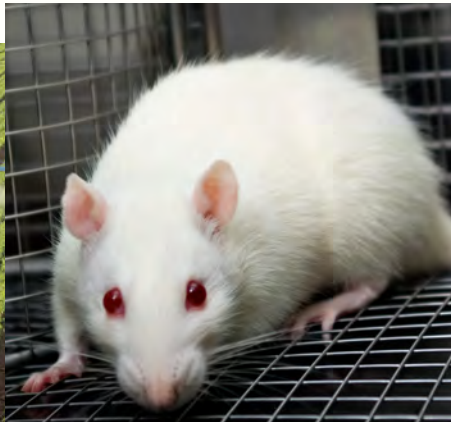




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# 3R Innovations & Best Practices in European Pesticide Regulation



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EUSAAT 2012 • 5-8 September 2012 • Linz, Austria



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# Overview » EU Pesticide Sector

## WHY FOCUS ON PESTICIDES?

- *Dozens of separate in vivo data (testing) requirements both for active ingredients & formulated products*
  - **Up to 10,000 animals** may be consumed to bring a new active ingredient to market
- *EU Directives from 1994/98 do not reflect contemporary technical progress*
- *Both EU biocides and plant protection directives were already scheduled for revision*





# Overview » EU Pesticide Sector

## REGULATORY SCHEMES

- **Biocides** = non-food pesticides
  - Directive 98/8/EC → Regulation (EC) No 528/2012
  - Revision by 'normal legislative procedure' (formerly 'co-decision')
  - DG Environment lead
- **Plant protection products (PPPs)** = food-use pesticides
  - Directive 91/414/EEC → Regulation (EC) No 1107/2009
  - New regulation adopted by normal legislative procedure, but revision of data req's by comitology procedure, leading to separate data req. regulations
  - DG SANCO lead



## Starting Point » 1994/98 Data Req's

1. Toxicokinetics	11. 28-day dermal <sup>CR</sup>	21. Chronic (1y) dog	31. Avian acute oral*
2. Acute oral*	12. 28-day inhal. <sup>CR</sup>	22. Carcinoma rat	32. Avian dietary
3. Acute dermal*	13. 90-day dermal <sup>CR</sup>	23. Carcinoma mouse	33. Avian repro
4. Acute inhalation*	14. 90-day inhal. <sup>CR</sup>	24. Repro 2-gen rat	34. Fish acute x2*
5. Skin irritation*	15. Vitro mutation x3	25. Prenat dev. rat	35. Fish chronic juv.
6. Eye irritation*	16. Vivo micronuc. <sup>CR</sup>	26. Prenat dev. rabbit	36. Fish early life stg.
7. Skin sensitisation*	17. Mouse spot <sup>CR</sup>	27. Neurotox hen <sup>CR</sup>	37. Fish lifecycle <sup>CR</sup>
8. 90-day oral rat	18. Vivo cytogen. <sup>CR</sup>	28. Dermal absorpt.	38. Fish bio[]
9. 90-day oral dog	19. Vivo germ cell <sup>CR</sup>	29. Addn'l studies <sup>CR</sup>	39. Mecososm <sup>CR</sup>
10. 28-day oral <sup>CR</sup>	20. Chronic (2y) rat	30. Livestock feed*	...

\*Active ingredient + finished product    CR = Conditional Requirement





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# ILSI-HESI Agricultural Chemical Safety Assessment Technical Cmtee.



*“In most cases, when the database is complete using the large number of animals mandated by the test guidelines, **only one study is used to set the RfD** [reference dose] **for each risk assessment**. The question then arises: Would it have been possible to eliminate the studies which were not used for risk assessment and still protect human health?”*

—Doe et al., Crit Rev Toxicol. 2006; 36: 37-68



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# HSI Campaign Objectives & Approach

**1. *Secure uptake of all applicable OECD 3R guideline methods – as well as other approaches supported by regulatory precedent or literature – during revision of EU directives on biocides & plant protection products***

**2. *Move away from redundant in vivo testing***

- Multiple exposure routes (oral + dermal + inhalation)
- Multiple species (rodent + dog or rabbit)

