



Science For A Better Life

# Endocrine Disruption – what's happening in Europe

March 2015





# Agenda

- Endocrine Disruption – sounds bad, but what does it mean?
- How does the EU plan to regulate EDs?
- The EU Impact Assessment
  - Roadmap
  - Industry proposal
  - Public consultation and impact assessment
- A way forward?



# Endocrine Disruption – what does it mean?

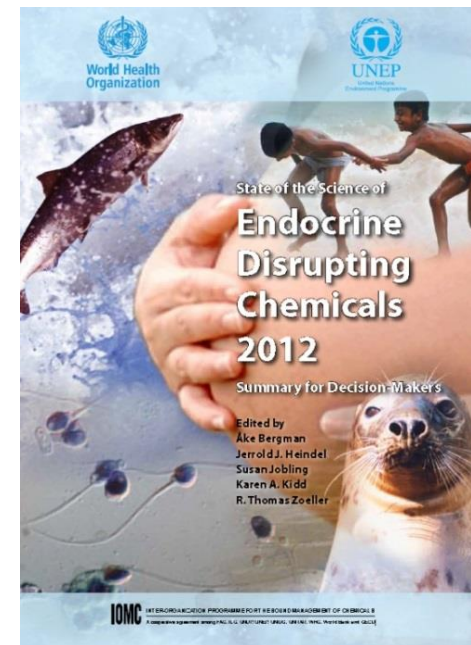
- We rely on our endocrine system to keep our bodies developing and working properly
- Our hormone levels are constantly fluctuating, for various reasons, some normal, some unexpected and transient – everything from daily cycles, puberty, menstrual cycles, stress, fear, excitement ....
- The problems arise when something interacts to cause an irreversible adverse effect, perhaps via an acute exposure at a particular time in embryonic development, or alternatively via chronic exposure over many years – but the effect(s) may not actually appear until many years later
- We maintain that the chronic and multi-generation studies that form part of the data requirements for pesticides are appropriate for detecting ED effects. And we actively contribute to the development of new guidelines as our knowledge continues to improve.

# Cause and effect?

WHO/UNEP report in 2002 provided a state of the art view on health concerns, diseases, that might have some link to endocrine disrupting chemicals

The 2012 update raised global concerns on ED chemicals

- Many ED-related human diseases are on the rise
  - Notably diabetes, autism, breast cancer, prostate cancer, testicular cancer, obesity ..
- Past observations of endocrine related effects in wildlife populations
- Numerous laboratory studies support the idea that chemical exposures contribute to endocrine disorders
- Internationally agreed and validated test methods capture only a limited range of the known spectrum of ED effects
- (or do they??)



# Pesticides - an easy target

- Diseases/conditions such as various cancers, diabetes, obesity are certainly increasing in prevalence. Indeed WHO considers the issue of overweight children and adults is reaching the scale of a Global epidemic.
- The WHO campaign focus is on sugar-rich foods/drinks and fast-food diets, with insufficient exercise. Lifestyle matters .... and life expectancy continues to increase ..
- But some have ED in their sights ..... with pesticides, generally, and multinationals, especially, to blame!



**If the real concern is health, then placing too much focus on pesticides is probably barking up the wrong tree at an easy target. Still, we (and the regulators) have a responsibility to ensure that correct use of our products does not endanger health or the environment!!**

# An Endless List of EDs?

## Illustration using Everyday Life Chemicals



### In vitro ED screen

- ER/AR binding
- hER transcriptional activation
- **Steroidogenesis**
- Aromatase
- ...

### In vivo ED screen

- Uterotrophic
- Herberger
- Pubertal male & female
- Amphibian metamorphosis
- FLC

### Apical toxicity studies

- Chronic & Cancer bioassays.
- Reproductive toxicity studies
- Subchronic studies

Paracetamol	Positive		Reduced AGD & fetal testicular testosterone
Gingerol	Positive	SAT Weight changes; ↑ testosterone	
Caffeine	Positive	Changes in SAT Weights (M), estrus cycle effects, delay in puberty (F)	↑ Incidence of Leydig cell hyperplasia, mammary tumors, pituitary adenomas
Capsaicin	Positive		
Eugenol	Positive		
Cinnamaldehyde	Positive		↑ testes & epididymis weights, ↑ sperm motility
Resveratrol	Positive		
Curcumin	Positive		
Cuminaldehyde	Positive		
Naringine, obacunone	Positive		
Quercetin	Positive		
Theobromine	Weak Positive		
Vitamin C	Weak Positive	↑ Testosterone	↑ Epididymal sperm count
Echinacoside	Weak Positive		
Saccharose	Negative		
Ibuprofen	Negative		
Vitamins B9, 6, 3	Negative		
Lipoic acid	Negative		
Gingkolide A	Negative		
Allyl sulfide/disulfide	Negative		

- From 24 randomly selected everyday chemicals several are endocrine active (*in vitro/in vivo*) and some induce adverse effects in long term studies.





