

International harmonisation, the road map for future acceptance of mixture testing by risk management



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International context

- The WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement)
 - Desiring the establishment of a **multilateral framework** of rules and disciplines
 - Desiring to further the use of harmonized sanitary and phytosanitary measures between Members, on the basis of **international standards, guidelines and recommendations** developed by the relevant international organizations, including the CAC
 - Members shall ensure that their sanitary or phytosanitary measures are based on an assessment ... of the risks to human, animal or plant life or health, taking into account **risk assessment techniques developed by the relevant international organizations**
 - Members shall ensure that any sanitary or phytosanitary measure ... is **based on scientific principles** and is **not maintained without sufficient scientific evidence**,



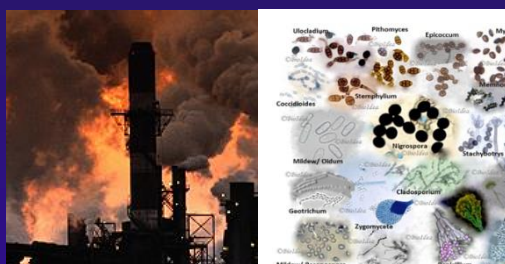
Consequences for international harmonisation

- Need to ensure consumer safety whilst not restricting international trade unnecessarily
- Assessments must be based on sound science (SPS agreement, etc)
- Need agreement on the scope of assessments
 - Exposure sources (silos), routes of exposure?
 - Basis for grouping chemicals?
 - Inclusion of non-chemical stressors?
- Practicalities of options available should the risk cup be exceeded



Exposure to multiple chemicals

- Drugs
- Cosmetics
- Household products
- Food ingredients
- ...

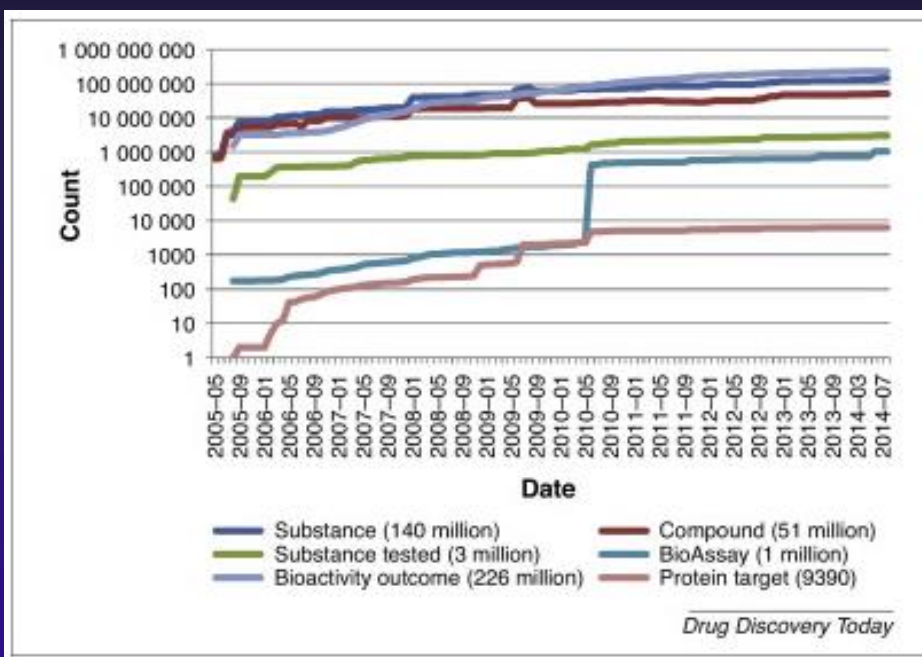
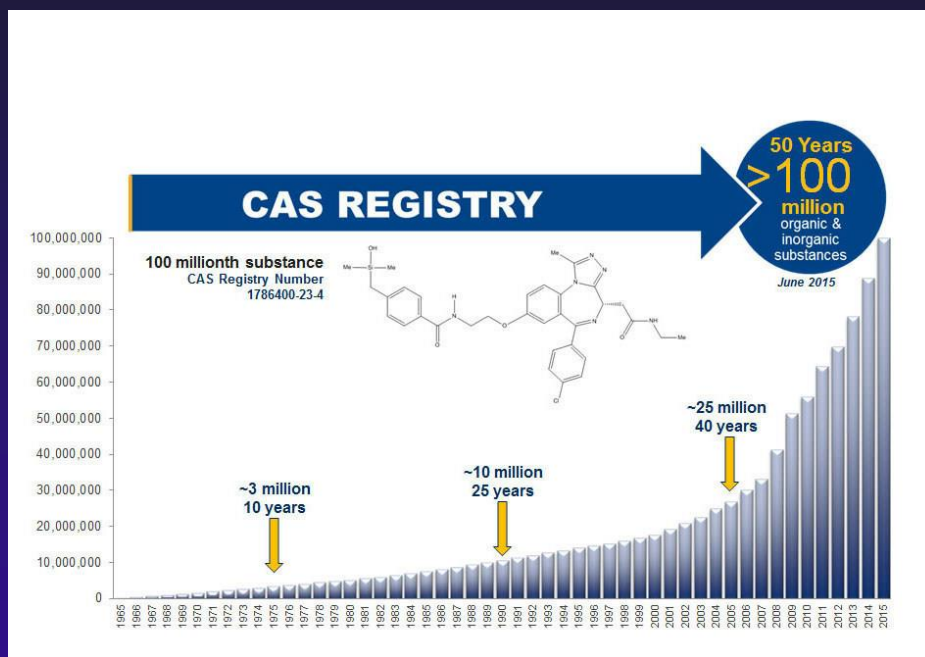