**3. *Encourage ‘thoughtful toxicology’***

- Using non-animal method data to waive particular tests
- Examine 2 or more endpoints within a single test
- Adopt more efficient & informative study designs
- Say ‘no’ to testing that is scientifically inappropriate

**IN COOPERATION  
WITH...**

Eurogroup &  
Deutscher  
Tierschutzbund  
AISE & ECPA  
EU Institutions  
Member State  
Authorities



# Case Study » Reproductive Toxicity

## STARTING POINT

- *Multi-generation study (2,600 rats) required as default approach*

## REVISED BIOCIDES REGULATION

- *“The **extended one-generation reproductive toxicity study** adopted at OECD level **should be considered as an alternative** approach to the multi-generation study” (Annex II, 8.10.2.)*



## DRAFT REVISED PPP DATA REQ's REGULATION

- *“The OECD extended one-generation reproductive toxicity study **may be considered as an alternative** approach to the multi-generation study” (Annex II, 5.6.1.)*

**POTENTIAL ANIMAL SAVINGS: 1,200**



# Case Study » Developmental Toxicity

## STARTING POINT

- *Teratology studies required in both rats (1,300) and rabbits (650)*

## REVISED BIOCIDES REGULATION

- *“Pre-natal developmental toxicity study, preferred species is rabbit... The **study shall initially be performed on one species**” (Annex II, 8.10.1.)*
- *“A decision on the need to perform additional studies on a second species or mechanistic studies should be based on the outcome of the first test and all other relevant available data (in particular rodent reprotox studies)” (Annex II, 8.10.3.)*



**POTENTIAL ANIMAL SAVINGS: 1,300**





# Case Study » Long-Term Toxicity

## STARTING POINT

- *Chronic studies required in both rats (160) and dogs (32)*

## REVISED BIOCIDES & PPP REGULATIONS

- *1-year dog study deleted (proposed by ENV & SANCO from outset)*



**POTENTIAL ANIMAL SAVINGS: 32**



# Case Study » Carcinogenicity

## STARTING POINT

- 2-year bioassay in both rats (400) and mice (400)



## DRAFT REVISED PPP DATA REQ's REGULATION

- “A second carcinogenicity study of the active substance shall be conducted using mouse as test species, **unless it can be scientifically justified that this is not necessary. In such cases, scientifically validated alternative carcinogenicity models may be used instead of a second carcinogenicity study**” (Annex II, 5.5.)

**POTENTIAL ANIMAL SAVINGS: 400**



# Case Study » Repeated Dose Toxicity

## STARTING POINT

- *No mention of endpoint-combining in data requirements, but provided for in OECD/EU test guidelines*

## REVISED BIOCIDES REGULATION

- *“In order to reduce testing carried out on vertebrate animals and in particular the need for free-standing single-endpoint studies, the design of the repeated dose toxicity studies **shall take account of the possibility to explore several endpoints within the framework of one study**” (Annex II, 8.9.)*

**POTENTIAL ANIMAL SAVINGS: ~80+**



# Case Study » Genotoxicity *In Vivo*

## STARTING POINT

- *Stand-alone in vivo studies*

## REVISED BIOCIDES REGULATION

- *“The study/ies do(es) not generally need to be conducted if... **valid in vivo micronucleus data is generated within a repeat dose study** and the in vivo micronucleus test is the appropriate test to be conducted to address this information requirement” (Annex II, 8.6.)*

## DRAFT REVISED PPP DATA REQ's REGULATION

- *“**Consideration shall be given to conducting an in vivo test as part of one of the short-term toxicity studies** described under point 5.3” (Annex II, 5.4.2.)*

**POTENTIAL ANIMAL SAVINGS: 80+**



# Case Study » Acute Dermal Toxicity

## STARTING POINT

- *Dermal lethal dose studies required for both AI & formulated products*

## RETROSPECTIVE ANALYSES BY HSI, ECVAM & OTHERS

- *Oral-dermal concordance assessments for 337 pesticides + 1,569 chemicals*
- *Results: Oral classifications  $\geq$  dermal for 97.9% of pesticides & 99.9% of chemicals (Seidle et al. ALTEX 2011, 28, 95-102)*
- *Conclusion: “Dermal acute systemic toxicity data almost never drive regulatory classification & labelling decisions in the chemicals, agrochemicals & biocides sectors”*





