Pesticide Testing on Human Subjects

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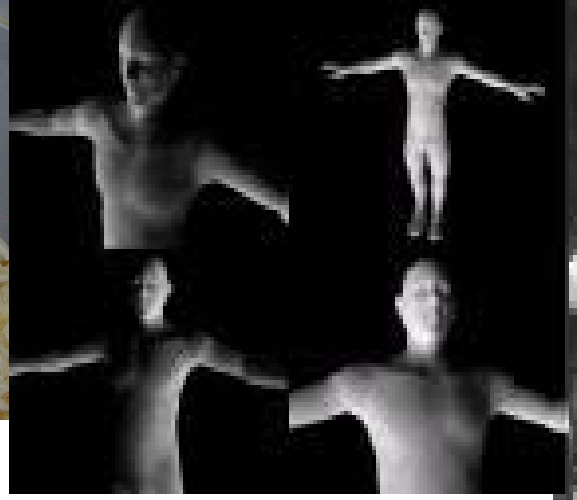
Bioethics

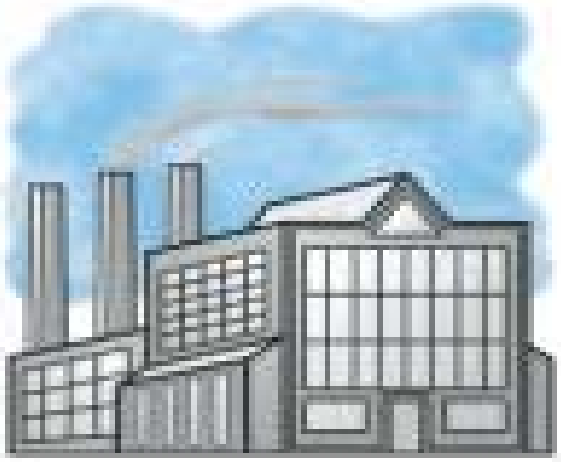
The ideas and opinions expressed in this lecture do not represent the views of the NIEHS, NIH, or federal government.

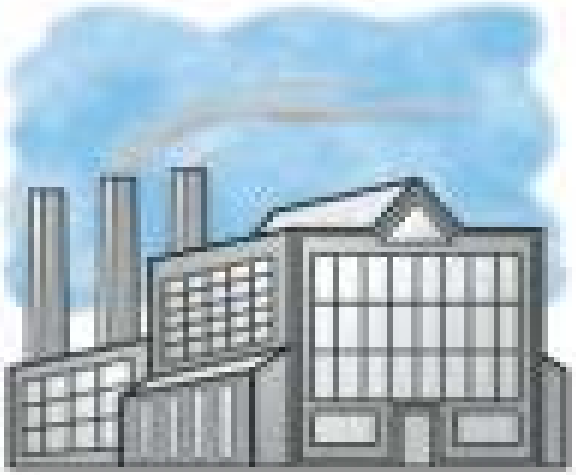
Background

- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) give the Environmental Protection Agency (EPA) the authority to control pesticide distribution, sale, and use.
- The EPA can study the consequences of pesticide usage and require users (farmers, utility companies, and others) to register when purchasing pesticides.
- All pesticides used in the U.S. must be registered (licensed) by EPA. Registration assures that pesticides will be properly labeled and that if in accordance with specifications, will not cause unreasonable harm to the environment (i.e. human health via exposure to pesticide residue on food).


- Manufacturers present the EPA with data concerning the safety of pesticides during the registration process.
- Manufacturers provide evidence concerning the no adverse effect level (NOAEL) level in rodents.
- The acceptable human exposure is derived by dividing the NOAEL dose by ten 3 times (3 safety factors): human-animal safety factor; human variation safety factor, and added in 1996, adult-child safety factor.
- The human exposure is supposed to be no more than 1/1000th the NOAEL dose.





- Prior to 1996, there were only 2 safety factors of ten.
- The Food Quality Protection Act (1996) added a third safety factor to provide extra protection for children.
- In response to the passage of this act, some pesticide companies started conducted pesticide exposure studies on human subjects, to provide evidence for lowering the human-animal safety factor.
- The economic motive for this research was to allow the companies to continue selling their products, since some pesticides may not be effective at the levels required by the FQPA.

Background

- In 1998, The Environmental Working Group (EWG) did an exposé on these studies, charging that they were unethical and poorly designed. Problems: health risks, lack of careful monitoring, potential coercion, small sample size.
- Some experiments included: oral administration of dichlorvos to 53 subjects, administration of orange juice laced with aldicard to 47 subjects.
- The media reported other pesticide experiments including managers for Novartis ingested diazinon, and a study sponsored by Dow AgroSciences, in which dozens of college-age volunteers were paid $460 to swallow a pill containing chlorpyrifos, a roach poison.

