Chemical Pollution and One Health
– from Reactivity to Proactivity
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Metabolic diseases: from chemical exposure to interventions

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Background

Metabolic diseases, in particular obesity and related diseases like type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), have increased during the past few decades across age segments, in both sexes, and in low- and high-income countries[1,2]. Interventions meant to tackle metabolic diseases around the globe have included identification of related genetic variation, incorporation of dietary policies, as well as stimulation of physical activity, as exemplified in a recent Cochrane review of obesity prevention in children[3]. Despite this, obesity trends have at best attenuated in some countries, and no country has been able to reverse them[1,2]. Importantly, pathologies under the umbrella of metabolic diseases, including CVD and T2DM[4,5,6] are the leading causes of morbidity and mortality in the world (WHO, 2020)[7].

Based on this evidence, the fundamental question posed to us as a society is how we can effectively tackle this burden of metabolic diseases. One of the hints to answering this question comes from recent evidence showing that the etiology of most non-communicable diseases relates to environmental exposures during embryonic development or infancy, on top of the genetic variation that could explain the susceptibilities of specific groups[8]. This is in line with the concept of Development of Origins of Health and Disease (DOHaD), which aims to understand how the incidence of diseases can be rooted in exposures occurring during early development[9]. Many of the compounds affecting our lives early in development are endocrine disrupting chemicals (EDCs), which mimic the action of our hormones when binding to cell receptors[10]. Because EDCs are part of many products used daily, such as plastics, electronics, pesticides and agrochemicals, they have become environmental contaminants[10]. EDC residues can persist in the environment for many years, bioaccumulate in organisms, and have detrimental effects for ecosystems, in general, and for human health, in particular. Additionally, bioaccumulation of many of these toxicants is known to occur in organisms used to feed human populations, such as fish, sea shells and vegetables.

The importance of investigating environmental contaminants is such that the World Health Organization (WHO) stated that understanding their effects is of 'high priority[11]. Despite these detrimental effects, the yearly production of new chemicals, of which many will have endocrine disrupting properties, is increasing at alarming rates. Of the tens of thousands of chemicals already on the marketplace, only around 2500 have been evaluated for health effects[12].

In relation to metabolic diseases, there is now plenty of evidence showing that environmental contaminants are involved in the etiology of obesity[12,13] and diabetes[14,15], in addition to well-known factors such excess calorie intake, food composition, and physical inactivity[16,17]. This current evidence follows years of research initiated by pioneering work in the 2000s that led to inception of the term 'obesogens' to describe environmental compounds able to trigger metabolic diseases[18]. At present, this concept is well-supported by experimental evidence in both human and animal studies[19]. An important fact emerging from studies investigating the obesogenic effects of environmental contaminants is that such effects are dose- and age-dependent. Additionally, many reports have also shown that the metabolic disruption produced by environmental contaminants can be transmitted across generations[20]. For example, experiments involving developmental exposure to the well-known pesticide Dichlorodiphenyltrichloroethane (DDT) in rodents have shown that obesity, measured as the accumulation of abdominal fat pads, increases three generations after the exposure[21]. Alarmingly, this phenomenon is not observed in the generation that was developmentally exposed, showing that metabolic effects can be hidden in the epigenome of the gametes until they are expressed generations after the exposure has ceased[22].

The idea of developing policy interventions that address exposure to EDCs to tackle metabolic diseases is in its infancy. A recent systematic review, however, generated high-quality evidence supporting the idea that changes in nutritional and other daily habits can successfully reduce exposure to EDCs[23]. These habits include dietary alterations such as consumption of organic

food, avoidance of canned food and beverages, modification of behavioral patterns in relation to personal care products, as well as avoidance of plastics (e.g., using glass or stainless-steel bottles and containers instead of plastic)[23]. The authors highlight the idea that societal interventions related to both education and/or regulatory policies aimed at reducing exposure to EDCs can have tangible effects. The question is whether this would also be reflected in a reduction in the incidence of metabolic diseases, and to what extent. Additionally, there is a need to know how such interventions could be integrated into current strategies that focus on nutritional and physical activities, thereby increasing the overall efficacy of societal interventions in this realm. The main aim of this workshop was to establish the conceptual basis for future development of societal interventions aimed at reducing the exposure to EDCs, the goal being to help tackle the global increase in metabolic diseases in human populations.

