Endocrine Active Compounds

Does the Dose make the Poison?

Thomas Hofmann
Experimental Toxicology and Ecology
BASF SE
Ludwigshafen, Germany

Advanced Course Endocrine Disruptors
Arbeitskreis Regulatorische Toxikologie

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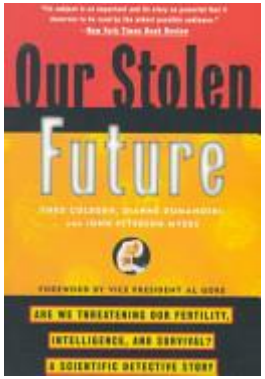
Outline

- Introduction
- Definitions
- Dose Response Relationships
  - Low Dose Effects
  - Thresholds
  - Critical Effect
- Animal Models and Relevance for Humans
- Conclusion

Introduction

- **History**
  - **1962 Rachel Carson: Silent Spring**
    - **Overuse of pesticides (DDT), thinning of egg shells**
  - **1980 Lake Apopka**
    - **Deaths of alligators after chemical spill**
    - **Infertility and other sexual disorders**
  - **1980 Papermill effluent**
    - **Androgenic effects in fish (gonopodium)**
  - **1996 Theo Colburn: Our Stolen Future**
    - **Alterations in functional and sexual development**



Introduction

- History (cont'd)
  - 1996 Endocrine Screening mandated by
    - Food Quality Protection Act
    - Safe Drinking Water Act
  - 1996 Weybridge Workshop
  - 2002 WHO-IPCS Global Assessment
  - 2012 Position Statement of the Endocrine Society
  - 2013 WHO-UNEP State of the Science Document
  - 2013 EFSA SC Hazard Assessment of Endocrine Disruptors

Key Discussion Points

- Non-monotonic dose-response curves (NMDRC)
- Low Dose Effects
- Thresholds
- Adversity
- . . . but discussion already starts with definitions

Definitions

- **Endocrine disruptor**
  - *'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' (WHO-IPCS, 2002)*
  - *'An exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action' (Zoeller et al., 2012)*

Definitions

- **Endocrine active substance (EFSA SC, 2013)**
  - *'. . . a substance having the inherent ability to interact or interfere with one or more components of the endocrine system resulting in a biological effect, but need not necessarily cause adverse effects'*
    - **Mode of action, not hazard itself**
    - **Ability to interact or interfere with the endocrine system, resulting in a biological effect**
    - **Not necessarily adverse (e.g. temporary modulation of feedback systems)**

Definitions

- **Adversity**
  - *'Change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences' (WHO-IPCS, 2009)*

Identifying Endocrine Disruptors (EFSA SC, 2013)

- **Criteria**
  - **Presence of an adverse effect**
  - **Presence of endocrine activity**
  - **Plausible / demonstrated causal relationship**
    - **Endocrine activity and adverse effect**

Identifying Endocrine Disruptors (EFSA SC, 2013)

- **Adversity**
  - **Should be observed in intact organisms (e.g. not castrated males)**
- **Modulation**
  - **In intact organisms (e.g. not castrated males, or in vitro)**
  - **Within homeostatic capacity**
  - **Temporary**
  - **Becomes adverse, if the organism is no longer able to compensate for changes**

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Non-Monotonic Dose-Response Curves (NMDRCs)

Dose Response Relationships

- **Paracelsus**
  - **'Alle Dinge sind Gift, und nichts ist ohne Gift. Allein die Dosis macht, daß ein Ding kein Gift ist.'**
  - **More simplified: 'The dose makes the poison'**
  - **Implies thresholds**
- **Endocrine active substances**
  - **Non-monotone dose-response curves described**
  - **Claim: 'No thresholds for hormonally active compounds'**

Non-Monotonic Dose Responses

- **What's different?**
  - **Exogenous compounds versus essential endogenous substances**
  - **Metals, morphogenic factors, hormones**
- **Zinc**
  - **Low dose effects due to deficiency**
  - **High dose effects due to 'true' toxicity**
- **Retinoic acid**
  - **Dysmorphogenesis below as well as above physiological levels**

