FACT SHEET NUMBER 1 – TOXICITY TESTING

Animals are used in pharmaceutical, agricultural and industrial research to predict human toxicity, and yet analysis suggests that animal models are poor predictors of drug and chemical safety for humans. The cost of animal research is high, financially, with time delays in drug approval, and in the loss of potentially beneficial drugs for human use.

Using animals to predict toxicity safety of human pharmaceuticals can:

1) Falsely identify a toxic drug as "safe"
2) Falsely label a potentially useful therapeutic agent as toxic.

An analysis of 2,366 drugs concluded that:
"Results from tests on animals (specifically rat, mouse and rabbit models) are highly inconsistent predictors of toxic responses in humans, and are little better than what would result merely by chance, or tossing a coin, in providing a basis decide whether a compound should proceed to testing in humans" ***(1)****. Similar results were found for non-human primates and dogs* ***(2)****."*

When a human-toxic drug is identified as "safe" by animal testing, the most likely outcome by far is that the drug will fail in clinical testing, often due to unacceptable adverse human effects, and sometimes significantly harming volunteer research subjects in the process. Drugs that survive clinical trials and attain market approval may still be recalled later due to toxicity identified only after months or years of human use.

Of 578 discontinued and withdrawn drugs in Europe and the USA almost half were withdrawn or discontinued in post-approval actions due to toxicity **(3)**. There are many notable examples of cases in which animal trials did not predict severe human toxicity, a few are listed below:

Isuprel Developed for treatment of asthma caused over 3,500 deaths in Great Britain alone, despite safety in rats, guinea pigs, dogs, and monkeys, all of

which had received doses far exceeding those administered in humans **(4,5)**.

Thalidomide Famously caused devastating phocomelia in an estimated 20,000 to 30,000 infants before it was withdrawn. However, animal tests failed to reveal significant teratogenicity in 10 strains of rats; 11 breeds of rabbit; 2 breeds of dog; 3 strains of hamsters; 8 species of primates; and various cats, armadillos, guinea pigs, swine, and ferrets **(6)**.

TGN1412 An antibody to treat human autoimmune disease given at 1/500th the dose found safe in animal testing to 6 human volunteers in a phase I trial **(7,8)**, rendering them all critically ill within minutes and leaving them all with long-term complications **(9–11)**.

BIA-102474-101 Developed for a range of disorders from anxiety to Parkinsonism, caused deep brain hemorrhage and necrosis in all 5 human volunteers during a phase I clinical trial after it was administered in doses that were 1/500th of the safe dose for dogs. One volunteer died **(12)**.

Fialuridine Developed for treatment of hepatitis B, caused the deaths of 5 volunteers during phase II clinical trials despite being safe in mice, rats, dogs, monkeys, and woodchucks in doses that were hundreds of times higher. Two other volunteers only survived after receiving liver transplants **(9)**.

When animal tests falsely identify a safe chemical as “toxic,” the almost certain outcome is abandonment of further development. Undoubtedly many potentially beneficial drugs have failed animal testing and been lost to patients, even though they would have been both safe and effective, the magnitude of this type of “error” is unknown. Many highly beneficial drugs would have failed animal testing and never been brought to market except that they were developed before animal testing was required E.g. penicillin (fatal to guinea pigs), paracetamol (toxic in dogs and cats), and aspirin (embryo toxicity in rats and rhesus monkeys).

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Contract research organisations account for most of the animal testing done in the United States and Europe. Statista, a global data portal for market and economic sector statistics, estimates the global markets for animal testing in 2018 at $7.4 billion for drug discovery, $11.2 billion for preclinical development and safety, $58.5 billion for clinical development, and $2.3 billion for central laboratory testing.

Reproducibility of animal studies within species, even when carried out under rigorous protocols, is questionable. Using a database of more than 800,000 animal toxicity studies performed for 350 chemicals under rigorous guidelines, a reviewer found toxicity was repeatable just 70% of the time in the same species **(13)**. Another reviewer found that results for a single chemical often differed with animal model, strain, dose, and delivery route. About 26% of chemicals demonstrated contradictory results on repeat testing in the same species.

The absence of toxicity in animals (dogs, rats, mice, rabbits and monkeys) provides essentially no insight into the likelihood of a similar lack of toxicity in humans: the former contributes no, or almost no, evidential weight in relation to the latter. Quantitatively, if, for example, a new drug has (based on prior information, such as similarity to other drugs, data from in vitro or in silico tests, and so on) a 70% chance of not being toxic in humans, then a negative test in any of these five species will increase this probability to an average of just
74%. The most controversial species, dogs and monkeys, the use of which, as opinion polls show, the general public object to particularly strongly, were the least predictive for humans in this respect, raising the probability from 70% to just 72% and 70.4% respectively **(15)**. Therefore, animal tests provide essentially no additional confidence in the outcome for humans, but at a great ethical, and financial, cost **(14)**.

