OECD RECENT ACTIVITIES ON ENDOCRINE DISRUPTERS TESTING AND ASSESSMENT

Anne Gourmelon, OECD

www.oecd.org/ehs

EFSA Stakeholders Meeting- Human Health and Environmental Risks of Endocrine Active Substances, 20 March 2013

OECD
BETTER POLICIES FOR BETTER LIVES

Recap' of recent OECD activities

- **1997-** OECD Task Force on EDTA established
- **2002-** Conceptual Framework on EDTA
- **2002-2013 (cont):** a number of Test Guidelines have been validated for the detection and characterisation of endocrine active substances
- **2009:** OECD workshop in Copenhagen:
  - Initiation of revision of the OECD Conceptual Framework
  - Starting point for the development of a guidance document related to ED testing

Relevant OECD Test Guidelines

	Human health	Environment
2007	TG 440 (E)	-
2008	Updated TG 407 (apical)	TG 211 (JH, ecdysteroid)
2009	TG 441 (A-aA) TG 455 (E)	TG 229 TG 230 (E, A, arom. inhibitors) TG 231 (T, aT)
2011	TG 456 (Steroid.)	TG234 (E, , A, arom. inhibitors)
2012	TG 457 (E-aE) TG 443 (apical)	

Recent relevant activities -TGs

- Validation and development of several *in vitro* Test Guidelines providing mechanistic information (e.g. TG 455, TG 456, TG 457): useful to support a mode of action
- Development of *in vitro* Test Guidelines containing functionally similar test methods (e.g. TG 455)
- Discussions of high-throughput methods similar to low- or medium-throughput methods that are under validation
- Endeavour to identify *in vitro* methods for thyroid disruption, no TG yet
- Validation of partial and life-cycle ecotoxicity test methods on-going

EDTA Conceptual Framework (rev. 2012) Levels 1 and 2

Mammalian and non mammalian Toxicology	
Level 1 Existing Data and Non-Test Information	• Physical & chemical properties, e.g., MW reactivity, volatility, biodegradability • All available (eco)toxicological data from standardized or non-standardized tests. • Read across, chemical categories, QSARs and other *in silico* predictions, and ADME model predictions
Level 2 *In vitro* assays providing data about selected endocrine mechanism(s) / pathways(s) (Mammalian and non mammalian methods)	• Estrogen or androgen receptor binding affinity • Estrogen receptor transactivation (OECD TG 455 – OECD TG 457) • Androgen or thyroid transactivation (If/when TGs are available) • Steroidogenesis in vitro (OECD TG 456) • MCF-7 cell proliferation assays (ER ant/agonist) • Other assays as appropriate

EDTA Conceptual Framework- Level 3

	Mammalian Toxicology	Non-Mammalian Toxicology
Level 3 *In vivo* assays providing data about selected endocrine mechanism(s) / pathway(s)[1]	• Uterotrophic assay (OECD TG 440) • Hershberger assay (OECD TG 441)	• Xenopus embryo thyroid signalling assay (When/if TG is available) • Amphibian metamorphosis assay (OECD TG 231) • Fish Reproductive Screening Assay (OECD TG 229) • Fish Screening Assay (OECD TG 230) • Androgenized female stickleback screen (GD 140)

1 Some assays may also provide some evidence of adverse effects.

EDTA Conceptual Framework- Level 4

Level 4 *In vivo* assays providing data on adverse effects on endocrine relevant endpoints [2]	• Repeated dose 28-day study (**OECD TG 407**) • Repeated dose 90-day study (**OECD TG 408**) • 1-generation reproduction toxicity study (**OECD TG 415**) • Male pubertal assay (see GD 150, Chapter C4.3)[3] • Female pubertal assay (see GD 150, Chapter C4.4)[3] • Intact adult male endocrine screening assay (see GD 150, Chapter Annex 2.5) • Prenatal developmental toxicity study (**OECD TG 414**) • Chronic toxicity and carcinogenicity studies (**OECD TG 451-3**) • Reproductive screening test (**OECD TG 421 if enhanced**) • Combined 28-day/reproductive screening assay (**OECD TG 422 if enhanced**) • Developmental neurotoxicity (**OECD TG 426**)	• Fish sexual development test (**OECD TG 234**) • Fish Reproduction Partial Lifecycle Test (when/If TG is Available) • Larval Amphibian Growth & Development Assay (when TG is available) • Avian Reproduction Assay (**OECD TG 206**) • Mollusc Partial Lifecycle Assays (when TG is available) [4] • Chironomid Toxicity Test (**TG 218-219**) [4] • Daphnia Reproduction Test (with male induction) (**OECD TG 211**) [4] • Earthworm Reproduction Test (**OECD TG 222**) [4] • Enchytraeid Reproduction Test (**OECD TG 220**) [4] • Sediment Water Lumbriculus Toxicity Test Using Spiked Sediment (**OECD TG 225**) [4] • Predatory mite reproduction test in soil (**OECD TG 226**) [4] • Collembolan Reproduction Test in Soil (**TG OECD 232**) [4]

[2] Effects can be sensitive to more than one mechanism and may be due to non-ED mechanisms.

