ATTACHMENT 3

Comments Before the National Academy of Sciences
Committee on the Use of Third Party Toxicity Research
with Human Research Participants
(Project STLP-Q-02-02-A)

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One of the central objectives of the Center for Regulatory Effectiveness is to strive to improve the quality of data and analysis agencies use to make regulatory decisions. This NAS project deals fundamentally with whether EPA and other government agencies can and should reject data and study findings relevant to their regulatory decisionmaking.

The committee faces a somewhat difficult task in separating the wheat from the chaff in the project charge. Many of the individual charge questions simply do not have a rational basis and therefore are not capable of an analytical response. For example, there is the question of whether the acceptability of data should depend on the type of substance tested. The answer is obviously No. Another example is whether acceptability should depend on whether the data were submitted before or after an EPA policy announcement. Of course not. Many of the charge questions raise legal issues of compliance with the Administrative Procedure Act, because under the APA it is the responsibility of an agency to provide a reasoned basis for its rules. So, for many of the charge questions the relevant issue is simply whether the agency has articulated a rational and legitimate basis for being able to reject relevant data.

On this point it should be noted that to date EPA has expressed "concerns", and made reference to "complex issues", but it has not articulated a rational basis for those concerns or specified why it believes the issues are complex. Most of the charge questions involve ethical principles that have been settled for decades, and fundamental legal precepts under the new Data Quality legislation, the Administrative Procedure Act, and other relevant legislation.

The visual presentation materials relating to this text are attached (4 pages).

Ethics

Are there ethical issues? Not really. There are personal views held by some individuals or

organizations, but they are not consensus views and do not have a rational basis. Such views have been based largely on innuendo, insinuation, and inaccuracy. An example is the assertion that third-party research involving environmental contaminants is ethically indefensible.

The human volunteer research under consideration here is consistent with ethical norms that have been in place for decades. Since the Nuremberg Code in 1949 there have been only three fundamental ethical issues: (1) Was there free and informed consent?; (2) Was the experiment designed to serve a peaceful purpose useful to society?; and (3) Was risk to participants minimized and their health carefully monitored?

The Nuremberg Code required that the experiment be designed "to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature." Some have suggested that the Code required a therapeutic benefit to test subjects. There is no such indication in the Code, and in practice it has never been so interpreted. Nor does the Code speak to commercial or regulatory motives. If commercial motives were impermissible, we would not allow most clinical trials of pharmaceuticals or medical devices.

Likewise, neither the Declaration of Helsinki nor the Common Rule indicate disapproval of human studies that are not intended to produce therapeutic results, and they both explicitly indicate otherwise.

- The Declaration of Helsinki promulgated by the World Medical Association explicitly allows research on healthy volunteers and for the purpose of "understanding of the aetiology and pathogenesis of disease" in contrast to research on potentially therapeutic agents. (A.6, B.16, B.18, 2000.)

- The Common Rule does not restrict human research to research for therapeutic purposes or research which will benefit the volunteers; and it explicitly provides for research that will not confer benefits on subjects, and it defines research simply as "systematic investigation . . . designed to develop or contribute to generalizable knowledge." (26 CFR §§ 26.102(d), 26.111(b), EPA version.)

- Pursuant to the Common Rule, many federal agencies, including EPA, have conducted non-therapeutic research with human volunteers for purposes of understanding the uptake, absorption, metabolism, and biological or adverse effect thresholds of many environmental contaminants. They have also routinely considered and used such research conducted by third parties.

- Third-party research on environmental contaminants has been approved and conducted by highly reputable medical researchers and institutions in both the U.S. and abroad. In the U.S., such research has often been approved and overseen by IRBs certified by federal agencies. There is

no rationale for a double standard for federal agencies vs. non-federal parties.

It should be noted here that the federal government has a large inter-agency committee charged with developing policy on human subjects research. This is the Human Subjects Research Subcommittee ("HSRS"), which is under the Committee on Science of the National Science and Technology Council. (See http://ohrp.osophs.dhhs.gov.) The HSRS is chaired by HHS, which had the original legal responsibility for developing the regulations now known as the Common Rule, and virtually every federal agency is a member, including OSTP and OMB. Thus, it is particularly surprising that the only federal agency sponsoring and controlling this NAS study is EPA. In this connection, it should also be noted that it was reported in the press that an EPA policy similar to the one under review here (but never formally made public) was sent to OMB for review in early 2001, and was rejected and withdrawn due mainly to objections from other federal agencies.

