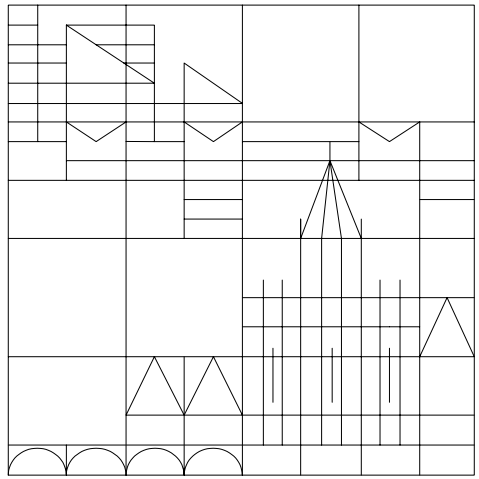
Good welfare equals good science: the 3R principle

Marcel Leist

Eur Life Science Circle, 27. Feb. 2008



University Konstanz

DOERENKAMP-ZBINDEN
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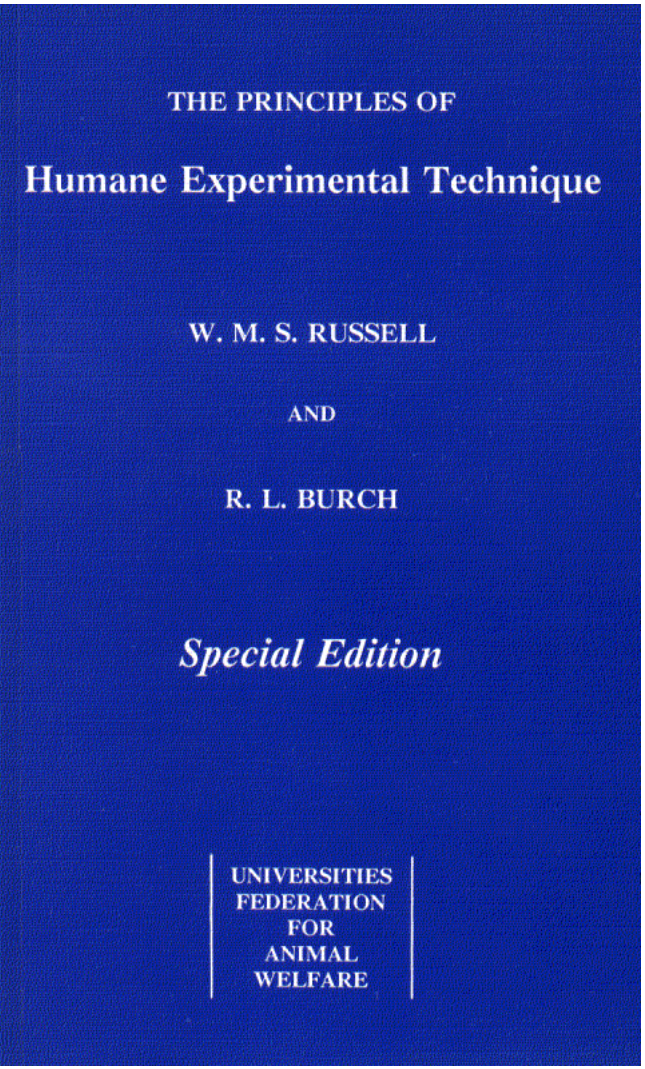
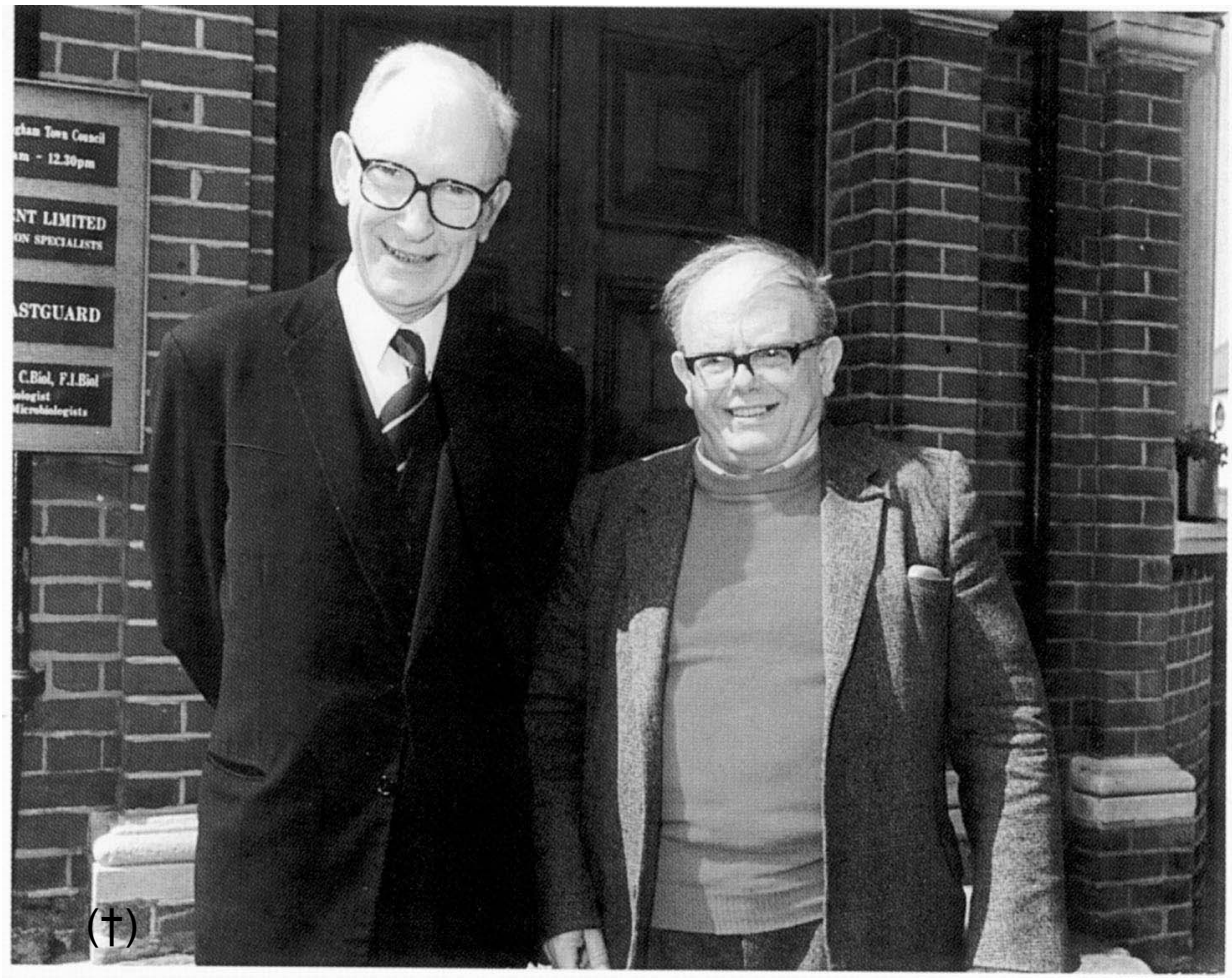
Doerenkamp-Zbinden Foundation

Animal protection and **good science**

- a conflict?

