



Improving *In Silico* Predictions in Developmental and Reproductive Toxicology

SOT 2019

Adrian Fowkes

Senior Scientist

adrian.fowkes@lhasalimited.org



Overview

- Collaborative poster describing the results from a data sharing initiative between Lhasa and a Lhasa member

- Highlights:

- Approaches for modelling developmental toxicity
- Benefits of data sharing
- Recommendations

Improving *In Silico* Predictions in Developmental and Reproductive Toxicology

Caren Villano¹, Brittany Richard², Adrian Fowkes³
¹ Bristol Myers Squibb, ² Bristol Myers Squibb Company, New Brunswick, NJ, ³ University of Bath, Bath, BA2 9AY, UK, ⁴ Lhasa Limited, ⁵ Covent School, Leeds, LS13 9PL

Abstract # 2404

1. Challenges facing *in silico* approaches for DART

Developmental and reproductive toxicity (DART) continues to be a challenging area for developing *in silico* models, partially due to a lack of data available across a broad chemical space. In addition, DART encompasses a wide range of complex endpoints, of which there is likely to exist multiple mechanisms leading to each adverse outcome (2). Therefore, for users to have confidence in using *in silico* approaches, predictive systems will have to cover large areas of chemical and biological space. While there is a large amount of publicly available DART data, a significant amount of critical information from DART studies, including those conducted by pharmaceutical companies, remain with the sponsor. A collaboration between Bristol Myers Squibb (BMS) and Lhasa Limited was established to highlight the benefits of data sharing for predicting DART (Figure 1).

Collaborative goals:

1. Broaden the chemical space available for evaluating *in silico* approaches for predicting DART
2. Improve *in silico* models to cover newly identified regions of chemical and biological space of concern
3. Share knowledge to support the development of alternative approaches

Figure 1: Integration of public and sponsor data from which models to improve *in silico* approaches to overcome data knowledge which together can further reduce risk assessments

2. QSAR approaches for predicting DART

Current *in silico* models for predicting DART use quantitative structure activity relationships (QSAR) and rely heavily on data derived from toxicity studies (Figure 2). Two general approaches exist:

1. Expert rule-based systems use a knowledge base containing QSAR and mechanistic knowledge captured experts.
2. Statistical approaches are trained directly on experimental data and algorithms identify relationships between chemical descriptors and toxicity endpoints.

Adverse outcome pathways (AOPs) describe sequences of measurable and essential events which can lead to an adverse outcome (Figure 3, 4). These pathways provide a framework to operationalise knowledge and predictive models relevant to toxicity endpoints.

AOP frameworks are transferable to both regulatory and risk assessment. For example, QSAR models can take advantage of the large volume of data in publicly available and built models provided for the interaction between a toxic molecule and a target of interest. Risk assessors working with complex toxic models can then utilize the knowledge within the AOP and its appropriate assays to progress a risk assessment.

Figure 2: Using QSAR to further DART risk assessments

3. Data curation and model validation

The compounds in the current BMS dataset were not present in any DART dataset held by Lhasa Limited and many areas of chemical space where toxic is known about the DART (ability of molecule) (Figure 3B). The BMS dataset adds value to existing knowledge both in terms of coverage of chemical space and in depth due to the types of studies available for each compound.

Figure 3: Comparison of chemical space covered by the BMS dataset and that in comparison to the public domain. (A) Bar chart showing the number of compounds in each dataset. (B) Scatter plot showing the relationship between BMS and public domain datasets.

Figure 4: Comparison of model coverage required by the BMS dataset and that in comparison to the public domain. (A) Bar chart showing the number of models in each dataset. (B) Scatter plot showing the relationship between BMS and public domain datasets.

Figure 5: Performance of models across the dataset created by the integration of the BMS dataset.

4. Adverse outcome pathway development

The compounds in the BMS dataset also revealed progress that prediction results, in order to identify areas of chemical and biological space not adequately covered by the *in silico* model. Existing developmental outcomes from the BMS dataset alongside data from the public domain 'failed' to identify any suitable structural alerts, due to the uniqueness of chemical space covered by the representative biosens. However, two pathways were identified that were not currently described in the AOP database. The pathways and key toxicity evidence for both AOPs are given below:

AOP: RET inhibition leading to malformation of the foetus and uterine tract

- Compounds binding to the RET receptor tyrosine kinase (RET) can impinge RET-mediated signaling pathways (7).
- Mouse foetal studies with impaired RET-mediated signaling exhibit cleft-lip and cleft-palate (8).
- Interactions between the uterine and endometrial mesenchyma enable formation of the foetus (9).
- Rat and rabbit embryological studies involving RET inhibition can result in uterine system malformations (10).

