CENTER FOR Science IN THE Public Interest

A Coordinated Research and Action Agenda to Build the Evidence Base Related to Metabolic Disrupting Chemicals

With the alarming prevalence of adult and childhood obesity in the U.S. and abroad, there is a critical need to understand its causes and pathogenesis. The obesogen hypothesis proposes that certain chemicals, called obesogens or metabolic disrupting chemicals (MDCs), may influence individual susceptibility to obesity by interfering with metabolic systems that regulate weight gain. This hypothesis proposes an additional paradigm to the "calories in, calories out" paradigm, which proposes that weight gain occurs as a direct result of calorie intake exceeding calorie expenditure. With support from the Passport Foundation beginning in 2019, the Center for Science in the Public Interest (CSPI) has sought to investigate the role of MDCs in the development of obesity by rigorously assessing the scientific evidence, ascertaining the strength of the evidence regarding the obesogen hypothesis, and developing consensus in the public health community around a research agenda to advance the science in this area. In 2020, CSPI compiled its findings from months of research into a memorandum that examined the supporting evidence for and limitations of the data related to the obesogen hypothesis. On July 1, 2021, CSPI held a half-day, virtual MDC convening with experts in the field to discuss and build consensus on the current understanding of MDCs and the future of MDC research, and to clarify recommendations for CSPI, researchers, and regulators on MDCs. Drawn from our own research, and with invaluable input from convening attendees, we developed this research agenda to identify potential research efforts that would address critical gaps in the MDC field. Our work has been informed by other key convenings, including a 2011 National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) workshop and a 2015 Institute of Medicine workshop. This document serves to inform leaders at the National Institutes of Health, the NTP, and the Food and Drug Administration and analogous institutions outside the U.S. as they consider funding research efforts and undertaking other activities in this area.

Research designs and considerations

- Randomized Controlled Trials (RCTs)
    - Conduct short-term RCTs in which participants are randomized to consume ad libitum controlled diets with varying acceptable doses of MDCs (e.g., propionate or another additive that is currently considered safe) in a multiple-arm crossover trial with a washout period. Compare primary outcomes of mean daily ad libitum energy intake between each diet period (within subject) as well as at the final week of each diet (between subjects). Perform cross tabulations by biomarkers that indicate exposure to specific MDCs in early life.
    - Conduct an overfeeding study, in which a short-term positive energy balance is imposed on participants with normal weight to mimic longer-term mismatched energy expenditure and intake. Randomize participants to consume varying tolerable/acceptable doses of MDCs. Evaluate whether weight change varies by exposure to MDCs.
- Leveraging population-based cohort studies as a cost-effective method to examine longitudinal relationships between MDC exposure and outcomes

    - Leverage population-based, prospective birth cohort studies (e.g., National Children's Study Archive, Environmental Influences on Child Health Outcomes (ECHO) cohorts) to conduct longitudinal analyses that examine associations between maternal exposure to MDCs during pregnancy (from collected biologic specimens including blood, urine, hair, and nail clippings, and environmental samples including air, dust, soil, food, and water at home places) and outcomes (e.g., weight change) in children and adults. Consider interactions with diets high in fat, refined carbohydrates, sugar-sweetened beverages, and/or ultra-processed foods.
    - Leverage population-based cohort studies to assess whether indicators of obesity vary by degree of exposure to suspected MDCs in biologic specimens in adults.
    - Leverage the National Health and Nutrition Examination Survey (NHANES) Biospecimen Program to consider the association between MDC exposure (analyzed via serum and urine samples) and indicators of obesity, adjusting for various nutrition- and health-related variables. Estimate the attributable fraction of MDCs to overweight and obesity.
- Controlling for confounders
    - Researchers should control for various important confounders such as parental smoking, parental BMI, exposures to air pollutants, parental and offspring diet, type 2 diabetes, consumption of pharmaceutical drugs known to lead to weight gain, and age. Both human and animal subjects should be observed beyond the pubertal period since some effects do not manifest until later in life.
- Implement a systematic review and evidence integration approach when evaluating the obesogenicity of substances, ideally employing the National Toxicology Program Office of Health Assessment and Translation (OHAT) handbook.
- Implementing the research designs above will require improved coordination, collaboration, and data sharing among clinicians, toxicologists, endocrinologists, epidemiologists, and agencies studying MDCs. The Endocrine Society is in a unique position to play larger role in bringing together basic, clinical, and MDC researchers.

Recommendations to the Federal government to improve research and assessment of MDCs

- In addition to the current opportunities to investigate environmental exposures related to obesity, NIEHS should host a workshop on MDCs to examine the progress made since its 2011 workshop and the 2015 IOM workshop, identify recommended screening and testing protocols for metabolic disruptors, and identify future research needs. The workshop should be informed by ongoing efforts to develop testing systems, such as the GOLIATH, EDCMET, and OBERON projects.
- This workshop should be followed by circulation of a request for application (RFA) to invite grant applications and ultimately stimulate research activity on MDCs.
- To encourage interdisciplinary research collaborations between toxicologists, environmental health scientists, nutrition scientists, and epidemiologists, various National Institutes, including NIEHS, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Institute of Child Health and Human Development (NICHD), should collaborate to fund clinical trials and other research.
- The FDA should fund the National Academies, in collaboration with the NIEHS and/or the Endocrine Society (ES), to develop recommendations for incorporating information on metabolic disruption into its assessments of food ingredients and packaging. This should include recommended screening and

testing protocols (including specific assays and endpoints) and guidance to companies that seek to introduce substances into the food supply to determine if they disrupt metabolism.

- FDA should require screening for direct and indirect measures of weight gain (e.g., using high throughput screening for biomarkers of metabolic disruption) by manufacturers seeking FDA approval for substances added to food and food packaging – at least for those with potential metabolic disruption effects.

This Research and Action Agenda was developed with generous contributions from (in alphabetical order):

- Jerrold Heindel, Ph.D. – Director of Commonweal's Healthy Environment and Endocrine Disruptor Strategies (HEEDS) program
- Kevin Hall, Ph.D. – Senior Investigator at the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)
- Maricel Maffini, Ph.D. – Independent consultant with more than 25 years of research experience in the fields of carcinogenesis, reproductive biology, and endocrine disruption
- Michele La Merrill, Ph.D., MPH – Associate Professor of Environmental Toxicology at the University of California, Davis
- Sarah Howard, M.S. – Director of Commonweal's Diabetes and Environment program
- CSPI Staff – Bonnie Liebman, MS (Director of Nutrition), Breanne Wright, Ph.D., MS (Deputy Director, Science Department), Caitlin Dow, Ph.D., MS (Senior Nutrition Scientist), Jensen Jose, JD (Regulatory Counsel), Lindsay Moyer, MS, RD (Senior Nutritionist), Lisa Lefferts, MSPH (Senior Scientist), Peter Lurie, M.D., MPH (Executive Director)