Using an AOP framework to identify the most human relevant test species – for confident single species DART assessments

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Are two species required for DART assessment?

The ICH S5 guidance generally requires developmental reproductive toxicity (DART) studies in two mammalian species: one rodent and one non-rodent. However, recent publications[1,2,3,4,5] have questioned the added value of a second species. The overall findings include:

- Rats and rabbits are typically equally sensitive to DART.
- True species-specific differences, where only one species demonstrates DART, are rare.
- Embryofoetal death is more prevalent in the rabbit, whereas growth retardation and variations are more prevalent in the rat.
- Study replication errors are usually the cause of observed species differences.

Given these findings, species specific mechanistic knowledge and knowledge of species-related potency findings for different potential mechanisms of action (MOAs) relating to DART could be used to build arguments to support the selection of a single, most appropriate species, in which to carry out a DART assessment.

The concept

We have developed a network of DART related AOPs that provides insight into mechanisms of toxicity and supports the interpretation of data from NAMs and traditional animal studies for regulatory decisions. With the addition of species sensitivity knowledge to AOPs, this network may enable single species safety assessments (Figure 1). We present a case study using a gonadotrophin releasing hormone (GnRH) AOP to assess whether AOP stressor can justify a single species DART assessment (Figure 2). If successful, this approach could be applied across the wider AOP network.

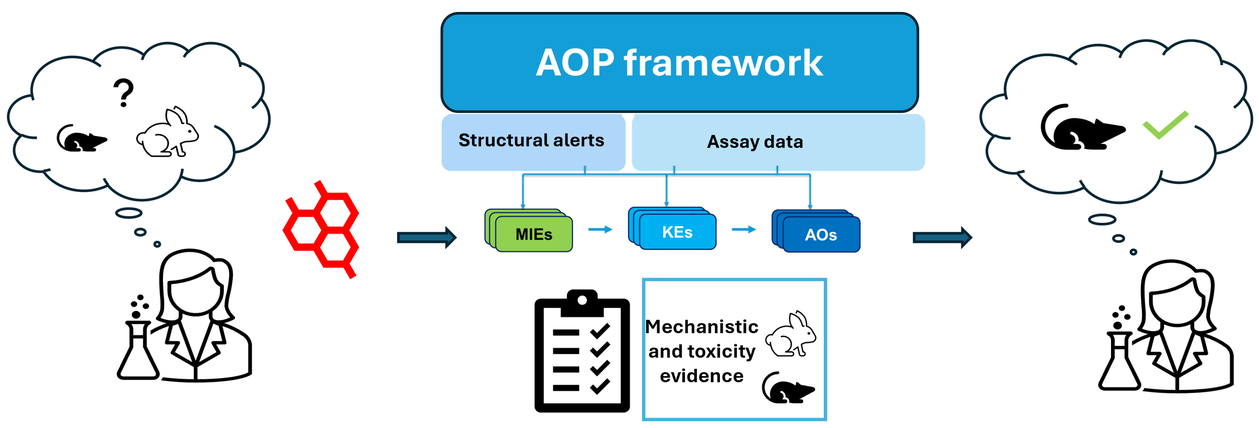

Figure 1. An AOP framework used to determine the most suitable species and support single species DART assessment.

To build confidence in single species risk assessments, we evaluate AOP-associated stressors and potency data to identify the most sensitive species for a particular MOA. Our approach scores stressor compounds against relevant factors (Figure 2) and combines these results to determine the most appropriate species for DART assessment. This assertion can then be tested using toxicity data for a target compound.

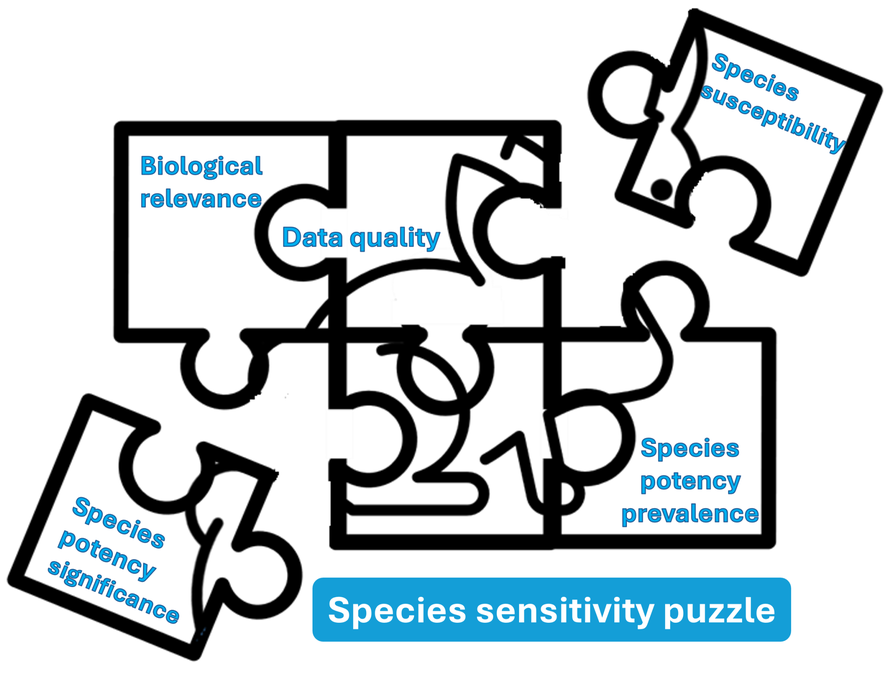

Figure 2. Factors evaluated to determine whether two species DART assessments are required for compounds with a particular MOA. Evaluating these factors help provide a confident argument to support single species DART assessments.

