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Review article: emulsifiers in the food supply and implications for gastrointestinal disease

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Summary

Background: Dietary emulsifiers are the latest food additives to be associated with intestinal, cardiovascular and metabolic health. Most recently, there are postulations around certain emulsifiers playing a role in the development of Crohn's disease.

Aim: To review the use of food-based emulsifiers, their content in the food supply and mechanisms by which they might exert potentially detrimental biological effects.

Methods: Information on emulsifiers and thickeners relevant to human health was critically examined.

Results: The term, "emulsifier," has been used loosely and has included thickeners as well as agents that truly promote emulsions. These comprise proteins, phospholipids and carbohydrates, alone or in combination, and play roles in optimising food appearance, texture and mouthfeel, delivering or disguising flavours and achieving palatable low-fat foods. Their presence in the food supply is common, but not "ubiquitous" as frequently stated. Strict regulations limit the amount added to foods, but the lack of established methodologies to measure the actual food content of these diverse compounds limits our knowledge of consumption. Emulsifiers and thickeners have effects on the gut microbiota, mucosal barrier and inflammatory pathways, and can induce disease in experimental models. However, differentiating pharmacological from physiological effects and translating findings in experimental animals to humans raise uncertainties about the relevance of such effects.

Conclusions: There is limited evidence to directly link emulsifiers and thickeners to human disease, but multiple potential pathogenic mechanisms. Knowledge of actual dietary intake and high-quality interventional studies is needed to enable the risks associated with their intake to be understood.

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1 | INTRODUCTION

The latest class of food additives to receive poor press are emulsifiers, due to the association of their ingestion with inflammatory bowel disease, specifically Crohn's disease, as well as cardiovascular and metabolic disease, as shown in epidemiological, animal and laboratory studies. For example, polysorbates affect permeability of cell lines in culture,[1] promote translocation of *Escherichia coli* across ileal epithelium and M cells in vitro,[2] and induce intestinal inflammation and metabolic syndrome in susceptible mice.[3] An epidemiological study associated increased use of dishwashers, which would reduce residual detergent on utensils and plates, with falling cardiovascular disease in UK.[4] However, several difficulties arise in understanding the potential role of emulsifiers in disease pathogenesis. These include inconsistencies in what is called an "emulsifier," limitations in our knowledge of the disposition and pharmacokinetics of emulsifiers after ingestion, and the commonly quoted statement that emulsifiers are "ubiquitous" in our food supply. The current review attempts to address multiple issues of relevance to the understanding of potential links of emulsifiers with disease.

2 | CONCEPT OF EMULSIONS AND THEIR VALUE IN FOOD

An emulsion describes a mixture of at least two immiscible liquids, in which small droplets of one liquid are dispersed within the other.[5,6] Emulsions are an integral part of many foods eaten and the liquids typically involved are oil and water. There are different types of emulsions as illustrated in Figure 1. When oil droplets are dispersed (the "dispersed" phase) into water (the "continuous" phase), the emulsion is called an *oil-in-water* (O/W) emulsion; examples include milk, mayonnaise, cream, dressings, sauces and soups.[6] When water droplets are dispersed in oil, this is referred to as a *water-in-oil* (W/O) emulsion, with margarine and butter being common examples.[6] *Multiple emulsions* are produced by multi-layering, usually involving W/O/W in food (Figure 1).

The principles of generating and stabilising emulsions of two immiscible liquids are illustrated in Figure 1 with high-speed homogenisation, disruptive forces are applied to the liquids causing small droplets to form.[6] However, the droplets within emulsions are often different specific gravity to the continuous phase and can separate by gravitational forces leading to creaming or sedimentation. The drops are also constantly moving and colliding with one another, with a consequence that they can flocculate, a process of aggregation into three-dimensional structures, or they can coalesce with their neighbours (also called "Ostwald ripening") (Figure 1). An example of the latter is the loss of creamy consistency of ice cream that has been frozen for a long time. It is, however, possible to form emulsions that will remain stable for an extended period of time by using substances known as *stabilisers*, a collective term describing agents with different modes of actions. Such agents include emulsifiers, texture modifiers and weighting agents, each of which increase the kinetic stability of emulsions via a different mechanism[6] (Figure 1).

