BUNDESINSTITUT FÜR RISIKOBEWERTUNG

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Legal and Practical Aspects of the Cut-off Criteria for Reproductive Toxic and Endocrine Disrupting Effects for Approval and Classification of Pesticides in Europe

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CUT – OFF CRITERIA

for substances with reproductive toxic and endocrine disrupting effects (points 3.6.4. and 3.6.5 of ANNEX II of REGULATION (EC) 1107/2009)

- **Legal and practical issues that still need to be resolved**
- **Possible procedures for implementing the cut – off**
- **Criteria for C&L for reproductive toxicity**
- **Consideration of hazard-based & risk-based cut - off**
  - Reproductive toxicity
  - Endocrine Disrupting Properties (ED)
- **Co-ordination between the new Regulations**
  - for Pesticides and CLP

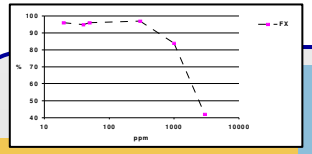
Current approval criteria: risk assessment

- **Directive 91/414/EEC**
  concerning the placing of plant protection products on the market

- *Risk assessment for pesticide approval …*
  - Directive 91/414/EEC concerning the "placing of plant protection products on the market" entered into force on 15 July 1991.
  - Dir. 91/414/EEC stipulates that a.s. contained in PPP must be assessed regarding the possible risk for humans, animals …..
  - Only when this risk assessment confirms that their use does not constitute a risk …, the a.s. entered in the EU positive list.
  - This means that preparations with these active substances may be approved in the individual Member States of the EU.

Current approval criteria: risk assessment

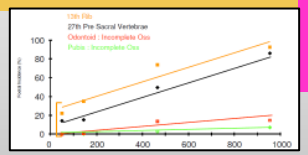
Dose-response relationship – Threshold Concept



Hazard identification

NOAEL for parental effects

NOAELs for reproductive effects



Absorption, bioavailability

Assessment Factor

Exposure assessment A

Exposure assessment B

Exposure assessment Z

External ARfD ADI

Route specific AEC

Systemic AOEL

Risk Characterisation

No concern

Annex I inclusion

Concern

No Annex I inclusion

Legal and practical issues that still need to be resolved

➢ **Directive 91/414/EEC vs. Regulation (EC) No. 1107/2009**
concerning the placing of plant protection products on the market

- Approval of pesticides should not depend primarily on carcinogenic, reprotoxic and endocrine disrupting properties when, instead, threshold values can be established above which a health risk is to be expected.
- The potential exposure of consumers, operators, workers and bystanders should also be taken into account.

Legal and practical issues that still need to be resolved

24.11.2009 EN Official Journal of the European Union L 309/1

I

(Acts adopted under the EC Treaty/Euratom Treaty whose publication is obligatory)

REGULATIONS

REGULATION (EC) No 1107/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 21 October 2009

concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC

- Substances should … present a **clear benefit for plant production** and … **not expected to have any harmful effect on human or animal health** ...
- … the **decision on acceptability or non-acceptability** of such substances should be taken at Community level **on the basis of harmonised criteria**.
- These criteria should be **applied for the first approval of a substance** under this Regulation.
- For active substances already approved, the criteria should be applied **at the time of renewal or review of their approval**.

Future approval criteria: Cut-off for CMR Cat 1 and ED

➢ **PPP - Regulation (EC) No. 1107/2009**
concerning the placing of plant protection products on the market

An active substance, safener or synergist shall only be approved if …

… it is not or has not to be classified as …

- *mutagen category 1A or 1B.*
- *carcinogen category 1A or 1B …**
- *toxic for reproduction category 1A or 1B …**
- *is not considered to have endocrine disrupting properties that may cause adverse effects in humans …**

… unless ... exposure of humans is negligible …*

Possible procedures for implementing the cut-off criteria

Definitions "Negligible exposure" for C & R & ED

- … the product is used in **closed systems** or in other conditions excluding contact with humans and
- where **residues** of the active substance, safener or synergist concerned on food and feed **do not exceed the default value** set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005

- Closed systems do not exclude necessarily exposure of bystanders and residents.
- A MRL of 0.01 mg/kg food for all compounds (PPP regulation) is not a health-based scientific decision criterion to protect consumers.
- A pragmatic and science-based definition of negligible exposure might be
  - based on TTC concept or
  - Exposure < 10 % (< 1%) ADI, ARfD, AOEL
  - NOAEL $_{\text{reprotox \& carcinogenicity}}$ / 1000

Future approval criteria: Cut-off for CMR Cat 1 and ED

efsa
European Food Safety Authority

ECHA

Hazard identification

Exposure assessment

Risk Characterisation

Classification and labelling for
Carcinogenicity
Mutagenicity
Reproductive Toxicity
....