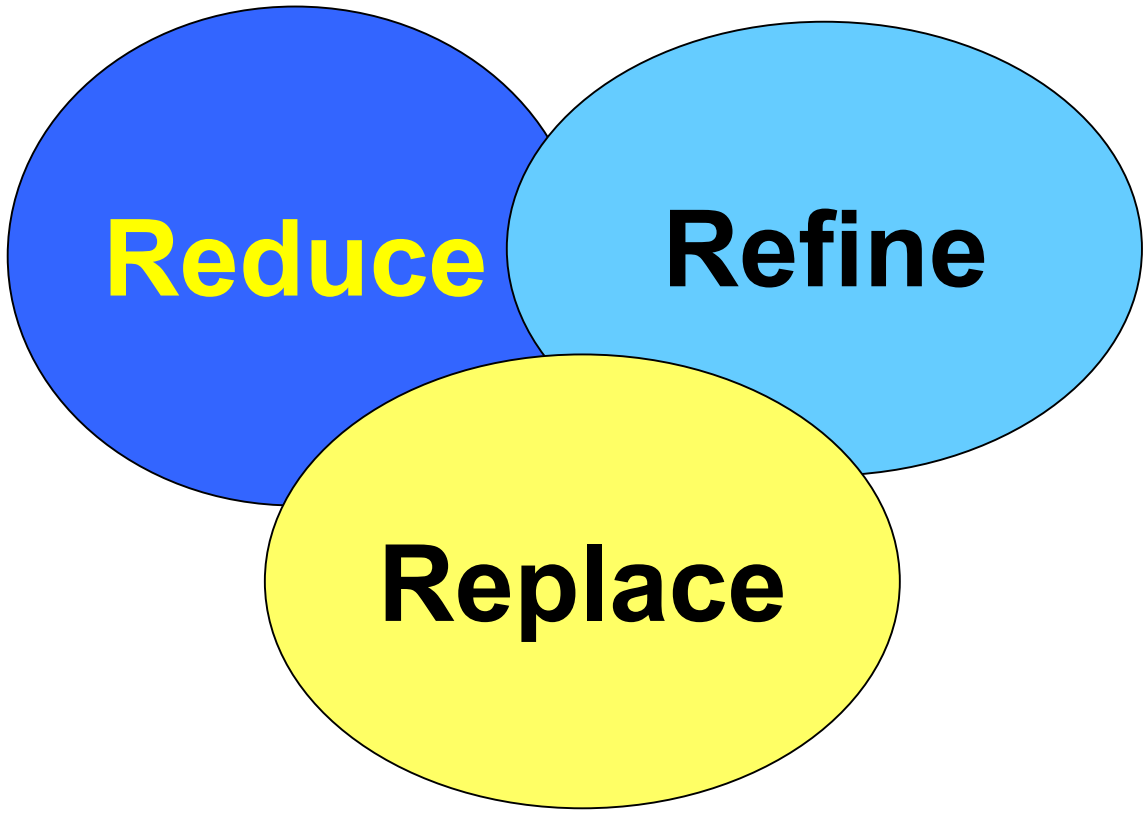
3R principle: *replace, reduce, refine*





William M. S. Russell & Rex L. Burch: ***The Principles of Humane Experimental Technique. London, 1959: Methuen & Co LTD***

In vitro methods as part of the 3R approach!



In vitro methods in drug discovery: why they remain relatively unnoticed

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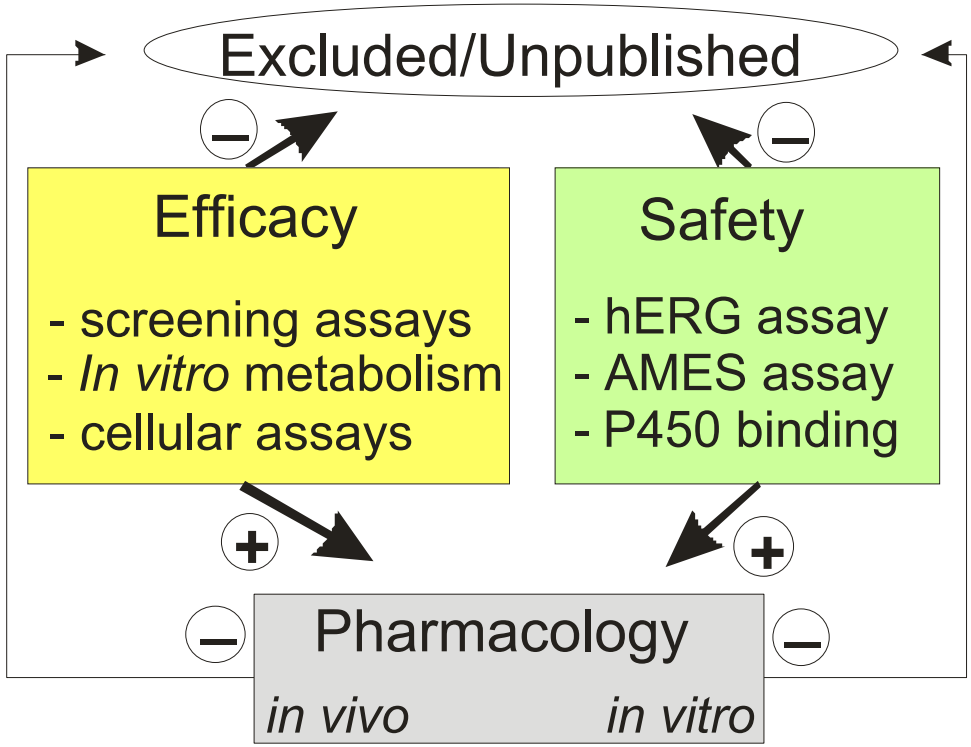


