes to use "default assumptions, including assumptions of a linear, no-threshold dose response, on a case-by-case basis....When available, EPA shall give explicit consideration to high quality studies that explore: a broad class of parametric dose-response models; a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the dose or exposure range; and models that investigate factors that might account for spatial heterogeneity."[73] This proposed new approach allows for assuming a safe threshold below which humans can be exposed to chemicals in circumstances where data may be sparse. This approach runs counter to EPA's own historic practice and to the best practice employed by the scientific community when conducting risk assessments. Specifically, the National Research Council has recommended that linear and conceptual models be used "unless data is sufficient to reject low-dose linearity."[74] The scientific research and risk assessment community have also reached a consensus that cancer and non-cancer risk assessment should be unified so that all compounds, not just carcinogens, should be subjected to benchmark dose modeling.[75] This means that researchers should not assume a safe threshold of exposure even for non-carcinogens such as lead and mercury.[76]

[73] 83 Fed. Reg. at 18,774.

[74] This has also been the position of the federal government since 1983. Eileen Abt, et al. *Science and Decisions: Advancing Risk Assessment*, 30 RISK ANALYSIS 1028 (2010); Committee on the Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences and National Research Center, *Risk Assessment in the Federal Government: Managing the Process* (1983), http://www.nap.edu/catalog/366/risk-assessment-in-the-federal-government-managing-the-process.

[75] EPA, Risk Assessment Forum, *Benchmark Dose Technical Guidance* (June 2012), https://www.epa.gov/sites/production/files/2015-01/documents/benchmark_dose_guidance.pdf; Eileen Abt, et al. *Science and Decisions: Advancing Risk Assessment*, 30 RISK ANALYSIS 1028 (2010).

[76] EPA, *supra* note 75; Eileen Abt, et al., *supra* note 75.

The approach EPA proposes also conflicts with the advice of EPA's own Science Advisory Board as well as the advice of the National Academies of Sciences, Engineering, and Medicine.[77] And, EPA's proposed new approach directly conflicts with the statutory mandates that it must protect develop rules that protect human health "with an adequate margin of safety."[78]

EPA's assertion in the proposed rule that there is "growing empirical evidence of non-linearity in the concentration-response function for specific pollutants and health effects" is dangerous and unsupported by scientific evidence.[79] In recent years, several toxicants such as lead and particulate matter air pollution have been shown to have either superlinear responses at low dose or no threshold.[80] The consensus of the academic scientific community has been for over a decade that threshold effects should not be presumed in the absence of robust concentration-response data.[81] Accordingly, this comment letter endorses and incorporates by reference the comments on this point that have been submitted by: The National Academies of Sciences, Engineering, and Medicine dated July 16, 2018, and the Center for Science in the Public Interest dated July 17, 2018.

VIII. THE RULE SHOULD BE WITHDRAWN

The proposed rule will undermine EPA's ability to fulfill its mission to protect human health, safety, and the environment by using the best available information and science. First, the proposed rule would exclude from EPA's consideration any reports, studies, analyses, and models that rely on confidential, inaccessible, or unavailable data but that historically have been considered the best available science and therefore used to support regulations and standards designed to protect public health and safety. Second, in so doing, the rule also eliminates EPA's access to fundamental information necessary for identifying and calculating the "health benefits" of rules and standards needed to protect public health. Finally, it threatens to impose significant costs on both the federal government and independent scientists. Worst of all, the proposed rule creates these multiple problems without providing any significant countervailing benefits.

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[77] EPA, *supra* note 75; Eileen Abt, et al., *supra* note 75.

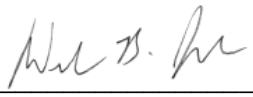
[78] For example, the Clean Air Act, 42 U.S.C. § 7409(b)(1) (setting NAAQS); the Safe Drinking Water Act, 42 U.S.C. § 300g-1(b)(4)(A) (setting Maximum Contaminant Level Goals ("MCLG's")).

[79] 83 Fed. Reg. at 18,770.

[80] Bruce P. Lanphear, et al., *Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis*, 113 ENVTL. HEALTH PERSP. 894 (July 2005), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1257652/; Joel Schwartz, *Assessing Confounding, Effect Modification, and Thresholds in the Association between Ambient Particles and Daily Deaths*, 108 ENVTL. HEALTH PERSP. 563 (June 2000), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1638159/pdf/envhper00307-0129.pdf; Qian Di, et al., *Association of Short-term Exposure to Air Pollution With Mortality in Older Adults*, JAMA NETWORK (Dec. 26, 2017), https://jamanetwork.com/journals/jama/fullarticle/2667069.

[81] Eileen Abt, et al., *supra* note 75.

For these and all of the reasons explicated above, the proposed rule should be withdrawn.

By: 

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The JAMA Forum

A Breath of Bad Air: Cost of the Trump Environmental Agenda May Lead to 80 000 Extra Deaths per Decade

David Cutler, PhD; Francesca Dominici, PhD

President Donald Trump and Environmental Protection Agency (EPA) Administrator Scott Pruitt have pledged to reexamine landmark environmental policies and to repeal regulations. In their view, excessive regulations are harming US industry, and thus reducing regulation will be good for business. As Donald Trump has said, seemingly without irony, "We are going to get rid of the regulations that are just destroying us. You can't breathe—you cannot breathe."

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As has become apparent, however, it is the changes Trump is proposing that are likely to make breathing more difficult. A central feature of his agenda is environmental damage: making the air dirtier and exposing people to more toxic chemicals. The beneficiaries, in contrast, will be a relatively few well-connected companies.

The Trump Agenda

In pursuit of its wide-ranging environmental agenda, the administration has already reversed or proposed to reverse more than 60 environmental rules. The full extent of the effects on health has not been tabulated and is hard to quantify, but guesses can be made for some of the larger ones (see the Table).

The largest health consequences are likely to come through changes in air quality. The Trump administration has announced its intention to repeal the Clean Power Plan rule, President Barack Obama's signature policy on climate change. The rule provides for the EPA to assign each state a goal for limiting emissions from existing power plants and gives the states latitude in meeting those goals, such as switching from coal to natural gas or building new wind or solar farms. Based on the regulatory impact analysis done by the EPA when the rule was implemented (as well as other analyses), repealing the rule would lead to an estimated 36 000 deaths each decade and nearly 630 000 cases of respiratory infection in children alone.

The administration is also targeting the control of air pollution from motor vehicles, indicating a desire to weaken greenhouse gas and fuel economy targets for automobiles. Nothing formal has been proposed, but Trump has spoken about rolling back new rules put in place by the Obama administration. Based on the regulatory impact analysis performed when those rules were proposed, it was estimated that they would lead to a reduction of 5500 deaths and 140 000 cases of respiratory ailments in children over a decade—benefits that would be lost if the rules are rolled back. Repealing these rules will also have negative effects on certain types of jobs, the environment (global warming pollution), and consumer savings. The administration is also planning to repeal the emission requirements for glider vehicles—rebuilt trucks that do not meet current environmental standards—a loophole that could lead to as many as 41 000 premature deaths per decade and 900 000 cases of respiratory tract symptoms.

Other elements of the administration's environmental agenda will also affect health, though it is hard to know by how much. Withdrawing from the Paris agreement on global warming, imposing tariffs on solar panels, and rolling back the "once in, always in" rule for industrial plants will all lead to increases in fine particulate matter and additional exposure to pollutants such as sulfur dioxide, nitrogen oxides, mercury, and others that adversely affect respiratory and cardiovascular health.

Water quality is also being targeted. The Trump EPA has proposed to rescind the Waters of the United States rule published in 2015, which brought more US streams and wetlands areas under the Clean Water Act. Rivers and streams are sources of drinking water for more than 130 million people and if polluted, might pose major health risks. The rule itself does not mandate any specific changes in water cleanliness, so we do not estimate a specific health consequence of repealing this rule.

Finally, the administration is proposing to withdraw or not implement regulatory actions affecting particular chemicals shown to be harmful to health, including lead, agricultural pesticides, and coal ash waste. Exposure to these hazardous substances will affect fewer people than the number of individuals affected by air pollution, but each will affect a concentrated number. As Christine Todd Whitman, head of the EPA under President George W. Bush, said: "You stop enforcing those regulations and [deaths] will go way up."

Overall, an extremely conservative estimate is that the Trump environmental agenda is likely to cost the lives of over 80 000 US residents per decade and lead to respiratory problems for many more than 1 million people. This sobering statistic captures only a small fraction of the cumulative public health damages associated with the full range of rollbacks and systemic actions proposed by the Trump administration.

An Attack on Science

One might imagine that the science that supported enactment of these rules would make repealing them difficult. But that is not the case. Even as it is targeting environmental rules, the Trump administration is taking aim at the use of science that supports public policy.

