New Pesticide Regulation:
Innovative Aspects and Emerging Problems

The envisaged impact on the activity of assessors

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JOINT MEETING SIMA-SITOX

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What's the impact of the cut-off criteria on the decision making process?

Impact on human health (Annex II 3.6.):

No active substances, classified as: Mutagen category 1A or 1B, carcinogen category 1A or 1B, reproductive toxin 1A or 1B or which are considered to be endocrine disruptors may be approved (except for specific cases)

- ✓ Regarding criteria for endocrine disruption, at EU level no specific harmonised criteria have been adopted yet , in the meantime the Regulation states that "substances classified 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."

SCHER (Scientific Committee on Health and Environmental Risks):

Opinion on "Endocrine Disrupting Chemicals: a Non-animal Testing Approach" (2005). Conclusions:

- ✓ "Endocrine disruption is not a toxicological endpoint per se, but is one class of the many mechanisms of action that may lead to the effects, which may result in adverse consequences";
- ✓ the application of an in vitro only approach gives information on the potential of a chemical to interact with the endocrine system, but only limited information on types and characteristics of possible adverse effects. It should not be only used as a basis for predicting adverse effects in the animal, which may or may not be the consequence of this interaction;
- ✓ the relation of the endocrine dependent toxicity to the general toxicity profile of the chemical needs to be characterized;

The **SCHER**, in agreement with **US EPA** and **OECD** recognized that an integrated non-animal test approach could be useful to prioritize chemicals for further testing with regard to toxicities to the endocrine system but modifications of some of the present protocols for animal toxicity testing already permit valid conclusions on this issue

Are tools for the assessment of endocrine disruptors currently available and accepted?

✓ OECD task force:

Current activities in the OECD Test Guidelines programme on endocrine disrupters to:

- Provide information and co-ordinating activities;
- Develop new and revised existing TG to detect endocrine disruptors;
- Harmonize hazard and risk characterization approaches

✓OECD high-priority activity: to **revise existing TG** and to develop new TG for the screening and testing of potential endocrine disruptors

OECD "**Enhanced TG 407**" "Repeated dose 28-day oral toxicity study in rodents" (2008) updated with parameters for endocrine effects:

- ✓ Additional parameters based on the respective target organs from the male and female reproductive tracts, the thyroid, and circulating hormone levels in order to detect endocrine activity of test substances with (anti)oestrogenic, (anti)androgenic, and (anti)thyroid activity.
- ✓ Allows to identify chemicals with a strong to moderate potential to act through endocrine mode of action on the gonads and the thyroid, gives indications for the dose-related potency and allows to put certain endocrine mediated effects into context with other toxicological effects.
- ✓ Substances with a low potency for an endocrine mode of action, i.e., having only marginal effects in the most comprehensive in vivo studies such as multi-generation studies, may not elicit clear endocrine-related effects.
- ✓ Evaluation of endocrine mediated effects should not be based on the results of TG 407 alone but should be performed with a weight-of-evidence approach incorporating all existing data to characterize potential endocrine activity.

Additional endpoints in study protocols for routine animal toxicity studies already required for classification and labelling and for hazard assessment

Endpoints recommended for the detection of endocrine disrupters (EDs) in TG 407

Mandatory endpoints	Optional endpoints
Weight	
- Testes - Epididymides - Adrenals - Prostate + seminal vesicles with coagulating glands	- Ovaries - Uterus, including cervix - Thyroid
Histopathology	
- Gonads: - Testes and - Ovaries - Accessory sex organs : - Epididymides, - Prostate + seminal vesicle with coagulating glands - Uterus, including cervix - Adrenal - Thyroid - Vagina	- Vaginal smears - Male mammary glands - Pituitary
Hormones measurement	
	- Circulating levels of T3, T4 - Circulating levels of TSH

The application of specific OECD TGs should be seen in the context of the

"OECD Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals"

OECD TG 441: "Hershberger Bioassay in Rats: A Short-term Screening Assay for (Anti)Androgenic Properties" (2009):

- ✓ a mechanistic in vivo screening assay for androgen agonists, androgen antagonists and 5α-reductase inhibitors.

OECD TG 440: "Uterotrophic Bioassay in Rodents: A short-term screening test for oestrogenic properties" (2007) :

