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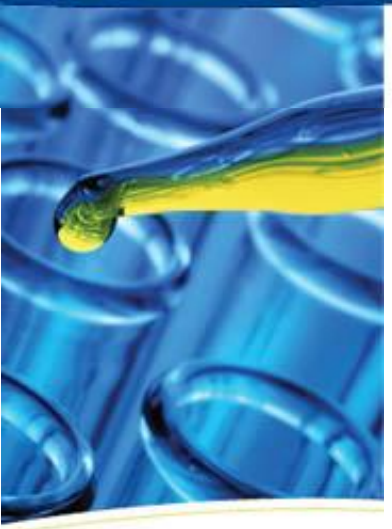
Europe Special Science Symposium
23-24 October 2008, Jolly Hotel du Sablon, Place du Sablon, Brussels

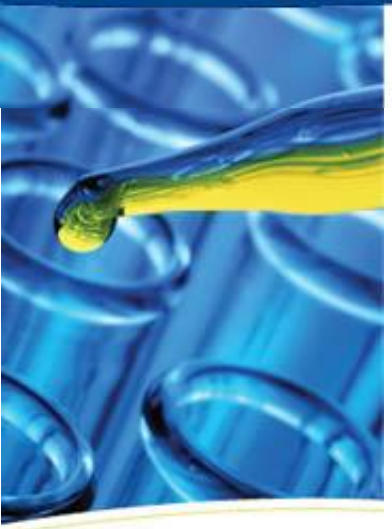


REACH and the NEED for ITS

- REACH places burden of proof on Industry
- Registration dossiers need to demonstrate safe use based on information on properties of their substances
- Huge data gaps to fill but huge opportunities to use alternative information…….ITS
- Extensive guidance has been developed for all endpoints
- Devil lies in the detail of the application for each individual (or group of) substances

Responsibility

- Industry to apply the guidance and implement the ITS, taking into account their own needs and Risk Management considerations!
- ECHA, its committees, MS Authorities and COM to play the judges
- Integration is the crux…….
- But how to apply WoE in a consistent, transparent manner ?

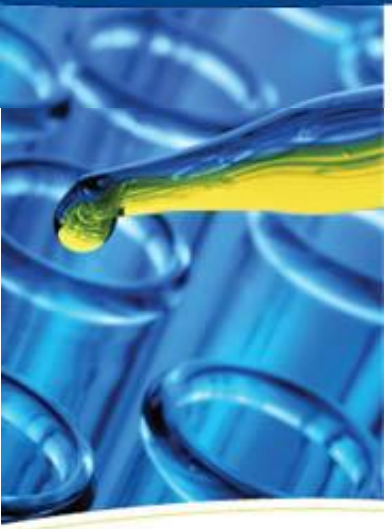


Requirements

- Data/information needs to be:
  - Reliable
  - Relevant
  - Adequate for C&L, PBT and CSA
  - Transparently presented
- Fit for purpose!
- Guidance provides directions and ideas for integration of information
- Conceptually simple, but on individual cases we deal with complex processes and complex techniques

Industry perspective

- ITS needs WoE approach involving multi-expert input
- Grouping approach promising
- In-vitro test particularly relevant to predict likelyhood of effects and for providing mechanistic information
- Some concerns about full transparency of QSARs and false pos/neg
- But in the end WoE by assessing relative values/weights of individual pieces of information should do the trick.
- But the process is not defined and agreed!



Optimising in-vivo testing

- Problem re-definition is key step in innovation
- Analyse carefully the need for and use of the test information
- Example within agricultural CSA process showed substantial improvements in use of animals
- Range of initiatives underway to help steering, selecting, interpreting animal and human data
- Possibilities suggested to use in/vitro and (Q)SAR approaches to better use (interpret?) the results of the systemic toxicity tests
- Substantial improvements possible in ecotox testing through application of aquatic tox test strategies
- Further ideas for optimising BCF testing (other species)

