

Dangerous Medicine:

Examples of Animal-Based “Safety” Tests Gone Wrong

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Biological differences between and within species require scientists to proceed with caution when interpreting the results of any experiment. Animals of different ages, sexes, developmental stages, and of different health status can all respond differently to experimental treatments. It is no surprise, then, that humans respond differently to administered pharmaceuticals than other animals. The surprise comes when scientists, physicians, and regulatory officials are willing to risk the health of patients by relying on animal experiments to predict the effects of drugs in humans—sometimes with grave results.

According to some estimates, adverse drug reactions are responsible for 2.2 million hospitalizations and 106,000 deaths annually.¹ Furthermore, as many as 50 percent of FDA-approved drugs are withdrawn or relabeled due to unanticipated side effects in humans.² A shockingly low 56 percent of known human teratogens are positive in one of six species surveyed.³ Below are a few selected examples to illustrate the dire need for better, more human-specific drug safety tests.

THALIDOMIDE

Perhaps the most famous teratogen, this drug was given to pregnant women in the 1950's to control nausea, causing more than 10,000 births with limb-reduction defects.^{4,5} After thalidomide was withdrawn from the market, tests in pregnant mice, rats, and guinea pigs were negative; finally, one strain of rabbit (the New Zealand white rabbit) was found to be susceptible. Cats, hamsters, rats, and mice were later found to be sensitive only to extremely high doses.³

ORAFLEX, OPREN (BENOXAPROFEN)

Even though year-long tests in rhesus monkeys and long-term rat studies⁶ gave no indication of risk, months after this non-steroidal anti-inflammatory (NSAID) was released onto the market in 1982, patients began experiencing severe liver toxicity and phototoxicity,^{7,8} eventually resulting in withdrawal of the drug, but only after more than 3,500 serious adverse events and 60 deaths occurred in Britain alone.⁹

FLENAC (FENCLOFENAC)

This NSAID, despite passing animal toxicity tests in 10 animal species (mice, rats, guinea pigs, ferrets, rabbits, cats, dogs, pigs, horses, and monkeys), produced severe liver toxicity in humans.¹⁰

BUTAZOLIDIN (PHENYLBUTAZONE)

This NSAID is commonly used in equine medicine to reduce pain and inflammation, but in humans can produce serious phototoxicity,¹¹ as well as serious or fatal liver¹² or bone marrow¹³ disease. Bone marrow toxicity was demonstrated in human cell cultures after the drug was released and produced more than 10,000 fatal cases of aplastic anemia.¹⁴⁻¹⁶

CYLERT (PEMOLINE)

Fifteen children suffered acute liver failure after taking this attention deficit hyperactivity disorder treatment, and 12 of those cases resulted in liver transplant or death.¹⁷ No animal tests that showed an indication of hepatic toxicity could be found.

REZULIN (TROGLITAZONE)

This drug, intended to treat type 2 (adult-onset) diabetes, was approved by the FDA in 1997. Rezulin lowered the blood sugar in rats without producing adverse effects, but reports of severe and even fatal liver failure appeared immediately after approval. Due largely to an aggressive investigation by the *Los Angeles Times* and after four label changes, Rezulin was withdrawn in 2000 after 391 deaths were attributed to the drug.¹⁸

PROPULSID (CISAPRIDE)

Propulsid was approved by the FDA in 1993 and was used primarily to treat gastric reflux

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Research Without Animals

Epidemiologic and Clinical Studies

Studies of human populations have provided important information about the causes of many diseases, such as the relationships between cholesterol and heart disease, the mechanism of transmission of HIV, and chemical exposures and birth defects.

Scientists can “see” abnormalities—and track treatment progress—in the brains of victims of Alzheimer's and Parkinson's diseases, schizophrenia, epilepsy, and brain injury¹ using sophisticated scanning technologies (CT, PET, and MRI). All drugs must undergo clinical testing before becoming approved; carefully crafted clinical research is the best way to determine human reactions to new drugs.

In Vitro Research

An enormous amount of valuable *in vitro* (test tube) research is conducted today. The National Disease Research Interchange provides more than 130 kinds of human tissue to scientists investigating more than 50 diseases, including cancer, diabetes, and glaucoma. Cell and tissue cultures are used

in children. Heart rhythm disturbances had appeared in clinical trials, but not in animal studies. By 1995, heart rhythm deaths in children became evident through adverse events reports. The drug remained on the market with five label changes, until being withdrawn in 2000 after causing over 300 deaths.¹⁸

INOCOR (AMRINONE)

This short-term therapy option for patients with severe heart failure produced severe and sometimes fatal thrombocytopenia (decreased blood clotting ability) in humans, despite no evidence of this effect in 2-year-long animal tests. Only after approval, and only in marmosets and a very specific, metabolically-compromised strain of rat, were similar effects found.⁷

BAYCOL (CERIVASTATIN)

Baycol was a popular drug approved in 1997 for the treatment of dyslipidemia (abnormal cholesterol levels), but it was withdrawn after substantial risk for severe or fatal rhabdomyolysis (muscle wasting) was revealed in patients. Muscle wasting was not seen in pre-clinical animal tests, including rats, mice, minipigs, dogs, or monkeys; only at very high doses were indications of effects on muscle tissue seen.¹⁹ The authors concluded that cerivastatin was well tolerated in all species. Post-withdrawal tests using rat and human muscle cells *in vitro* revealed that rat cells are 200 times more resistant to the drug's effects.²⁰ Eventually more than 100 deaths were linked to cerivastatin.

Such a high error rate begs the question: How many possibly life-saving therapies have clinicians never investigated because of toxicities in other animal species? Penicillin, which was originally discovered in 1929, wasn't used until 1939 because of its ineffectiveness in curing infected rabbits. If it had been "safety" tested in cats, guinea pigs, or hamsters, it would have been abandoned as toxic.²¹

Furosemide (Lasix) is one of our most important diuretics, used to reduce fluid retention during heart failure and other diseases. Though experiments in mice show extensive liver damage, decades of clinical use have proven its safety for humans.^{22,23}

One of our most relied-upon pain relievers, Aspirin (Acetylsalicylic acid), causes teratogenic malformations in mice, rats, dogs, cats, rabbits, and monkeys.³

What You Can Do

- More funding must be dedicated to the development of better, human-based drug safety tests. Write your federal legislators to explain this urgent need.
- Encourage the National Institutes of Health to fund studies using non animal methods, such as the examples listed at the right. Contact NIH here:

Elias Zerhouni, Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

- Support only health charities that fund non-animal research. A full list of those with the Humane Charity Seal of Approval can be found at www.HumaneSeal.org.

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Research Without Animals

continued

to screen new therapies and to test for product safety. Genetic microarrays are being used to predict liver toxicity by measuring gene expression in human liver cells.²

In Silico (Computer) Technologies

Computers can often predict the toxicity of chemicals, including their potential to cause cancer or birth defects, based on their molecular structure. Computer simulations can also predict the metabolism and distribution of chemicals in human tissues.

Safety Testing

Safety tests using human cells are more accurate than animal tests. In the Multicenter Evaluation of *In Vitro* Cytotoxicity tests (MEIC), researchers evaluated 68 different methods to predict the toxicity of 50 different chemicals.³ Rat LD50 tests—lethal dose tests currently used—were only 59 percent accurate, but a combined human cell test was 83 percent accurate in predicting actual human toxicity.^{4,5}

Pharmagene Laboratories conducts new drug development exclusively using human tissues and computer technologies. With tools from molecular biology and biochemistry, Pharmagene investigates how new drugs affect the actions of human genes or the proteins they make. These techniques replace animal tests in many cases.

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