Annex I Inclusion

Classification for reproductive toxicity

- **CLP - Regulation (EC) No. 1272/2008**
  on classification, labelling and packaging of substances and mixtures

- Harmonised classification and labelling for active substances used in plant protection products and biocidal products

- In this classification system, reproductive toxicity is subdivided under two main headings:

  (a) Adverse effects on sexual function and fertility;

  (b) Adverse effects on development of the offspring

Hazard categories for reproductive toxicants

- **Category 1A**: **Known** human reproductive toxicants

  - The classification is largely based on evidence from **humans**.
- **Category 1B**: **Presumed** human reproductive toxicants
  - The classification is largely based on data from **animal** studies.
  - **clear** evidence of an adverse effect … in the absence of other toxic effects, or
  - adverse effect is considered not to be a secondary non-specific consequence.
  - mechanistic information raises doubt about relevance for humans, classification in Category 2 may be more appropriate.
- **Category 2**: **Suspected** human reproductive toxicants
  - **some** evidence from humans or experimental animals,
  - possibly supplemented with other information, and
  - evidence is not sufficiently convincing to place the substance in Category 1.
  - effects in the absence of other toxic effects, or
  - considered not to be a secondary non-specific consequence.

Classification for fertility effects

- **Adverse effects on sexual function and fertility**

Any effect of substances that has the potential to interfere with sexual function and fertility.

This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

Classification for developmental effects (1)

ECHA

- **Adverse effects on development of the offspring**

Developmental toxicity includes, in its widest sense,
any effect which interferes with normal development of the conceptus,
either before or after birth, **and** resulting from exposure
of either parent prior to conception, or
exposure of the developing offspring during prenatal development, or
postnatally, to the time of sexual maturation …

Therefore, for pragmatic purpose of classification,
developmental toxicity essentially means
adverse effects induced during pregnancy, **or**
as a result of parental exposure …

Classification for developmental effects (2)

➢ **Adverse effects on development of the offspring**

The major manifestations of developmental toxicity include:

- death of the developing organism,
- **structural abnormality,**
- altered growth, and
- functional deficiency.

Classification for developmental effects (3)

➢ **Maternal toxicity**

Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity.

Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g.

- *irreversible effects such as **structural malformations**,*
- *embryo/foetal lethality,*
- *significant post-natal functional deficiencies.*

Classification for developmental effects (4)

- **Maternal toxicity**

Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific ***maternally-mediated mechanism*** *has been demonstrated.*
In such a case, classification in Category 2 may be considered more appropriate than Category 1.

…when a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects.

Consideration of hazard-based cut-off criteria
Reproductive toxicity
CLP - Regulation (EC) No. 1272/2008

Annex I; 3.7 Reproductive toxicity

For the purpose of classification hazard classes Reproductive Toxicity are differentiated into:

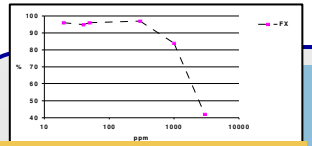
- CAT 1
  may damage fertility or unborn child
- CAT 2
  suspected of damaging fertility or unborn child
- Additional category effects on or via lactation

Classification	Category 1A or Category 1B	Category 2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Hazard Statement	H360: May damage fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.

