Numbers behind Infographic
Assuming "Future" is around 10 years from now
For explanation of "scaling" see the end of the document

CURRENT PREDICTIVE POWER

Human Concordance of animal testing: 60%

Calculated: 53% average, 71% combined: average ~ 60%

Estimate based on:
Olson, H., et al. 2000. Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals. Regulatory Toxicology and Pharmacology 32, 56–67

- Non-rodents, 63%; rodents, 43%; together, 71%
- Note: this is retrospective concordance of positive findings, does not take into account false negatives, and is not predictive capability

Current concordance of ToxCast: ~55%

Calculated, most appropriate: 54%, but don't want to give impression of confidence in accuracy by giving a precise number.

Calculation from:
Thomas et al. Russell S. Thomas, Michael B. Black, Lili Li, Eric Healy, Tzu-Ming Chu, Wenjun Bao, Melvin E. Andersen, and Russell D. Wolfinger. A Comprehensive Statistical Analysis of Predicting In Vivo Hazard Using High-Throughput In Vitro Screening. Toxicological sciences 128(2), 398–417 (2012) doi:10.1093/toxsci/kfs159

- ToxCast assays performance predicting 60 in vitro endpoints for ~300 chemicals
- The overall median balanced accuracy for the in vitro assays across the 60 in vivo endpoints was 0.504 with a median sensitivity and specificity of 0.130 and 0.921
- endpoints with a nearly equal number of positive and negative chemicals, the median balanced accuracy was 0.540 with a median sensitivity and specificity of 0.717 and 0.363.
- for QSARS: The balanced accuracy showed that 56 of the 60 endpoints were predicted at a level less than 0.55

BITS OF DATA* PER WEEK

*Bits of data only, not interpretation: these are not equivalent with respect to regulation: animal "bit" are used to regulate, ToxCast "bits" are used in combination for prioritization for testing.

Animal tests: 2500 (average)

Lowest: 4 (acute tox), high (carcinogenicity): 4,885
Average is approximately 2500

Estimates based on:
OECD TG Acute oral: average 8 rodents X 1 endpoint each/ 2 weeks = 4 per week

OECD TG 451: Carcinogenicity:
Endpoints:

Morbidity/mortality 2 x daily = 1464 x 400 = 585,600
Signs of toxicological relevance 1 x daily = 732 x 400 = 292,800
[Tumor onset, location, dimensions progression] =
Weight, food consumption, water consumption 1 X weekly = 3 x 104 x 400 = 124,800
Urine samples: [@ interim kill] and 10 per sex per dose x 11 endpoints at end = 880
Gross necropsy: once: external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents = 10 X 400 = 4000
54 organs saved
All tissues from the high dose and control groups; 200 x 54 = 10,800
[could be dozens of data points per slide if there are findings]

- All tissues of animals dying or killed during the study: varies from 0 – 200 X 54 = say 20% on average = 2,160
- All tissues showing macroscopic abnormalities including tumors;
- When treatment-related histopathological changes are observed in the high dose group, those same tissues are to be examined from all animals in all other dose groups;
- In the case of paired organs, e.g., kidney, adrenal, both organs should be examined.

Data reporting:

- body weight/body weight changes;
- food consumption, calculations of food efficiency, if made, and water consumption, if applicable;
- dose/exposure
- toxicokinetic data if available;
- ophthalmoscopy;
- haematology (at 3, 6, 12, 18 and 24 mos);
- clinical chemistry (at 3, 6, 12, 18 and 24 mos);
- Urinalysis (at 3, 6, 12, 18 and 24 mos)

- Signs of toxicity;
- Incidence (and, if scored, severity) of any abnormality;
- Nature, severity, and duration of clinical observations (whether transitory or permanent);
- Terminal body weight;
- Organ weights and their ratios, if applicable;
- Necropsy findings; Incidence and severity of abnormalities;
- Non neoplastic histopathological findings;
- Neoplastic histopathological findings;
- Correlation between gross and microscopic findings;
- Detailed description of all treatment-related histopathological findings including
- severity gradings;
- Report of any peer review of slides;

From J. Bucher at NTP: It currently takes from 18 months to 2 years to design, plans and organize a study and do the upfront analytical chemistry. Assuming no pre chronic dose selection studies are needed, the study takes 2 years, unless one starts with perinatal dosing in which case add 2 months. The lab generally takes 18 mo- 2 years to read the pathology and send in a report, and then it takes us about 2 years to verify pathology and write reports. Give or take a year here and there. John

From Nigel Walker: One correction
It usually, for a non perinatal study, takes 9-12 months for the lab to read the path and generate the GLP report.

From Sue Marty – In our lab, it takes approximately 2.5 years from protocol signing to final report for a chronic/oncogenicity study without perinatal dosing.