Some have suggested that agencies should not consider or use third-party volunteer research for the purpose of determining a regulatory safety standard. This suggestion resolves into a kind of ethical Catch 22:

- As a matter of ethics, risk to study subjects should be minimized – preferably so subjects are not likely to experience significant adverse health effects.

- It should be considered unethical to design a human study so as to look for or determine a NOAEL.

Such a proposition is at odds with ethical norms. It is also inconsistent with the practice of government agencies in developing regulatory standards or guidance.

It must also be considered that in addition to the ethical considerations in protecting human study subjects, science has a broader set of ethics that more commonly comes under the rubric of scientific integrity. Such integrity demands the consideration and weighing of all significant relevant information. Federal agencies have therefore, in the past, always considered all of the available relevant data, including small observational epidemiologic studies and even case reports in addition to human volunteer studies.

The real ethics issue here appears to be simply confirmation of appropriate ethics oversight under existing norms.

The Law and Scientific and Regulatory Integrity

Society often expresses its ethical norms through the law, and there are a number of provisions of federal legislation, and case law, that address the need to consider all significant relevant scientific data.

The most recent of such provisions are in the Data Quality legislation and the OMB and EPA implementing guidelines, the origins of which go back to 1995. The Paperwork Reduction Act of 1995 contained provisions requiring OMB to issue regulations and guidance to all federal agencies for the purpose of ensuring and maximizing the quality of the information they disseminate. It also made it the responsibility of all federal agencies to comply with the OMB regulations and guidance and to issue their own conforming regulations and guidance. (44 U.S.C. §§ 3504, 3506, 3516). However, the 1995 legislation contained no deadlines for implementation of these mandates.

As of 1999, OMB had issued only extremely sparse guidance to agencies in a Circular (Circ. A-130), with little opportunity for public notice and comment, and federal agencies had not issued conforming regulations and guidance. Consequently, Congress, in sec. 515 of the Omnibus Appropriations Act for FY 2001, basically ordered OMB and the agencies to get on with implementing the mandates in the 1995 Act under specific timeframes. (P.L. 106-554, 44 U.S.C. § 316 note.)[1]

On September 28, 2001, OMB issued interim final data quality guidance to all federal agencies required by the 1995 and 2000 legislation. (66 FR 49718.) On January 3, 2002, OMB issued revised final guidance. (67 FR 369, republished with technical corrections 67 FR 8452.) The January 3, 2002 OMB guidance, which was issued after EPA's December 14, 2001 announcement of its "interim policy" on acceptability of third-party human volunteer studies, contained a new requirement: Agencies were required to "adopt or adapt" for health and safety risk assessments the principles enacted by Congress in 1996 for risk assessments under the Safe Drinking Water Act of 1996 ("SDWA"). (67 FR at 8458 1st col., 8460 2d col.) As set out in the OMB guidelines, the SDWA directed agencies to include in risk assessments supporting SDWA regulations "each significant uncertainty . . . and the studies that would assist in resolving the uncertainty" and "peer-reviewed studies known to the [agency] that support, are directly relevant to, or fail to support any estimate of [risk] effects and the methodology used to reconcile inconsistencies in the scientific data." Third-party human studies come within these new requirements.

On October 15, 2002, EPA issued its final agency-specific conforming data quality guidelines. 67 FR 63657. The EPA guidelines adopt the two SDWA requirements quoted above from the OMB guidelines. At p. 23. The EPA guidelines also state in two places that the agency's risk assessments will employ a weight-of-the-evidence approach that considers "all relevant information" and its quality. Pp. 21 and 26.

