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Endocrine disruptors

Characterizing the effect of endocrine disruptors on human health: The role of epidemiological cohorts

Caractérisation de l'effet des perturbateurs endocriniens sur la santé humaine : l'apport des cohortes épidémiologiques

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ABSTRACT

Research on endocrine disruptors (EDs) developed from numerous disciplines. In this concert of disciplines, epidemiology is central to inform on the relevance for humans of mechanisms and dose-response functions identified in animals, to characterize the health impact (number of attributable disease cases), the cost associated with ED exposure, and the efficiency of the measures taken to limit exposure. Here, we present epidemiological tools to draw valid inference regarding effects of potential EDs. Epidemiology is generally observational, requiring care to control confounding bias. Many potential EDs have a short biological half-life; approaches relying on repeated biospecimens sampling allow limiting exposure misclassification and the resulting bias. For non-persistent compounds, couple–child cohorts are a central study design. Cohorts can now rely on molecular biology approaches to characterize exposures and intermediate pathways, which corresponds to the advent of molecular epidemiology and allows stronger interactions between epidemiology, toxicology, and molecular epidemiology to characterize the health effects of EDs.

Mots clés :
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RÉSUMÉ

La recherche sur les perturbateurs endocriniens (PE) s'est développée avec l'apport de différentes disciplines. Dans cette pluridisciplinarité, l'épidémiologie a un rôle à jouer pour éclairer la pertinence des mécanismes d'action de PE identifiés dans d'autres modèles, caractériser les relations dose–réponse, l'*impact sanitaire* à l'échelle de la population (nombre de cas attribuables à l'exposition aux PE et coût économique associé) et l'efficacité de mesures pour limiter l'exposition. Nous présentons les outils épidémiologiques permettant de tirer des conclusions valides pour l'humain sur les substances suspectées d'être des PE. Une spécificité de l'épidémiologie est sa nature essentiellement

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observationnelle, nécessitant une attention particulière dans le contrôle des biais de confusion. Un autre point central est lié à la nature peu persistante dans l'organisme de beaucoup de PE potentiels. Des approches, s'appuyant sur un recueil répété d'échantillons biologiques chez chaque sujet, permettent de limiter l'erreur de mesure et les biais pouvant en résulter. Du point de vue du *design* d'étude, l'approche centrale pour la problématique des PE non persistants est celle de la cohorte couple–enfants. Ces cohortes peuvent s'appuyer sur les développements de la biologie moléculaire pour caractériser exposition et mécanismes intermédiaires, ce qui correspond à l'avènement de l'épidémiologie moléculaire, permettant des interactions plus fructueuses entre épidémiologie, toxicologie et biologie moléculaire.

1. Introduction

1.1. Endocrine disruption research: a multidisciplinary field

Although research on substances now identified as endocrine disruptors (EDs) already existed in the mid-20th Century, the terminology "endocrine disruptors" was first used in the scientific literature in 1993 [1]. EDs are defined by the World Health Organisation as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" [2]. Compared to other dangers for health, a specificity of this definition is the combination of the existence of adverse effects and of information on the mechanism of induction of these effects. Other dangers are generally either defined in terms of adverse effects (e.g., carcinogens) or in terms of mechanism (e.g., mutagenic substances, but not carcinogens). This specificity highlights the need for research on EDs to work both at the scale of organisms (or populations), which is most convenient to highlight adverse health effects (what toxicology, ecotoxicology, ecology, demography and epidemiology typically do) and at finer scales, which is usually required to identify biological mechanisms. Note that (eco)toxicology and epidemiology are now increasingly able to help identifying biological mechanisms [3,4].

1.2. What molecular and (eco)toxicological studies can tell us about EDs

Historically, ED research developed from a variety of disciplines including ecotoxicology, toxicology, molecular biology, epidemiology, and clinical research. Studies relying on molecular, cellular, organ and animal models as well as wildlife observations brought crucial findings about EDs. (i) At the molecular and cellular levels, structural and cell-based assays identified exogenous substances with affinity for key molecular components of the endocrine system such as nuclear receptors and enzymes implied in hormone metabolism or synthesis [5]. (ii) At the level of organs, studies finely documented the impact and mechanisms of action of chemicals on the endocrine system [6]. (iii) At the level of organisms, toxicological experiments described the toxicokinetics of the suspected EDs and their biological and health effects (including development, fecundity, metabolic disorders and behaviour) over large ranges of doses, alone or in mixtures, during specific developmental windows, over up to several generations [7–9]. (iv) At the ecosystem level, ecotoxicological research has identified EDs in the environment and described their impact on wildlife (e.g., the decrease in bird populations in the US Great lakes due to organochlorine exposures [10], or imposex in sea molluscs because of tributyltin (TBT) exposure [11]).

1.3. What molecular and (eco)toxicological studies cannot address efficiently

Although the above-mentioned issues are central, specific questions important for research on EDs, for risk assessment and to inform risk management cannot be efficiently tackled with the above-mentioned approaches. These include the actual exposure patterns and levels in humans [12]; the shape and slope of dose-response functions in humans [13]; the health impact (risk, or disease cases attributable to exposure to EDs) and the related economic cost for society [14]; the existence of possible synergy between EDs and specific lifestyle factors; the efficiency of specific prevention measures on human populations (e.g., informing the public, modifying one's diet...) [15].

These questions can be specifically addressed by (human) population-based approaches such as those of epidemiology and closely-related disciplines. Historically, for example, these approaches have been central to document the diethylstilboestrol [16], and Minamata [17] crises. Other important questions, related, e.g., to the decision-making processes regarding substances with endocrine-disrupting properties, are within the scope of social sciences and will not be discussed here.

1.4. The epidemiological approach

Epidemiology can be defined as a science aiming at studying patterns and causes of diseases in human populations, and at identifying approaches to limit disease incidence. We make no distinction between epidemiology and clinical research on patients, which we consider to be the application of epidemiology to a specific population and possibly specific "exposures", such as drugs. Although generally of observational nature, epidemiologists have for a long time also used experimental and quasi-experimental approaches (see 2 below).

In this article, we will discuss some of the main challenges of epidemiological research, focusing on control for confounding bias (section 2), study design (section 3), and exposure misclassification (section 4), illustrating to