EDTA Conceptual Framework (2002)

Increasing knowledge on MoA

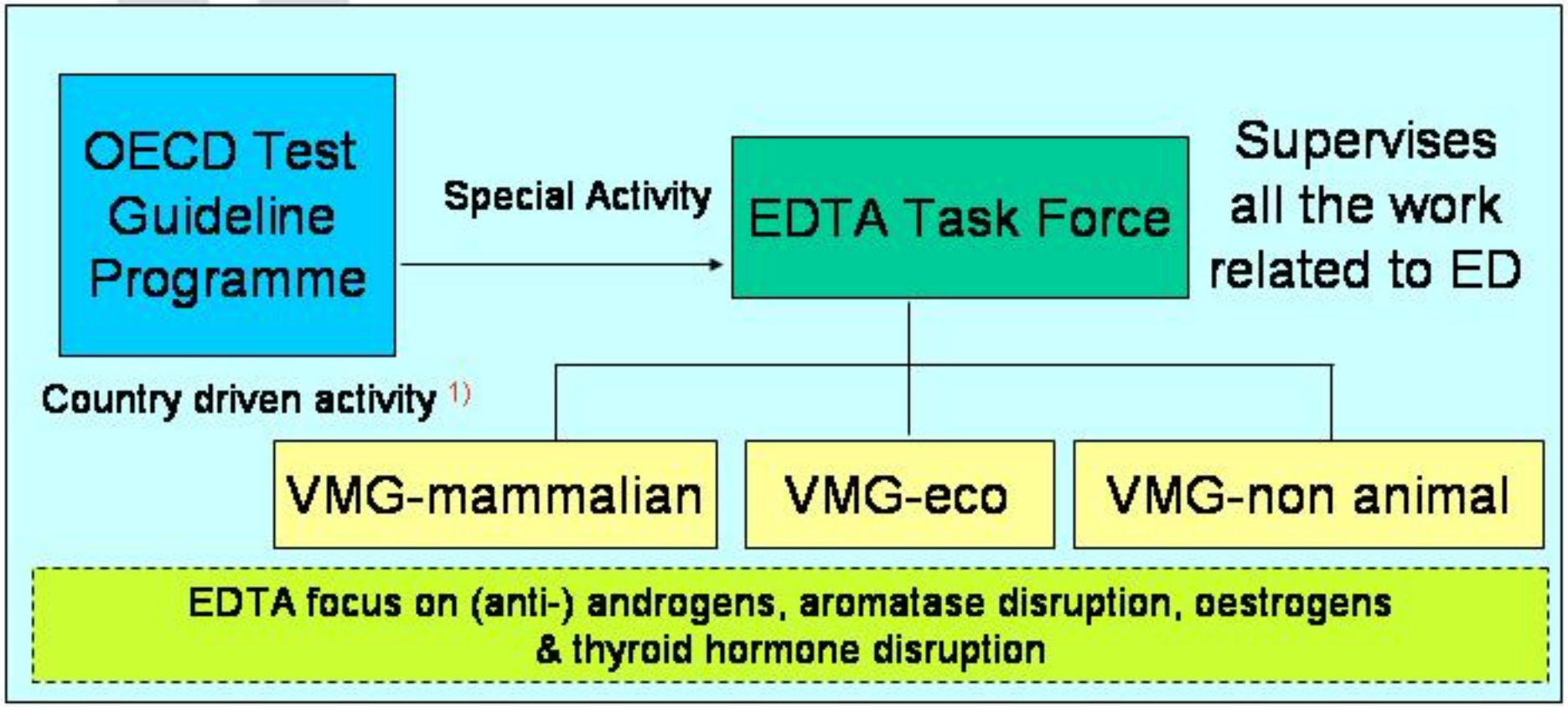
5 levels of increasing biological complexity:

- Level 1: existing info, QSARs
- Level 2: in vitro assays on ER, AR binding
- Level 3: in vivo assays about single endocrine mechanisms
- Level 4: in vivo assays about multiple endocrine mechanisms
- Level 5: in vivo assays on adverse effects about endocrine and other mechanisms for risk assessment