- Agrochemicals
- Industrial emissions
- Effluent
- Natural toxins
- ...





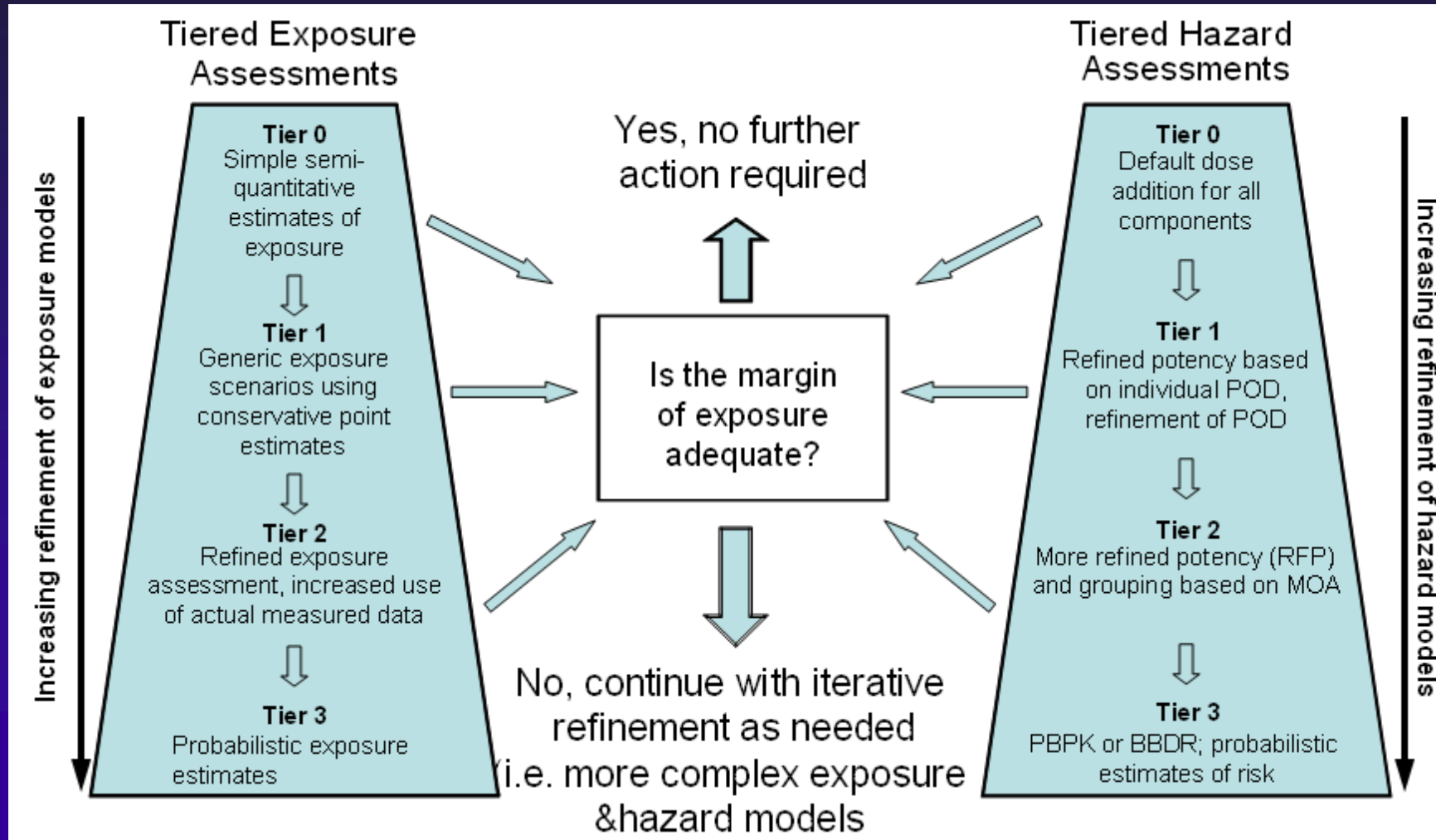
Increasing numbers of chemicals

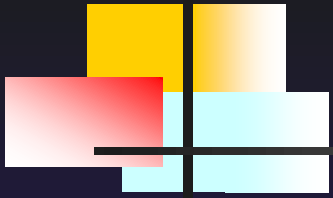


- Add to this uncharacterized environmental degradation products, metabolites and process intermediates

