R&D toxicity test to be eliminated

In a rare collaboration between animal rights organizations and scientists, the US has joined a growing worldwide movement to eliminate the use of a toxicity test called the lethal dose–50 (LD_{50}) test, and embrace alternative methods that require fewer animals. Animal rights groups estimate that about 5 million animals per year have been used in LD_{50} tests in the US alone.

The LD_{50} determines the dosage of a chemical that kills half the animals in a test group—the bigger the dose required, the lower the chemical's toxicity. Test groups typically comprise 50–200 animals, often rats. The test is being phased out internationally and will no longer be used by regulatory agencies for classification and labeling of drugs and chemicals.

The International Organisation for Economic Co-operation and Development (OECD), an international trade organization that includes the US, Japan and several member states of the European Union, intends to eliminate the LD_{50} from its test guidelines by September 2002. After that time, data generated by the old method can be rejected by government authorities and less animal-intensive studies used instead.

Officially, the test is not required by the US Food and Drug Administration (FDA) to evaluate new medicines and is no longer used by many biomedical researchers and drug companies. ''The FDA usually requires different information,'' says veterinarian Bill Stokes, director of the National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (ICCVAM). ''They want to know the LD_{10} [the dose at which 10% of animals die]—they're more interested in knowing when you start getting toxic effects.''

Replacing LD_{50} will be one of three measures of toxicity that use as few as 14 animals. In the 'up-and-down' method, animals are exposed to incremental doses of a substance every 48 hours, and the dose that kills the animals is observed. This method takes more time but uses as few as 6–9 rats. Stokes explains, ''If an animal dies, you reduce your dose by that same factor and continue until you've had three deaths, or three survivals.'' This method was reviewed in July 2000 by an ICCVAM panel, which asked that a computer software program be developed to establish test doses. This software has now been created by the US Environmental Protection Agency and ICCVAM announced on 21 August that it was fine-tuning the technique, which uses only eight rats per compound tested.

The 'fixed-dose procedure', first proposed by the British Toxicological Society in 1984, is another stepwise analysis—this one based on dosing at a series of fixed dose levels, with five animals dosed at each level. This approach avoids the use of death as an endpoint, instead relying on the observation of signs of toxicity. The 'acute toxic class method' uses three animals per step and is based on biometric evaluations of fixed doses.

Marlene Cimons, Washington, DC

HHMI to improve teaching

Based on the premise that undergraduate teaching receives scant recognition of its importance, the Howard Hughes Medical Institute (HHMI) has announced that it is to spend $20 million bolstering the skill.

Scientists actively involved in research are invited to apply for an HHMI teaching post, worth $1 million over 4 years, to develop new and exciting ways to teach undergraduates. Eighty four universities have been invited to nominate tenured professors and 20 such positions will be created.

HHMI believes that faculty who are "creative in research" have something "very special" to bring to the undergraduate classroom in the forms of scientific discovery, communication and sharing the excitement for research. As part of the program, the professors will meet several times a year to share their experiences.

Stephanie Irvine, Denver

Pfizer in "unethical" trial suit

In the latest complaint of clinical-trial misconduct, 30 families have filed a lawsuit against the world's largest pharmaceutical company, Pfizer, alleging unethical treatment of children involved in a 1996 clinical trial of the company's oral antiobiotic drug trovafloxacin (Trovan) in Nigeria.

The suit charges that Pfizer did not obtain informed consent from the sick children's parents and that a failure to adhere to the study protocol resulted in brain damage, hearing loss and the death of 11 of the 2,000 children in the study.

Filed in New York City, the suit alleges that Pfizer was hasty in setting up the clinical trial in order to take advantage of a meningitis epidemic. In its rush to test a potential blockbuster drug, the suit charges, the company failed to give the families the option of seeking an "effective and approved alternative" treatment. The suit seeks "punitive damages" without naming a dollar figure, and asks the court to order that Pfizer "provides ongoing medical care to evaluate the liver and joint function of the children enrolled in the experiment."

The case came to light in a series of stories in the *Washington Post* in December 2000, which examined clinical trials in countries such as Africa, Costa Rica, Thailand and China. The paper concluded that, in general, US researchers were not ensuring that overseas study subjects gave informed consent.

In a written statement, Pfizer maintains that the trial was "designed and conducted in accordance with good medical practice and ethical norms," and denies the families were unaware that their children were part of a study. The company notes that the mortality rate for children in both arms of the study—which compared Trovan to the antibiotic ceftriaxone—was 6% compared to an untreated mortality rate of 10–30% for that particular epidemic. The company did admit to "some protocol deviations and record keeping errors" but claims they did not "compromise patient care or the scientific conclusions of the trial."

The US Food and Drug Administration approved Trovan in 1997, but declined to approve its use in children. Worldwide sales of the drug in 1998 were $160 million, but the product was withdrawn from the market in Europe in 1999 because of associated liver problems.

Tinker Ready, Boston