Endocrine-active substances

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www.ilsi.eu

Hazard and risk

Hazard = potential to cause harm

Risk = likelihood * potential

Risk assessment

Hazard identification
Hazard characterisation

Uncertainty factor

Reference value (e.g. ADI)
RV = NOAEL/UF

Exposure assessment
Risk characterisation

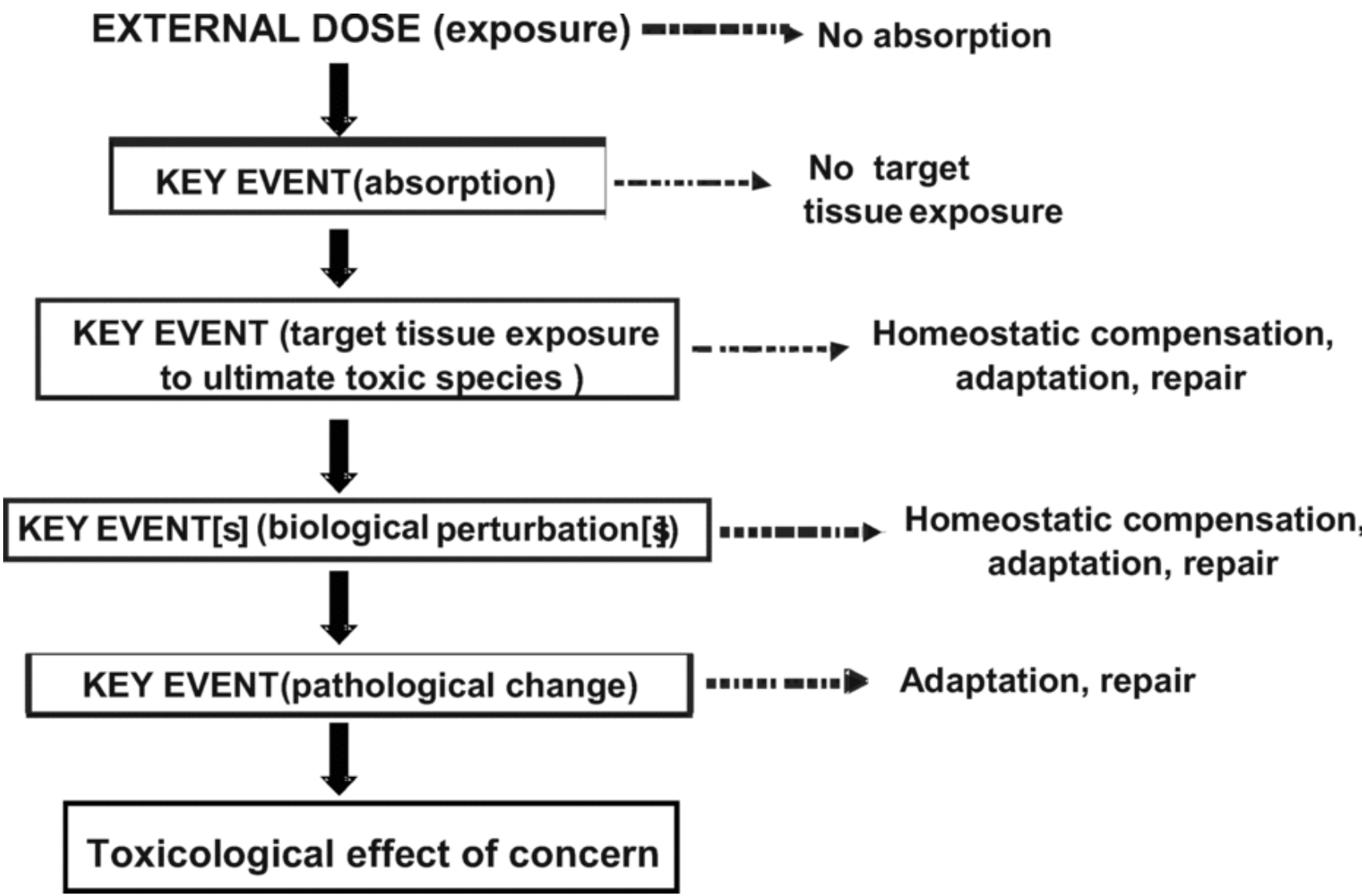
Scientific foundation of reference values

