OSIRIS Webtool:
An integrated Framework for non-testing methods

Dinant Kroese

TNO| knowledge for business

Focus:

not on the webtool primarily

on human health endpoints

Outline

Context: *REACH, ITS & 'Non-Testing'*

Objectives OSIRIS / Webtool

WoE approaches

Conclusions / Next steps

REACH context

Core tools under REACH

- The Chemical Safety Assessment is the tool used to ***determine*** the safety of the chemical
- The Chemical Safety Report is the tool used to ***record/document*** the Assessment to EChA
- The Safety Data Sheet is the tool used to ***communicate*** safe use to downstream users (DU)

Chemical Safety Assessment

to *determine* the safety of the chemical

has 2 major objectives..

C&L assessment (PBT & vPvB)

and

DNEL/DMEL derivation (PNEC)

Chemical Safety Assessment

(Annex VI)

1. Gather and share available information
2. Consider information requirements *cf* tonnage-bands *(Annexes VII-X)*
3. Identify information gaps
4. Generate new testing data / propose testing strategy
   (*Annexes VII & VIII / Annexes IX & X*)

REACH Standard Information Requirements

(Annexes VII – X)

Tonnage	Human Health
1 – 10 tpa Annex VII	• *In vitro* skin and eye irritation • Skin sensitization • *In vitro* mutagenicity • Acute toxicity (one route)
10 – 100 tpa Annex VIII	• *In vivo* skin and eye irritation • Further *in vitro* mutagenicity • Acute toxicity (2nd route) • Sub acute toxicity (28d) • Reproductive toxicity screen
100 – 1000 tpa Annex IX	• *Further mutagenicity tests* • Sub-chronic toxicity (90d) • Reproductive toxicity tests

>1000 tpa
 	
Annex X
	• Further mutagenicity tests
	• Further reproductive toxicity tests
	  • *Carcinogenicity may*
	  • *Chronic toxicity may*

REACH Standard Information Requirements

(Annexes VII – X)

(REACH art.13, 25 & Annex XI) Animal tests as last resort!

Tonnage	Human Health
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Annex X
	• Further mutagenicity tests
	• Further reproductive toxicity tests
	  • *Carcinogenicity may*
	  • *Chronic toxicity may*

REACH Standard Information Requirements

General rules for adaptation

(Annex XI)

1. Testing does not appear scientifically necessary

2. Testing is technically not possible

3. Substance-tailored exposure-driven testing

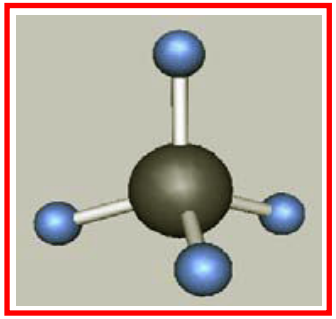
Magic word = ITS

Strategy to efficiently gather required information

Available sources of information

Human data

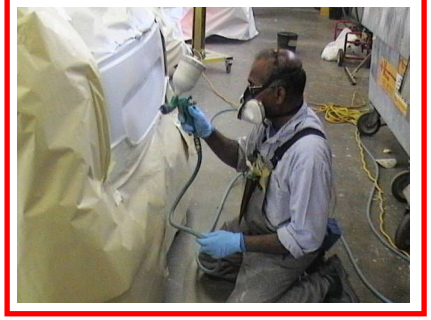
*Non-Testing (**NT**) information*



(Q)SAR

In vitro

Exposure (-based waiving)