NMDRCs - Low Dose Effects

- **Definition**
  - In the range of human exposures
  - At doses lower than usually used in standard tests
- **Hormones**
  - High receptor affinity
  - Active at low doses
    - Effects of Diethylstilbestrol and Bisphenol A on prostate weights
    - Intrauterine position phenomenon

Thresholds

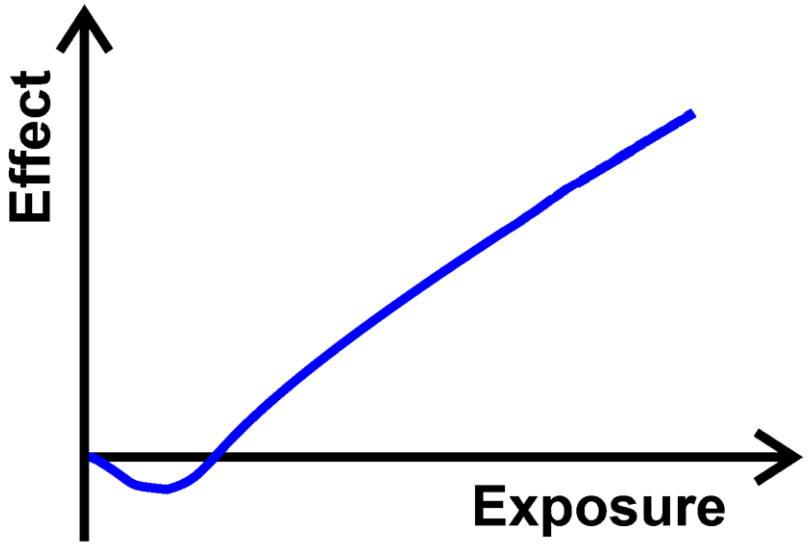
- **Claim: 'No thresholds for endocrine active compounds'**
  - **Endogenous hormone level is already above threshold**
  - **Added effect to an existing background level**
- **However**
  - **Thresholds experimentally proven**
    - **Numerous non-genotoxic agents**
    - **Numerous 'Endocrine Disrupting Chemicals'**

Thresholds – Defense mechanisms

- **Balance of hormone homeostasis**
  - **Exposures without adverse effects are possible**
  - **Overload of homeostatic and detoxifying mechanisms**
    - **Adverse effects**
  - **Question: when becomes the response adverse**
- **Buffer capacity**
  - **Free radicals, reactive oxygen species, and reactive products produced in the normal metabolism of food**

Threshold Discussion

- **Hormesis**
  - Decrease in adverse effects in the low dose region
  - Hormetic response necessitates a threshold for an adverse effect



- **In summary**
  - Discussions of low-dose effects are highly controversial and have not provided convincing arguments against a threshold approach

Critical Effect

- **Critical Effect**
  - First adverse effect that occurs at increasing dose
  - In the most sensitive species

- **Hazard Characterization**
  - Should be based on the leading adverse effect(s)
  - Risk management based on these effects should also protect against endocrine effects occurring at higher dose levels