- The Reference Value approach is based on the premise that most toxicological endpoints have a true biological threshold
- A recent ILSI publication explains the importance of thresholds in detail
  - Crit. Rev. Food Sci. Nutr. 49, 2009
  - http://www.informaworld.com/smpp/title~db=all~content=g914018566

ILSI Threshold Working Group

- **Chemical Group:** Alan Boobis (Imperial College London), George Daston (Procter & Gamble), and Julian Preston (EPA)
- **Nutrient Group:** Sanford Miller (U Maryland), Joseph Rodricks (ENVIRON), Ian Munro (CANTOX), A. Catharine Ross (Pennsylvania State), Robert Russell (Tufts), and Elizabeth Yetley (retired NIH)
- **Allergen Group:** Steven Gendel (FDA CFSAN), Geert Houben (TNO), and Steve Taylor (U Nebraska)
- **Pathogen Group:** Bob Buchanan (U Maryland), Arie Havelaar (RIVM), Mary Alice Smith (U Georgia), and Richard Whiting (Exponent)
- **ILSI Research Foundation:** Stephen Olin and Elizabeth Julien

Mode of action and key events



Case studies

- Chemicals
  - Non-DNA-reactive carcinogen (chloroform)
  - DNA-reactive carcinogens
  - Endocrine disruptors (binding to estrogen receptor)
- Nutrients
  - Vitamin A (retinol) toxicity
- Pathogens
  - General discussion of toxigenic, toxicoinfectious, and invasive bacteria
  - Listeria monocytogenes
- Food Allergens
  - Key events for elicitation

Endocrine-active substances "endocrine disruptors"

- Endocrine-active substance effects
  - Interfering with hormone or receptor turnover
  - Receptor stimulation or inhibition
- Substances acting on steroid receptors have received most attention

