Information on OECD Work Related to Endocrine Disrupters

(2012)

Introduction

1. The protection of human health and the environment from endocrine disrupters[1] is currently a high priority for regulatory authorities in most OECD countries/regions, and it is being proposed by UNEP as a SAICM policy emerging issue[2]. Indeed, the OECD Test Guidelines Programme has spent approximately half of its resources since 1996 to develop Test Guidelines and other tools to support countries' needs related to testing and assessment of chemicals for endocrine disruption.

How work is carried out

2. The work on endocrine disrupters testing and assessment is overseen by the Working Group of National Coordinators of the Test Guidelines Programme (WNT) and managed by four main expert groups:

- An advisory group on endocrine disrupters testing and assessment (EDTA AG)
- A validation management group on ecotoxicity testing
- A validation management group on non-animal testing.
- A validation management group for mammalian testing (nearly no longer active).

3. The EDTA AG is an advisory group to the WNT and to the VMGs. National experts nominated by the National coordinators and the European Commission, and representatives from the Business and Industry Advisory Committee, Environmental NGOs, and International Council on Animal Protection in OECD Programmes participate in the work.

Outcome of OECD work

4. In addition, after more than 10 years working on the validation and development of methods for screening and testing chemicals for endocrine disruption, the *Workshop on OECD Countries' Activities Regarding Testing, Assessment and Management of Endocrine Disrupters*, held in September 2009 in Copenhagen, recommended further work for OECD, in particular (i) the development of a guidance

[1] WHO definition used as working definition by OECD: "An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

[2] http://www.saicm.org/index.php?content=meeting&mid=124&menuid=&def=1

document for the assessment of endocrine disrupters, (ii) the revision of the 2002 Conceptual Framework for Testing and Assessment of Endocrine Disrupters, and (iii) the development of a detailed review paper on endpoints that are not included in existing Test Guidelines [see Workshop Report No. 118 in the Series on Testing and Assessment at:

http://www.oecd.org/document/46/0,3746,en_2649_37465_47830318_1_1_1_37465,00.html

5. In parallel with the continuous development of Test Guidelines for the screening and testing of endocrine disrupters, the documents recommended by the Copenhagen workshop have been developed, as presented in paragraphs 6-14 below.

Conceptual Framework for Testing and Assessment of Endocrine Disrupters

6. A Conceptual Framework (CF) for the Testing and Assessment of Endocrine Disrupters was adopted in 2002. The CF is not a testing strategy; it is not prescriptive and simply reflects the type of information the tests provide at the different levels, such as informing endocrine toxicity outcome pathways, moving from *in silico* to *in vitro* and *in vivo*. It should be noted that information on mechanisms/pathways is particularly important for assessing chemicals for endocrine disruption.

7. A draft revised CF was agreed at the April 2011 meeting of the Advisory Group on Endocrine Disrupter Testing and Assessment (EDTA AG). It includes all published Test Guidelines listed in Table 1 of this document; test methods for which inclusion in the Test Guidelines work plan has been approved or provisionally approved by the Working Group of National Coordinators of the Test Guidelines Programme (WNT) (Table 2 and paragraph 14); some existing Test Guidelines not specifically developed for screening/testing of chemicals for endocrine disruption (Annex, Table 3), and a few non OECD test methods. The draft revised CF will be attached as an annex to the *Guidance Document on Standardized Test Guidelines for Evaluating Chemicals for Endocrine Disrupters* (see next section of this document).

8. The revised description of the five levels of the draft CF is as follows:

Level 1. Existing data and non test information

Level 2. *In vitro* assays providing data about selected endocrine mechanism(s)/pathway(s)

Level 3. *In vivo* assays providing data about selected endocrine mechanism(s)/pathway(s)

Level 4. *In vivo* assays providing data on adverse effects on endocrine relevant endpoints

Level 5. *In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over extensive parts of the life cycle of the organisms.

9. Information/tools from lower levels can be used to determine what specific higher level tests are needed for a specific chemical to increase evidence that it is/it is not an endocrine disrupter. This approach is illustrated in the *Guidance Document on Standardized Test Guidelines for Evaluating Chemicals for Endocrine Disruption* (see below).

Guidance Document on Standardized Test Guidelines for Evaluating Chemicals for Endocrine Disruption

10. This draft Guidance Document (available at:

http://www.oecd.org/document/12/0,3746,en_2649_37465_1898188_1_1_1_37465,00.html)

was developed by two consultants in close cooperation with the EDTA AG. It is expected to be published in 2012.

