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Review

Food contact materials and gut health: Implications for toxicity assessment and relevance of high molecular weight migrants

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A B S T R A C T

Gut health is determined by an intact epithelial barrier and balanced gut microbiota, both involved in the regulation of immune responses in the gut. Disruption of this system contributes to the etiology of various non-communicable diseases, including intestinal, metabolic, and autoimmune disorders. Studies suggest that some direct food additives, but also some food contaminants, such as pesticide residues and substances migrating from food contact materials (FCMs), may adversely affect the gut barrier or gut microbiota. Here, we focus on gut-related effects of FCM-relevant substances (e.g. surfactants, N-ring containing substances, nanoparticles, and antimicrobials) and show that gut health is an underappreciated target in the toxicity assessment of FCMs. Understanding FCMs' impact on gut health requires more attention to ensure safety and prevent gut-related chronic diseases. Our review further points to the existence of large population subgroups with an increased intestinal permeability; this may lead to higher uptake of compounds of not only low (<1000 Da) but also high (>1000 Da) molecular weight. We discuss the potential toxicological relevance of high molecular weight compounds in the gut and suggest that the scientific justification for the application of a molecular weight-based cut-off in risk assessment of FCMs should be reevaluated.

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1. Introduction

The gastrointestinal (GI) tract is the first system in the body to be exposed to and affected by the chemicals ingested with food and drinks. Food components, including natural ingredients, as well as additives and contaminants, constitute the main source of chemical agents that can interfere with the structure and function of GI compartments. Among these, the gut, comprised of the small and the large intestine, is subjected to the longest contact times during the intestinal passage of food. The gut is also the major point of uptake of orally delivered chemicals, from where they can be internalized to subsequently interact with other organs and body systems. In the last decade, the biomedical community has witnessed a resurgence of interest in the research on the disruption of gut health and its role in the etiology of several diseases of public concern (Bischoff et al., 2014; Sellers and Morton, 2014; Turner, 2009). The influence of environmental factors, including chemical exposures, is being increasingly recognized as well.

Several types of food ingredients and direct food additives have been demonstrated or suggested to affect gut physiology and health (Csaki, 2011; Lerner and Matthias, 2015; Lewis et al., 1995; Vignal et al., 2016). Gut health may also be affected by food contaminants, including some pesticide residues, mycotoxins, and metals (Akbari et al., 2017; Lu et al., 2015; Sellers and Morton, 2014). Another important source of food contaminants, receiving less attention so far in this regard, is the heterogeneous group of food contact chemicals (FCCs) that can migrate from various food contact materials (FCMs) and articles (FCAs) into food during the production, transport, processing, storage, packing, preparation, and serving (Seltenrich, 2015). FCCs include not only the substances knowingly used during manufacture of FCMs, i.e., intentionally added substances (IAS), but also the so-called non-intentionally added substances (NIAS), such as impurities, reaction by-products, and degradation products (Grob et al., 2010; Nerin et al., 2013). Processed and packaged foods constitute a significant source of human exposure to FCCs (Hartle et al., 2016; Rudel et al., 2011; Zota et al., 2016), and it has been estimated that food contamination due to FCCs may be at least 100 times higher than that due to pesticide residues (Grob et al., 2006).

This review focuses on the question of whether FCCs may interfere with gut health, and, consequently, whether gut health is a relevant endpoint to be considered in the risk assessment of FCCs and FCMs. We will first introduce the crucial aspects of gut health, followed by an overview of studies demonstrating the effects of food additives and contaminants, with a focus on FCCs. We will then discuss the implications of these findings for the safety assessment of FCMs, touching on (i) whether gut-related effects should be explicitly considered in the toxicity assessment of FCMs, and (ii) whether the prevailing assumption that high molecular weight (Mw) compounds are not absorbed in the gut and may be therefore exempt from risk assessment still remains scientifically justified.

2. Crucial aspects of gut health and their role in human diseases

This section focuses on the intestinal permeability, gut microbiota, and their influence on the immune responses occurring in the gut-associated lymphoid tissue (GALT). Proper functioning of this interconnected system is crucial to the maintenance of immune homeostasis (Asselin and Gendron, 2014; Wittkopf et al., 2014), and a disruption of one or more of its components, or of the communication between them, has been implicated in the etiology of several human diseases (Farhadi et al., 2003; Kurashima et al., 2013). Furthermore, it has been suggested that exposures to environmental chemicals, many of them often present in food, are likely to be among the significant contributors to this concerning development, as will be discussed in the next subsections.

2.1. Intestinal permeability, gut microbiota, and immune responses

Gut lumen contains a complex mixture of chemical substances which are delivered with food, secreted by the body's glands, or generated by gut microbiota (see Fig. 1). Gut microbiota is a dynamic community of microorganisms normally inhabiting the colon (large intestine). The resident gut microorganisms perform many functions vital for the health of the human host. For example, they aid digestion and produce essential nutrients such as vitamins and short-chain fatty acids (Andoh, 2016; Louis et al., 2010; Rowland et al., 2017). They also send signals to both closely (e.g., gut (Ulluwishewa et al., 2011), GALT (Macpherson and Uhr, 2004)) and distantly (e.g., brain (Scott et al., 2017)) located organs, influencing their structure and function. Some gut microorganisms are also able to metabolize different xenobiotics introduced with the diet (Lu et al., 2015). These reactions may result not only in detoxification, but also in the appearance of toxic transformation products (Zheng et al., 2013). In this way, gut microbiota may influence bioavailability of a xenobiotic compound and, consequently, its effects on the human host (Claus et al., 2016; Klaassen and Cui, 2015; Li et al., 2016; Snedeker and Hay, 2012). Since food can also be a source of external microorganisms, another function of the resident gut microbiota is to prevent the overgrowth of the potentially pathogenic external flora (Kamada et al., 2013). Thus, healthy gut microbiota contributes to the barrier function of the gut, as it helps to protect the host from both noxious compounds and pathogenic microorganisms. However, although gut microbiota itself is an indispensable component of a healthy gut, the microorganisms need to be kept inside the gut lumen, i.e. “behind the barrier”, because uncontrolled translocation of microorganisms through the gut wall and their contact with the underlying immune system may result in adverse local and even systemic immune reactions (Brenchley and Douek, 2012; Dheer et al., 2016).

Interaction with gut lumen contents allows the organism to assimilate nutrients and to communicate with gut microbiota, but the body must also protect itself from the entry of potentially