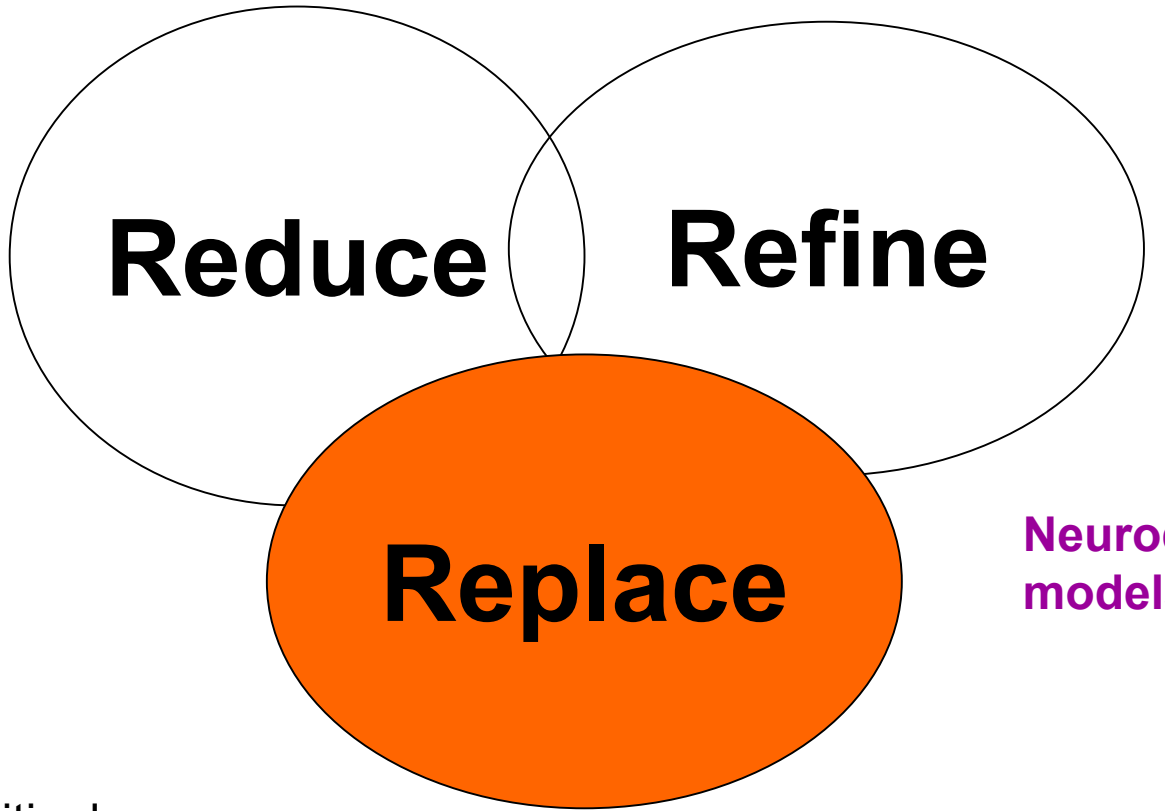
Antibody production

BOTOX

Vaccine batch control

Hormone bioactivities

Pyrogenicity



Angiogenesis

Neurodegeneration models

Anti-parasitic drugs

Oncology

Avoidance of prejudice:

„....in vitro systems do not predict systemic toxicity....., in vivo systems are better“

Example: TeGenero TGN1412

The Journal of Immunology (2007), 179, 3325

"Cytokine Storm" in the Phase I Trial of Monoclonal Antibody TGN1412: Better Understanding the Causes to Improve PreClinical Testing of Immunotherapeutics

Richard Stebbings, Lucy Findlay, Cherry Edwards,[1] David Eastwood, Chris Bird, David North, Yogesh Mistry, Paula Dilger, Emily Liefooghe, Isabelle Cludts, Bernard Fox, Gill Tarrant, Jane Robinson, Tony Meager, Carl Dolman, Susan J. Thorpe, Adrian Bristow, Meenu Wadhwa, Robin Thorpe, and Stephen Poole[2]

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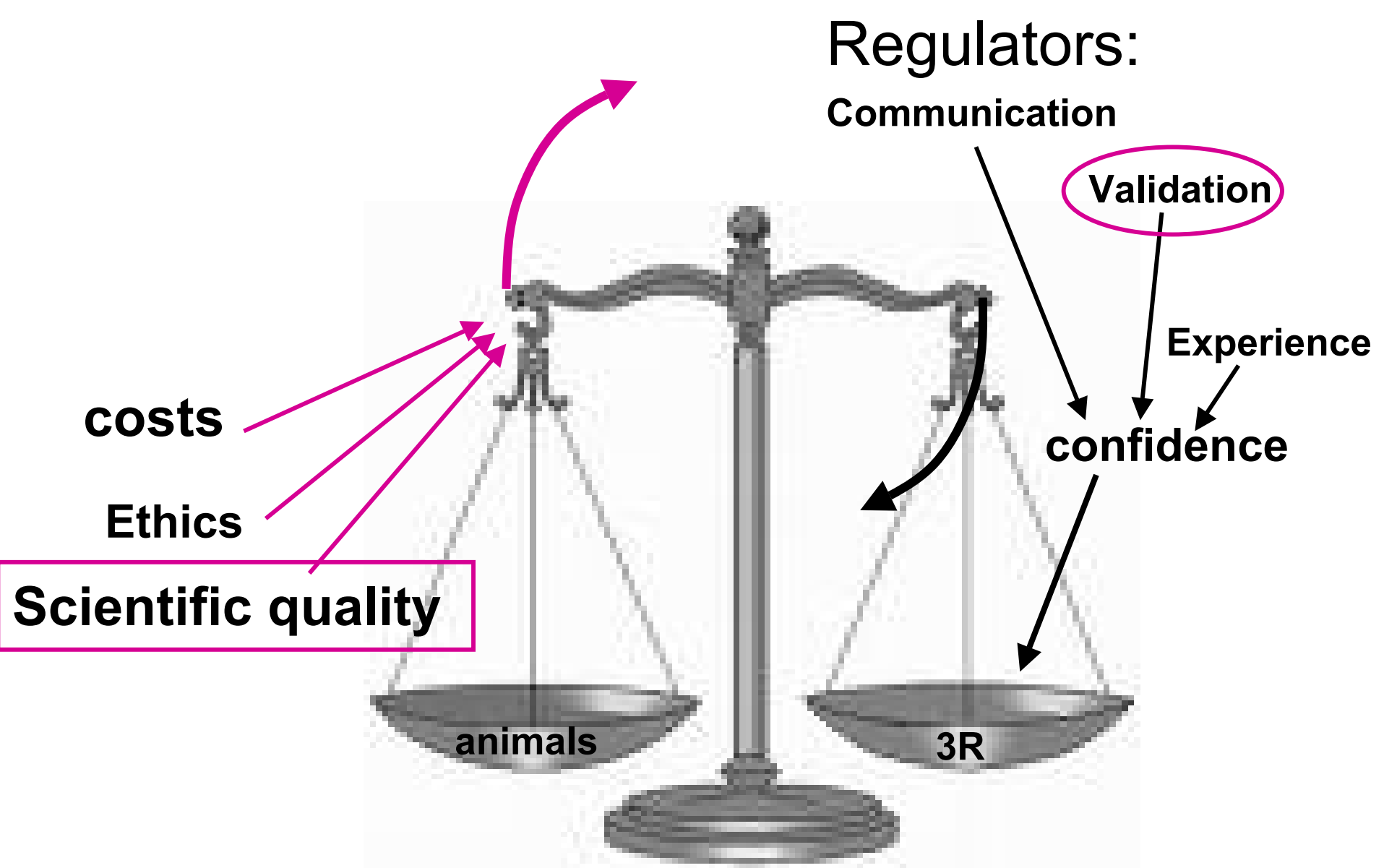
The CD28-specific mAb TGN1412 rapidly caused a life-threatening "cytokine storm" in all six healthy volunteers in the Phase I clinical trial of this superagonist, signaling a failure of preclinical safety testing. We report novel in vitro procedures in which TGN1412, immobilized in various ways, is presented to human white blood cells in a manner that stimulates the striking release of cytokines and profound lymphocyte proliferation that occurred in vivo in humans. [redacted] the potential to act upon the immune system. Data from these novel procedures, along with data from in vitro and in vivo studies in nonhuman primates, suggest that the dose of TGN1412 given to human volunteers was close to the maximum immunostimulatory dose and that TGN1412 is not a superagonist in nonhuman primates. *The Journal of Immunology*, 2007, 179: 3325–3331.



Major drivers for 3R

Problems with in vivo assays....:

Quantitative extrapolation of *in vitro* whole embryo culture embryotoxicity data to developmental toxicity *in vivo* using the Benchmark Dose approach.

A.H. Piersma et al, (2007) Toxicol. Sci.

Example:

Quantitative extrapolation of *in vitro* whole embryo culture embryotoxicity data to developmental toxicity *in vivo* using the Benchmark Dose approach.

