Exposure to Thyroid-Disrupting Chemicals: A Transatlantic Call for Action

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THERE HAS BEEN A DRAMATIC surge of studies reporting the epidemiology, putative mechanisms on hormone action, and potential adverse effects of endocrine-disrupting chemicals (EDCs) over the past few decades. The Endocrine Society has recently summarized the available evidence regarding effects of EDCs in several key areas: (i) obesity and diabetes, (ii) female reproduction, (iii) male reproduction, (iv) hormone-sensitive cancers in females, (v) prostate, (vi) thyroid, and (vii) neurodevelopment and neuroendocrine systems (1). However, significant limitations regarding our understanding of disease burden, strength of the evidence, and, in some areas, directionality of association remain in many of these endocrine systems.

Given the critical role of thyroid hormone action in the brain during early growth and development, the impact of thyroid hormone-disrupting chemicals (TDCs) is potentially harmful, particularly among pregnant women and their infants. Sources of exposure may include environmental and/or dietary routes. Environmental TDC exposure can occur from use of manufactured industrial products (e.g., plastics, flame retardants, coolants), agricultural practices (e.g., pesticides), personal care products (e.g., sunscreens, antimicrobials), and from tobacco smoke (which contains thiocyanate metabolites). Dietary exposure may result from EDC contamination into the food chain and food packaging materials, and ingestion of natural goitrogens (i.e., thiocyanate, isoflavones) in sufficient amounts to result in thyroid hormone axis dysfunction.

Although there is emerging evidence of the adverse thyroidal hormone axis effects of perchlorate, phthalates, bisphenol A, antimicrobials, brominated flame retardants, and perfluorinated chemicals (2), it is virtually impossible to change policy making until strong causal relationships are clearly established. Rigorous human studies regarding causality and/or associations of most TDCs are lacking.

We thus advocate for the international thyroid community to lead new and confirmatory collaborative research in this

area. An integration of basic (3), epidemiologic, and clinical hypotheses and approaches is needed, specifically regarding the impacts of TDCs and their potential exacerbation by iodine deficiency during pregnancy and early childhood. The fact that nearly 40% of the world's population still has inadequate nutritional iodine intake renders these individuals and risk groups even more vulnerable toward the adverse effects of TDCs, some of which might act as co-goitrogenic compounds interfering with the feedback regulation of the hypothalamus–pituitary–thyroid axis. In addition, interactions between the complex effects of TDC exposure and thyroid autoimmunity should be explored by taking into consideration various factors such as major sex differences in thyroid hormone-related diseases, the age of exposure, latency from exposure, synergistic effect of different EDC mixtures, nontraditional dose–response dynamics, and transgenerational effects (1).

The magnitude of the effects of TDC exposure remains incompletely understood, but the potential individual and socioeconomic implications are great. The costs of neurodevelopmental disease and IQ loss attributable to two TDCs, a flame retardant and an organophosphate pesticide, were recently estimated to be more than €150 billion per annum in the European Union (4). This call to focus on an important and timely topic in thyroidology requires the joint efforts, interests, engagement, and expertise of the global scientific thyroid community.

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References

1. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT 2015 EDC-2: The Endocrine Society's

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- Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr Rev* **36**:E1–E150.
2. Pearce EN, Braverman LE 2009 Environmental pollutants and the thyroid. *Best Pract Res Clin Endocrinol Metab* **23**: 801–813.
 3. Bianco AC, Anderson G, Forrest D, Galton VA, Gereben B, Kim BW, Kopp PA, Liao XH, Obregon MJ, Peeters RP, Refetoff S, Sharlin DS, Simonides WS, Weiss RE, Williams GR, American Thyroid Association Task Force on Approaches and Strategies to Investigate Thyroid Hormone Economy and Action 2014 American Thyroid Association Guide to investigating thyroid hormone economy and action in rodent and cell models. *Thyroid* **24**:88–168.
 4. Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L 2015 Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab* **100**:1256–1266.

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