NC3Rs

Reviewing the use of two species in toxicology studies supporting drug development

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Introduction

The UK's National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs) and the Association of the British Pharmaceutical Industry (ABPI) are collaborating to review the utility of two species in regulatory toxicology studies.

The purpose is to explore circumstances when data from a single species could be sufficient to enable safe progression in humans, for a broader range of molecule types than current practice and at different stages of development.

An international working group was convened in 2017, consisting of representatives from 25 pharmaceutical and biotechnology companies, 4 contract research organisations, 2 consultancies, 2 academic and 4 regulatory bodies (Europe and USA).

Here we present preliminary, brief results from the data sharing exercise conducted to gather information on current practices, species used and the value of data from two species.

Methods

Data was collected by questionnaire, during May to August 2017. Participants were requested to submit information from their most recent molecules (compounds) to have completed packages of toxicology studies (performed post-2012 to reflect current guidelines) at the following stages of progression: a) pre-First-in-Human (FIH) studies, b) FIH package or c) post-FIH longer-term studies. No compound-identifying factors (names or chemical structures) were collected and all data was blinded upon receipt at the NC3Rs.

Results

Eighteen organisations submitted data for 172 compounds (Figure 1): 53% from USA, 44% from Europe and 3% from Japanese-based companies. The dataset includes compounds from five different molecule types (Figure 1) and multiple therapeutic indications (Figure 2).

114 compounds were in active development whilst 58 had stopped (Table 1). The majority of compounds (93) had completed the First-in-Human (FIH) package of toxicology studies, whilst a further 47 were in later development and had conducted post-FIH longer-term toxicology studies.

Two species were used by 89 (97%) small molecules, 5 (83%) ADCs, 12 (80%) recombinant proteins and all 13 synthetic peptides, but just for 14 (30%) mAbs (Figure 3). The rodent and non-rodent species used are illustrated in Figures 4a and 4b.

For compounds using two species (Table 2), one small molecule (following ICHM3 guidelines), 2 ADCs and 5 mAbs (all following ICHS6 guidelines) reduced to a single species during the package. All other compounds retained use of two species: 94 followed ICHM3 or ICHS9 guidelines whilst 31 followed ICHS6 guidelines (including 11 compounds at post-FIH stage).

Figure 1
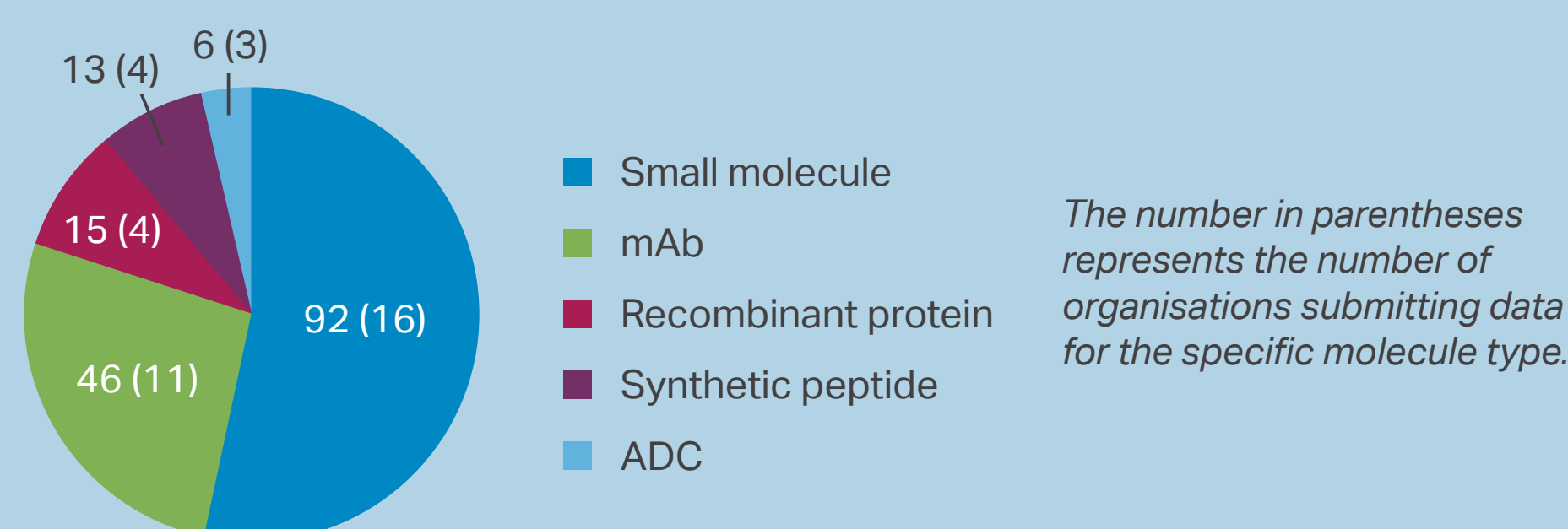The number of compounds per molecule type within the dataset.

