RSESS – March 16, 2009

The Great Debate:

Can Clinical trials be run safely without data from dog studies?

CON: Due Diligence for Effective Risk Management

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Can Clinical trials be run safely without data from dog studies?

“Drugs are pure, safe and effective for their intended uses” -- Food, Drug and Cosmetic Act (amended)

First consideration among all in clinical trials is human safety

Can Clinical trials be run safely without data from dog studies?

First consideration in clinical trials is human safety

'Safety' doesn't mean the NCE is totally safe.

It means that the toxicological properties of the NCE have been examined in non-clinical test systems (rodent, non-rodent) and are understood wrt –

- dose (exposure)-response,
- possible target organ toxicity (adverse outcomes),
- i.d. useful, predictive biomarkers (e.g., LFTs)
- preliminary margins of safety, and
- the likelihood of incurring lasting harm

RSESS – The Great Debate – 'Due Diligence for Risk Management'

Can Clinical trials be run safely without data from dog studies?

First consideration in clinical trials is human safety

- NCEs (small molecules) and biologicals are demonstrated to be pharmacologically active in *in vitro and/or vivo* model systems, and presumed so also in human subjects

- However we don't know precisely how pharmacological activity in humans may be manifested;
  - Are there known class (chemical, pharmacologic) effects; prior human experience with similar compounds?
  - One species (rat) may over- or under-predict
  - NCEs are 'unknown' at the start wrt their cross-species pharmacologic (toxicologic) properties

- Animal toxicity studies by design explore high dose effects and define the essential toxicologic properties (target organs, some biomarkers) and provide safety margins (wide or narrow) of NCEs for FIH studies

Can Clinical trials be run safely without data from dog studies?

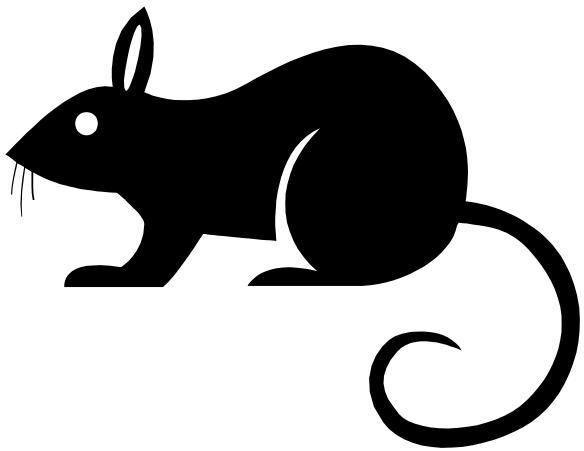
First consideration in clinical trials is human safety

- Human clinical trials do have a long history of safety – but sometimes unexpected serious AE's occur
- The long practice of conducting toxicity studies to MTD/MFD in two nonclinical species has underwritten this historical safe outcome
- without non-rodent (dog) data in general toxicology studies we are walking on the high wire without a safety net