However, not all compounds in this chemical class cause uterine malformations.

RET inhibition class	RET inhibition class
RET inhibition class	RET inhibition class
RET inhibition class	RET inhibition class
RET inhibition class	RET inhibition class
RET inhibition class	RET inhibition class

Openning evidence in this way highlights the importance between the observed toxicity and mechanistic knowledge. The approach of information gathered for RET inhibition could be due to effects on multiple targets. RET inhibitors can also inhibit USF9, which is believed to cause developmental toxicity via the disruption to angiogenesis (11).

AOP: SGLT-2 inhibition leading to adverse renal system development

- SGLT2 glucose transporter-2 (SGLT-2) is primarily expressed in the proximal tubules of the kidney and is responsible for glucose reabsorption into the bloodstream (12). Inhibition of the transporter increases the concentration of glucose in the filtrate, which results in an increase in the volume of urine produced.
- Pharmacological targeting (SGLT-2) used in postnatal developmental toxicity studies, produced renal pelvic dilations in juvenile rats (13).

Compound	High renal developmental toxicity
Compound	High renal developmental toxicity
Compound	High renal developmental toxicity
Compound	High renal developmental toxicity
Compound	High renal developmental toxicity

The adverse outcomes observed have been attributed to the toxicity of the quantity of urine to handle larger volumes of urine during development (14). These findings highlight a potential risk for use of these compounds during pregnancy due to the functional maturation of the renal tubules occurring in early foetal development. It is needed to establish a greater understanding of the human relevance and quantitative nature of these findings.

5. Collaboration perspectives

Conclusions:

1. Increasing the availability of DART data through data sharing supports the development of *in silico* models and disease knowledge through the construction of AOPs.
2. Pharmaceutical use unique unique regions of chemical space, which can hinder the generation of structural alerts due to the lack of appropriate endpoints.
3. AOP frameworks can integrate both knowledge and data to enable models to cover relevant areas of chemical and biological space. That data elements are provided allow relevant information to be made decisions.
4. Two BMS were highlighted during this collaborative. RET inhibition and SGLT2 inhibition. The supporting evidence for these mechanisms were curated into an AOP framework.

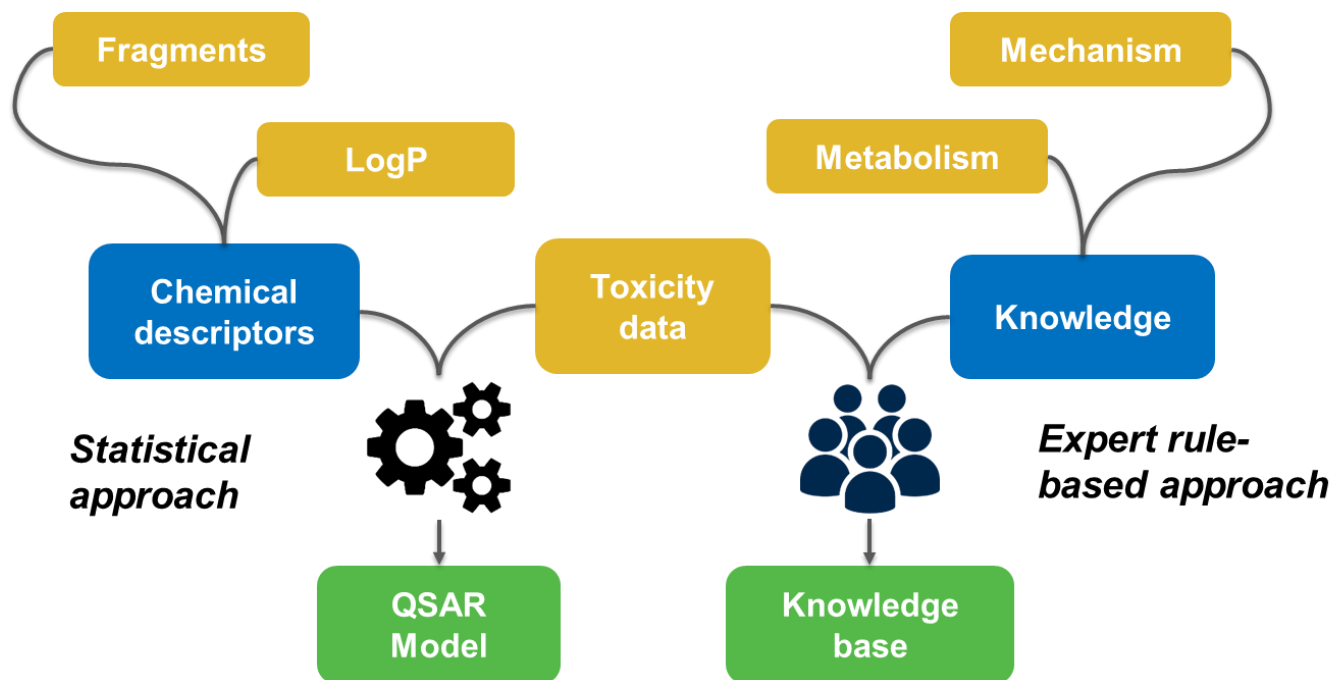
Recommendations:

1. Data sharing should aim to support decision-making for risk assessment, and therefore should include toxicity, mechanism, response and observed study data for both toxicants and non-toxicants.
2. Development of alternative approaches for predicting developmental toxicity should account for both descriptors to quantify pathways and mechanistic processes that can lead to adverse renal system development.

References: (1) Sijdel et al. *Worm Dev Biol*. 2018; 132: 1640-1652. (2) Ashby et al. *Environ Toxicol Chem*. 2002; 21(9): 1991-2000. (3) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (4) Taylor et al. *Hum Reprod*. 2017; 32(12): 2317-2324. (5) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (6) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (7) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (8) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (9) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (10) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (11) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (12) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (13) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139. (14) Villano et al. *Regul Toxicol Pharmacol*. 2017; 87: 127-139.

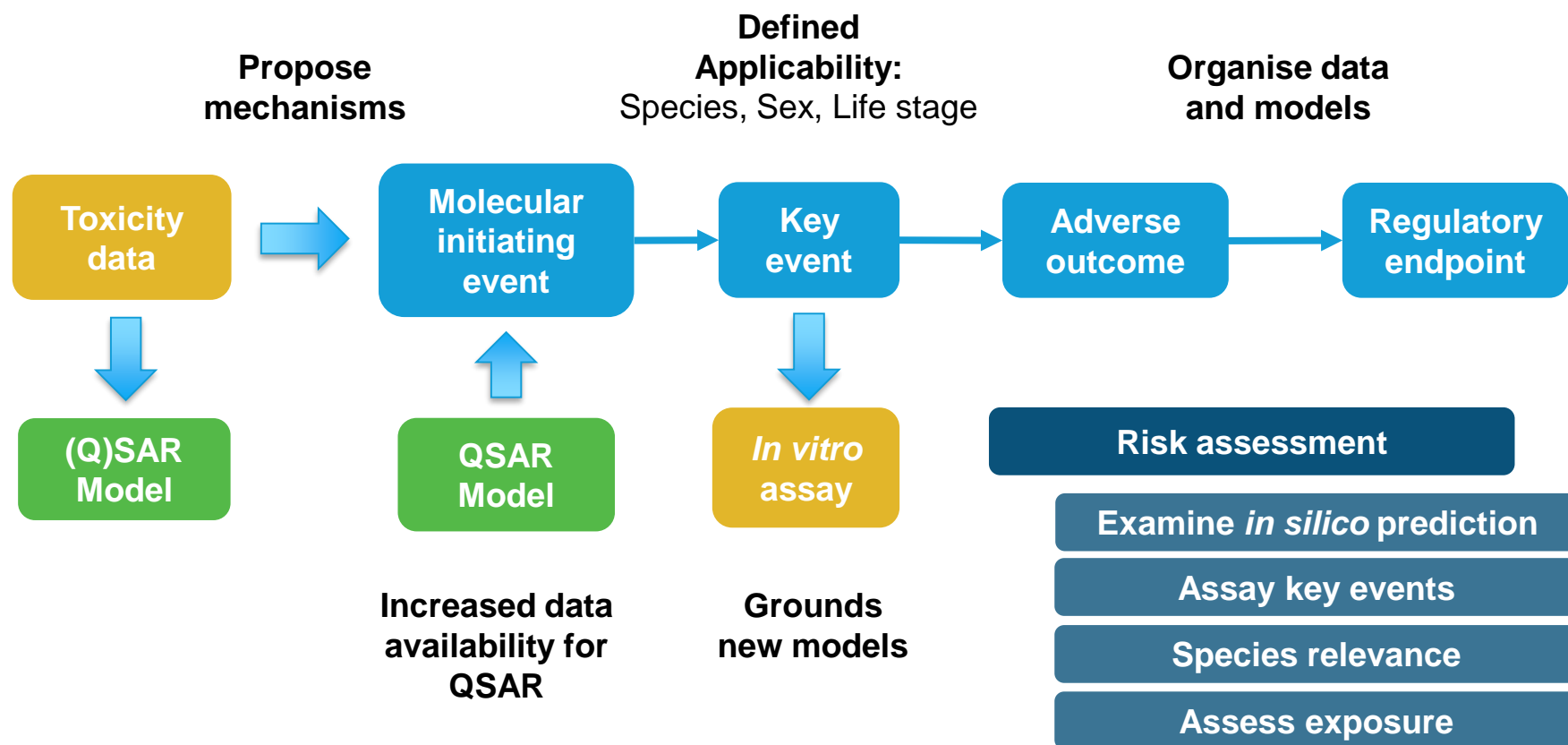
Background

- Current off-the-shelf approaches for predicting DART rely heavily on data derived from toxicity studies



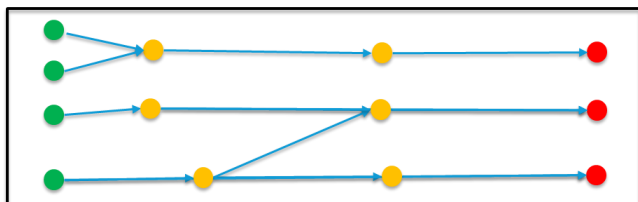
Background

- AOP-based approaches support QSAR approaches to cover a broader range of chemical and biological space



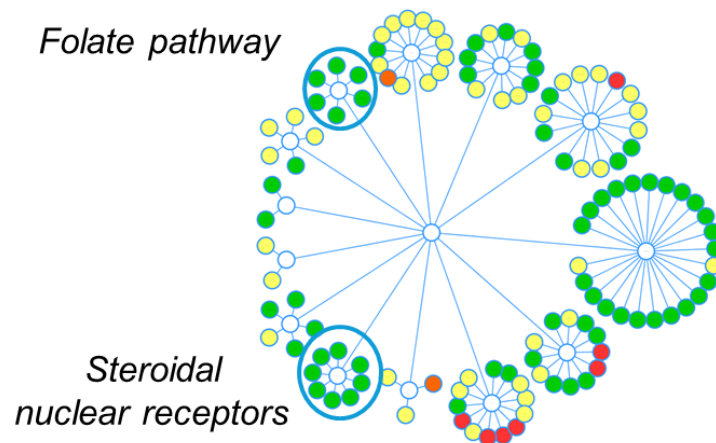
Background

- Lhasa have synthesised a putative AOP network for DART
 - Extracted mechanisms from Derek Nexus
 - Performed literature review



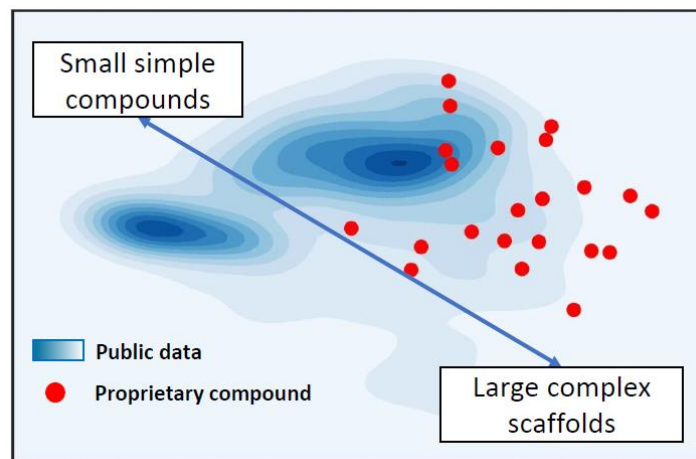
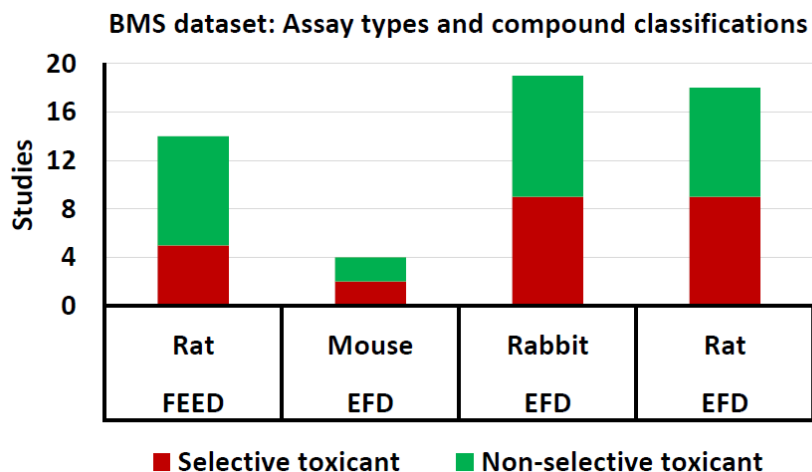
Event Type	DART
MIE	57
KE	119
AO	5

