

August 29, 2005

MEMORANDUM TO THE FILE

SUBJECT: Consistency of EPA's Proposed Human Studies Rule with the Nuremberg Code

On August 2, 2005, the President signed into law the Department of Interior, Environment, and Related Agencies Appropriations Act, 2006, Pub. L. No. 109-54 (Appropriations Act), which provides appropriated funds for the Environmental Protection Agency and other Federal departments and agencies. Section 201 of the Appropriations Act addresses EPA activities regarding intentional dosing human toxicity studies for pesticides as follows:

None of the funds made available by this Act may be used by the Administrator of the Environmental Protection Agency to accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject. The Administrator shall allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule. Such rule shall not permit the use of pregnant women, infants or children as subjects; shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation; and shall establish an independent Human Subjects Review Board. The final rule shall be issued no later than 180 days after enactment of this Act.

This memorandum discusses the basis for EPA's conclusion that its proposed rule, Protections for Subjects in Human Research, is consistent with the principles of the Nuremberg Code. After quoting each of the ten principles in the Code (in italics), the Agency sets forth its analysis of how the proposed rule is consistent with the principle.

Permissible Medical Experiments

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study.

EPA ANALYSIS:

Although this introductory material does not express a "principle," it does reflect a viewpoint with which EPA agrees—that it is possible to conduct some types of research with

humans ethically, and that when research is ethically conducted it may contribute valuable information for the good of society that is unprocurable by other means.

All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

EPA ANALYSIS:

EPA's proposal would extend the requirements of the Common Rule to covered research; these requirements include an obligation on researchers to obtain fully voluntary and fully informed consent from subjects. The Common Rule addresses issues relating to legal capacity to consent, voluntariness, the range of information sufficient to make consent "informed," and who has responsibility for obtaining such voluntary consent. See 40 CFR §26.116.

Where the Nuremberg Code calls for explaining the "nature, duration, and purpose of the experiment" the Common Rule at 40 CFR §26.116(a)(1) requires "[a] statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental." Where the Nuremberg Code calls for explaining "all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment" the Common Rule at 40 CFR §26.116(a)(2) requires "[a] description of any reasonably foreseeable risks or discomforts to the subject." EPA believes that these requirements are consistent with principle # 1 of the Nuremberg Code.

2. The experiment should be such as to yield fruitful results for the good of

society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

EPA ANALYSIS:

The Common Rule at 40 CFR §26.111(a)(2) provides that an Institutional Review Board (IRB) shall not approve proposed research unless “Risks to subjects are reasonable in relation to anticipated benefits.” As the National Academy of Sciences’ 2004 report makes clear, the benefits to be considered by an IRB (and also by EPA during protocol review under proposed 40 CFR §26.124(b)) include results that benefit society at large, as well as benefits (if any) to the individual test subjects. See generally, NAS report, chapter 4. EPA will approve proposals for research with human subjects and accept reports of such research only if it determines that the research either is likely to yield—or, in the case of reports, has yielded—fruitful results for the good of society. The proposed rule is thus consistent with principle # 2 of the Nuremberg Code.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.

EPA ANALYSIS:

While Common Rule requirements do not directly address principle # 3, the protocol review process which would be established by proposed 40 CFR §26.124(b) includes review of research proposals by both EPA and an independent Human Studies Review Board (HSRB). In this review both EPA and the HSRB would have access to all available laboratory animal studies on the potential toxicity of the pesticide, since such information is required to be submitted to the Agency in support of regulatory actions affecting pesticides. See e.g., FIFRA sections 3(c)(5) and 6(a)(2). EPA and the HSRB would then consider these data in determining whether the proposed research met the requirement in the Common Rule to minimize risks to subjects and whether the proposed design was scientifically sound and justified by the anticipated results.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

EPA ANALYSIS:

The Common Rule at 40 CFR §26.111(a)(1) provides that an IRB shall not approve proposed research unless “risks to subjects are minimized.” The proposed rule is thus consistent with principle # 4 of the Nuremberg Code.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

EPA ANALYSIS:

While the Common Rule has no provision corresponding exactly to this prohibition of research which is likely to lead to death or disabling injury, such a prohibition is implicit in two of the provisions of the Common Rule. These provisions state that an IRB shall not approve proposed research unless “risks to subjects are minimized” and “risks to subjects are reasonable in relation to anticipated benefits.” See 40 CFR §§ 26.111(a)(1) and (a)(2). EPA cannot conceive of any societal benefit which could justify undertaking research with pesticides when there was an *a priori* reason to believe death or disability would result. EPA would not approve research involving such risks under any circumstances. The proposed rule is thus consistent with principle # 5 of the Nuremberg Code.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

EPA ANALYSIS:

The Common Rule at 40 CFR §26.111(a)(2) provides that an IRB shall not approve proposed research unless “Risks to subjects are reasonable in relation to anticipated benefits.” As the NAS report makes clear, the benefits to be considered by an IRB (and also by EPA during protocol review under proposed 40 CFR §26.124(b)) include results that benefit society, as well as benefits to individual test subjects. See generally, NAS report, chapter 4. EPA considers the phrase “the humanitarian importance of the problem to be solved by the experiment” in Nuremberg principle # 6 to be equivalent to the phrase “for the good of society” in Nuremberg principle #2, and regards the Common Rule requirement to consider “anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result” as capturing the intent of both phrases.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

EPA ANALYSIS:

This principle is reflected in both the requirements of 40 CFR §26.111(a)(2), quoted above, and 40 CFR §26.111(a)(6), which provides that an IRB shall not approve proposed research unless it includes “adequate provision for monitoring the data collected to ensure the safety of subjects.” Thus, the IRB (and both EPA and the HSRB, when they review proposals for research with human subjects) will not approve the proposed research design unless it would ensure appropriate medical oversight of the research, include “stopping rules” to ensure the safety of subjects, and collect information needed for an investigator to determine that test subjects were experiencing unanticipated adverse effects that might indicate potential for more serious harm.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

EPA ANALYSIS:

The discussion above concerning principle # 7 also applies to principle # 8. During the course of review of proposals for research with human subjects, established by proposed 40 CFR §26.124(b), EPA and the HSRB will evaluate the qualifications of the researchers who will conduct the proposed research to ensure that they are competent to carry out the study in a manner that will adequately protect the test subjects.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

EPA ANALYSIS:

The Common Rule at 40 CFR §26.116(a)(8) requires that the informed consent materials provided to test subjects contain “a statement that participation is voluntary, refusal to participate will involve no penalty, or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time” The proposed rule is thus consistent with principle # 9 of the Nuremberg Code.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

EPA ANALYSIS:

The discussion above concerning principle # 7 also applies to principle # 10. During the course of review of proposals for research with human subjects, established by proposed 40 CFR §26.124(b), EPA and the HSRB will evaluate the adequacy of proposed “stopping rules” that would govern when to terminate the research because of risks to test subjects. EPA would not approve any research unless it contained safeguards sufficient to ensure that the experiment did not cause injury, disability or death.

In summary, after careful consideration of each of the ten principles in the Nuremberg Code, EPA concludes that, if adopted in a final rule, the provisions contained in its proposal, “Protections for Subjects in Human Research,” would satisfy the mandate in the Agency’s 2006 Appropriations Act to promulgate a regulation “consistent with . . . the principles of the Nuremberg Code with respect to human experimentation.”