[3] Depending on the guideline/protocol used, the fact that a substance may interact with a hormone system in these assays does not necessarily mean that when the substance is used it will cause adverse effects in humans or ecological systems.

[4] At present, the available invertebrate assays solely involve apical endpoints which are able to respond to some endocrine disrupters and some non-EDs. Those in Level 4 are partial lifecycle tests, while those in Level 5 are full- or multiple lifecycle tests.

EDTA Conceptual Framework – Level 5

Level 5		
In vivo assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism [2]	• Extended one-generation reproductive toxicity study (**OECD TG 443**)[5] • 2-Generation reproduction toxicity study (**OECD TG 416 most recent update**)	• FLCTT (Fish LifeCycle Toxicity Test) (when TG is available) • Medaka Multigeneration Test (MMGT) (when TG is available) • Avian 2 generation reproductive toxicity assay (when TG is available) • Mysid Life Cycle Toxicity Test (when TG is available)[4] • Copepod Reproduction and Development Test (when TG is available)[4] • Sediment Water Chironomid Life Cycle Toxicity Test (**OECD TG 233**) [4] • Mollusc Full Lifecycle Assays (when TG is available) [4] • Daphnia Multigeneration Assay (if TG is available) [4]

[2] Effects can be sensitive to more than one mechanism and may be due to non-ED mechanisms.

[4] At present, the available invertebrate assays solely involve apical endpoints which are able to respond to some endocrine disrupters and some non-EDs. Those in Level 4 are partial lifecycle tests, while those in Level 5 are full- or multiple lifecycle tests.

[5] The Extended one-generation reproductive Toxicity Study (OECD TG 443) is preferable for detecting endocrine disruption because it provides an evaluation of a number of endocrine endpoints in the juvenile and adult F1, which are not included in the 2-generation study (OECD TG 416) adopted in 2001

Relevant recent activities – Guidance Documents

- Guidance Document on Standardized Test Methods for the Evaluation of Chemicals for Endocrine Disruption, No. 150

  - **Objective:** to provide guidance to on how to interpret the outcome of individual tests and how to increase evidence on whether or not a substance may be an ED.

    Testing strategies or guidance on interpretation from a suite of tests are **not** given.

  - **Generic** and **specific** guidance: under specific guidance, **various scenarios** are proposed for a given test outcome, depending on the existing available information, **possible conclusions are proposed**, as well as the immediate **next step to increase evidence**.

Scenarios	Result of ER binding assay	Existing Results		Possible conclusions	Next step which could be taken to increase evidence	Other considerations
		Mechanism (*in vitro* mechanistic data)*	Effects (*in vivo* effects of concern)**			
A	+	+	+	Interaction with ER combined with effects on AR/T/S and potential for adverse effects via multiple mechanisms.	Perform assay from upper levels *e.g.* UT assay (level 3) or female PP assay (level 4) or (ext)-1 or 2-gen assay (level 5).	If existing data is from level 5 then may be sufficient information to conclude evidence of concern for ED. If existing data is from level 4 assay then level 5 assay should provide definitive information for ED assessment. If existing data is from UT assay then level 4 assay will provide data on multiple modalities. Consider route of exposures for existing effects data and possible implications of kinetic differences.

Test outcome

Other available information

Possible conclusion

Proposed next step

Extract from the specific guidance in OECD GD No. 150

Relevant recent activities – Guidance Documents

- Case studies (No. 181) using the guidance document:
  - Prochloraz
  - 4-tert-Octylphenol
  - Perchlorate

- Fish Toxicity Testing Framework, No. 171, including a generic testing strategy, and elements for testing endocrine active substances

Other relevant activities – Development of AOPs

- Under the Extended Advisory Group on Molecular Screening and Toxicogenomics
  - Programme on the development of Adverse Outcome Pathways, launched in 2012

- Workplan includes AOPs on endocrine-related effects
  - AOP on depressed TH synthesis and subsequent adverse neurodevelopmental outcomes in mammals
  - AOP linking aromatase inhibition, AR agonism, ER antogonism, or Steroidogenesis inhibition, to Impaired reproduction in fish

Other relevant activities – Hazard Assessment

- Project on the combined assessment of chemicals with same mode of action:
  - Targeted on countries' current activities on phthalates
  - Denmark, Canada and Australia expressed interest
  - Objective is to compare approaches and identify opportunities for working together

- Possibility to use the OECD Cooperative Chemicals Assessment Meeting for the hazard assessment of endocrine disrupters, but need commitment from countries and stakeholders in various OECD countries.

OECD ED activities in the near future

- 2013:
  - Meeting of the VMG on ecotoxicity testing in October, to finalise discussions on the validation of the fish life-cycle test, invertebrates life-cycle test
  - Meeting of the VMG-non animal in October-November to continue discussion on various *in vitro* assays for ER, AR binding, scoping of thyroid assays
  - Teleconference of the EDTA Advisory Group in October to take stock of progress in the US with the EDSP, and progress in Europe on definition of endocrine disrupters, and activities in other regions, and discuss opportunities for further work at OECD

Thank you for listening!

Email: anne.gourmelon@oecd.org