Approach

In this workshop, we gathered experts from different backgrounds to promote an evidence-based discussion about the effect of exposures to contaminants on the incidence of metabolic diseases in humans. The idea was to identify gaps in public policies and provide concrete suggestions and recommendations on how we can translate into public policy and practice the evidence showing that chemicals in the environment can produce metabolic diseases.

Before the workshop, five invited key participants were asked to provide questions they thought would be relevant to discuss among the workshop participants. These questions were received and combined into the three following questions, which were the matters under discussion in the workshop:

Q1. What type of tools and methodologies are needed to efficiently characterize and screen the adverse health impacts of chemical exposure in exposed individuals and their descendants? Consider not only old chemicals, but also the amount of new chemicals produced each year.
Q2. How can scientists promote the incorporation of metabolic disruptors into current regulations, in order to monitor, reduce and mitigate their effects as well as to empower individuals to make informed choices that limit their exposures?
Q3. How can clinicians and healthcare providers incorporate discussions about exposure to obesogens/environmental toxicants into routine patient care, offer guidance on risk reduction strategies, and integrate the evaluation of environmental obesogen exposure into routine health assessments?

The workshop was opened by an introduction to the topic by Dr. Carlos Guerrero-Bosagna (Uppsala University), who presented these three questions to the 28 participants from 8 countries: Brazil, Chile, Costa Rica, the Netherlands, Nigeria, Spain, Sweden, and the US. Most of the participants were from academia, but also from the public health sector, Swedish government agencies, companies, and one representative from the World Bank.

The workshop continued with 15-minute seminars held by the five invited key participants:

Prof. Juliette Legler from Utrecht University (the Netherlands) opened by stating that there are over 30,000 papers mentioning health outcomes associated with exposure to EDCs. She envisioned ways to move the field of metabolic disruption forward, which would involve not only showing that EDCs produce adverse effects and their mode of action, but also showing that such adverse effects are a direct consequence of the EDC mode of action. Because there are no OECD validated non-EATS methods to assess metabolic disruption, she made the case that the OECD conceptual framework for testing and assessing EDCs needs to be improved by incorporating the concept of metabolic disruption. To accomplish this, the independent development of assay candidates by researchers worldwide is needed, as well as the compilation of data produced by such assays to properly evaluate the 'weight of evidence' relating adverse effects and EDC mode of action.

Then, Prof. Tuulia Hyötyläinen (Örebro University) continued by talking about the advantages and possibilities of using metabolomics as a read out after environmental exposures, which includes individualized assessments and interventions. Importantly, she pointed out that the most of the impacts of toxicants in humans are indirect and mediated by changes in microbiota and the derived signaling metabolites. Given this complexity, she also called for the development of better assessment tools, at the biological, chemical and eco-toxicological levels.

Subsequently, Dr. Isaac Olufadewa from Nigeria presented the Slum and Rural Health Initiative, pointing to the importance of evidence-based and community-led solutions to tackle non-communicable diseases. Particularly in Africa, he sees challenges, such as accelerated development, legal issues, infectious diseases, inadequate education, but also opportunities, for example collaboration with other countries, in order to leverage policies and programs focused on reducing EDC usage and exposures.

This was followed by a presentation by Dr. Bárbara Echiburú from the University of Chile, who highlighted the accelerated pace of increasing metabolic diseases in Chile, which affect more women than men. She highlighted Polycystic Ovary Syndrome (PCOS) as an important example of metabolic disease, mentioning that PCOS is the most prevalent disease in overweight women. She introduced the idea that metabolic alterations during pregnancy can enhance the incidence of metabolic diseases in the offspring, particularly in relation to PCOS.

IMAGE CREDIT: ISTOCK PHOTOS

The last talk was by Dr. Josep Jimenez Chillarón from the University of Barcelona (Spain), who pointed to the importance of considering the theory of DOHaD for understanding the etiology of metabolic diseases. He also presented examples of transgenerational transmission of effects of metabolic disruption in mice, which are observed even three generations after the exposure has ceased.

Outcome of workshop discussions

Discussion related to Q1

There is a serious problem with the speed at which screening for dangerous chemicals can be performed. For example, for the utilization of screening methods by the European Chemicals Agency (ECHA), the OECD needs to first certify a validated method. At the moment, the responsibility for method validation relies on individual researchers and multi-effort research projects. However, these efforts take a very long time, from the development stage to implementation by regulatory agencies.