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…also **heterogeneity in the design of the available *in vivo* studies** underlies much of the scatter, and this **puts a limit on validating *in vitro* data** as predictors of *in vivo* data. **Further analysis** of the *in vitro-in vivo* correlation would therefore **require high quality *in vivo* data,** …..

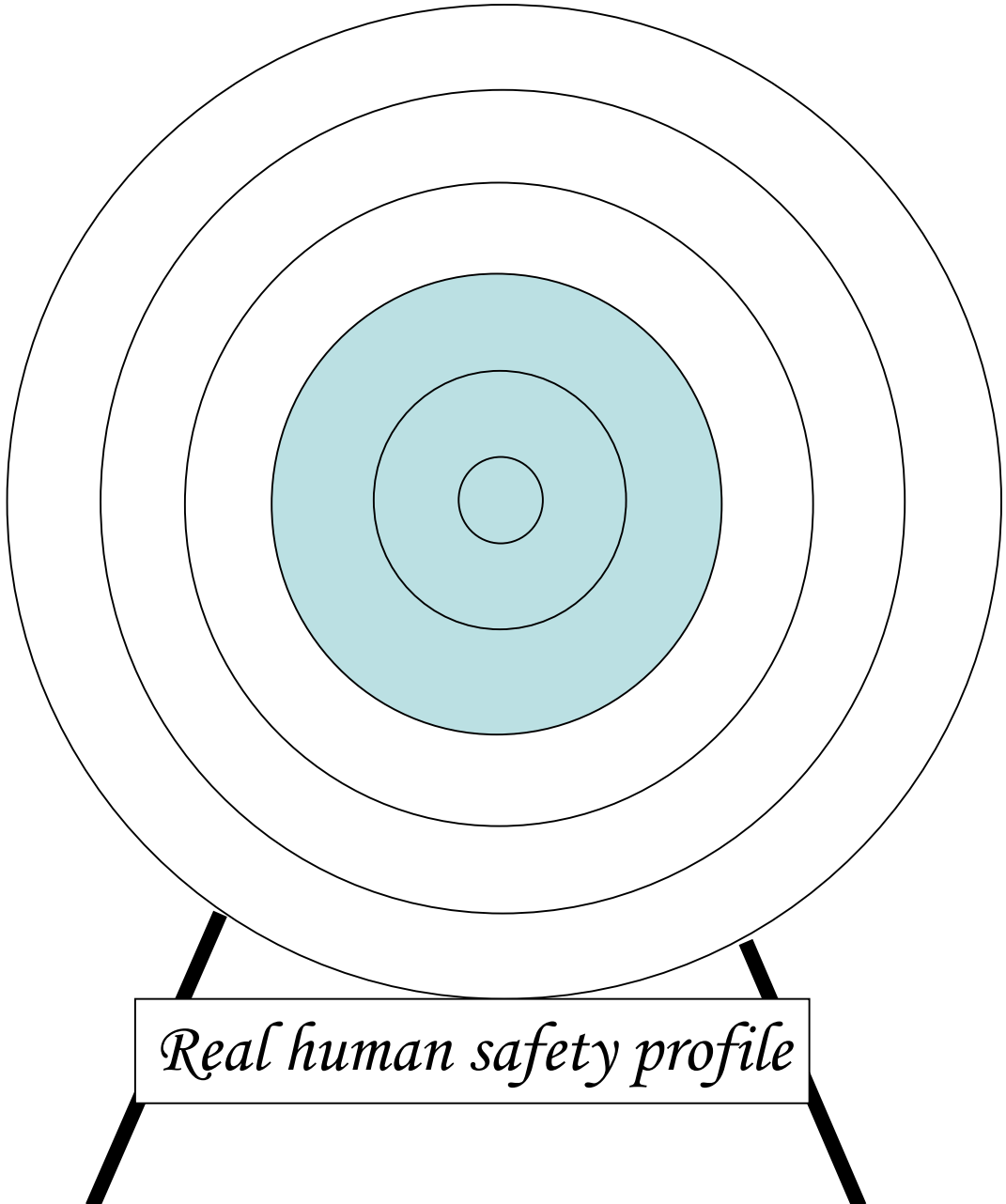
Major obstacles for in vitro tests:

The validation problem

Method ⟶ Validation ⟶ Acceptance

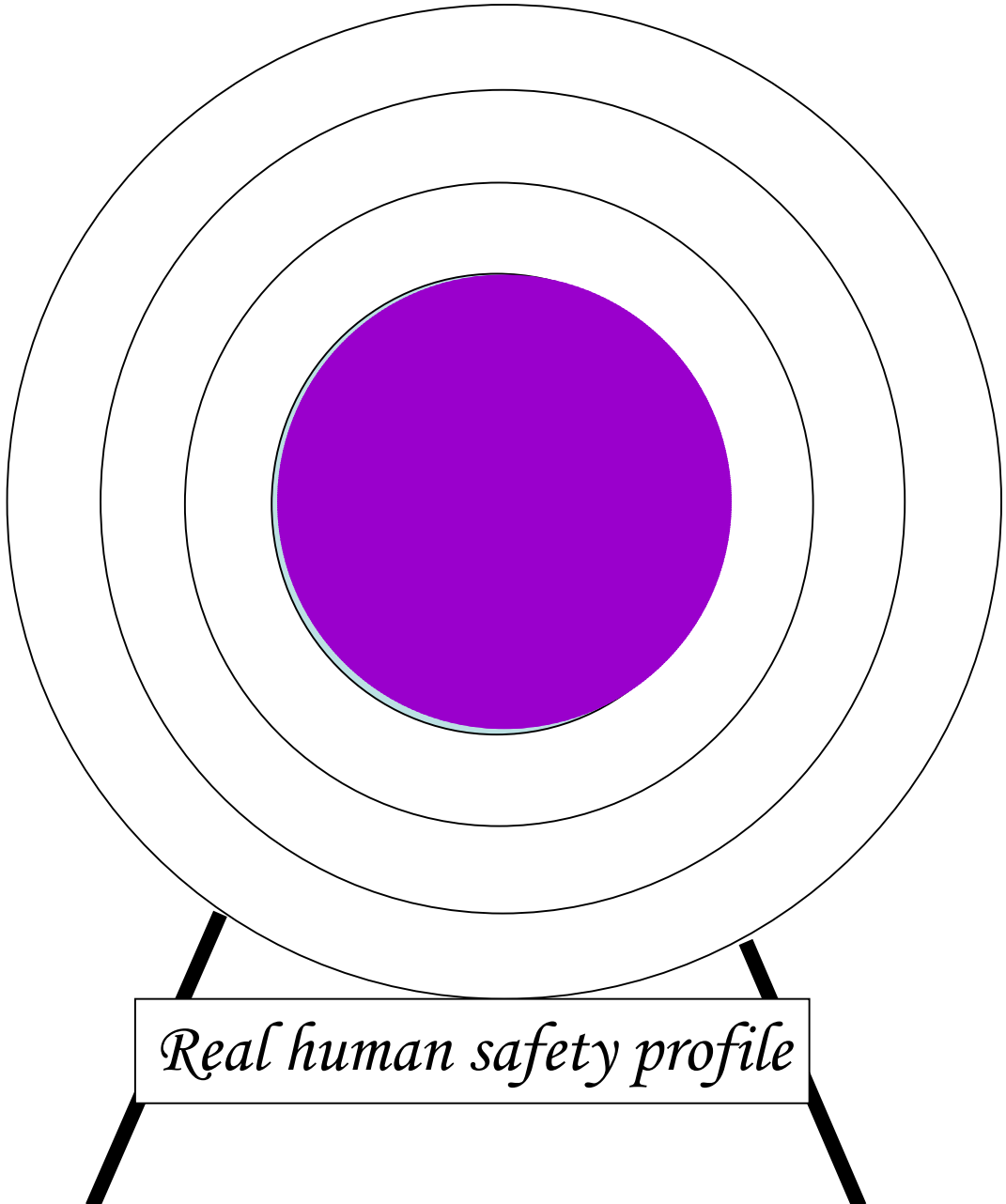
The validation dilemma:

Are we going to hit?