The IPCS framework when co-exposure is likely

Tiered exposure and hazard based considerations: mixture or component based



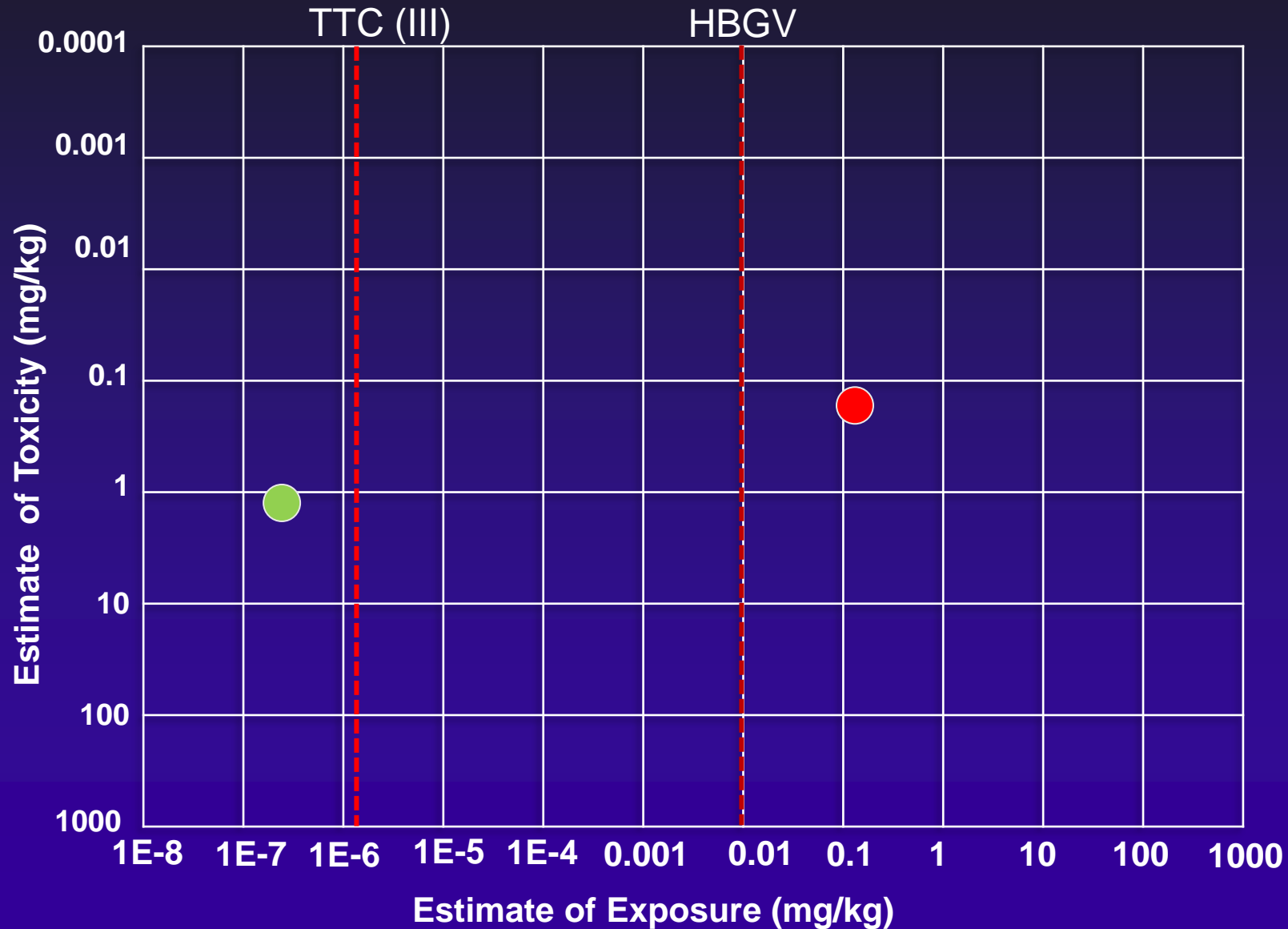


Start with exposure

- Use pattern
 - Is exposure even possible?
- Physicochemical properties
 - Is systemic exposure possible?
- Threshold of toxicological concern
 - Is exposure so low that it can be ignored?
 - If additivity is a potential concern, consider comparing exposure with a fraction of the TTC
- Health based guidance values
 - If exposure to a single chemical exceeds its HBGV (e.g. TDI), address this issue before CRA



Inclusion based on exposure





Combined assessment groups – Different approaches

- Cumulative Assessment Group (CAG): A subset of chemicals selected from a larger group for inclusion in a refined quantitative estimate of risk
 - Inclusion approach (must meet specific criteria to be **included**)
- Cumulative Assessment Group (CAG): A group of chemicals considered for a cumulative assessment, which may be refined during the assessment
 - Exclusion approach (must meet specific criteria to be **excluded**)



