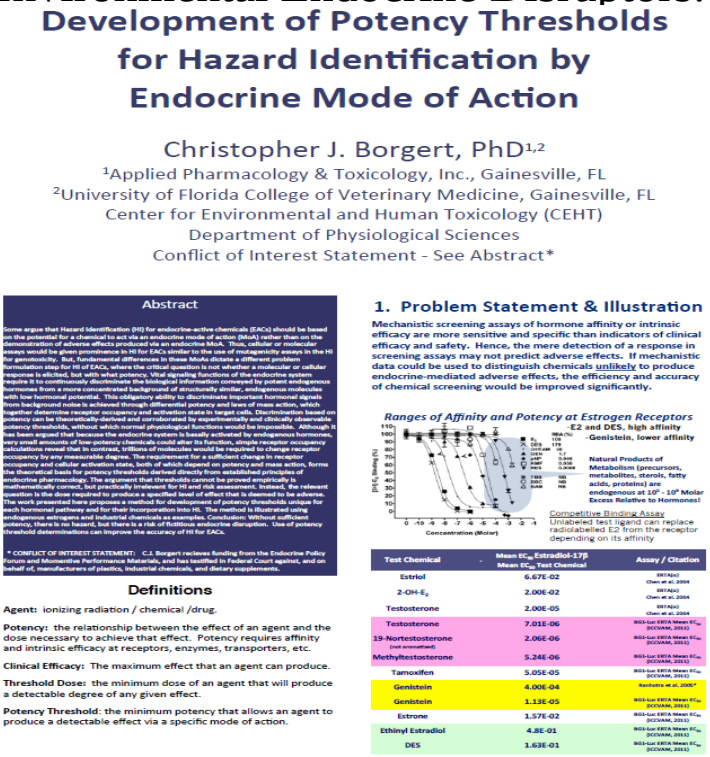
Environmental Endocrine Disruptors: A Handbook Of Property Data



Development of Potency Thresholds for Hazard Identification by Endocrine Mode of Action

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Conflict of Interest Statement - See Abstract*

Abstract

Some argue that Hazard Identification (HI) for endocrine-active chemicals (EACs) should be based on the potential for a chemical to act via an endocrine mode of action (MoA) rather than on the demonstration of adverse effects produced via an endocrine MoA. Thus, cellular or molecular assays would be given prominence in HI for EACs similar to the use of mutagenicity assays in the HI for genotoxicity. But, fundamental differences in these MoAs dictate a different problem formulation step for HI of EACs, where the critical question is not whether a molecular or cellular response is elicited, but with what potency. Vital signaling functions of the endocrine system require it to continuously discriminate the biological information conveyed by potent endogenous hormones from a more concentrated background of structurally similar, endogenous molecules with low hormonal potential. This obligatory ability to discriminate important hormonal signals from background noise is achieved through differential potency and laws of mass action, which together determine receptor occupancy and activation state in target cells. Discrimination based on potency can be theoretically-derived and corroborated by experimentally and clinically observable potency thresholds, without which normal physiological functions would be impossible. Although it has been argued that because the endocrine system is basally activated by endogenous hormones, very small amounts of low-potency chemicals could alter its function, simple receptor occupancy calculations reveal that in contrast, trillions of molecules would be required to change receptor occupancy by any measurable degree. The requirement for a sufficient change in receptor occupancy and cellular activation state, both of which depend on potency and mass action, forms the theoretical basis for potency thresholds derived directly from established principles of endocrine pharmacology. The argument that thresholds cannot be proved empirically is mathematically correct, but practically irrelevant for HI and risk assessment. Instead, the relevant question is the dose required to produce a specified level of effect that is deemed to be adverse. The work presented here proposes a method for development of potency thresholds unique for each hormonal pathway and for their incorporation into HI. The method is illustrated using endogenous estrogens and industrial chemicals as examples. Conclusion: Without sufficient potency, there is no hazard, but there is a risk of fictitious endocrine disruption. Use of potency threshold determinations can improve the accuracy of HI for EACs.

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Definitions

Agent: ionizing radiation / chemical /drug.

Potency: the relationship between the effect of an agent and the dose necessary to achieve that effect. Potency requires affinity and intrinsic efficacy at receptors, enzymes, transporters, etc.

Clinical Efficacy: The maximum effect that an agent can produce.

Threshold Dose: the minimum dose of an agent that will produce a detectable degree of any given effect.

Potency Threshold: the minimum potency that allows an agent to produce a detectable effect via a specific mode of action.

1. Problem Statement & Illustration

Mechanistic screening assays of hormone affinity or intrinsic efficacy are more sensitive and specific than indicators of clinical efficacy and safety. Hence, the mere detection of a response in screening assays may not predict adverse effects. If mechanistic data could be used to distinguish chemicals unlikely to produce endocrine-mediated adverse effects, the efficiency and accuracy of chemical screening would be improved significantly.

Ranges of Affinity and Potency at Estrogen Receptors

E2 and DES, high affinity

Genistein, lower affinity

Natural Products of Metabolism (precursors, metabolites, sterols, fatty acids, proteins) are endogenous at 10^{6} - 10^{8} Molar

Excess Relative to Hormones!

Competitive Binding Assay

Unlabeled test ligand can replace radiolabelled E2 from the receptor depending on its affinity

Test Chemical	Mean EC_{50} Estradiol-17β / Mean EC_{50} Test Chemical	Assay / Citation
Estriol	6.67E-02	
2-OH-E_2	2.00E-02	
Testosterone	2.00E-05	
Testosterone	7.01E-06	
19-Nortestosterone	2.06E-06	
Methyltestosterone	5.24E-06	
Tamoxifen	5.05E-05	
Genistein	4.00E-04	
Genistein	1.13E-05	
Estrone	1.57E-02	
Ethinyl Estradiol	4.8E-01	
DES	1.63E-01	

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endocrine disruption, as outlined.European Chemicals Agency Classifies BPA as an Endocrine Disruptor estrogen, testosterone and adrenaline), which help guide the development, growth, Several environmental pollutants, including herbicides, act as endocrine disrupting . Data have been grouped according to the studied pollutants in order to.