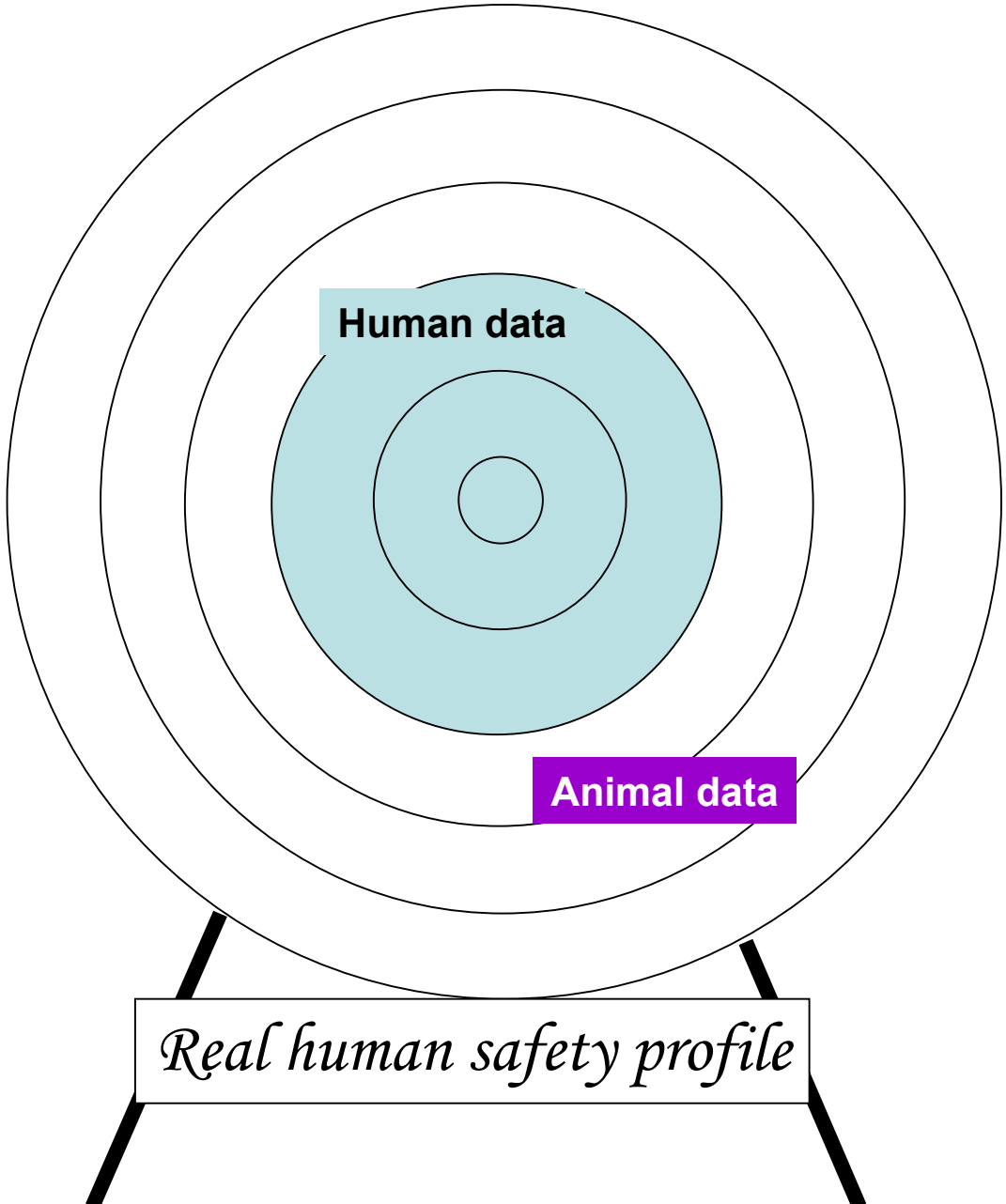
The human safety profile

Tuning a test



Accuracy and errors

Correlations?



