Basic principles of the safety assessment of drugs

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Björn Dahl, PhD
Senior Project Director
Global Safety Assessment
AstraZeneca R&D

Outline of presentation

Safety assessment in the discovery and development of drugs

Target

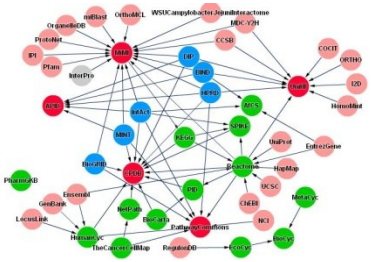
Lead chemistry

Cmpd selection

Cmpd characterisation / regulatory documentation / risk assessment

New indications, formulations, combinations, impurities, degradation products, patient populations, paediatrics etc

Target Safety Assessment

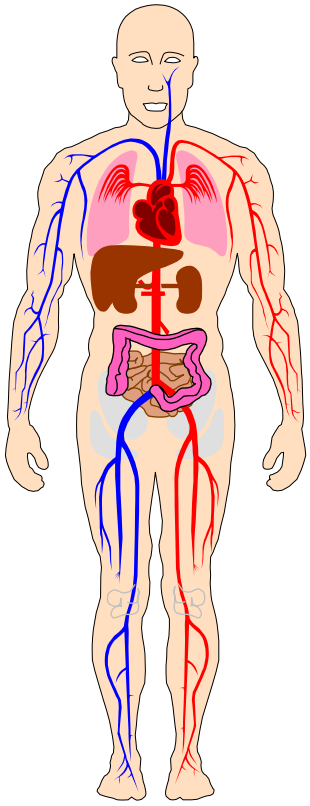


Some components

- overall target function/biology in health and disease
  - pathway mapping/interaction with other pathways
  - information from ko/ transgenic models
  - human target variations - implications

- target distribution
  - explicitly not only confined to intended pharmacological tissue/ organ
  - identifying relevant species for toxicological characterisation
  - in health and in disease

- functionally / structurally related targets
  - selectivity (off target pharmacology)



→ critical issues addressed experimentally when possible

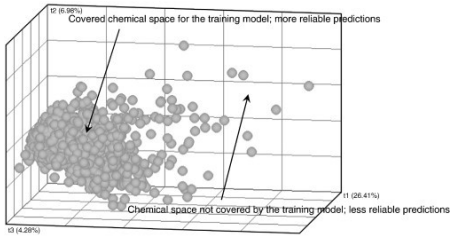
→ build/refine safety plans moving forward

Chemistry Safety Assessment

Components of early avoidance of chemical structure safety liabilities:

• chemical structures are analysed continuously ***in silico*** for possible structure-related safety concerns:

- genotoxicity
- hERG channel blockade
- reactive metabolite formation
- phospholipidosis
- bone marrow toxicity
- structural similarity to problematic molecules
- DMPK properties
- and more ……



→ experimental follow up of potential issues
→build/refine safety plans moving forward

Optimisation of lead compounds

Screening ***in vitro*** for e.g.

- Genotoxicity
- hERG and other ion channels
- Cyto tox
- Immunotox
- Hepatic tox
- Bone marrow tox
- Transporters
- Metabolism/CYPs
- Reactive metabolites
- Off target pharmacology/secondary pharmacology
- Cross-species comparisons where applicable

Fit for purpose ***in vivo*** studies, e.g.

- To early address target or chemistry related safety concerns identified
- To extract relevant safety information as part of PK/PD characterisation in *in vivo* (disease) models
- To build confidence in safety before expanding into larger regulatory animal studies

Internal decision making up to this point

Safety characterisation of candidate drug

Objective

- Provide and assess safety information relevant for conducting safe clinical trials and supporting marketing applications.

Animal data generally more in focus at:

- First dose to man (healthy volunteers, patients)
- Increased duration/doses
- First dose to women of childbearing potential
- First dose to children
- Assessing reproductive and carcinogenic risks

Clinical safety data evolve during development and eventually override some of the toxicology data

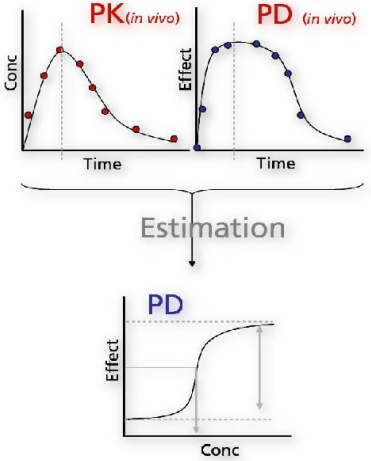
Drug safety surveillance of marketed drugs continues for the life-time of the products