Scott Pruitt recently signed a controversial rule stipulating that policy can be based only on research for which the underlying data have been made accessible to the general public. The idea is to

Proposed Changes in Environmental Protections and Possible Effects

Area	Actions	Projected Effects
Air Quality	Repeal of Clean Power Plan	• Increases exposure to small atmospheric particulate matter • An estimated 36 000 deaths over a decade • An estimated 630 000 cases of respiratory ailments in children over a decade
	Rollback of CAFE[a] standards for automobiles	• Increases exposure to small atmospheric particulate matter and ozone • An estimated 5500 deaths over a decade • An estimated 140 000 cases of respiratory ailments in children over a decade
	Repeal of emission requirements for glider vehicles	• Allows noncompliant diesel trucks on the roads • An estimated 41 000 premature deaths over a decade • An estimated 900 000 cases of respiratory ailments over a decade
	Loosening of other air pollution rules (eg, power plants, solar power tariffs)	• Potential for industrial plants to increase emissions by 4 times • Endangering those living near power plants (areas of high poverty)
Water Quality	Repeal of Waters of the United States rule	• Exposes water sources for approximately 117 million US residents • At least 1 million people in each of 21 different states depend on small streams for their drinking water
Chemicals	Scale back of lead-risk reduction program	• Leaves an estimated 4 million households with children at risk of exposure to high levels of lead • Approximately 500 000 children currently have elevated blood lead levels
	Delay or reduction of chemical bans	• Exposes toddlers and older children to 11 to 15 times the recommended levels of chlorpyrifos (because of denial of ban on use in agriculture) • Exposes public to 3 carcinogens (methylene chloride, trichloroethylene, and N-Methylpyrrolidone) used in furniture stripping, grease removal, and dry cleaning (action delayed)
	Weakening of rules on coal ash waste	• More than 100 million tons of coal ash are produced annually, resulting in more than 100 documented cases of coal ash poison contamination in the drinking water, wetlands, creeks, and rivers between 1948 and 2008

[a] There is substantial uncertainty with respect to the extent of the rollback of the Corporate Average Fuel Economy (CAFE) rules. Projected health effects are calculated based on the assumption of full achievement of CAFE standards vs rollback of those standards.

remove most observational studies of health effects of air pollution exposure from being considered in regulatory settings, unless the individual health records are made publicly available. This is a nearly impossible task because the health data are collected under the agreement to maintain patient confidentiality. With no evidence of harms (because of constraints on presenting the available evidence), regulations cannot be sustained. On April 23, 985 scientists sent him a letter urging him to abandon the proposal.

Fortunately for those interested in public health, the regulatory process will take many years. Whoever is sworn in as President in January 2021 will have a large effect on whether the Trump administration's full environmental agenda goes into effect.

Implications for Physicians and Policy

For physicians, the manifestation of these changes is likely to be an increase in disease and number of deaths. Respiratory and cardiovascular problems are most likely, but a wide variety of conditions are likely to be seen. Poor, black, or elderly populations are likely to be affected the most. People working with chemicals in industrial settings will also be affected, as will people who live in areas with high concentrations of power plants such as the Ohio River Valley from Indiana to Pennsylvania, and in the southeast from Alabama and Georgia to Maryland.

One could debate the merits of these tradeoffs if there were a large number of people who would benefit economically from these changes. In practice, however, any economic benefits are not likely to accrue to those most in need. Employment is down in many fossil fuel industries because technology has made workers less necessary for production, not because of environmental regulations. And even if a large number of coal jobs were restored, it would come at the expense of employment in new industries such as wind and solar, which are already being hurt by the Trump administration policies. Not having to comply with environmental rules will increase corporate profits, but not worker bank accounts.

Overall, the ultimate effects of the Trump administration's policies seem clear, even through the haze they will create. ■

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Air Pollution and Mortality in the Medicare Population

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ABSTRACT

BACKGROUND

Studies have shown that long-term exposure to air pollution increases mortality. However, evidence is limited for air-pollution levels below the most recent National Ambient Air Quality Standards. Previous studies involved predominantly urban populations and did not have the statistical power to estimate the health effects in underrepresented groups.

METHODS

We constructed an open cohort of all Medicare beneficiaries (60,925,443 persons) in the continental United States from the years 2000 through 2012, with 460,310,521 person-years of follow-up. Annual averages of fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [$PM_{2.5}$]) and ozone were estimated according to the ZIP Code of residence for each enrollee with the use of previously validated prediction models. We estimated the risk of death associated with exposure to increases of 10 μg per cubic meter for $PM_{2.5}$ and 10 parts per billion (ppb) for ozone using a two-pollutant Cox proportional-hazards model that controlled for demographic characteristics, Medicaid eligibility, and area-level covariates.

RESULTS

Increases of 10 μg per cubic meter in $PM_{2.5}$ and of 10 ppb in ozone were associated with increases in all-cause mortality of 7.3% (95% confidence interval [CI], 7.1 to 7.5) and 1.1% (95% CI, 1.0 to 1.2), respectively. When the analysis was restricted to person-years with exposure to $PM_{2.5}$ of less than 12 μg per cubic meter and ozone of less than 50 ppb, the same increases in $PM_{2.5}$ and ozone were associated with increases in the risk of death of 13.6% (95% CI, 13.1 to 14.1) and 1.0% (95% CI, 0.9 to 1.1), respectively. For $PM_{2.5}$, the risk of death among men, blacks, and people with Medicaid eligibility was higher than that in the rest of the population.

CONCLUSIONS

In the entire Medicare population, there was significant evidence of adverse effects related to exposure to $PM_{2.5}$ and ozone at concentrations below current national standards. This effect was most pronounced among self-identified racial minorities and people with low income. (Supported by the Health Effects Institute and others.)

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A Quick Take is available at NEJM.org

The adverse health effects associated with long-term exposure to air pollution are well documented.[1,2] Studies suggest that fine particles (particles with a mass median aerodynamic diameter of less than 2.5 μm [$PM_{2.5}$]) are a public health concern,[3] with exposure linked to decreased life expectancy.[4-6] Long-term exposure to ozone has also been associated with reduced survival in several recent studies, although evidence is sparse.[4,7-9]

Studies with large cohorts have investigated the relationship between long-term exposures to $PM_{2.5}$ and ozone and mortality[4,9-13]; others have estimated the health effects of fine particles at low concentrations (e.g., below 12 μg per cubic meter for $PM_{2.5}$).[14-18] However, most of these studies have included populations whose socioeconomic status is higher than the national average and who reside in well-monitored urban areas. Consequently, these studies provide limited information on the health effects of long-term exposure to low levels of air pollution in smaller cities and rural areas or among minorities or persons with low socioeconomic status.

To address these gaps in knowledge, we conducted a nationwide cohort study involving all Medicare beneficiaries from 2000 through 2012, a population of 61 million, with 460 million person-years of follow-up. We used a survival analysis to estimate the risk of death from any cause associated with long-term exposure (yearly average) to $PM_{2.5}$ concentrations lower than the current annual National Ambient Air Quality Standard (NAAQS) of 12 μg per cubic meter and to ozone concentrations below 50 parts per billion (ppb). Subgroup analyses were conducted to identify populations with a higher or lower level of pollution-associated risk of death from any cause.

Methods

Mortality Data

We obtained the Medicare beneficiary denominator file from the Centers for Medicare and Medicaid Services, which contains information on all persons in the United States covered by Medicare and more than 96% of the population 65 years of age or older. We constructed an open cohort consisting of all beneficiaries in this age group in the continental United States from 2000 through 2012, with all-cause mortality as the outcome. For each beneficiary, we extracted the date of death (up to December 31, 2012), age at year of Medicare entry, year of entry, sex, race, ZIP Code of residence, and Medicaid eligibility (a proxy for low socioeconomic status). Persons who were alive on January 1 of the year following their enrollment in Medicare were entered into the open cohort for the survival analysis. Follow-up periods were defined according to calendar years.

Assessment of Exposure to Air Pollution

Ambient levels of ozone and $PM_{2.5}$ were estimated and validated on the basis of previously published prediction models.[19,20] Briefly, we used an artificial neural network that incorporated satellite-based measurements, simulation outputs from a chemical transport model, land-use terms, meteorologic data, and other data to predict daily concentrations of $PM_{2.5}$ and ozone at unmonitored locations. We fit the neural network with monitoring data from the Environmental Protection Agency (EPA) Air Quality System (AQS) (in which there are 1928 monitoring stations for $PM_{2.5}$ and 1877 monitoring stations for ozone). We then predicted daily $PM_{2.5}$ and ozone concentrations for nationwide grids that were 1 km by 1 km. Cross-validation indicated that predictions were good across the entire study area. The coefficients of determination (R^2) for $PM_{2.5}$ and ozone were 0.83 and 0.80, respectively; the mean square errors between the target and forecasting values for $PM_{2.5}$ and ozone were 1.29 μg per cubic meter and 2.91 ppb, respectively. Data on daily air temperature and relative humidity were retrieved from North American Regional Reanalysis with grids that were approximately 32 km by 32 km; data were averaged annually.[21]

For each calendar year during which a person was at risk of death, we assigned to that person a value for the annual average $PM_{2.5}$ concentration, a value for average ozone level during the warm season (April 1 through September 30), and values for annual average temperature and humidity according to the ZIP Code of the person's residence. The warm-season ozone concentration was used to compare our results with those of previous studies.[10] In this study, "ozone concentration" refers to the average concentration during the warm season, unless specified otherwise.

