Principles of pharmacology and toxicology govern effects of chemicals on the endocrine system

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In collaboration with leading European and US/Canadian Toxicologist

Tasks of Toxicology

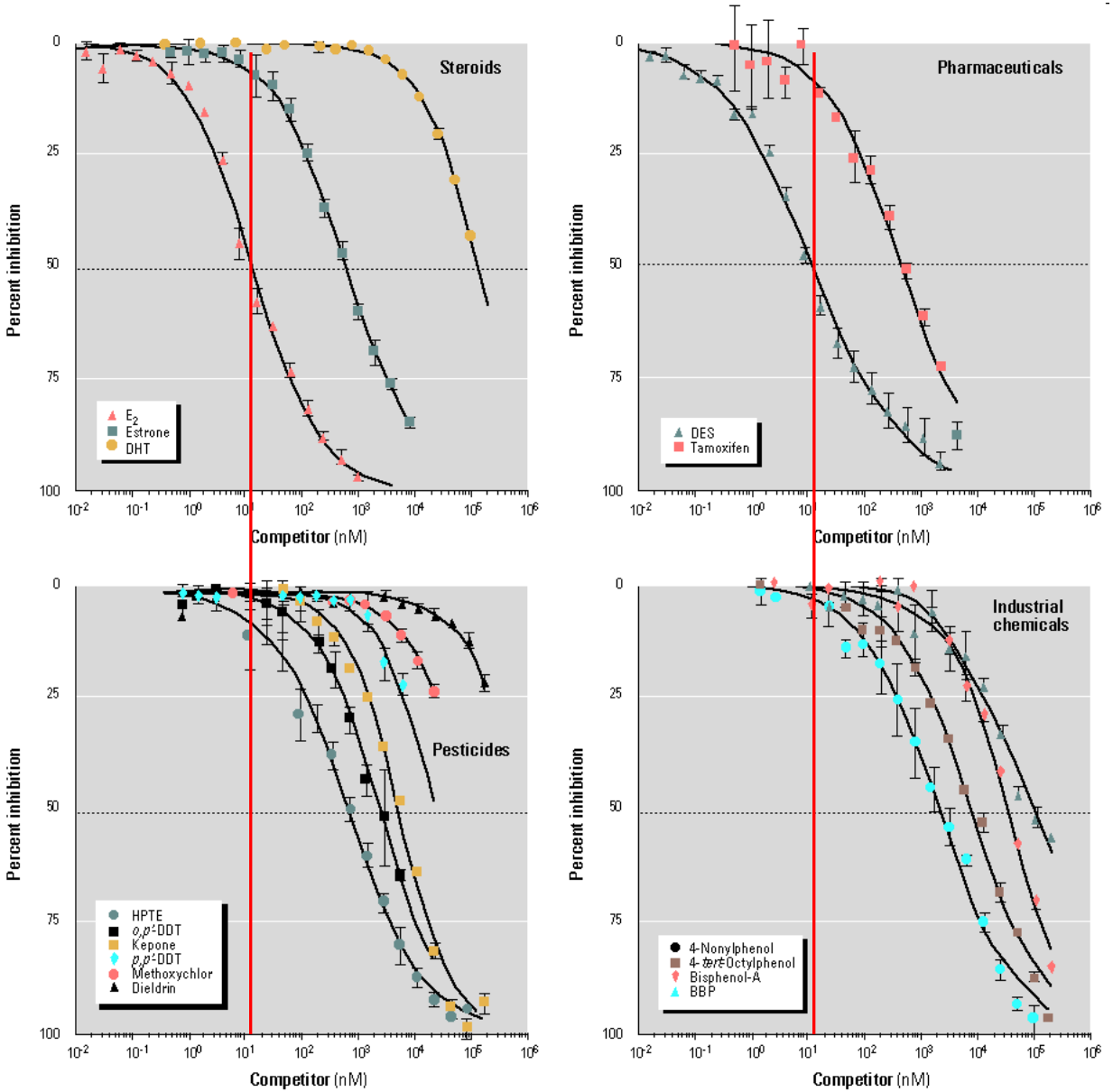
- The Toxicologist core job and interest is to **protect humans and the environment from adverse health effects** with the **highest integrity** and using the **best scientific evidence** available:
- To characterize adverse effects of chemicals used as pharmaceuticals, plant protection products, and in consumer applications by evaluating and developing
  - underlying modes of actions
  - relevant and sensitive assays
- To perform risk assessments based on hazard information and appropriate information on exposure using **weight of evidence** approaches assessing **all available scientific** information