Regulatory guidelines - framework

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- ICH M3(R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals
- And many more detailed international and regional guidances

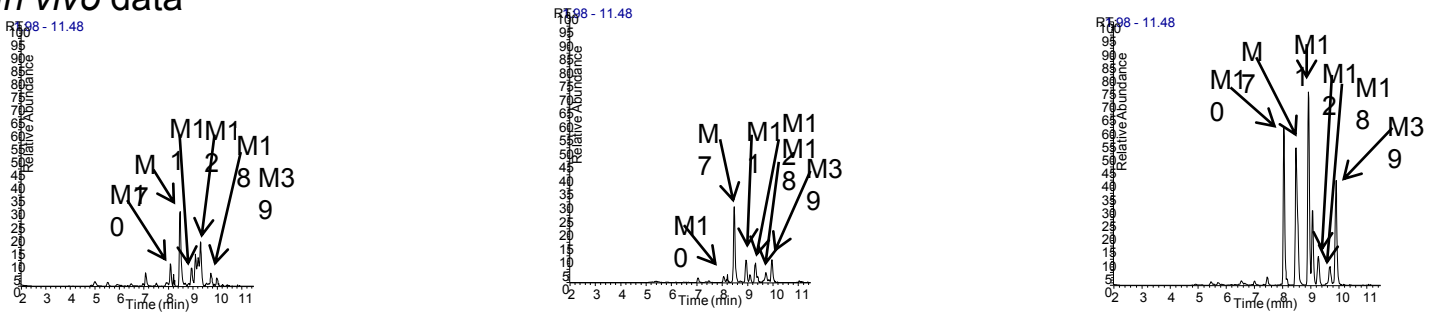
Considerations selecting animal species

- Pharmacologically responsive?
  - To address concerns around exaggerated pharmacology



- Appropriate local and systemic exposure to the drug
  - Ensure adequate exposure margins in the relevant tissues/compartments is achievable using the proposed route of administration in man.
  - Supplement by alternative route if needed and feasible
  - Take into account local vs systemic exposure, half-life, exposure profiles, max/min levels, protein binding etc.

- Coverage of human relevant metabolites?
  - Compare cross-species including man
  - Microsomes
  - Hepatocytes
  - *In vivo* data



Chromatograms obtained from analysis of Human, Rat and Dog steady state plasma samples

Safety Pharmacology

Studies that investigate the potential **undesirable pharmacodynamic effects on physiological functions** at exposures in the therapeutic range and above

- Studies on the mode of action and or effects in relation to the **desired therapeutic target**
- Studies on the mode of action and/or effects **not related to the desired therapeutic target** (with focus on vital functions such as CV, Respiratory, CNS)
- Usually single dose/short-term studies in rodents and non-rodents

- **Identify** undesirable pharmacodynamic properties relevant to human safety
- **Evaluate** adverse pharmacodynamic effects observed in toxicology and/or clinical studies
- **Investigate mechanisms** of adverse pharmacodynamic effects

General toxicity studies

One rodent and one non-rodent species

- Generally rats and dogs
- Duration equal or longer than intended clinical trial (up to 6 months in rodents and 9/12 months in non-rodents)

Dose levels:

- Relevant route of administration
- Therapeutic up to Max Tolerable/Limit/Fesible Dose
- Exposure rather than dose levels
- Generally 1 control and 3 treatment groups (+ recovery)

Aim:

- Systemic exposure levels
- Target(s) of toxicity
- Incidences and severities
- Dose-dependency
- Time-dependency
- Species specificity
- Reversibility

General toxicity studies continued
Evaluations - endpoints

- clinical signs
- body weight
- food & water consumpt.
- ophthalmoscopy
- ECG (non-rodents)
- toxicokinetics
- clinical pathology
  - haematology
  - blood chemistry
  - urinalysis
- pathology
  - necropsy/gross pathology
  - organ weights (12-20)
  - microscopic pathology (40-45 different tissues from each animal)
- ad hoc as appropriate
  - non std biomarkers
  - special stainings
  - male fertility
  - explorative samples
  - Met ID
  - safety pharm endpoints

Genetic toxicology

Drug:

in vitro assays

- Ames Test (bacteria) – gene mutation
- Mouse Lymphoma TK locus test or Chromosomal aberrations in human lymphocytes (mammalian cells) – chromosomal damage
- +/- metabolic activation system

***in vivo* assays**

- Micronucleus assay (rats or mice, bone marrow)

Genotoxic Impurities:

- *In silico* and *in vitro* assessment of Potential Genotoxic Impurities (PGI) from manufacturing route or degradation processes
- Control under Threshold of Toxicological Concern (TTC) (some times down to ppm levels of active drug)

Reproductive toxicology

- Fertility – dosing of males and females before and during mating, but also evaluation of reproductive organs in general tox studies: usually in rats

- Embryofoeteal development – dosing of females during major organ development – evaluation of offspring: usually in rats and rabbits

- Peri and postnatal development: including reproductive performance of offsping (2nd generation)

- Generally, studies on fertility and embryofoetal development before inclusion of women of childbearing potential although exceptions do exist

Carcinogenicity

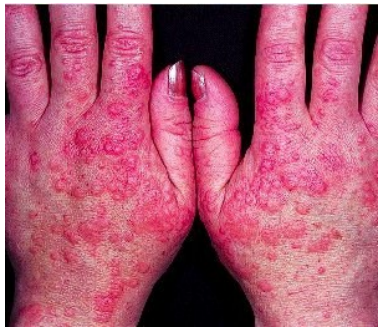
- Studies in rodents with life time exposure ~ 2 years
  - Usually rats and mice (2 studies)
  - 500-600 animals/study
  - Tumour incidence – histopathological evaluation of most tissues
  - Performed at a late stage of development – takes ~3 years to complete
  - Options for alternative tests, eg 6 month test in transgenic mice models sensitive to tumour development
    - Can replace one of the studies
  - ICH S1 revision under discussion

Phototoxicity

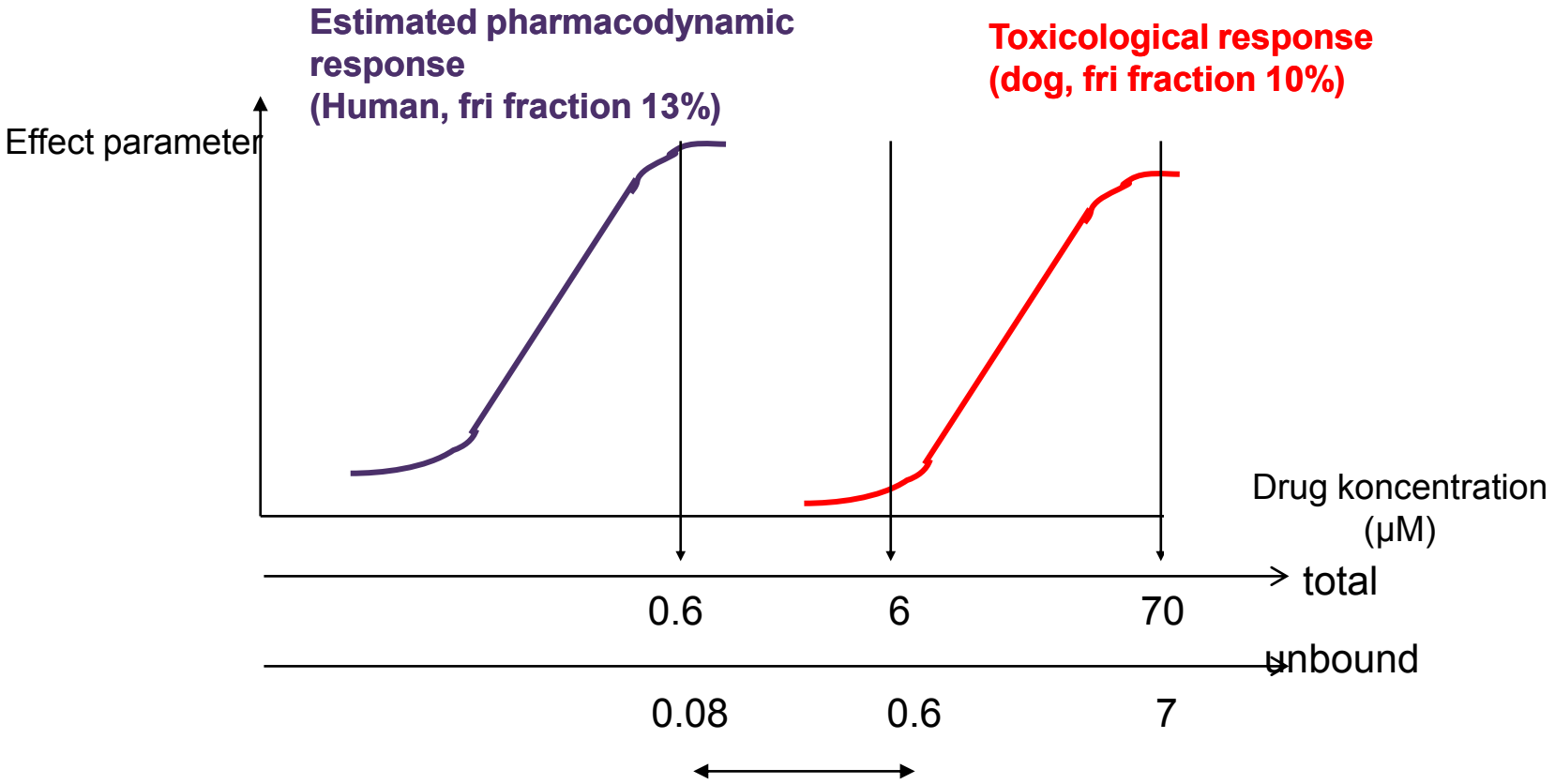
Assessment for potential phototoxicity part of the standard package

