

# Mechanistic Expert Call Datasets Support *in silico* Prediction of Teratogenicity for a Wider Chemical Space

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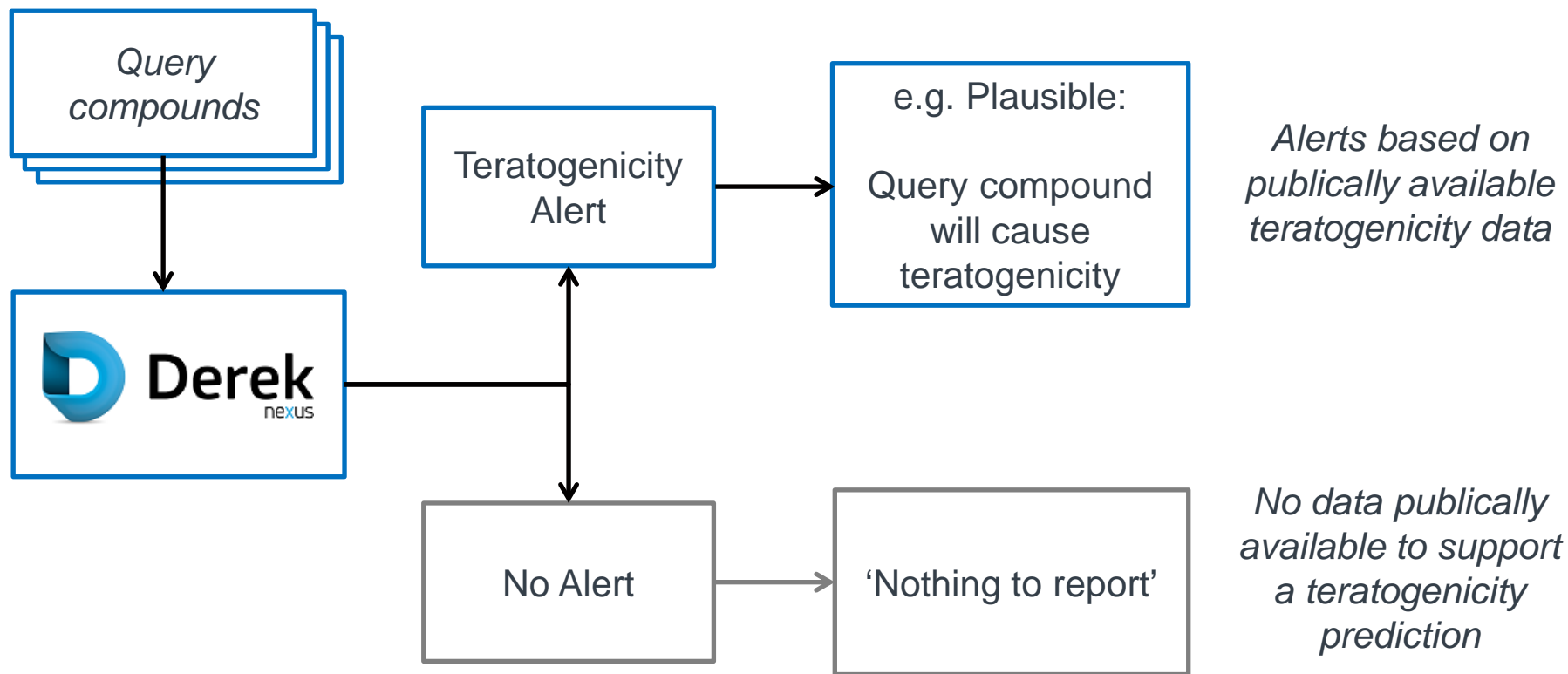