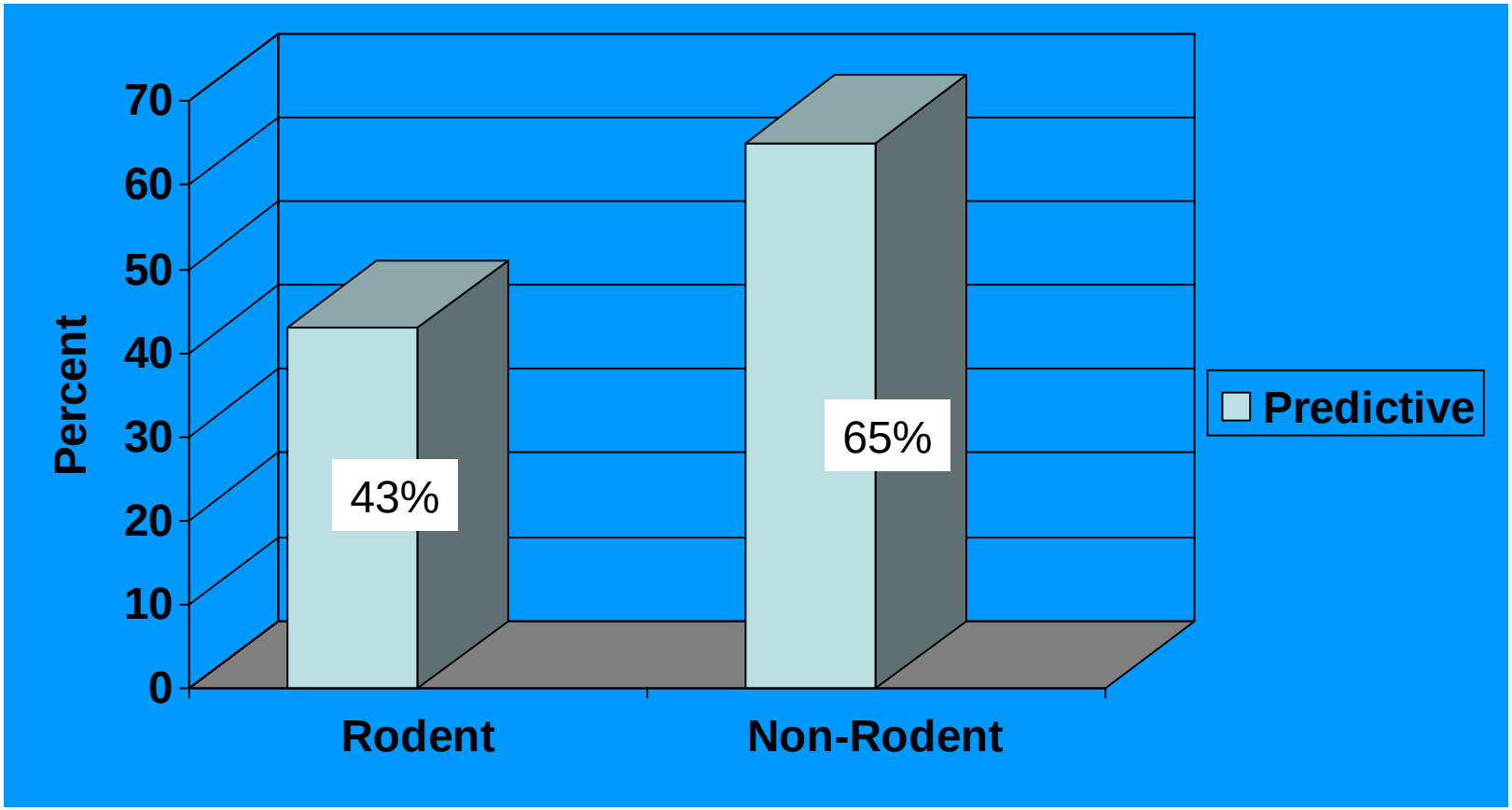
Is this just a dramatic overstatement?

Can Clinical trials be run safely without data from dog studies?
First consideration in clinical trials is human safety

- What may happen if we removed the dog from the nonclinical strategy?

