

Clarification of the Mission Statement

12/10/2001

In 1998 the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) recommended the following assays for consideration in the endocrine disruptor screening program:

- Aromatase^{*},
- Steroidogenesis,
- Estrogen receptor binding and reporter gene (ER),
- Androgen receptor binding and reporter gene (AR),
- Fish reproduction screen,
- Frog metamorphosis,
- Hershberger,
- Uterotrophic,
- Pubertals - male^{*},
- Pubertals - female,
- Adult 14-day intact male^{*},
- *In utero* through lactation^{*},
- Mammalian 2-generation,
- Avian 2-generation,
- Amphibian chronic,
- Invertebrate chronic and,
- Fish chronic.

* alternative assays

Work on the development and validation of some of the assays is already well underway and the EDMVS will need to be integrated into these activities in a manner that corresponds to the stage of development of each of the assays. In addition, where there is international interest in an assay, the assays being developed for EDSP must harmonize with the international guidelines being developed for endocrine disruptor screening and testing through the OECD.

The work of validation can be broken down into four phases and the work of EDMVS will be organized around these phases as delineated in the objectives of the Mission Statement:

- 1) initial protocol development (Detailed Review Paper),
- 2) the pre-validation reports,
- 3) the validation reports, and
- 4) the integrated summary report.

EPA is seeking the advice and recommendations of the EDMVS on all four phases of the validation process for: aromatase, steroidogenesis, fish reproduction screen, frog thyroid, *in utero* through lactation, avian 2-generation, amphibian chronic, invertebrate chronic, and fish chronic assays.

For the pubertal assays (both male and female), a formal DRP will not be presented. EPA is planning on bypassing the development of formal DRP for these pubertal assays because two NHEERL papers essentially address most of the components of a DRP. Thus, the EDMVS will be involved in phases 2-4 for the pubertal assays. The DRP phase for the mammalian 2-generation is not planned due to the large volume of information.

The estrogen/androgen receptor binding assays or reporter gene assays (referred to as ER/AR) are being validated by ICCVAM. The Hershberger assay has been prevalidated and the uterotrophic assay has been validated through the OECD. The development of the adult 14-day intact male assay has been supported by industry. EPA will develop a paper comparing the results of the adult 14-day intact male, pubertal male and the OECD 407 assay to determine if they can substitute for each other in the Tier 1 battery.

Finally, the EDMVS' advice and recommendations will be requested on the assay composition of the Tier I screening battery. Candidates for the Tier I screening battery includes (at this time) the following assays: Hershberger, uterotrophic, ER/AR, aromatase, steroidogenesis, pubertal male/female, fish reproduction screen, frog thyroid, adult 14-day intact male and possibly the *in utero* through lactation assay (for which a tier has not yet been determined).

Interaction with OECD

One of the challenges of managing the EDSP validation effort will be the coordination and integration of the US efforts with those of the OECD. Three screening level assays (uterotrophic, Hershberger, fish screen) and four tier 2 tests (mammalian, avian, fish, amphibian) being considered for use in the EDSP will be developed as OECD guidelines. These will be managed through the Endocrine Disruptor Testing and Assessment Workgroup (EDTA). Subordinate to the EDTA are the ecotox Validation Management Group (VMG-eco) and the mammalian Validation Management Group (VMG-mam). In addition there may be expert workgroups (e.g., fish, avian) to design protocols and otherwise serve as subcommittees to the VMGs.

It is useful to divide the OECD work into three categories.

Work nearly completed at OECD

These are assays which are well along in the OECD validation program. This includes the uterotrophic and Hershberger assays. The uterotrophic assay has completed validation and the Hershberger has completed prevalidation. The validation studies for the Hershberger have been designed and approved by the EDTA. As the major decisions have already been made for this work, the EDMVS will be kept informed of these efforts but will not be consulted on these programs.