Background

- In 1998, the EPA decided that it would not accept third party data from human dosing studies. Before 1998, the EPA had accepted 3rd party data on a case-by-case basis, The consequence is that the agency's previous practice of considering third-party human studies on a case- by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide. But the EPA had no formally adopted the Common Rule for 3rd party dosing studies.
- In 2001, the EPA asked the National Research Council (NRC) to study the issue and stated that it would not consider third party data until the NRC had completed its report.

Background

- **<u>Croplife America vs. EPA</u> (U.S. Fed. Ct. App. Dist. Columbia, 2003). Several agricultural organizations sue the EPA, claiming that it engaged in inappropriate rule-making and must issue a rule with appropriate procedures (notice, public comment, etc.)**
- **The Federal Court ordered the EPA to engage in appropriate rule making. The previous case-by-case policy would remain in effect until a new policy is issued.**

Background

- 2004. The NRC issues its report. It says that some types of 3rd party dosing studies can be conducted, provided that they meet stringent scientific and ethical standards.
- The NRC recommends that the EPA adopt the Common Rule for 3rd party data and establish a committee to review third party studies prior to IRB review.

Background

- 2004. The EPA went ahead the formal rule making procedure. It gave notice of a rule consistent with the mandate by the federal court (case-by-case basis with the Common Rule as a guide).
- July 2005. EPA proposes adopting the Common Rule and subparts protecting children, pregnant women, and fetuses for third party research. The EPA decides to defer adoption of the subpart protecting prisoners because 1) this subpart is problematic and is being revised and 2) third parties have not tested pesticides on prisoners since 1978. It also proposes that all 3rd party studies be submitted to the EPA for review after IRB review.

Background

- September 2005. EPA modifies the proposed rule.
- Common Rule adopted for all EPA research (1st, 2nd or 3rd party) on dosing studies involving environmental substances (not just pesticides). What is an environmental substance? Oxygen, water, pollen, mosquito repellant, food?
- Prohibits dosing studies on children, pregnant women, or prisoners.
- This is stronger than the subparts B, C, D of the Common Rule, which would allow some dosing experiments on children, pregnant women, or prisoners.

Background

- Children's Environmental Exposure Research Study (CHEERS). EPA-sponsored, with collaboration from Duval County, Florida Health Dept (Jacksonville) and CDC.
- Field monitoring study of the effects of pesticides (and other chemicals) on young children in the home environment.
- Plans to recruit 60 young children with high pesticide use in the home. A control group of low pesticide use would also be recruited.
- Parents would not be required to begin using pesticides or continue using pesticides. It was not an intentional dosing study. In fact, the EPA would carefully screen participants to make sure that they were already using pesticides (if in that group).

Background

- Even though it was not an intentional dosing study, it was portrayed as such by the media.
- Soon reporters and blogs were describing it as an experiment in which parents would be paid to expose their children to pesticides. No one bothered to check the original stories for accuracy. The EPA did not respond effectively to these charges.
- Extensive study procedures: interviews, taking collecting samples around the home and taking blood and urine samples. Parents were required to videotape their children's activities and keep a pesticide purchasing and food journals.
- 5 home visits over a two-year period.
- Parents would be warned of any unsafe pesticide levels in blood or urine or unsafe pesticide practice.

Background

- Parents would be paid $970 to complete all of the activities and receive a video camera, t-shirts and mugs.
- Approved by 5 different IRBs.
- The American Chemistry Council (ACC) would pay $2 million to help support the study.

Background

- **Environmental and Children's Health groups protested the CHEERS study.**
- **CHEERS became a political cause and symbol of the Bush Administration's environmental policies.**
- **Congressional hearing were held, led by Sen. Barbara Boxer (D-Cal).**
- **CHEERS researchers were compared to the Nazis.**
- **Boxer and others threatened to stop the nomination of Steve Johnson as the new EPA director if he did not stop the CHEERS study.**
- **Johnson cancelled the study on April 9, 2005.**

Background

- Boxer also proposed an amendment to *Interior-Environment Appropriations bill (P.L. 109-54)* that would place a one-year moratorium on the EPA funding human pesticide dosing studies or considering on 3rd party human dosing data. The amendment would also ban intentional dosing studies on children, infants, or pregnant women, and require the EPA to follow guidance from the Nuremburg Code and the National Academy of Sciences, and establish an independent review board to review intentional dosing studies.
- The amendment passed.

