Regulatory Challenges of CLH

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Introduction

Toxicological and eco-toxicological testing is performed according to a double shopping list

1) a predefined list of studies which need to be performed
2) a fairly narrow description of how each study must be performed (OECD guidelines)

Nearly all (new) active ingredients are developed for global use

Interpretation of what the high (maximum tolerated) dose in a regulatory study varies from country to country

Inevitably this results in compliance with the most stringent demand on high dose testing
High Dose Testing

Criteria of what constitutes the “Maximum Tolerated Dose” vary from:

1) **Country to country**
   EU, USA and Japan do not have common criteria for MTD; USA is open for an informed discussion on dose level setting, and allows for adjustments based on kinetics – there is no such process or guarantee in the EU

2) **Study type**
   Systemic toxicity: 10% decrease in bw development
   Developmental toxicity: ...the highest dose level should ideally induce some overt maternal toxicity such as slight weight loss, but not more than 10% maternal deaths

3) **Species**
   Minimal signs of toxicity in dogs are sufficient to claim an MTD
Relevance of Results

The problem with CLH is not related to low dose, specific and selective effects.

How to assess the relevance of (high dose) effects with respect to CLH?

! Human relevance is assumed by default!

How do we demonstrate absence of relevance?
Relevance of Results

(1) Toxicodynamics

Investigate MoA/AoP to understand the chain of key events causally linked to the adverse effect.

Key events then need to be investigated concerning human relevance.
Relevance of Results

(2) Toxicokinetics

Differences between mammalian species (rat, mouse, dog) are often explained by differences in ADME

→ Investigate ADME in species demonstrating CLH relevant effect and compare to human situation.

Qualitative difference may be used to address human relevance

Example: a metabolite causing adverse effect is not formed in humans
Relevance of Results

(2) Toxicokinetics

How do we deal with quantitative differences?

We all know that the dose makes the poison, how is dose taken into account in CLH?
(2) Toxicokinetics of MCPA

\[
\text{AUC}_{(0 - \infty)} \quad [\mu\text{g equiv. x h/g}] \quad \text{(plasma)}
\]

- rat; 5 mg/kg b.w.: 130
- dog; 5 mg/kg b.w.: 2,500
- rat; 100 mg/kg b.w.: 5,400
- dog; 100 mg/kg b.w.: 20,500

➔ Renal elimination of MCPA: dog << rat
➔ Renal elimination of MCPA in man ~ rat
➔ Dog is not a suitable test species!

Not using dog data for risk assessment was acceptable for regulatory authorities. Would you also consider CLH findings in such a case as non relevant?
Hurdles

AoP / MoA research is complex and often involves new technologies which are not well known to the larger community of decision makers.

The bar for the perfect explanation of findings may be too high, attenuating rather than stimulating good research.

Emotions (perception of severity of findings) play a role.

Appealing a decision when new data become available is difficult.

CLH is a “yes / no” process, reality is probabilistic.
Suggestions for a Path Forward

Communication is key!
(how can industry better cooperate with RAC to ensure that the right issues are addressed with appropriate research?)

AoP / MoA investigations and results are often complicated and complex

Appropriate time is needed to communicate these results to decision makers

The process needs to be transparent and documented

Good science should be rewarded
Further potential improvements

Can potency be introduced in the CLH process?

EU hazard classification involves identification of the hazards and comparison of those hazards (including degree of hazard) with defined criteria. Classification should give guidance on hazard identification as well as degree of hazard.

Potency is the most important indicator of degree of hazard.

It is included in criteria for acute lethality and general toxicity.

EU classification for carcinogenicity and reproductive toxicity does not discriminate across the wide range of potencies seen (6 orders of magnitude).

Therefore potency should be included in the classification process.

Reg Tox Pharmacol, 70, 457 – 467, 2014
Incorporating potency into EU classification for carcinogenicity and reproductive toxicity.
Conclusion

- Our current way of (high dose) toxicity testing is causing more problems than it serves in informing about relevant risks.

- Mode of action / Human Relevance Framework analysis is a tool to reduce/overcome these limitations

- Improvements of the current CLH process can be achieved by introducing potency resulting in more realism in the outcome

- Communication between decision makers and industry needs to be improved

- Good science should be rewarded
Thank you!