# How does the EU plan to regulate EDs

- A need to discriminate between chemicals with the potential to interact with the endocrine system, and those that can actually cause harm (“irreversible, adverse effects”), since many chemicals in everyday foods can have endocrine activity
- Plant Protection and Biocides Regulations in EU will deal with endocrine disruption as an exclusion criterion (“cut-off”)
- Under REACH (currently) which regulates industrial chemicals and US EPA EDSP, a substance can be identified as ED (Substance of Very High Concern, SVHC for REACH) and then authorised (or not) via risk assessment with appropriate mitigation measures, taking account of expected exposure and socio-economic impact. **1107 and 528 do not allow for this**, since the cut-off applies before any risk assessment, therefore we need to integrate these elements into the criteria that identify an ED **for regulatory purposes**
- **Criteria that are set for pesticides and biocides are then supposed to be applied to industrial chemicals and cosmetics in future. Industrial chemicals have much less data per dossier than pesticides (room for “doubt”) and cosmetics are not allowed to conduct animal, in vivo, tests**

# A need for focus, prioritisation



BPD-BPR began a 10 year program in 2000, received half the dossiers expected, and has extended the program to 24 years, already. The US EPA's Endocrine Disrupter Screening Program has 10,000 chemicals to screen! We need criteria that help us focus on regulating/removing the substances of real concern.





# Roadmap – what are the options?

## Criteria:

Option	Details/Comments
1	No criteria specified; the interim criteria for PPPR to apply (C2 and R2 or R2 with adverse endocrine effects)
2	A single category ('known or presumed') based on the WHO/IPCS definition.
3	A multiple category approach based on the WHO/IPCS definition. <ul style="list-style-type: none"><li>• Category 1: endocrine disruptors ; Category 2: suspected endocrine disruptors; Category 3: endocrine active substances;</li></ul>
4	WHO/IPCS definition to identify EDs and inclusion of potency as an element of hazard characterization (hazard identification and characterization)

## Regulatory decision-making

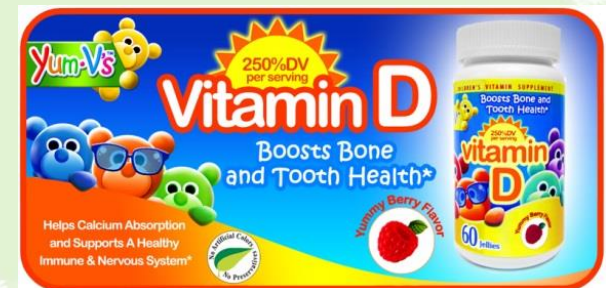
Option	Details/Comments
A	No policy change required (Baseline). The hazard based provisions in 1107 on regulatory decision making are not changed.
B	Introduction of elements of risk assessment into sectorial legislation as opposed to basing on hazard alone. Introduction of negligible risk to replace negligible exposure?
C	Introduction of further socio-economic considerations, including risk-benefit analysis, into sectorial legislation. Exemption from the ban for cases where not approving the substance would have a disproportionate negative impact on society?



# The Risks of the Hazard-Based Approach

- Vitamin D3 is a substance with endocrine activity and potential for disruption and ***it is absolutely essential for proper bone development!!!!***
- However, it also has uses in rodenticide baits since **high doses** cause hypercalcemia and death
- Current proposals based upon intrinsic hazard could result in a total ban for biocide use, or at least a ban on use by non-professionals in Europe

**Meanwhile health authorities encourage us to feed it to our children every day at the right dose for them – and that's good!!**



# How could a natural ED be approved for biocide use?



When Cholecalciferol was evaluated for biocide uses, the hormonal mode of action was recognised, and the initial classification proposal was C2, R2.

Fortunately, some common sense prevailed and, in spite of the ED potential, it was recommended for approval:

**approval could be achieved via derogation « necessary to prevent or control a serious risk to public health » which is not available for PPPs and does not apply to amateur uses under biocides.**

**estimated exposure is considered acceptable (not negligible) and within current tolerable upper intake level (i.e. there is an established a threshold)**