11. This document was developed to support regulatory authorities' decisions related to the hazard of specific chemicals and toxicologically-relevant metabolites when they receive test results from a Test Guideline or draft Test Guideline for the screening/testing of chemicals for endocrine disruption. The guidance is worded to permit flexible interpretation in the context of different domestic legislation, policies and practice.

12. It also provides guidance on how to interpret the outcome of individual tests, taking into account existing information, and how to increase evidence on whether or not a substance may be an endocrine disrupter. It recommends test methods that may be performed if regulatory authorities need more evidence. The test methods are defined precisely so that countries' eventual testing requirements can be harmonised and hence ensure the Mutual Acceptance of Data.

Detailed Review Paper on the State of Science on Novel *in vitro* and *in vivo* Screening and Testing Methods and Endpoints for Evaluating Endocrine Disrupters

13. The project to develop this document is led by the United States, in cooperation with the European Commission. To date, OECD work related to endocrine disrupters focused on oestrogen/androgen and thyroid pathways. However, other endocrine and neuro-endocrine pathways may also have adverse outcomes, such as symptoms of metabolic syndrome, reproductive dysfunction, altered fetal development.

14. The document is developed by consultants, in close consultation with the EDTA AG. The draft chapters of the document are available at:

http://www.oecd.org/document/12/0,3746,en_2649_37465_1898188_1_1_1_37465,00.html

Test Guidelines Specifically Developed or Updated for the Screening or Testing of Chemicals for Endocrine Disruption

15. A number of test Guidelines have been published in 2007-2011 (See Table 1) and are available free of charge at: http://www.oecd-ilibrary.org/content/package/chem_guide_pkg-en

Table 1: Published Test Guidelines specifically developed or updated for the screening or testing of chemicals for endocrine disruption

TG	Title	Adoption year
440	Uterotrophic Bioassay in rodents: A short-term Screening Assay for Oestrogenic Properties	2007
407 (updated)	Repeated Dose 28-day Oral Toxicity Study in Rodents	2008
211 (updated)	Daphnia Magna Reproduction Test	2008
441	Hershberger Bioassay in rats: A Short-Term Screening Assay for (Anti)Androgenic Properties	2009
229	Fish Short Term Reproduction Assay	2009

230	21-Day Fish Assay: A Short-Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition	2009
231	Amphibian Metamorphosis Assay	2009
455	Stably Transfected Human Oestrogen Receptor-α Transcriptional Activation Assay for the Detection of Oestrogenic Agonist Activity of Chemicals	2009
233	Sediment-Water Chironomid Life-Cycle Toxicity Test Using Spiked Water or Spiked Sediment	2010
234	Fish Sexual Development Test	2011
456	H295R Steroidogenesis Assay	2011

16. The work plan of the Test Guideline Programme includes projects for other Test Guidelines for screening/testing chemicals for endocrine disruption (See Table 2).

Table 2: Projects for Test Guidelines for the screening or testing of chemicals for endocrine disruption, which are included in the work plan

Project	Lead Country
Fish Life-Cycle Test/Medaka Multi-Generation Test	USA/JPN /DEU
Larval Amphibian Growth and Development Assay	USA/JPN
Mysid Life Cycle Toxicity Test	USA
Copepod Reproduction and Development Test	SWE
Avian 2-Generation Reproductive Toxicity Assay	USA
Human Recombinant Oestrogen Receptor Alpha Binding Assay	USA/EC/ DEU/JPN
STTA Assay for the Detection of Oestrogen Agonists and Antagonists	USA
STTA Assay for the Detection of Androgenic and Anti-Androgenic Activity	JPN
STTA Assay for the detection of Anti-Oestrogenic activity of chemicals	JPN
MCF-7 Cell Proliferation Assay for the Detection of Oestrogen Receptor Agonists and Antagonists	USA
Chimpanzee Recombinant Androgen Receptor Binding Assay	DEU/GBR/ FRA
Mollusc Reproductive Toxicity Tests – Development and Validation of Test Guidelines	DEU/GBR/ FRA/DNK
Xenopus Embryonic Thyroid Signalling Assay	FRA

17. At the April 2011WNT meeting, inclusion of some new projects in the work plan has also been provisionally approved pending further information:

- New TG: Androgen Receptor Transactivation Assay (ARTA) Validation (USA)
- New Test Guideline for a Fish Reproduction/Partial Lifecycle Test (USA)