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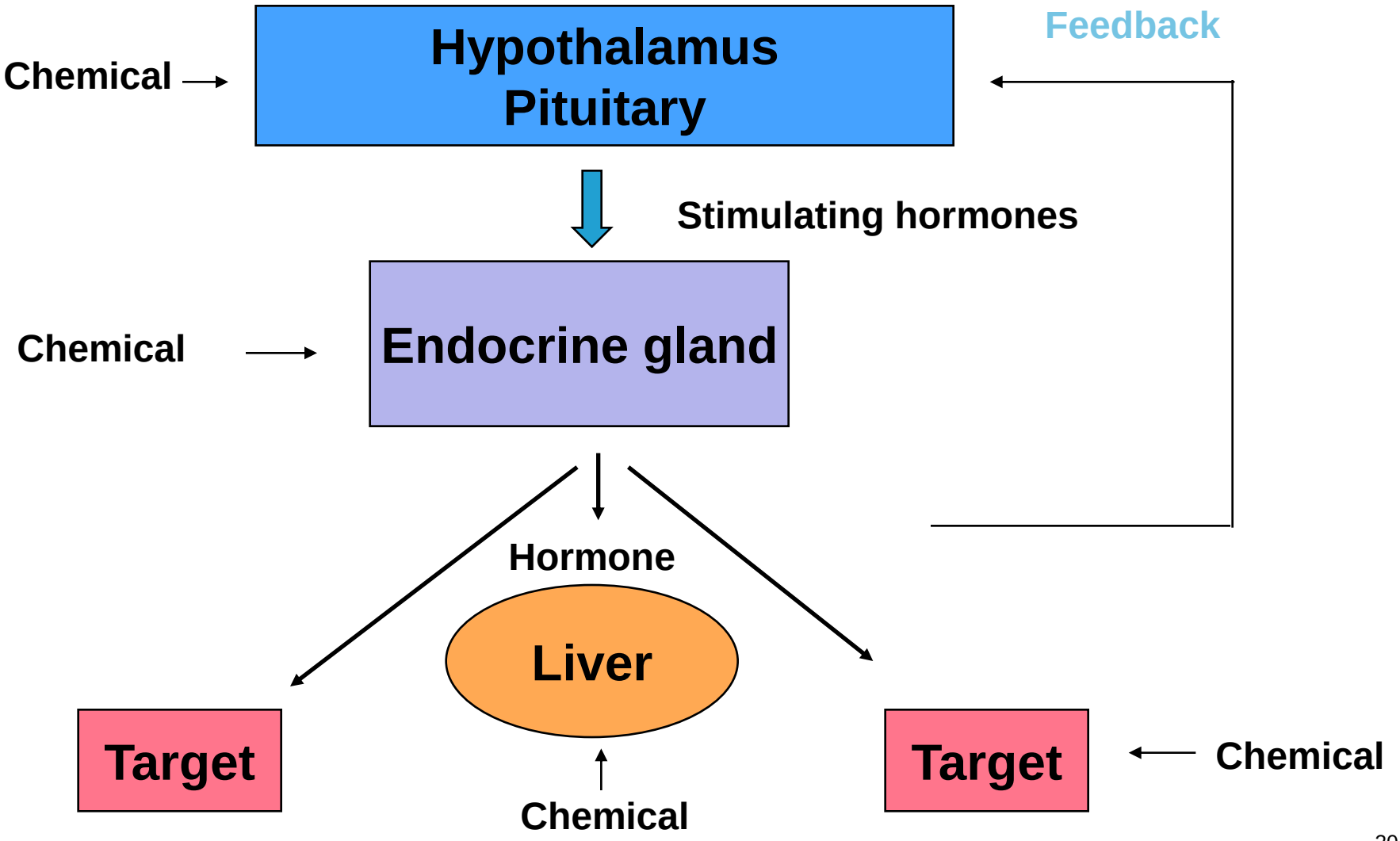