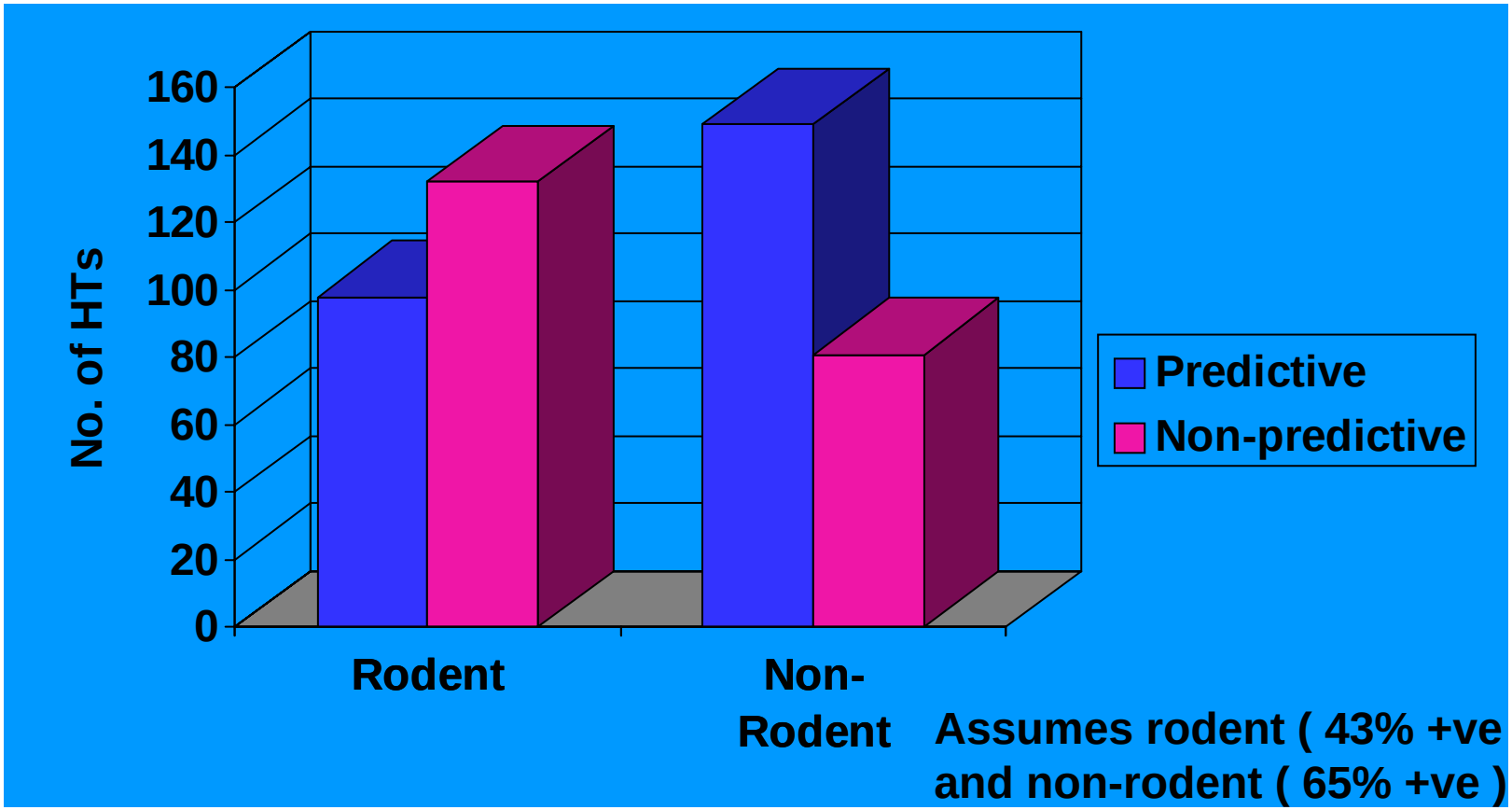


Prediction by Individual Species



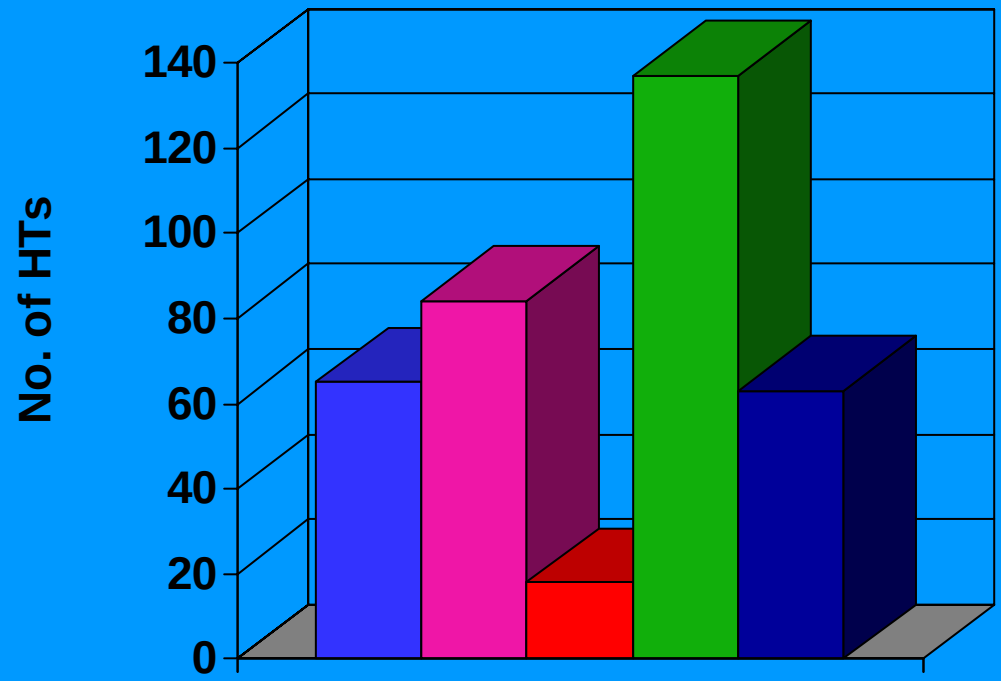
- Reg Tox Pharma **32**, 56-67, 2000

Prediction / Non-prediction by Species