Grouping & read across

ITS

Strategy to efficiently gather required information

Step 1: Gather all available Testing and Non-Testing information

*If **not** sufficient* ↓ *for **C&L** and **RC** cf REACH*

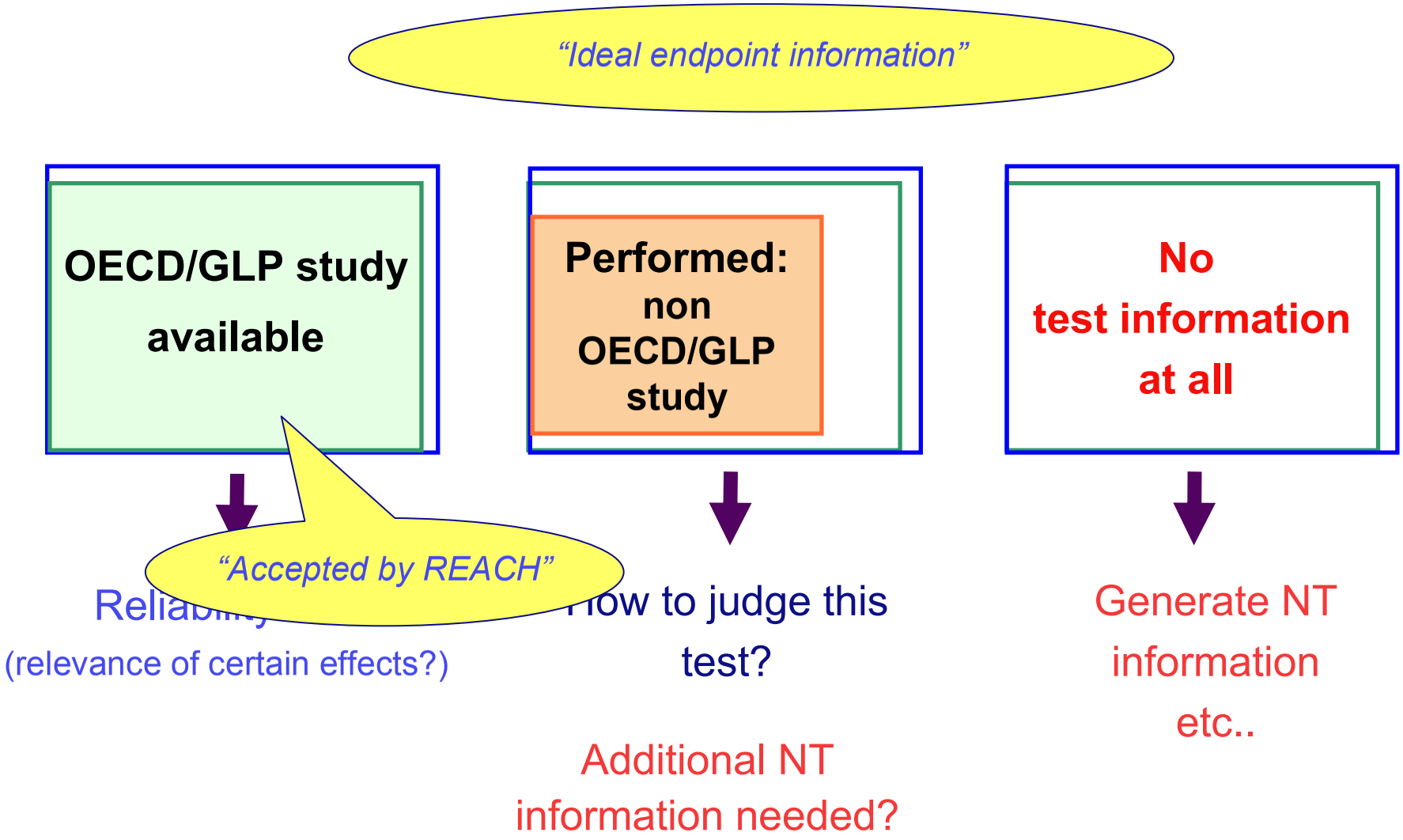
(*Testing is technically possible*)

Step 2: Is Exposure-Based Waiving an option?

*If **not** possible* ↓

Step 3: Perform / Propose Testing as last resort!!

ITS: 3 starting situations (per endpoint)



How to weight & combine information from different sources?

REACH objectives
C&L, RC

+

= sufficient ???

Non-GLP / *Non*-OECD

+

= sufficient ???

+

= sufficient ???