Consideration of hazard-based and risk-based cut off criteria

Reproductive toxicity

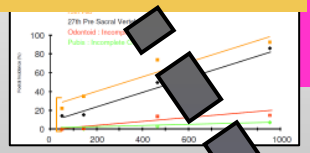
Cat. 1



Hazard-based Classification

NOAEL for parental effects

NOAELs for reproductive effects



Absorption, bioavailability

Assessment Factor

10X

Exposure assessment A

Exposure assessment B

Exposure assessment Z

External ARfD ADI

Route specific AEC

Systemic AOEL

Risk Characterisation

TTC

No concern

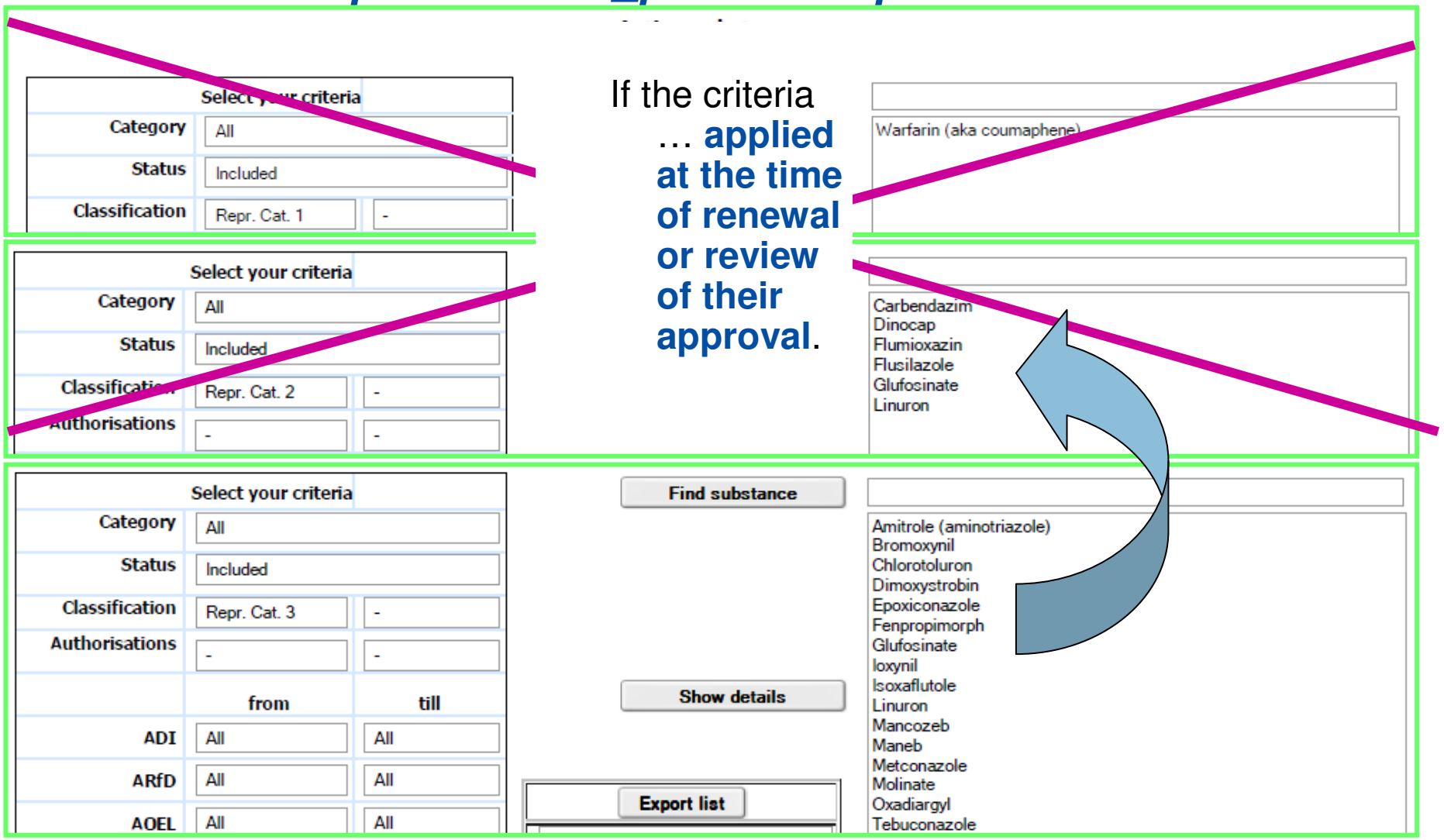
Concern

Decision on approval

Consideration of hazard-based cut-off criteria

Reproductive toxicity

ec.europa.eu/sanco_pesticides/public/index.cfm



If the criteria … **applied at the time of renewal or review of their approval**.