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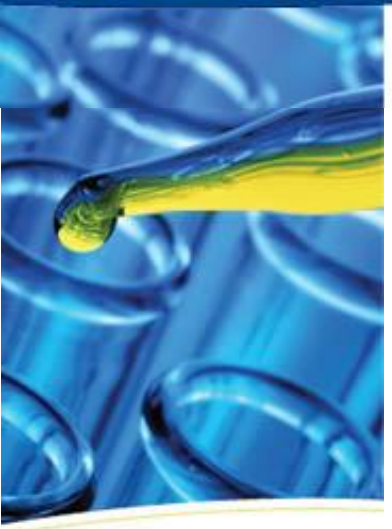
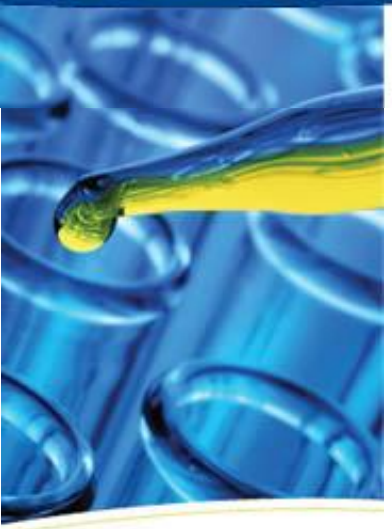


Discussion points:

- Optimized test may be:
  - more complicated (practicability)
  - more expensive than the standard test
  - may take more time (sequential methods)
- Regulatory acceptance optimized test may be too late for REACH
- Should the optimized test cover more or less than the standard test
- Missing information in optimized test may be supplemented by alternative tests



- Extended F1:
  - Choice between principle (test all possible endpoints within reproductive cycle) and pragmatism (saving many animals by excluding endpoints highly unlikely to contribute to RA or C&L).
  - Comprehensive data analysis needed.
  - and then optimization of design.
  - TG too late? Unlikely because of political pressure?
  - Test is more complicated/costly and this may hamper implementation.

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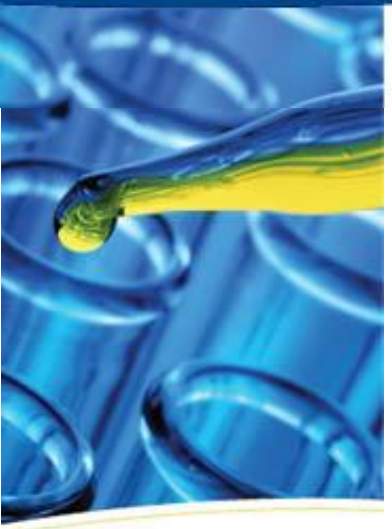
Application of in *vitro assays* in REACH

(from presentations, posters, T Murk)

- Mechanistic alerts in TTC approaches
- Role in ITS (Bayesian N); helps focussing *in vivo* tests (species, endpoint, duration)
- Facilitates grouping of compounds based on toxicological mechanism
  - Adds to rational read across (biol., endp., chem.)
  - In case the critical tox-mechanism is identified => *in vitro* testing (QSAR for group of compounds)
  - *In vitro=>in vivo* (Q)SAR

- *Can seriously reduce animal use and costs, but….*



Application of in *vitro assays* in REACH

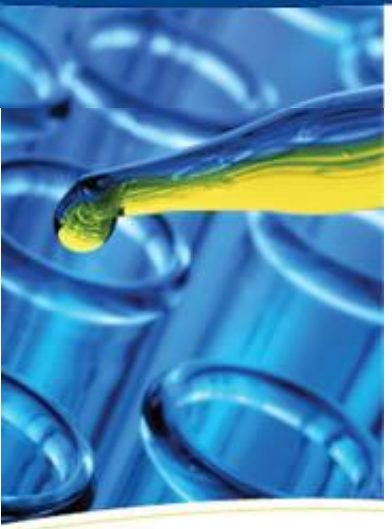
Provided:

- Well defined endpoints and protocols
- EU ringtests performed
- Chemically certified standards

Requires more effort:

- Need for tests with suitable (intra-cellular) *in vitro* metabolisation (bio-activation)
- Identify & develop missing *in vitro* assays for main toxicological pathways (relevant triggers)
- Stimulate combination with fate/PBTK-modelling =>comparison *in vitro* effect levels & predicted or measured blood levels given certain exposure

Further discussion needed on how to implement studies in a regulatory testing strategy?