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Global Regulator expectation is that two animal species, rodent and non-rodent, be used for safety/toxicity testing, before progression to human clinical trials. Use of dogs and non-human primates (NHPs) have been shown to add just 2% and 0.4% respectively to the weight of evidence of existing probabilities that new drugs might be safe. This negligible contribution is statistically insignificant to safety assurances, and causes massive needless animal suffering and death, increased monetary costs and also time delays to product development.

A very complex and intensely bureaucratic regulatory system has been built up to control the safety testing of products ranging from industrial chemicals to pharmaceuticals and vaccines. Many animal tests are currently required for risk assessment to support the marketing and use of these products. To replace the accepted animal tests requires considerable effort to reassure the regulatory authorities that the alternative methods provide an adequate assessment of risk, and to overcome bureaucratic inertia.

Intensive efforts are needed to accelerate the validation and regulatory acceptance of alternatives through bodies such as the OECD and ICH, as well as ECVAM and the European Commission. This includes showing human relevant data matches previously obtained data from animal use, this ignores the fact that NAMS are human relevant and that animal models are not predicative of human biology.

References

1. Bailey J, Thew M, Balls M. An analysis of the use of animal models in predicting human toxicology and drug safety. Altern Lab Anim 2014;42: 189-99. https://www.wellbeingintlstudiesrepository.org/cgi/viewcontent.cgi?article=1123&context=acwp_arte

FACT SHEET NUMBER 1 – TOXICITY TESTING

2. Bailey J, Thew M, Balls M. Predicting human drug toxicity and safety via animal tests: can any one species predict drug toxicity in any other, and do monkeys help? Altern Lab Anim 2015;43: 393–403. https://www.wellbeingintlstudiesrepository.org/cgi/viewcontent.cgi?article=1023&context=acwp_lab

3. Siramshetty BV, Nickel J, Omieczynski C, et al. WITHDRAWN—a resource for withdrawn and discontinued drugs. Nucl Acids Res 2016;44: D1080-6 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4702851/

4. Greek R, Pippus A, Hansen LA. The Nuremberg Code subverts human health and safety by requiring animal modeling. BMC Med Ethics 2012; 13:16. https://bmcmedethics.biomedcentral.com/articles/10.1186/1472-6939-13-16

5. Stolley PD. Asthma mortality: why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 1972;105:883–90.

6. Schardein J. Drugs as Teratogens. Cleveland,OH: CRC Press, 1976:49.

7. Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in phase 1 trial of the anti-CD28 monoclonal antibody TGN1312. N Engl J Med 2006;355:1018–28. https://www.nejm.org/doi/10.1056/NEJMoa063842

8. Dayan CM, Wraith DC. Preparing for first-in-man studies: the challenges for translational immunology post TGN1412. Clin Exp Immunol 2008;151:231–4. https://academic.oup.com/cei/article/151/2/231/6457596

9. Attarwala H. TGN1412: from discovery to disaster. J Young Pharm 2010;2:332–6.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964774/

10. Allen F. "Like a horror film": what was the "Elephant Man" drug testing trial, what is TGN1412 and what happened to the men involved? The Sun (UK). February 21, 2017.
https://www.thesun.co.uk/news/2917810/elephant-man-drug-testing-trial-tgn1412/

11. Vial T, Descotes J, Braun F, Behrend M. Chapter 37. Drugs that act on the immune system:37—-cytokines and monoclonal antibodies. Side Effects Drugs Annu 2007;29:383–423.

12. Eddleston M, Cohen AF, Webb DJ. Implications of the BIA-102474-101 study for review of first-into-human clinical trials. Brit J Clin Pharm 2016; 81:582–6.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4799914/

13. Meigs L, Smirova L, Rovida C, Leist M, Hartung T. Animal testing and its alternatives—the most important omics is economics. ALTEX 2018; 35:275–305.
https://www.altex.org/index.php/altex/article/view/1134

14. Jarrod Bailey and Michael Balls. Recent efforts to elucidate the scientific validity of animal-based drug tests by the pharmaceutical industry, pro-testing lobby groups, and animal welfare organisations. 2019
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397470/

15. Bailey J, Thew M, Balls M. An analysis of the use of dogs in predicting human toxicology and drug safety. Altern Lab Anim. 2013;41:335–50.
https://www.wellbeingintlstudiesrepository.org/cgi/viewcontent.cgi?

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article=1026&context=acwp_lab

Please also look up an excellent paper that draws many toxicity failures together:

Limitations of Animal Studies for Predicting Toxicity in Clinical Trials. Gail A. Van Norman

2020: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7185927/