A platform for next generation carcinogenicity assessments

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Introducing Lhasa and Kaptis

An educational not-for-profit charity

Our purpose: **To enable informed decision making on chemical safety**

A tool to support expert review and decision making for chemical risk assessments

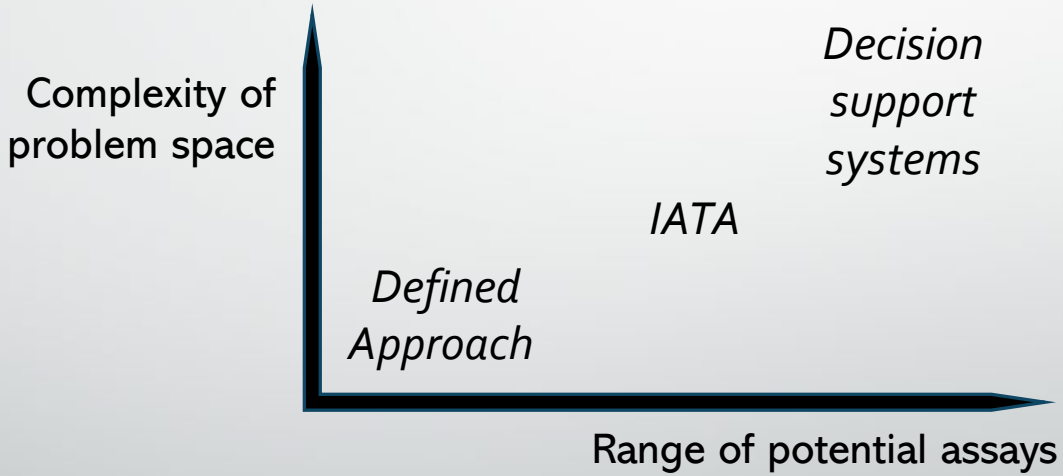
..adding automation, expert knowledge, data and decision-support to IATAs

The problem:

Increasingly, non-animal studies can provide sufficient evidence to make a decision about chemical safety.

However, it is not always easy to

- Access and apply biological (mechanistic) knowledge
- Identify relevant assays
- Contextualise data from these assays *(understanding relevance, specificity…)*
- Identify uncertainty *(addressing conflicting results, gaps in knowledge…)*
- Make an informed decision aligned to regulatory guidance that follows best practice