Consideration of hazard-based cut-off criteria
Endocrine Disrupting Properties

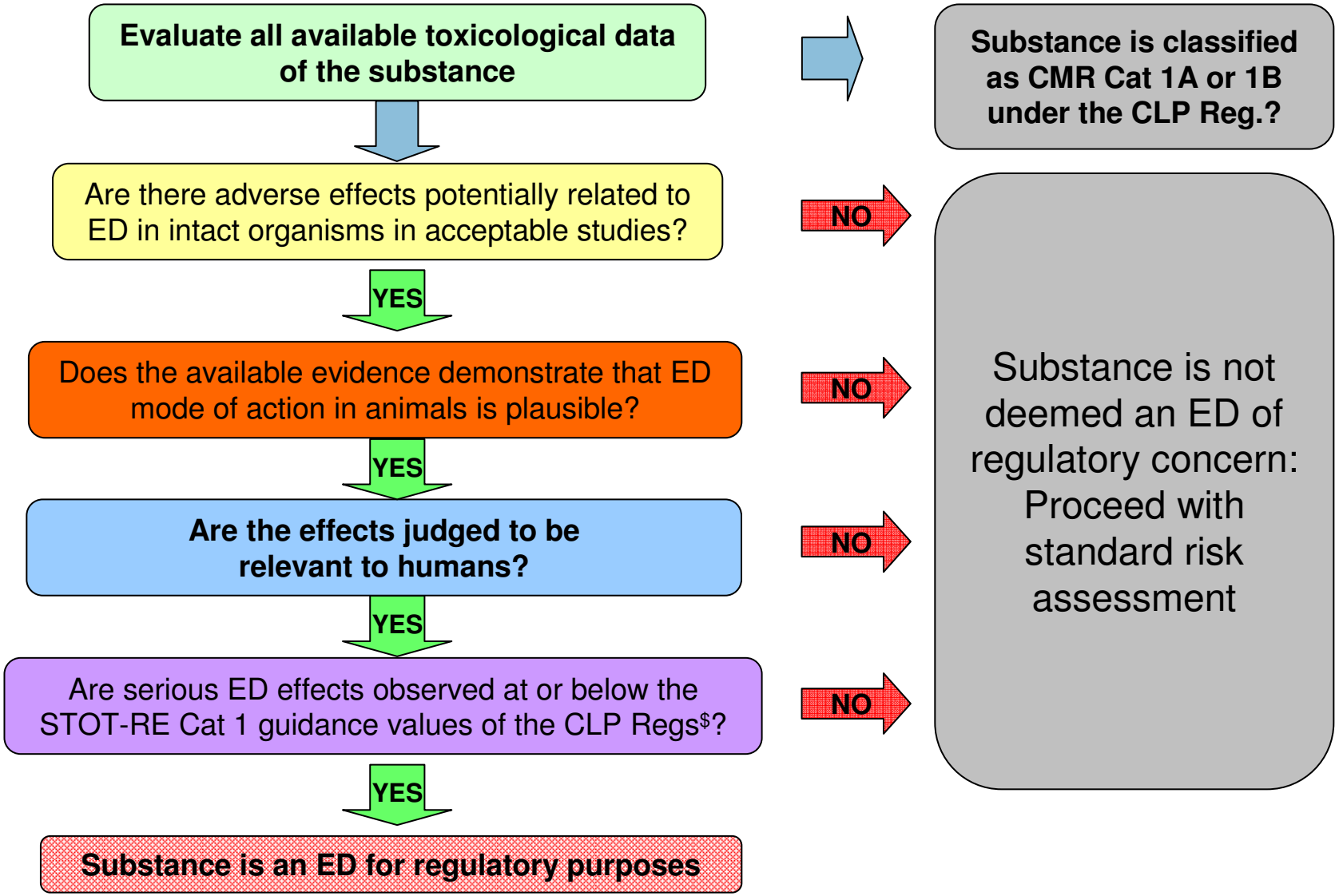
➢ PPP - Regulation (EC) No. 1107/2009

➢By 14 December 2013, the Commission shall present …
a draft of the measures concerning **specific scientific criteria**
for the determination of ED properties to be adopted ...

➢ Pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as
carcinogenic category 2 and toxic for reproduction category 2,
shall be considered to have endocrine disrupting properties.