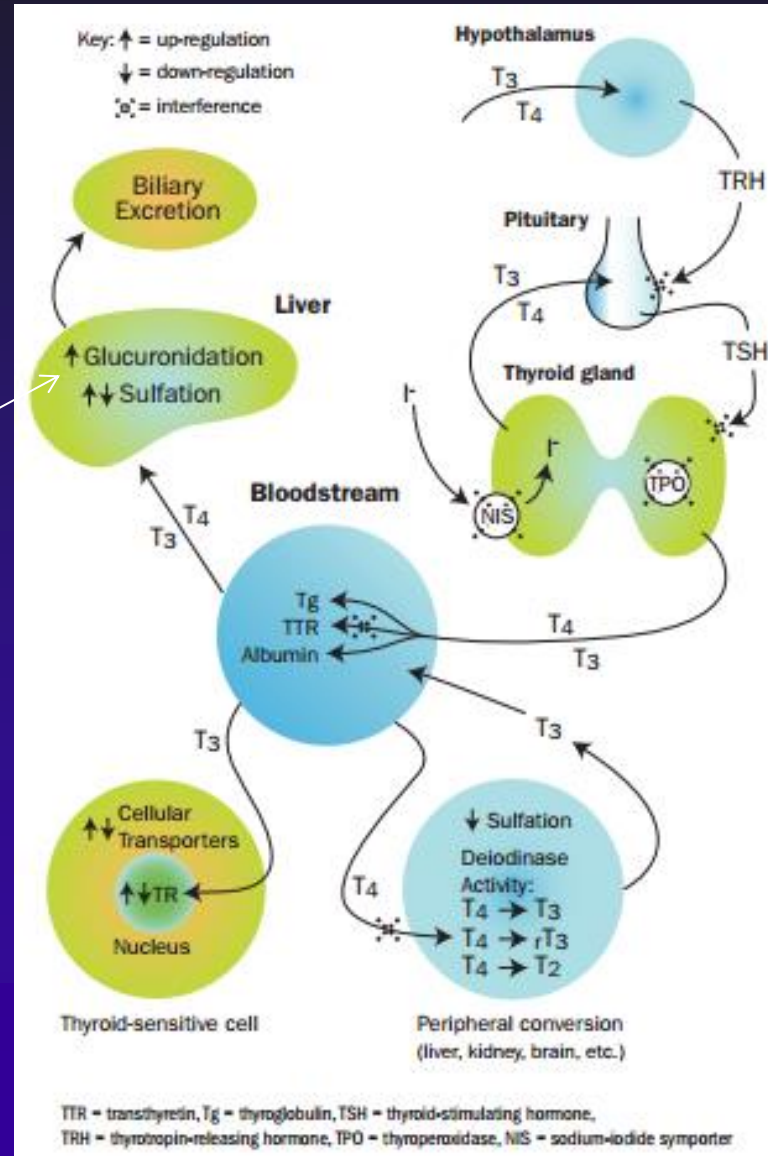
EFSA CAGs for pesticides

- Tiers
 - Level 1 = organ/organ systems level
 - Level 2 = refinement at the effect level
 - Level 3 = common mode of action
 - Level 4 = common mechanism of action
- Nervous system: 67 substances, with 6 specific effects: 42 with repeat-dose motor effects
- Thyroid system: 57 substances with 2 specific effects: 53 affecting follicular cells and/or T3/T4 system
- Liver system: 106 substances with 15 specific effects: 99 causing hypertrophy, 45 causing degeneration, 58 causing cholestasis, 40 causing fatty changes
