

# Why Animal Experiments Fail in Birth Defect Research

PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

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## INHERENT PROBLEMS

I. There are inherent problems with animal experiments in defining and solving the problem of birth defects:

A. "Karnofsky's law" is frequently stated in developmental teratology. This law holds that everything is teratogenic if given in the right dose to the right species at the right time. It follows that because all agents have the potential for toxicity in some organism at some dose, the production of positive results in developmental toxicity studies is only a matter of finding a sensitive state in a sensitive species and of using an adequately high dose of the toxicant.<sup>1</sup>

B. There are many sources of error in using animal tests to predict teratogenicity:

1. Species differences:

It is almost invariable to see rats and rabbits used as the test animal, although mice may be used in place of rats. The choice of rats and rabbits as the primary testing species is not because they are considered to be so similar to humans, but because they are easy to handle and because their use has generated an enormous, although not necessarily correct, database.<sup>1</sup>

Species differences in animal tests for causes of birth defects are present for many reasons:

- a. Differences in genotype from one species to another and even one strain to another can affect susceptibility to teratogens.<sup>1</sup>
- b. Different species develop at different rates and along different schedules. These differences can affect the interpretation of animal data because chemicals appear to exert their effect on the fetus at different stages of development.<sup>1</sup>
- c. Humans may be more sensitive than other animals because of the longer period of human development.<sup>1</sup>
- d. Species-specific differences in the placenta may affect the results of animal tests.<sup>2</sup>

2. The route of administration to the animal may not be the likely human route. It is not unusual to see

drugs given to animals in teratogenicity tests intraperitoneally, intravenously, or via gastric tubes.<sup>1</sup> Studies in which solvents whose usual source of human exposure is through inhalation or dermal absorption, may be given to animals intravenously or via gastric tubes.<sup>3</sup>

3. The dosing schedule in animals may not mimic the schedule in humans. Although animals are usually given the chemical once a day, daily dosing is unusual for human exposure, either therapeutic or environmental, and results from this bolus dosing may be misleading.<sup>1</sup> For example, some agents are teratogenic only if the peak concentration reached in fetal tissues exceeds a threshold level, even briefly. For others, prolonged exposure at lower doses may be more predictive of toxic sequelae.

4. One of the doses usually used in animal tests is that which produces some toxicity in the mother, however, this may not be applicable to the human situation where the same maternal effect may not be observed.<sup>1</sup>

5. Routine animal handling itself may cause developmental effects. Stress imposed by food or water deprivation or by restraint has adverse effects on pregnancy outcome.<sup>1</sup>

6. Animal studies may not be sufficiently sensitive to detect subtle developmental toxicity such as learning or behavioral problems, occurring at low dose exposures.<sup>1</sup>

C. Studies have been done to predict the reliability of animal data:

In a now classic review on the use of animal teratogenicity testing, Brown and Fabro summarized information collected by the FDA and the Council on Environmental Quality. In identifying human teratogens, mice tests were correct in 85%, rat tests in 80%, rabbit tests in 60%, hamster tests in 45%, and monkey tests in 30%. When the same criteria were applied to predict nonteratogens, mice and hamster tests were correct in 35%, rat tests in 50%, rabbit tests in 70%, and monkey tests in 80%. (Note that predicting these

results by simply flipping a coin would prove correct 50% of the time.)<sup>1</sup>

d. An additional problem with animal tests is their impracticality. Animal teratogenicity tests require a large investment of time, animals, and money (about \$60,000 to test one chemical in rats and rabbits). Considering the tens of thousands of chemicals in widespread use (many of them untested) and the addition of about 1,000 new chemicals per year, testing all of them is simply not practical.<sup>1</sup>

E. Animals are also used in the research areas of fetal and newborn diseases again with the problem of nontransferability of the data to humans. *Nelson's Textbook of Pediatrics* states, "Much of our knowledge of fetal physiology has been obtained from animals and often is not directly applicable to man."<sup>5</sup>

II. In contrast to animal experiments, epidemiologic studies have provided consistently crucial information:

A. Virtually all known developmental hazards were identified and/or characterized through studies of human populations.<sup>1</sup>

B. Epidemiologic studies were responsible for identifying, among other things the thalidomide disaster, fetal alcohol syndrome, fetal hydantoin syndrome, fetal rubella syndrome, the association of folic acid with neural tube defects, and the effects of DES and methyl mercury on development.<sup>4,6</sup>

C. One of the most popular reference sources among genetic counselors is *Drugs in Pregnancy and Lactation, A Reference Guide to Fetal and Neonatal Risk* by Briggs, Freeman, and Yaffe. This important book presents no animal data, but rather relies solely on human data.<sup>1</sup>

III. Scientists are turning to in vitro tests to improve both predictability and practicality because of inherent problems and inaccuracies in animal testing.

A. In vitro studies offer many advantages. They are less expensive, faster, and more reproducible than animal tests.

B. Some in vitro screens have achieved successful application in labs where they are used to assess the relative "toxicity" of chemicals within a family defined on the

basis of structure, functionality, or pharmacologic activity.<sup>7</sup>

C. "In the long run understanding of the mechanisms of toxic action and consequently the recognition of essential endpoints and criteria as indicators of specific toxicologic potential, largely based on in vitro assays, may hopefully lead to the development of completely different data sets and hazard identification schemes that would be far superior to the current animal tests. Nevertheless, none of the above will lead to a better world for the experimental animal, when scientists in toxicology are not really convinced of the necessity to reduce the use of animals in their research. . . . What is needed most of all is respect for the life of animals and consequently a positive attitude towards developments that could lead to a reduction of animal use."<sup>7</sup>

D. It is not clear that any of the in vitro tests in existence today are sufficiently developed at this time to identify human toxicity with ease or certainty.<sup>1</sup> A significant greater amount of resources need to be devoted to this area.

#### IV. Conclusion

Reliance on the faulty information obtained from animal tests puts human health in jeopardy in addition to causing the death and suffering of many animals. In addition, the progress of science is slowed as money that could be better spent on clinical studies as well as the development of more reliable in vitro tests is being wasted on animal tests.

#### References

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### WHAT PCRM WOULD LIKE THE MARCH OF DIMES TO DO

We would like March of Dimes to shift funding from animal experiments into methods that will have an impact on decreasing birth defects, including epidemiological studies, birth defects monitoring systems, in vitro studies to predict what chemicals cause birth defects and social and educational programs that serve to prevent birth defects through proper prenatal care and reducing high risk behavior.

We would also ask the March of Dimes to develop a plan for eliminating animal experiments. As a part of that plan we ask that they report the extent of animal use in the experiments it funds, including cost, number and species of animals used, as well as descriptions of all current and planned animal experiments.