As part of a sensitivity analysis, we also obtained data on $PM_{2.5}$ and ozone concentrations from the EPA AQS and matched that data with

each person in our study on the basis of the nearest monitoring site within a distance of 50 km. (Details are provided in Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

STATISTICAL ANALYSIS

We fit a two-pollutant Cox proportional-hazards model with a generalized estimating equation to account for the correlation between ZIP Codes.[22] In this way, the risk of death from any cause associated with long-term exposure to $PM_{2.5}$ was always adjusted for long-term exposure to ozone, and the risk of death from any cause associated with long-term exposure to ozone was always adjusted for long-term exposure to $PM_{2.5}$, unless noted otherwise. We also conducted single-pollutant analyses for comparability. We allowed baseline mortality rates to differ according to sex, race, Medicaid eligibility, and 5-year categories of age at study entry. To adjust for potential confounding, we also obtained 15 ZIP-Code or county-level variables from various sources and a regional dummy variable to account for compositional differences in $PM_{2.5}$ across the United States (Table 1, and Section 1 in the Supplementary Appendix). We conducted this same statistical analysis but restricted it to person-years with $PM_{2.5}$ exposures lower than 12 μg per cubic meter and ozone exposures lower than 50 ppb (low-exposure analysis) (Table 1, and Section 1 in the Supplementary Appendix).

To identify populations at a higher or lower pollution-associated risk of death from any cause, we refit the same two-pollutant Cox model for some subgroups (e.g., male vs. female, white vs. black, and Medicaid eligible vs. Medicaid ineligible). To estimate the concentration-response function of air pollution and mortality, we fit a log-linear model with a thin-plate spline of both $PM_{2.5}$ and ozone and controlled for all the individual and ecologic variables used in our main analysis model (Section 7 in the Supplementary Appendix). To examine the robustness of our results, we conducted sensitivity analyses and compared the extent to which estimates of risk changed with respect to differences in confounding adjustment and estimation approaches (Sections S2 through S4 in the Supplementary Appendix).

Data on some important individual-level covariates were not available for the Medicare cohort, including data on smoking status, body-mass index (BMI), and income. We obtained data from the Medicare Current Beneficiary Survey (MCBS), a representative subsample of Medicare enrollees (133,964 records and 57,154 enrollees for the period 2000 through 2012), with individual-level data on smoking, BMI, income, and many other variables collected by means of telephone survey. Using MCBS data, we investigated how the lack of adjustment for these risk factors could have affected our calculated risk estimates in the Medicare cohort (Section 5 in the Supplementary Appendix). The computations in this article were run on the Odyssey cluster, which is supported by the FAS Division of Science, Research Computing Group, and on the Research Computing Environment, which is supported by the Institute for Quantitative Social Science in the Faculty of Arts and Sciences, both at Harvard University. We used R software, version 3.3.2 (R Project for Statistical Computing), and SAS software, version 9.4 (SAS Institute).

RESULTS

COHORT ANALYSES

The full cohort included 60,925,443 persons living in 39,716 different ZIP Codes with 460,310,521 person-years of follow-up. The median follow-up was 7 years. The total number of deaths was 22,567,924. There were 11,908,888 deaths and 247,682,367 person-years of follow-up when the $PM_{2.5}$ concentration was below 12 μg per cubic meter and 17,470,128 deaths and 353,831,836 person-years of follow-up when the ozone concentration was below 50 ppb. These data provided excellent power to estimate the risk of death at air-pollution levels below the current annual NAAQS for $PM_{2.5}$ and at low concentrations for ozone (Table 1).

Annual average $PM_{2.5}$ concentrations across the continental United States during the study period ranged from 6.21 to 15.64 μg per cubic meter (5th and 95th percentiles, respectively), and the warm-season average ozone concentrations ranged from 36.27 to 55.86 ppb (5th and 95th percentiles, respectively). The highest $PM_{2.5}$ concentrations were in California and the eastern and southeastern United States. The Mountain region and California had the highest ozone concentrations; the eastern states had lower ozone concentrations (Fig. 1).

Table 1. Cohort Characteristics and Ecologic and Meteorologic Variables.

Characteristic or Variable	Entire Cohort	Ozone Concentration		$PM_{2.5}$ Concentration	
		≥50 ppb*	<50 ppb	≥12 $\mu g/m^3$	<12 $\mu g/m^3$
Population					
Persons (no.)	60,925,443	14,405,094	46,520,349	28,145,493	32,779,950
Deaths (no.)	22,567,924	5,097,796	17,470,128	10,659,036	11,908,888
Total person-yr†	460,310,521	106,478,685	353,831,836	212,628,154	247,682,367
Median yr of follow-up	7	7	7	7	7
Average air-pollutant concentrations‡					
Ozone (ppb)	46.3	52.8	44.4	48.0	45.3
$PM_{2.5}$ ($\mu g/m^3$)	11.0	10.9	11.0	13.3	9.6
Individual covariates‡					
Male sex (%)	44.0	44.3	43.8	43.1	44.7
Race or ethnic group (%)§					
White	85.4	86.6	85.1	82.0	88.4
Black	8.7	7.2	9.2	12.0	5.9
Asian	1.8	1.8	1.8	2.1	1.6
Hispanic	1.9	2.0	1.9	1.9	1.9
Native American	0.3	0.6	0.3	0.1	0.6
Eligible for Medicaid (%)	16.5	15.3	16.8	17.8	15.3
Average age at study entry (yr)	70.1	69.7	70.2	70.1	70.0
Ecologic variables‡					
BMI	28.2	27.9	28.4	28.0	28.4
Ever smoked (%)	46.0	44.9	46.2	45.8	46.0
Population including all people 65 yr of age or older (%)					
Hispanic	9.5	13.4	8.4	8.4	10.0
Black	8.8	7.2	9.3	13.3	6.3
Median household income (1000s of $)	47.4	51.0	46.4	47.3	47.4
Median value of housing (1000s of $)	160.5	175.8	156.3	161.7	159.8
Below poverty level (%)	12.2	11.4	12.4	12.5	12.0
Did not complete high school (%)	32.3	30.7	32.7	35.3	30.6
Owner-occupied housing (%)	71.5	71.3	71.6	68.6	73.2
Population density (persons/km^2)	3.2	0.7	3.8	4.8	2.2
Low-density lipoprotein level measured (%)	92.2	92.0	92.2	92.2	92.2
Glycated hemoglobin level measured (%)	94.8	94.6	94.8	94.8	94.8
≥1 Ambulatory visits (%)¶	91.7	92.2	91.6	91.7	91.7
Meteorologic variables‡					
Average temperature (°C)	14.0	14.9	13.8	14.5	13.7
Relative humidity (%)	71.1	60.8	73.9	73.7	69.6

* Summary statistics were calculated separately for persons residing in ZIP Codes where average ozone levels were below or above 50 ppb and where $PM_{2.5}$ levels were below or above 12 μg per cubic meter. The value 12 μg per cubic meter was chosen as the current annual National Ambient Air Quality Standard (NAAQS) (e.g., the "safe" level) for $PM_{2.5}$. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters) and ppb parts per billion.

† The number for total person-years of follow-up indicates the sum of individual units of time that the persons in the study population were at risk of death from 2000 through 2012.

‡ The average values for air pollution levels and for ecologic and meteorologic variables were computed by averaging values over all ZIP Codes from 2000 through 2012.

§ Data on race and ethnic group were obtained from Medicare beneficiary files.

¶ The variable for ambulatory visits refers to the average annual percentage of Medicare enrollees who had at least one ambulatory visit to a primary care physician.