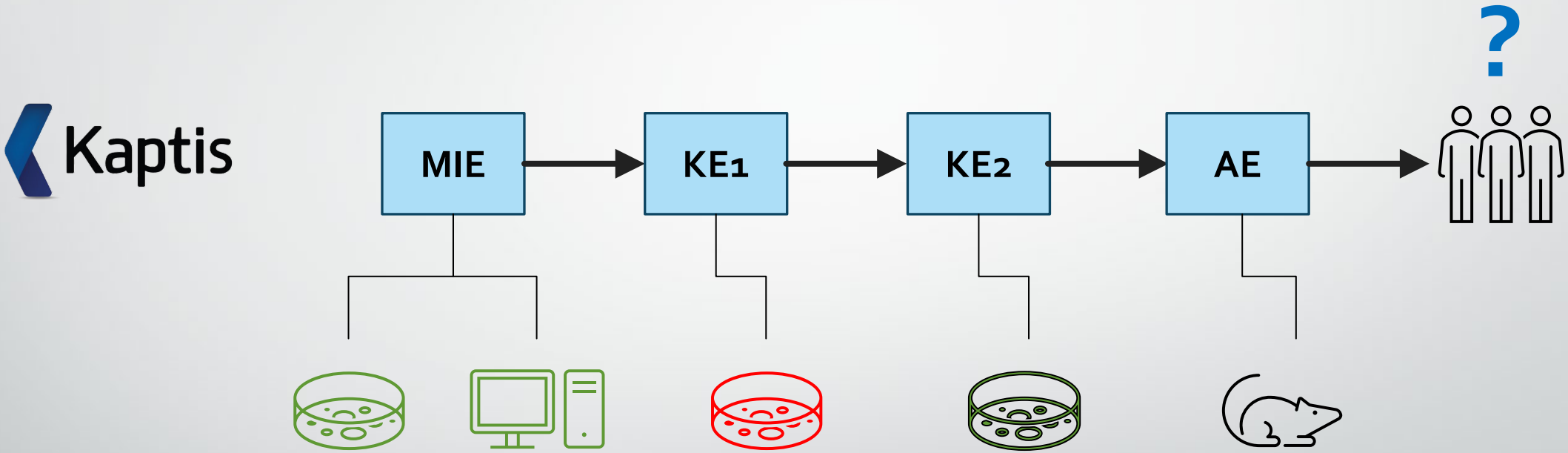


Decision-support systems provide knowledge, contextualise data and a framework that supports decisions.

From model performance to decision support – The rise of computational toxicology in chemical safety assessments

The solution:

- **Decision-support systems** provide support to both submitters and reviewers.
  - *…with access to knowledge, a framework to organise data, and guides to support decisions*



- AOPs have been widely accepted as an efficient and intuitive approach to **organise knowledge**.
- This same framework can also **integrate data** and provide **structured support for decisions**

MIE = molecular initiating event KE = key event AE = adverse event

Method Description:

Kaptis

A computational tool to support decisions on chemical safety assessment

..combining knowledge, automation & best practice

Method Description:

1. **Use AOPs** as a knowledge framework
    - *AOPs helps us organise knowledge of toxicity including mechanistic causes*
2. **Integrate assays** that measure Key Events
    - *Associating assays to key events allows us to contextualise and rank their value (WoE)*
3. **Add data**
    - *Organising data for a compound of interest*
4. **Apply reasoning** using pre-defined best practice
    - *Select expert-defined arguments to challenge or strengthen a position (or add own)*
5. **Review** for coverage, conflicts and strength of evidence
    - *Use the AOP view of the data to assess coverage and resolve conflicts*
6. **Make a decision**
    - *Determine the outcome (including the need for further testing)*
7. **Report** the decision
    - *Organise the information needed to defend the decision*

..combining knowledge, automation & best practice

Specific application

ICHS1B(R1)

S1B-R1_FinalGuideline_2022_0719.pdf (ich.org)

Context of Use: The requirement

ICH S1B(R1) allows data from non-animal studies to support a decision on carcinogenic risk

- A weight-of-evidence approach can remove the need for a 2-year rat carcinogenicity study.
- There are 3 possible conclusions about the carcinogenic potential in humans:

Likely	Uncertain	Unlikely
"…a 2-year rat carcinogenicity study **would not** add value"	"…a 2-year rat carcinogenicity study **would** add value to human risk assessment"	"…a 2-year rat carcinogenicity study **would not** add value"

ICH S1B(R1) guidance

Structuring expert review using AOPs: Enabling robust weight-of-evidence assessments for carcinogenicity under ICH S1B(R1), 2024

Context of Use: Confident decisions

Applying Kaptis to meet ICH S1B(R1) guidance

Kaptis

- Is aligned with the ICH S1B(R1) regulatory guidance
- Provides peer-reviewed knowledge and guided expert review to support decision-making
- It also provides in silico predictions in the absence of any experimental data
  - *This can supplement in vitro data for regulatory submission, guide assay selection and strengthen decisions*
- The science behind Kaptis been published in peer-reviewed literature:

Decision making

Employing an adverse outcome pathway framework for weight-of-evidence assessment with application to the ICH S1B guidance addendum, 2021

Knowledge framework

Development of a Network of Carcinogenicity Adverse Outcome Pathways and its Employment as an Evidence Framework for Safety Assessment, 2022

Expert review

Structuring expert review using AOPs: Enabling robust weight-of-evidence assessments for carcinogenicity under ICH S1B(R1), 2024