We need tools that:

- Weight information
  - *from tests*
  - *from models / methods*
  - *from categories approaches*
  - *etc.*
- Can add weights of different sources of information
- Can decide if total weight of information is “sufficient”
- If not → help find most efficient way of filling “information gap”

This is the central objective of:

SIXTH FRAMEWORK PROGRAMME

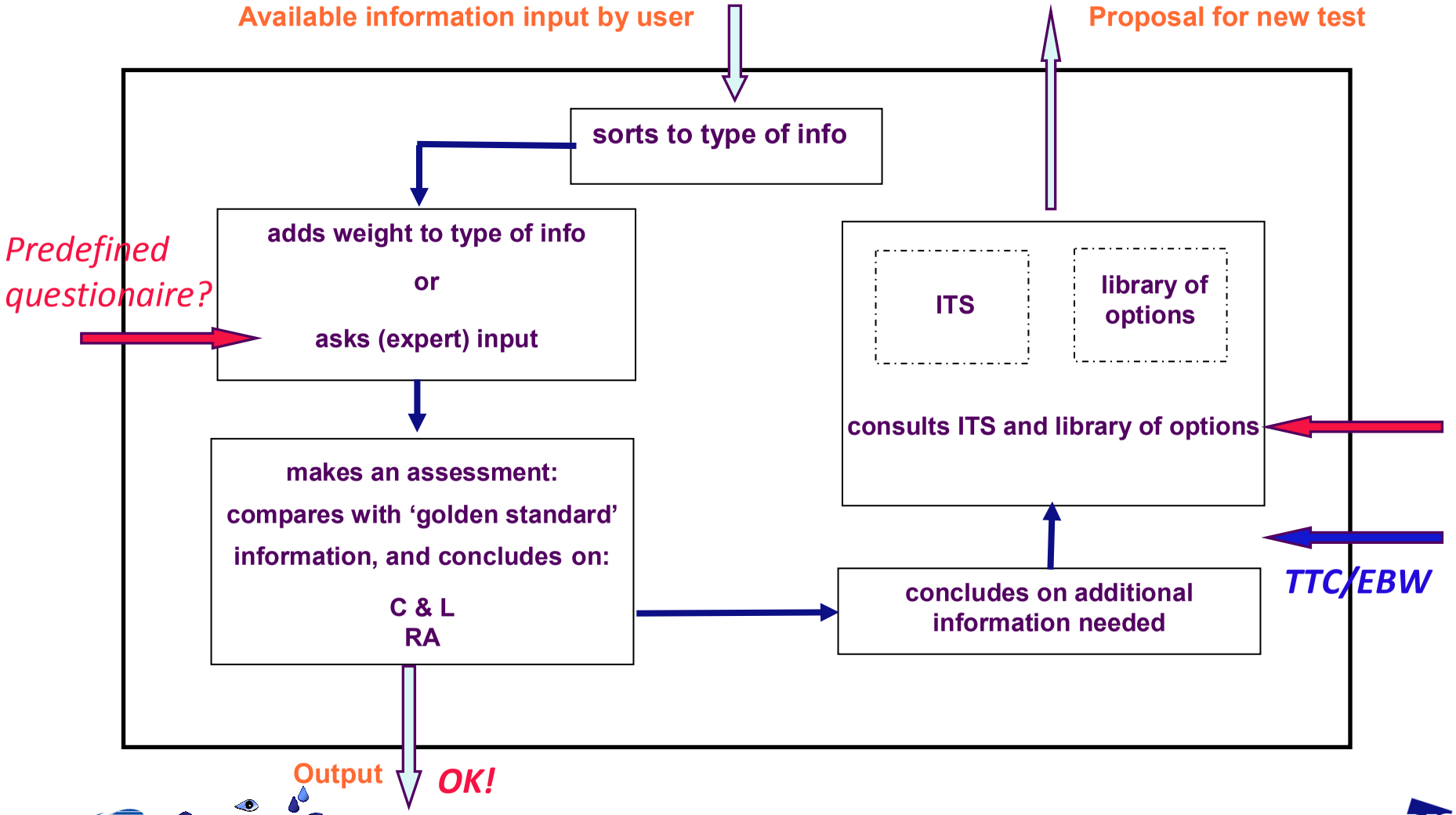
OSIRIS

Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information

2007-2011

Ultimate goal: OSIRIS webtool

simpple



SIXTH FRAMEWORK PROGRAMME

OSIRIS

TNO

Generating focus within OSIRIS

At the first Stakeholder Workshop (Stuttgart 07):

Focus on most critical endpoints: CMRS!