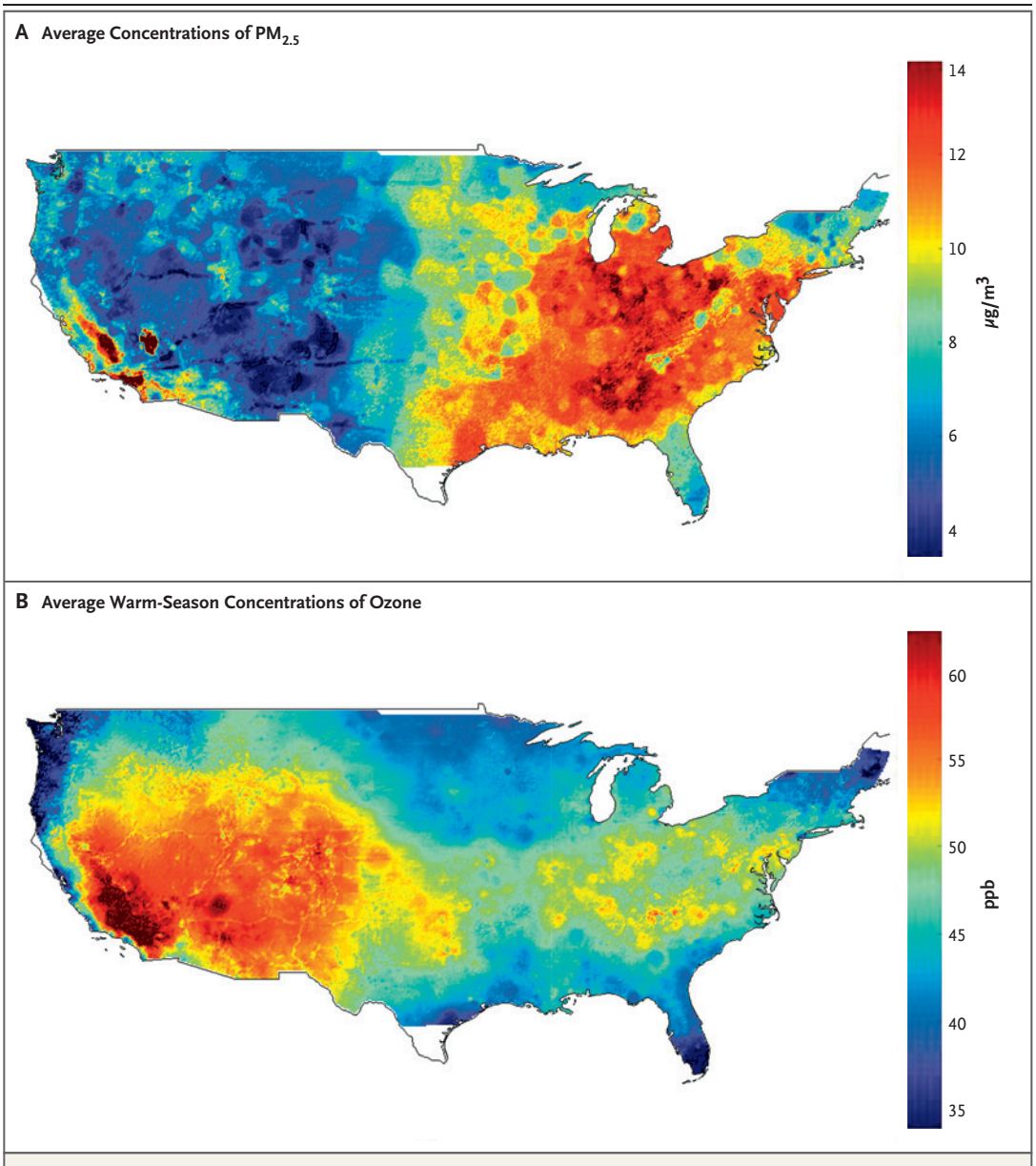

Figure 1. Average $PM_{2.5}$ and Ozone Concentrations in the Continental United States, 2000 through 2012.

Panel A shows the average concentrations of fine particulate matter (particles with a mass median aerodynamic diameter of less than 2.5 μm [$PM_{2.5}$]) in micrograms per cubic meter, as estimated on the basis of all daily predictions during the study period. Panel B shows the concentration of ozone levels in parts per billion as averaged from April 1 through September 30 throughout the study period.

In a two-pollutant analysis, each increase of 10 μg per cubic meter in annual exposure to $PM_{2.5}$ (estimated independently of ozone) and each increase of 10 ppb in warm-season exposure to ozone (estimated independently of $PM_{2.5}$) was associated with an increase in all-cause mortality of 7.3% (95% confidence interval [CI], 7.1 to 7.5) and 1.1% (95% CI, 1.0 to 1.2), respectively. Estimates of risk based on predictive, ZIP-Code–specific assessments of exposure were slightly higher than those provided by the nearest data-monitoring site (Table 2). When we restricted the $PM_{2.5}$ and ozone analyses to location-years with low concentrations, we continued to see significant associations between exposure and mortality (Table 2). Analysis of the MCBS

Table 2. Risk of Death Associated with an Increase of 10 μg per Cubic Meter in $PM_{2.5}$ or an Increase of 10 ppb in Ozone Concentration.*

Model	$PM_{2.5}$	Ozone
	hazard ratio (95% CI)	
Two-pollutant analysis		
Main analysis	1.073 (1.071–1.075)	1.011 (1.010–1.012)
Low-exposure analysis	1.136 (1.131–1.141)	1.010 (1.009–1.011)
Analysis based on data from nearest monitoring site (nearest-monitor analysis)†	1.061 (1.059–1.063)	1.001 (1.000–1.002)
Single-pollutant analysis‡	1.084 (1.081–1.086)	1.023 (1.022–1.024)

* Hazard ratios and 95% confidence intervals were calculated on the basis of an increase of 10 μg per cubic meter in exposure to $PM_{2.5}$ and an increase of 10 ppb in exposure to ozone.
† Daily average monitoring data on $PM_{2.5}$ and ozone were obtained from the Environmental Protection Agency Air Quality System. Daily ozone concentrations were averaged from April 1 through September 30 for the computation of warm-season averages. Data on $PM_{2.5}$ and ozone levels were obtained from the nearest monitoring site within 50 km. If there was more than one monitoring site within 50 km, the nearest site was chosen. Persons who lived more than 50 km from a monitoring site were excluded.
‡ For the single-pollutant analysis, model specifications were the same as those used in the main analysis, except that ozone was not included in the model when the main effect of $PM_{2.5}$ was estimated and $PM_{2.5}$ was not included in the model when the main effect of ozone was estimated.

subsample provided strong evidence that smoking and income are not likely to be confounders because they do not have a significant association with $PM_{2.5}$ or ozone (Section 5 in the Supplementary Appendix).

SUBGROUP ANALYSES

Subgroup analyses revealed that men; black, Asian, and Hispanic persons; and persons who were eligible for Medicaid (i.e., those who had low socioeconomic status) had a higher estimated risk of death from any cause in association with $PM_{2.5}$ exposure than the general population. The risk of death associated with ozone exposure was higher among white, Medicaid-eligible persons and was significantly below 1 in some racial subgroups (Fig. 2). Among black persons, the effect estimate for $PM_{2.5}$ was three times as high as that for the overall population (Table S3 in the Supplementary Appendix). Overall, the risk of death associated with ozone exposure was smaller and somewhat less robust than that associated with $PM_{2.5}$ exposure. We also detected a small but significant interaction between ozone exposure and $PM_{2.5}$ exposure (Table S8 in the Supplementary Appendix). Our thin-plate–spline fit indicated a relationship between $PM_{2.5}$, ozone, and all-cause mortality that was almost linear, with no signal of threshold down to 5 μg per cubic meter and 30 ppb, respectively (Fig. 3, and Fig. S8 in the Supplementary Appendix).

DISCUSSION

This study involving an open cohort of all persons receiving Medicare, including those from small cities and rural areas, showed that long-term exposures to $PM_{2.5}$ and ozone were associated with an increased risk of death, even at levels below the current annual NAAQS for $PM_{2.5}$. Furthermore, the study showed that black men and persons eligible to receive Medicaid had a much higher risk of death associated with exposure to air pollution than other subgroups. These findings suggest that lowering the annual NAAQS may produce important public health benefits overall, especially among self-identified racial minorities and people with low income.

The strengths of this study include the assessment of exposure with high spatial and temporal resolution, the use of a cohort of almost 61 million Medicare beneficiaries across the entire continental United States followed for up to 13 consecutive years, and the ability to perform subgroup analyses of the health effects of air pollution on groups of disadvantaged persons. However, Medicare claims do not include extensive individual-level data on behavioral risk fac-

