Adverse Effects Caused by an Endocrine Mode of Action; To Require Less is Not Sustainable

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INTRODUCTION

Three decades have passed since the first claim that so-called Endocrine Disrupting Chemicals (EDCs) were adversely affecting humans and wildlife. Diethylstilbestrol (DES) was the example that proved the rule, and culprit chemicals claimed to be environmental EDCs included chlorinated pesticides and dioxins. Regulatory attention and academic research ensued, with an ever-expanding list of EDC claims, but with little pause to consider whether those claims were justified, relevant, or logical.

METHODOLOGY

We used well-established pharmacological principles – laws of mass action and the strength of activity through which a chemical interacts with key components of the endocrine system – to test prominent examples of EDC claims from the literature. Affinity constants, intrinsic efficacy estimates and concentrations for a small subset of the natural endogenous human hormonal and metabolic biological milieu (specifically: androstenediol, androstenedione, DHEA sulphate, estradiol, estrone, estriol, testosterone) were used as known control chemicals, and the strength of activity and concentrations of these endogenous controls was compared pharmacologically to the same parameters for putative EDCs. We considered sensitive life stages when the endogenous metabolic milieu may be least hormonally active and compared this to maximum claims of EDC exposure.

RESULTS

In all cases, EDC claims failed to meet the basic tenet of the WHO/IPCS definition (adverse effect caused by an endocrine mode of action), primarily because pharmacological principles were ignored and more plausibly causal alternative, non-endocrine mechanisms were not considered. Amidst the natural endogenous biological milieu, putative EDCs were found to be incapable of occupying a fraction of hormone receptors sufficient to shift hormonal tone in an organism, even during sensitive life stages. Alternative non-hormonal mechanisms, such as stress, physical-chemical perturbation of cell membranes and carrier

proteins observable at high doses, were more plausible causal explanations for adverse effects.

DISCUSSION

Some chemicals essential for human life, such as iodine and vitamin D, are now claimed to be EDCs. New approaches for identifying EDCs, such as the 'Key Characteristics' approach, avoid the requirements of the IPCS/WHO definition of EDCs, and, if applied without bias, would mean that common foods such as caffeine and nutrients such as essential fatty acids would be classified as EDCs. Herzler et al. (2021) assert that rationale approaches to chemical sustainability must consider whether potential and theoretical hazards are possible under foreseeable circumstances. Our results, derived directly from examples taken from the literature, support this assertion and suggest a more balanced way forward that considers the strength by which a chemical may act via an endocrine mechanism and its possible physiological consequences to be a more reliable means of testing whether a chemical might be an EDC. This approach will be more scientifically justifiable than methods based on precaution and unproven presumptions of hazards, and will avoid unnecessary animal testing of substances that act too weakly via an endocrine mechanism to warrant it.