At subsequent OSIRIS Meetings:

Focus on Proof-of-Concept instead of concrete ITSses for CMRS!

Generating focus within OSIRIS

At interpillar meeting in Liverpool 08:

P-o-C for a categorical, and for a continuous dataset!

Categorical dataset: sensitisation (as model C&L endpoint)

Continuous dataset: repeated dose toxicity (as model RC endpoint)

Main reason: availability of data and expertise!

How to develop a tool for a categorical endpoint that:

- Weights information
  - *from tests*
  - *from models / methods*
  - *from categories approaches*
  - *etc.*
- Can add weights of different sources of information
- Can decide if total weight of information is “sufficient”
- If not → help find most efficient way of filling “information gap”

Approach chosen:

Probabilistic one using Bayesian statistics:

“What is the probability that

a predicted response that the substance is a sensitizer or not, is true?”

Approach chosen:

1. Score of the substance in a test: 'yes' or 'no' (i.e. sensitizing)
   &
   Score of that test relative to the required OECD/GLP test as 'GS' ('Gold Standard')

   'Sensitivity/Specificity cross table'

2. 'Quality factor' score of that test:

   describing performance of specific test and its result

   - *no. of animals*
   - *applicability domain*
   - *reporting..*

   ~ Klimisch rating

Categorical CMRS endpoints and 'GS'

(Annexes VII – X)

Tonnage	Human Health	'Gold Standard'
1 – 10 tpa Annex VII	• Skin sensitization • *In vitro* mutagenicity	LLNA, OECD 429 GM Bacteria, OECD 471
10 – 100 tpa Annex VIII	• Further *in vitro* mutagenicity • Reproductive toxicity screen	CA/MN Mamm cells, OECD 473/487 GM Mamm cells, OECD 476 Reprotox screen, OECD 421
100 – 1000 tpa Annex IX	• Further mutagenicity tests • Reproductive toxicity tests	*If pos in vitro: in vivo,* OECD 474/475 Prenatal developm tox, OECD 414 (2-gen tox, OECD 416)
>1000 tpa Annex X	• Further mutagenicity tests • Further reproductive toxicity tests • *Carcinogenicity may be required*	*If pos in vitro: in vivo,* OECD 474/475 2-gen tox, OECD 416 Carcinogenicity, OECD 451

How to develop a tool for a continuous endpoint that:

- Weights information
  - *from tests*
  - *from models / methods*
  - *from categories approaches*
  - *etc.*
- Can add weights of different sources of information
- Can decide if total weight of information is “sufficient”
- If not → help find most efficient way of filling “information gap”

Approach chosen:

Probabilistic one using Bayesian statistics:

"What is the probability that

the observed NOAEL (LOAEL) is the true NOAEL (LOAEL) ?"