Increasing relevance at population level

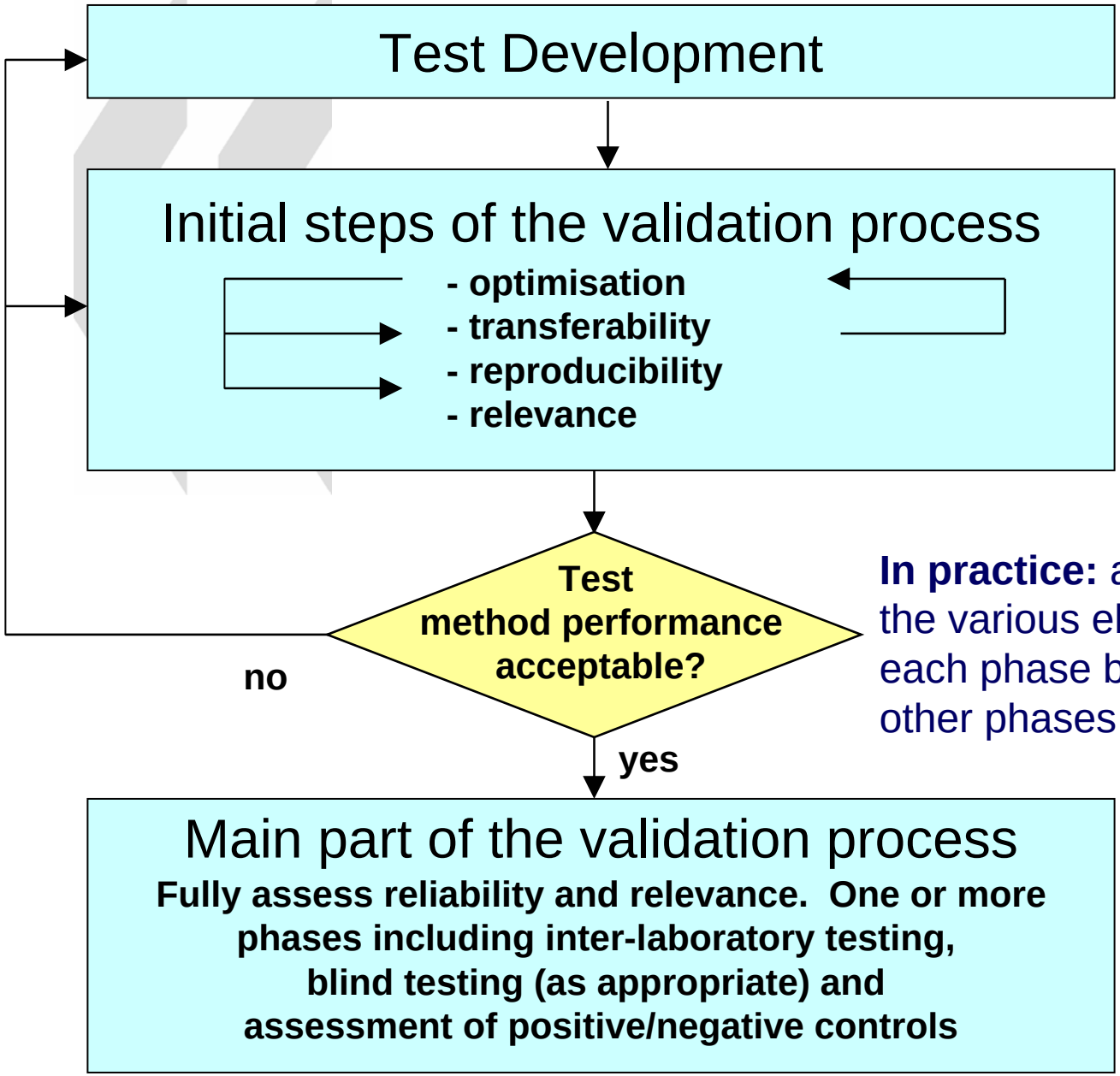
= assays and tests are tools that regulators can pick-up as they need for conducting for HA/RA

Endocrine Disruptor Testing & Assessment (EDTA): A Special OECD Task Force



1) OECD member countries make proposals to develop new or update existing TG; proposals are prioritized by countries and a lead is designated for the work.

OECD Guidance Document 34



Goal: ensure that each of the validation principles has been adequately addressed

In practice: a continuum between the various elements of validation; each phase builds on results of other phases of the work

Challenges

- Test methods need to cover a range of species commonly used in OECD member countries;

  → species present different advantages & limitations;

