Incorporation of metabolism into guideline studies – an opportunity to increase robustness of read across approaches

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The Balance of REACH

- **Meet the requirements of the REACH legal text**
  - **Perform robust hazard characterisations to underpin robust risk assessment**
- **Don't conduct unnecessary animal testing**
  - **Clear responsibility to exhaust alternative approaches before testing**

Consistent with the Three R's of toxicology

Maintaining the balance using 'read across'

- Read Across – strong foundation in Science
  - Potential for Toxicity linked to
    - Phys Chem properties
    - Reactivity
    - Presence of known 'toxiphores' or potential for metabolism to one
    - Potential for receptor binding
    - Etc.
  - Understanding of how structural and physical properties affect toxicity = the basis of (Q)SAR tools

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Voutchkova AM, Osimitz TG, Anastas PT. (2010). Toward a comprehensive molecular design framework for reduced hazard. Chem Rev. 110(10):5845-82

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Building a category/selecting analogues - Rationales

- 'From structure comes function'
  - a common functional group
  - a constant pattern in the changing of the potency of the properties across the category
  - the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals
- Why does structure influence function?
  - One of many reasons reason → Handled by body in a similar way
    - Phys Chem properties and structure impact bioavailability, distribution, metabolism and excretion

The Challenge with using Read Across

- Biological systems – Complex
  - Predictions based on structure/Phys Chem properties not always accurate
    - Particularly for more 'complex' endpoints
  - Using read across for these complex endpoints – more challenging
- With read across comes uncertainty

How to decrease uncertainty?

- ADME data – very useful in supporting read across
  - Do category members have common metabolic pathways?
  - Is bioavailability and tissue distribution similar?
  - Does one member convert to another, or both convert to the same metabolite?
  - How fast/how much?
- BUT – ADME studies can take a long time, can require additional animal use, can have significant costs

REACH Annexes VII-X:

- Requirement for ADME assessment 'based on available data'
- No requirement for a new study
- *Potential barrier to running a new study?*
  - *In vitro* vs *in vivo*
    - animal use sensitivity vs usefulness of data
  - Bespoke ADME studies
    - Can be Expensive
    - Complex – No 'Standard guidelines', Significant analytical requirements
    - Time consuming

A significant investment!

Opportunity for generating ADME without additional studies

- Other regulatory programs with significant test data requirements including ADME
  - Why not build ADME into range finding studies?
    - No 'additional animals' or special dosing requirements
    - Fits into existing study design (few modifications needed)
- Can we do this for REACH substances?
  - Use in supporting read across?
    - ADME 'Add-on' catered to specific questions
      - Bioavailability
      - Demonstrate similarity in metabolism
      - Identify metabolites (quantitative assessment)
      - Rate and Extent of metabolism
    - Can be done with or without radiolabel

Use of metabolism 'Add-on' in Practice: Case study

- Di-EPh
  - 100-1000t substance – Registration in 2013
  - Initial situation: Minimal data available
- Structural similarity to another substance (EPh) with complete dataset (REACH Annex VII-X and beyond – including ADME)
- Can a case for the use of read across be built?

Read Across Hypothesis

- 'Analogue approach' with support from additional structurally related substances
- Expert assessment of Di-EPh metabolism
  - predicted to metabolise to EPh or to a structurally similar metabolite
    - A lot known about EPh metabolism and toxicity
    - EPh → acid metabolite (major route)
    - Metabolism to acid = detoxification pathway
  - Prediction for Di-EPh
    - Di-EPh → EPh → acid metabolite

      or → acid metabolite
    - Several other possible pathways also identified
- Toxicity trend with other structurally similar substances
    - Mono>Di>Tri
  - Expectation that Di-EPh is less toxic than EPh

Strategy

- Annex VII and VIII studies performed
  - OECD 422 modified to include toxicokinetics
  - Allow comparison of toxicity profiles
    - Any differences – is the predicted trend substantiated?
    - Are the metabolic pathways the same?
    - Does the one substance metabolise to the other?
- If the toxicity data are consistent and the metabolism data supportive – use read across for sub-chronic and developmental toxicity

The ADME study

Rangefinder for OECD 422 – Diet study

Urine collected on TD 14 (metabolism cages)
Blood samples taken on TD14 (6.30am, 1.30 pm and 3.30pm) and Terminal (TD15)

Analysis of metabolites and parent based on predicted metabolic pathway (high confidence based on knowledge of chemistry)
Excretion T 1/5 and AUC derived for parent and metabolites

- At least 40-50% absorption
- Detected in blood and urine
  - Di-EPh
  - Di-EPh Acid metabolite
  - acid metabolite of EPh

Di-EPh → EPh → acid metabolite
AND → acid metabolite

Outcome

- Bioavailability
  - Systemic availability ***at least*** 40-50% - overall likely to be closer to 90%
    - Billiary excretion not measured
  - Compare with EPh - >90%
- Tox profile
  - Less toxic relative to EPh taking rat strain and bioavailability into consideration
  - No difference in target organs
  - Trend consistent with other structurally related chemicals
- Conclusion
  - Common metabolic pathway, common or structurally related metabolites
  - Toxicity profile supports read across
  - Use of read across represents a 'conservative' assessment

Opportunities and Challenges of this approach under REACH

- ADME 'Add-on' only available for new studies
- Alternative is a bespoke ADME study
  - Potentially uses animals and can be time consuming and expensive
- No guarantee of success
  - Interpretation of data vs guidance vs needs of regulatory audience
  - How comprehensive should assessment of metabolism be?
  - May show read across 'not justified'
  - balance the risk for additional testing in the future against testing today
- How to be applied in a 2018 requirement context?
  - Cost of generating ADME data may be disproportionate to required tests
  - Timing issues if ADME data do not support read across…

Opportunities and Challenges of this approach under REACH

BUT

- ADME form basis of categories using 'Metabolic justification'
  - Metabolism ***information*** needed to support hypothesis
- ADME data add significantly to WoE for other types of categories
  - Reduce uncertainty?
  - Inform Mode of Action understanding
- 'Add on' Study design variable
  - Simple to more 'Complex' depending on question

Further Opportunities

- In assessment of read across justifications
  - If read across justification not sufficient
    - Would ADME help?
    - Understanding the type of data and how it helps
      - Is there an opportunity to perform before rejecting read across?
      - Can it be added in to one of the requested studies – staged approach to testing?

THANK YOU FOR YOUR ATTENTION