Regulatory Agencies Use Outdated Flawed Approaches to Assess Chemical Safety

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Regulatory agencies such as the FDA and EPA in the US and EFSA in the EU are supposed to protect the public from toxic chemicals. Tragically, however, agency scientists are required to adhere to models of the way toxic chemicals were proposed to act in prior centuries, going back to the early 1500s.

These outdated concepts about how to assess the toxicity of chemicals have been shown to be false for a class of toxic chemicals of great concern – endocrine disrupting chemicals. Endocrine disruptors are chemicals that interfere with the functioning of hormones that control development and then afterward control bodily functions throughout the remainder of life. Chemicals that disrupt these essential regulators of life contribute to the epidemic of chronic diseases plaguing the world, and also result in an increased risk of death from viral diseases such as COVID-19 [1].

Some examples of the over 1000 chemicals that have endocrine disrupting activity [2] are three very high volume chemicals found in most people who are examined: bisphenol A (BPA), which disrupts estrogen, androgen and thyroid hormone function [3], phthalates, which disrupt androgen hormone function [4], and perchlorate, which disrupts thyroid hormone function [5].

Using 21th century principles and methods, independent scientists have shown that these chemicals pose a serious threat to the health of people, pets, wildlife and the environment by polluting household products, food, water, soil and air [6, 7]. But the standard operating procedures and decision making of regulatory agencies around the world are based upon disproven assumptions and outdated methods to assess whether chemicals are safe. Chemical risk assessments by these regulatory agencies are thus grossly misleading [3].

Five major false principles guide the work of regulatory agency personnel in chemical risk assessments:

1. Males and females should respond the same when exposed to an endocrine disrupting chemical. This is a strange proposition given that there are marked differences between males and females in the hormones being disrupted (for example, the androgen and estrogen sex hormones). Specifically, in the Federal Register the FDA stated its position regarding endocrine disrupting chemicals: "For an observed effect to be toxicologically relevant (i.e.,

potentially adverse),… the observed effect should occur in both sexes of test species" [8]. In contrast, a central feature of findings from research on endocrine disruptors is that the response of males and females to disruption by these toxic chemicals is markedly different, or even completely opposite [9].

2. There is a "safe" or "threshold" level of exposure for endocrine disrupting chemicals. However, experiments show that any exposure will disrupt the already "above the threshold for causing effects" hormones that create the sex differences in the bodies of males and females and then control adult sexual function [10]. There is extensive evidence that minute perturbations in blood levels of sex hormones (below a part per trillion) during fetal sexual development has lifetime consequences [11, 12]. The concept of a "no effect" threshold exposure dose is thus illogical for a male who experiences disruption of androgen action or a female that experiences disruption of estrogen action.

3. Higher doses always lead to a greater response; dose-response relationships are assumed to always be monotonic, i.e., the direction of the effect never changes [8]. The traditional approach in toxicology of examining effects of only very high toxic doses of chemicals has been used by regulatory agencies to predict that less of a response will *always* occur at lower doses. Testing a few very high toxic doses is used to predict a theoretical "safe" threshold dose that is not actually directly tested (this "safe" daily dose is called the Acceptable or Tolerable Daily Intake Dose; ADI or TDI). For hormones, hormonally active drugs, and endocrine disrupting chemicals, high doses can cause the opposite effect seen at lower doses, which is the basis for tight control of the therapeutic dose of hormonal anticancer drugs for breast (Tamoxifen) and prostate (Lupron). These hormonally active drugs stimulate cancer at low doses (called "flare"), but have the opposite effect of inhibiting cancer at high therapeutic doses. If doctors followed the principles of toxicology when administering these drugs, they could kill their patients if the exposure dose got into the "flare" range. There are numerous examples of non-monotonic dose-response relationships for hormones, vitamins, drugs and endocrine disrupting chemicals [13].

4. Testing procedures for chemical toxicity used in risk assessments are referred to as "guideline protocols" that include extensive and expensive record keeping; this was established in the 1970s in response to fraudulent reports by commercial toxicology laboratories based on non-existent research [14]. These guideline procedures are cleverly referred to as "Good Laboratory Practices or GLP", even though those conducting the research may not have the required expertise and the experimental design may be inappropriate. A common design flaw in GLP studies is the absence of appropriate controls [15-17]. Regulatory agencies typically only use findings from industry funded GLP studies in chemical risk assessments. The guideline protocols are outdated and not focused on relating exposures to diseases caused by endocrine disrupting chemicals.

