Evidence for Obesogens: Interpretations and Next Steps

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Traditionally toxicologists have embraced the presumption that “Alle Ding sind Gift, und nichts ohn’ Gift; allein die Dosis macht, das ein Ding kein Gift ist” or “All things are poison, and nothing [is] without poison; only the dose makes a thing not be poison,” as first proposed by Paracelsus in 1538, but hypothesized nonmonotonic, low dose adverse effects of some substances challenge this premise. Three perspectives on environmental chemicals as “obesogens” are presented in this issue. Schug and Heindel suggest there is compelling evidence demonstrating many industrial and agricultural chemicals act as obesogens and provide hypotheses on how endocrine disruption, particularly during early development, could lead to obesity later in life. On the other hand, Sharpe and Drake are skeptical of the current evidence linking environmental chemicals to obesity, emphasizing two primary criticisms: (1) Animal model studies have largely relied on high dose levels that do not reflect routes and magnitudes of exposures experienced by humans and (2) Epidemiological studies linking chemicals to obesity are likely confounded by exposures that are comparable to those experienced in human populations.

Same Evidence, Different Perspectives

These perspectives highlight the range of informed opinions even when the very same evidence is presented. For example, both Schug/Heindel and Sharpe/Drake cite Tremblay et al. (1), as evidence supporting and refuting organochlorines (OCs) as obesogens, respectively. Tremblay et al. measured sleeping metabolic rate (SMR) before and after a weight-reducing program and found that the decrease in SMR, beyond what would be predicted by weight loss alone—i.e., the adaptive reduction in thermogenesis upon weight loss, is positively correlated with OC plasma levels. Contrary to Schug and Heindel’s interpretation of this data that OCs can lead to a higher probability of regaining lost pounds after weight loss, heightened adaptive thermogenesis predicts resistance to losing weight due to reduced energy expenditure. Alternatively, Sharpe and Drake state Tremblay’s work suggests OCs increase thermogenesis, thus leading to increased weight loss, but in fact adaptive thermogenesis here refers to decreases in energy expenditure upon decreased energy intake. Yet another, possibly more straightforward interpretation of Tremblay’s results would be that adaptive thermogenesis is primarily determined by fat loss, and since ingested OCs are primarily stored in fat cells, greater concentrations of OCs are seen in blood after greater fat loss. Exposure and elimination of lipophilic compounds are determined by fat intake and fat loss, respectively, therefore epidemiological studies going forward should explicitly address potential confounding with both dietary fat intake and fat loss via weight reduction programs or other mechanisms, such as breastfeeding. Birth cohort studies may be informative in this regard, as long as sufficient variation in exposures can be captured across all levels of potentially confounding variables. Interestingly, initial OBELIX birth cohort results show an inverse relationship between PCB levels and birth weight. The next challenge is development of ethical and practical study designs to adequately control for potential confounding.

What Type of Evidence can We Practically and Ethically Generate?

Despite the divergent interpretations of individual studies and the differences in the overall conclusions drawn in these three perspectives, it is clear we have imperfect knowledge. As Richard Sharpe points out, the large number of positive association studies for Bisphenol A (BPA) and obesity as evidence for causality belies the fact that plausibility is tenuous due to confounding by diet, and even longitudinal studies will have difficulty teasing apart the contribution of diet versus BPA exposure (2). Thus an important question is what type of evidence is critical to move the community forward? While a randomized controlled trial (RCT) would be optimal for determining causality such as in the classic case of smoking as a cause of lung cancer, ethical concerns make RCTs unrealistic when examining the effects of many environmental chemicals, because often there are not demonstrated or even plausible benefits from exposure, only hypothesized adverse health effects. For example, ethical concerns resulted in the suspension of the Children’s Environmental Exposure Research Study (CHEERS) due to the perception that

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participants would be encouraged to use pesticides, even when the design was to characterize routine pesticide exposure. Randomized intervention study designs to reduce exposure may be useful in determining causality, although a recent family-based trial discovered food contamination actually led to increased exposure to BPA in the dietary replacement arm (3). Additionally, practical limitations, including the importance of developmental time of exposures, the long lag between exposure and effect, and the suggestion of non-monotonic dose-response curves, also limit the feasibility of the standard RCTs in evaluating environmental contaminants as obesogens.

Natural or quasi experimental study designs may offer alternative methods for satisfying some causality criteria when RCTs are not a reasonable option. For example, studies examining the hypothesized effects of breastfeeding and other factors on obesity highlight that these designs can offer inferential strength which lies midway between that of a pure RCT and an ordinary observational epidemiological design (4,5).

**Conclusion**

On a final note, making a clear distinction between drawing a conclusion on causality and how and when evidence is used when making a decision is important. Although current evidence may not be sufficient for drawing a conclusion on the obesogenic potential for some environmental contaminants, a decision to limit exposures, either individually or at the societal level, is a different question, and hinges on (1) balancing both the estimated benefits and risks associated with the decision and (2) the immediacy at which the decision needs to be made (i.e., do I buy a BPA-free bottle today versus should a standard be set to limit exposure to potential obesogens). Decision-making at the governmental level requires varying levels of evidence, for example aligning with the US Department of Justice Rules of Evidence, or the US Environmental Protection Agency weight of evidence approach. Ideally, generation of scientific evidence that merits causal conclusions will play a key role in decision-making processes in the future.

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