

protect the general public? Should the same standard apply if intentional exposure to an environmental pollutant occurs at ambient levels, or at elevated levels? If research involves intentional exposure to a pesticide, does it matter if exposure results from use of the pesticide in conformity with approved label directions?

c. Should the Agency apply the same standard of acceptability independent of the pathway of exposure? For example, should the same standard apply when exposure is oral, or dermal, or by inhalation?

d. Should the Agency apply the same standard of acceptability independent of the effects being evaluated? For example, should the same standard apply to a study measuring transitory changes in blood chemistry or levels of a substance in urine that applies to studies measuring longer-lasting changes? Should the same standard apply to a study of localized skin irritation that applies to a study of systemic dermal toxicity? Should the same standard apply to studies measuring organoleptic effects, such as taste or smell, that applies to studies of toxic effects? Should the same standard apply to measurements of toxic effects and to measurements through genomic or proteomic assessments?

e. Should conduct of research in compliance with the provisions of the Common Rule or another standard for the protection of human subjects be accepted as evidence of its ethical acceptability?

f. Should the Agency consider whether research has been performed consistent with an EPA guideline for data development in determining its acceptability? For example, EPA has published guidelines for certain kinds of human studies required for pesticide registration; should conduct of a required study in compliance with an EPA guideline be accepted as evidence of its acceptability?

g. Should the Agency apply the same standard of acceptability independent of a study's statistical power?

h. Should the Agency apply the same standard of acceptability whether or not a human study design is able to measure the same endpoints in humans that have been observed in animal testing of the same substance? For example, if the most sensitive adverse effects shown in animal studies have been detected through histopathological evaluation of brain tissue, is subsequent research involving intentional exposure of human subjects acceptable?

i. Should the Agency apply the same standard of acceptability to intentional dosing studies independent of whether

there are alternative methods of obtaining data of comparable scientific merit that would not require deliberate exposure of humans? If not, to what extent, if any, should the cost of the alternate method be a factor?

j. What special considerations, if any, should the Agency apply in judging the acceptability of studies when some or all of the subjects are from populations likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons?

3. *Should the standard of acceptability vary depending on the provenance of the research?*—a. Should the Agency apply the same standard of acceptability without regard to who or what organization sponsors or supports the research? Since 1991, human research conducted or supported by the U.S. government has been subject to the Common Rule. Should the same standard apply to research conducted or supported by others? Should a single standard apply independent of whether the sponsor is a commercial enterprise, a non-profit organization, another government in the United States (such as state, tribal, or local), or the government in another country? Should the same standard apply without regard to the test sponsor's interest in a regulatory matter that could be affected by EPA's consideration of the data?

b. Should the Agency apply the same standard of acceptability independent of who or what organization conducts the research? For example, a research organization--public or private--holding a "Federal-Wide Assurance" from the Department of Health and Human Services's Office of Human Research Protections usually promises to comply with the Common Rule in all its human research. Should third-party work conducted by a research organization holding a Federal-Wide Assurance be assessed by the same standard that applies to other third-party human research?

c. Should the Agency apply the same standard of acceptability without regard to where the research was conducted? For example, does it matter whether research is conducted entirely in the United States or partially in the United States? If it is conducted outside the United States, does it matter in what country it is conducted? What are the advantages and disadvantages of judging the acceptability of human studies based on a single uniform standard versus prevailing local standards (e.g., in different countries)?

d. Should the Agency apply the same standard of acceptability without regard

to the reasons the research was conducted? If not, how might the Agency determine intent?

e. Should the Agency apply the same standard of acceptability to submitted research without regard to who submitted it? For example, should the same standard apply to submissions from regulated industry, from public interest groups, from the public, or from other governments? Should the Agency apply the same standard of acceptability independent of whether the study was submitted voluntarily, or in response to a particular regulatory requirement of EPA?

f. Should the Agency apply the same standard of acceptability to human research which is not submitted, but which the Agency obtains at its own initiative from the scientific literature or other sources, independent of how or where EPA obtains it?

4. *Should the standard of acceptability vary depending on EPA's potential use of the data?*—a. Should the Agency apply the same standard of acceptability independent of whether the results of the study would support a more or less stringent regulatory position? For example, should the same standard apply whether the data indicate that the substance tested is more risky or less risky than is indicated by other available data?

b. Should the Agency apply the same standard of acceptability without regard to how EPA intends to use the results, e.g., to reduce or remove the traditional tenfold interspecies uncertainty factor, to provide an endpoint for use in calculating a Reference Dose or Reference Concentration for the test substance, to provide a dose-response function for use in quantitative risk assessment, or for some other purpose?

5. *Should the standard of acceptability vary depending on EPA's assessment of the risks and benefits of the research to the subjects or to society?*—a. Should the Agency apply a standard of acceptability based on a comparison of the anticipated benefits of the research in relation to the risks to human subjects, provided the risks are minimized and informed consent is obtained?

b. Should the Agency independently assess the risks of the research to the subjects and the benefits of the research to the research subjects or to society, or should it defer to the judgment of Institutional Review Boards or similar oversight panels?

c. If EPA were to assess independently the risks and benefits of human research, on what range of information should it base its assessment? How might EPA obtain