- Reproductive & developmental systems: 129 substances with 9 specific effects
- Also groupings for effects on: adrenals, eyes



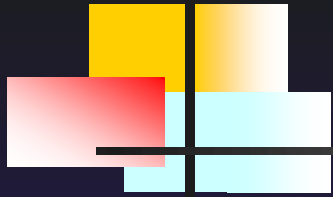
Same or similar mode of action

UGT
 synthesis
 ↑
 CAR/PXR
 ↑
 Inducer
 e.g. PB

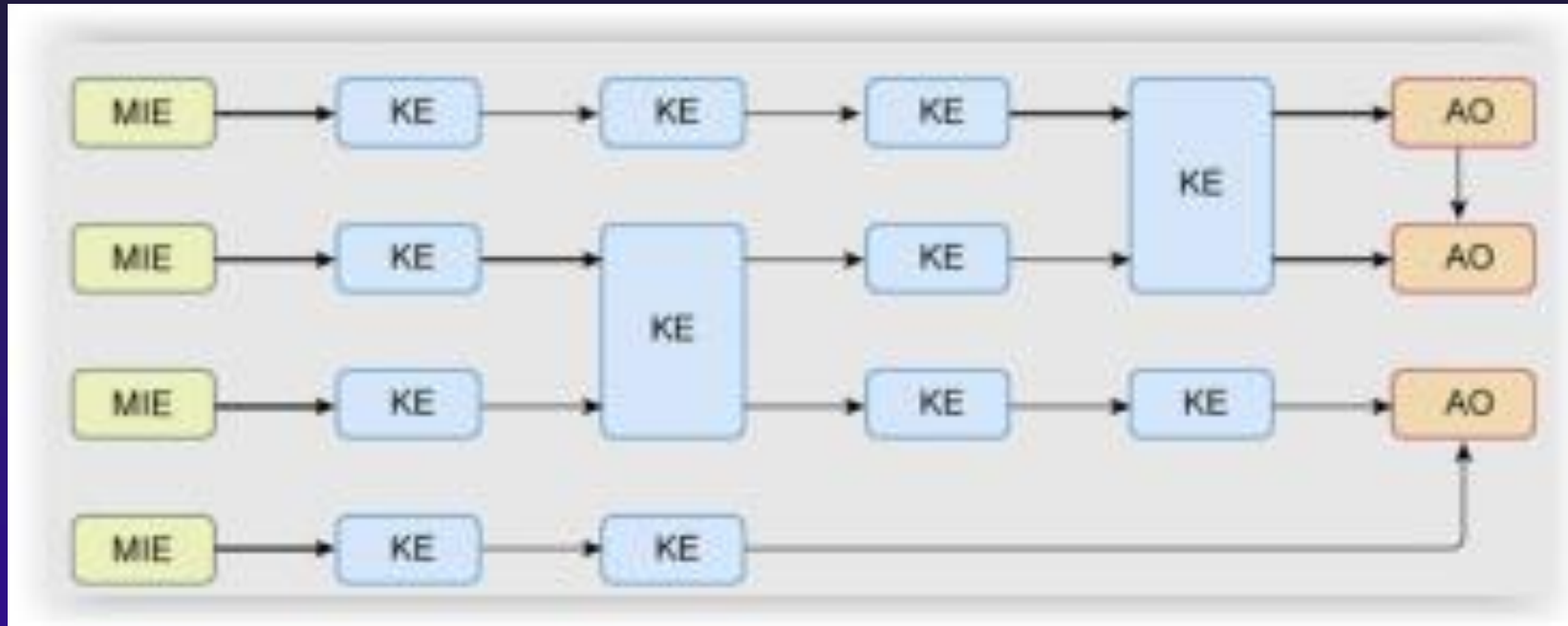


TTR = transthyretin
 Tg = thyroglobulin
 TSH = thyroid-stimulating hormone
 TRH = thyrotropin-releasing hormone
 TPO = thyroperoxidase
 NIS = sodium-iodide symporter