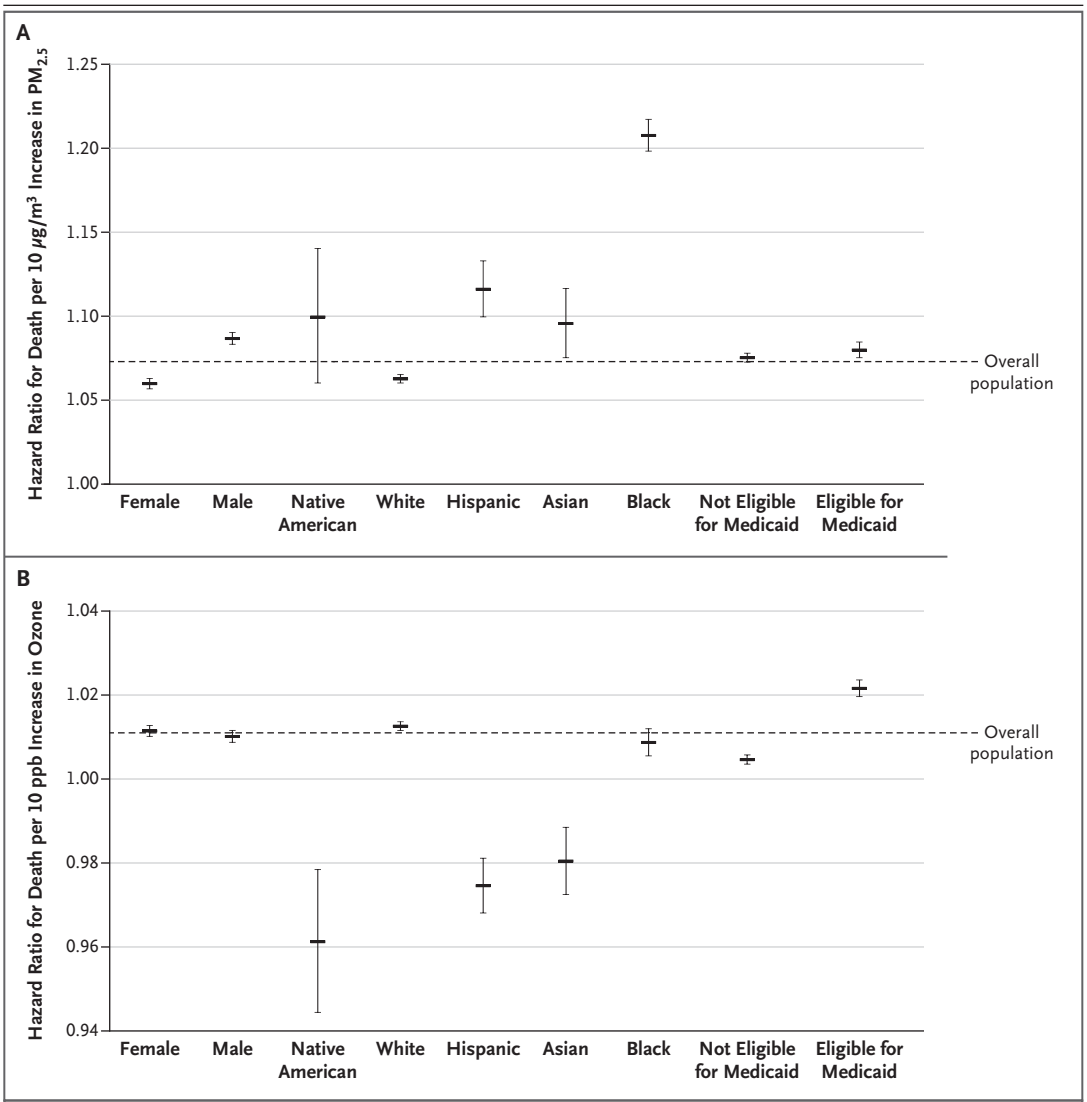

Figure 2. Risk of Death Associated with an Increase of 10 μg per Cubic Meter in $PM_{2.5}$ Concentrations and an Increase of 10 ppb in Ozone Exposure, According to Study Subgroups.

Hazard ratios and 95% confidence intervals are shown for an increase of 10 μg per cubic meter in $PM_{2.5}$ and an increase of 10 parts per billion (ppb) in ozone. Subgroup analyses were conducted by first restricting the population (e.g., considering only male enrollees). The same two-pollutant analysis (the main analysis) was then applied to each subgroup. Numeric results are presented in Tables S3 and S4 in the Supplementary Appendix. Dashed lines indicate the estimated hazard ratio for the overall population.

tors, such as smoking and income, which could be important confounders. Still, our analysis of the MCBS subsample (Table S6 in the Supplementary Appendix) increased our level of confidence that the inability to adjust for these individual-level risk factors in the Medicare cohort did not lead to biased results (Section 5 in the Supplementary Appendix). In another study, we analyzed a similar Medicare subsample with detailed individual-level data on smoking, BMI, and many other potential confounders linked to Medicare claims.[23] In that analysis, we found that for mortality and hospitalization, the risks of exposure to $PM_{2.5}$ were not sensitive to the additional control of individual-level variables that were not available in the whole Medicare population.

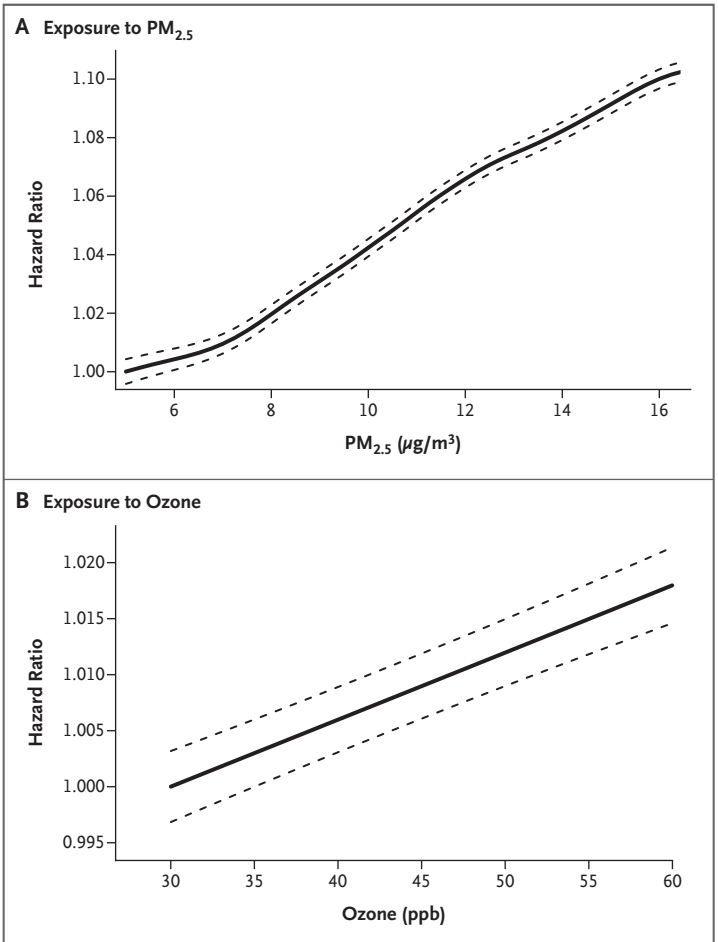

Figure 3. Concentration–Response Function of the Joint Effects of Exposure to $PM_{2.5}$ and Ozone on All-Cause Mortality.

A log-linear model with a thin-plate spline was fit for both $PM_{2.5}$ and ozone, and the shape of the concentration-response surface was estimated (Fig. S8 in the Supplementary Appendix). The concentration–response curve in Panel A was plotted for an ozone concentration equal to 45 ppb. The concentration–response curve in Panel B was plotted for a $PM_{2.5}$ concentration equal to 10 μg per cubic meter. These estimated curves were plotted at the 5th and 95th percentiles of the concentrations of $PM_{2.5}$ and ozone, respectively. The complete concentration–response three-dimensional surface is plotted in Fig. S8 in the Supplementary Appendix.

We also found that our results were robust when we excluded individual and ecologic covariates from the main analysis (Fig. S2 and Table S2 in the Supplementary Appendix), when we stratified age at entry into 3-year and 4-year categories rather than the 5 years used in the main analysis (Fig. S3 in the Supplementary Appendix), when we varied the estimation procedure (by means of a generalized estimating equation as opposed to mixed effects) (Tables S3 and S4 in the Supplementary Appendix), and when we used different types of statistical software (R, version 3.3.2, vs. SAS, version 9.4). Finally, we found that our results were consistent with others published in the literature (Section 6 in the Supplementary Appendix).[5,17,24-28]

There was a significant association between $PM_{2.5}$ exposure and mortality when the analysis was restricted to concentrations below 12 μg per cubic meter, with a steeper slope below that level. This association indicated that the health-benefit-per-unit decrease in the concentration of $PM_{2.5}$ is larger for $PM_{2.5}$ concentrations that are below the current annual NAAQS than the health benefit of decreases in $PM_{2.5}$ concentrations that are above that level. Similar, steeper concentration-response curves at low concentrations have been observed in previous studies.[29] Moreover, we found no evidence of a threshold value — the concentration at which $PM_{2.5}$ exposure does not affect mortality — at concentrations as low as approximately 5 μg per cubic meter (Fig. 3); this finding is similar to those of other studies.[18,30]

The current ozone standard for daily exposure is 70 ppb; there is no annual or seasonal standard. Our results strengthen the argument for establishing seasonal or annual standards. Moreover, whereas time-series studies have shown the short-term effects of ozone exposure, our results indicate that there are larger effect sizes for longer-term ozone exposure, including in locations where ozone concentrations never exceed 70 ppb. Unlike the American Cancer Society Cancer Prevention Study II,[9,10] our study reported a linear connection between ozone concentration and mortality. This finding is probably the result of the interaction between $PM_{2.5}$ and ozone (Section 7 in the Supplementary Appendix). The significant, linear relationship between seasonal ozone levels and all-cause mortality indicates that current risk assessments,[31-33] which incorporate only the acute effects of ozone exposure on deaths each day from respiratory mortality, may be substantially underestimating the contribution of ozone exposure to the total burden of disease.