Fraunhofer Institut Toxikologie und Experimentelle Medizin

repeated dose toxicity database analysis

RepDose

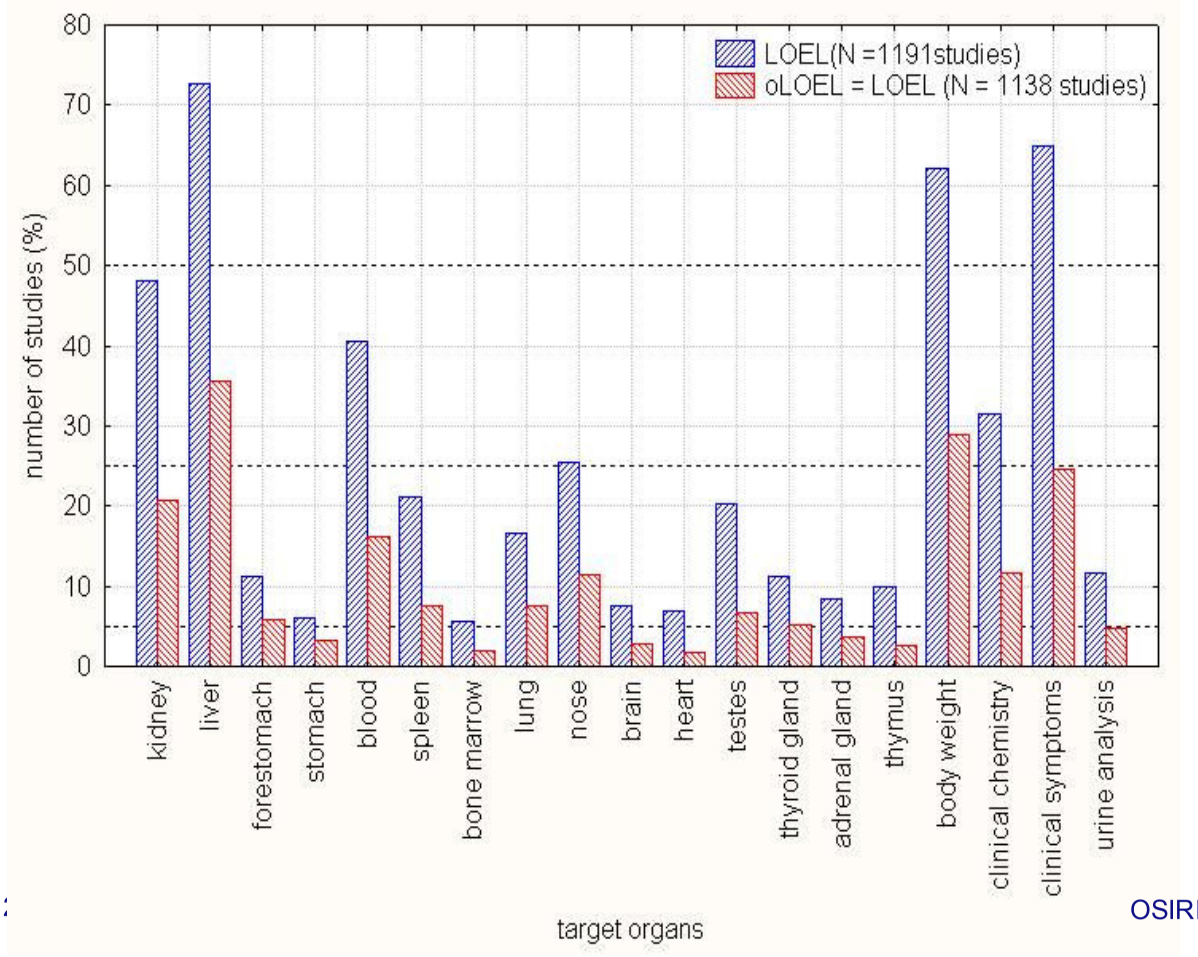
Target organs most frequently determining NOAEL:

Liver
Body weight
Clinical symptoms
Kidney
Blood

↓

Provides a way to assign weight to any non-OECD/ GLP test data …!

and even Non-test data?!



Approach chosen:

1. Score of the substance in a test: 'NOAEL' or 'LOAEL'
   &
   Score of that test relative to the required OECD/GLP test as 'GD' ('Gold Standard')

   'Organ-coverage statistics'

2. 'Quality factor' score of the specific test:

   describing performance of specific test and its result

   - *no. of animals*
   - *'applicability domain'*
   - *reporting ..*

   ~ Klimisch rating

Progress so far?

Using the ITS structure as template:

Step 1: Gather all available Testing and Non-Testing information

*If **not** sufficient* ↓ *for **C&L** and **RA** cf REACH*

(*Testing is technically possible*)

Step 2: Is Exposure-Based Waiving an option?