- Does the cmpd absorb UV/VIS light in significant amounts (MEC>1000)?
- Does it distribute to tissues exposed to sunlight?
- In vitro assessment
- In vivo assessment

Apply precautions if needed in clinical trials



Safety margins - Risk assessment



Safety margin: 10x

Correction free fraction (unbound): 7.5x

Example prediction of human exposure at FTIM

Pharmacokinetic models – allometric scaling – predictions to man

1

Primary PK parameters in animals (CV%)

	CL mL/min/kg	VDss mL/kg	$t_{1/2, \lambda 2}$ (h)
Cynomolgus monkey	3.6 (45)	87 (24)	19.4 (47)
Mouse	12 (8)	138 (13)	10.2 (12)
Rat	5.6 (5.4)	73 (9.4)	11 (16)
Rat [a)]	5.7 (13)	77 (22)	11 (40)

Predicted human PK

	CL (mL/h/kg)	Vss (mL/kg)	$t_{1/2, \lambda 2}$ (h)
Human*	1.5	53	29

* Predicted from allometric scaling

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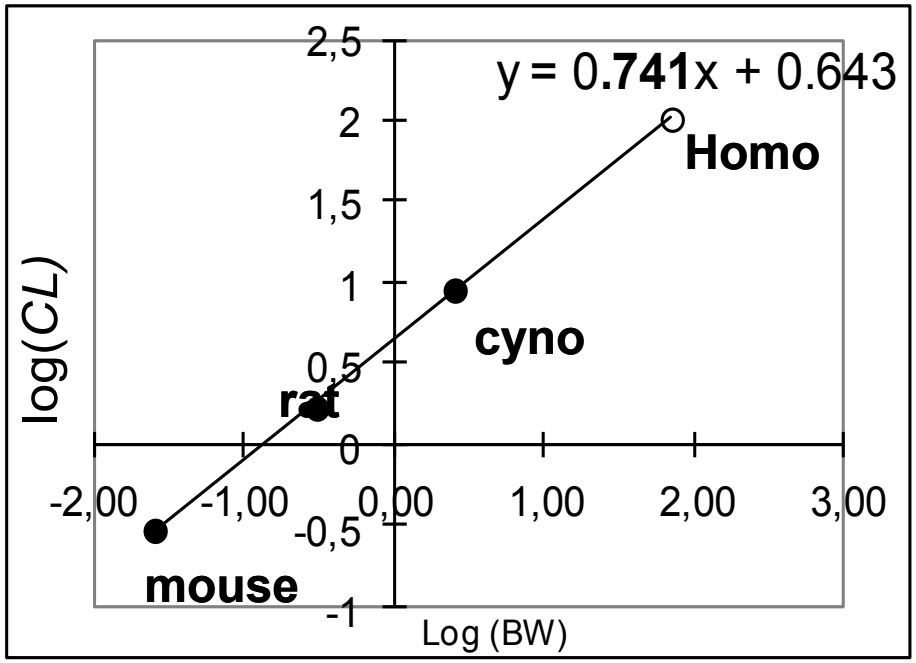

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What is an appropriate safety margin/exposure limit?