The enormous sample size in this study, which includes the entire Medicare cohort, allowed for unprecedented accuracy in the estimation of risks among racial minorities and disadvantaged subgroups. The estimate of effect size for $PM_{2.5}$ expo-

sure was greatest among male, black, and Medicaid-eligible persons. We also estimated risks in subgroups of persons who were eligible for Medicaid and in whites and blacks alone to ascertain whether the effect modifications according to race and Medicaid status were independent. We found that black persons who were not eligible for Medicaid (e.g., because of higher income) continued to have an increased risk of death from exposure to $PM_{2.5}$ (Fig. S4 in the Supplementary Appendix). In addition, we found that there was a difference in the health effects of $PM_{2.5}$ exposure between urban and rural populations, a finding that may be due to compositional differences in the particulates (Table S3 Supplementary Appendix).

Although the Medicare cohort includes only the population of persons 65 years of age or older, two thirds of all deaths in the United States occur in people in that age group. Although our exposure models had excellent out-of-sample predictive power on held-out monitors, they do have limitations. Error in exposure assessment remains an issue in this type of analysis and could attenuate effect estimates for air pollution.[34]

The overall association between air pollution and human health has been well documented since the publication of the landmark Harvard Six Cities Study in 1993.[25] With air pollution declining, it is critical to estimate the health effects of low levels of air pollution — below the current NAAQS — to determine whether these levels are adequate to minimize the risk of death. Since the Clean Air Act requires the EPA to set air-quality standards that protect sensitive populations, it is also important to focus more effort on estimating effect sizes in potentially sensitive populations in order to inform regulatory policy going forward.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the funding agencies. Furthermore, these agencies do not endorse the purchase of any commercial products or services related to this publication.

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ATTACHMENT 3

Partial List of Studies That May Contain Protected Health Information and That Have Been Relied on by the Environmental Protection Agency (EPA) and Cited in EPA Documents

The following studies were cited in supporting or decision making EPA documents.

Safe Drinking Water Act (SDWA)

Six Year Review #1 Health Effects Technical Support Document

- Barrett JH, Parslow RC, McKinney PA, et al. 1998. Nitrate in drinking water and the incidence of gastric, esophageal, and brain cancer in Yorkshire, England. *Cancer Causes Control.* 9:153-159.
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Six Year Review #2 Health Effects Technical Support Document

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Contaminant Candidate List Examples

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Perfluorooctanoic Acid Health Effects Support Document

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Environmental Health

EDITORIAL Open Access

Delayed discovery, dissemination, and decisions on intervention in environmental health: a case study on immunotoxicity of perfluorinated alkylate substances

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Abstract

Identification and characterization of environmental hazards that impact human health must rely on the best possible science to inform and inspire appropriate public health intervention. The perfluorinated alkylate substances (PFASs) are persistent emerging pollutants that are now being recognized as important human health hazards. Although the PFASs have been produced for over 60 years, academic research on environmental health aspects has appeared only in the most recent 10 years or so. In the meantime, these persistent chemicals accumulated in the global environment. Some early studies e.g., on population exposures and toxicity, were not released to the public until after year 2000. Still, the first PFAS risk assessments ignored these reports and relied on scant journal publications. The first guidelines and legal limits for PFAS exposure, e.g., from drinking water, were proposed 10 years ago. They have decreased substantially since then, but remain higher than suggested by data on human adverse effects, especially on the immune system, that occur at background exposure levels. By now, the best-known PFASs are being phased out, and related PFASs are being introduced as substitutes. Given the substantial delays in discovery of PFAS toxicity, in dissemination of findings, and in regulatory decisions, PFAS substitutes and other persistent industrial chemicals should be subjected to prior scrutiny before widespread usage.

Late emergence of early evidence

Industrial chemicals are often regarded inert or safe, unless proven otherwise, i.e., the so-called "untested chemicals assumption," although this belief is of course not logical [1, 2]. A high-priority group of environmental chemicals, the perfluorinated alkylate substances (PFASs), constitute a clear example how narrow reliance on published toxicity studies can be misleading and result in insufficient and delayed protection of public health [3]. New insight on PFAS immunotoxicity shows that the path from discovery of toxicity to decisions on intervention can be stalled for decades (Table 1).

After the beginning of commercial PFAS production in the 1950s, a brief review article from 1980 [4] for the first time mentioned industry-sponsored studies, some of which were carried out in monkeys. Perfluorooctanoic acid (PFOA) showed specific toxicity to the reticuloendothelial system (i.e. immune system) [5]. In this 90-day study, compound-related microscopic lesions were seen in bone marrow, spleen and lymph nodes, thus clearly suggesting immunotoxicity, although functional tests were not carried out. A parallel study on perfluorooctanoic sulfonic acid (PFOS), also from 1978, was aborted due to mortality of the monkeys at all doses (the lowest being 10 mg/kg/day) [6]. These two internal reports were eventually shared with the U.S. Environmental Protection Agency (EPA) in 2000 [7] and then became accessible to the public.

A medical thesis from 1992 mentioned the evidence from the monkey study and noted: "No follow-up studies of these observations have been reported" [8]. The thesis analyzed clinical examination data from PFOA production workers and found clear associations between increased PFAS concentrations in the blood and decreased

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Table 1 Time course of important developments regarding PFAS exposure and health risks [5, 6, 8, 10, 11, 13, 15, 16, 28, 31, 32, 44, 50]

Year	Exposure evidence	Reference
1968	Organic fluoride compounds discovered in human blood	[11]
1976	Organofluorines determined in blood from production workers	[10]
1981	PFOA found in umbilical cord blood when female worker gives birth	[13]
1993	Transfer of PFOS into milk observed in goats	[10]
1998	PFOS found in blood from the general population	[10]
2003	PFAS in blood from Red Cross blood donors	[16]
2004	PFAS detected in human milk	[15]
2014	Breastfeeding shown to be major source of PFAS exposure in infants	[31]
	Immunotoxicity	
1978	Immunotoxicity and other adverse effects in monkeys exposed to PFOA, and mortality in monkeys exposed to PFOS	[5, 6]
1992	Leukocyte cell count changes in PFOA production workers	[8]
2008	Mouse study shows immunotoxicity at serum PFAS concentrations similar to elevated human exposures	[50]
2012	Immunotoxicity reported in PFAS-exposed children	[28]
2013	Benchmark Dose calculations suggest that guidelines are far from protective	[44]
2017	PFAS exposure during infancy associated with subsequent immune deficiency	[32]

Unpublished information is shaded

leukocyte counts. The results were not reported in a scientific journal. However, in connection with a recent law suit, a draft manuscript on this study has been released ("Peripheral blood lymphocyte count in men occupationally exposed to perfluorooctanoic acid" [9]). The draft concluded: "PFOA is associated with alterations in peripheral blood lymphocyte numbers in PFOA production workers, suggesting that cell-mediated immunity may be affected by PFOA". Other company materials outlined in an expert report include the comment "We're working with [the author] regarding some of the wording" [10]. Evidently, an agreement was not reached, and the findings were not published.

Human exposure to organofluorine compounds was discovered as early as 1968 [11] and was later confirmed in a more extensive study [12]. However, the exact identity and the sources were unknown at the time. Soon thereafter, PFASs were identified in blood from production workers, and in 1981 also in umbilical cord blood at a female worker's childbirth [13]. Although the latter finding signified placental passage and prenatal PFAS exposure, this observation was not revealed until 20 years later, after which it was soon confirmed in a larger study [14]. Of additional public health significance, an unpublished study on goats from 1993 showed that PFOS was transferred into milk [10], and this pathway was verified in humans, again many years later [15].

New insight into a hidden hazard

By about 2000, the widespread occurrence and persistence of PFASs in the environment became known [7], as reflected also by the presence of PFASs in serum samples from blood banks [16]. Only after this time, and especially during the most recent 10 years, did the scientific literature on PFASs expand (Fig. 1) [17]. Immune system deficits in PFOA-exposed mice were at first observed in studies of peroxisome proliferator activation [18]. Later, experimental studies of PFOS showed reductions in lymphoid cell numbers and de novo antibody synthesis [19], and a study in mice from 2009 demonstrated that PFOS exposure reduced the survival after influenza A infection [20]. Then followed in vitro evidence of adverse effects in human white blood cells [21]. Although the 1978 monkey study [5] could have been obtained from the U.S. EPA, none of these studies referred to these original findings.