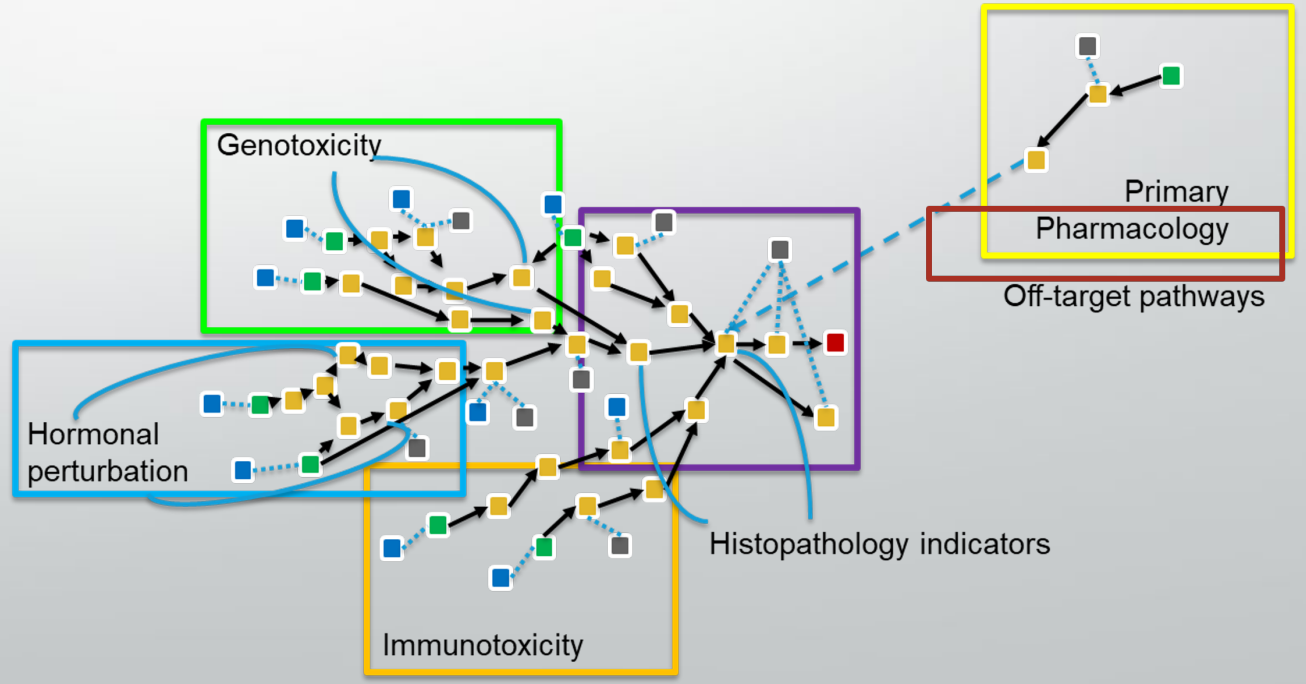
Context of use:
A. How is your method intended to be used?

- **To make a decision about carcinogenic potential under the ICH S1B(R1) addendum**
  - This requires assessment against 6 factors.
  - Kaptis aligns mechanistic knowledge to those 6 factors via expert-curated AOPs
  - Kaptis supports the decision using best practice as defined by industry experts

ICH S1B(R1) Factors in guidance document

Genotoxicity	Histopathology
Hormonal perturbation	Primary Pharmacology
Immunotoxicity	Off- target pathways

ICH S1B(R1) Factors projected onto AOP network in Kaptis



Context of use:
B. What regulatory testing need does your method address?

The assessment of carcinogenic potential under ICH S1B(R1) guidance by…

- Providing access to mechanistic/carcinogenicity knowledge.
  - *Public knowledge + private knowledge + expert interpretation.*
- Guiding decision making through the application of best practices as defined by experts.
  - *Quality of decision-making ↑ , Consistency ↑ , Confidence in the decision ↑*
- Ensuring the decision is transparent and explained.
  - *Standardised report designed to meet the needs of regulators.*

Context of use:
C. What regulatory space does your method address?

- Kaptis is designed to support decisions on chemical safety for a wide range of toxicities.
- Augmenting the IATA approach with peer-reviewed knowledge and expert-defined decision making.