Some general considerations:

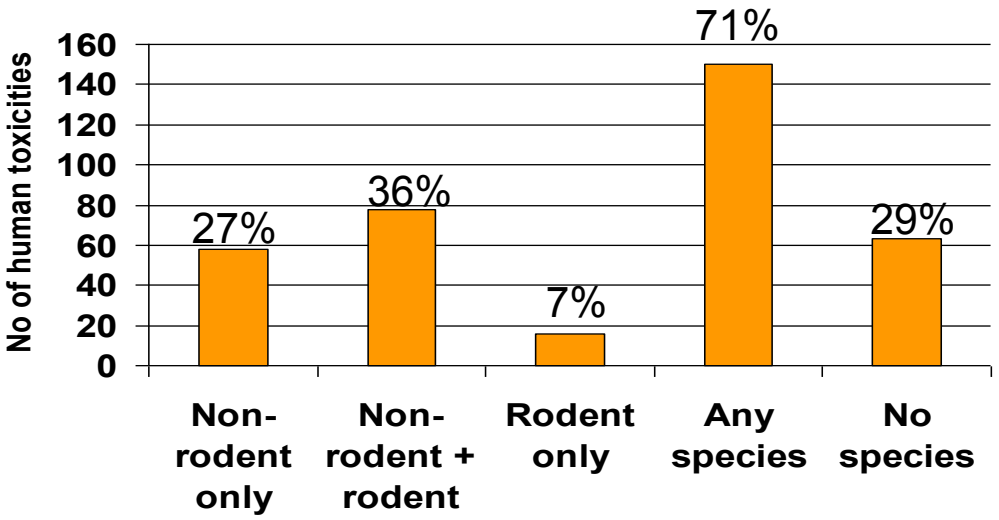
- Patient population, indication
- Human relevance or not
- Human vs animal sensitivity
- Exaggerated pharmacology or unspecific toxicology
- Adaptive vs. degenerative
- Reversibility
- Biomarker sensitivity and predictivity, if available

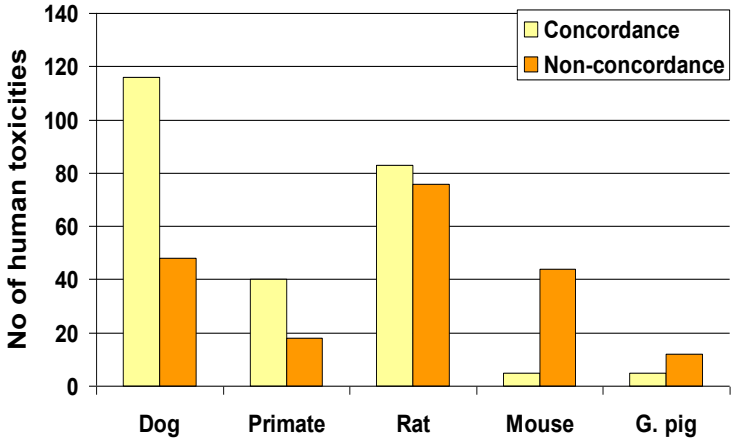
- Risk to occur in the study population at suggested dose levels?
- Potential consequences if it occur?
- Risk/benefit for the patients?
- How to detect, predictive or diagnostic markers available?
- How to act if it occur, recovery following drug withdrawal, antidotes?

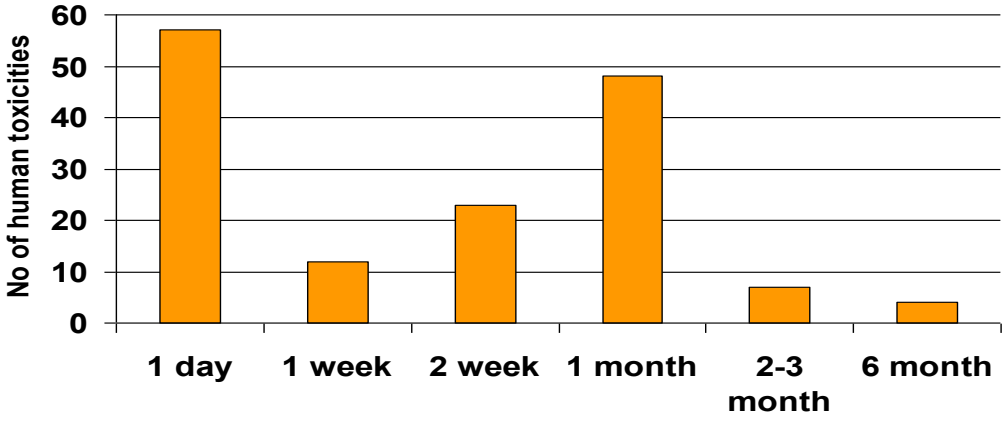
Acceptable safety margins and exposure limits set case-by-case

Risk assessment not only for next clinical trial but also for ”line of sight”

Concordance of toxicity: animal vs man







Olsson et al., Regulatory Toxicology and Pharmacology 32, 56-67 (2000)

Sola dosis facit venenum

“The dose makes the poison”