The OMB and EPA guidelines with their commitment to use all relevant data followed the December 14, 2001 EPA announcement that it would not use third-party human volunteer data until

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[1] The sec. 515 provisions mirrored recommendations contained in the House report for the previous fiscal year appropriations bill. H.R. Rep. 592, 105th Cong., 2d Sess. at 49-50. OMB had not complied with those recommendations.

following an NAS study and possible rulemaking by the Agency. The EPA announcement also specifically recognized that it might subsequently be "legally required" to use such data. Consequently, CRE filed, in May 2002, a petition under section 553 of the Administrative Procedure Act for recission of the EPA announcement and rule on the basis that under the Data Quality legislation and the OMB implementing rules consideration of such data was now "legally required" for all risk assessments. EPA has not yet responded to the CRE petition.

Of course, the statutory provisions of the Safe Drinking Water Act of 1996 which were imported into the data quality guidelines apply to any EPA risk assessment that is to be used in setting drinking water standards. It would be odd if different standards for acceptance and use of scientific data applied to drinking water regulations but not to other environmental regulations.

As noted during the December meeting by Mr. Abramson, FIFRA provisions indicate clearly that Congress considered use of human volunteer test data to be acceptable for FIFRA decisionmaking, since it specified the terms under which it could be used (fully informed and free consent). 7 U.S.C. § 136j(a)(2)(P).

The Food Quality Protection Act of 1996 specifically requires EPA to consider "the available data from studies" in setting pesticide residue tolerances, and also "available information concerning the relationship of the results of such studies to human risk . . . ." 21 U.S.C. § 346a(2)(D). Third-party human volunteer studies certainly come within these requirements.

Executive Order 12866, promulgated in 1993, although not judicially enforceable, contains administrative mandates to be followed by all federal agencies in making regulatory decisions. It requires that all federal agency regulatory decisions be based on "the best reasonably obtainable scientific . . . information." Sec. 1(b)(7), 58 FR 51735, Oct. 4, 1993.

More generally, the Administrative Procedure Act ("APA") and its judicial interpretations require agencies to consider all significant relevant data in order to avoid rulemaking which is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706. Agencies simply cannot ignore significant relevant data in developing rules.[2]

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[2] *Simpson v. Young*, 854 F.2d 1429, 1434 (D.C. Cir. 1988); *Int'l Ladies Garment Workers Union v. Donovan*, 722 F.2d 795, 814 (D.C. Cir. 1983), *cert. denied*, 469 U.S. 820 (1984); *County of Suffolk v. Secretary of the Interior*, 562 F.2d 1368 (2d Cir. 1977), *cert. denied*, 434 U.S. 1064 (1978); *Consumers Union of United States, Inc. v. Consumer Product Safety Commission*, 491 F.2d 810, 812 (2d Cir. 1974); *Crutchfield v. U. S. Army Corps of Engineers*, 214 F.Supp. 593, 620 (E.D. Va. 2002).

Although EPA titled its moratorium on consideration and use of third-party human volunteer test data a "policy" in its December 14, 2001 announcement, a statement of general agency policy is a "rule"

Additionally, the APA and its judicial interpretations require as a basic principle that an agency articulate a reasoned basis for a rule in order to avoid its being found arbitrary, capricious, or an abuse of discretion. Moreover, when an agency establishes a new policy and rule that is a departure from a previously well-established policy or practice, it must articulate a cogent basis for changing its position. It is notable that EPA has not articulated any reasoned basis for its current ban on third-party human test data, which is a change from its prior well-established practice; instead, the current policy appears to have been driven by PR campaigns organized by entities who feel that consideration of human research might sometimes result in less stringent regulatory standards.

Thank you. Does the Committee have any questions or requests for further information or supporting documentation or citations?

Attachments

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under the definitions in the APA. 5 U.S.C. § 551.

All of the ethical guidelines and rules noted previously are aimed at the persons or entities who conduct or sponsor human volunteer studies; they do not contain any legal authority for a U.S. federal agency to reject relevant data. It is not clear where EPA would derive any general authority to reject data relevant to a rulemaking, authority to promulgate a rule allowing it to reject such data, or even authority to promulgate rules governing the ethical conduct of third parties. Congress gave legal authority to HHS to enact the original version of what has now become the "Common Rule", but that authority applied only to testing sponsored by HHS. The only authority that Congress has given to EPA for rejection of relevant human volunteer data submitted by third parties is contained in FIFRA, and is limited to rejection on grounds of failure to ensure free and fully informed consent.