Carcinogenicity assessments

- Pharmaceuticals
  - **ICHS1B (R1)**
- Agrochemicals
  - ReCAAP
- Non-genotoxic carcinogens
  - OECD IATA EWG

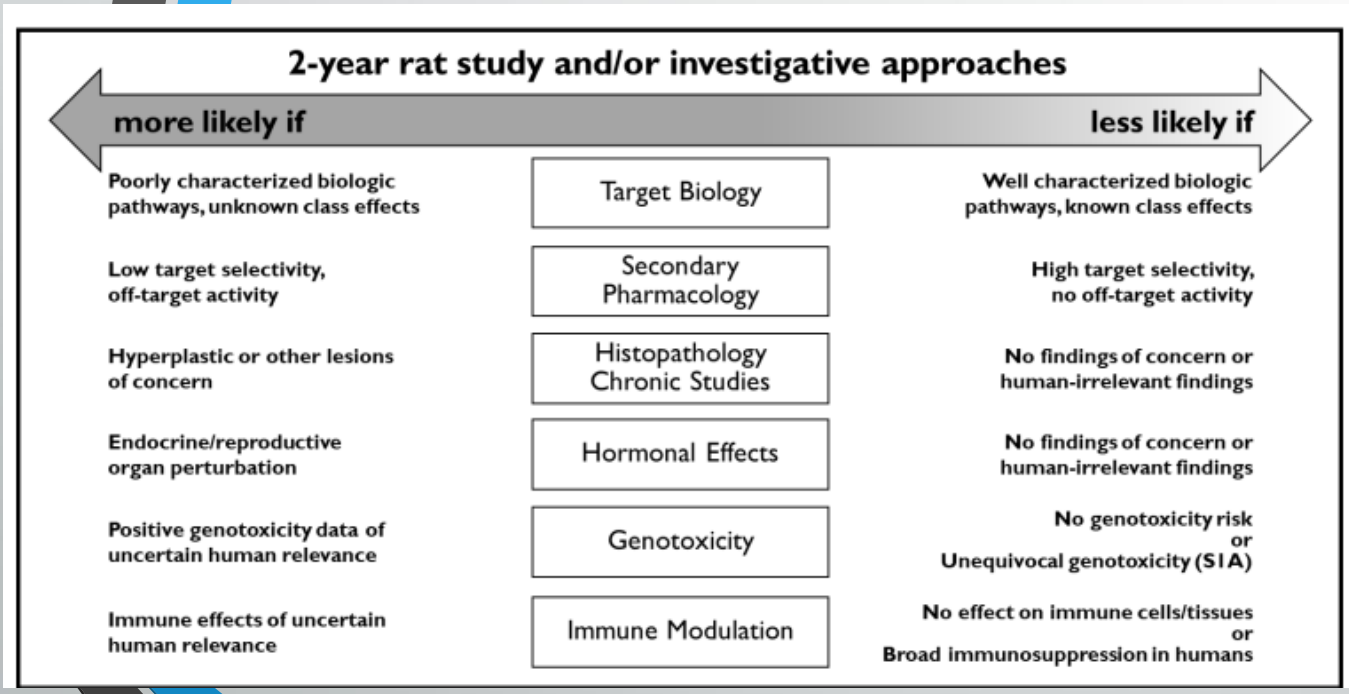
Endpoints in development

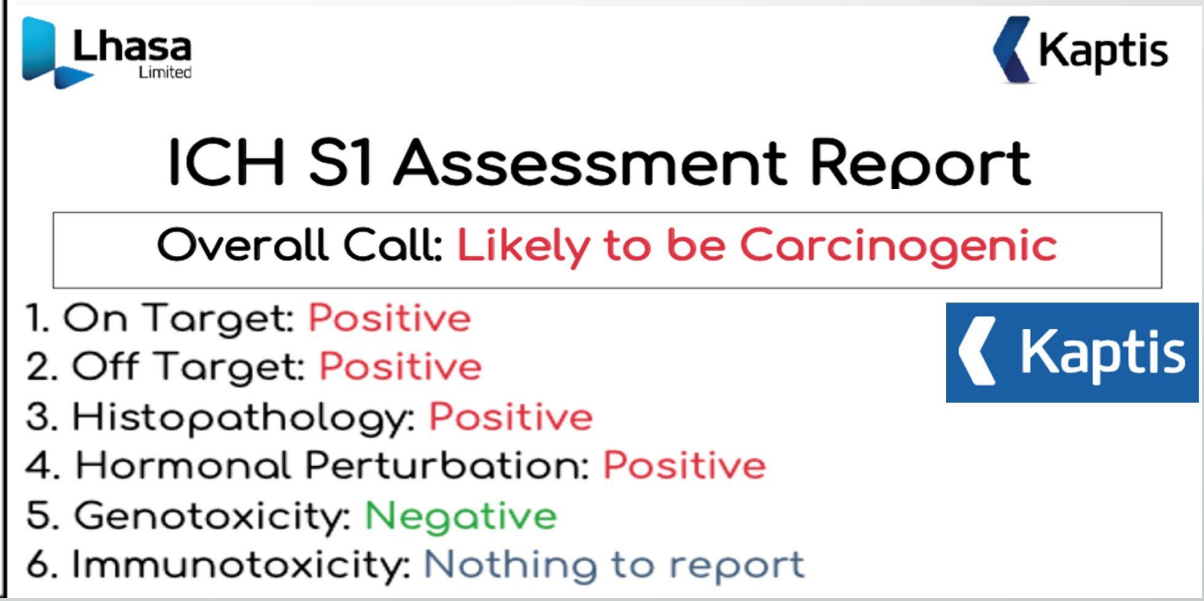
- Skin sensitisation
  - OECD #497
- DART
  - ICH S5

Context of use:

D. Has data generated by your method been used for regulatory submissions?

Yes, reports generated by Kaptis has been used by the pharmaceutical industry for submissions as part of the ICH S1B (R1) addendum.



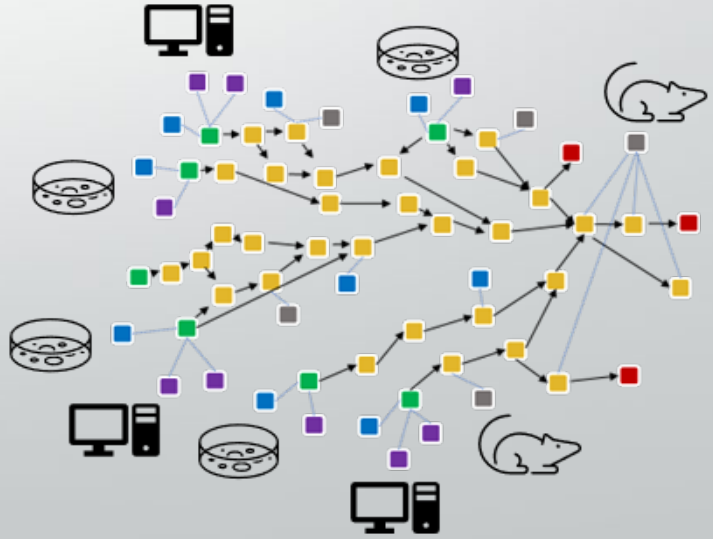


S1B-R1_FinalGuideline_2022_0719.pdf (ich.org)

Kaptis report

Biological relevance:
A. Mechanistic understanding

- AOPs are a framework to organise mechanistic knowledge
  - *AOPs explicitly describe mechanisms of action through the pathways*
- AOPs allow assays to be contextualised across these mechanistic pathways
  - *This approach allows data gaps to be identified and conflicting results reconciled*
  - *Kaptis contains 60 assays relevant for the assessment of carcinogenicity*
- Mechanistic causes of carcinogenicity are well understood
  - *Kaptis contains 37 AOPs representing all known major pathways*
  - *Comprehensive AOPs have been developed by Lhasa scientists*



Development of a Network of Carcinogenicity Adverse Outcome Pathways and its Employment as an Evidence Framework for Safety Assessment, 2022

