

Good Medicine

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The Next Thalidomide Could Be Just around the Corner...

Animal-Based Drug Tests Miss Half of All Birth Defects

By Jarrod Bailey Ph.D.

Since the 1960s, when thousands of babies with malformed limbs and other birth defects were born to women taking the sedative and anti-nausea medication thalidomide, all drugs and other chemicals have increasingly been subject to safety testing in animals.

Researchers have tested chemicals on a wide variety of pregnant animals in hopes of determining how “safe” the substances may be for humans. The object has been to identify any “teratogens,” substances that cause birth defects. Over the decades, they’ve compiled vast amounts of data on substances ranging from pharmaceuticals to pesticides and plastics. And tens of millions of rodents, monkeys, dogs, cats, pigs, cows, sheep, and ferrets—to name but a few of the species—have inhaled, or been force-fed or injected with, thousands of such chemicals in order to assess their effects on the development of the animals’ unborn offspring.

These tests rely, of course, on the basic assumption that their results are applicable to pregnant human beings. A comparison of animal test data with what is known about human birth defects reveals how flawed this assumption is. My colleagues and I recently conducted a comprehensive review of animal experiments used to test 1,396 different substances. Our findings showed:

- Almost half of all animal experiments involving substances known to cause human birth defects indicate that they are “safe.”
- Almost half of all animal experiments using substances known to be safe in humans indicate that they are dangerous.
- Finally, almost one-third of all substances tested yielded varying results, depending on the species.

No Better Than a Coin Toss

Our survey exposes a testing system that performs so poorly that one could almost obtain a similarly successful predictive rate by flipping a coin. Indeed, virtually every human teratogen was initially identified as a result of epidemiology and clinical case studies—that is to say, despite, rather than because of, animal testing.

In the case of thalidomide, it wasn’t until 12,000 babies were born with missing and deformed limbs and other birth defects that the drug was pulled from the market. Animal testing prior to its release had revealed a very low level of toxicity, and subsequent “retrospective” experiments using pregnant animals were largely negative and eventually showed characteristic limb defects in only a few specific breeds of rabbits and monkeys. Where teratogenesis did occur, the effects were highly variable, inconsistent, and often of low incidence and only when extremely high doses had been administered.

Far from serving to protect millions of human children from premature death or a life of suffering and disability, animal testing may actually be one of the major causes of such tragedies. The consequences are many: Harmful drugs and chemicals are reaching the marketplace because of erroneous suggestions of safety in animals. Conversely, potentially beneficial drugs may well be discarded before they can be used. And many substances remain without a firm classification of risk, due to the disarray in animal test results; after all, how does one conclude that a substance does or does not pose a risk to humans when the animal results are a mix of positives and negatives?

The problem stems from fundamental biology: There are simply too many differences in physiology and biochemistry for animals to be good predictors of what will cause birth defects in humans. No nonhuman animal species absorbs, metabolizes, or eliminates test substances like a human.

Long History of Failure

Notable examples of the discordance found in teratology include:

- Cortisone, a prescribed steroid, that is harmless in humans but teratogenic in every animal species tested.
- Diazepam (Valium), the ubiquitous tranquilizer that can cause human birth defects when taken by women early in a pregnancy. Birth defects are seen in the offspring of mice and hamsters, but only at doses of dozens to hundreds of times greater than the human dose. Similarly large doses have no teratogenic effect on rats or rabbits.
- Aspirin, a classic teratogen in numerous species (mice, rats, rabbits, cats, and dogs), which is not classed as a teratogen in humans.

Better Tests Are Available

Better test methods exist. The best of them, the Embryonic Stem Cell Test (EST), utilizes cells that can be grown indefinitely in the laboratory. In official validation tests conducted by the European Centre for the Validation of Alternative Methods, this test was found to have an accuracy of 78 percent—a significant improvement on the animal-based equivalent. In addition, it is much cheaper, easier and quicker to perform, and more repeatable and reliable.

The advent of the EST appears to be timely: 400 new drugs and between 50,000 and 70,000 new chemicals are introduced to the market each year. Even if animal tests were predictive, they would have a tough time keeping pace with these numbers. Clearly, it's time to embrace safer new technologies to minimize risk and make sure another thalidomide crisis never occurs.

The findings summarized in this article are to be published in a full and extensive review in the European scientific journal Biogenic Amines in May 2005.

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