➢ In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as **toxic for reproduction category 2 and which have toxic effects on the endocrine organs**,
may be considered to have such endocrine disrupting properties.

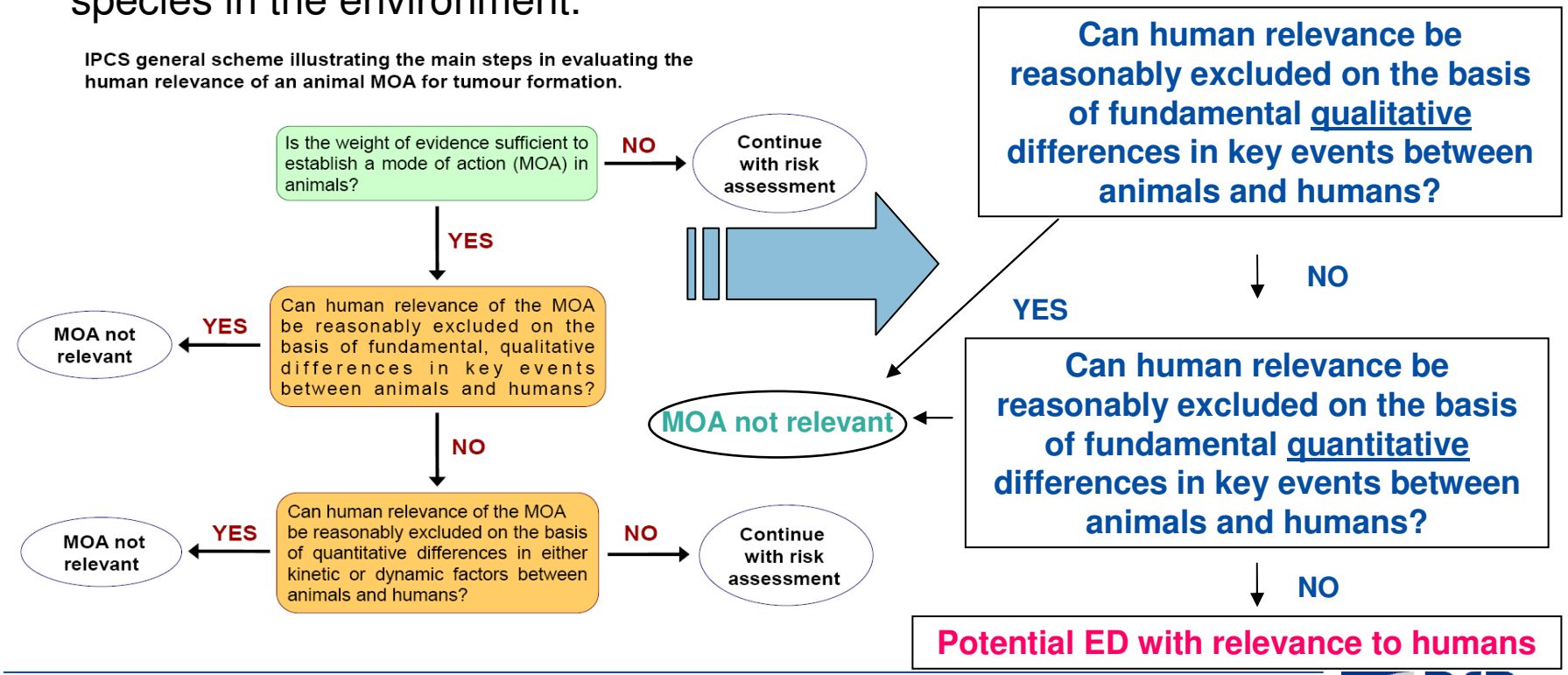
Joint DE-UK Proposal for potency-based cut-off criteria
Endocrine Disrupting Properties



Joint DE-UK Proposal for potency-based cut-off criteria
Endocrine Disrupting Properties

Analysis of relevance for humans

- Use IPCS human relevance framework for robust and transparent conclusion (Boobis *et al.*, 2008);
- If no information, assume human relevance;
- If effects not relevant to humans, they could still be relevant to non-target species in the environment.



