National Centre for the Replacement Refinement & Reduction of Animals in Research

Incidence of new toxicities in biologics and small molecules upon long-term dosing

Helen Prior, Briony Labram and Fiona Sewell
The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), London, UK

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Introduction

A recent international consortium[1] reviewed the use of two species in drug development, concluding that current ICHS6(R1) approaches for use of a single species for long-term toxicity studies could be used more widely for biologics and other modalities, including small molecules[2]. The cross-company dataset was examined to investigate how often new toxicities are identified in long-term (13, 26 or 39 week) toxicity studies in rodents and non-rodents and whether use of only one species would miss toxicities of concern for human safety.

Methods

Short-term studies were defined as ≤6 weeks and long-term studies as 13-39 weeks.

For rodents (31 molecules) and non-rodent (33 molecules) separately, toxicities in different target organs (high-level definitions, e.g. haematology, immune system etc) were compared between study durations and molecules were classified into those where new toxicities were identified in long-term studies, and those where no new effects were observed.

For 29 molecules with short and long-term studies in both rodent and non-rodent, the number of unique target organ toxicities identified in short-term studies were combined, and the identification of new toxicities in either rodent or non-rodent long-term study was noted. A hypothetical exercise was then conducted to evaluate if new toxicities would potentially be missed if only one of the species had been progressed to long-term studies.

Results

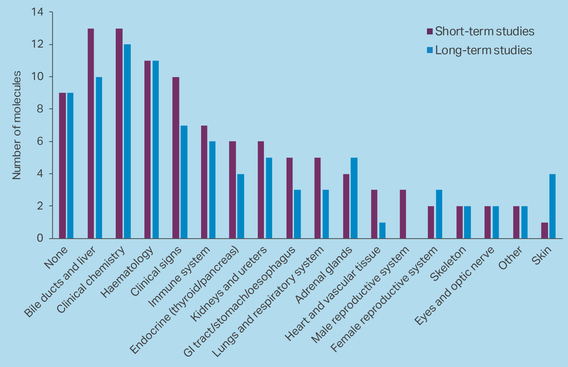


Figure 1. Common rodent target organ toxicities in short and long-term studies.

Table 1. The number of molecules with new toxicities identified in rodent long-term studies.

	21 small molecules		10 biologics	
Toxicities	**New[a]**	**None**	**New[b]**	**None**
	7	14	4	6
Target organs	Bile ducts/liver (3) Skin (2) Female repro (2) Hematology (2) Endocrine (1) Clinical chemistry (1) Kidneys/ureters (1) Adrenal glands (1) Eyes/optic nerve (1)		Skin (2) Skeleton (1) Adrenal glands (1) Other (1)	

[a] single new toxicity in 4 molecules, multiple new toxicities in 3 molecules

[b] single new toxicity in 3 molecules, multiple new toxicities in 1 molecule

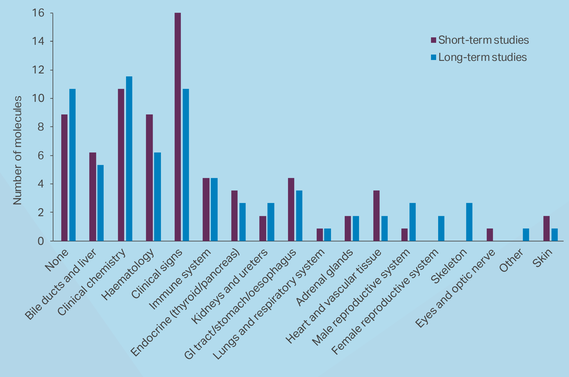


Figure 2. Common non-rodent target organ toxicities in short and long-term studies.

Table 2. The number of molecules with new toxicities identified in non-rodent long-term studies.