Possible solutions to this were suggested, including the development of screening tools that utilize artificial intelligence and in silico prediction. Moreover, the development of screening tools that are not to be validated by the OECD was suggested – tools that could be used by companies already at the stage of chemical development, before they are accepted to be used by chemical assessment agencies. This would also help the screening in countries where government chemical assessment agencies do not exist. The suggested safety evaluation during the manufacturing process would be similar to what is already done by the pharmaceutical industry when they conduct case studies.

This connects with the next topic raised, which concerns who bears responsibility for the detrimental effects produced after exposure to environmental chemicals, the costs of which are, in the end, paid by society and governments, which need to cope with the burden of diseases. The point was raised that manufacturing companies should bear responsibility for these effects (in a lifetime perspective and transgenerationally) and should be proactive in preventing them. We should move forward as a society towards that aim, beginning by encouraging industry-academia partnerships for the development and utilization of early screening methods, promoting political pressure for legislation that recognizes the responsibility of the manufacturers, and ultimately, advancing towards financial compensation for the detrimental consequences of chemical exposures.

In a globalized world, however, the problem extends beyond country borders. Although countries may regulate (to different levels) the production and import of chemicals in/to their markets, thus far, no country or economic zone has developed regulations on the chemicals contained in imported, already manufactured products. For instance, even though Europe has

banned using BPA to make baby bottles, nothing prevents an individual from importing a baby bottle containing BPA from countries outside Europe.

Discussion related to Q2

One of the main problems related to effectively communicating the dangers of environmental exposures, in order to mitigate their effects on the population, is to establish their causality in relation to metabolic disorders, particularly considering that some countries are very cautious about communicating risks to the population. Although the 'weight of evidence' approach would be ideal, using this method for every substance would require considerable time, at the same time as there is an urgent need to speed up the identification of these health hazards, to regulate their production, and to reduce the number of dangerous chemicals in consumer products.

One option proposed to create public awareness and protection against suspected EDCs was to label products with warning statements such as 'This product may contain EDCs'. Importantly, communication of the risks of EDCs should be strategic and done with caution to ensure that no blame be placed on specific societal groups, for example, pregnant women, given the important developmental component of metabolic disruption. The development and commercialization of tests that could indicate individuals' personal levels of exposure to compounds that are known or suspected to be metabolic disruptors would also help the population gain awareness about their levels of exposure.

To translate science to policy, scientists should rely more on the communication power of scientific societies, for example, the Endocrine Society. Additionally, scientists should bring the topic of EDC-induced metabolic disruption to international organizations, such as to WHO or European Food Safety Authority (EFSA) committees in which they participate as well as to meetings with policymakers.

Discussion related to Q3

An important communication venue raised in the discussion was to inform the general population of the dangers of metabolic disruptors via medical practitioners, whose opinions and advice are generally highly regarded by the general population. However, there was agreement among participants that, across countries, bachelor's level education for medical doctors lacks curriculum content in relation to environmentally-induced diseases. This prevents proper dissemination of information on the problem from medical practitioners to patients. Therefore, inclusion of courses on the health effects of environmental exposures in the curriculum for medical practitioners is greatly needed, as they should have updated information when informing patients about the health risks of environmental exposures. This would involve researchers creating courses geared towards medical practitioners, including doctors, nurses and nutritionists, both when they are bachelor students as well as practitioners undergoing specialization.

It is nevertheless challenging to condense all the information available into clear and straightforward recommendations that could be shared with patients. Additionally, life stage differences should be considered for such recommendations, as they may vary for pregnant women, fetuses, breast-feeding babies, toddlers, adolescents, adults, and people with specific conditions (e.g., cardiovascular diseases, cancers). Importantly, the ability of these detrimental health effects to be transgenerationally transmitted should also be considered. All in all, due to the programming nature of metabolic diseases, childhood should be a priority period for an integral health and environmental assessment as well as intervention. In order to assess the risk of exposures, the participants were in general agreement that the elaboration of standardized and scientific questionnaires would be beneficial. It is important to point out that private individuals offering environmental assessment services already employ questionnaires, however these are not formulated by scientists. The suggested questionnaires should be accompanied by guidelines, also created based on scientific knowledge, to help guide medical practitioners' decisions concerning how patients can prevent their particular environmental exposures. However, for all of this to occur, the scientific community needs to agree on the levels of different exposures that would be considered of low risk (baseline) or harmful. This was one of the points most agreed upon by participants.

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