Coordination between PPP– and CLP–Regulation

Workshop on Harmonised Classification and labelling (CLH)
of active substances in Plant Protection Products
12. April and 13. April 2011 at the BfR in Berlin
Cooperation at the European level in the assessment of human health hazards
of active substances in Plant Protection Products (PPP)
under the Regulation (EC) No 1107/2009 and the harmonised classification and labelling of
active substances under the Regulation (EC) No 1272/2008

- **Goals of the Workshop:**
- to finalise discussion on how the two processes can most efficiently be linked between RMS, EFSA and ECHA.
- to raise awareness in MSs (CAs for PPP evaluation and for C&L) and to communicate importance of the issue and the possible solutions.
- to discuss and recommend solutions regarding formatting problems a (how to facilitate compilation of PPP and C&L dossiers in form and content).
- to discuss possibilities and practicalities for submission of IUCLID 5 dossiers to support technical preparation of dossiers for C&L and Annex I inclusion.
- to improve harmonised interpretation and reporting for of CMR studies, discuss scientific principles of interpretation to avoid conflicting interpretations e.g. for **Reproductive Toxicity** ..

Workshop Classification of Pesticides

Break out group 1

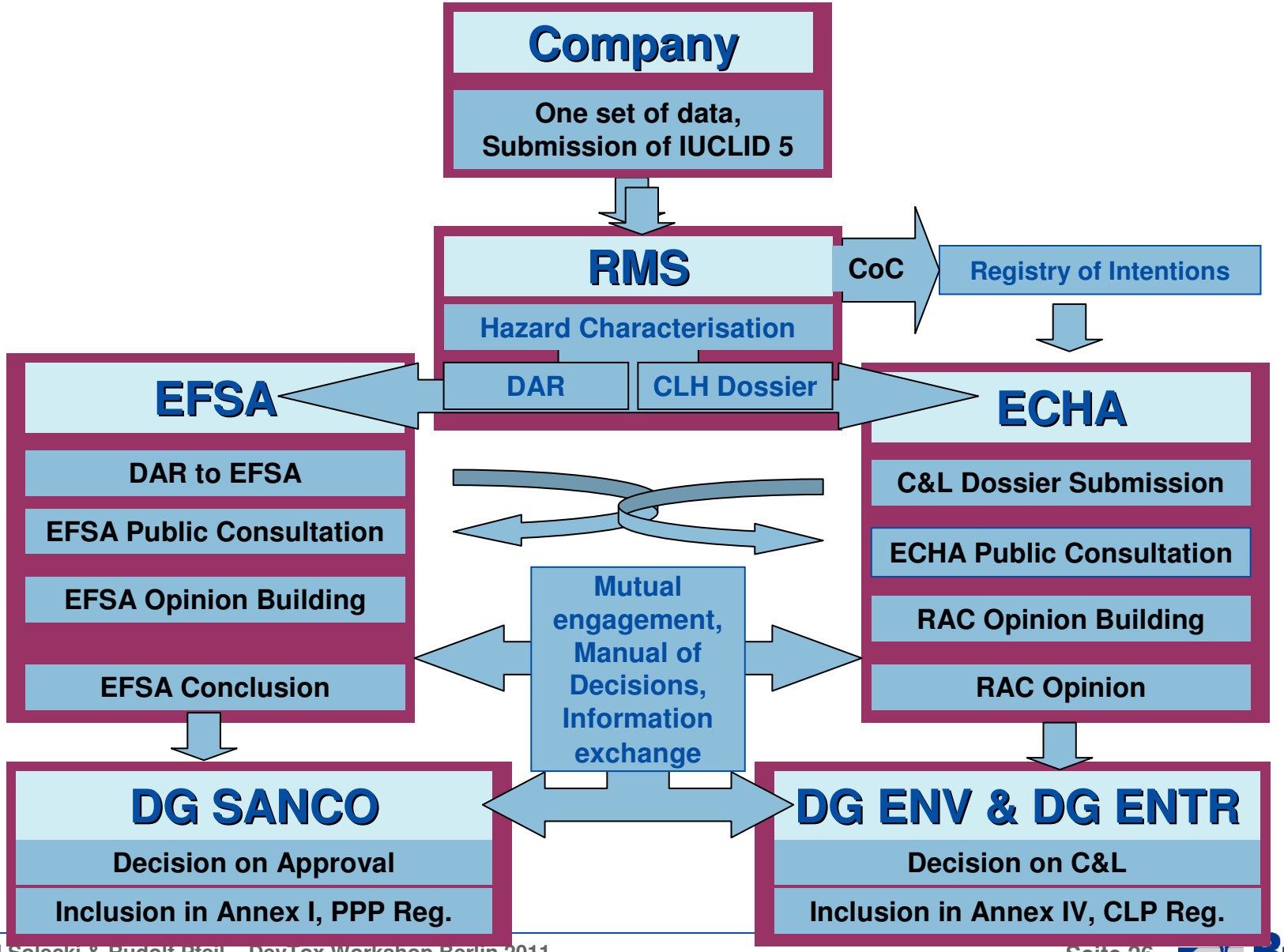
- **Scope**
  - **streamlining and integration of the procedures for active substances in PPP for Annex I inclusion under the Reg. (EC) No 1107/2009 and for Classification and Labelling (C&L) .**
- **Main goals**
  - how 2 processes could most efficiently be linked between RMS, EFSA, ECHA as prepared by ECHA discussion paper and reflected in the outline paper
  - to consider the anticipated workloads stemming from the PPP programmes in relation to the capacity of the ECHA process with a view to ensuring
    - appropriate planning,
    - management and
    - prioritisation procedures.
  - to raise awareness in Member States and to communicate the importance of the issue and possible solutions.
  - to prepare a draft working document on the both processes.