Ethical Issues

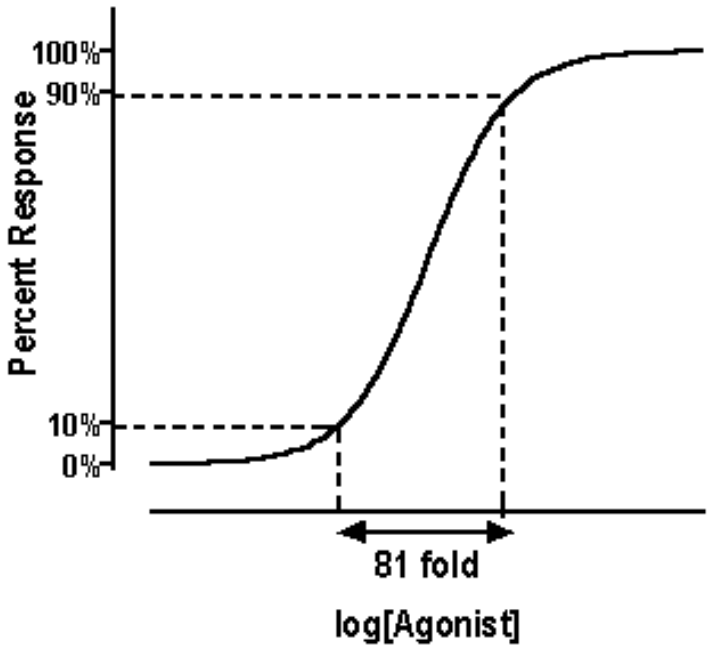
Benefit/risk.

- Risks of intentional dosing studies, if done properly (i.e. careful subjection selection and clinical monitoring), are much lower than Phase I drug studies on healthy subjects.
- Intentional dosing studies escalate the dose until an adverse effect is observed, such as presence of a metabolite in the blood or urine or symptoms, such as dizziness or nausea.
- Pharmacokinetic studies (absorption, metabolism, elimination)
- Pharmacodynamic studies (how the drug affects the body)

Ethical Issues

Benefit/risk.

- Phase I drug studies on healthy subjects escalate the dose until an maximum tolerable dose (MTD) is observed, such as liver or kidney toxicity, neurological effects, changes in blood pressure or heart rate, intolerable symptoms.
- The goal is to find a safe dose.
- Objection: so the studies are safer than Phase I drug studies, but we're not talking about approving a new drug, which can benefit patients and society. Pesticide studies only benefit industry!?



Ethical Issues

Benefit/risk.

- The studies may benefit society as well.
- Better knowledge of how pesticides affect people can lead to better regulation of pesticides, which can improve public health.
- Can help the EPA establish safe levels of pesticide exposure.
- Industry is hoping that the studies will provide evidence for increasing allowable exposures, but the studies might support the opposite conclusion. The studies could lead to tougher regulation of pesticides.

Ethical Issues

Benefit/risk.

- Studies could improve public health by enhancing our general understanding of how pesticides affect people. Animal studies offer useful data, but they can only go so far.
- Knowledge from human studies can be useful in the development of better animal models. It is important to be able compare animal and human responses to find the best animal for modeling human toxicity and pathology. Better animal models can improve public health.

Ethical Issues

Benefit/risk

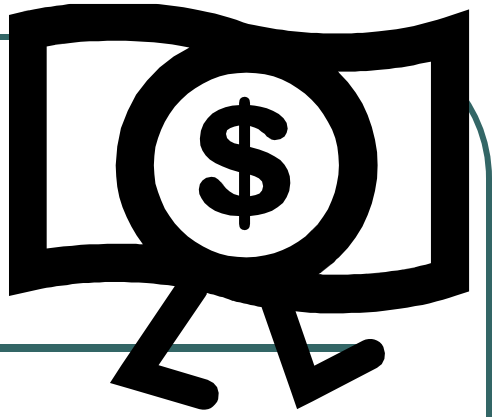
- If the studies are not scientifically necessary, then they are of questionable benefit. One might argue that the public health benefits could be obtained through animal experiments, epidemiological studies, or observational (field studies).
- Reply: yes, these other studies can be very useful, but they have limitations, due mostly to lack of control of variables. Dosing studies are controlled experiments.
- For example, a farm worker may be exposed to many different chemicals at unknown dosages. There may also be variations in heat, diet, exercise, smoking, etc.