Assumes rodent (43% +ve) and non-rodent (65% +ve) always used.

Preclinical Species in which Human Toxicity predicted (n = 230)



Species showing corresponding toxicity

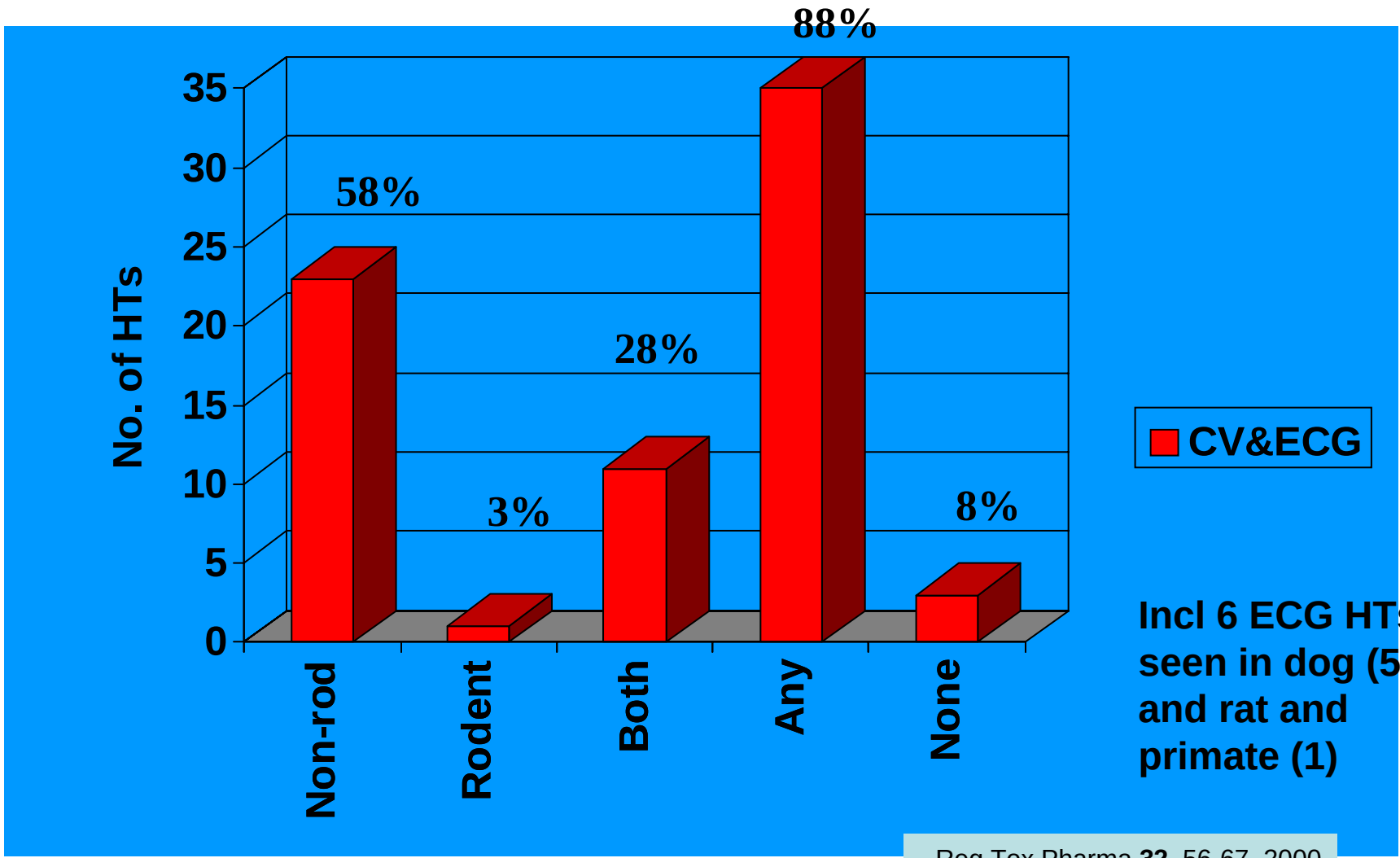
Total 73%+ve
(95% CI =)

