Vitenskapskomiteen for mat og miljø
Norwegian Scientific Committee for Food and Environment

VKM Protocol 2023

Protocol for a scoping review of research on gastrointestinal effects of selected emulsifiers, stabilisers, and thickeners

From the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and Environment

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The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and Environment
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Preparation of the opinion

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to draft the protocol. The project group consisted of VKM members and VKM staff. The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics assessed and approved the final opinion.

Authors of the opinion

The authors have contributed to the opinion in a way that fulfils the authorship principles of VKM (VKM, 2019). The principles reflect the collaborative nature of the work, and the authors have contributed as members of the project group and/or the VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics.

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

Table of Contents

Abbreviations and/or glossary

Abbreviations

ADI	acceptable daily intake
bw	bodyweight
EST	emulsifiers, stabilisers, and thickeners
EU	European Union
GI	gastrointestinal
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
PECO	Population, Exposure, Comparator, Outcome
PES	processed Eucheuma seaweed
RoB	risk of bias

Glossary

Emulsifiers, stabilisers, and thickeners: Food additives that affect the texture of food.

Emulsifier: Food additives preventing liquids that normally don't mix, such as water and oil, from separating. Compounds used as emulsifiers are amphiphilic in nature. In food systems emulsifiers are used to form stable lipid droplets in liquid systems, so called oil-in-water emulsions such as mayonnaise, or to keep water droplets stable in oil-in-water emulsions such as margarine.

Gastrointestinal tract: A tube that is specialized along its length for the sequential processing of food. It consists of a series of hollow organs stretching from the mouth to the anus. including mouth, oropharynx, esophagus, stomach, duodenum, small and large intestines, rectum, and anus (Berne and Levy, 2000; Vander et al., 1990).

The digestive system: is the gastrointestinal tract and the several accessory glands and organs that add secretions to these hollow organs. Included organs and glands are the following: mouth, oropharynx, esophagus, stomach, duodenum, small and large intestines, salivary glands, pancreas, liver, gallbladder, rectum, and anus (Boron and Boulpaep, 2016).

Gastrointestinal tract effects: Include effects on digestion and absorption of food, gastrointestinal tract illness, effects on intestinal microbiota, effects on immune status, and gastrointestinal tract well-being (Bischoff, 2011).

Risk of bias: Systematic errors in the conduct of a study that can lead to misleading results and conclusions.

Scoping review: A type of knowledge synthesis that follows a systematic approach to map evidence on a topic and identify main concepts, theories, sources, and knowledge gaps (Tricco et al., 2018b).

Stabiliser: Food additives that maintain the consistency, texture, and appearance by preventing separation such as creaming or settling of different ingredients in foods. In emulsions, stabilisers prevent the dispersed lipid droplets from rising upward and form a cream layer. In other food systems stabilisers prevent settling of dispersed particles (e.g. settling of cocoa particles in chocolate milk). Stabilisers work similarly to thickeners by increasing the viscosity or gel-like properties of the product.

Thickener: Food additives that increase the viscosity or gel-like properties of the final product.

1 Introduction and aim

1.1 Emulsifiers, stabilisers, and thickeners (EST)

Emulsifiers, stabilisers, and thickeners (EST) are additives that affect the consistency of food, and which are used in a number of foods on the Norwegian market. Emulsifiers facilitate the mixing of water and oil, thickeners increase viscosity or gel-like properties, and stabilisers prevent separation of food constituents due to gravity (precipitation of particles or creaming of lipid droplets in emulsions). Examples of EST are carrageenan (E 407), processed Eucheuma seaweed (E 407a), and sodium carboxymethyl cellulose (E 466).