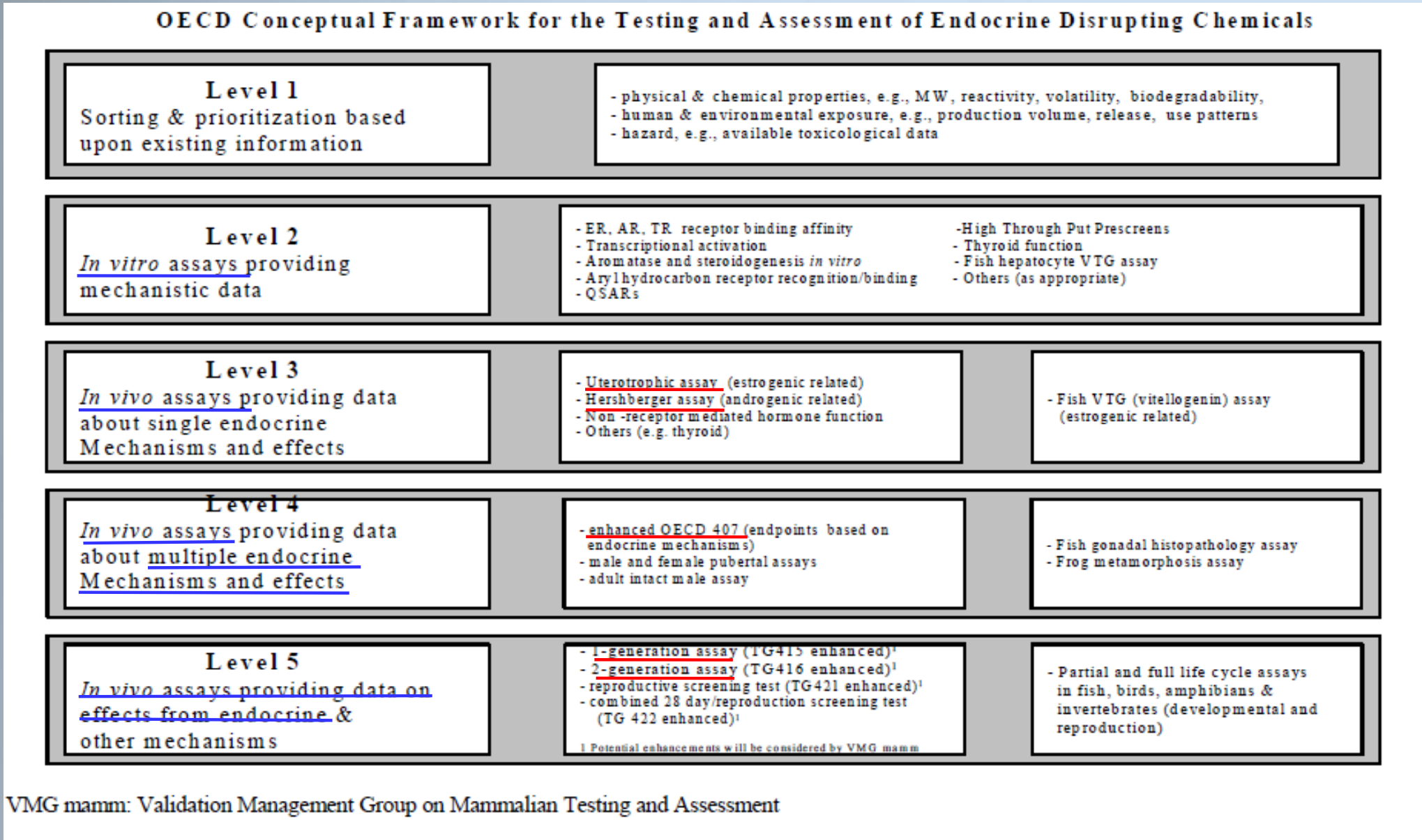
- ✓ an in vivo assay providing data about a single endocrine mechanism, i.e. oestrogenicity.

OECD TG 455: "Stably Transfected Human Estrogen Receptor-α Transcriptional Activation Assay for Detection of Estrogenic Agonist-Activity of Chemicals" (2009):

- ✓ an in vitro assay, providing mechanistic information proposed for the detection of estrogenic transcriptional activation regulated by estrogen receptors.

"OECD Conceptual Framework for the Testing and Assessment of EDC"

Battery of tests to identify substances with potential to interact with the endocrine system, leading to risk assessments for human health or the environment.



VMG mamm: Validation Management Group on Mammalian Testing and Assessment

EFSA has established an internal task force to initiate the development of a common strategy towards endocrine active substances.

Mode of action; weight-of-evidence approach:
Scientific Opinion on Bisphenol A (EFSA Journal, September 2010; 8(9):1829):
Conclusions on endocrine-mediated action of BpA:

- ✓ Bisphenol A (BpA) is used in the manufacture of plastics, to produce reusable drinking bottles, infant feeding bottles and other food storage containers.
- ✓ In the absence of a correlation with functional adverse effects, the relevance of the observed (from in vitro and in vivo studies on receptors, hormones, proteomic, genomic) biochemical and molecular changes for human health cannot be assessed.
- ✓ Because of the lack of a common clearly defined mode of action of BpA at low doses, the toxicological relevance of the BpA effects described cannot be evaluated and the results cannot be taken into consideration for derivation of a TDI.

Human relevance when the toxicity profile seems to be species-specific?

An example: The role of thyroid-pituitary disruption by UDPGT induction in thyroid tumor promotion in rats

- ✓ Some substances induce thyroid tumors through a disruption of the thyroid-pituitary hormonal feedback mechanism of circulating T4 in the rat.
- ✓ The proposed mode of action for thyroid tumor promotion after exposure to UDPGT inducers is that, after induction of UDPGT, there is increased T4 elimination (metabolism of T4 via glucuronidation :T4-UDPGT) followed by decreased serum T4 which results in increased serum thyroid-stimulating hormone (TSH). This, in turn, stimulates increased follicular cell proliferation that can then drive tumor formation.
- ✓ This unique toxicity profile seems to be species-specific because the thyroxine in rodents is metabolized rapidly and the human thyroid is less sensitive to prolonged TSH stimulation than that of the rat.
- ✓ The role of thyroid-pituitary disruption in tumor development in humans is much less convincing than in animals.

Thank you…

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Comparative assessment (candidates for substitution)?

- ✓ There is considerable doubt at present as to which substances will be classified as candidates for substitution, not least because the criteria for establishing which substances will be considered endocrine disruptors have yet to be agreed. Areas for further development: determining definitive provisions for endocrine disruptors in humans (Annex II, point 3.6.5)
- ✓ Plant protection products may be subject to a comparative assessment and substitution where there are other products presenting significantly lower risk for human health or the environment. Comparative assessment will be applied at member state level.