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

VKM Report 2025:03

Update of the scoping review of research on gastrointestinal effects of selected emulsifiers, stabilisers, and thickeners

Camilla Svendsen, Monica Andreassen, Ellen Bruzell, Eva Denison, Tove Gulbrandsen Devold, Berit Granum, Gro Haarklou Mathisen, Monica Hauger Carlsen, Trine Husøy

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

This updated scoping review gives an overview of research on gastrointestinal effects of emulsifiers, stabilisers, and thickeners, specifically agar (E 406), sodium alginate (E 401), carrageenan (E 407), processed Eucheuma seaweed (E 407a), sodium carboxymethyl cellulose (E 466), gellan gum (E 418), guar gum (E 412), and xanthan gum (E 415).

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Scientific Opinion of 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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Update of the scoping review of research on gastrointestinal effects of selected emulsifiers, stabilisers, and thickeners

Preparation of the report

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to draft the report. 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 report.

Authors of the report

The authors have contributed to the report 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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The assessment and approval of the report was performed in accordance with the VKM routine for approval of risk assessments (VKM, 2018).

Disclaimer

Parts of the text and tables in the current report are identical to the original scoping review (VKM et al., 2023).

Acknowledgement

VKM would like to thank Senior Librarian Nataliya Byelyey (Norwegian Institute of Public Health, the library) for valuable help in performing the literature searches.

VKM would like to thank the referees Dr. Jon-Vidar Gaustad (Norwegian Medical Products Agency) and Prof. Dr. Ursula Gundert-Remy (Institute of Clinical Pharmacology and Toxicology, Charité–Universitaetsmedizin Berlin, Germany) for their valuable comments through critical review of the draft report. VKM emphasises that the referees are not responsible for the content of the final report. In accordance with VKM's routines for approval of a risk assessment (VKM, 2018), VKM received their comments before evaluation and approval by VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics, and before the report was finalised for publication.

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.

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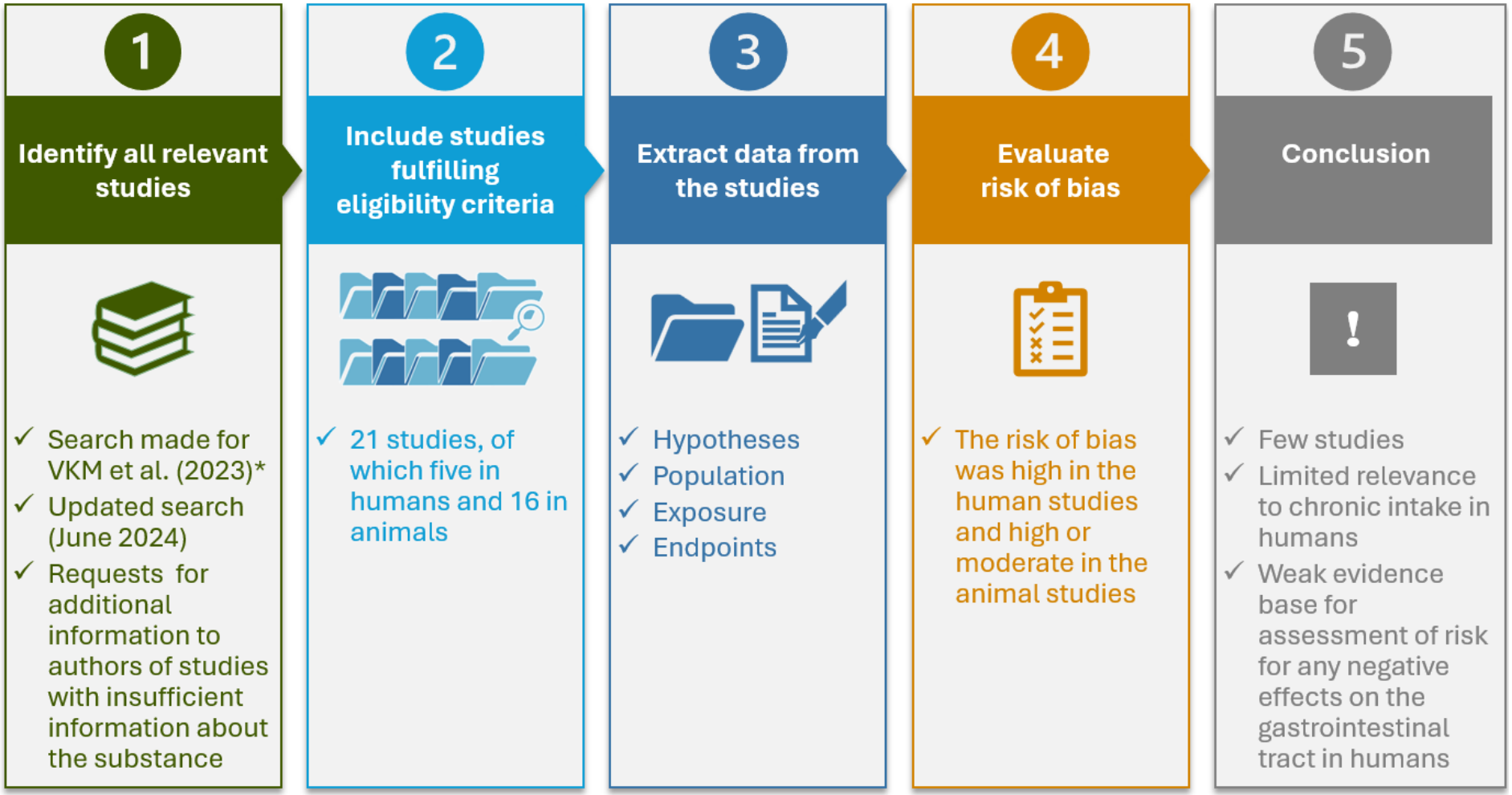
Graphical abstract