Example AOP: Topoisomerase II binding leading to carcinogenicity with supporting data for Ciprofloxacin overlayed

Topoisomerase II binding assay: **Positive**

Topoisomerase II-DNA cleavage complex binding → Topoisomerase II-DNA cleavage complex stabilisation

Chromosome aberration test: **Positive**

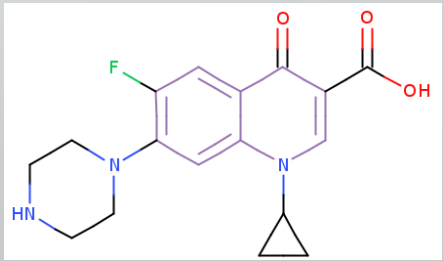
Chromosome structural damage → Micronucleus formation

Micronucleus assay: **Positive**

Malignant neoplasm

Rodent carcinogenicity study: **Positive**

AOP and KERs are derived from experimental evidence including studies using reference compounds



Ciprofloxacin

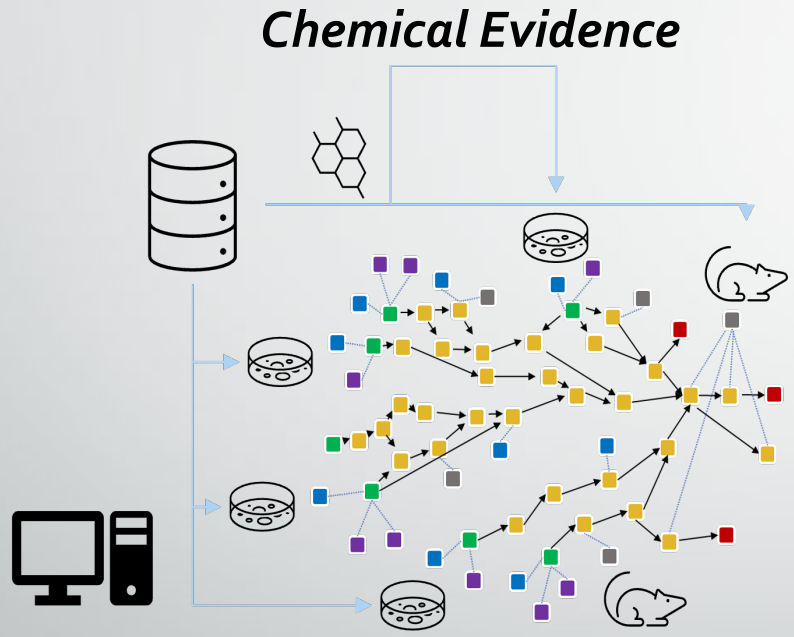
Number of AOPs for each factor

Factor	Number of AOPs	Representative example AOP
Genotoxicity	18	Topoisomerase II binding leading to carcinogenicity
Histopathology Chronic Studies	37	Peroxisome proliferator-activated receptor alpha (PPAR alpha) activation leading to carcinogenicity
Hormonal Effects	12	Oestrogen receptor (ER) activation leading to carcinogenicity
Immune Modulation	4	Calcineurin deactivation leading to carcinogenicity
Secondary Pharmacology	20	Dopamine type 2 receptor activation leading to carcinogenicity

Note that AOPs can contribute to more than one factor in the network

Biological relevance:
B. Reference compounds

- Reference compounds have been used to develop the decision support system
  - *AOP knowledge is derived from the experimental observations from reference compounds*
  - *Kaptis contains assay data from over 17,000 compounds which supports reasoning and expert review*