The number in parentheses represents the number of organisations submitting data for the specific molecule type.

- Small molecule: 92 (16)
- mAb: 46 (11)
- Recombinant protein: 15 (4)
- Synthetic peptide: 13 (4)
- ADC: 6 (3)

Figure 2
The therapeutic indications of the compounds within the dataset.

* includes not disclosed (3), bleeding disorders/ haematology (2), urology (3), gastrointestinal (1) and gynaecology (1).
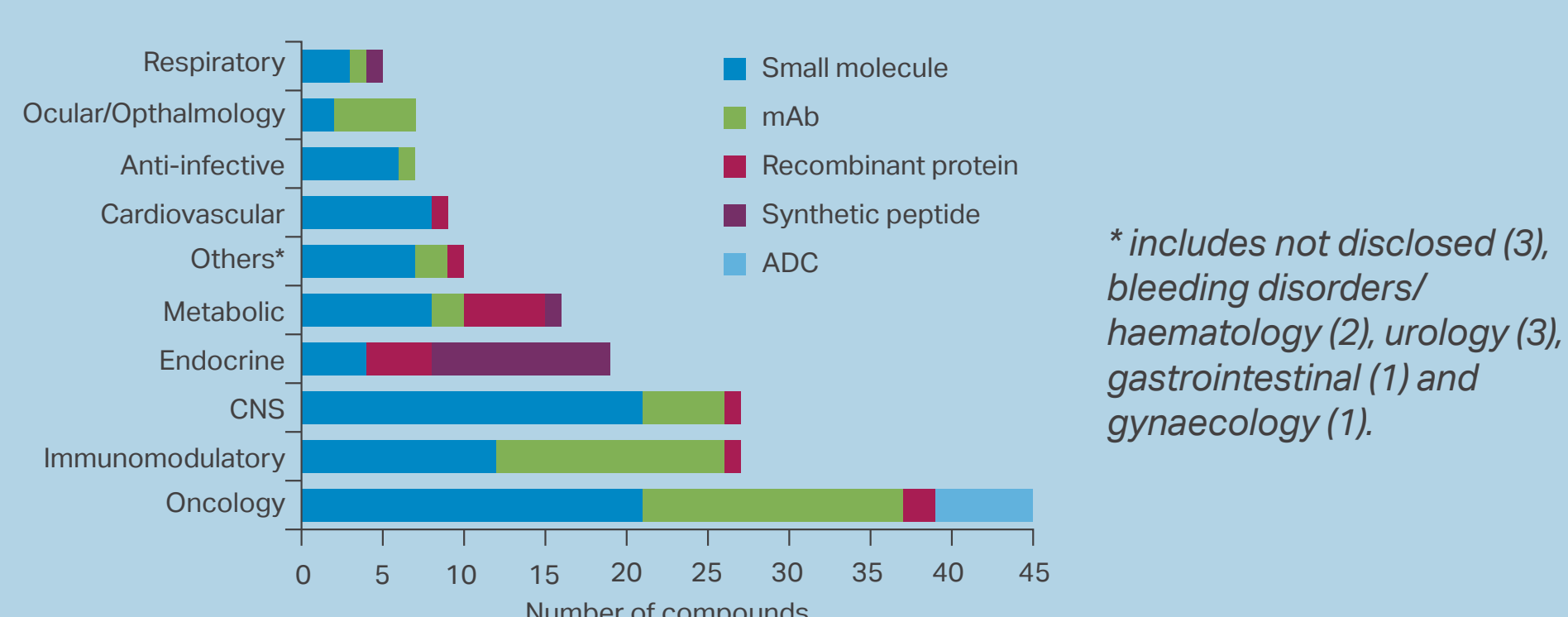
Figure 3
The number of species used for compounds for different therapeutic indications.
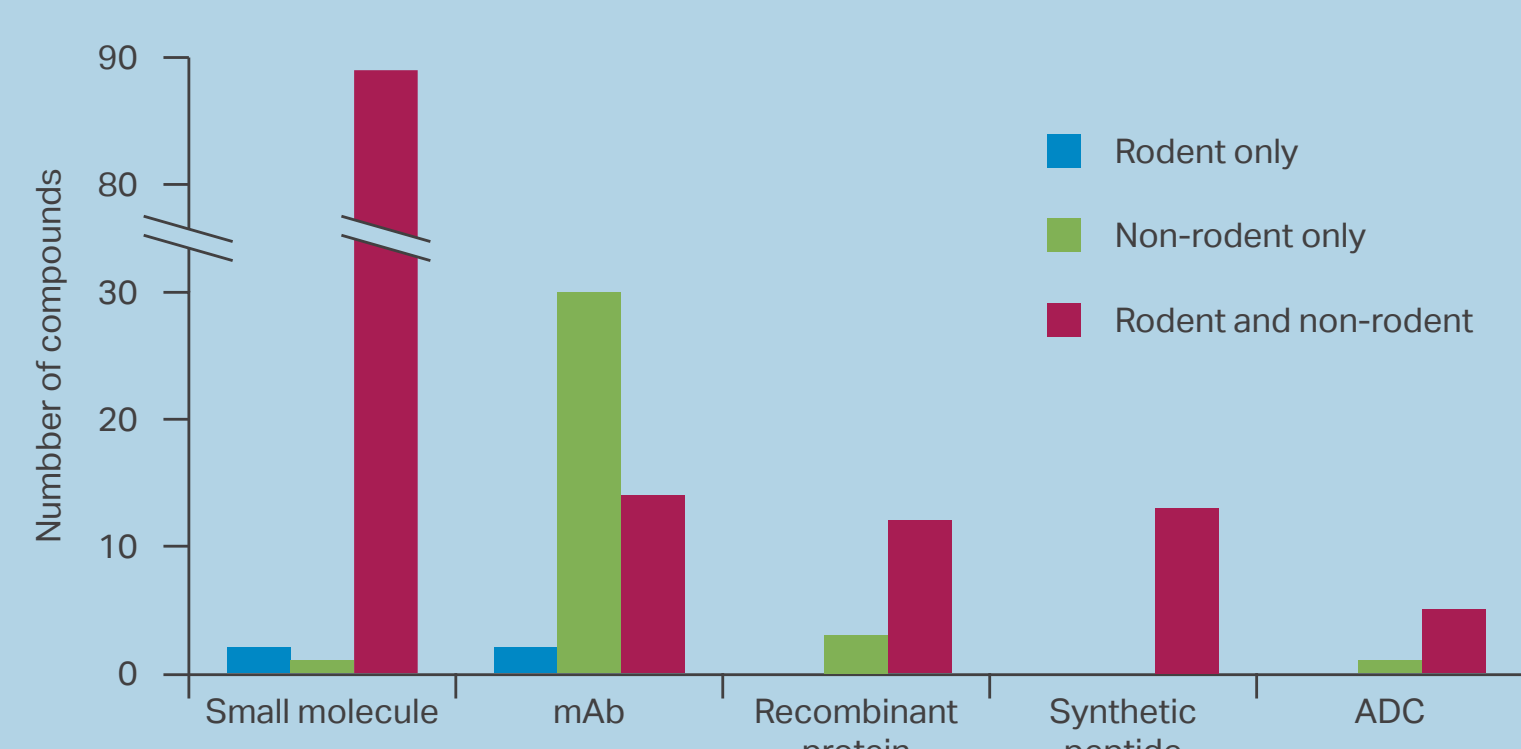