Workshop Classification of Pesticides

Break out group 2

- **Scope**
  - **scientific and practical issues in assessment and interpretation of CMR studies and requirements concerning adequate scientific content according to Reg. (EC) No 1107/2009 and Reg. (EC) No 1272/2008.**
- **Main goals**
  - how to **facilitate compilation of CLH dossiers** by the RMS;
  - how to integrate **additional relevant documents from the pesticide process**,
  - to facilitate the **harmonised preparation of dossiers** for both procedures.
  - to improve **harmonised interpretation and reporting** of CMR studies, including **Reproductive Toxicity**
  - to **discuss scientific principles of interpretation** of relevant studies, e.g., **Reproductive Toxicity**
  - to **avoid conflicting interpretations and different reporting** of same studies, e.g., **Reproductive Toxicity**.

Workshop Classification of Pesticide



Coordination between PPP Regulation and CLP

Concluding remarks C&L Workshop (1)

- **Aim:**
  Proposals for C&L from EFSA and ECHA should be identical, at best.

- **How to reach this aim?**
  1. Improvement of **procedural issues**
  2. Improvement of **scientific issues**

- **Procedural issues:**
  1. Processes (PPP, CLP) should be run in **cooperation**.
  2. **Revision of the DAR** is necessary in order to meet CLP requirements.
  3. **IUCLID-file** should also be submitted for **PPP** assessment in order to save work for RMS.

Coordination between PPP Regulation and CLP

Concluding remarks C&L Workshop (2)

- **Scientific issues:**

  1. **Identical data base** (for PPP and CLP decisions) is essential for receiving identical conclusions.

  2. **Harmonized application of CLP criteria** is essential for receiving identical conclusions.

- **Workshop output:**

  Publication of results: CIRCA and COM SANCO website

- **save all background documents of the workshop and the report in a public folder in CIRCA at the following address:**

http://circa.europa.eu/Public/irc/sanco/eccoman1/library?l=/new_section

Coordination between the Regulations for PPP & biocides

- Proposal for a regulation of the European Parliament and of the Council concerning the placing on the market and use of **biocidal products**
- New: Hazard based "exclusion criteria" for the biocide approval

Article 5

1) The following active substances shall not, …, be included in Annex I:
   a) … classified as, carcinogen category 1A or 1B;
   b) … classified as, mutagen category 1A or 1B;
   c) … classified as, toxic for reproduction category 1A or 1B;
   d) … identified … as having endocrine disrupting properties;
   e) … fulfill the criteria for being PBT or vPvB …
   f) … are persistent organic pollutants …..

2) However … included in Annex I … if .. one of the following conditions is met:
   a) … exposure of humans … in a biocidal product…, is negligible, in particular … used in closed systems or strictly controlled conditions;
   b) … active substance is necessary to control a serious danger …;
   c) … not including … would cause disproportionate negative impacts

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Thank you for your attention!

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