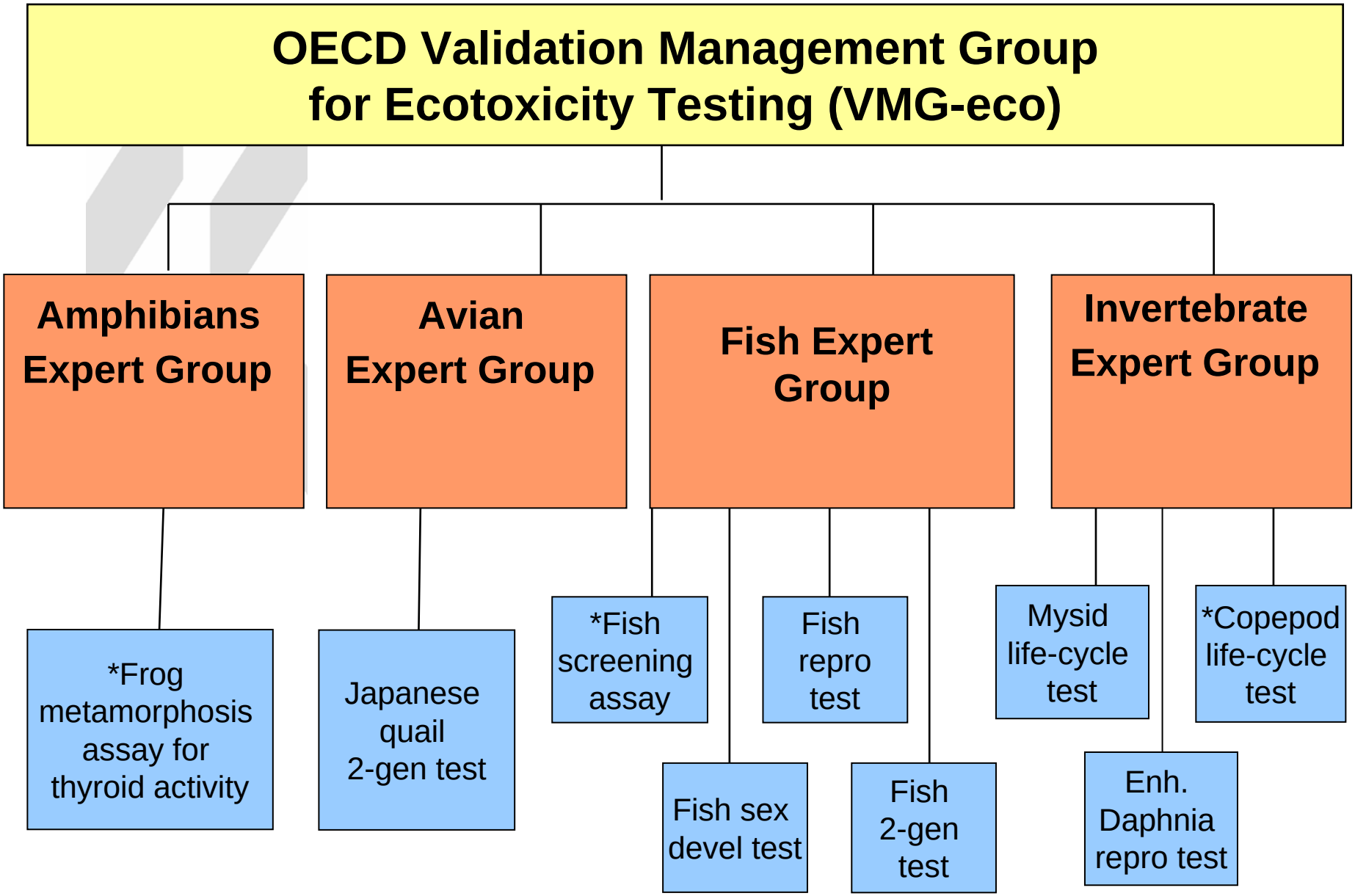
- Validate methods that can be internationally accepted and adopted;

  → participating laboratories from diverse geographical areas;

  → assays must stay simple enough to be used globally;

- Validate methods to demonstrate their relevance and reliability (reproducibility).

  → long stepwise process: labour- and cost- intensive;



* Inter-laboratory validation work & reporting in progress

In vivo Fish screen for ED (1)

- Validation completed for the 21-day fish screening assay;
- 21-d exposure duration;
- ♂/♀ analysed separately;
- Endpoints evaluated: vitellogenin (VTG), secondary sex characteristics (SSC), gonad histology, spawning status;
- Inter-laboratory work – range of reference substances
- Model species
  - fathead minnow
  - medaka
  - zebrafish

In vivo Fish Screen for ED (2)

- Phase 1A and Phase 1B – Highlights:

Substance/ response	**MoA**	**VTG**	**2y sex characters**	**Gonad histology**	**Spawning status**
17-β estradiol	E	↑ ♂(32ng/l)	Not measured	↑ oocyte atresia	n.a.
Trenbolone	A	↓ ♀(500ng/l)	↑ ♀		n.a.
4-tert-pentylphenol	Weak E	↑ ♂(320µg/l)	↓ ♂(1mg/l)	↑ %spermatogonia ↑ (immat.) oocyte atresia	↓ FHM
Prochloraz	Ar. inhibitor	↓ ♀(300µg/l)	-	↑ %spermatozoa ↑ (immat.) oocyte atresia	↓ all sp.
Fadrozole	Ar. inhibitor	↓ ♀(100µg/l)	-		↓ all sp.
Flutamide	Anti-androgen	↑ ♂/♀but not reproducibly	↓ but not reproducibly	↑ %spermatogonia ↑ (immat.) oocyte atresia	↓ FHM