Ethical Issues

Informed Consent

- In some of the 3rd party studies, the subjects were employees of the company sponsoring the experiment.
- Coercion would be a significant problem in studies like these.
- In the CHEERS study, critics argued that the $970 + other benefits constituted coercion or undue influence, especially since many of the families would be economically disadvantaged.
- $970 sounds like a lot of money, but it may have worked out to a pay rate of about $20 to $40 per day. All 5 IRBs said this amount was not excessive.

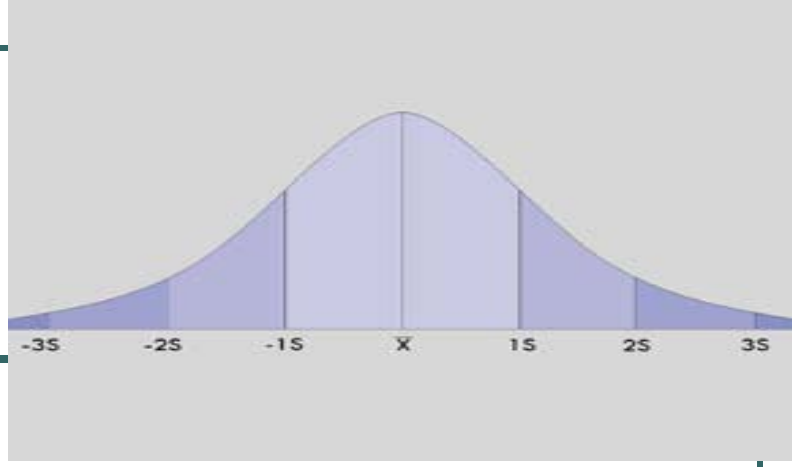
Ethical Issues



Conflict of interest (COI)

- The sponsors will find ways of biasing the studies to promote their own interests and short-change the public.
- Reply: steps can be taken to prevent bias, such as independent design and monitoring of studies, independent analysis of data, and no restrictions on publication. Companies should not be allowed to skew the data or suppress unwanted results.
- One can learn from COIs in the testing of new drugs.
- COI was a major concern in the CHEERS study.
- However, the ACC would not have been significantly involved in the design of the study, interpretation of the data, or dissemination of results.
- Nevertheless, the appearance of a COI was a cause for concern.

Ethical Issues



Study design.

- Some of the studies submitted to the EPA by industry may have been statistically underpowered (sample size too small).
- Any studies should have the appropriate sample size (not too large or too small).
- Too large (unnecessary exposure to risk); too small (may not produce statistically significant results).
- Question: can we learn anything useful from small samples? Maybe.

Ethical Issues

Vulnerable populations.

- The EPA has proposed that it might accept data on intentional dosing studies involving children, pregnant women, or fetuses.
- Would such studies ever be ethical?
- Key issue: risk. If the studies are minimal risk, they would be ok.
- More than minimal risk, they are more difficult to justify and might not be allowable under the Common Rule subparts.
- **45 CFR 46.406 §46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.**
- **HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:**

Ethical Issues

Vulnerable populations.

- **(a) The risk represents a minor increase over minimal risk;**
- **(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;**
- **(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and**
- **(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.**

Ethical Issues

Vulnerable populations.

- CHEERS was classified as minimal risk because it was not viewed as an intentional dosing study.
- The risks were the risks of data collecting procedures, not the risks of exposure to pesticides in the home.
- Would exposure to pesticides in the home be a minimal risk?
- It might be if one use the relativistic interpretation of the daily life definition of minimal risk, since children living in homes where pesticide use is high might ordinarily encounter exposure to pesticides during the daily life.
- Problem: this interpretation would take advantage of the fact that these children normally face risks higher than other children face.

Ethical Issues

Community Involvement

- The CHEERS researchers worked with the public health department, local government, clinics, hospitals and others with community connections.
- The Jacksonville area was supportive of the study.
- Opposition came from outside, especially environmental groups and others interested in making a political issue out of the study.

Ethical Issues

Community Involvement

- Could community involvement have been better?
- The community members have helped with designing and publicizing the study to avoid even the appearance of intentional dosing.
- The community could have provided information on the appropriateness of the economic incentives.

Conclusion

- Pesticide research of any kind will always be controversial due to the controversies surrounding pesticide use.
- Some groups and people will always oppose studies that could benefit pesticide companies.
- But some studies might have significant public health benefits.
- Understanding how pesticides affect children is a very important problem.
- All types of studies should adhere to the highest scientific and ethical standards, including the Common Rule.
- Effective communication with the media and the public is crucial, to avoid misinterpretations like those found in the CHEERS study.