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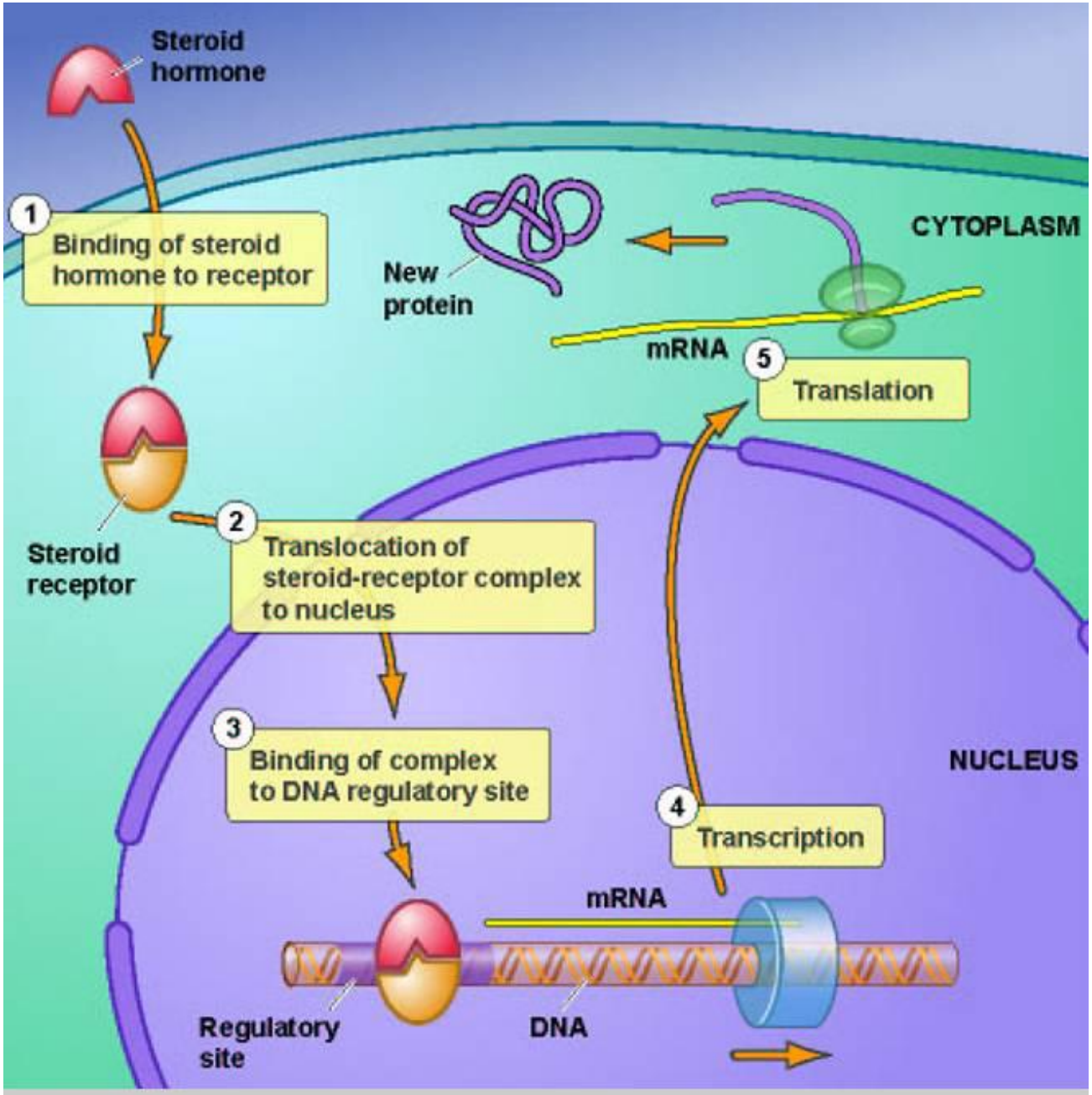
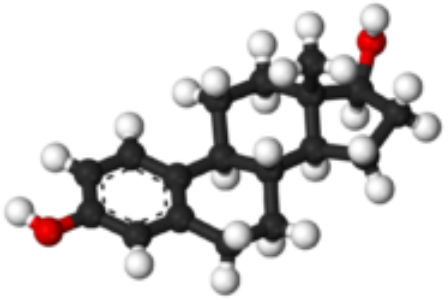


Source: "Module 6," < http://www.thepepproject.net/ >

Key events for endocrine disruptor action

- Internal exposure
- Binding to receptor
- Translocation to nucleus
- Binding to regulatory site on DNA
- Change in transcription to RNA
- (Change in translation to protein)
- Change in cell function
- Change in organ function within normal range
- Toxicity

Estradiol (main estrogen)



