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Food packaging and migration of food contact materials: Will epidemiologists rise to the neotoxic challenge?

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In the early 1990s, several groups of scientists –including epidemiologists and pneumologists– began to publish a series of prospective studies reporting increased incidence of cardiovascular diseases in human populations associated with exposure to low levels of airborne particles [1, 2]. Prior to these publications, toxicological studies had primarily focused on pulmonary effects of particulates in laboratory animals—and the results from those studies indicated that real-world air pollution levels in many places were too low to cause harm to humans. This created something of a paradox, seemingly: epidemiologists finding adverse effects whose biological mechanisms were not apparent at the time. Over the next several years, the epidemiological and clinical evidence on cardiovascular effects associated with particulates increased [2], leading to the design of toxicological and other laboratory studies aiming to understand mechanisms of the effect of particulates on the cardiovascular system. Epidemiological data challenged assumptions and furthered knowledge about the mechanisms of toxicity. And ultimately the toxicologists began asking and answering different questions. Laboratory and population studies were enriching each other, as they should. As a result, we now have a good understanding of cardiovascular risks from particulates, and corresponding policies and regulation addressing the protection of citizens from air pollution [3-5].

Food contact materials and human health: a new challenge for epidemiological research

As ubiquitous as particulate air pollution (or more), but until recently with a much lower profile, food contact materials (FCMs) have long posed a silent challenge to researchers concerned with human health, nutrition, and the environment. FCMs are articles used in packaging, food storage, processing or preparation equipment that directly come into contact with human aliments. Most often FCMs are made of plastic or have a synthetic material in direct contact with the foodstuff; for example, as can coating, laminate in beverage cartons or the closures of glass jars. Importantly, most FCMs are not inert. Chemicals contained in the FCM, like monomers, additives, processing aids or reaction by-products, can diffuse into foods [6, 7]. Known as *migration*, this chemical diffusion is accelerated by increased temperatures and depends on storage time, chemical properties of the FCM and the foodstuff, as well as on the physical characteristics of the FCM (pore size, thickness, and surface area) [6, 7]. Some, but not all FCM migrants, are regulated, for example as *indirect food additives* (in the US).

FCMs are a significant source for chemical food contamination [8, 9], although legally they are not considered as contaminants. As a result, humans consuming packaged or processed foods are chronically exposed to synthetic chemicals at low levels throughout their lives [10], including the most sensitive periods of development. These facts may be of relevance to scientists interested in the developmental origins of health and disease hypothesis (DOHaD), life-course effects of in-utero and childhood environmental exposures, plasticity, epigenetics, and related processes [4,

11-18]. As such, FCMs are a novel exposure source in the sense that they have received little attention so far in studies concerned with human health effects. Their integration into epidemiological and non-epidemiological research is highly relevant. The current dearth of epidemiological publications on FCMs is surely not justified on scientific grounds.

Lifelong, low-dose exposure to FCM is of concern for several reasons. Firstly, acknowledged toxicants are legally used in FCMs in Europe, the US and other regions (notably, China). In the US, several types of asbestos are authorized as indirect food additives for use in rubber [19]. Formaldehyde, another known carcinogen, is widely present at low levels in plastic bottles made of polyethylene terephthalate (PET) [20]; formaldehyde also migrates from melamine formaldehyde tableware [21]. Considering how widely beverages are consumed from PET soda bottles, this may amount to a significant, yet unrecognized exposure of the population.

Secondly, numerous controversially discussed chemicals are present in FCMs. Several of these are endocrine disrupting chemicals (EDCs) [22-24]. For example the EDCs nonylphenol, bisphenol A, tributyltin, triclosan and several different phthalates [25-28] are legally and intentionally used in FCMs in Europe or the US. Whereas for some of these substances the science is being debated and policy makers struggle to satisfy needs of stakeholders, consumers remain exposed to these chemicals on a daily basis, mostly unknowingly.

Thirdly, the total number of known chemical substances intentionally used in FCMs exceeds 4,000 [29, 30]; in addition, FCMs also contain an unknown number of polymerization by-products, impurities and break down compounds [7, 31]—collectively known as Non-Intentionally Added Substances (NIAS). Improvements in analytical chemistry have led to the constant reduction of detection limits, thereby revealing the presence of NIAS migration into food [7, 32, 33].

Given the low levels of toxicants generally found in foods, the difficulty of analyzing chemicals in a complex food matrix, and the considerable effort that analytical method development requires, it is not surprising that little is known about most NIAS. Especially, their toxicological hazards often remain unknown, while both industry and regulators are struggling to ensure safety of marketed products using exposure assessment and chemical risk assessment concepts on unknown compounds [34]. FCMs are another relevant source of widespread exposure to chemical mixtures.

At the same time, chemical risk assessment is being challenged by several recent scientific findings addressing chemical toxicity:

EDCs mimic hormones' property to affect biological systems at low doses, thus causing subtle changes that may lead to adverse effects at later stages in life [26, 27, 35, 36]. Research on the DOHaD has revealed the fragility of early life stages to chemical exposures [14, 17, 37, 38]. A consequence of such exposure in the womb can be chronic disease later in life. Furthermore, the observed effects may follow non-monotonic dose-response curves, thereby defying current practices of testing at high doses to extrapolate to the low doses of actual exposure [35]. What is more, EDC-induced physiological changes are not on the radar of common toxicology, which casts serious doubts about the adequacy of current chemical regulatory procedures [36, 39, 40]. We therefore propose to call EDC effects *neotoxic*, thereby capturing their unique properties, mechanisms of action and effects, as well as the obligation to think outside traditional mechanistic and risk assessment paradigms when addressing chemical risk. Accordingly, neotoxicants are synthetic chemicals that cause adverse effects through mechanisms different from those commonly tested by traditional toxicology, and which have been introduced into the anthroposphere through industrialization and weak global regulation.