Figure 4a
The rodent species used for compounds from different molecule types.
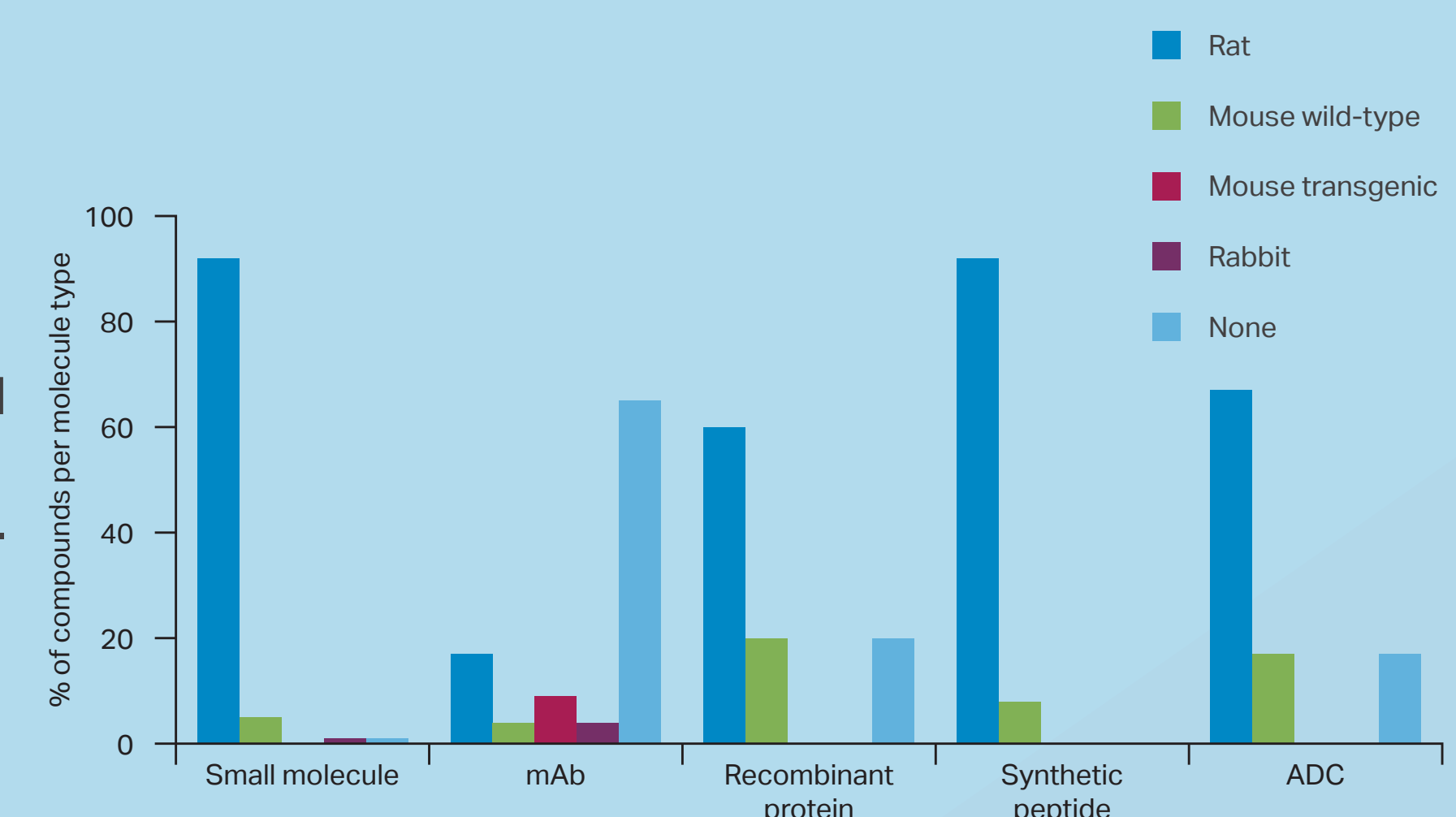