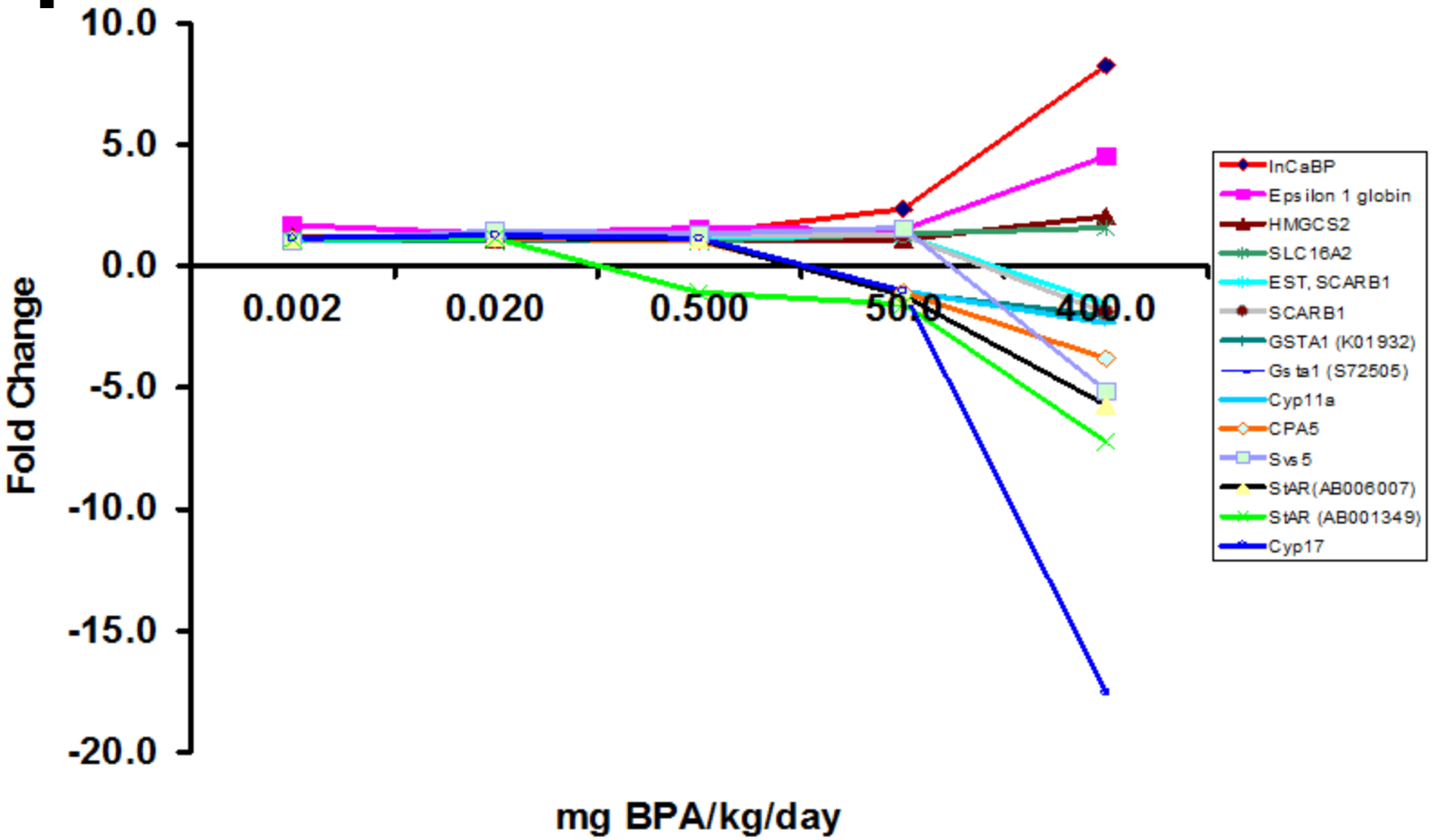
- Estradiol blood plasma levels fluctuate during the menstrual cycle from 70-1480 pmol/L*
- Estradiol levels in males 50-200 pmol/L*
- 50 pmol/L = 30,000,000,000,000 molecules/L
- Endocrine-active substances occur naturally in some foods at umol/L range
- Endocrine-active substances should be considered against this background
- Non-threshold response is extremely unlikely

*http://www.gpnotebook.co.uk/simplepage.cfm?ID=570818627&linkID=24801&cook=yes

Critical determinants of endocrine disruptor threshold

- There is evidence that several of the key events in endocrine disruption exhibit a threshold
- It is not possible to determine which of these is the critical determinant (if any), from available data
- For this, studies in which each event was studied in isolation would be necessary

Threshold dose-response in gene expression in rat foetal testis



- Estradiol and genistein also show threshold
- Gene responses were monotonic
- Morphological changes were not observed

Naciff et al 2005 Tox Sci 86:396

Conclusions

- Endocrine-active substances are extremely potent
- However, they cause harm only when a threshold is exceeded
- Therefore, a safe level can be established
- As in other cases, a risk-based approach is possible

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das Tauſent fünffhundert vnd
XXXVIII. Jar. Gepracticiert durch
den Hochgelörtē Doctorem
Paracelſum.
Mars. Saturnus.

"The dose is the poison"