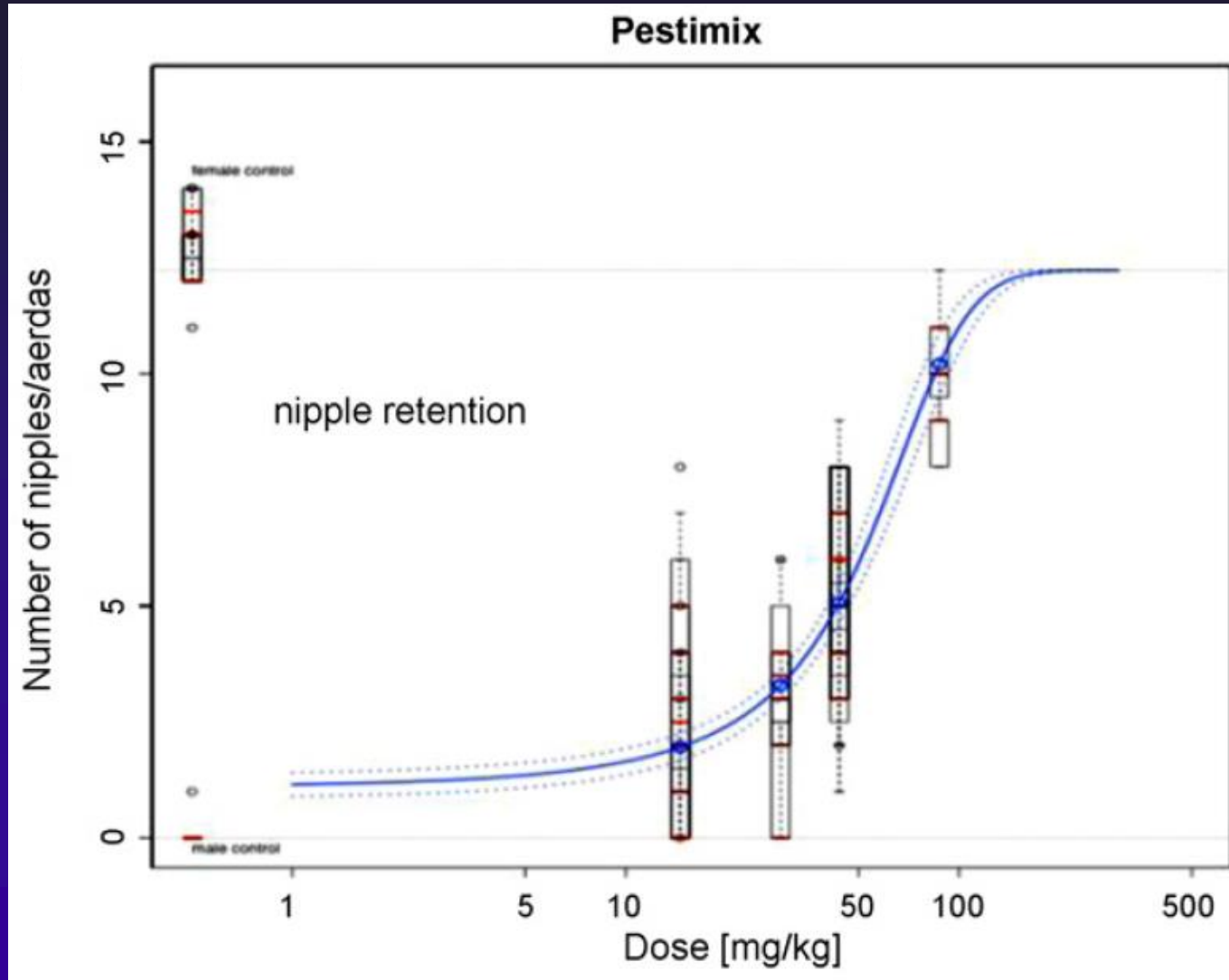
Patrick, 2009



Common MOA/AOP

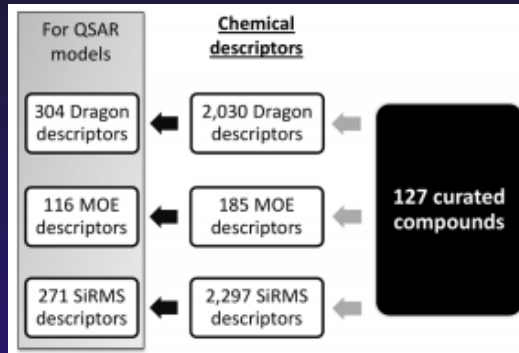


Effects of mixture of dissimilarly-acting substances on nipple retention in male rat offspring