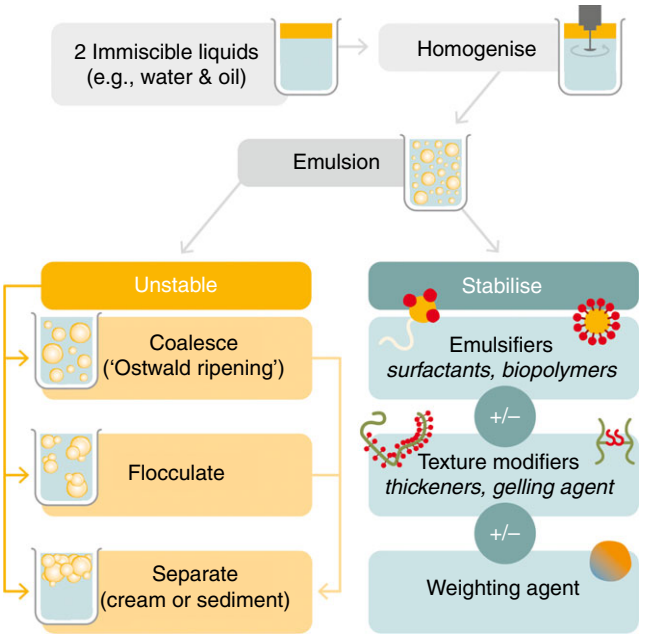

FIGURE 1 Schematic of the creation and fate of emulsions. Most emulsions are unstable, leading to coalesce, flocculate or separate. Emulsions can be stabilised by addition of emulsifiers, texture modifiers and/or weighting agents. Emulsifiers adsorb to droplet surface and stop aggregation, texture modifiers increase viscosity and weighting agents set oil droplets to the same specific gravity as water

2.1 | Emulsifiers

In order to function as an emulsifier, a substance must have the ability to adsorb to the surface of droplets as they are formed during homogenisation and thereby protect them from aggregating with their neighbours.[6,7] In an O/W emulsion, an emulsifier would need to have surface activity at the oil-water interface in order to have this functionality. Most emulsifiers are amphiphilic molecules (ie, having both hydrophilic and hydrophobic parts) capable of adsorbing to an oil-water interface.[6] They not only enhance the stability of emulsions by protecting emulsion droplets from aggregation, but also assist in the formation of emulsions by reducing interfacial tension during homogenisation.[6,8] Emulsifiers can be broadly divided into two subcategories[6]—surfactants and amphiphilic biopolymers—and are described in Table 1:

1. *Surfactants:* They consist of a hydrophilic "head" or polar group and a lipophilic "tail" group.[8] The head group may be anionic, cationic, zwitterionic (ie amphoteric) or nonionic.[6,8] Surfactant molecules adsorb to oil-water interfaces with the hydrophilic end located in the aqueous phase and the hydrophobic/lipophilic end located in the oil phase.[8] Surfactants help to prevent aggregation of droplets by producing repulsive force between droplets.
2. *Amphiphilic biopolymers:* Some biopolymers are also surface-active as they are amphiphilic,[7] and may be proteins, polysaccharides or protein-polysaccharide complexes. Naturally-occurring surface-active proteins (such as egg or casein) were the first emulsifiers

TABLE 1 Substances commonly used to stabilise emulsions in food and beverages

Substance	Class	Description	Examples	E number
Emulsifiers—surfactants	Nonionic	No charge at its hydrophilic head	• Mono- and di-glycerides of fatty acids	• 471
			• Monoglyceride esters (acetic acid, lactic acid, succinic acid)	• 472a, 472b, 472f, 363
			• FA esters (polyglycerol, propylene glycol, sucrose)	• 473, 475, 476, 1520
			• Ethoxylated sorbitan esters (polysorbates (Tween) 20, 60, 65, 80)	• 432, 433, 435, 436
			• Sorbitan esters (Span)	• 491-495
	Anionic	Contains negatively charged functional group at the hydrophilic head	• FA salts - sodium stearoyl lactylate, calcium stearoyl lactylate	• 481, 482
			• MG esters - citric acid diacetyl tartaric acid	• 472c, 472e
	Cationic	Contains positively charged functional group at the hydrophilic head	• Lauroyl arginate	• 243
	Zwitterionic (amphoteric)	Contains a hydrophilic head with two oppositely charged groups	• Lecithin	• 322
			• Lysolecithin	• No E number
Emulsifiers—amphiphilic biopolymers	Proteins	Forming viscoelastic absorbed layer	• Milk (casein, whey) • Meat and fish (eg, gelatin) • Egg • Plants (eg, soy protein)	—
	Protein-polysaccharide complexes	Protein-polysaccharide ratio forms viscoelastic properties	• Gum arabic	• 414
			• Xanthan gum	• 415
	Polysaccharides[a]	High viscosity & prevents oil droplets from coalescing	• Some pectins (eg, acetylated pectin from sugar beet, depolymerised citrus pectin)	• 440
			• Galactomannans (eg, guar gum)	• 412
			• Modified starches	• 1400-1500
			• Modified celluloses (eg, methylcellulose)	• 460-469
Texture modifiers	Thickening & gelling agents	Increases viscosity by reducing rate of sedimentation or forming a gel	• Modified celluloses[a] (eg, carboxymethylcellulose, hydroxypropyl, methylcellulose, hydroxypropyl cellulose)	• 466, 463, 464
			• Pectin[a], guar gum[a], xanthan gum[a]	• 440, 412, 415
			• Agar, gelatin[b], casein[b]	• 406
			• Carrageenan	• 407
Weighting agents		Increases the specific gravity of oils to prevent separating from other components, usually in nonalcoholic beverages	• Sucrose acetate isobutyrate	• 444