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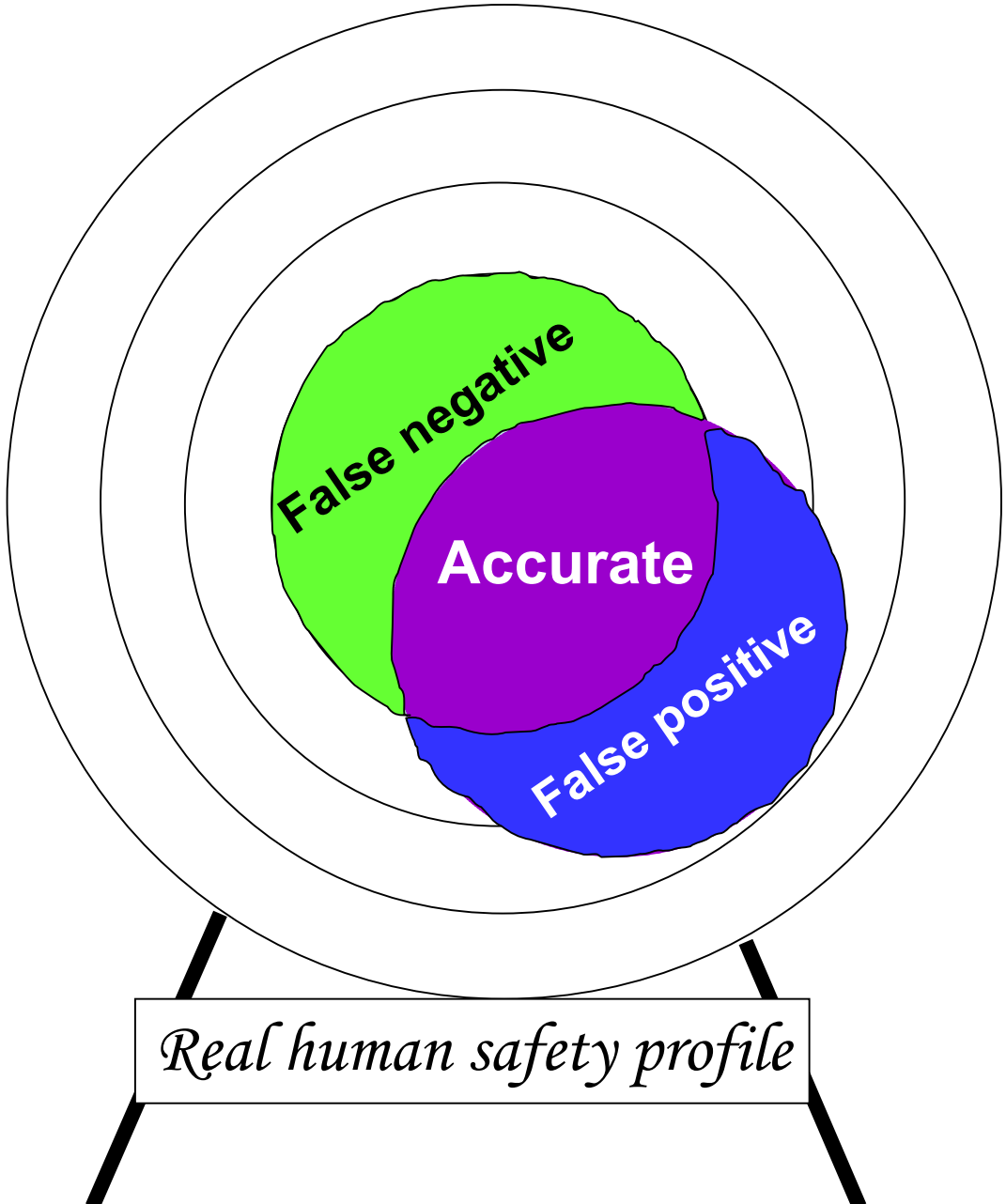
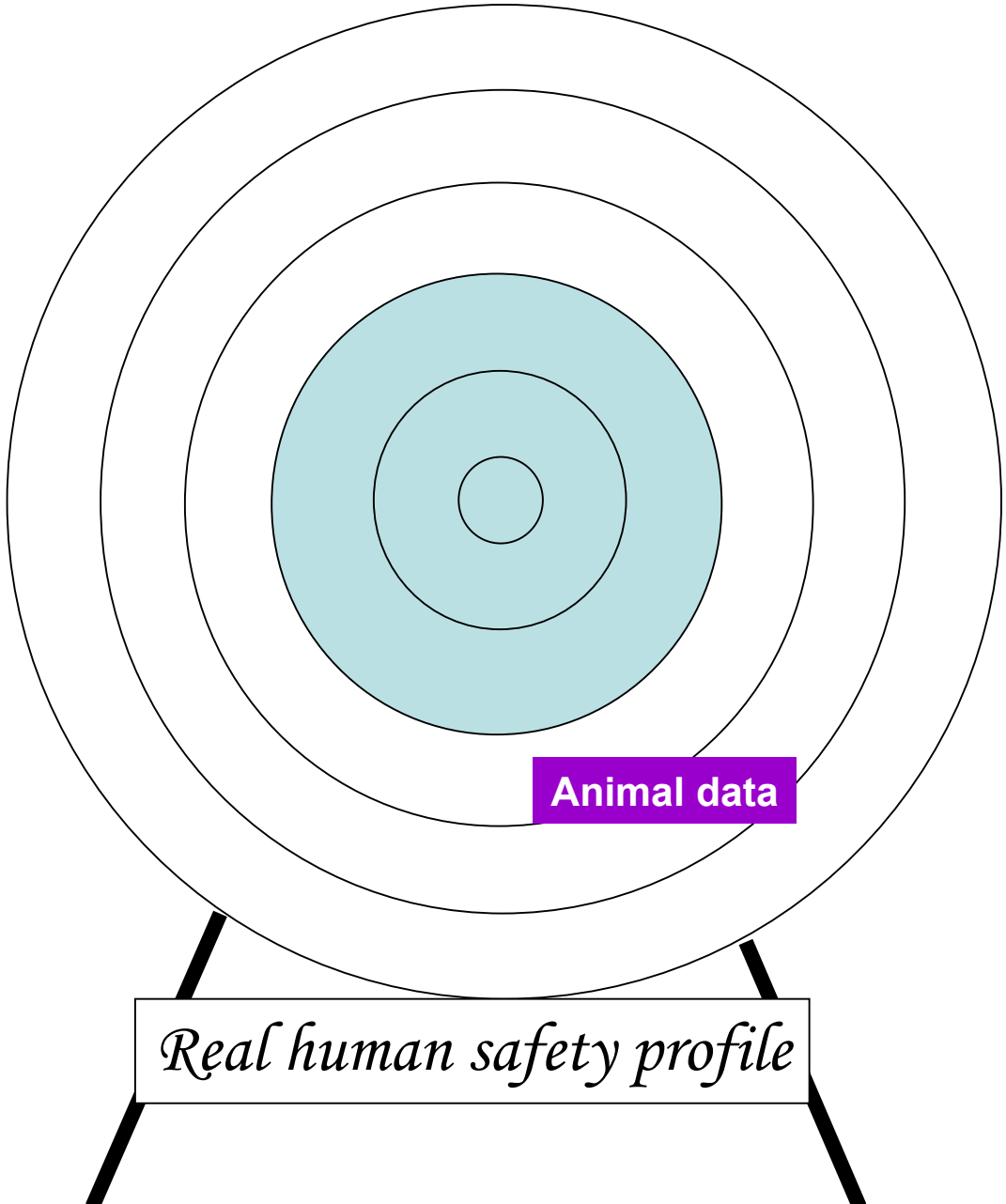
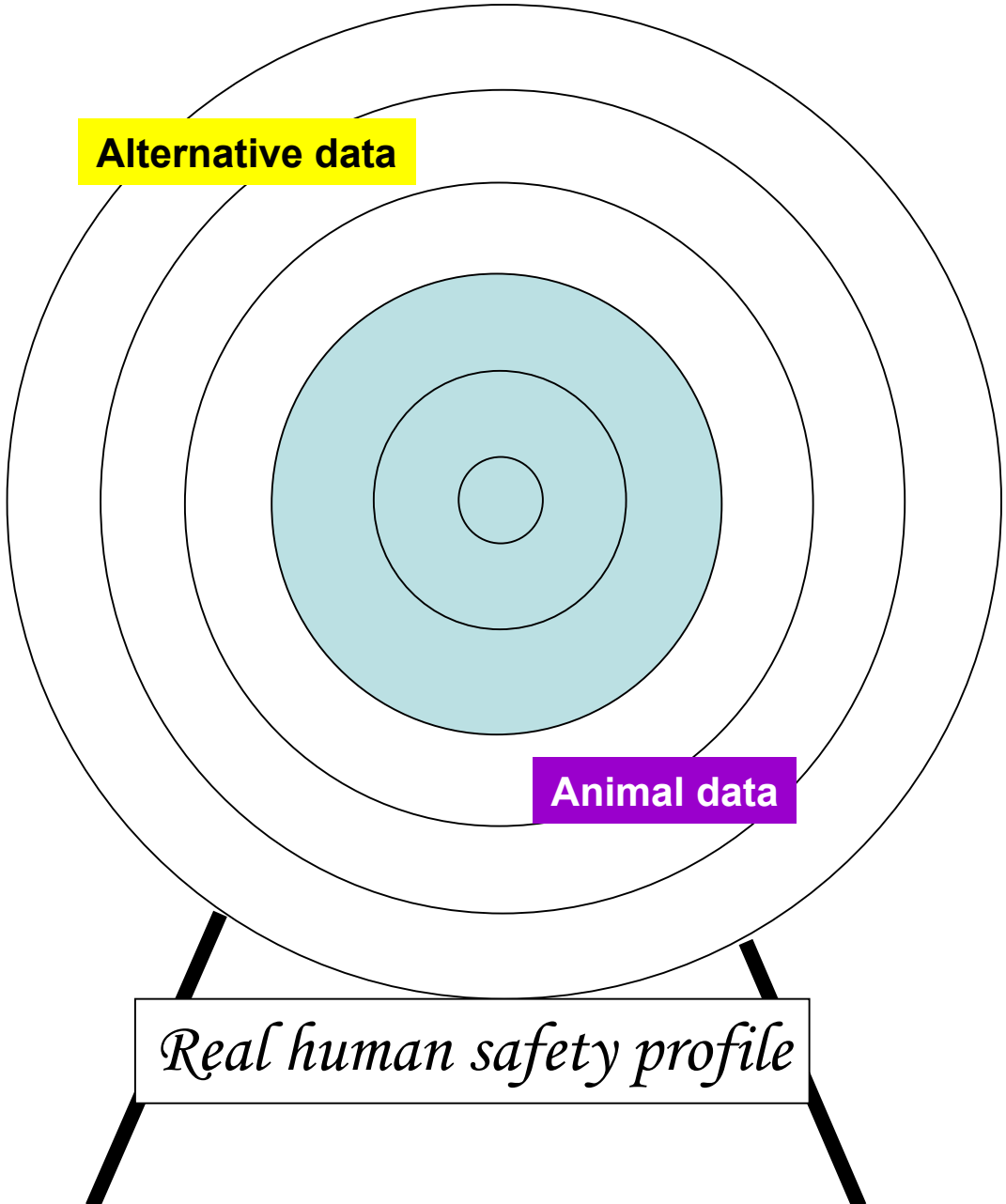


