# Can we expand the use of one species for post-First-in-Human (FIH) studies, within and beyond ICHS6?

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## Introduction

The UK 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[1].

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 is current practice and at different stages of development.

Within ICHS6 guidelines, one species may be used for longer-term studies if toxicity profiles are 'comparable' in two species in short term studies. Here we present a detailed analysis of target organ toxicities identified at First-in-Human (FIH) stage, to identify the incidence of similar target organ toxicities between species in short term studies and to determine whether other guidelines could also adopt this principle.

## Methods

Data were collected by questionnaire (May to August 2017). Participants submitted information from their most recent molecules (compounds) to have completed packages of toxicology studies (performed post-2012 to reflect current guidelines). No compound-identifying factors (names or chemical structures) were collected and all data were blinded upon receipt at the NC3Rs.

The dataset was sorted to identify molecules that used two species for short-term (2-13 week) toxicology studies to support FIH submission. The target organ toxicities in the two species were compared and noted as 'none', 'same', 'similar' or 'different' (see footnote to Table 1). The assumptions used were 1) if toxicities are different in the two species at FIH this provides scientific justification for the continuation of post-FIH studies using two species, and 2) if toxicities are similar in the two species at FIH this provides scientific justification for the reduction to one species for post-FIH studies. No assessment of severities or relative importance of target organs for decision-making was made.

A blinded exercise was performed for 35 molecules with additional longer-term ('post-FIH') data (13-39 week). The toxicities in the two species at FIH were reviewed and a decision to continue the post-FIH studies in two species or to reduce to one species was made. The actual post-FIH study outcomes were then revealed and concordancy tables created (Tables 3 and 4).

## Results

Eighteen organisations submitted data for 172 compounds; 115 of these (from five different molecule types) used two species for their FIH toxicology studies (Figures 1 and 2). ICHM3 or ICHS9 guidelines were followed by all 75 small molecules and three synthetic peptides. ICHS6 guidelines (alone or in combination with ICHS9) were followed by all the mAbs, recombinant proteins and ADCs, plus 9 synthetic peptides.

Toxicities were similar ('none', 'same' and 'similar' definitions combined) in both species for 32, 85, 36, 42 and 25% per molecule-type, respectively (Table 1). For 11 molecules following ICHS6 that progressed to post-FIH studies, four mAbs, one recombinant protein and one synthetic peptide had similar toxicities at FIH, yet only two mAbs reduced to one species (Table 2).

The blinded exercise decisions to reduce to one species or not were 100% accurate for mAbs, recombinant proteins and synthetic peptides, and 70% accurate for small molecules.

## Discussion

Molecules following ICHM3 and ICHS9 (all the small molecules and three synthetic peptides in our dataset) do not currently have the option to use one species for post-FIH studies. This data indicates that FIH study toxicities are similar in the two species for approximately 33% of these molecules and therefore that there could be opportunities to reduce to one species for post-FIH studies on a case-by-case basis.

Molecules following ICHS6 (all the mAbs, recombinant proteins and ADCs, plus 9 synthetic peptides in our dataset) do have the option to use one species for post-FIH studies. A higher number (74%) of these molecules had similar toxicities at FIH, yet a relatively small number did reduce to one species for post-FIH studies.

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. We propose that when toxicities are similar in two species at the FIH stage, subsequent studies could proceed in a single species with low risk to human safety.

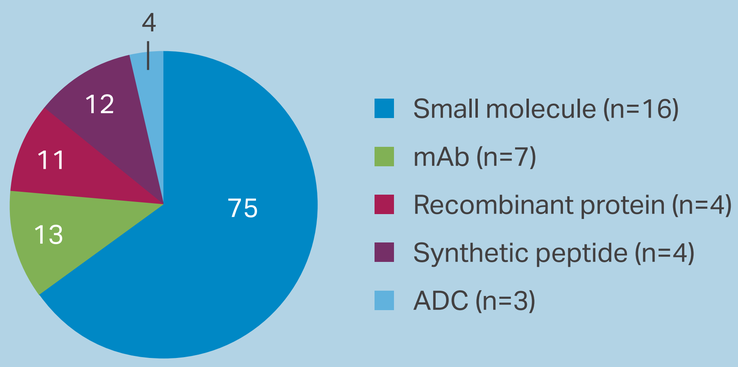


**Figure 1:** Number of compounds per molecule type with FIH data in two species.

n *represents the number of organisations submitting data for the specific molecule type.*