[a]Surface activity may be due to presence of protein contaminants.
[b]Can be classified as both texture modifiers and emulsifiers.[6,7]

utilised in the food industry,[8] and proteins extracted from milk, meat, fish, eggs or plants are all still commonly used in the food industry to this day.[6] There is controversy over polysaccharides as emulsifying agents. In general, polysaccharides are not surface-active, but stabilise emulsions via modifying texture. However, some have clear demonstration of surface activity whereas its origin in others, such as gum arabic and xanthan gum, may be from protein contaminants or proteins covalently bound to the polysaccharide backbone.[6,7] Other polysaccharides, such as carrageenan, may be poorly surface-active when used alone,[9] but can be added to proteins to improve their emulsifying activity.[7,10]

2.2 | Texture modifiers

Texture modifiers stabilise emulsions by increasing the viscosity of the continuous (aqueous) phase, which reduces the rate at which particles

sediment, cream or form a gel. In that way, they can be even more effective than surfactants or proteins in conferring long-term stability on emulsions.[7] They can also alter the texture or mouthfeels of food products.[6] These may be thickening agents that act via its large molecular dimension (see Table 1) or gelling agents that increase viscosity or form gels because of intermolecular cross-links.

2.3 | Weighting agents

Weighting agents balance the densities of the dispersed and continuous phases. The most common agent used is sucrose acetate isobutyrate that increases the specific gravity of the flavouring oils used in citrus beverages and prevents those oils separating from other beverage components and rising to the surface.

2.4 | Food value of emulsions

The production of stable emulsions in the food industry is important for many reasons, some of which are outlined in Table 2.

2.5 | Gastrointestinal fate of emulsifiers and thickeners

Knowledge of the fate of emulsifiers and thickeners in the gastrointestinal tract is critical to understanding their possible role in disease pathogenesis.

2.5.1 | Surfactant emulsifiers

Nearly all the surfactant-type emulsifiers have a fatty acid nonpolar region with a hydrophilic head. Using polysorbates as the model for such emulsifiers, the fatty acid component is digested via the standard fat digestion mechanisms in the upper gut and the vast majority will be degraded. The polar head is released in an inert form and the vast majority of this will pass through the gastrointestinal tract without being absorbed or metabolised. However, this is not true for all surfactants. Choline released from digestion of phosphatidylcholine as part of lecithin is metabolised by intestinal bacteria to produce trimethylamine, which is absorbed (further discussed under Potential Mechanisms for Disease Pathogenesis). Data on the fate of many emulsifiers are not readily available.

2.5.2 | Amphiphilic biopolymers

Proteins used as emulsifiers (such as whey or casein) will be digested via the proteolytic enzymatic mechanisms in the stomach and duodenum. The polysaccharide emulsifiers are generally indigestible (no suitable small intestinal hydrolases) and hence will be delivered to the colon largely intact. However, as outlined above, the surface activity of most may well reside in bound or contaminating proteins, which would also be subject to normal protein digestion. Thus, the emulsifying action would be destroyed in the small intestine.

2.5.3 | Thickeners and gelling agents

Most thickening agents are nonstarch polysaccharides (NSPs) that are indigestible. Some, such as guar gum, will be fermented by the gut microbiota and others, such as carrageenan and modified celluloses, are not degraded and will remain present in the intestinal lumen throughout their gastrointestinal transit. These NSPs are likely to be able to enter the mucous layer, particularly those that are more readily hydrated. Carboxymethylcellulose (CMC) has received considerable attention because of this property and its consequent ability to alter functional properties of the mucus (discussed later). The ability to make gels (ie, gelling agents) is shared by proteins (such as gelatin), which will be digested in the proximal gastrointestinal tract, and some polysaccharides such as carrageenan.

2.5.4 | Weighting agents

Sucrose acetate isobutyrate has been used for decades in citrus beverages and has been studied in various animal models and humans. It is extensively metabolised within the gastrointestinal tract mostly to sucrose and acylated sucrose.

