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On behalf of the Environmental Protection Network

I am Dr Bernard Goldstein. My background includes being appointed U.S. Environmental Protection Agency (EPA) Assistant Administrator for the Office of Research and Development (ORD) by President Reagan under the leadership of EPA Administrator Bill Ruckelshaus, serving as chair of the Clean Air Science Advisory Committee (CASAC) under Administrator Ann Gorsuch, and being an elected member of both the National Academy of Medicine and the American Society for Clinical Investigation.

I am here today as part of the Environmental Protection Network (EPN), an organization comprised of over 450 EPA alumni volunteering their time to protect the integrity of the EPA, human health and the environment, providing an informed and rigorous defense against current Administration efforts to undermine public health and environmental protections.

In my previous presentation to the Science Advisory Board (SAB) on June 5, 2019, I emphasized that it is highly inappropriate to advance a major new plan on how to utilize the scientific literature for regulatory purposes without asking advice from the SAB about the whole plan. Limiting the SAB to only help EPA get around an impediment to this ill-considered plan goes beyond being inappropriate. You were being treated as technicians who can fix a complex measuring device but have no say in how the device is used or how its findings are interpreted.

I will approach the primary topic of today's meeting on two levels. One is to discuss major practical problems that need more emphasis. I will follow this by expanding on some of the ethical issues I believe are likely to be central to the willingness and ability of scientists to share environmental health study information. Note that I start with the recognition that none of the proposed approaches under consideration inherently can guarantee no risk of release of personal information. For example, personal information from a seemingly fully protected study of Alaskan Native populations at risk from the Exxon Valdez oil spill was required to be released by the judge considering the resulting toxic tort suit.

Practical Problems

Let me raise some practical problems that, in part, have been touched upon by others. I will start by focusing on the industry response to a specific study performed by Zhang and her colleagues[1] that had much impact on the 2010 International Agency for Research on Cancer meeting in the majority vote in favor of formaldehyde as being a cause of human leukemia. For the record, I voted with the minority, as I believed that the Zhang et al. study required replication, by which I mean a different study on a different population – something that industry has refused to do. Although Zhang et al. have broadened their study and reported confirming their findings.

[1]Zhang L. et al (2010). Occupational exposure to formaldehyde, hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells. Cancer Epidemiol Biomarkers Prev. 19:80-88

Briefly, it is a cross-sectional study finding that workers in a Chinese factory which had significantly elevated formaldehyde levels had lower blood counts as compared to a similar factory population without formaldehyde exposure. They also found chromosomal findings in the formaldehyde-exposed workers consistent with leukemogenesis.

Industry was strongly advised to simply repeat the study in a different population. Instead they have spent far more money hiring consultants to perform studies to pick holes in the Zhang et al. study. These include procedural issues such as the number of metaphases that were counted – but that would not make a difference if those doing the counting were blind as to whether the source was from a formaldehyde-exposed worker or not. Eventually, through a FOIA request to the NCI, the formaldehyde industry was able to get the raw data on recent exposure levels. They claimed there was no relation between blood counts and the exposure levels.[2] This was touted by an American Chemical Society press release and said to show the importance of obtaining the raw data from investigators who allegedly hid confounding evidence. [3] But their claim was unjustified. An effect of a leukemogen on peripheral blood counts reflects damage to bone marrow stem cells occurring over the full time of exposure, which for each worker was at least one year. Without a Job Exposure Matrix, or some other way to estimate longer-term exposure, the correct approach was a cross-sectional design.[4]

In fact, the reanalysis by the consultants hired by the formaldehyde industry confirmed the low blood counts in the formaldehyde-exposed workforce – although they buried that part of the reanalysis in the supplemental findings only available online. (If you do follow up on the letter I wrote with my analysis and their response, please note that they are wrong when they state that I agreed with their concerns about the Zhang et al. chromosomal findings.)

The Zhang et al publication had 34 co-authors from 7 different institutions and 3 different countries (the US, China and the Netherlands). So let's start with the question of how would EPA get the raw data? Would the 34 different investigators need to give their permission? What if just one of the 34 decided that they did not want to make their raw data available to industry to continue the nit-picking defamation that has already been part of the formaldehyde story? Would only the IRBs in the one US institution (NCI) and the one Chinese institution (the Guangdong Poison Control Center) need to or want to do so?