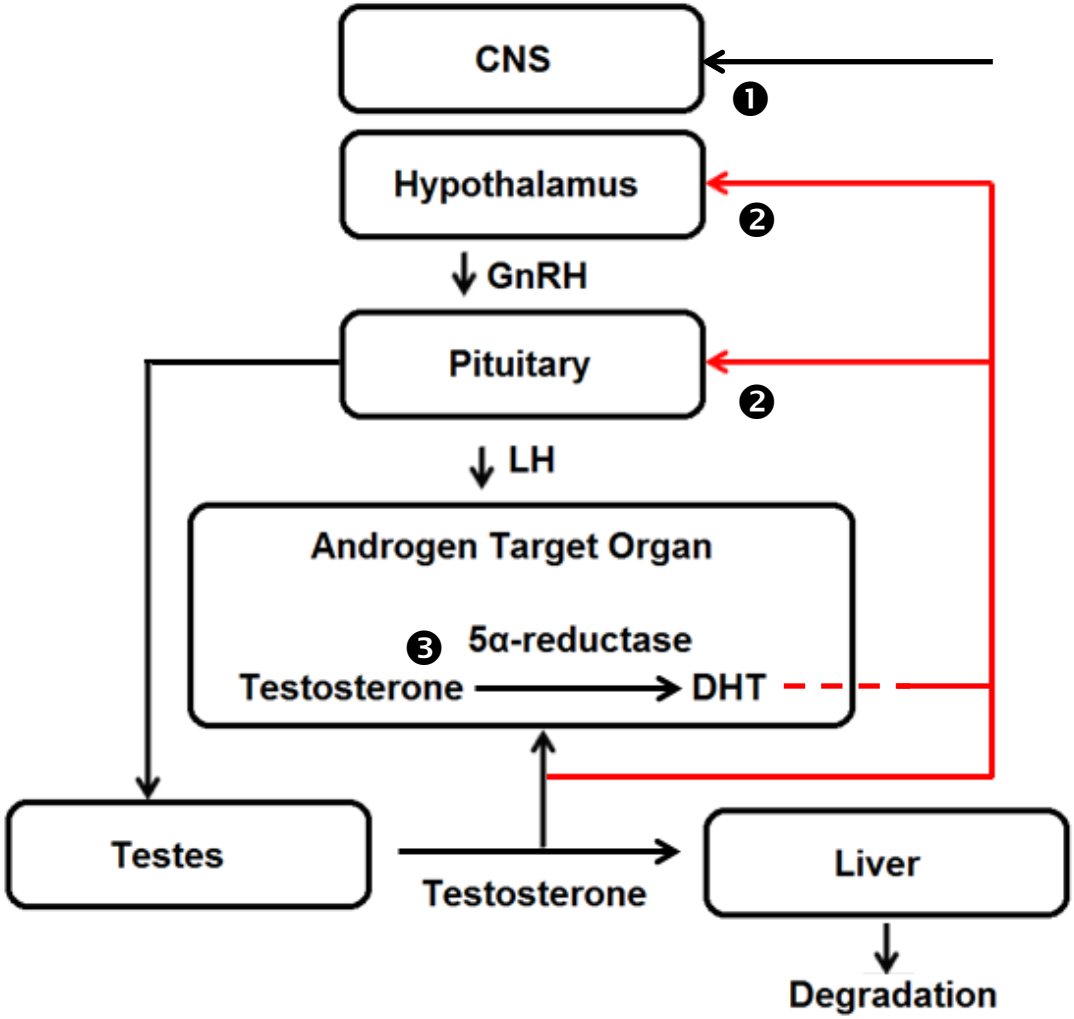
Animal Models and Relevance to Humans