Animal models of human safety



Correlation of models of human safety

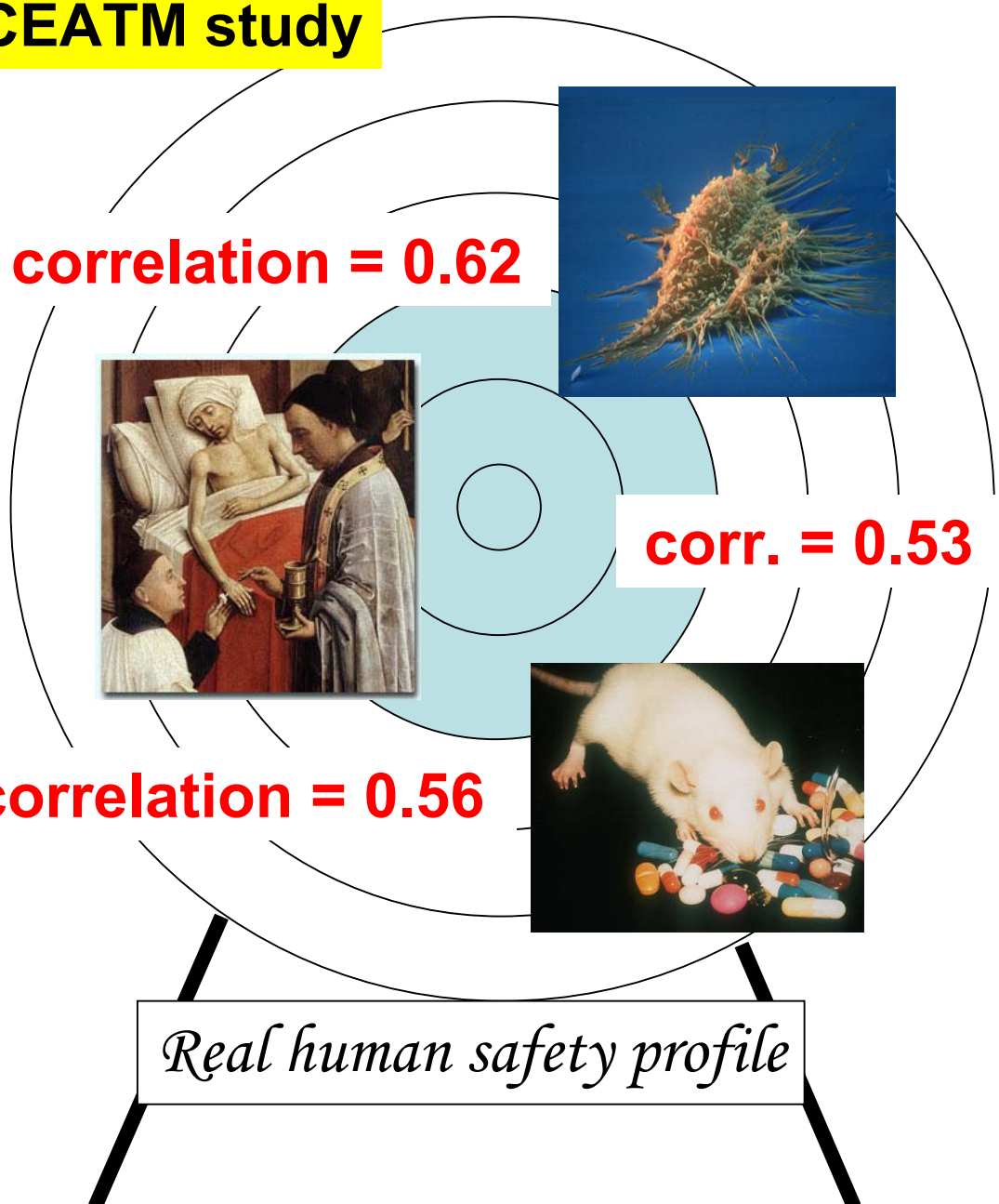
Real world scenarios!