Chemicals targeting the same site of action are known for their ability to act additively when present in mixtures [41, 42]. Current chemical risk assessment practices assume that there is a threshold for exposure to an individual chemical below which the chemical's toxicity is considered unproblematic. In Europe, chemical migration from FCMs into food resulting in levels below 10 ppb is not considered toxicologically relevant [43]. For some reason, it is also assumed to be clinically irrelevant. However, humans are not exposed to single chemicals in isolation. Especially for FCMs, many different substances migrate, but are not necessarily detected [44]. In fact, several studies have shown that the total toxicity of all migrates from a given FCM in *in vitro* assays cannot be fully explained by the known/identified migrants [45, 46].

Establishing causality between lifelong (and largely invisible) exposure to FCMs and human chronic diseases is challenging for several reasons, including the fact that reference populations completely unexposed to FCM are generally inexistent—everybody is exposed to synthetic chemicals from FCMs, usually at low doses. What is more, large inter-individual and social differences in internal concentrations of food contact substances may exist in most populations, as it is the case for commonly detected environmental contaminants in foods and people [47-49]. Progress is thus urgently needed in population-based exposure assessment and biomonitoring of FCMs. It is a major challenge −for epidemiology, toxicology and other health and life sciences− to tease out the actual cause-effect relationships between food contact chemicals and chronic diseases like cancer, obesity, diabetes and neurological and inflammatory disorders [13, 16, 17].

Epidemiology can contribute to improving knowledge on the role of food contact chemicals in diseases of complex etiology

In the developed world chronic diseases are responsible for around 2/3 of deaths, with about 16% of deaths occurring before age 60 [50]. While most chronic, non-communicable diseases are rightly considered "diseases of complex etiology" (and, therefore, have multiple causes), there is strong evidence linking these disorders with chronic exposure to environmental pollutants [26, 51]. The World Health Organization and the United Nations Environment Programme (UNEP) recently concluded in their 2012 State of the Science on Endocrine Disrupting Chemicals report that EDCs are a global public health threat [50]. EDCs and other neotoxicants are commonly used or present in FCMs [22-24]; their safety for this use often has not been established [52]. The direct health consequences of this exposure to neotoxicants via FCMs are currently unknown. Considering that today most foods are packaged [53] and the entire population is likely to be exposed, it is of utmost importance that current knowledge gaps are reliably and rapidly filled.

Unraveling the role of FCMs in the development of chronic disease is of high scientific and public interest. In contrast to other challenges in nutritional and environmental epidemiology, chemical exposures from FCMs offer the benefit of a fairly discrete and measurable route of exposure. Methodological progress is feasible. We propose, specifically, that in addition to using Food Frequency Questionnaires and other dietary assessment methods (dietary intake records, 24-hour recalls) and technologies [54], dietary habits should additionally be characterized according to FCMs, and supplemented by biomonitoring efforts. Such task will include analyses of the uses of materials in contact with food throughout the food supply chain (processing, packaging, storage), and food packaging in stores, at home, the workplace and other settings. Furthermore, studies should also measure − through validated instruments and procedures − the frequency of consumer practices such as storage in freezers, heating foods in plastic dishes and containers, use of plastic films, as well as packaging preferences when buying foods and beverages (e.g., higher or lower preference for unpackaged foods, glass, cans and plastic packages). In Europe, for example, the FACET database can support such efforts: this newly established database from the EU-funded research project *Flavorings, Additives and Food Contact Materials Exposure Task* (FACET) contains levels of food packaging migrants from FCM and links them with food consumption data [55, 56]. Subsequently, statistical analyses would integrate these types of information with data traditionally used in nutritional, environmental and molecular epidemiology.

Innovative research could also expand knowledge on toxic mechanisms; e.g., on estrogenic, androgenic, thyroid, and glucocorticoid effects of chemicals migrating from FCMs; on the homeostasis of glucose and lipid metabolism, energy homeostasis, and insulin resistance; on the

role of agonists and antagonists of nuclear receptors in modulation of nuclear receptor function and endocrine diseases, including non-nuclear steroid membrane receptors and non-steroid receptors; on metabolic and mitochondrial dysfunction, inflammation, adipogenesis and adipose macrophages [12-14, 16, 17, 26-28, 35, 36, 41, 42, 57].

Also, given the economic and cultural influences on food consumption, social epidemiology should develop a research agenda on FCMs, health and wellbeing.

Integrating knowledge about FCM chemical composition and migration into food in epidemiological studies is in our view an opportunity and a duty for the epidemiological research community. Eventually, such research will strengthen primary prevention policies by reducing chemical exposures resulting from a manageable source. It will also advance basic and applied knowledge on the molecular and physiological mechanisms that link some environmental chemicals and human diseases.

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