Figure 4b
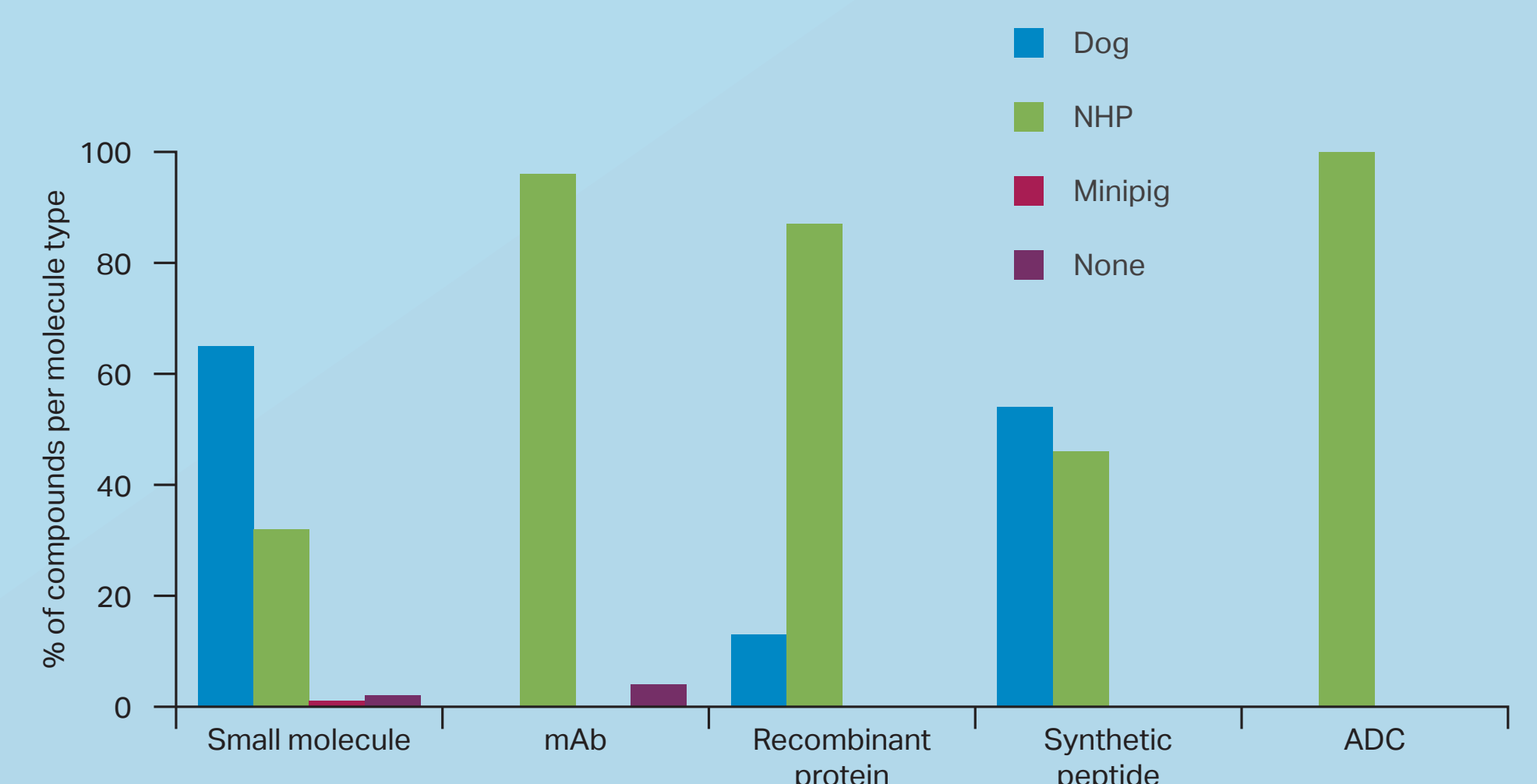The non-rodent species used for compounds from different molecule types.