Model correlation

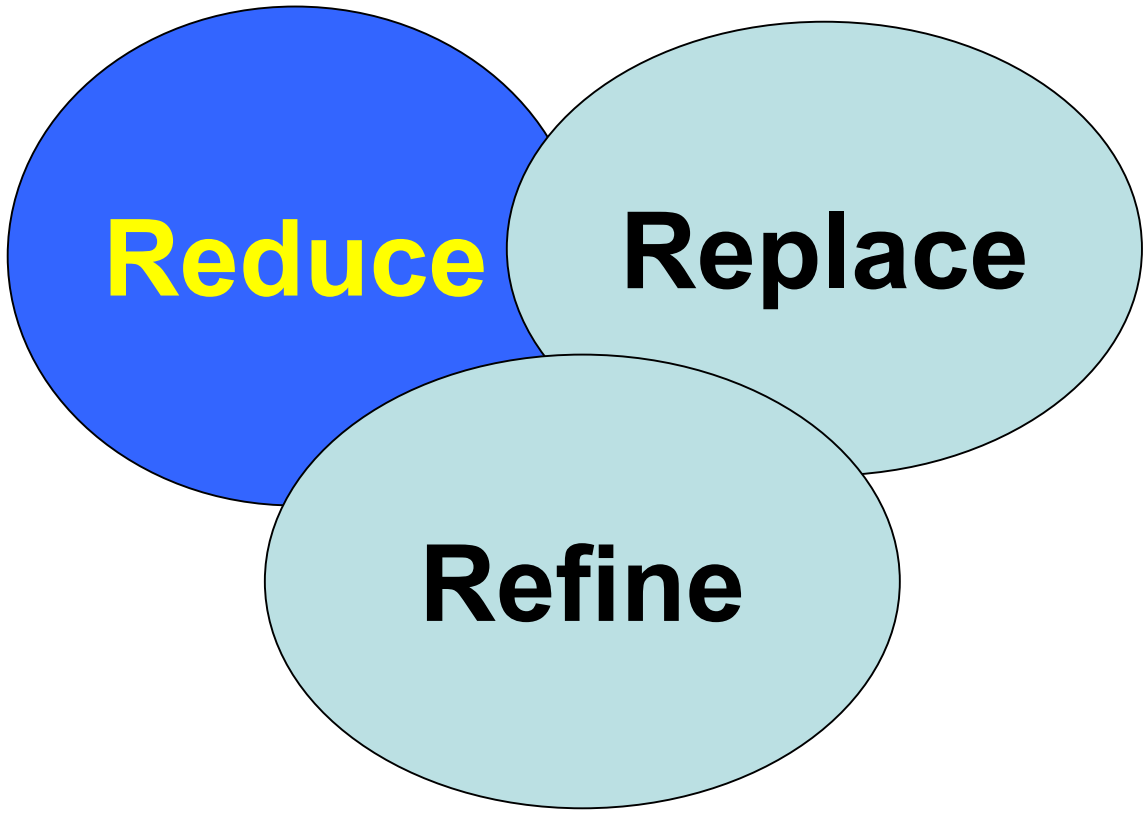
Examples from ECVAM/NICEATM study

Comparison to in vitro data



Personal communication T. Hartung; n = 45

In vitro methods in the reduction domain?

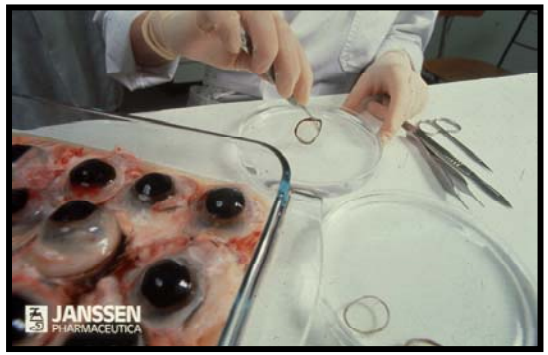


Example: Test of eye irritation

Rabbit model

Classification
(R41/R36)

Example: Test of eye irritation (EU)



In vitro models → Rabbit model

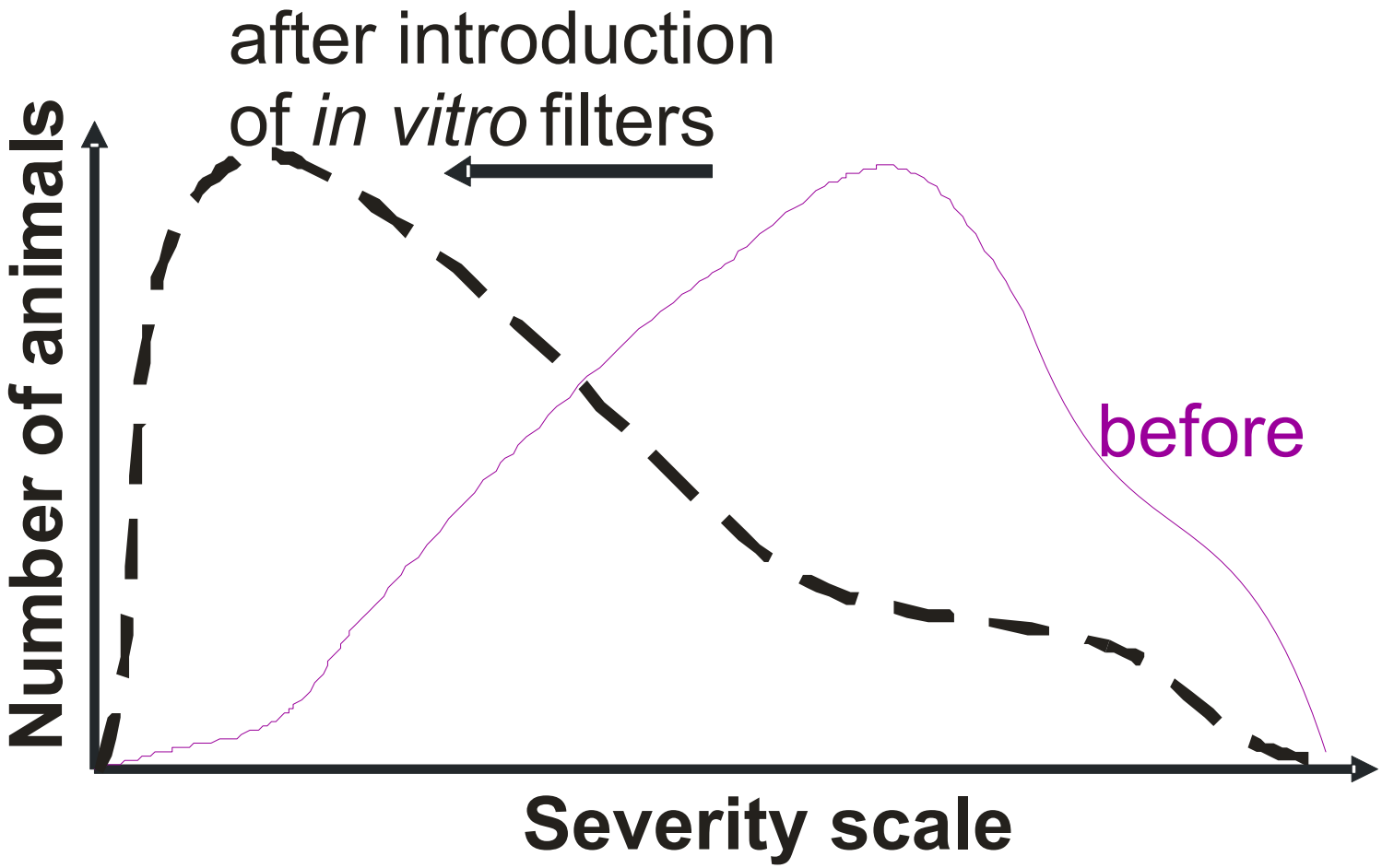
93%

7%

Classification
(R41)

Classification
(R41/R36)

Not each animal experiment is the same



What‘s to come?

The dawning of the age of research without animal suffering .....

POLICYFORUM

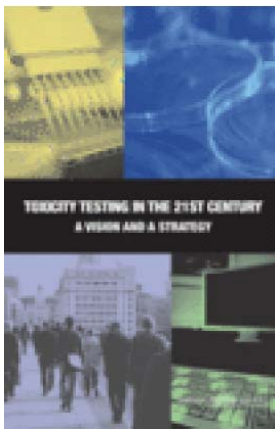
TOXICOLOGY

Transforming Environmental Health Protection

Francis S. Collins,[1*†] George M. Gray,[2*] John R. Bucher[3*]

15 FEBRUARY 2008 VOL 319 SCIENCE www.sciencemag.org
Published by AAAS

We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments.



TOXICITY TESTING IN THE 21ST CENTURY
A VISION AND A STRATEGY

Committee on Toxicity Testing and Assessment of Environmental Agents
Board on Environmental Studies and Toxicology
Institute for Laboratory Animal Research
Division on Earth and Life Studies

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