- Non-rodent only 28%
- Non-rodent plus rodent 37%
- Rodent only 8%
- Any species 73%
- No species 27%

Positive non rodents only were dog (53) ,primate (12) or both (2). Rodents only were rat (13), mouse (3), guinea pig (4) and rabbit (1).

- Reg Tox Pharma **32**, 56-67, 2000

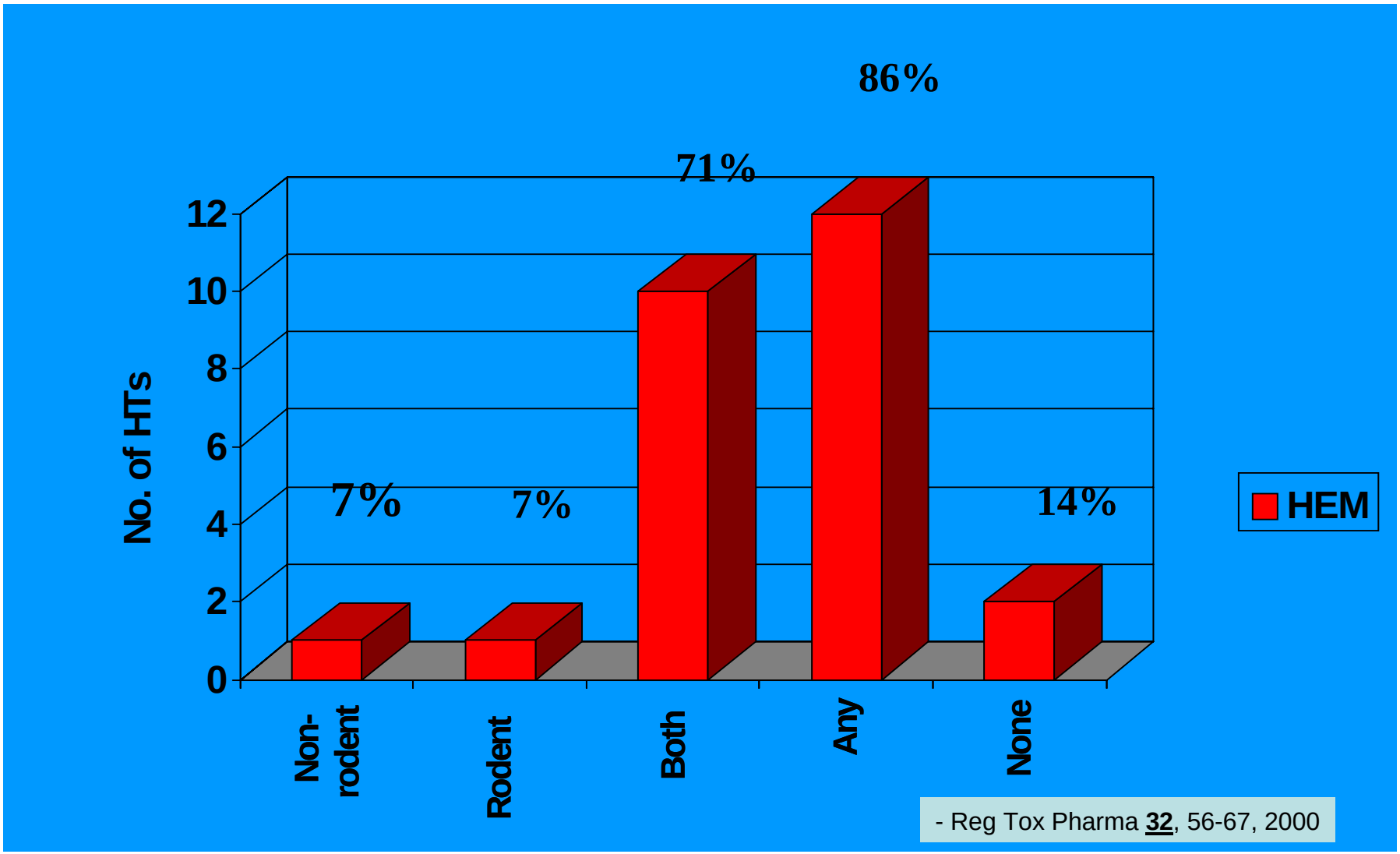
Predictivity of Cardiovascular Human Toxicity by Preclinical Species (n=40)