# Case Study » Acute Dermal Toxicity

## DRAFT REVISED PPP DATA REQ's REGULATION

- ***“The acute dermal toxicity of the active substance shall be reported unless waiving is scientifically justified (for example where oral LD<sub>50</sub> is greater than 2000 mg/kg)” (Annex II, 5.2.2.)***

## REVISED BIOCIDES REGULATION

- ***“Before a new dermal acute toxicity study is carried out, an in vitro dermal penetration study should be conducted to assess the likely magnitude and rate of dermal bioavailability” (Annex II, 8.7.)***

**POTENTIAL ANIMAL SAVINGS: 30**



# Case Study » Skin Sensitisation

## STARTING POINT

- *GP Max/Buehler tests (32 guinea pigs), both AI & formulated products*

## REVISED BIOCIDES REGULATION

- *“The assessment of this endpoint shall comprise the following consecutive steps:*
  - 1. an assessment of the available human, animal and alternative data*
  - 2. in vivo testing*

*The Murine Local Lymph Node Assay (LLNA) **including, where appropriate, the reduced variant of the assay**, is the first choice method for in vivo testing...” (Annex II, 8.3.)*

**POTENTIAL ANIMAL SAVINGS: 24**



# Case Study » Skin/Eye Irritation

## STARTING POINT

- *Rabbit Draize tests (3 animals each), both AI & formulated products*

## REVISED BIOCIDES REGULATION

- *“The assessment of this endpoint **shall be carried out according to the sequential testing strategy** for dermal [eye] irritation set out in the Appendix to Test Guideline B.4 [B.5]” (Annex II, 8.1. & 8.2.)*

**POTENTIAL ANIMAL SAVINGS: 3 each**



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# Case Study » Finished Products

## STARTING POINT

- *New in vivo testing for all (or most) acute endpoints*

## REVISED BIOCIDES REGULATION

- *Broad provision for **classification by calculation**:*

*“Testing of the product/mixture does not need to be conducted if there are valid data available on each of the components in the mixture to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected” (Annex III, 8.1. through 8.7.)*



**POTENTIAL ANIMAL SAVINGS: 100+**



# Case Study » Fish Acute Toxicity

## STARTING POINT

- *Fish lethal concentration test (42 animals)*

## REVISED BIOCIDES REGULATION

- *“When short-term fish toxicity data is required the **threshold approach (tiered strategy)** should be applied” (Annex II, 9.1.1.)*



**POTENTIAL ANIMAL SAVINGS: 30**





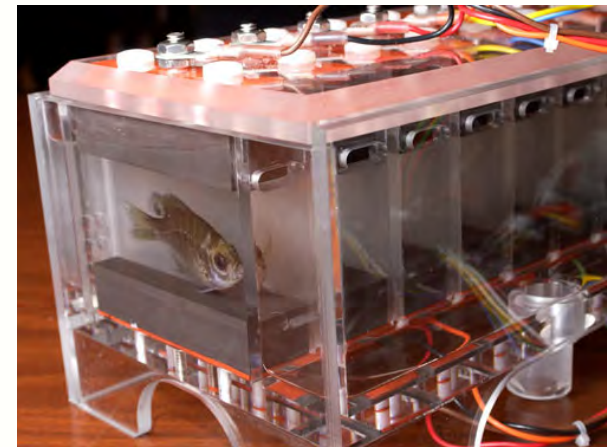
# Case Study » Fish Bioconcentration

## STARTING POINT

- *Fish study (42 animals)*

## REVISED BIOCIDES REGULATION

- *“The experimental determination may not need to be carried out **if it can be demonstrated on the basis of physico-chemical properties (e.g. log Kow <3) or other evidence** that the substance has a low potential for bioconcentration” (Annex II, 9.1.4.)*



**POTENTIAL ANIMAL SAVINGS: 12**



## Case Study » Effects on Birds

### STARTING POINT

- *Avian acute oral (60 animals), dietary (80 animals) & repro (1,400 animals) studies generally required*

### REVISED BIOCIDES REGULATION

- *Endpoints downgraded to “ADS” (conditional tier 2)*
- *“For [avian reproduction] the study does not need to be conducted if the dietary toxicity study shows the  $LC_{50}$  is above 2000 mg/kg” (Annex II, 9.4.)*