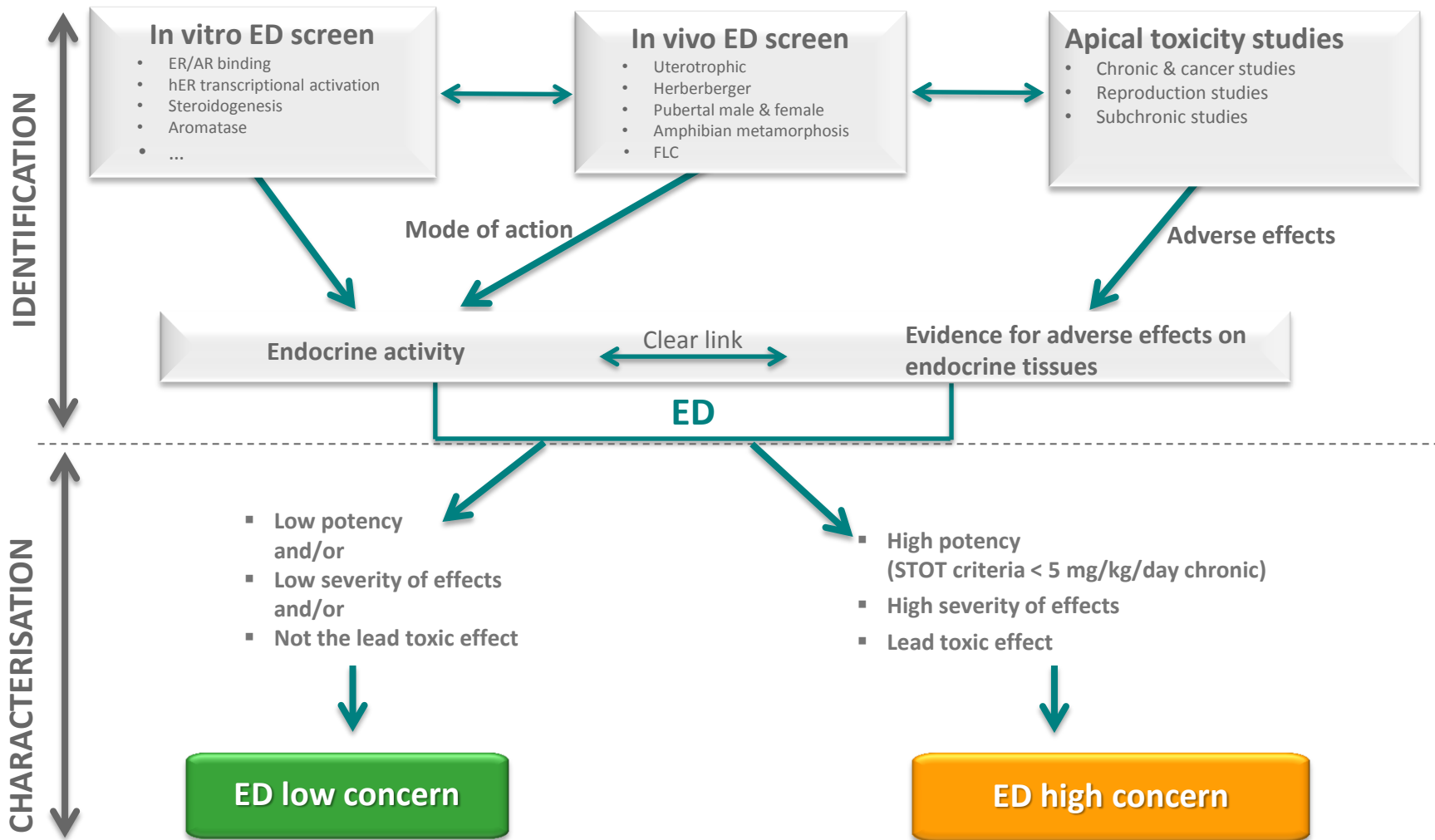
**use might be considered acceptable if sufficient risk reduction measures are applied**

**use is important as an alternative to anti-coagulant rodenticides (resistance, secondary poisoning issues)**

**PS. These are the proposals from KEMI (Sweden is Evaluating Member State for cholecalciferol)**



# ECETOC proposal for criteria based on full hazard assessment





# Some of the PC Comments ...

- It seems bizarre that triazole fungicides when applied to crops are more harmful than a lady with thrush applying the fungicide to her vagina. (agricultural producer – organization/association)
- Endocrine disrupting chemicals must be regulated extremely carefully, fully adopting the precautionary principle, because their unchecked use could actually threaten the future of humanity and our ability to reproduce. (journalist).
- In this scientific day and age I think banning a chemical purely on a hazard based criteria without further risk assessment of the chemical taking place is living in the dark ages (agronomist).
- Your questions are NOT made to permit normal citizen to tell you what they know: that the risk is huge and precaution should prevail over lobbies
- If we have something which is potentially useful, the object should be to see if it is possible to make it safe, not to ban it.





# Impact Assessment Process

- 1) Substance by Substance Evaluation (JRC, Q4 2014 – Q3 2015)
  - 700 Substances to be checked against the 4 Options from Roadmap (all pesticides and biocides plus approx 200 „representative“ industrial chemicals)
- 2) Socio-Economic Impact Assessment (External contractor, Q3 2015 – Q3 2016)
  - Assessing the socio-economic impact that the implementation of one the different options may have

**But beware – pesticides have data-rich dossiers and it would cost a small fortune (plus overwhelming test lab facilities) to conduct chronic and multi-generation tox tests on all the industrial chemicals that might be « suspected » EDs due to lack of evidence!!**



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Thank you!