18. A number of existing Test Guidelines may also provide useful information for the assessment of endocrine disrupters (see Annex, Table 3). They are available free of charge at: http://www.oecd-ilibrary.org/content/package/chem_guide_pkg-en

19. Other publications related to testing and assessment of endocrine disrupters, e.g. Guidance documents, detailed review papers, validation and peer review reports are available (see Annex, Tables 4 and 5) and at:

http://www.oecd.org/document/46/0,3746,en_2649_37465_47830318_1_1_1_37465,00.html

<u>Annex</u>: Existing Test Guidelines that may provide useful information and other documents related to endocrine disrupter testing and assessment

Table 3: Adopted Test Guidelines that may provide useful information, although not specifically developed for screening/testing chemicals for endocrine disruption
One-Generation Reproduction Toxicity Study (TG 415), 1983
Two-Generation Reproduction Toxicity (TG 416), last update in 2001
Reproduction/Developmental Toxicity Screening Test (TG 421), 1995
Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (TG 422), 1996
Carcinogenicity and Reproductive Toxicity Studies (TG 451-453), updated in 2009
Prenatal Development Toxicity Study (TG 414), updated in 2001
Repeated Dose 90-Day Oral Toxicity Study in Rodents (TG 408), updated in 1998
Development Neurotoxicity Study (TG 426), 2007
Avian Reproduction (TG 206), 1984
Chironomid Toxicity Test (TG 218-219), 2004
Extended One –Generation Reproductive Toxicity Study (TG 443), 2011

Table 4: Guidance Documents published in the OECD Series on Testing and Assessment
No. 148: Guidance Document on the Androgenised Female Stickleback Screen, 2011
No. 123: Guidance Document for the Diagnosis of Endocrine-Related Histopathology of Fish Gonads, 2010
No. 115: Guidance Document on the Weanling Hershberger Bioassay in Rats: A Short-Term Screening Assay for (Anti)Androgenic Properties, 2009
No. 106: Guidance Document for Histologic Evaluation of Endocrine and Reproductive Tests in Rodents, 2009
No. 82: Guidance Document on Amphibian Thyroid Histology, 2007
No. 71: Guidance Document on the Uterotrophic Bioassay - Procedure to Test for Antioestrogenicity, 2007

Table 5: Detailed review papers, background review documents, validation reports, and peer review reports published in the OECD Series on Testing and Assessment
No. 161, Peer Review Report on the Stably Transfected Transcriptional Activation (STTA) Assay for the Detection of Androgenic and Anti-Androgenic Activity of Chemicals and Agreement of the Working Group of National Coordinators on the follow-up to the peer review (2011)
No. 158, Report of Progress on the Interlaboratory Validation of the OECD Harpacticoid Copepod Development and Reproduction Test (2011)
No. 143, Peer Review Report for the Validation of the Fish Sexual Development Test and Agreement of the Working Group of National Co-ordinators of the Test Guideline Programme on the Follow-up of the Peer Review (2011)
No. 142, Report of the Phase 2 of the Validation of the Fish Sexual Development Test for the Detection of Endocrine Active Substances (2011)
No. 141: Report of the Phase 1 of the Validation of the Fish Sexual Development Test for the Detection of Endocrine Active Substances (2011)