Important evidence emerged after the discovery of PFAS contamination in the Mid-Ohio River Valley and

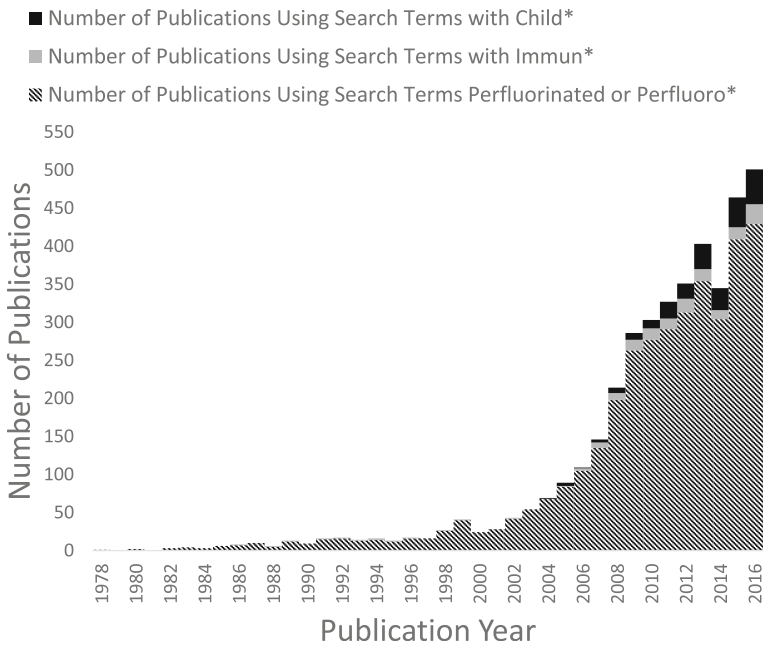

Fig. 1 Number of publications on PFASs over time, according to the Web of Science database (between 1978 and 2017), using the search terms "perfluorinated or perfluoro"* and restricting to environmental sciences, toxicology, or public, environmental, and occupational health categories. This search was further refined using the search terms "immun*" and "child*"

the court-mandated health examinations [22]. In regard to immunotoxicity, an interim report showed that increased PFOA exposure was associated with changes in serum concentrations of immunoglobulins [23]. A more focused study determined antibody responses to flu vaccination [24]. Elevated serum-PFOA concentrations were associated with a reduced antibody titer rise, particularly to an A influenza virus strain, with an increased risk of not attaining the antibody level needed to provide long-term protection. A later study on 12 adult volunteers with background exposures showed that two of the subjects failed to respond to a tetanus-diphtheria booster and that the steepness of the antibody responses was negatively associated with the serum-PFAS concentrations [25]. Cross-sectional data have also suggested lower vaccination antibody concentrations at elevated background PFAS exposures [26].

The first prospective study assessing children's antibody responses to routine childhood immunizations reported in 2012 that a doubling in exposure to PFOS and PFOA was associated with an overall decrease by up to 50% in the specific vaccine antibody concentration [27, 28]. When mutually adjusted, the regression coefficients for PFOA and PFOS changed only little [27]. Booster vaccine responses in children at age 5 years were lower at elevated serum-PFAS concentrations [28, 29]. A smaller Norwegian study of about 50 children aged 3 years also showed tendencies toward lower vaccination antibody concentrations at higher exposures during pregnancy [30]. As PFASs are now known to be transferred to the infant via human milk [31], it seems likely that PFAS exposures in early infancy represent a particular hazard to the adaptive immune system [32]. If true, the routine modeling of lifetime exposures for risk assessment is inappropriate, as it ignores the presence of vulnerable time windows.

PFAS exposure can also impact the body's ability to fight off common infections, such as colds and gastroenteritis, as seen in the Norwegian study [30]. A larger, prospective study in Denmark found that increased maternal serum concentrations of PFOA and PFOS were significantly associated with a higher frequency of fever and symptoms in the children [33], in agreement with a subsequent study from Japan that relied on retrospective assessment of the disease incidence [34]. In contrast, a substudy from the Danish National Birth Cohort examined the hospitalization rates for a variety of infections, such as airway infection, middle ear infection, and appendicitis, through to age 11 years and showed no association with PFOS and PFOA in early pregnancy serum from the mother [35]. However, a recent report from the project team raised doubt about the validity of the PFAS analyses [36].

Delayed interventions

Despite the support from both experimental and epidemiological data [37], most regulatory risk assessments of PFASs have focused on other target organs and have

emphasized toxicity testing in rodents [4]. The first opinion from the European Food Safety Authority (EFSA) in 2009 [38] listed a single report on immunotoxicity under "Other endpoints". That same year, the EPA issued provisional health advisories and concluded that "epidemiological studies of exposure to PFOA and adverse health outcomes in humans are inconclusive at present" [39]. Neither report referred to the 1978 monkey study that had become available in 2000. Early and more recent guidelines and recommended limits for PFOS and PFOA are shown in Table 2.

The EPA prepared more detailed risk assessment reports for PFOA and PFOS in 2014 [40, 41]. These drafts conclude that the two major PFASs exhibit immunotoxicity in experimental models and that the epidemiological evidence is additive, although mixed exposures complicate the attribution of effects to specific PFASs. A similar conclusion was reached by an ATSDR ToxProfile on the perfluoroalkyls in 2015 [42]. The coverage of human immunotoxicity was very brief, and no mention of this potential was made in the sections on public health implications. Although the monkey studies were cited, the risk assessment reports did not refer to the 1992 study of exposure-associated immune cell abnormalities in workers.

More recently, the National Toxicology Program (NTP) in 2016 reviewed the immunotoxicity information on PFOS and PFOA and concluded that both are "presumed" to constitute immune hazards to humans [37]. The term "presumed" is the strongest below "known" in the NTP vernacular. Both PFASs suppress the antibody response in animal studies, while the evidence in humans is "moderate", as all studies are observational (not experimental) and refer to mixed PFAS exposures. The revised ATSDR ToxProfile [43] just released concluded that decreased antibody response to vaccines is a potential outcome from exposure to all five PFASs commonly found in human blood samples. However, ATSDR stopped short of using epidemiology evidence for derivation of exposure limits.

Table 2 Guideline values expressed in terms of acceptable concentrations of PFOS and PFOA in drinking water (ng/L),[a] as compared with the estimated limit based on benchmark dose calculations for immunotoxicity in children [44]

Authority	Year	PFOS	PFOA
Australia			
	2016	70	560
Canada	2016	600	200
U.S. EPA	2009	200	400
	2016	70	70
ATSDR	2015	70	100
	2018	11	7
Minnesota	2008	300	300
	2017	27	35
New Jersey	2007	-	40
	2017	13	14
EFSA	2009	70	700
	2018	6.5	3
BMDL-based	2013	< 1	< 1

[a]Estimated from total intake limits, assuming 20% exposure contribution from water (rounded values)

Regulatory agencies frequently use benchmark dose calculations as a basis for generating exposure limits [38]. This approach relies on fitting a dose-response function to the data, and the benchmark dose (BMD) is defined as the dose that leads to a specific loss (or degree of abnormality) known as the benchmark response (BMR) in the outcome variable. The lower one-sided 95% confidence limit of the BMD is the benchmark dose level (BMDL), which is used as the point of departure for calculation of exposure limits. Relying on the vaccine antibody responses, BMDLs for PFOS and PFOA were calculated in 2013 to be about 1 μg/L serum [44], i.e., levels that are exceeded by a majority of the general population [45]. However, at first, these results were disregarded because of the absence of an unexposed control group [42], a condition that would be impossible to meet. Another concern was the high correlation between exposure components, such as PFOA and PFOS [40, 41, 43]. Still, mutual adjustment is possible and shows clear negative impacts of both of these major PFASs on immune system responses [27], and other calculations show virtually unchanged BMDLs for PFOA and PFOS after such adjustment [46].

In an updated opinion on PFOS and PFOA [47], EFSA used separate BMD calculations for several outcomes in humans, including immunotoxicity, relying on summary data in deciles or quartiles. For the vaccine response data [28], EFSA assumed that all subjects in the lowest decile exposure group had the same exposure, and the BMDs were similar to the average serum concentration in that group. For this reason, EFSA's calculated BMDs are several fold higher than the ones obtained from the continuous dose-effect relationship [44]. Still, the new tolerable intake limits are substantially lower than other published guidelines (Table 2), though quite similar to the Minimal Risk Levels developed by ATSDR [43].

The "untested chemicals assumption", as highlighted by the National Research Council [1] has clearly been inappropriately relied upon in past risk assessments of PFASs, and these substances must now be added to the list of environmental hazards [48] where standard risk assessment has failed. As a major reason, early evidence on PFAS toxicity was kept secret for 20 years or more, and even after its release, it was apparently overlooked.

A related reason is the absence of academic PFAS research on the immune system and other sensitive target organs until about 10 years ago. Further, regulatory agencies relied on experimental toxicity studies and disregarded emerging epidemiological evidence. As a result, even some of the current guidelines are orders of magnitude above exposure levels at which associations with adverse effects have been reported.

The PFASs therefore constitute an unfortunate example that risk assessment may be inappropriate to assess human health risks from chemical exposures when crucial documentation has not yet been published. Recognizing the weaknesses of conventional risk assessment, scientists from the U.S. EPA recently recommended to consider the full range of available data and to include health endpoints that reflect the range of subtle effects and morbidities in humans [48]. The present summary of delayed discovery, dissemination and decision-making on the PFASs indicates that a more comprehensive assessment of adverse health risks is urgently needed and that PFAS substitutes, as well as other persistent industrial chemicals, should not be considered innocuous in the absence of relevant documentation [49].

Conclusions

Early research on environmental PFAS exposures and their health implications became available at a substantial delay and was not taken into account in initial regulatory decisions on exposure abatement. Only in the last 10 years or so has environmental health research focused on the PFASs and revealed important human health risks, e.g., to the immune system. Although guideline values for PFASs in drinking water have decreased over time, they remain too high to protect against such toxicity. While the most commonly used PFASs will remain in the environment for many years, new PFAS substitutes are being introduced, although little information on adverse health risks is available. Given the serious delays in the discovery of PFAS toxicity, their persistence in the environment, and their public health impact, PFAS substitutes and other persistent industrial chemicals should be subjected to prior research scrutiny before widespread usage.