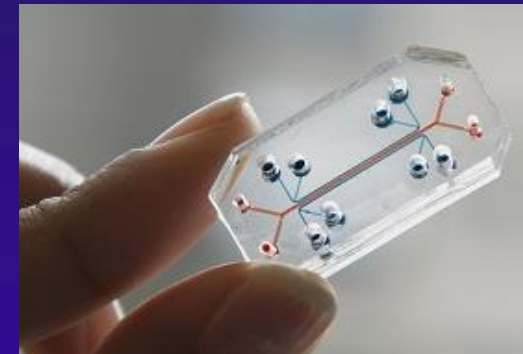
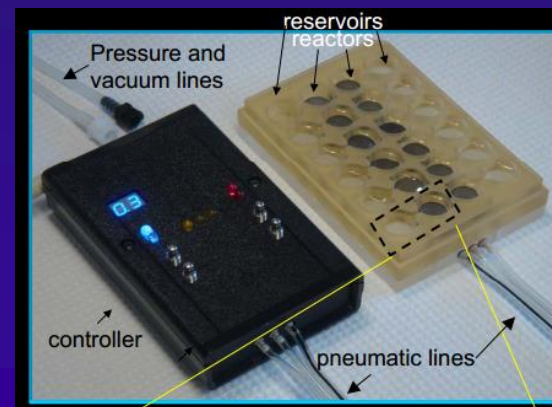
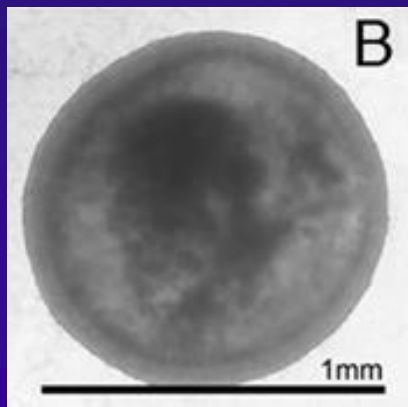
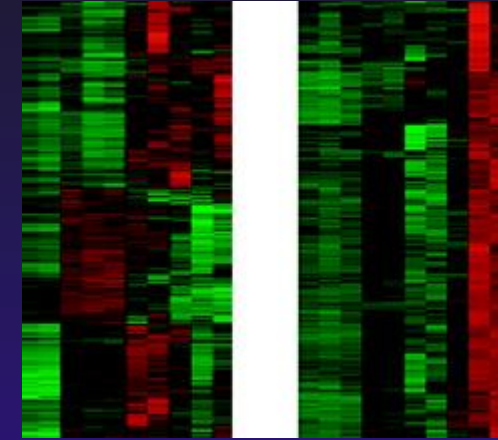
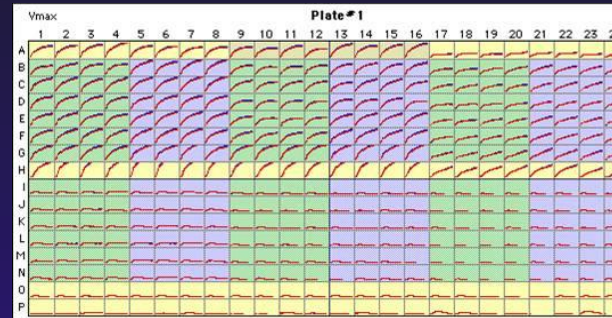