The European Food Safety Authority (EFSA) has established acceptable daily intakes (ADI) for some EST. However, following publications of studies reporting negative effects of some EST on the gastrointestinal (GI) tract (Bhattacharyya et al., 2017; Chassaing et al., 2022), concerns have been raised regarding the use of these substances. This concern led some Norwegian food manufacturers to reduce the use of certain EST. Possible replacements are agar (E 406), sodium alginate (E 401), gellan gum (E 412), guar gum (E 412), and xanthan gum (E 415). All the above-mentioned food additives are authorised as food additives in the European Union (EU) in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives (Regulation (EC) No 1333/2008).

1.2 Gastrointestinal (GI) tract effects

GI tract effects are diverse in type and extent. Adversity ranges from clinically manifested diseases to symptoms of unknown severity, while examples of positive effects are feeling of well-being and disease prevention. Below is one way of categorising a non-exhaustive list of GI tract effects (Bischoff, 2011):

1. Diagnosed chronic diseases, such as colorectal cancer, food allergy, food intolerance (e.g., coeliac disease) and inflammatory bowel disease (IBD) i.e., Crohn's and ulcerative colitis.
2. GI effects and symptoms, often reversible and without a defined diagnosis, such as nausea, vomiting, diarrhoea and abdominal pain. One or more of these symptoms also include irritable bowel syndrome.
3. (Non-symptomatic) GI alterations such as changes in the microbiota, mechanical barriers, immunity, or fecal biochemical composition.
4. Other effects.

1.3 Aim of the scoping review

The aim of the scoping review is to systematically map literature addressing GI tract effects caused by agar (E 406), sodium alginate (E 401), carrageenan (E 407), processed Eucheuma

seaweed (E 407a), carboxymethyl cellulose (E 466), gellan gum (E 412), guar gum (E 412), and xanthan gum (E 415). The following elements will be addressed:

- The extent and characteristics of the research literature on GI tract effects of the selected EST regarding
    - populations
    - data on exposures
    - comparisons of exposure
    - outcomes
    - study designs
- Study hypotheses
- The extent to which the design and conduct of the studies are likely to have prevented bias (the degree of systematic errors)

2 Methods

We will conduct a scoping review according to the "Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist" (Tricco et al., 2018a). The software EPPI-Reviewer (Thomas, 2022) will be used for the study selection, data extraction, risk of bias evaluation, and the synthesis of findings.

A scoping review is a type of knowledge summary that maps and describes existing literature and research activity on a particular theme. In a scoping review, the evidence on a topic is mapped in a systematic way, and main concepts, theories, sources, and knowledge gaps are identified (Colquhoun et al., 2014; Levac et al., 2010; Tricco et al., 2018b). Scoping reviews are conducted using scientific, systematic, and transparent methods enabling critical appraisal of methods, results, and conclusions. In this way, scoping reviews resemble systematic reviews except that scoping reviews do not synthesise results in a meta-analysis or assess the confidence in the effect estimates for each outcome. Scoping reviews often have a broader scope than systematic reviews and aim to describe the available research literature in a field.

2.1 Eligibility criteria

Studies addressing GI tract effects of agar (E 406), sodium alginate (E 401), gellan gum (E 412), guar gum (E 412), xanthan gum (E 415), carrageenan (E 407), Eucheuma seaweed (E 407a), and carboxymethyl cellulose (E 466) will be included in the scoping review. The eligibility criteria are given in Table 2.1-1.

Table 2.1-1. Eligibility criteria for studies on GI effects.

Population	Humans of all age groups, males, and females Mammals Ex vivo GI tract model systems (human faecal samples)
Exposure	• Oral intake of agar (E 406), sodium alginate (E 401), gellan gum (E 412), guar gum (E 412), xanthan gum (E 415), carrageenan (E 407), Eucheuma seaweed (E 407a), and carboxymethyl cellulose (E 466), tested separately • Dietary sources containing agar (E 406), sodium alginate (E 401), gellan gum (E 412), guar gum (E 412), xanthan gum (E 415), carrageenan (E 407), Eucheuma seaweed (E 407a), and carboxymethyl cellulose (E 466) • The substance tested must be approved for use as food additive in certain foods in Norway/EU
Comparison	Placebo, no treatment, dose comparison
Outcomes	Any GI tract effects, including but not restricted to:

	• Diagnosed chronic diseases, such as colorectal cancer, food allergy, food intolerance (e.g., coeliac disease) and inflammatory bowel disease (IBD) i.e., Crohn's and ulcerative colitis • GI effects and symptoms, often reversible and without a defined diagnosis, such as nausea, vomiting, diarrhoea and abdominal pain. One or more of these symptoms also include irritable bowel syndrome. • (Non-symptomatic) GI alterations such as changes in the microbiota, mechanical barriers, immunity, or fecal biochemical composition • Other effects
Study design	• Human controlled studies • Animal experimental studies • Ex vivo GI tract model studies • Systematic reviews
Publication year	No restriction
Country	No restriction
Language	Danish, English, Norwegian and Swedish

A publication qualifies as a systematic review if 1) a specific research question and the specific criteria used for selecting studies are described, 2) the authors have performed a systematic literature search, and 3) it includes a quality assessment of the selected studies (Lasserson et al., 2022).

2.2 Information sources

We aim to search the electronic databases from MEDLINE (Ovid), Embase (Ovid), and Web of Science from inception to search date. The search strategies will be drafted in cooperation with a research librarian, who will conduct the literature searches.

The electronic database searches will be supplemented by checking reference lists of included studies and searching the web sites of organisations, such as WHO and EFSA.

2.3 Literature search

Research librarian Bente Foss has developed the literature search strategy in collaboration with the project group. We will search the electronic databases MEDLINE (Ovid), Embase (Ovid), and Web of Science. The planned search strategy for MEDLINE (Ovid) is included in Appendix 1.

2.4 Selection of sources of evidence

Authors will independently, in pairs of two, assess 1) titles and abstracts for relevance, and 2) full text articles against eligibility criteria (Table 2.1-1). Disagreements will be resolved by consensus or by consulting a third author.

2.5 Data charting process

The project group will jointly develop and test a data charting form. Authors will extract data from a sample of the included publications to ensure that the data extraction is consistently applied. Discrepancies will be resolved through discussions. If necessary, the data-charting form will be modified. Following calibration of the data extraction, one author will extract the data and a second author will independently check the data extraction for accuracy and completeness. Disagreements will be resolved by consensus or by consulting a third author.

When sufficient data are not reported in a study, we will attempt to obtain them by contacting the corresponding author.

2.6 Data items

2.6.1 Systematic reviews

We will extract the following data on study characteristics of each systematic review:

- authors
- title
- journal
- year of publication
- funding
- reported conflict of interest
- main objective(s), including PECOs (population, exposure, comparator, outcome)
- number and study designs of primary studies included
- years of publication of the studies included (range)
- EST included in the review
- list of the main outcomes/endpoints considered
- list of key findings that relate to the systematic review questions
- the risk of bias tool used

We will extract the following data on details of the primary studies included in the systematic review (information will be extracted from the systematic review):

- the country where the study was conducted
- the year/s the study was conducted
- any stated hypotheses regarding GI tract effects

- population, including number of participants
- exposure, including administration of the substance (in food or tested separately), dose, duration of exposure, and follow-up
- comparison, including placebo, no treatment, dose comparison
- outcomes measured as described in Table 2.1 regarding
    - diagnosed chronic diseases
    - GI symptoms
    - (non-symptomatic) GI alterations
    - other effects
- reported findings regarding effects on the outcomes included in this scoping review

2.6.2 Primary studies

We will extract the following data on study characteristics of each primary study:

- authors
- title
- journal
- country
- year of publication
- funding
- reported conflict of interest
- main objective(s)
- any stated hypotheses regarding GI tract effects
- population, including number
- exposure, including administration of the substance (in food or tested separately), dose, duration of exposure, and follow-up
- comparison, including placebo, no treatment, dose comparison
- outcomes measured as described in Table 2.1-1 regarding
    - diagnosed chronic diseases
    - GI symptoms
    - (non-symptomatic) GI alterations
    - other effects
- reported findings regarding effects on the outcomes included in this scoping review

2.7 Risk of bias

Risk of bias will be evaluated to get an overview of the extent to which the design and conduct of the studies are likely to have prevented bias (the degree of systematic errors).