Case study – GnRH AOP species sensitivity

The GnRH AOP was identified as a suitable candidate around which to build a case-study. Stressors of the GnRHR were identified and relevant data was gathered. The compound abarelix was removed from the initial investigation to be used as the target compound later in the case study. 10 compounds which had both rat and rabbit data were identified and taken forward for assessment.

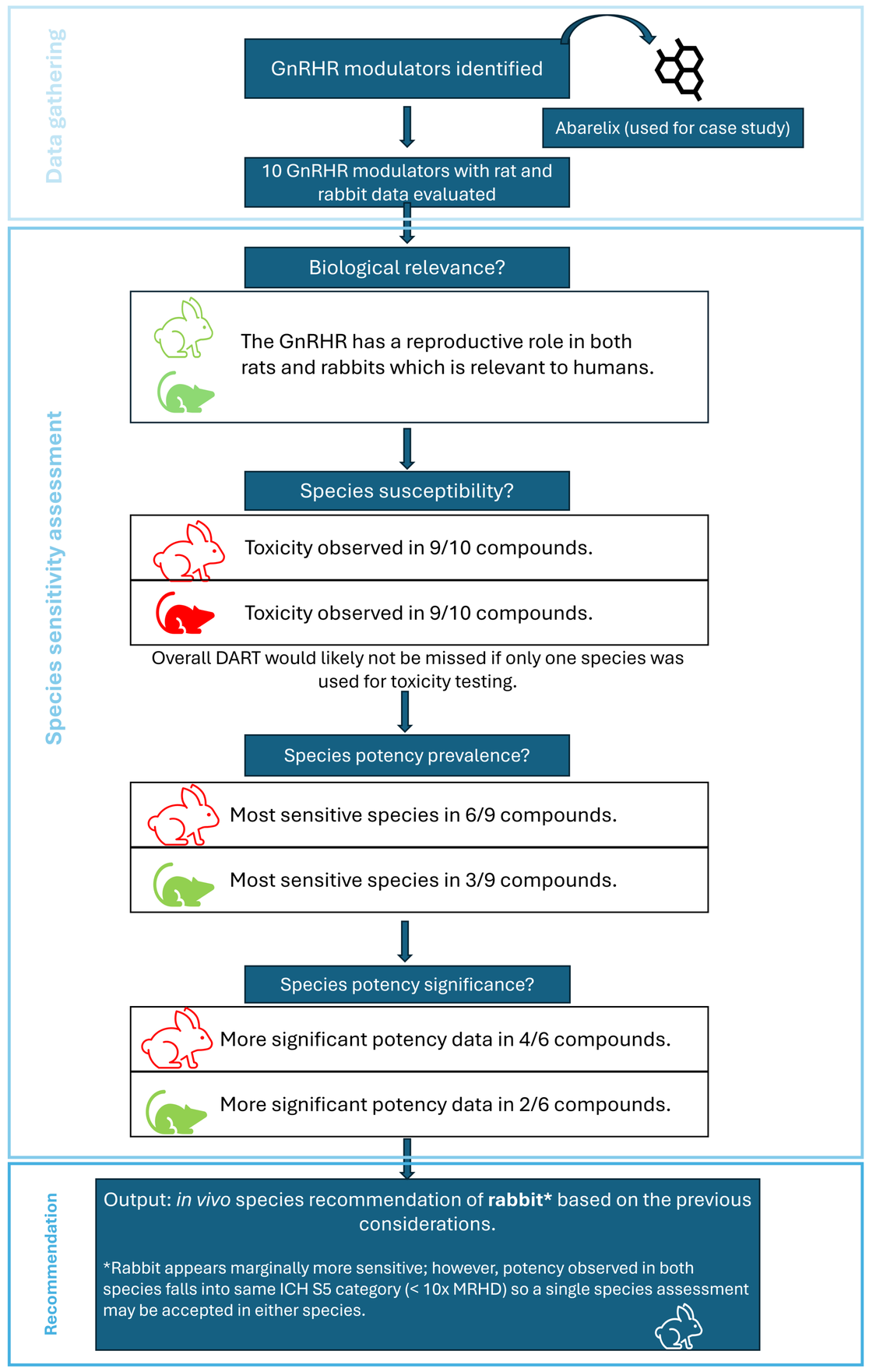

Figure 3. Workflow determining the most suitable test species for *in vivo* for GnRH pathway stressors.

Case study - Abarelix

Based on the above recommendation, the rabbit was suggested as the species for DART assessment of Abarelix. A data search was conducted for this compound to determine if this recommendation was supported. All data was sourced from the FDA[6].

In this instance, MRD values show the rat is the most sensitive species, not the rabbit. Using our workflow to suggest the rabbit could still support a single species DART assessment, as the MRD values for most compounds are < 10x MRD and potency differences between rat and rabbit are minimal. A single species DART assessment may be sufficient for regulatory submissions in either species.

The ICH S5 R3 guideline states that a single species assessment is appropriate if toxicity is observed at exposures similar to the maximum recommended human dose. As all the associated data is within 10-fold of the MRD, we have confidence to support a single species DART assessment.

Conclusion

An AOP framework not only facilitates the interpretation of relevant data but also strengthens the scientific rationale, thereby supporting confident regulatory decisions regarding the sufficiency of single species DART assessments. We will continue to develop and refine our methodology for other DART AOPs to further enhance the robustness and reliability of our approach. By sharing our experience, we aim to encourage collaboration and help build confidence across the field in adopting single species DART assessments where appropriate.

References

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