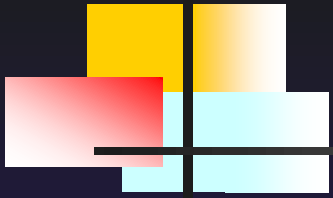
Hass et al, 2012

AOP/MOA using emerging methods in toxicity testing

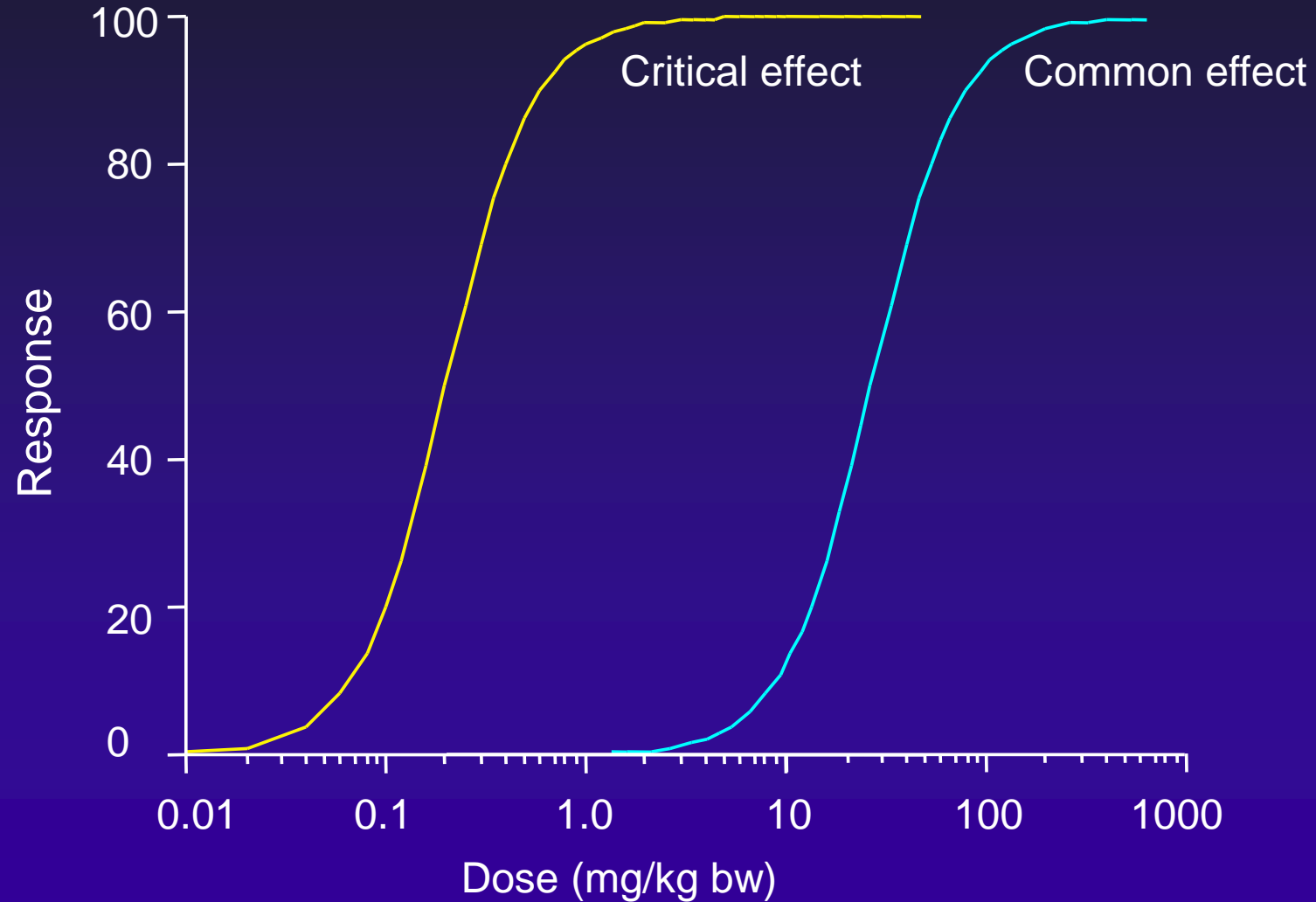


$$\log IC_{50} = -1.46\epsilon_{HOMO} - 0.032V_m - 3.644$$





Common vs critical effect





Road map for harmonisation of mixture assessment

- Agreement on how compounds should be grouped for cumulative risk assessment
 - Exposure criteria
 - Use of information on mode of action/adverse outcome pathways
 - Minimum information to include or exclude common mode of action
 - How should the possibility of synergy be addressed
- Definition of mixture of concern – which chemicals, which exposure routes and over what time period
- What is the chemical domain of consideration
 - Human medicines, nutrients, other natural constituents of the diet, etc?
 - Legislative compartmentalisation/silos
- Probabilistic versus deterministic exposure (and hazard) assessment
 - ACROPOLIS MCRA for exposure