Incl 6 ECG HTs seen in dog (5) and rat and primate (1)

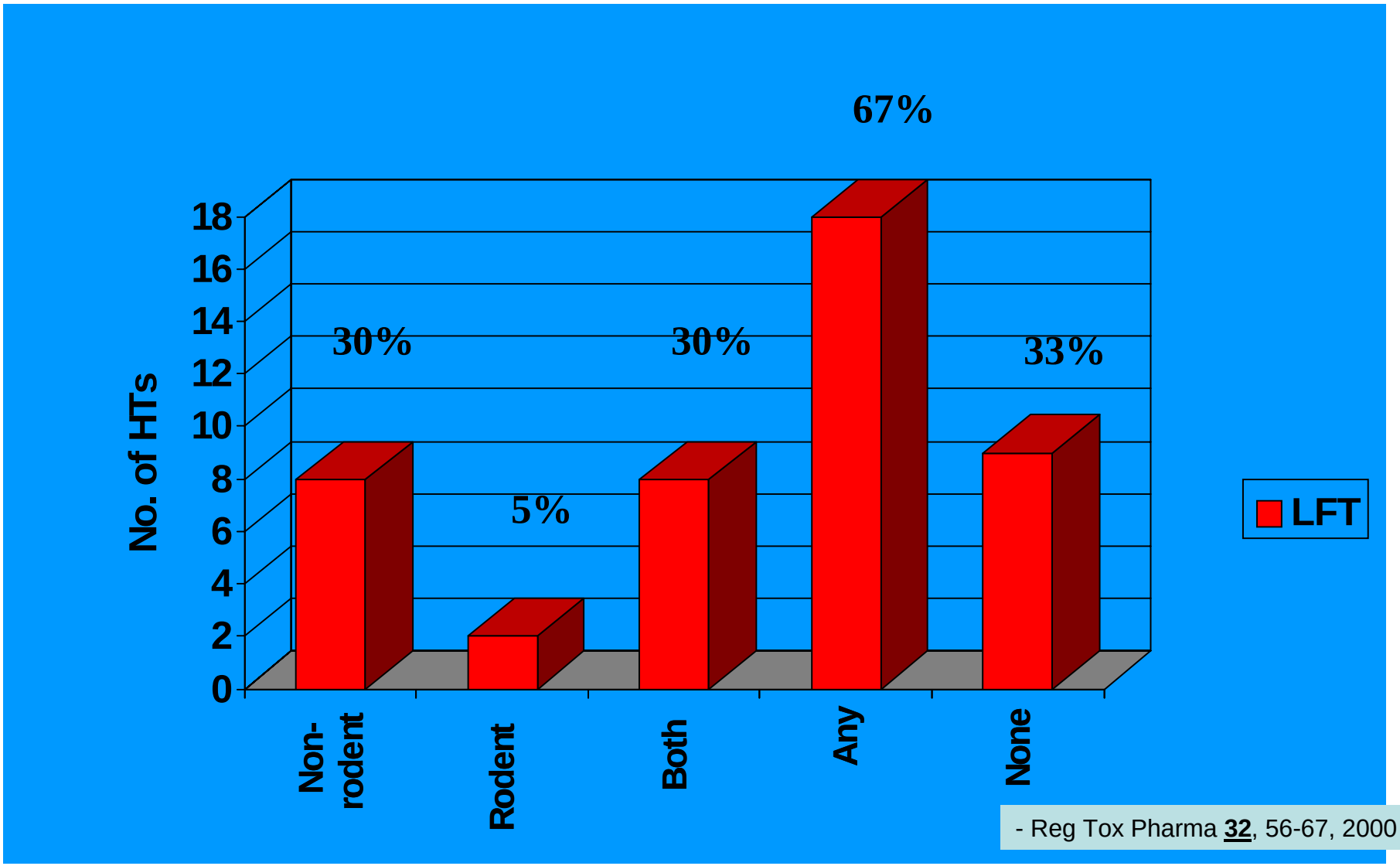
- Reg Tox Pharma **32**, 56-67, 2000

Predictivity of Hematologic Human Toxicity by Pre-clinical Species (n = 14)



- Reg Tox Pharma **32**, 56-67, 2000

Predictivity of LFT Human Toxicity by Pre-clinical Species (n = 27)