# Outline

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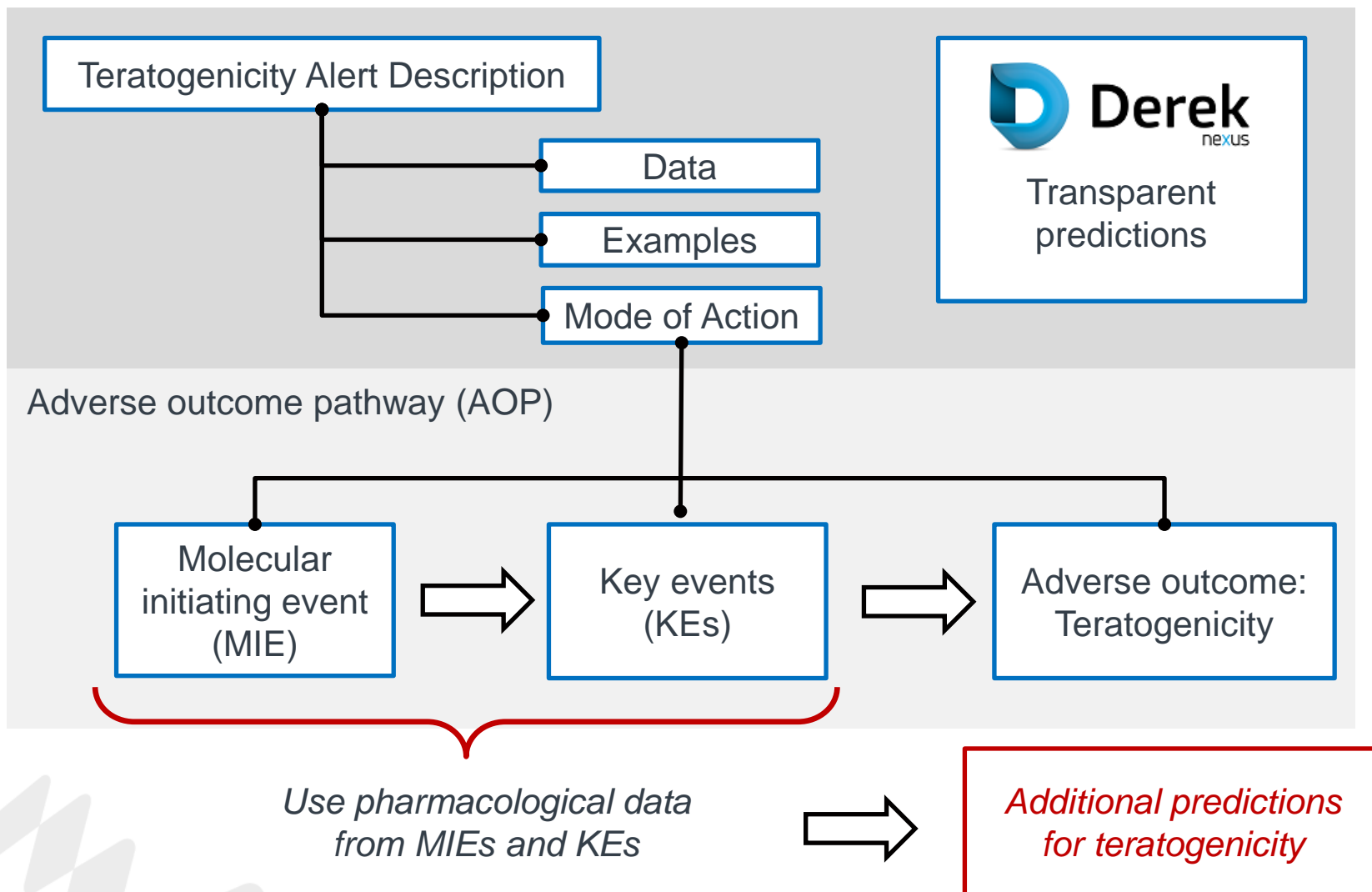
1. Teratogenicity alerts in Derek Nexus
  2. Workflow for implementing new molecular initiating event (MIE)-based alerts for Derek Nexus
  3. Performance of MIE specific custom knowledge bases (KBs)
  4. Conclusions & Future Work
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# Teratogenicity endpoint in Derek Nexus (2014)