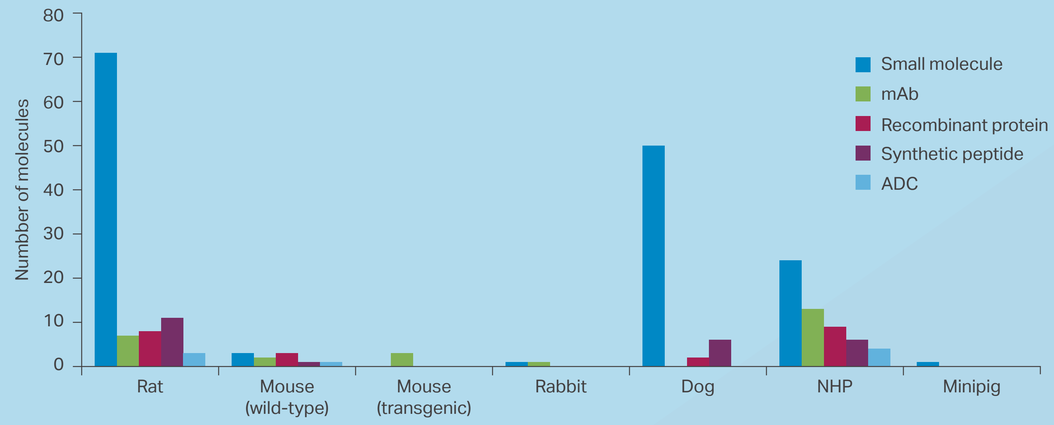


**Figure 2:** The species used for FIH studies by molecule type.

**Table 1:** Target organ toxicities identified in the two species for FIH studies.

| | None | Same | Similar | Different |
|---|---|---|---|---|
| **Small molecule (75)** | 3 | 11 | 10 | 51 |
| **mAb (13)** | 8 | 3 | - | 2 |
| **Recombinant protein (11)** | 1 | 1 | 2 | 7 |
| **Synthetic peptide (12)** | 4 | - | 1 | 7 |
| **ADC (4)** | - | 1 | - | 3 |

**Definitions of the table categories:**

None = absence of target organ toxicities in both species
Same = toxicities identified in the same target organs in both species
Similar = toxicities in both species, mostly the same (only one additional or different target organ toxicity in one of the species).
Different = No target organ toxicities in one species and at least one in the other species, or more than one target organ toxicity different in the two species.

**Table 2:** The species used for post-FIH studies (molecules following ICHS6).

| Molecule type | Toxicities in the two species at FIH | Species used for post-FIH studies |
|---|---|---|
| **mAb** | None | Rat only |
| **mAb** | None | Mouse and NHP |
| **mAb** | None | Rat and NHP |
| **mAb** | Same | Rat only |
| **mAb** | Different | Rat and NHP |
| **mAb** | Different | Mouse and NHP |
| **Recombinant protein** | None | Mouse and NHP |
| **Recombinant protein** | Different | Mouse and NHP |
| **Synthetic peptide** | Similar | Rat and NHP |
| **Synthetic peptide** | Different | Rat and NHP |
| **Synthetic peptide** | Different | Rat and NHP |

| Decision following review of FIH data | Concordant | Non-concordant |
|---|---|---|
| **Drop to one species** | No effects in either of the two species used in chronic toxicology studies OR effects only identified in the species chosen to progress. (Sponsor used one species so matched decision).<br><br>3Rs opportunity 'safely' taken | Effects identified in the species chosen to drop, therefore potential safety concerns would be missed.<br><br>Missed potential safety concerns |
| **Retain two species** | Different effects identified in the two species used in chronic toxicology studies, therefore retaining two species was justified.<br><br>Justified use of two species | Effects identified in only one species, or neither species, therefore this is a missed 3Rs opportunity to reduce to one species.<br><br>Missed 3Rs opportunity |

**Table 3:** Criteria for the blinded exercise (the potential to reduce to one species or to retain two species for the post-FIH studies).

**Table 4:** Outcomes from the blinded exercise (the potential to reduce to one species or to retain two species for the post-FIH studies).

| | | Concordant | Non-concordant |
|---|---|---|---|
| **Small molecules** | | | |
| Drop to one species | 14 | 9 (64%) | 5 (36%) |
| Retain two species | 9 | 7 (78%) | 2 (22%) |
| **Other molecules*** | | | |
| Drop to one species[1] | 8 | 8 (100%) | - |
| Retain two species[2] | 4 | 4 (100%) | - |

*The mAbs, recombinant proteins and synthetic peptides have been collated into an 'other molecules' category.
[1] These were five mAbs and three synthetic peptides.
[2] These were one mAb, two recombinant proteins and one synthetic peptide.

## Acknowledgements

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## References

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