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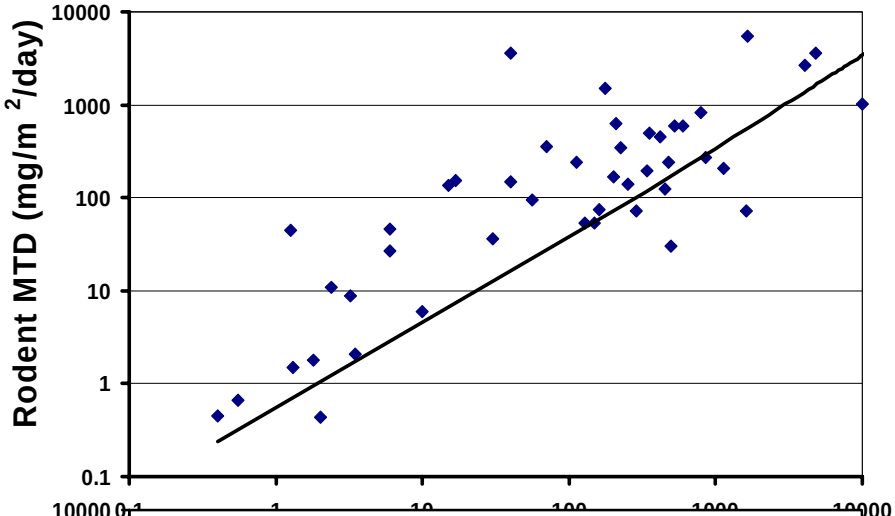
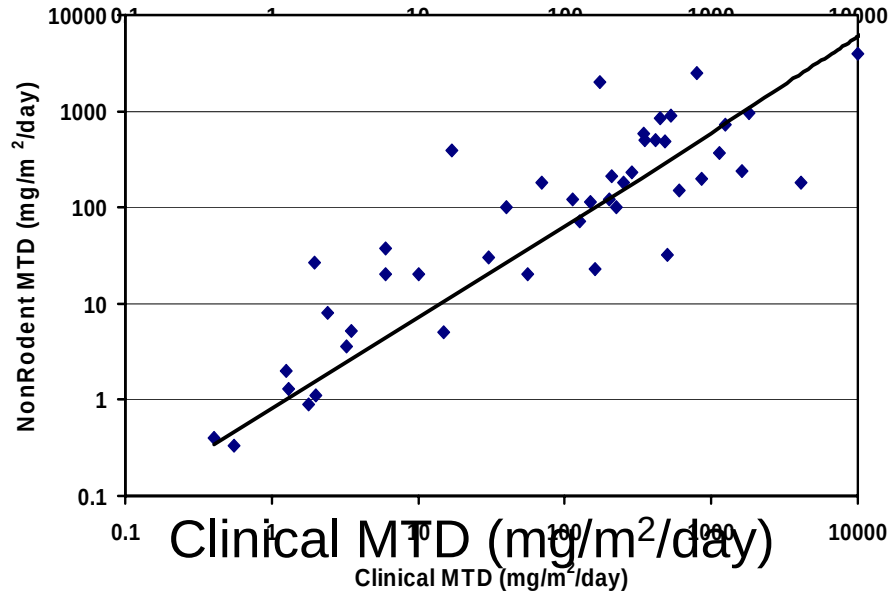
MTD- Rodent Human Correlation from : Smith and Tomaszewski, Preclinical and Clinical Toxicity Correlations for Cancer Drugs Developed by NCI. (2002)