3 | KNOWLEDGE OF STABILISERS IN THE FOOD SUPPLY

3.1 | Stabilisers used

Emulsifiers and thickeners are naturally occurring in foods, as those found in eggs, meat and milk, but are also food additives. Recent evaluation of manufactured food in the US have shown that the seven most commonly used additive emulsifiers and thickeners are: CMC, polysorbate 80, lecithin, mono- and diglycerides of fatty acids, stearoyl lactylates, sucrose esters and polyglycerol polyricinoleate. Of these, lecithin and mono- and diglycerides are the two most widely used, with estimated intakes of 55 and 80 mg/kg/body weight (bw) day, respectively, compared to only 8 mg/kg/bw day of polysorbate 80.[11] While it has not been formally assessed elsewhere, these also appear to be the most commonly found emulsifiers and thickeners in Australia and the UK. While it may be assumed that such consumption has increased with the influx of manufactured foods over the past century, the US dietary exposure seems not to have changed over the past 10 years.[11]

3.2 | Identification and safety of stabilisers

In Europe, the UK, Australia and New Zealand, food additives are designated a number by the International Numbering System, which is defined by the Codex Alimentarius. These numbers may be used in place of the actual food additive name on food packaging. Most stabilisers are allocated an International Numbering System number 400-499, with some exceptions that sit outside that range, including lecithins (examples in Table 1). While food additive descriptions are

TABLE 2 Some uses and techniques in which emulsions are of value in the food industry

Technique of using emulsions	Food value
Enhance the appearance of the product by avoiding separation and other manifestations of instability	eg, A mayonnaise in which the oil and water separate would be unattractive to buy and use in food preparation. Shelf life may be enhanced
Improve the organoleptic characteristics (ie, taste, colour, odour and mouthfeel) of food	An essential part of the food experience
Use multiple emulsion techniques to control the release of or protect labile ingredients	Encapsulate unpleasant aroma and/or bioactive compounds and sensitive food components to improve nutritional value
Replace O/W emulsions with W/O/W so that the oil content is reduced without affecting the physical characteristics of the product	Produce low-fat emulsions without affecting the mouthfeel of the full-fat equivalent

stipulated by this European numbering system, each national regulatory agency use their own method of enforcing additive identification on labels and assessment of safety. For example, in many European countries, food manufacturers may use a previously unused food additive until the appropriate regulatory agency assesses its safety and determines whether it is to be placed on a "banned list". In contrast, Food Standards Australia New Zealand (FSANZ) must approve additives before use and generally follows the safety assessments completed by the Joint FAO/WHO Expert Committee on Food Additives, although may also complete their own assessments. In the US, the Food and Drug Administration (FDA) regulates food additives independently and all food additives must obtain their premarket approval. The only exemptions are additives termed "Generally Recognised As Safe" (GRAS), a list of food substances established in 1958 and deemed as such by an expert committee. Both CMC and lecithin are GRAS, but additives have been removed from the list if subsequently shown to be unsafe. Regulatory agencies require that the minimum amount of substance that is necessary to achieve the technical effect is used, although it is unclear how this is determined for each additive. In Australia, identification of emulsifiers is compulsory, except if present within a compound ingredient (ie, an ingredient made up of at least two ingredients) that constitutes less than 5% of the final product and does not provide a technological function, as decided by the manufacturing company. The US and European standards are very similar. Hence, additive emulsifiers present as a small ingredient may not be identified on ingredients lists. An example of this is the case of the aforementioned citrus soft drinks that use stabilisers as a weighting agent. Indeed, many citrus soft drinks do not have additive stabilisers listed on their ingredients lists, yet the flavour remains stable and evenly dispersed through the bottle.

Most emulsifiers and thickeners have no defined level of toxicity, because the highest dose required to produce an adverse effect is above the level experimental animals can reasonably consume. Acceptance of safety has been thrown into question following the recent publication by Chassaing et al, in which polysorbate 80 and CMC both induced colitis in genetically predisposed mice.[3] Past data investigating the safety of CMC and polysorbate 80 have not indicated any adverse effects, other than diarrhoea and weight loss in rats fed polysorbate 80 for 2 years.[12–15] These rodents were not genetically predisposed to disease, so it is likely that toxicity levels are different for select populations and re-evaluation of emulsifiers previously considered to be safe is required. Mono- and diglycerides have been assessed in animal studies, showing that ingestion of levels of 15% of the diet showed liver enlargement but no significant histopathological change.[16] In humans, it is thought that the likely unwanted effects of mono- and diglycerides are from increasing long-chain saturated fatty acids.[16] For lecithin, no adverse effects have been seen in acute toxicity studies in animals provided both orally or parentally.[16] No human studies have been conducted as it is considered that the clinical experience of lecithin is sufficient proof of safety. The weighting agent, sucrose acetate isobutyrate, has been studied in detail and no known toxicity, although, in dogs, has reversible hepatic effects.[17]

3.3 | Food composition of stabilisers

Various stabilisers may be used in food depending on their characteristics. For example, they may be used to keep the oil mixed in salad dressings and nut butters, or to help incorporate fat into the dough of baked goods. Emulsifiers and thickeners are added to many manufactured foods, but the six main food categories where they are generally present include breads and other baked goods, fat spreads, mayonnaises and salad dressings, ice creams and other dairy desserts, confectionery and beverages. Some foods, such as ice cream, will always contain emulsifiers. However, there is generally considerable inconsistency in the presence and type of stabilisers used in manufactured foods, as illustrated in Figure 2. Table 3 describes the common applications of stabilisers within the six food categories.