- Risk of bias will be evaluated for all systematic reviews and human studies.

- Risk of bias will be evaluated for animal studies published in the period 2013 until today. If the number of animal studies is high, the risk of bias evaluation will be limited to a random selection of 25-50% (depending on the total number of identified publications).

The risk of bias evaluation of systematic reviews will be performed using the ROBIS tool (Whiting et al., 2016) whereas the evaluation of primary studies will be performed according to the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (OHAT handbook; (NTP, 2019)).

Authors will independently, in pairs of two, perform the risk of bias evaluation. Disagreements will be resolved by consensus or by consulting a third author.

2.8 Synthesis of findings

We will summarize the charted data to provide information on the body of research on GI tract effects of the selected EST as follows:

- Present the sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage (Page et al., 2021).
- Summarise characteristics of the studies, reporting populations, exposures, comparisons, and outcomes studied within each study design.
- Present the hypotheses addressed according to health outcome.
- Present the overall risk of bias categorisation of included studies.

Text, figures, and tables will be used to present the results. In line with recommendations for scoping reviews we will not conduct any analysis or synthesis of the results identified or assess our confidence in the findings (Tricco et al., 2018b). Using EPPI-reviewer (Thomas, 2022), we will arrange the studies into categories according to study design, the outcomes reported, type of exposure, and study population. At least two authors, independently of each other, will categorise the selected publications. Any disagreements will be resolved by discussion. An overview of the categories is given in Table 2.8-1. The categories will be piloted on a set of the included studies and improved when needed.

Table 2.8-1. Categories that will be used to present the findings. P: postnatal days

Codebook for EPPI-Reviewer – evidence map		
Level 1	***Level 2***	***Level 3***
Type of publication		
Systematic review		
Primary study	Human controlled study	Parallel
		Crossover
	Animal study	
	Ex vivo GI tract model study	
Publication year		

2023		
2022		
2021		
2020		
2019		
2018		
2017		
2016		
2015		
2014		
2013		
2012 or earlier		
Search date, systematic review		
2023		
2022		
2021		
2020		
2019		
2018		
2017		
2016		
2015		
2014		
2013		
2012 or earlier		
Search date not reported		
Population		
Human	**Age**	
	Infant (0-1 y)	
	Toddler (>1-3 y)	
	Children (>3-13)	
	Adolescent (>13-18)	
	Adult (>18-65)	
	Elderly (>65)	
	Not reported	
	Sex	
	F (Female)	
	M (male)	
	M+F	
	Not reported	
	Health status	
	Healthy	
	Not reported	
	Other	

Animal	**Species**	**Age, start of exposure**
	Non-human primates	Infancy (0-12 months)
		Young (1 to 8 years)
		Adult (>8 years)
		Not reported
	Dog (Beagle)	Pre-weaning
		Young (from weaning (~8 weeks) to 3 years)
		Adult (>3 years to 9 years)
		Old (≥9 years)
		Not reported
	Rat	Pre-weaning
		Young (from weaning (~P21) to 5 weeks)
		Adult (≥6 weeks to 18 months)
		Old (≥19 months to 24 months)
		Very old (>24 months)
		Not reported
	Mouse	Pre-weaning
		Young (from weaning (~P21) to 5 weeks)
		Adult (≥6 weeks to 18 months)
		Old (≥19 months to 24 months)
		Very old (>24 months)
		Not reported
	Rabbit	Pre-weaning
		Young (Young (post weaning (~P28) to 1 year)
		Adult (>1 year to 10 years)
		Old (>10 year)
		Not reported
	Guinea pig	Pre-weaning
		Young (Young (post weaning (~P21) to 4 months)
		Adult (>4 months to 14 months)
		Old (>15 months)
		Not reported
	Pig	Pre-weaning
		Young (post weaning 4 weeks) to 6 months)
		Adult (>6 months to 14 months)
		Old (>15 months)
		Not reported
Exposure, substance	**Exposure, administration**	**Exposure, dose**
Agar (E 406)	Single substance	Additional categories may be included, e.g., according to knowledge on the purity of the tested substance and the doses tested
	Food	
Carrageenan (E 407)	Single substance	
	Food	
Eucheuma seaweed (E 407a)	Single substance	
	Food	