Rodent MTD (mg/m^2/day)



Non-Rodent MTD (mg/m^2/day)



Clinical MTD (mg/m^2/day)

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First consideration in clinical trials is human safety

- A glimpse based on our experience -- What happens if we removed the dog from the nonclinical strategy ('rat only' tox studies)?
- The rat alone only predicts about 40% of known human toxicities
- The usefulness of the rat alone to identify human toxicities is variable:

Rat is useful (some toxicities):
- CNS
- Respiratory (tend to overprediction)
- GI
- Hemic
- Endocrine (selected examples)

Rat is not so useful:
- Cardiovascular
- Dermal
- Liver (high false +)
- GI (dog is better)
- Renal (overprediction)
- Respiratory (false –, and overprediction

-**Greaves, P Nature Rev Drug Discov. 3, 226-236, 2004 & other references**

Can Clinical trials be run safely without data from dog studies?

First consideration in clinical trials is human safety

- Consider what we've learned from history & experience with two species toxicology studies –
  1. Two species work better than one to identify human-relevant toxicity
  2. Dogs are more predictive of AE's in humans than are rats
  3. More sensitive species should drive selection of Ph 1 starting dose, and escalation speed
  4. We don't learn much about toxicity that is new (and relevant to human toxicity) beyond one-month duration toxicity studies

- Reg Tox Pharma **32**, 56-67, 2000, and other sources

First consideration in clinical trials is human safety

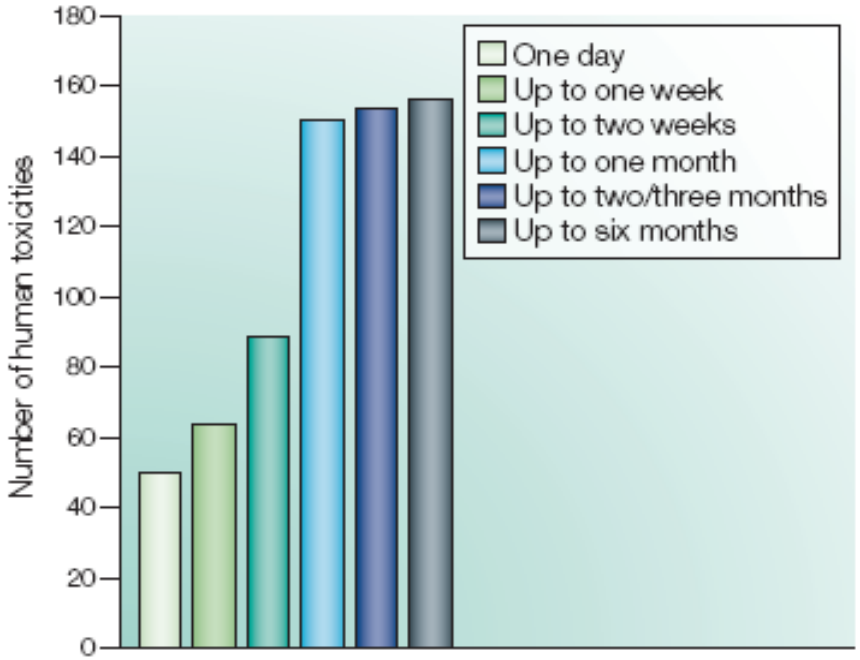

Figure 5 | **Time to first detection of animal toxicity.** The number of toxicities that can be detected in animal systems reaches a plateau at the one-month stage of the study. By this time, 94% of toxicities were detected, but prior to this time some toxicities were not apparent. On the first day, 25% of these observations were from safety pharmacology rather than from toxicology studies. Modified, with permission, from REF. 12 © (2002) Elsevier Science.

-Greaves, P Nature Rev Drug Discov. 3, 226-236, 2004

First consideration in clinical trials is human safety

- Do animals help us to identify human safety of medicines? - Yes
- Are toxicity studies in rats alone able to assure safety of medicines in early clinical development

  - Not really
- Is there a better way to conserve animal use in non-clinical development?

– Yes, expanded use of dogs and rats early; identify more sensitive species; then reduce/modify requirements for two species chronic testing