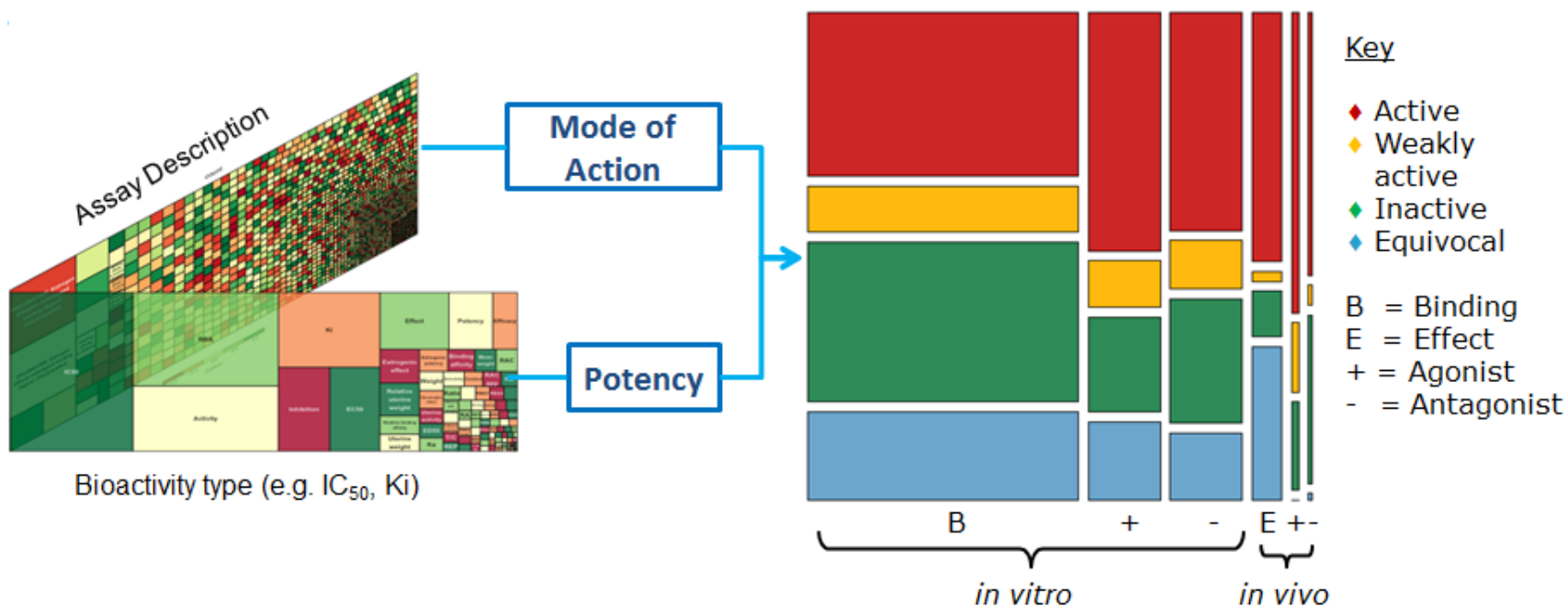
Teratogenicity alerts in Derek Nexus are based on the limited *in vivo* toxicity data available in the public domain

# Teratogenicity alerts in Derek Nexus





# Lhasa Mechanistic Expert Call Datasets



## ChEMBL data:

>26000 experiments in ER responsive assays

Knowledge Enrichment

## Purposeful Mechanistic dataset:

9388 data points  
6952 compounds



# MIEs relevant to teratogenicity

- Datasets and expert models created for three MIEs:
  - Oestrogen receptor modulation (ERM)
  - Androgen receptor modulation (ARM)
  - 5alpha-Reductase inhibition (5aRI)

Table 1. Analysis of the Lhasa mechanistic expert activity calls datasets.