Interference of chemicals with the endocrine system

- An interference of chemicals with the endocrine system is just **one of many possible modes of action** resulting in potentially adverse (or therapeutic) effects
- Most modes of action in toxicology involve complex mechanisms, potential windows of susceptibility, and potentially sensitive subgroups
- **Receptor-mediated toxicities** are widely characterized **in many toxic responses** (e.g. modes of action for the nervous and immune system, liver and cardiotoxicity)
- There is **abundant information on the principles of receptor-interactions** from long-standing state-of-the-art experience in pharmacology and toxicology

Binding of a number of different compounds to the human Estrogen Receptor

Competitive Binding Assay: Human recombinant estrogen receptor



Definitions

- *"An EDC is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes **adverse** effects in an **intact organism**, or its progeny,…."* (WHO/IPCS, 2002).
- An adverse effect is a *"change in the morphology, physiology, growth, development, reproduction, or life span of an organism, … that results in an **impairment of functional capacity**,….."* (WHO/IPCS, 2004).
- Consequently, *"Contrasted to adverse effects, **non-adverse effects can be defined as** .. biological effects that do not cause biochemical, morphological, or physiological changes that affect the general well-being, growth, development or life span …."* (Lewis *et al.*, 2002).

Consequences for classification and labeling

- Classification and labeling (C&L) for Carcinogenic, Mutagenic or Reproductive (CMR) properties is based on adverse effects observed in studies of appropriate sensitivity and quality
- As an interference with the endocrine system is a **mode of action**, it per se **does not represent an adverse effect**
- Accordingly, modes-of-action should not be used as a basis for C&L of chemicals. A special classification as “endocrine disruptor” is inconsistent with the established and proven procedures of C&L, and thus **MUST** be avoided (Autrup et al., Tox Sciences 2015)
- If a chemical interfering with the endocrine system results in adverse effects, these **WILL** trigger C&L

Issues with risk assessment

- “Critical effect, severity, (ir)reversibility and potency aspects are part of the hazard characterization of EDCs. To inform on risk and level of concern for the purpose of risk management decisions, risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. **EDCs can therefore be treated like most other substances of concern for human health and the environment**, i.e. be subject to risk assessment and not only to hazard assessment.“ [EFSA 2013].

Issues with risk assessment cont.

- Many natural food ingredients (e.g. isoflavonoids (phytoestrogens), some mycotoxins such as zearalenone) can also cause adverse effects by interference with the endocrine system
- In contrast to many industrial chemicals potentially interfering with endocrine endpoints (e.g. Bisphenol A, EFSA, 2015), **safety margins** of exposure for natural food ingredients chemicals **are small** (e.g. zearalenone)

Conclusions

(Autrup et al., Tox Sciences 2015)

- Appropriately designed and conducted toxicity studies **MUST** include determination of the **potency** by which a chemical induces adverse effects
- Appropriate toxicity testing covers potential adverse effects on the endocrine system, which could manifest as reproductive and developmental toxicities
- Whenever such toxicities are identified based on well-developed and robust endpoints, this will result in the classification of the respective chemical as a “Reproductive/Developmental Toxicant”
- Therefore, interference with the endocrine system is only one of many mechanisms potentially causing adverse effects.
- Chemicals interfering with the endocrine system can be subjected to the ***well-established and widely accepted procedures for risk assessment***