Hormonal Balance



Animal models – Leydig cell tumors in rats



❶ Dopamine agonists (Mesulergine)

❷ Antiandrogens (Flutamide)

❸ 5α-reductase inhibitors (Finasteride)

Leydig cell tumors in rats

- Androgen receptor antagonists (Flutamide)
  - Increase of LH and testosterone
- 5α-reductase inhibitors (Finasteride)
  - Reduction of the androgenic signal
  - Increase of LH
- Dopamine agonists
  - Increase in LH
- Prolonged stimulation of Leydig Cells
  - Hypertrophy, hyperplasia, and finally neoplasia
  - Examples: Linuron, Vinclozolin

Leydig cell tumors in rats

- **Relevance for humans**

	Rats	Humans
Leydig cell tumor incidence	Sprague-Dawley: 5.3% Wistar: 5.9% Fisher 344: 76.8%	0.00004%

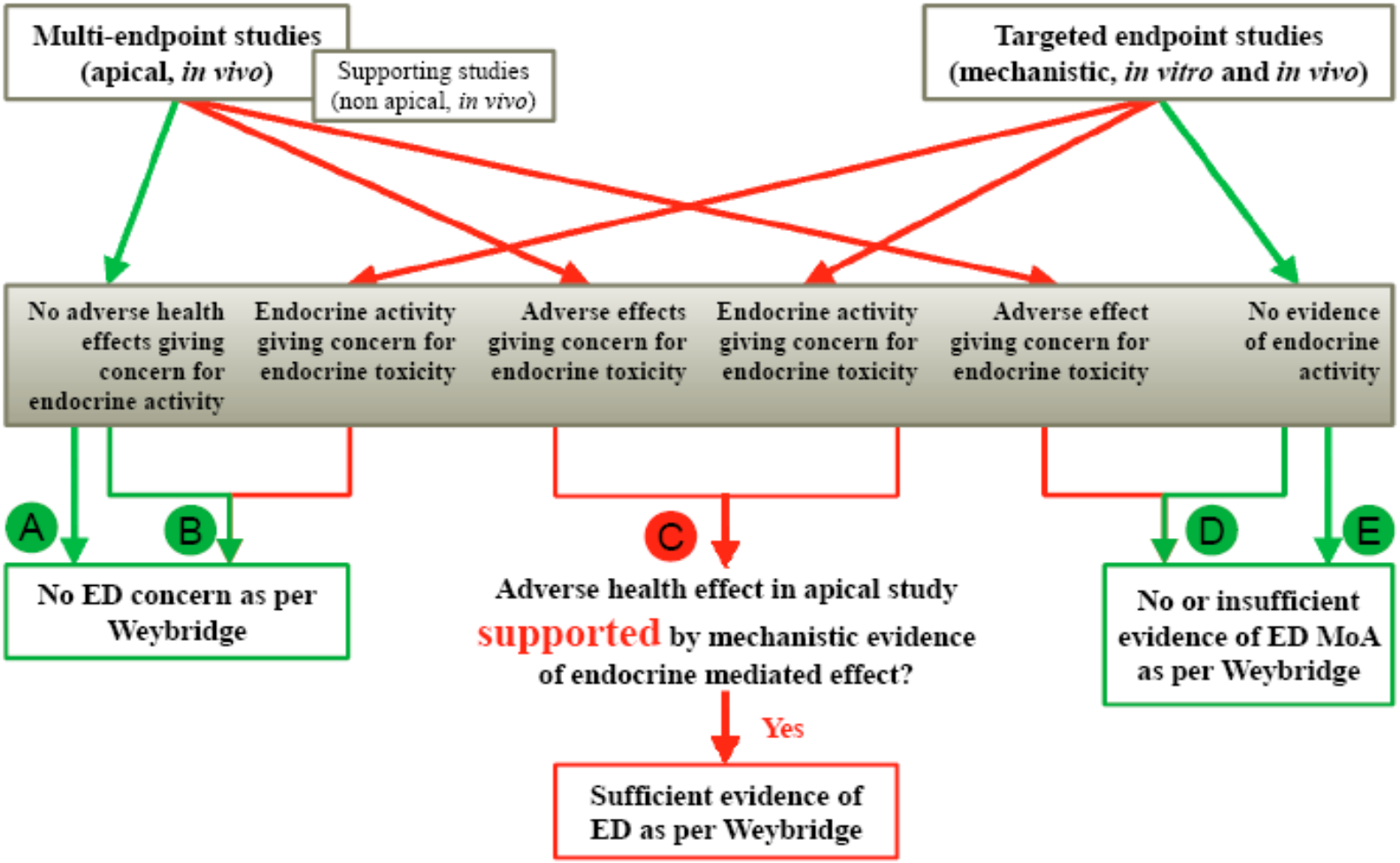
Leydig cell tumors in rats

- **Relevance for humans**

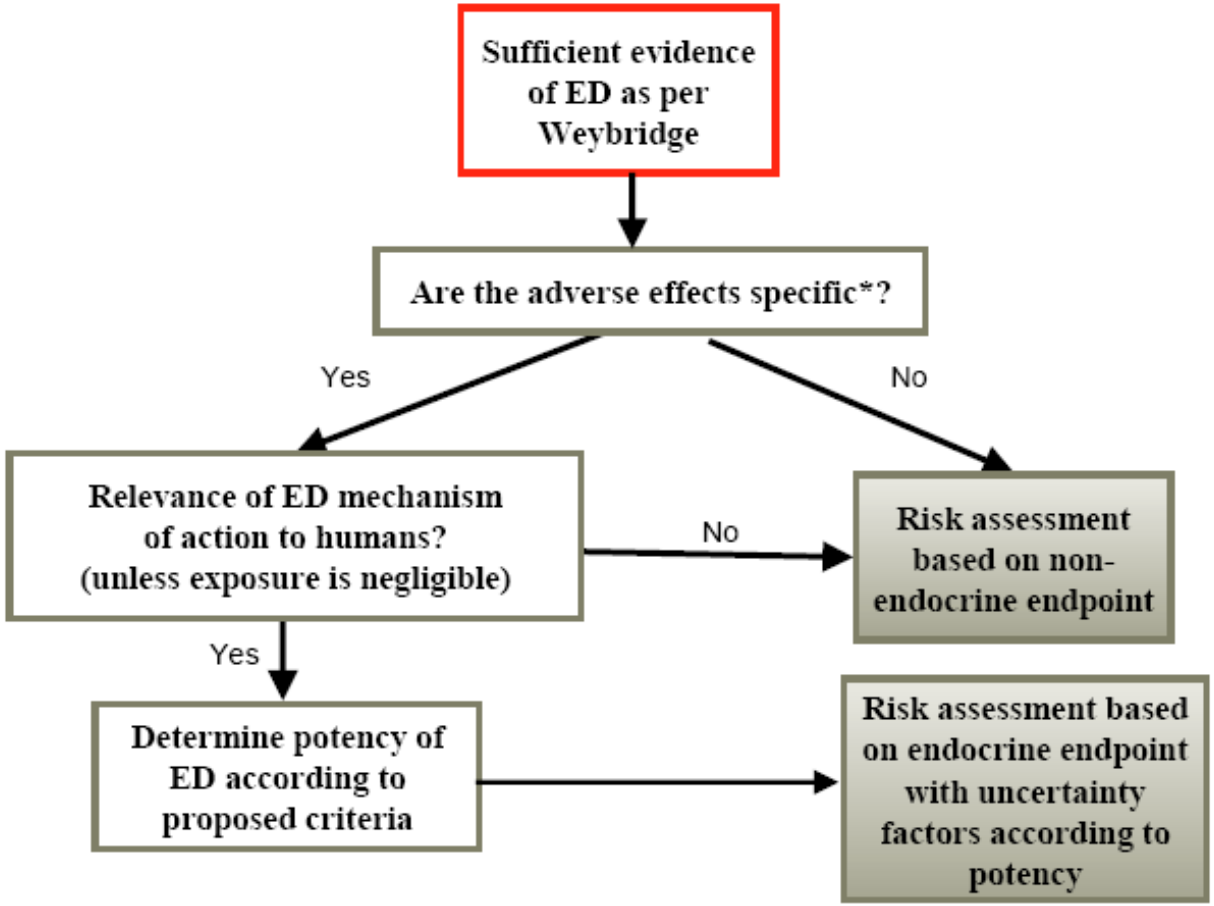
Result of LH increase	Tumor incidence	
	Rats	Humans
Androgen insensitivity syndrome (AIS) (defective androgen receptor)	100%	2.3%

- **LH increase in rats:** **Leydig cell tumors**
- **LH increase in humans:** **Leydig cell hyperplasia**

Identifying Endocrine Disruptors – ECETOC Proposal (1/2)



Identifying Endocrine Disruptors – ECETOC Proposal (2/2)



Conclusion

- **Endocrine activity**
  - **Not a toxicologically defined endpoint, but a Mode Of Action, which may or may not result in adverse effects**
  - **Discussions about low-dose effects are controversial and have not provided convincing arguments against a threshold approach**
  - **Adverse effects and thresholds can be assessed in adequately designed regulatory toxicity studies**
  - **Endocrine effects detected in animals are not necessarily relevant for humans**