No. 136: Validation Report of The Chironomid Full Life-Cycle Toxicity Test, 2010
No. 135: Detailed Review Paper on Environmental Endocrine Disruptor Screening: The use of Oestrogen and Androgen Receptor Binding and Transactivation Assays in Fish, 2010
No. 133: Peer Review Report for the H295R Cell-Based Assay for Steroidogenesis, 2010
No. 132: Report of the Multi-Laboratory Validation of the H295R Steroidogenesis Assay to Identify Modulators, 2010
No. 128: Validation Report of the 21-day Androgenised Female Stickleback Screening Assay, 2010
No. 127: Peer Review Report of the Validation of the 21-Day Androgenised Female Stickleback Screening Assay, 2010
No. 121: Detailed Review Paper on Molluscs Life-Cycle Toxicity Testing, 2010
No. 118: Workshop Report on OECD Countries Activities Regarding Testing, Assessment and Management of Endocrine Disrupters, Part I and Part II, 2010
No. 111: Report of the Expert Consultation to Evaluate an Estrogen Receptor Binding Affinity Model for Hazard Identification, 2009
No. 110 : Report of the Validation Peer Review for the Hershberger Bioassay (Weanling Model), 2009
No. 109: Literature Review on the 21-Day Fish Screening Assay and Fish Short-Term Reproduction Assay, 2009
No. 108 : Report of the Validation of the Hershberger Bioassay (Weanling Model), 2009
No. 97: Detailed Review Paper on the Use of Metabolising Systems for In Vitro Testing of Endocrine Disruptors, 2008
No. 95: Detailed Review Paper on Fish Life-Cycle Tests, 2008
No. 94: Report of the Validation Peer Review for the 21-Day Fish Endocrine Screening Assay and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report, 2008
No. 93: Report of the Validation of an Enhancement of OECD TG 211: Daphnia Magna Reproduction Test, 2008
No. 92: Report of the Validation Peer Review for the Amphibian Metamorphosis Assay and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report, 2008
No. 91: Report of the Validation of the Amphibian Metamorphosis Assay (Phase 3), 2008
No. 90: Background Review Document on the Rodent Hershberger Bioassay, 2008
No. 86: Report of the OECD Validation of the Rodent Hershberger Bioassay: Phase 2: Testing of Androgen Agonists, Androgen Antagonists and a 5 α-Reductase Inhibitor in Dose Response Studies by Multiple Laboratories, 2008
No. 85: Report of the Validation Peer Review for the Hershberger Bioassay, and the Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report, 2007
No. 83: Summary Report of the Peer Review Panel on the Stably Transfected Transcriptional Activation Assay for Detecting Estrogenic Activity of Chemicals, and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-Up of this Report, 2007
No. 81: Summary Report of the Validation Peer Review for the Updated Test Guideline 407, and Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report, 2007
No. 78: Final report of the Validation of the 21-day Fish Screening Assay for the Detection of Endocrine Active Substances. Phase 2: Testing Negative Substances, 2007
No. 77: Final Report of the Validation of the Amphibian Metamorphosis Assay: Phase 2 - Multi-chemical Interlaboratory Study, 2007
No. 76: Final Report of the Validation of the Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances: Phase 1 - Optimisation of the Test Protocol, 2007

No. 73: Report of the Validation of the Rat Hershberger Assay: Phase 3: Coded Testing of Androgen Agonists, Androgen Antagonists and Negative Reference Chemicals by Multiple Laboratories. Surgical Castrate Model Protocol, 2007
No. 68: Summary Report of the Uterotrophic Bioassay Peer Review Panel, including Agreement of the Working Group of the National Coordinators of the Test Guidelines Programme on the Follow-up of this Report, 2006
No. 67: Report of the Uterotrophic Bioassay: Additional Data Supporting the Test Guideline on the Uterotrophic Bioassay in Rodents, 2007
No. 66: OECD Report of the Validation of the Rodent Uterotrophic Bioassay: Phase 2 - Testing of Potent and Weak Oestrogen Agonists by Multiple Laboratories, 2006
No. 65: OECD Report of the Initial Work Towards the Validation of the Rodent Uterotrophic Assay - Phase 1, 2006
No. 62: Final OECD Report of the Initial Work Towards the Validation of the Rat Hershberger Assay: Phase-1, Androgenic Response to Testosterone Propionate, and Anti-Androgenic Effects of Flutamide, 2006
No. 61: Report of the Validation of the 21-Day Fish Screening Assay for the Detection of Endocrine Active Substances (Phase 1B), 2006
No. 60: Report of the Initial Work Towards the Validation of the 21-Day Fish Screening Assay for the Detection of Endocrine active Substances (Phase 1A), 2006
No. 59: Report of the Validation of the Updated Test Guideline 407: Repeat Dose 28-Day Oral Toxicity Study in Laboratory Rats, 2006
No. 57: Detailed Review Paper on Thyroid Hormone Disruption Assays, 2006
No. 55: Detailed Review Paper on Aquatic Arthropods in Life Cycle Toxicity Tests with an Emphasis on Developmental, Reproductive and Endocrine Disruptive Effects, 2006
No. 47: Detailed Review Paper on Fish Screening Assays for the Detection of Endocrine Active Substances, 2004
No. 46: Detailed Review Paper on Amphibian Metamorphosis Assay for the Detection of Thyroid Active Substances, 2004
No. 38: Detailed Background Review of the Uterotrophic Bioassay, 2003
No. 21: Detailed Review Paper: Appraisal of Test Methods for Sex Hormone Disrupting Chemicals, 2000