DART MIEs grouped by their biological role



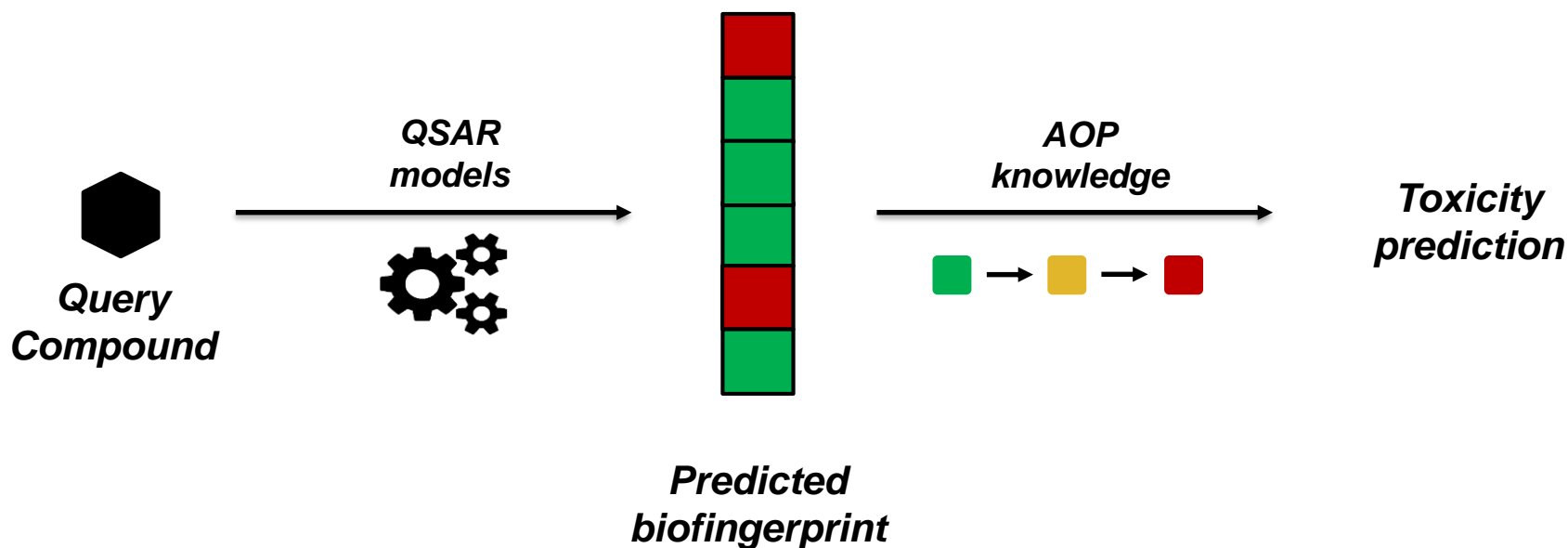
Working with members

- How well do Lhasa's models perform against a member's chemical space?
- Reprotoxicity data was curated from a Lhasa member's database.