LMEAD	Number of substances	Active substances (Equivocals removed)	Response type known for active substances	Data points verified
ERM	6952	55%	51%	46%
ARM	4849	62%	68%	64%
5aRI	1261	83%	NA	66%

**Knowledge injection by Lhasa scientists has led to the production of purposeful and high quality training sets**



# MIEs relevant to teratogenicity

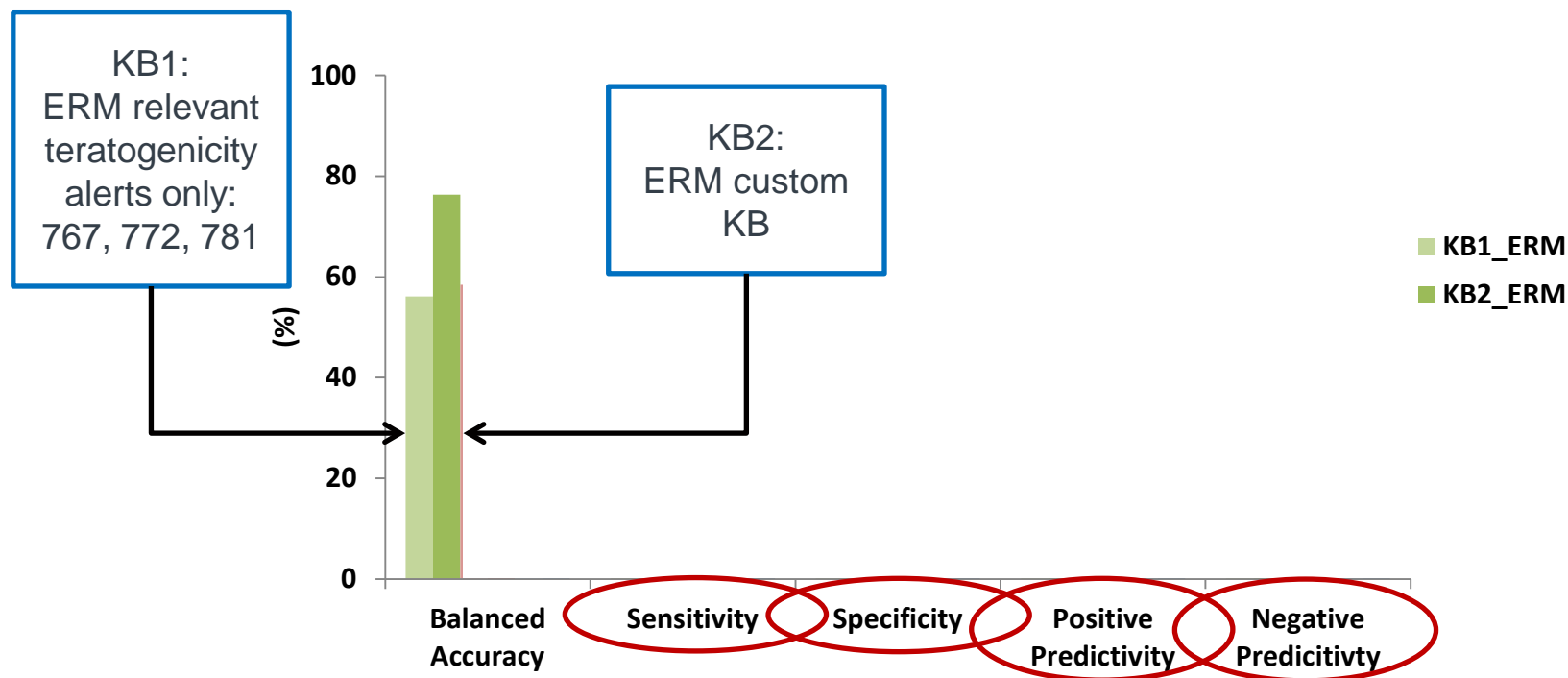
- Datasets and expert models created for three MIEs:
  - Oestrogen receptor modulation (ERM)
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Table 2. Composition of the three MIE specific Derek Nexus custom knowledge bases.