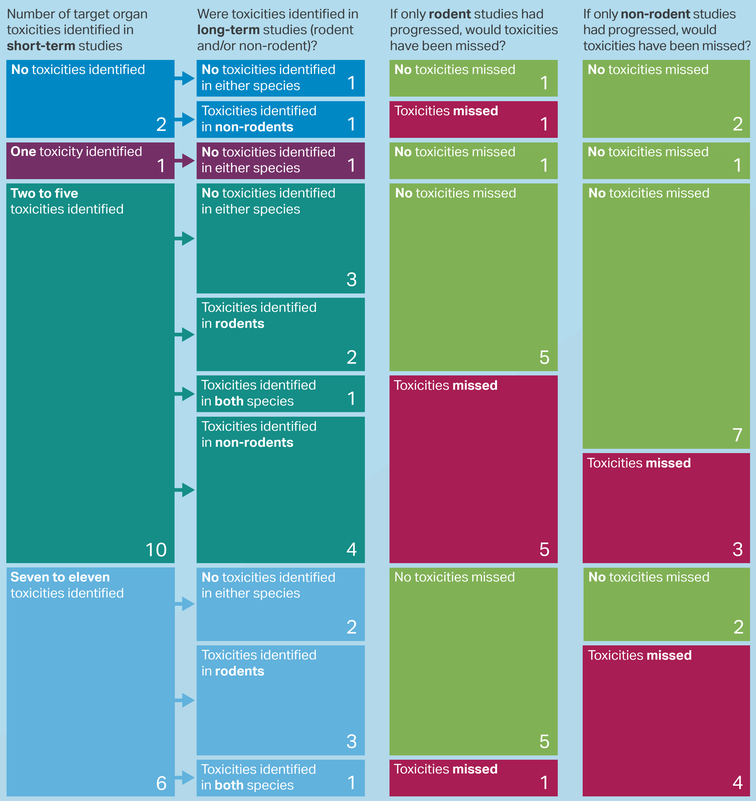
	19 small molecules		14 biologics	
Toxicities	**New[a]**	**None**	**New[b]**	**None**
	7	12	4	10
Target organs	Immune system (2) Male repro (2) Kidneys/ureters (2) Female repro (1) Hematology (2) Bile ducts/liver (1) Clinical chemistry (1) Clinical signs (1) Adrenal glands (1) Idiopathic canine polyarteritis (1) GI tract/stomach/oesophagus (1) Skeleton (1)		Bile ducts/liver (2) Skeleton (2) Skin (1) Female repro (1) Heart/vascular tissue (1) GI tract/stomach/ oesophagus (1) Lungs and respiratory system (1)	

[a] single new toxicity in 3 molecules, multiple new toxicities in 4 molecules

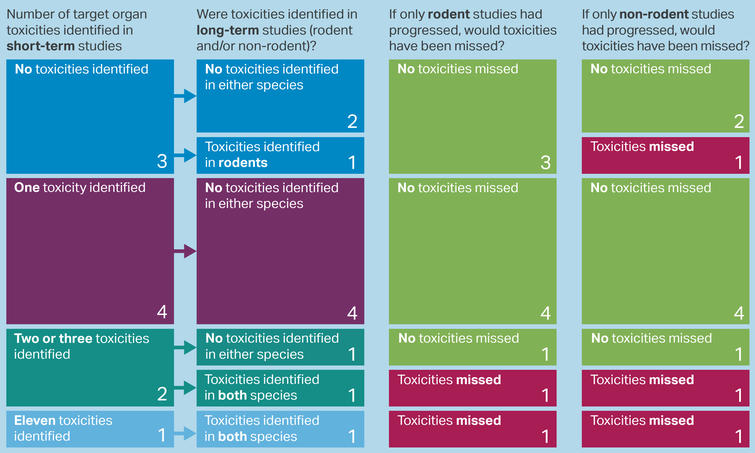
[b] single new toxicity in 2 molecules, multiple new toxicities in 2 molecules

Results

Of 19 small molecules tested in both rodent and non-rodent short and long-term studies



Of 10 biologics tested in both rodent and non-rodent short and long-term studies



Discussion

New toxicities are identified in longer-term studies in each species; the relative importance or impact of the new toxicity(ies) on molecule progression was not available within the dataset. There are no new toxicities identified in long-term studies for a significant proportion of molecules: 60% biologics and 67% small molecules (rodent) or 71% biologics and 63% small molecules (non-rodent).

When two species are used for short-term studies there are opportunities to reduce to only one species for longer-term studies. A key concern is how to identify the most appropriate species to progress from short-term study data such that human safety is not compromised.

For biologics, new long-term toxicities may have potentially been missed in 20% if the rodent only had progressed, or in 30% if the non-rodent only had progressed. For small molecules, new long-term toxicities may have been missed in 37% if the rodent only had progressed, or in a different 37% if the non-rodent only had progressed.

References

1. Prior *et al.* (2018). Reviewing the Utility of Two Species in General Toxicology Related to Drug Development. *International Journal of Toxicology* 37: 121-124.

2. Prior *et al.* (2020). Opportunities for use of one species for longer-term toxicology testing during drug development: a cross-industry evaluation. *Regulatory Toxicology & Pharmacology*, DOI 10.1016/j.yrtph.2020.104624.