SIDLEY AUSTIN LLP
SIDLEY

SIDLEY AUSTIN LLP
1501 K STREET, N.W.
WASHINGTON, D.C. 20005
(202) 736 8000
(202) 736 8711 FAX

Sender's Email
Sender's Direct Tel

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Comments for Workshop on "Improving the Use of Science in the Administrative Process."

These comments are submitted in response to the statement that the Workshop aims "to explore other ways to improve the use of science in the administrative process." The comments focus on issues that are germane to EPA's Integrated Risk Information System (IRIS) because that is the area in which I have had experience, but because they focus on problems with relying on the published scientific literature, they should be applicable to the administrative systems that rely wholly or in large part on published scientific literature as the basis for reaching their conclusions. Undoubtedly my training as a lawyer will be evident in the way I look at and approach these problems.

1. **Publication Bias.** In conducting a human health risk assessment under IRIS, EPA starts by conducting a literature search and assembling the scientific papers that report a chemical's effects on humans and relevant animal species. This appears to be a fair way to review the scientific understanding of the chemical's possible effects on humans and animals, but it fails to take account of publication bias. This well known phenomenon favors publication of studies showing "positive" results – an association between the chemical and a biological effect – over those that do not. In risk assessments, the determination of the dose at which there is no observable effect is very important. Reviewing only the published literature can be highly misleading on that central issue. "Because the results of research in this field [clinical trials] have been so consistent, it is probably safe to conclude that publication bias is real and widespread. … Conclusions about the efficacy and safety of medical intervention are based on data presented in the scientific literature. The validity of these conclusions is threatened if publication bias results from investigators or editors making decisions about publishing study results on the basis of the direction or strength of the study findings. … The results of clinical trials should not be suppressed in this way." Dickersin and Min, "Publication Bias: The Problem That Won't Go Away," 703 Annals of the New York Academy of Sciences 135, 143-145 (1993); see, e.g., Sena et al, "Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy," PLos Biol 8(3) e1000344 (2010) ("published results of interventions in animal models of stroke overstate their efficacy by around one third"). EPA needs to capture the results of research showing, at given doses, that a chemical has no effect on human or animal biological systems. Dickersin and Min urge the establishment of a government run registration system for studies that are not published in the scientific press. Requiring researchers who receive government financial support to report their unpublished results to the funding agency, and make them readily available to the public, would be a first step in this direction.

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2. **Multiple Comparisons.** A researcher on, say, the neurodevelopment effect of a chemical on children or rats can have the treated subjects perform 20 different tests; at a 95% confidence level, the researcher finds one association which is written up and published without reporting on other tests that did not show an association. Having made 20 comparisons at the 95% confidence level, at least one association is likely to be spurious – the result of random chance. But if one does not know how many tests or comparisons were made, there is no basis for making a fair judgment as to the strength or value to give to the reported positive result. There is no requirement in law or custom that directs researchers to report the number of comparisons they made, and publication bias discourages the ambitious academic from reporting a large number of comparisons which would result in sober analysts putting lesser weight on the positive results reported. EPA needs to know how many comparisons a researcher made and what the results were. This could be achieved in large measure by requiring that government-supported researchers report such data; in addition, EPA could, as a matter of routine, ask the researchers to provide this information before it relied on the published results in a weight-of-the-evidence review.

3. **Meta-Analysis.** In a weight of the evidence review, replication of results has great weight in persuading the reviewer that the results are sound; conversely, failure to replicate results detracts markedly from the weight that a study will be given. Being able to tell whether results are replicated or not replicated depends on having common metrics used in the studies; e.g., administering the same dose under the same conditions at the same age. This is very rarely done, thereby erecting barriers to accurate determination of the weight that should be given to experimental results. See e.g., Goodman et al, "Using Systematic Reviews and Meta-Analysis to Support Regulatory Decision Making for Neurotoxicants; Lessons Learned from a Case Study of PCBs," 118 Environmental Health Perspectives 728 (2010). Again the federal agencies that support research financially should require that experiments that closely resemble ones done in the past be conducted and reported with sufficient common metrics to allow effective meta-analysis. Of course, this would not preclude encouraging innovative approaches to measuring and reporting whatever else the authors or the funding agency choose to focus on.

4. **Review of data relied on in critical studies.** EPA typically relies on one or a few "critical studies" in performing its analysis and reaching conclusions as to the risks to human health that are presented by a chemical. EPA reviews the printed reports found in the peer reviewed journals carefully, but it very rarely asks to see the underlying data. To a lawyer, this seems perverse – a bias against examining the actual data that is said to support the Agency's conclusion. With no falsification, there are a number of ways to present data that will affect such data's ultimate implications. Statistical treatment is the most obvious example. Not surprisingly, in the one instance I am aware of where data was asked for it was statistical treatment that was focused on: "This peer review used a unique and novel approach to evaluate the validity of this very important and controversial environmental health issue. Fifteen principal investigators of primary research groups active in the this field were asked by the organizing committee to provide their individual animal data on selected parameters for independent statistical reanalysis by the statistics subpanel." Melnick et al., "Summary of the National Toxicology Program's Report of the Endocrine Disruptors Low-Dose Peer Review," 110 Environmental Health Perspective 427 (2002). This independent statistical review had significant consequences: "These analyses provide greater insight on the experimental data than is typically apparent in most peer-reviewed research articles; consequently, the statisticians' report was critical for each of the subpanel reviews." Ibid at 428. Human health risk assessments are of major importance to the public health and frequently result in many millions of dollars of expenditure by companies

guarding against the risks that EPA identifies. It is clearly important to make these judgments as accurate as possible. In these circumstances, at least for the critical studies, the Agency should routinely ask that the data underlying the printed article should be produced; EPA should then examine the data and the reported results should only be relied on where they are fully supported by the data.

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Angus Macbeth