AOP-based model

Predictive models annotated to appropriate key events can act as entry points to the AOP network

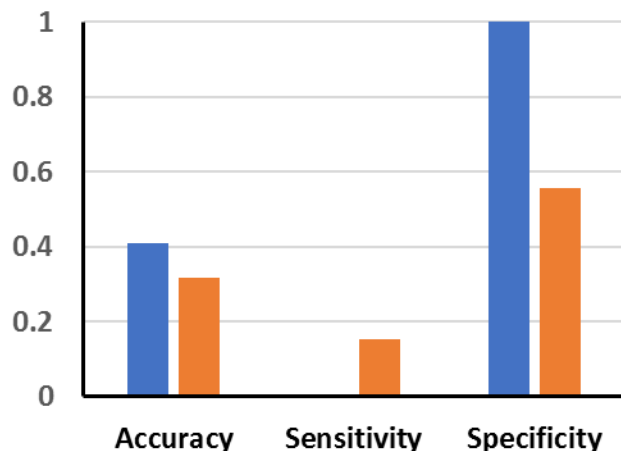


Model performance

The performance of the AOP-based model, and Derek Nexus, was evaluated against public and member data

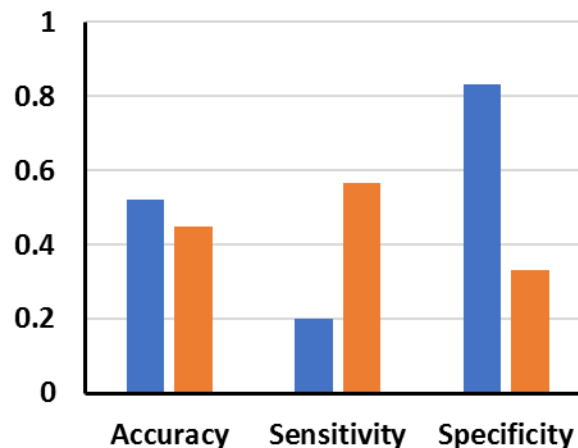
Member dataset

	TP	FP	TN	FN
Derek Nexus	0	0	9	13
AOP model	2	4	5	11



Public dataset

	TP	FP	TN	FN
Derek Nexus	6	5	25	24
AOP model	13	10	20	17



Performance of *in silico* models against the datasets curated in this study.
TP = True positives, FP = False positives, TN = True negatives, FN = False negatives.

The AOP network contains additional mechanisms allowing the AOP-based model to cover wider areas of chemical space

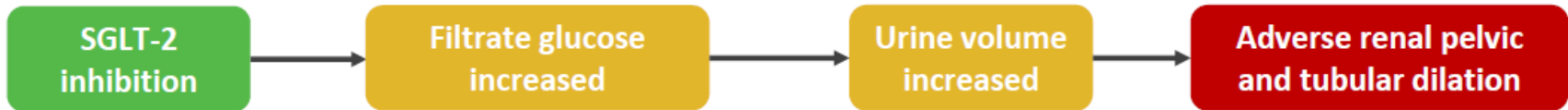
New knowledge

AOP: RET inhibition leading to malformations of the kidney and urinary tract



Species: Mammal, Sex: Male and Female, Life stage: Embryo-fetal

AOP: SGLT-2 inhibition leading to adverse renal system development



Species: Mammal, Sex: Male and Female, Life stage: Renal development

Acknowledgements

- Caren Villano
- Brittany Rickard
- Lhasa Limited members who have shared DART data

Interested in knowing more or supporting this initiative

adrian.fowkes@lhasalimited.org



shared **knowledge** • shared **progress**

Lhasa Limited

Granary Wharf House, 2 Canal Wharf

Leeds, LS11 5PS

Registered Charity (290866)

Company Registration Number 01765239

+44(0)113 394 6020

info@lhasalimited.org

www.lhasalimited.org



Work in progress disclaimer

This document is intended to outline our general product direction and is for information purposes only, and may not be incorporated into any contract. It is not a commitment to deliver any material, code, or functionality, and should not be relied upon. The development, release, and timing of any features or functionality described for Lhasa Limited's products remains at the sole discretion of Lhasa Limited.



Collaborative Working Disclaimer

The purpose of this meeting is to [INSERT]. In order to avoid a breach of competition law, participants are reminded not to disclose commercially sensitive or confidential information, or intentions about future market conduct (including information about products under development, pricing, sales strategy or customers). This meeting is not intended to lead to any agreement or understanding as to market conduct.

Confidentiality Statement

All Lhasa Limited members are subject to confidentiality provisions as outlined in their software sponsorship agreement(s). It is the responsibility of all participants in a Lhasa Limited project to:

- Ensure they understand their confidentiality obligations.*
- Ensure they understand the confidential status of their own information and that it is appropriate to share such information.*
- Treat information related to a Lhasa Limited project with care and only share such information with prior agreement from Lhasa when this would be beneficial for such projects.*