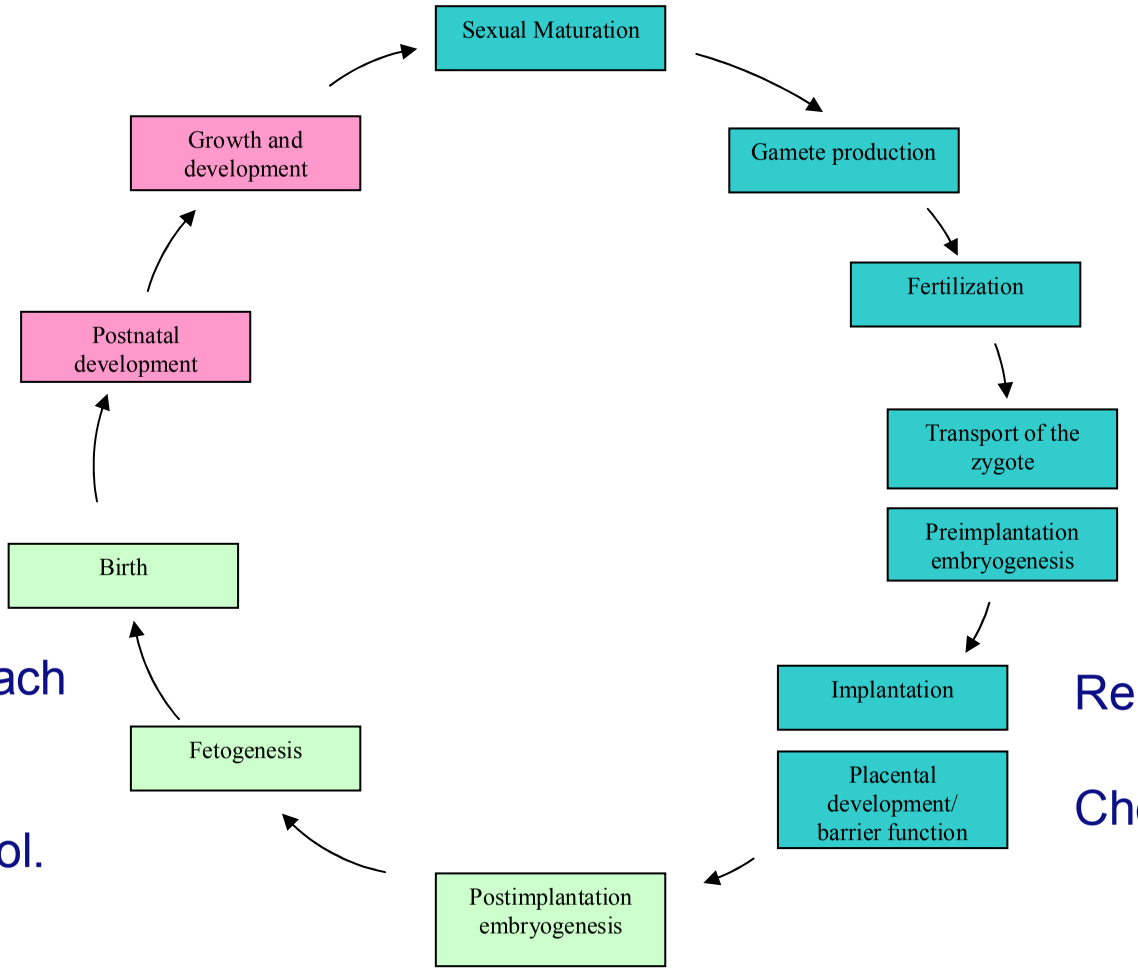
*If **not** possible* ↓

Step 3: Perform / Propose Testing as last resort!!

Tools for CMRS ITSses to be developed

		Proof-of-concept endpoint		Proof-of-concept endpoint		
ITS		**S**	**M**	**Rep Dose Tox**	**C**	**R**
		categorical	**categorical**	**continuous**	**continuous**	**continuous**
Step 1	T + NT	Sens/Spec cross table & Quality Factors	*conform* ***S*** ***Note:*** *widely accepted in vitro tests available*	'Coverage approach' & Quality Factors tbd	Conform **Rep dose tox**	? Conform **Rep dose tox** possible?
Step 2	EBW?	? *'TTC' for induction or challenge? Differentiation: high – low potency?*	? *See endpoint Carcinogenicity*	! 'Whole db' & Cramer(-like) approach	! Conform **Rep dose tox** approach	? **Rep dose tox** approach possible
Step 3	'T'	Decision analysis to choose … red LLNA, **LLNA** or GPMT..?	? *Depends on in vitro data / which MoA?* GM / SCA / NCA	What to choose? no. of animals, selected organs, duration of test?	What to choose? no. of animals, selected organs, duration of test?	What to choose? what test? Distinction to MoA?