4 | METHODOLOGIES FOR MEASUREMENT OF STABILISERS

The measurement of the concentration of emulsifiers and thickeners in foods is needed for the purposes of regulation (to ensure compliance to safe limits) and food safety (eg, to ensure degradation products are not present). However, for the purposes of the clinical evaluation of safety during everyday dietary consumption, it is a basic principle that the actual concentration of food substances and the amount being consumed are measured, particularly if the clinical or biological effects of those substances is being assessed. An example of the importance of accurate food characterisation is the analysis of FODMAP content in food, as such data have been critical to the design and subsequent success of a therapeutic diet.

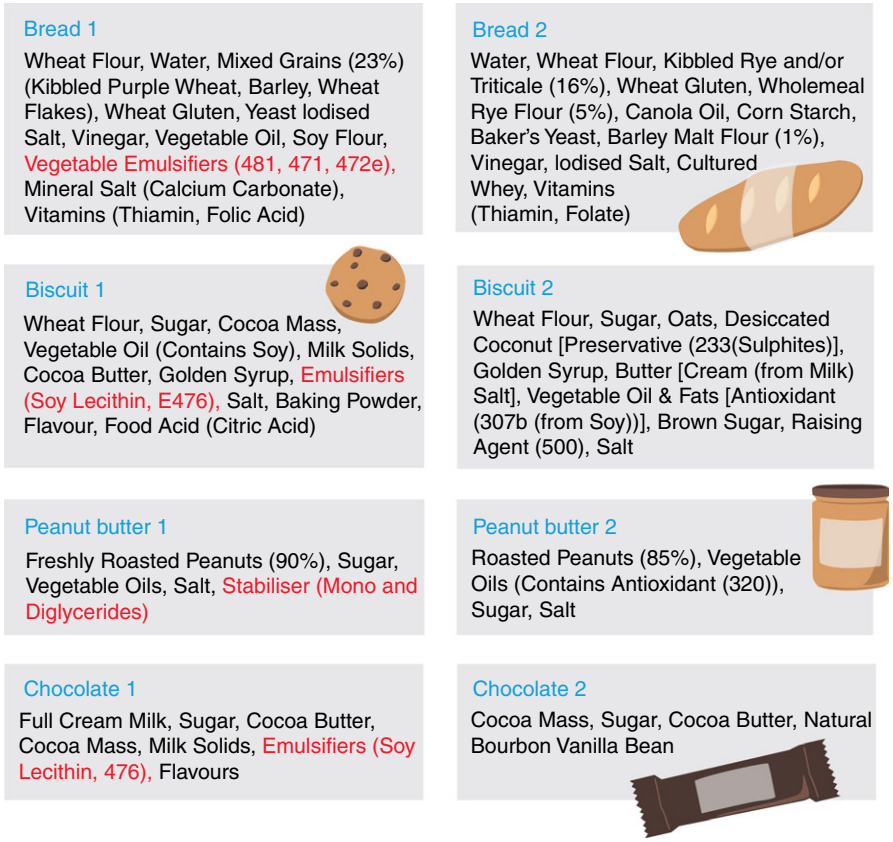

FIGURE 2 Examples of ingredients lists of emulsifier-containing and emulsifier-free food products

Unfortunately, measurement is difficult. The first step involves extraction of fat and the emulsifiers from food, with use of various solvents. Separation of nonlipid emulsifiers within complex matrices, initial separation will also be required using, for example, enzymatic digestion.[8] For polysaccharide thickeners like CMC, extraction involves enzymatic digestion of associated protein followed by a "clean-up" process to separate from other gums like carrageenan.[18]

Multiple detection and quantification methodologies have been applied depending upon the nature of the emulsifier or thickener,[8] but gaining a quantitative catalogue of contents is near impossible for reasons of their diversity, of the methodological challenges associated with individual additives in both their extraction and quantification, and the variability and changeability of their use in the food industry. As an alternative, a specific agent identified in the food label of a food can be assumed to be found at the upper level of its usual range as dictated by safety limits. This method was applied by the Food Drug Administration in one of the few estimates of population intake of specific emulsifiers and thickeners.[11] This imprecise method of estimation is dictated by regulatory limits, which will confound examination of, for example, dose-dependent effects in clinical intervention studies.

5 | POTENTIAL MECHANISMS FOR DISEASE PATHOGENESIS

Four broad mechanisms for disease pathogenesis associated with emulsifying and thickening agents have been described. These are illustrated in Figure 3.