4 years to generate data = 209 weeks
5 years to complete entire study from beginning to interpretation
Minimum: 585,600 + 292,800 + 124,800 + 880 + 4000 + 10,800 + 2160 = 1,021,040/209 = 4,885

NCATS (NCCT): ~ 1.4 million

Current actual NCATS: 900,000 to 1,800,000 per week, average 1.35 million/week

Estimate from Geoff Spencer, NCATS:
NCATS current screening capacity from:
~10,000 chemicals x 15 concentrations x 3 replicates x 2-4 readouts = 900,000 to 1,800,000 bits of data per week

COST PER CHEMICAL:

Animal studies: $3,000,000
Full pesticide dossier: $3,000,000 (see attached spreadsheet)

Non-animal: $6,000
Near future non-animal: 63,000
With scaling 10-fold less that the HGP*, in 10 years the cost will be $6,300

Note: it will not just be a reduced cost issue, but also an increase in efficiency as fewer, less expensive tests are needed as predictive capacity increases.

Estimate based on:

- toxcast screen: 10,000
- 2000 per 3-d culture test: say 2 for eye, 3 for skin: 10,000
- in vitro genotox: minimum 2: 20,000
- Predicting cost of in vitro developmental tox, reprotox, immunotox, neurotox, or cancer in it's entirety is not realistically feasible at this point – but say theoretically that it would be possible to get at these using a combination of 3-D reconstructed organs:
- organ chips: (from HuRel) 1000 X say, 8 organs = 8,000
- toxicokinetics:
- cost estimates for circulating human-on-chip systems: hard to estimate but say 8 organs plus circulation plus analysis: 15,000 (probably very low)
- Minimum: 10,000 + 10,000 + 20,000 + 8,000 + 15,000 = 63,000

Note: when AOPs have been constructed, and outcomes can be reliably predicted from a series of in vitro mechanistic assays, an assessment could be done using fewer assays.

TESTING CAPACITY
Note: again, at the moment comparing apples to oranges – one can regulate on RCB data, but not on ToxCast data. Calculations below include the assumption that pathway understanding will improve to the point where in vitro results can be used to make most regulatory decisions.

Animal studies: 20 (average)
Estimated: 0.1 to 17

Estimate based on:
From Andrew Rowan:

> In about 30 years of using the NCI Cancer Bioassay system, we have generated data on around 500 chemicals (= 17 per year) but have managed to generate a human risk assessment on no more than one-fifth of the bioassay data sets.

On the other hand, it takes about 10 years to complete a dossier for a pesticide active. So that is 0.1 chemical/year.

So average the two over 10 years: 171/10 = 17 per year, rounded up to 20

ToxCast: 4,000

Estimated: 4,000

Estimate based on ToxCast so far:

> Richard Judson, Keith Houck, Matt Martin, Thomas Knudsen, Russell S. Thomas, Nisha Sipes, Imran Shah, John Wambaugh andKevin Crofton. ***In Vitro* and Modelling Approaches to Risk Assessment from the U.S. Environmental Protection Agency ToxCast Programme. Basic & Clinical Pharmacology & Toxicology Volume 115, Issue 1, pages 69–76, July 2014**
>
> 2007 – 2014: 7 years = 365 weeks
> 700 assays or assay endpoints
> 1800 chemicals in different concentrations, some 1, some as many as 11
> Some chems screened in a subset of assays
> Total: 1,526,359 chemical/assay pairs /365 = 4,182 per week
>
> **From R. Judson (US EPA):** this an interesting question that doesn't have a single answer. Your basic arithmetic below is correct for ToxCast / Tox21 – we have about 1-2 million assay/chemical combinations, so you get ~2500-5000 chemical-assay combinations / week. Having said that, we had people generate data in spurts, so none of the labs were running our sample full time. Even the NCGC lab has only been running Tox21 samples a fraction of the time (much more time is spent developing each assay than running the 10K library). Because of this, if NCGC had 20K or even 100K chemicals (which would include all chemicals in commerce and more), they could still have run the same set of assays in the same time.

FUTURE PREDICTIVE POWER

Animal: could say 70%
the point here is that this is not likely to improve much over time

Pathway-based: >90%
Already ToxCast can predict ER activity with ~ 90% accuracy according to Browne, et al. **2015. Screening chemicals for estrogen receptor bioactivity using a computational model. *Environ. Sci. Technol.* 49(14):8804-14.**

The system will continue to improve over time, but will always be imperfect so will asymptotically approach 100%.

***Economy of Scale: need to determine based on human genome project**
From: A.N. Rowan. 2015. Ending the Use of Animals in Toxicity Testing and Risk Evaluation

The potential of the new approaches, exemplified by the ToxCast program, to improve toxicity testing and risk assessment can be estimated by looking at what has happened as a result of the Human Genome Project (HGP). It cost approxi- mately $300 million to sequence the first human genome (the entire HGP cost being around $3.8 billion). Since the completion of the HGP in 2001, the cost of sequencing a human genome has dropped to a little more than $1,000 (a 300,000-fold improvement in cost per genome).
(http://www.genome.gov/images/content/cost_per_genome_oct2015.jpg)
Over 14 years.

Hayden EC. The $1,000 genome. Nature 2014;507:7492; available at http:/ /www.nature.com/news/technology-the-1,000-genome-1.14901 (last accessed 1 Mar 2015).
US$10 million in 2007 to 1000 in 2015 → 10,000 x in 7 years.

Let's round up to 10 years: 10,000,000 → 10,000 in 10 years, and reduce that further by 10X → 1,000 in 10 years to be conservative.