Endpoint	Alerts in Custom KB	Number of existing teratogenicity alerts	Number of new MIE alerts	Potential new MIE alerts
ERM	48	3	9	36
ARM	23	2	7	14
5aRI	24	1	16	7

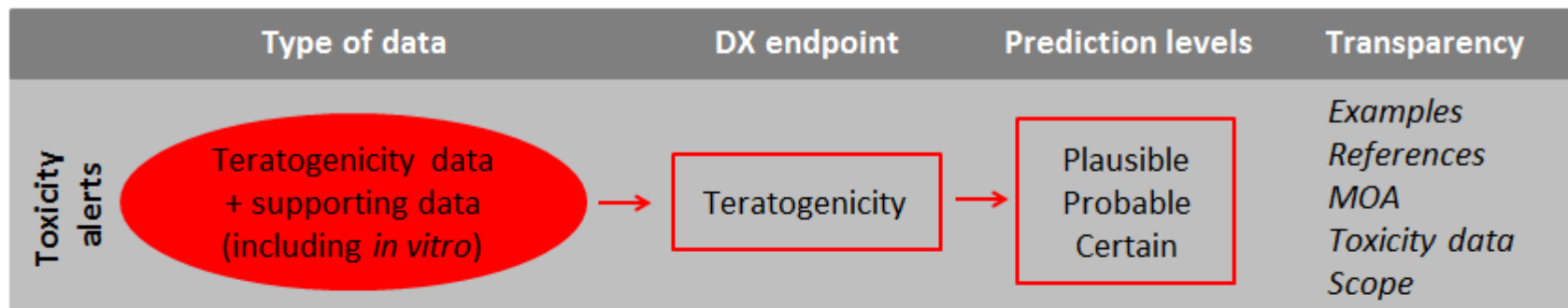
**New MIE-based alerts allow for additional teratogenicity predictions**

# Performance of each MIE custom KB



Performance of each custom knowledge base (KB2) created for the 3 MIEs compared to the relevant Derek Nexus teratogenicity alerts (KB1 - 2014 certified KB).

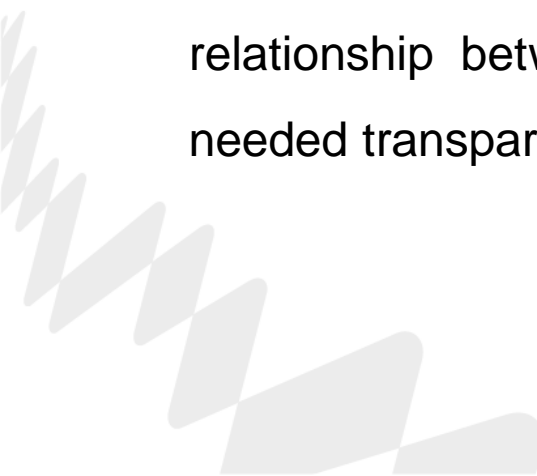
# Transparent reasoning in Derek Nexus





# Conclusions


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- Successfully used pharmacological data to support teratogenicity predictions for a wider chemical space using three different MIEs.
  - MIE-based alerts for teratogenicity are now present in the 2016 Derek Nexus release:
    - 9 alerts for oestrogen receptor modulation
    - 16 alerts for 5alpha-reductase inhibition
  - Reasoning rules have facilitated tailored predictions for both MIE endpoints and teratogenicity. In addition, they explain clearly the relationship between MIE and toxicity while maintaining the much needed transparency.
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## Future Work


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- Validate the individual MIE custom KBs using data from additional sources
  - Assess the performance of the custom KBs against datasets from Lhasa Limited members
  - Investigate other MIEs relevant to teratogenicity, e.g.
    - **Glucocorticoid receptor modulation**
    - **Aromatase inhibition**
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# Acknowledgements

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- Lead Scientist
    - Bashir Surfraz
  - Past and present team members
    - Alex Cayley
    - Jeffrey Plante
    - Alun Myden
    - Emma Hill
  - The Knowledge Team
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**Questions?**



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

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