New Work at OECD

These are assays that are early in the process. In all of these cases, protocols for prevalidation have not yet been designed. This area is perhaps the most difficult to integrate. In all, the US is the lead country and EPA will be the major player, but OECD will have primacy on coordinating this work and must be engaged from beginning to end.

EPA believes that the most logical role for EDMVS is to provide advice to EPA to inform the US position at VMG and EDTA meetings. The EDMVS role would be most significant where no expert group exists and the initial study design is left to the lead country to propose. It should also be noted that several EDMVS members are in fact members of the EDTA. This overlap should assist in communication and coordination.

New Work at EPA

These are assays like the mammalian 2-gen test that are on the horizon at OECD but are not yet in the official OECD work plan. EPA will make substantial progress on these assays before OECD seriously engages in work. For this phase of the work, it is proposed that we regard this as a US activity with EDMVS as the primary vehicle for deliberation and stakeholder input. EPA will keep OECD informed of our activity and will bring our efforts to the EDTA at the appropriate time.

Coordination with ICCVAM

ICCVAM will prepare all documentation and hold an expert consultation and peer review of the ER, AR binding and related reporter gene assays. ICCVAM is also represented on EDMVS and may be briefed at key points in the validation process.

Tier I Screening Battery - Assays and Phases for EDMVS' Advice and Recommendations

Assays	DRP / Initial Protocol Development	Prevalidation [special studies]	Validation	Integrated Summary Report
Aromatase (EPA)	yes	yes	yes	yes
Steroidogenesis (EPA)	yes	yes	yes	yes
Fish Reproduction (EPA lead for OECD)	yes	yes [comparison of protocols (repro vs vitellogenin)] [Demonstration in fathead minnows] [Comparison of species]	yes	yes
Frog Thyroid (EPA lead for OECD)	yes	yes	yes	yes
Pubertals (m & f) (EPA)	no ¹	yes [Multi-dose study] [Array study] [Restricted Feeding Study] [Single dose study (completed)]	yes -Comparison paper (Pubertal, adult male, 407)	yes
Adult 14-day intact male²	no ²	no ²	yes ³	yes ³
ER / AR Binding⁴	no ⁴	no ⁴	no ⁴	yes
Hershberger⁵ (OECD)	no ⁵	no ⁵	no ⁵	yes
Uterotrophic⁵ (OECD)	no ⁵	no ⁵	no ⁵	yes
EDMVS will Review Tier I screening battery for composition				
Tier ? In Utero through Lactation (EPA)	yes	yes	yes	yes

¹ For the pubertal assays (both male and female), EPA is relying on a DRP equivalent; two NHEERL papers essentially address most of the components of a DRP.

² Development of the adult 14-day intact male assay has been supported by industry.

³ EPA will develop a paper comparing the results of the adult 14-day intact male, pubertal male and the OECD 407 assay to determine if they can substitute for each other in the Tier I battery. This will serve as the Integrated Summary Report for this assay.

⁴ The estrogen/androgen receptor binding assays or reporter gene assays (referred to as ER/AR) are being validated by ICCVAM.

⁵ The Hershberger has been prevalidated by OECD with the intention of completing validation. The uterotrophic assay has completed a validation process through the OECD.

Tier II - Assays and Phases for EDMVS' Advice and Recommendations

Assays	DRP / Initial Protocol Development	Prevalidation [special studies]	Validation	Integrated Summary Report
Mammalian- 2-generation (EPA and OECD)	no ¹	yes [One generation extension] [Propylthiouracil (PTU) demo (Complete)]	yes	yes
Avian 2-generation (EPA lead for OECD)	yes	yes [avian dosing study] [comparison of species (almost complete)]	yes	yes
Fish Chronic (EPA lead for OECD)	yes	yes	yes	yes
Amphibian Chronic (EPA lead for OECD)	yes	yes	yes	yes
Invertebrate Chronic (EPA lead for OECD)	yes	yes	yes	yes

¹ A formal DRP is not planned. EPA is relying two NHEERL papers which essentially address most of the components of a DRP. EPA may become the OECD lead for this assay.