Carboxymethyl cellulose (E 466)	Single substance	
	Food	
Sodium alginate (E 401)	Single substance	
	Food	
Gellan gum (E 412)	Single substance	
	Food	
Guar gum (E 412)	Single substance	
	Food	
Xanthan gum (E 415)	Single substance	
	Food	
Exposure, number of doses	**Exposure, duration**	
Single		
Multiple	2 to 7 days	
	8 to 15 days	
	16 days to one month	
	>1 month to 3 months	
	>3 months to 6 months	
	>6 months to 1 year	
	>1 year	
Comparison		
Placebo		
No treatment		
Dose comparison		
Outcome		
Diagnosed chronic disease	Colorectal cancer	
	Food allergy	
	Food intolerance	
	Inflammatory bowel disease	Crohn's
		Ulcerative colitis
GI effects and symptoms	Nausea	
	Vomiting	
	Diarrhoea	
	Abdominal pain	
(Non-symptomatic) GI alterations	Changes in microbiota	
	Mechanical barriers	
	Immunity	
	Faecal biochemical composition	
Other	Other	
Risk of bias		
	Low	

Risk of bias (systematic reviews)	Unclear	
	High	
Risk of bias (primary studies)	Tier 1	
	Tier 2	
	Tier 3	

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Appendix: Literature search

Search strategy for Ovid MEDLINE(R) (1946 to 16.02.2023) is presented below.

Result: 3150 primary studies and 3 systematic reviews

1	**Agar/ or Carrageenan/ or Carboxymethylcellulose Sodium/ or Alginates/**	**36141**
2	(agar or "900-18-0" or "E406" or carr#g?e?n* or "900-07-1" or "E407" or "carboxymethyl cellulose" or carboxymethylcellulose or K679OBS311 or "E466" or "E407a" or processed Eucheuma seaweed? or sodium alginate? or "E412" or gellan gum? or "E412" or guar gum? or xanthan gum? or "E415").tw,kf.	96790
3	1 or 2	113367
4	exp Gastrointestinal Tract/	688300
5	((GI or gastrointestinal or digestive or alimentary or aliment) adj (tract? or tractus or canal?)).tw,kf.	103020
6	4 or 5	759325
7	3 and 6	3943
8	limit 7 to "therapy (maximizes sensitivity)"	1455
9	("randomized controlled trial" or "controlled clinical trial").pt. or (randomized or randomised or randomly or rct or placebo or trial or groups).tw,kf,bt.	3678541
10	8 or (7 and 9)	1685
11	exp Rodentia/ or Mice/ or Animals/ or Rats/ or Rabbits/ or Dogs/ or Haplorhini/ or Swine/ or Guinea Pigs/	7258870
12	("ex vivo" or "exvivo" or cell? or "in vivo" or invivo or mouse or mice or animal? or rat? or rabbit? or dog? or pig? or monkey? or rodent* or leporidae? or haplorhini).tw,kf.	10269866
13	11 or 12	12612573
14	7 and 13	2774
15	10 or 14	3153
16	limit 15 to "reviews (maximizes specificity)"	3
17	Meta-Analysis/ or Network Meta-Analysis/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kf,bt.	488143
18	16 or (15 and 17)	3
19	15 not 18	3150