**POTENTIAL ANIMAL SAVINGS: 1,500+**



# Summary



## BIOCIDES

- Potential **best-case** animal use reduction of ~40%
- Possibly largest-ever one-time cut in in vivo data requirements in a regulated product sector

## PPPs

- More modest relative to biocides

## BUT...

- We're not living in a perfect world
- Real-world animal use reduction unlikely to be substantial until other global markets adopt equivalent 3R measures



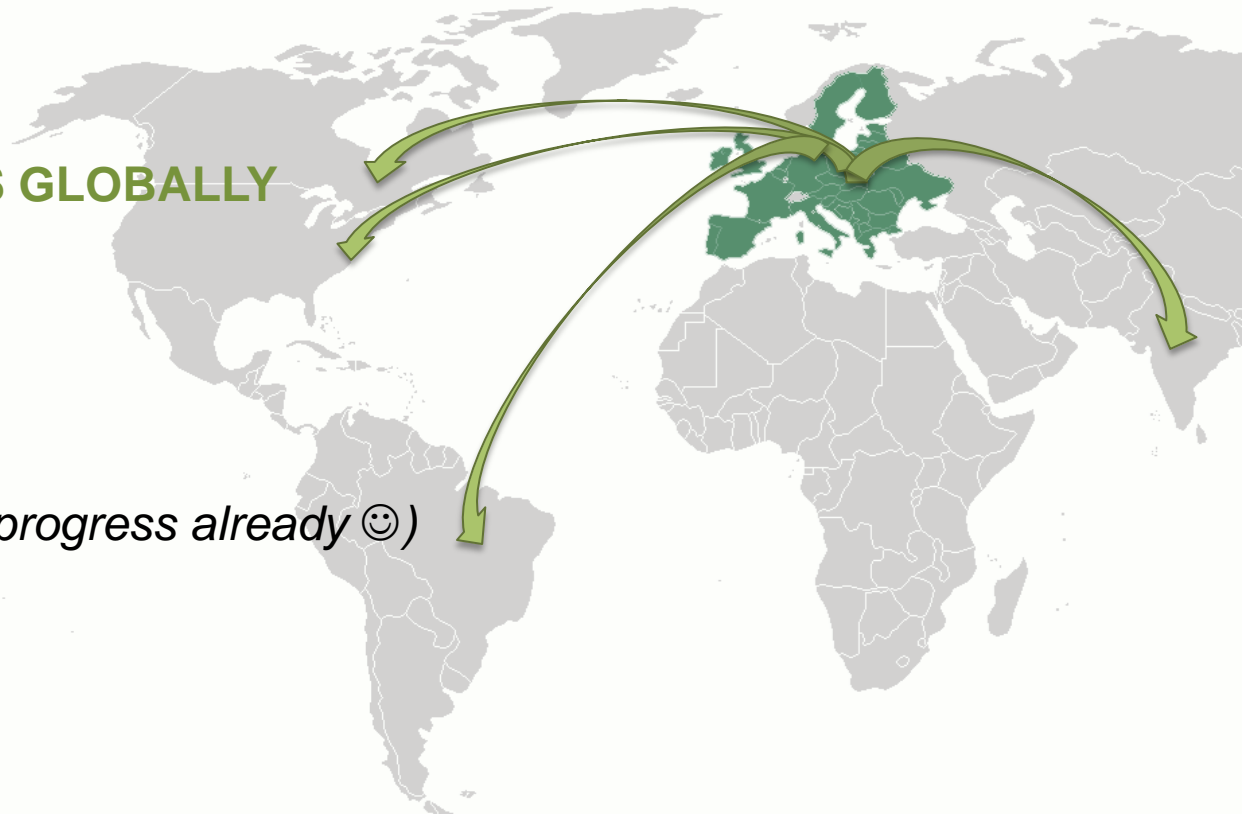
# Next Steps

## EXTEND PRECEDENTS TO OTHER EU REGULATIONS

- *REACH*

## EXTEND PRECEDENTS GLOBALLY

- *Brazil*
- *Canada*
- *India*
- *United States (some progress already 😊)*
- ...



[ End Animal Testing ]



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