5. There must be a large number of animals used in toxicological GLP studies for the findings to be used by regulatory agencies in risk assessments and accepted as "valid and reliable" (true and repeatable). In sharp contrast, the National Institutes of Health (NIH), that funds biomedical research in the US, *requires* scientists to establish the smallest number of animals needed to

achieve statistically significant findings (called "power analysis") in order to obtain funding for the research. Requiring the use of an arbitrary large number of animals results in the death of excessive numbers of animals and clearly violates NIH research grant-funding guidelines; often 50 animals per group are examined in regulatory agency and industry-funded toxicology studies [18]. In addition, the arbitrary high number of animals being tested by regulatory agencies and chemical industries may actually be too small for some low frequency outcomes, such as rare cancers, that might be the focus of the study. Requiring a non-science based arbitrary number of animals to be tested is thus a profoundly illogical as well as, for academic researchers, an illegal and ethically indefensible demand by regulatory agencies. But the requirement for academic NIH-funded researchers to not test excessive numbers of animals is used by regulatory agencies to dismiss results from large numbers of NIH-funded studies showing that endocrine disrupting chemicals cause a wide range of diseases [3].

The consequence of adhering to the above false premises is that the predicted "safe" daily exposure levels (ADI or TDI) for endocrine disrupting chemicals estimated by regulatory agencies are dramatically higher than what would be calculated using all of the published science. Specifically, academic scientists in the US who participated with the FDA in an approximately 30-million dollar collaborative study of BPA (the CLARITY-BPA study) showed conclusively that the FDA's current estimated lowest adverse effect dose of BPA [18] is at least 20,000 fold higher than the dose shown to cause harm by CLARITY-BPA researchers [19].

Similar findings from the FDA's CLARITY-BPA "core guideline" portion of this collaborative research project were declared by the FDA to be "not biologically plausible" [18], because the findings were not consistent with traditional toxicological models of how toxic chemicals should act (for example, the dose-response relationship would have to be monotonic to be accepted). Rejecting data because they don't fit a 500-year-old model of toxic chemical action violates the scientific method. In science, models are tested in experiments and abandoned when consistently contradicted by experimental research and clinical findings.

The Endocrine Society (representing over 17,000 physicians and scientists who treat and study endocrine disorders and diseases) has issued repeated Society statements that regulatory agencies in the US and EU refuse to acknowledge. The Endocrine Society seeks to have these agencies incorporate 21st century principles of endocrinology into the process of determining the hazards (health effects) of endocrine disrupting chemicals [6, 7]. The core principles that are used to dictate how the FDA, EPA and EFSA assess the safety of endocrine disrupting chemicals violate the basic principles used by endocrinologists who study chemicals that cause endocrine diseases, and this disconnect from reality is completely unacceptable.

It is well beyond time for these regulatory agencies to be focused on protecting the health of people and the environment rather than focusing their efforts on protecting their prior regulatory decisions and never admitting that they had previously made a mistake. Adherence to outdated regulatory decisions makes it appear that these agencies are primarily protecting the profits of corporations that they are supposed to be regulating. It is unacceptable for regulatory agency employees to use centuries old ideas to declare chemicals as safe at some "estimated" threshold dose that is completely divorced from current research showing the wide array of harm caused by

these chemicals in large numbers of peer-reviewed academic research publications [19, 3]. Sadly, regulatory agencies in the US and EU will have to be forced to change their anti-scientific approaches to regulating endocrine disrupting chemicals by Congressional action in the US and legislative action by Parliament in the EU. While the EU has made some attempts to update its chemical regulatory system, nothing like this is happening in the US.

The dramatic increase in diseases and disorders related to exposure to endocrine disrupting chemicals, including reproductive disorders in men and women (low sperm production, infertility, miscarriage, endometriosis, polycystic ovarian disease), metabolic disorders (obesity, diabetes, cardiovascular, liver, kidney and immune disorders), and neurologic disorders (autism, attention deficit hyperactivity disorder, Parkinson's disease, Alzheimer's disease and dementia) demand action by legislators. Left to their own current practices, these regulatory agencies will continue to reject 21st century science as the basis for regulating endocrine disrupting chemicals in common use that are clearly hazardous and implicated in the increasing incidence of numerous endocrine-related diseases [2].

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