5.1 | Alteration of intestinal mucosal barrier function

The intestinal barrier has multiple components. These include the mucosa-associated microbiota, mucus and its associated anti-microbial contents such as IgA and defensins, the epithelium with its tight junctions and cellular components of both innate and acquired immune system arranged in the intraepithelial compartment, the lamina propria and the mucosa-associated lymphoid tissue. All components are potentially affected by the presence of dietary emulsifiers and thickeners, but dissecting which change is cause and which is effect is challenging.

The ability of the mucus layer to inhibit the movement of molecules and bacteria from the lumen to the epithelium may be reduced by emulsifiers and thickeners. The absorption of phytochemicals such as curcumin can be markedly enhanced by their presentation in micellar form using polysorbate 80.[19–21] Likewise, the absorption of furosemide can be enhanced by the concomitant use of emulsifiers.[22] The thickener, CMC, integrates into the mucus layer by virtue of its very high water-holding capacity. Its other properties of being nonfermentable and not binding bile acids or cholesterol have led to the belief that CMC is harmless in the GI tract.[23,24] However, CMC does appear to support the encroachment of bacteria into the mucus layer as shown by closer proximity of bacteria to the epithelium, small intestinal bacterial overgrowth and mucosal inflammation in genetically susceptible mice.[3,25] Reasons for such effects appear to be a combination of effects on the bacteria (described later) and the microenvironment within which its sits (ie, the mucus layer).

Emulsifiers might also have effects on the cell membranes of the epithelium. Indeed, M cells generated in vitro permitted a marked increase in translocation of *E coli* across them when exposed to low concentrations of polysorbate 80, as did follicular-associated epithelium when human ileal biopsies mounted in Ussing chambers.[2] Whether this represented an effect of the emulsifier on the epithelial cells or on the behaviour of the bacteria was not investigated in this study.

5.2 | Alteration of the functional characteristics of the gut microbiota

The effects of the emulsifiers on cell membranes of bacteria or the provision of specific nutrient groups by thickeners might alter the pathogenicity of specific bacteria and/or change the compositional structure of the microbiota. In the mucosal simulator of the human intestinal microbial ecosystem (M-SHIME), CMC and polysorbate 80 induce increased expression of bioactive flagellin, which increases the ability of the bacteria to penetrate the mucus.[26] CMC seems to do this directly and, therefore, must not be quite as inert as originally thought. While, CMC is not fermented by bacteria, it may still provide carbohydrates to support bacterial growth and/or functional change. This is consistent with the promotion of growth of Neisseria gonorrhoea in tampons impregnated with CMC.[27] Polysorbate 80 appears to have a similar effect on flagellin, but does so in conjunction with other changes to microbial composition.[26]

5.3 | Induction of mucosal inflammation

It is presumed that the mucosal inflammation that is associated with the exposure of emulsifiers and thickening agents in animal models is a direct consequence of the alteration of barrier function and of increased aggressiveness of bacteria with greater translocation. However, some proteins with strong emulsifier activity, such as egg-yolk phosvitin, have direct effects on a macrophage-like cell line by increasing nitric oxide production and increasing phagocytosis in a dose-dependent manner.[28] The in vivo significance of this is unknown. Soybean lecithin, but not milk lecithin, induces increased adiposity and inflammation in mice fed high-fat diets.[29,30] The underlying mechanism of this phenomenon is not understood, but may involve barrier dysfunction since the stimulation by milk lecithin of goblet cells to release mucus is not evident for soybean lecithin. Interestingly, the pro-inflammatory effect of a high-fat diet may relate to the emulsifier content of the fats used.[30]

5.4 | Effects of metabolic products of the agents

The metabolism of polar groups on emulsifying agents potentially may lead to pathogenic molecules that can be absorbed. The known example is lecithin (phosphatidylcholine), which is digested by intestinal lipases to choline-containing nutrients. These can be further metabolised by the intestinal microbiota to trimethylamine, a molecule that is readily absorbed and oxidised in the liver to