Complex Reproductive Cycle



Coverage approach for repro: Dang *et al*, Reproduct.Toxicol. 2009

ReProTect (FP6)

ChemScreen (FP7)

Tools for CMRS ITS to be developed

		Proof-of-concept endpoint		Proof-of-concept endpoint		
ITS		**S**	**M**	**Rep Dose Tox**	**C**	
		categorical	**categorical**	**continuous**		
Step 1	T + NT	Sens/Spec cross table & Quality Fact…	*conform* ***S*** ***Note:*** *widely accepted in vitro tests available*	'Coverage approach' & Quality Factors tbd	**Rep dose tox**	Conform **Rep dose tox** possible?
Step 2	EBW?	*'TTC' for induc… or challeng… Differenti… high – low …tency?*	*See endpoint Carcinogenicity*	! 'Whole db' & Cramer(-like) approach	! Conform **Rep dose tox** approach	? **Rep dose tox** approach possible
Step 3	'T'	Decision analysis to choose … red LLNA, **LLNA** or GPMT..?	? *Depends on in vitro data / which MoA?* GM / SCA / NCA	What to choose? no. of animals, selected organs, duration of test?	no … …ed organs, duration of test?	… Distinction to MoA?

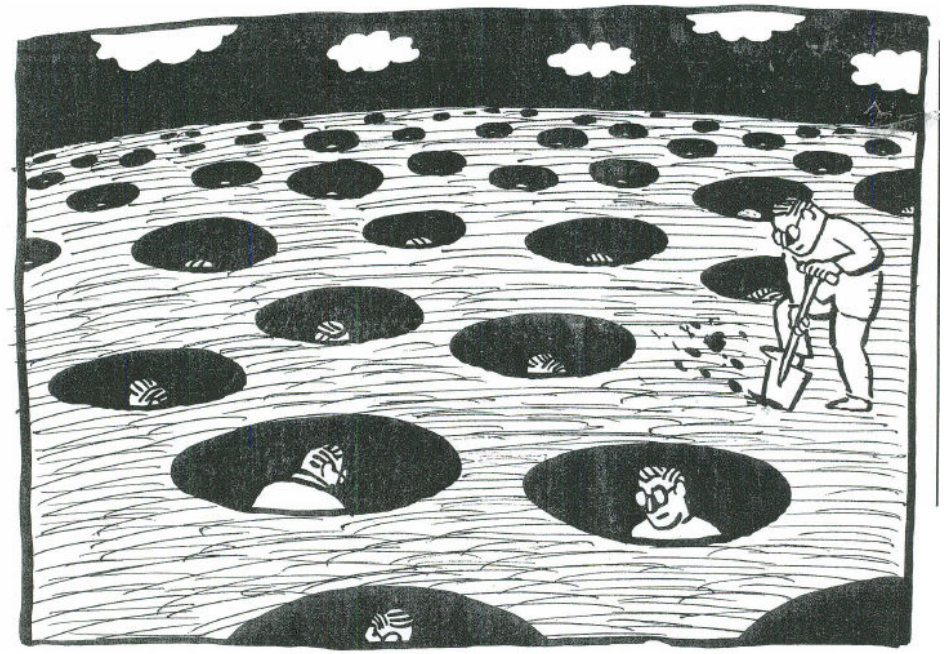
What are the NT options?

What are options?

What are options?

Conclusions / Next steps

- A clear focus and template for our objectives (given data, time ….).



statisticians, toxicologists, software engineers, chemists etc…. their languages and hobbies….

Conclusions / Next steps

- A clear focus and template for our objectives (given data, time ….).
- WoE approach for categorical endpoints: nearly finished.
- WoE approach for continuous endpoints identified; yet to make statistically-founded.
- ITSses for sensitisation, mutagenicity, BCF, and aquatic tox are introduced in the webtool (http://osiris.simmple.com; *not yet public*). One continuous human health endpoint needs to be incorporated asap (to allow validation by P5).
- TTCs / Exposure-based Waiving options need to be incorporated.
- Adapted *in vivo* testing: what are the options?
- What is an acceptable probability (weight)?

Refinement
Reduction and
Replacement of animal testing

Leading to better alternatives

Thank you for your attention

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