Computational toxicology and categories

- Different kinds of categories (structural, mechanistic, toxicologically meaningfull)
- Challenge to perform species to species or even endpoint to endpoint extrapolation
- Place for in chemico techniques?
- Mantra: mechanistically based!
- Much progress made on reporting formats: transparency is key!
- Useful outline for application of non-testing strategy
- Need for more automated workflows to guide users through many different tools
- Use of structural alerts will help formation of categories and subcategories

TTC

- Provides useful means for grouping chemicals
- Can be useful for screening data-poor chemicals
- Applicability for REACH not yet clear/fully assessed

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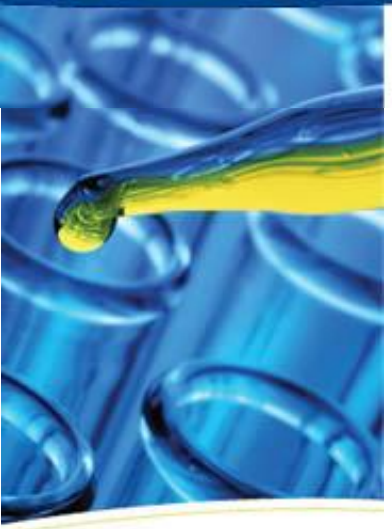

Exposure based waiving

- EBW implemented in REACH but….
- To prevent testing substantial investment in exposure assessment is needed
- Use of Exposure and effect distributions may improve decision-making
- Integration of EBW in ITS needs still more consideration

Weight of evidence

- Important to **transparently** document and communicate WoE
- **Paradigm change** from expert to more formal approaches
- Tools to integrate, compare all information pieces with their relative weights **still in development phase** (prototypes available)
- **Clearly potential to reduce costs and animal testing**

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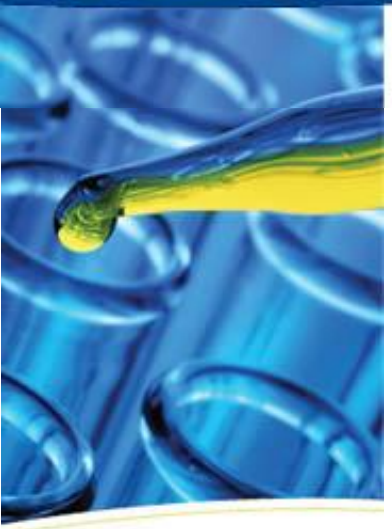

Decision-framework

- Input assumptions (prior)
- Impact of input assumptions
- Importance of including biological relevance in statistical models
- Background mathematics are insufficiently transparant for an end-user
- Useful for **faster decision-making**
- Investigates a **larger number of potential strategies**

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Risk characterisation

- RC in REACH provides some new needs and challenges
- Provide good overview of complexity and choices made in the RC decisions
- Address uncertainty but focus on the outcome
- Alternative approaches acceptable but proper scientific justification needed to convince the ‘judges’

Risk Communication

- Risk Governance Framework
- Scientific basis is necessary but will not convince the public since perception is driven by other factors
- Trust and credibility are key
- ….but can only be earned!

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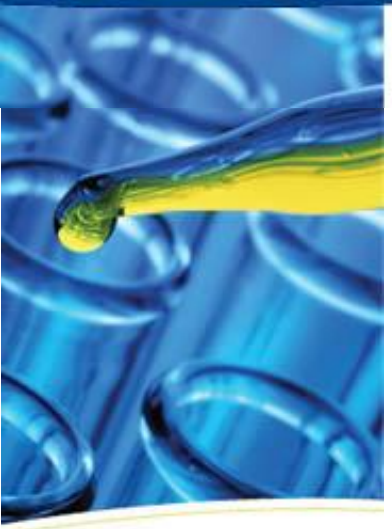

Conclusions

- Many useful initiatives ongoing to build pillars for the ITS temple
- But do we have the architectural plan?
- Can we convince people to live in it?