Note that it is not unusual for the IRB of a US institution to defer to another institution's IRB, particularly one such as the NCI. But would they do so if the data might be pertinent to a regulation and could end up being used by anyone? After all, the possibility arises that this could lead to release of information about the participants, or just provide enough information so that hackers could now break through the veil of secrecy imparted by US rules. Note, of course, that these rules are different throughout the world. In Europe some of the rules are particularly stringent. While an IRB in the Netherlands University, with investigators involved in the study, may have been willing to defer to the NCI, would they do so if they believed that the data could be turned over to anyone in the public? Will they do so in the future? Not surprisingly, in view of the worldwide growth of environmental science, international studies with or without significant US collaboration are becoming an ever-increasing percentage of total environmental health research. Isn't one of the inevitable outcomes of EPA's proposal a cumbersome barrier to being able to put together a team of

[2]Mundt KA, et al. (2017). Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes? Crit. Rev. Toxicol. 47:592-602.

[3]https://www.americanchemistry.com/Media/PressReleasesTranscripts/ACC-news-releases/New-Study-Challenges-Formaldehyde-Cancer-Findings.html

[4]Goldstein, BD (2018) Mundt et al paper: "Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells. (Letter). *Crit Rev Toxicol 4*8:339-340

international investigators for studies of humans that are potentially relevant to EPA's environmental regulation?

Now let us assume that the raw data on the Zhang et al. study were not available via FOIA, and the proposed transparency rule were in existence. Why would the authors agree to have their data made available to EPA? So they could waste time from their careers battling industry-paid consultants? In particular, would the non-US authors agree?

Another practical problem has to do with an unforeseen threat. I previously pointed out that, to me, perhaps the most challenging part of being head of ORD was to try to anticipate the inevitable new potential environmental problem that no one had thought of. I presented a scenario to you in which peer-reviewed studies from different non-US countries had caused these countries to begin their regulatory processes and led to pressure from the US Congress and the public for EPA to respond. Would EPA require the raw data from foreign scientists not necessarily willing to share? Even if the Administrator made an exception, would that stand up to legal scrutiny if there were a negative study published by the industry, perhaps underpowered, which was willing to share its data? And, to further complicate the matter, what if EPA had recently recognized the potential problem and had competitively funded an American scientific group to begin its study, but they had yet to publishable results? Wouldn't these be the best scientists to give advice? But, of course, they would be barred to do so by this EPA's new rule forbidding those receiving EPA funding from any EPA advisory process. Note that for-profit consultants who might have done the industry study would not be barred.

I also have been involved in the analysis of the Deepwater Horizon disaster,[5] including service on a recent NRC committee evaluating the use of dispersants. Central to the difficulty in interpreting the risks to the cleanup workers is that while the spill began in April 2010, the NIEHS was not able to get into the field for its investigation of worker health until early 2011. A significant part of the delay was due to sorting out HIPAA issues, which hopefully will not occur in future disaster responses. Recall bias is a common problem in epidemiological studies of potential risk factors, a problem that is compounded by the length of time between the possible exposure and the epidemiological investigation. In my view this delay contributed to recall bias and added greatly to uncertainties as to the strength of the findings of NIEHS and Coast Guard investigators about the purported health effects. Will the possibility that investigators or IRBs disagree about whether their study would conform to EPA's new requirements contribute further to delays in the response of scientists to environmental disasters?

The Ethical Basis for the Oversight and Actions of Institutional Review Boards

Institutional Review Boards use of ethical concepts as a basis to decide on the appropriateness of human research studies has evolved through recent decades. These ethical constructs are central to decisions as to whether and how to perform research.

At the beginning of my academic career as a hematologist, I was peripherally involved in a study, approved by the then new NYU IRB, about whether the iron status of menstruating women, irrespective of their specific hemoglobin level, affected their exercise physiology. The makers of Geritol, an iron supplement, asked me to also do a separate study on whether their product actually increased hemoglobin levels, as they had never formally done such a study and were involved in a regulatory issue as to whether their advertising claims were excessive. The NYU IRB turned it down on the basis that the outcome was certain and therefore did not meet what is now known as the ethical criterion of "equipoise," also called the uncertainty

[5]Goldstein, B.D., Osofsky, H.J., & Lichtveld, M.Y. The Gulf oil spill. *New England Journal of Medicine*, 364(14):1334-1348

principle, which is often defined as requiring a state of genuine uncertainty.[6] The same presumably would be true today for an IRB faced with a proposal to study whether benzene causes leukemia. Any study of reasonable statistical power would be expected to find the well-known causative relation between benzene and leukemia, and an underpowered study could be considered to be unethical.