Abbreviations

BMD: Benchmark dose; BMDL: Benchmark dose level; BMR: Benchmark response; EFSA: European Food Safety Authority; EPA: Environmental Protection Agency; NTP: National Toxicology Program; PFAS: Perfluorinated alkylate substance; PFOA: Perfluorooctanoic acid; PFOS: Perfluorooctanoic sulfonic acid

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Authors' Contributions

The author read and approved the final manuscript.

Competing interests

The author is an editor-in-chief of Environmental Health. The author recently served as a health expert for the State of Minnesota in a lawsuit against a PFAS-producing company.

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OUR CORE PRACTICES

Core practices are the policies and practices journals and publishers need to reach the highest standards in publication ethics. We include cases with advice, guidance for day-to-day practice, education modules and events on topical issues, to support journals and publishers fulfil their policies.

1. ALLEGATIONS OF MISCONDUCT

Journals should have a clearly described process for handling allegations, however they are brought to the journal's or publisher's attention. Journals must take seriously allegations of misconduct pre-publication and post-publication. Policies should include how to handle allegations from whistleblowers.

FIND OUT MORE: publicationethics.org/misconduct

2. AUTHORSHIP AND CONTRIBUTORSHIP

Clear policies (that allow for transparency around who contributed to the work and in what capacity) should be in place for requirements for authorship and contributorship as well as processes for managing potential disputes.

FIND OUT MORE: publicationethics.org/authorship

3. COMPLAINTS AND APPEALS

Journals should have a clearly described process for handling complaints against the journal, its staff, editorial board or publisher.

FIND OUT MORE: publicationethics.org/appeals

4. CONFLICTS OF INTEREST/COMPETING INTERESTS

There must be clear definitions of conflicts of interest and processes for handling conflicts of interest of authors, reviewers, editors, journals and publishers, whether identified before or after publication.

FIND OUT MORE: publicationethics.org/competinginterests

5. DATA AND REPRODUCIBILITY

Journals should include policies on data availability and encourage the use of reporting guidelines and registration of clinical trials and other study designs according to standard practice in their discipline.

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6. ETHICAL OVERSIGHT

Ethical oversight should include, but is not limited to, policies on consent to publication, publication on vulnerable populations, ethical conduct of research using animals, ethical conduct of research using human subjects, handling confidential data and of business/marketing practices.

FIND OUT MORE: publicationethics.org/oversight

7. INTELLECTUAL PROPERTY

All policies on intellectual property, including copyright and publishing licenses, should be clearly described. In addition, any costs associated with publishing should be obvious to authors and readers. Policies should be clear on what counts as prepublication that will preclude consideration. What constitutes plagiarism and redundant/overlapping publication should be specified.

FIND OUT MORE: publicationethics.org/intellectualproperty

8. JOURNAL MANAGEMENT

A well-described and implemented infrastructure is essential, including the business model, policies, processes and software for efficient running of an editorially independent journal, as well as the efficient management and training of editorial boards and editorial and publishing staff.

FIND OUT MORE: publicationethics.org/management

9. PEER REVIEW PROCESSES

All peer review processes must be transparently described and well managed. Journals should provide training for editors and reviewers and have policies on diverse aspects of peer review, especially with respect to adoption of appropriate models of review and processes for handling conflicts of interest, appeals and disputes that may arise in peer review.

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10. POST-PUBLICATION DISCUSSIONS AND CORRECTIONS

Journals must allow debate post publication either on their site, through letters to the editor, or on an external moderated site, such as PubMed Commons or PubPeer. They must have mechanisms for correcting, revising or retracting articles after publication.

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Core practices

COPE's role is to assist editors of scholarly journals and publishers/owners - as well as other parties, such as institutions and funders, albeit less directly - in their endeavour to preserve and promote the integrity of the scholarly record through policies and practices that reflect the current best principles of transparency and integrity. COPE's new recommendations are intended to reflect these aims, in a practical way. COPE have therefore reviewed the Code of Conduct and Best Practice Guidelines for Editors and Code of Conduct for Journal Publishers and have consolidated them into one, much shorter, document entitled "Core Practices". [Available to download as an A4 poster.] Connected to each of these core practices will be hyperlinks to the detailed documents and resources COPE already publish, which are arrived at through extensive consultation, and which we will be building into a comprehensive, yet responsive library. The full range of COPE resources can be found here. .The Core Practices are applicable to all involved in publishing the scholarly literature: editors and their journals, publishers (and institutions).

COPE's Core Practices should be considered alongside specific national and international codes of conduct for research and is not intended to replace them.

Background to why the Code of Conduct for Journal Editors has been replaced with the Core Practices.

Journals and Publishers should have robust and well-described, publicly documented practices in all the following areas for their journals:

1. Allegations of misconduct

Journals should have a clearly described process for handling allegations, however they are brought to the journal's or publisher's attention. Journals must take seriously allegations of misconduct pre-publication and post-publication. Policies should include how to handle allegations from whistleblowers.

Latest resources

- Association of Research Integrity Officers 2018 (Event)
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- In the news: May 2018 Digest (News)

View all Allegations of misconduct resources

2. Authorship and contributorship

Clear policies (that allow for transparency around who contributed to the work and in what capacity) should be in place for requirements for authorship and contributorship as well as processes for managing potential disputes

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- Association of Research Integrity Officers 2018 (Event)
- In the News: July Digest (News)
- ISMTE North American Conference (Event)

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Journals should have a clearly described process for handling complaints against the journal, its staff, editorial board or publisher

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- In the news: April 2018 Digest (News)
- Complaints and appeals (News)
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4. Conflicts of interest / Competing interests

There must be clear definitions of conflicts of interest and processes for handling conflicts of interest of authors, reviewers, editors, journals and publishers, whether identified before or after publication

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Journals should include policies on data availability and encourage the use of reporting guidelines and registration of clinical trials and other study designs according to standard practice in their discipline

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- Letter from the COPE co-Chairs: July 2018 (News)
- In the News: July Digest (News)
- Creating and implementing data research policies: COPE webinar report (News)

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7. Intellectual property

All policies on intellectual property, including copyright and publishing licenses, should be clearly described. In addition, any costs associated with publishing should be obvious to authors and readers. Policies should be clear on what counts as prepublication that will preclude consideration. What constitutes plagiarism and redundant/overlapping publication should be specified

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A well-described and implemented infrastructure is essential, including the business model, policies, processes and software for efficient running of an editorially independent journal, as well as the efficient management and training of editorial boards and editorial and publishing staff

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9. Peer review processes

All peer review processes must be transparently described and well managed. Journals should provide training for editors and reviewers and have policies on diverse aspects of peer review, especially with respect to adoption of appropriate models of review and processes for handling conflicts of interest, appeals and disputes that may arise in peer review

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10. Post-publication discussions and corrections

Journals must allow debate post publication either on their site, through letters to the editor, or on an external moderated site, such as PubPeer. They must have mechanisms for correcting, revising or retracting articles after publication

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Joint statement on EPA proposed rule and public availability of data

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We are writing in response to a proposed rule announced by the Environmental Protection Agency (EPA) in a 24 April 2018 press release (*1*). The release reads, "The rule will ensure that the regulatory science underlying Agency actions is fully transparent, and that underlying scientific information is publicly available in a manner sufficient for independent validation."

Data sharing is a feature that contributes to the robustness of published scientific results. Many peer-reviewed scientific journals have recently adopted policies that support data sharing, consistent with the Transparency and Openness Promotion (TOP) standards. These standards, however, recognize the array of workflows across scientific fields and make the case for data sharing at different levels of stringency; in not every case can all data be fully shared. Exceptional circumstances, where data cannot be shared openly with all, include data sets featuring personal identifiers.

We support maintaining the rigor of research published in our journals and increasing transparency regarding the evidence on which conclusions are based. As part of these goals, we require that all data used in the analysis must be available to any researcher for purposes of reproducing or extending the analysis. Importantly, the merits of studies relying on data that cannot be made publicly available can still be judged. Reviewers can have confidential access to key data and as a core skill, scientists are trained in assessing research publications by judging the articulation and logic of the research design, the clarity of the description of the methods used for data collection and analysis, and appropriate citation of previous results.

It does not strengthen policies based on scientific evidence to limit the scientific evidence that can inform them; rather, it is paramount that the full suite of relevant science vetted through peer review, which includes ever more rigorous features, inform the landscape of decision making. Excluding relevant studies simply because they do not meet rigid transparency standards will adversely affect decision-making processes.

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1. U.S. Environmental Protection Agency, News Releases, "EPA Administrator Pruitt proposes rule to strengthen science used In EPA regulations" (2018); www.epa.gov/newsreleases/epa-administrator-pruitt-proposes-rule-strengthen-science-used-epa-regulations.

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Joint statement on EPA proposed rule and public availability of data

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