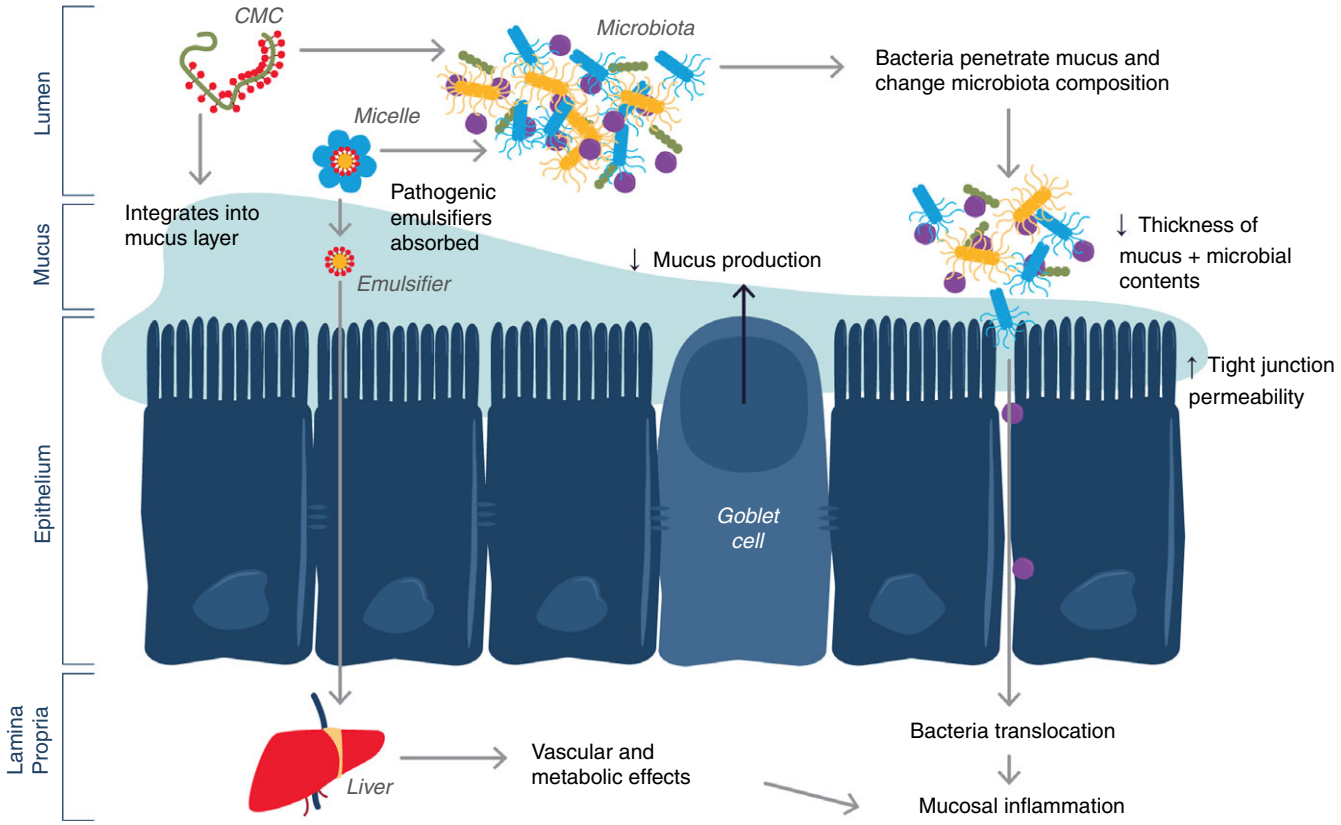

FIGURE 3 Potential pathogenic mechanisms associated with emulsifiers and thickeners

TABLE 3 Description of foods commonly containing emulsifiers and the emulsifier properties

Food category	Food type	Commonly added emulsifier (E number)	Property of stabiliser
Baked goods	Bread	471, 472e, 481, 482	• Strengthening and softening dough for crumb-structure • Retaining moisture for freshness
	Biscuits	472e, 473	
	Cakes	472b, 475	
Fat-based spreads	Margarines	322, 471, 472c, 472b, 475, 476	• Providing stability • Improving spreadability, particularly in low-fat varieties • Optimising whipping • Reducing water content to prevent splattering • Reducing splattering when brought to a high temperature
	Nut butters	471	
	Shortening (solid vegetable-based fat)	322, 471, 472b, 475	
Dairy desserts	Ice cream	471, 432-436, 473	• Enabling aeration of fat, protein, sugars and gum and provide smooth, creamy and fine texture • Reducing rate of melting and reducing freezing time • Incorporating air bubbles into aerated desserts and providing a fine, regular and highly stable air structure that does not collapse • Thickening, gelling and improving mouthfeel
	Other desserts	472a, 472b, 477	
Mayonnaises and salad dressings		405, 415, 322, 471, 472e	• Stabilising the product in place of egg yolk
Confectionery	Caramels, toffees, gummy lollies	471, 473	• Controlling stickiness and improve flavour release • Delaying "bloom," which describes the white spots on the surface of chocolate that commonly develops with time or with temperature fluctuations
	Chocolate	322, 476, 472c, 442, 492	
Beverages	Soft drinks	444	• Contributing to flavour of citrus and kola drinks that remain stable and uniform during varying storage temperatures • Stabilising potassium bitartrate (KHT) stabilisation (tartaric acid crystallisation) • Lengthening shelf life and increasing stability of cream-based liqueurs[33]
	Wine	466	
	Spirits	481, 477	

trimethylamine-N-oxide (TMAO). There is now strong evidence for the direct atherogenic, thrombotic, renotoxic and other effects of TMAO, and its circulating levels are associated with cardiac and metabolic diseases.[31] Such levels are related to the dietary intake of choline-containing nutrients, which in turn influence the functional ability and composition of the microbiota to metabolise choline to trimethamine. While these may be components of essential nutrients (such as L-carnitine in red meat), this example does illustrate the pathogenic potential of metabolites of emulsifiers.