I believe that the equipoise issue might well be used by an IRB to refuse to allow investigators to hand over raw data to EPA. Although often controversial, many IRBs interpret their mandate as including whether the proposed study is scientifically valid. If not, there would then be no ethical basis on which to expose humans to any risk – including having their personal information at risk of disclosure. For example, the IRB might turn down a study that has too little statistical power to be likely to answer the question, such as studies that had previously been done with many pharmaceutical agents or with a small workforce exposed to a new chemical. They would also turn down a study that was inherently biased.

University IRB's do not necessarily allow investigators to automatically use data on subjects that have previously been gathered for one purpose to be used for a new purpose not part of the original protocol. But is sharing the raw data with the general public a new study, or simply part of the process of replication of existing data?

Based upon the principle of equipoise, the IRB would perhaps have two grounds to oppose turning over the data to EPA. One is the degree of certainty, based upon past behavior, as exemplified by formaldehyde, that the regulated industry would hire consultants whose future success depended on finding and exaggerating minor blemishes or potential confounding factors suggested by the raw data. Such confounders are inherent in any study that cannot be done in a random double-blind fashion – which is true for virtually all environmental health studies (see my previous June 5, 2019 SAB testimony; and let me emphasize that not all consultants are inherently biased). In other words, the already existing evidence that such disclosure leads to a biased study could be construed as grounds for the IRB to refuse permission. The second is that reanalysis of the same data does not constitute replication of an environmental health study, which is claimed to be the rationale for the study. In environmental health, replication is usually achieved by multiple studies by different investigators on different populations using different scientific approaches – not by recounting the same numbers. Equipoise is further unlikely to be achieved when it is only industry that can afford to hire scientific consultants to reanalyze data.

Although I am very familiar with IRBs as an investigator and as an institute director, department chair, and dean who has tangled with many an IRB, I do not consider myself an expert. But neither are you. There are experts who have studied the subject of the ethical issues involved and the decisions that can and are being made by IRBs around the US. These experts could and should be consulted in the appropriate open fashion, perhaps through the National Academy of Medicine or through a subcommittee appointed to advise the SAB. But once again, this EPA leadership has seen fit to rush headlong into making major changes without enlisting the help of scientific advisory processes that have characterized EPA's first 50 years. Please do not be complicit in their doing so.

Finally, at the last SAB meeting, I repeated a point I had made earlier that environmental health studies of humans almost never can consist of the double-blind studies required by the FDA, and so are inherently more subject to confounding. Administrator Wheeler followed my comments by demonstrating that he felt

[6]Freedman B. (1987) Equipoise and the ethics of clinical research. New Engl J Med 317:141-145. See also Djulbegovic et al (2000). The uncertainty principle and industry-sponsored research. Lancet 356:635-638, for an influential study that demonstrated the biases inherent in industry-sponsored pharmaceutical research

free to make a statement directly to the SAB at the June 5th meeting that shows his complete ignorance of the issue.[7]

> "FDA routinely uses the double-blind scientific studies for their work where they have two teams of researchers replicating the same data, both teams don't know each other exist and where they are."

He then added,

> "… federal research would be more accepted by the public if you used the double-blind standard for everything,"

Now, I am not playing "Gotcha." He is, of course, not a health scientist. But he is the head of EPA. He could have avoided making such an embarrassing mistake by simply asking any EPA health scientist, or health scientist members of SAB, or perhaps any of the many epidemiologists who were formerly part of CASAC's ozone and particulate subcommittees before these were abolished. But he did not. Whatever the reason, it demonstrates his repetitive failure to enlist the advice of knowledgeable scientists, advice called for by Congress and an integral part of the consensus approaches inherent in an effective and unbiased EPA science advisory process. It also emphasizes to the environmental health research community how foolish it would be to cooperate by releasing raw data to an organization that can be so politicized and so anti-science.

Let me conclude by thanking you for serving on the SAB and for your attention to my comments.

[7]Dr Bernard Goldstein. How EPA Administrator Wheeler Completely Misinterprets the Science. The Hill. June 20, 2019. https://thehill.com/opinion/energy-environment/449465-how-epa-administrator-wheeler-completely-misinterprets-science