Table 1: The distribution of compounds across the three phases of toxicology studies.

	Number of compounds in active development				Number of compounds stopped in development			
	Pre-FIH	FIH	Post-FIH	Active total	Pre-FIH	FIH	Post-FIH	Stopped total
Small molecule	12	26	25	63	11	18	0	29
mAb	0	19	10	29	1	11	5	17
Recombinant protein	3	4	1	8	1	5	1	7
Synthetic protein	2	3	5	10	0	3	0	3
ADC	0	4	0	4	2	0	0	2
Total for phase	17	56	41	114	15	37	6	58

Pre-FIH: compounds that have completed early non-GLP studies (not yet started FIH studies)
FIH: compounds that have completed pivotal GLP studies and/or FIH trials
Post-FIH: compounds that have completed pivotal long-term studies and/or Phase II/III trials

Table 2: The reduction from two to one species for different molecule types at the three toxicology phases.

	Guidelines followed				Compounds at pre-FIH that reduced to one species	Compounds at FIH that reduced to one species	Compounds at post-FIH that reduced to one species
	Total	ICHM3	ICHS6	ICHS9			
Small molecule	89	68		21	0 / 21	0 / 43	**1** / 25 [a]
mAb	14		14		**1** / 1 [b]	**4** / 7 [c]	**2** / 6 [d]
Recombinant protein	12		12		0 / 3	0 / 7	0 / 2
Synthetic protein	13	3	10		0 / 2	0 / 6	0 / 5
ADC	5		2*	3	0 / 1	**3** / 4 [e]	

* these compounds also followed ICHS9 guidelines.
[a] progressed in dog only; [b] progressed in NHP only; [c] one progressed in rat and three in NHP only;
[d] both progressed in rat only. [e] all progressed in NHP only.

Discussion

This information provides a starting point to examine the question around how many species need to be used for regulatory toxicology studies, and if the typical two species approach could be replaced more frequently with a one species approach.

For small molecules, two species use was the common approach (as expected), irrespective of therapeutic indication. For large molecules, single species use was evident in many cases (some mAbs), but not for others (recombinant proteins, synthetic peptides and ADCs). For these molecules, where two species had been used initially, there were few incidences of reducing to one species in later stages of development.

Understanding the differences or similarities in toxicities between species may highlight reasons for low adoption of regulatory guideline opportunities (single species chronic studies for biologicals) and may provide evidence to promote consideration to apply the use of one species to a wider range of molecule types (e.g. small molecules) or therapeutic areas (e.g. oncology).

Supporting human safety is the key focus of regulatory toxicology studies and the opportunity to use one species, or reduce from two to one species, requires careful consideration. Further analysis and reflection of the complete dataset is ongoing. Future publications will describe these results and provide recommendations for potential scenarios when the use of one or two species may be appropriate.

Acknowledgements

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