6 | CAVEATS TO CONSIDER

Hypothetical issues that require consideration in the pathogenic capabilities of emulsifying and thickening agents include the following:

1. *The actual amount of emulsifiers and thickeners ingested in the diet is poorly documented:* The content of emulsifiers and thickeners in food is not quantified (see discussion above under "Methodologies for measurement of emulsifiers and thickeners"), but must, by law, be restricted to "safe" concentrations. They are used in food processing to achieve the desired organoleptic effect. One of the few reports of actual dietary intake of common emulsifiers quantified daily intake by assuming food containing emulsifiers had "maximum-use levels".[11] In other words, the published results of daily intake represented the worst-case scenario if the emulsifier concentrations were indeed within the legal limits. Additionally, emulsifiers and thickeners are not always used alone and multiple types are commonly ingested in any one food product or meal. Furthermore, the relationship of the amounts fed to mice or concentrations exposed to cells in vitro in experimental studies to actual exposure is uncertain. The risk that pharmacological rather than physiological effects are being reported has to be seriously considered. Thus, there is a real need for methods to be developed and applied to their accurate quantification within food.
2. *There is no information of the effects of multiple emulsifiers and thickeners:* They may have additive, synergistic or even antagonistic effects, especially given their wide variation of structure of type and differing mechanisms of action.
3. *The behaviour of the agent when ingested independently of an emulsion may be different to that when ingested as an emulsion:* In animal and in vitro studies, emulsifiers or thickeners are given or exposed to cells/tissue other than in an emulsion—usually in the drinking water or dissolved in the culture medium. In vivo, the

fate of the agent used and its behaviour in the gastrointestinal tract may be quite different when ingested in the context of food. A surfactant provided alone will seek lipid and hydrophilic substrates that it would not have had access to if ingested in its bound form. This may be less relevant to thickening agents since their mode of actions in emulsions is very different.

4. *The likely concentration of the agent at sites of potential pathogenicity must be considered:* Most emulsifiers are effectively destroyed by digestive processes in the proximal small intestine and would be unlikely to be present in concentrations that would be pathogenic locally in the more distal intestine. This is particularly the case in the terminal ileum regarding development of Crohn's disease. Thickening agents like CMC and carrageenan are different in that they are not apparently metabolised and so have the potential to have effects all along the gastrointestinal tract.

7 | TRANSLATION TO THE COMMUNITY

Multiple individual food components may have deleterious effects on the gastrointestinal tract when they are tested under experimental conditions outside the context of actual food, as illustrated with emulsifiers and thickeners. This offers the opportunity to utilise such information falsely as scientific proof of their toxicity (ie, so-called pseudoscience) to support campaigns of fear to change eating habits. This approach is concerning but unfortunately common.[32] On the evidence to date, our messages to the community should remain vague and nonspecific due to our limited knowledge of food composition, relevance of various emulsifiers and thickeners on pathogenesis of disease and their role in prevention and therapy. "Common sense" messages that are in line with current recommendations for healthy eating, such as limiting manufactured foods containing additives, will continue to be our general advice until the evidence base for a pathogenic contribution of emulsifiers and thickeners to illness is established and the development of targeted therapeutic diets and subsequently controlled trials performed to better direct us.

8 | CONCLUSIONS

The term, "emulsifier," has been used loosely and has included thickeners as well as agents that truly do promote emulsions. Their presence in the food supply is common, but not "ubiquitous" as frequently stated. Emulsifiers and thickeners comprise a broad range of molecules that include protein, phospholipid and carbohydrates alone or in combination. These agents play important roles in optimising food appearance, texture and mouthfeel not only for foods with the need to prevent overt separation of lipid and water components like mayonnaise, but also for the optimal delivery of flavours and nutrients, and for achieving palatable low-fat foods. There are strict regulations that limit relative content in foods, but the lack of established methodologies to measure the actual food content of these diverse compounds limits the understanding of how much is being consumed within a population or by an individual. There are multiple mechanisms by which emulsifiers and thickeners modulate the biology of the gut microbiota and physiological processes of the human and experimental models in which they induce disease. However, differentiation between pharmacological and physiological effects, and uncertainties of translating phenomena in experimental animals to humans raise uncertainties about the relevance of such effects. Addressing such uncertainties will require better knowledge of actual exposure, an understanding of interactions between individual emulsifiers and thickeners and interventional studies where they are delivered in the real-world context of food examining their physiological and pathophysiological effects in humans.

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