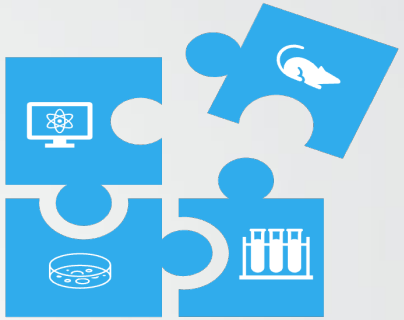
In Silico Models

No. of Alerts	442
No. of Key Events	48

Assays

No. of Assays	60
No. of Measurements	65
No. of Compounds	17049

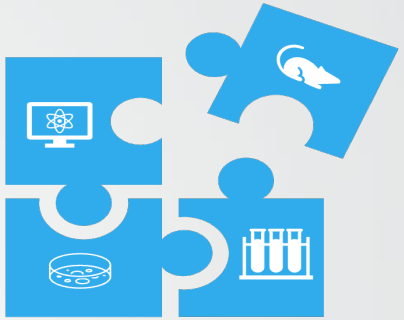
Biological relevance:
C. Comparison to existing laboratory animal methods



- It is accepted that non-animal studies can avoid the need for 2-year carc studies
  - *This is embedded within the ICHS1B(R1) guidance document*
- Laboratory assays (in vitro or in vivo) each have individual strengths & limitations
  - *Kaptis provides the expert knowledge needed to assess their relevance and limitations*
- Currently no single assay can assess all known mechanisms that drive carcinogenicity
  - *Kaptis allow relevant assays to be identified to ensure adequate testing*
- Integrating and reasoning between data generated in diverse assays requires expert knowledge
  - *Kaptis provides the evidence and expert analysis that few individuals possess*
- Transparent, robust and reproducible decisions require a systematic and shared framework
  - *Kaptis provides a common framework for analysis, decision-making and review*

- **Safety decisions are no longer limited to observational studies in animals**
  - *Kaptis is an enabling technology that provides access to knowledge and supported decision-making*

Biological relevance:
C. Comparison to existing laboratory animal methods

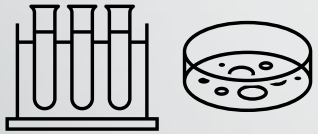


2 year rodent bioassay

"In 58% of cases, the EPA considered animal carc. data inadequate to support a classification of probable human carcinogen or non-carcinogen".

Animal Carcinogenicity Studies: 1. Poor Human Predictivity

in vitro



in silico

	Sens. (%)	TP
Derek Nexus	76	291
Kaptis (351 Derek alerts with automated reasoning)	85	323
Kaptis (351 Derek alerts + in vitro data with automated reasoning)	85	326

IARC Human Relevant Data Set

TP = true positives

Technical characterisation

Sources of variability:

- Kaptis reduces variability by providing a common framework and access expert-curated knowledge and data alongside predictions to enable **confident** and **transparent** decision-support.

Robustness:

- Kaptis uses **consistent rules** to combine evidence based on key criteria, ensuring uniform reasoning and data import across users.

Intra-laboratory reproducibility:

- Different Lhasa members using Kaptis reached **consistent conclusions** on carcinogenicity assessments, demonstrating **uniformity** across internal and external users.

Transferability:

- Kaptis generates comprehensive, transparent, and reliable **reports** suitable for regulatory submission or internal circulation within organizations.

Kaptis supports all phases of regulatory decision-making for ICH S1B(R1):

Assess carcinogenicity risk for a novel compound

- ICH S1B(R1)
  - Regulatory decision
  - Prioritisation

1 Requirement

2 Information Gathering

Gather information

- Use all available knowledge and data
- Expert-curated public data embedded in Kaptis
- Ability to add proprietary data
- Evidence is contexualised & valued

Decision 4

Assessment 3

Standardised report designed to support regulatory review

- Achieve harmonised conclusions
- Decisions are transparent
- Reduce unnecessary animal testing

Assess against the 6 factors

- Expert-guided review using published best practice established through collaboration
- Conflicting data can be rationalised
- Knowledge gaps highlighted

Outcomes we are seeking today

- Greater understanding on how & where decision-support systems can help you
  - *We would like to work with you to define acceptance criteria for such AI tools*
- Feedback on your needs and expectations
  - *What do you need (as a regulator) to trust an AI tool?*
- Collaboration and on-going engagement
  - E.g. publications on 'best practice' and how to assess a decision-support system are planned

Kaptis

A tool to support expert review and decision making on chemical risk assessments

For more information contact

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