**VKM et al. (2023). Scoping review of research on gastrointestinal effects of selected emulsifiers, stabilisers, and thickeners*

Summary

This scoping review was commissioned by the Norwegian Food Safety Authority. The aim was to update a previous scoping review of research literature on the effects of emulsifiers, stabilisers and thickeners (EST) on the gastrointestinal (GI) tract, specifically agar (E 406), sodium alginate (E 401), carrageenan (E 407), processed Eucheuma seaweed (E 407a), sodium carboxymethyl cellulose (E 466), gellan gum (E 418), guar gum (E 412), and xanthan gum (E 415). The effects could be beneficial, adverse or neutral. A scoping review contrasts with a safety evaluation that consists of assessment of biological and chemical properties, potential toxicity of any organ, and dietary exposure estimates. It does not report on measures of the strength of the relationship between EST exposures and effects on the GI tract.

The literature search covered the period from March 1, 2023 (end of search of the previous review) to June 11, 2024. The search strategy and the eligibility criteria were the same in the previous and the updated scoping reviews. Fifteen studies fulfilling the eligibility criteria were identified in the previous scoping review (VKM, 2023). In addition, 214 studies fulfilled all eligibility criteria except the criterion that the substance tested must be in accordance with the regulations for food additives in the EU and Norway. The information about the substance tested in these studies was insufficient, and to obtain this information for the present update, the VKM sent requests by email to the corresponding authors of the publications, whenever such contact information was available. If delivery failed, an effort was made to identify a new email address to which the request was re-sent. Six additional studies from five publications were included following receipt of requested information. No studies were included from the updated literature search. Four of the included studies examined effects of sodium alginate (E 401) and guar gum (E 412) in humans and two other studies examined effects of guar gum (E 412) and carboxymethyl cellulose (E 466) in pigs.

From both the previous scoping review (VKM, 2023) and the present update, 21 controlled studies fulfilling the eligibility criteria were identified: five studies in humans and 16 in animals. The dose ranges reported or estimated, across all ESTs in the human and animal studies (four different species), were 36-214 mg/kg bw per day and 51-6000 mg/kg bw per day, respectively. The study durations of the human controlled studies were between 1 day and 1 week, i.e. acute exposures only. Study durations were subchronic (exposure ≥13 weeks) in four of the animal experimental studies and subacute (≤12 weeks) in the remainder.

The endpoints addressed in the human studies were:

- Faecal weight and consistency
- Gastric emptying (time and frequency)
- Glucose and insulin homeostasis
- Satiety and appetite

The endpoints addressed in the animal studies were:

- Changes in gut microbiota composition or number of bacteria
- Enzymatic activity (digestive, microbial, cell proliferation, and inflammatory)
- Intestinal utilisation and fermentation of nutrients
- Macroscopic changes (stomach, small intestine, colon)
- Microscopic changes (digestive tract) including inflammation
- Mucosal weight, content (colon)
- Presence of blood or mucus in faeces
- Tumor promotion in cancer-induced mice (genetic or chemical)

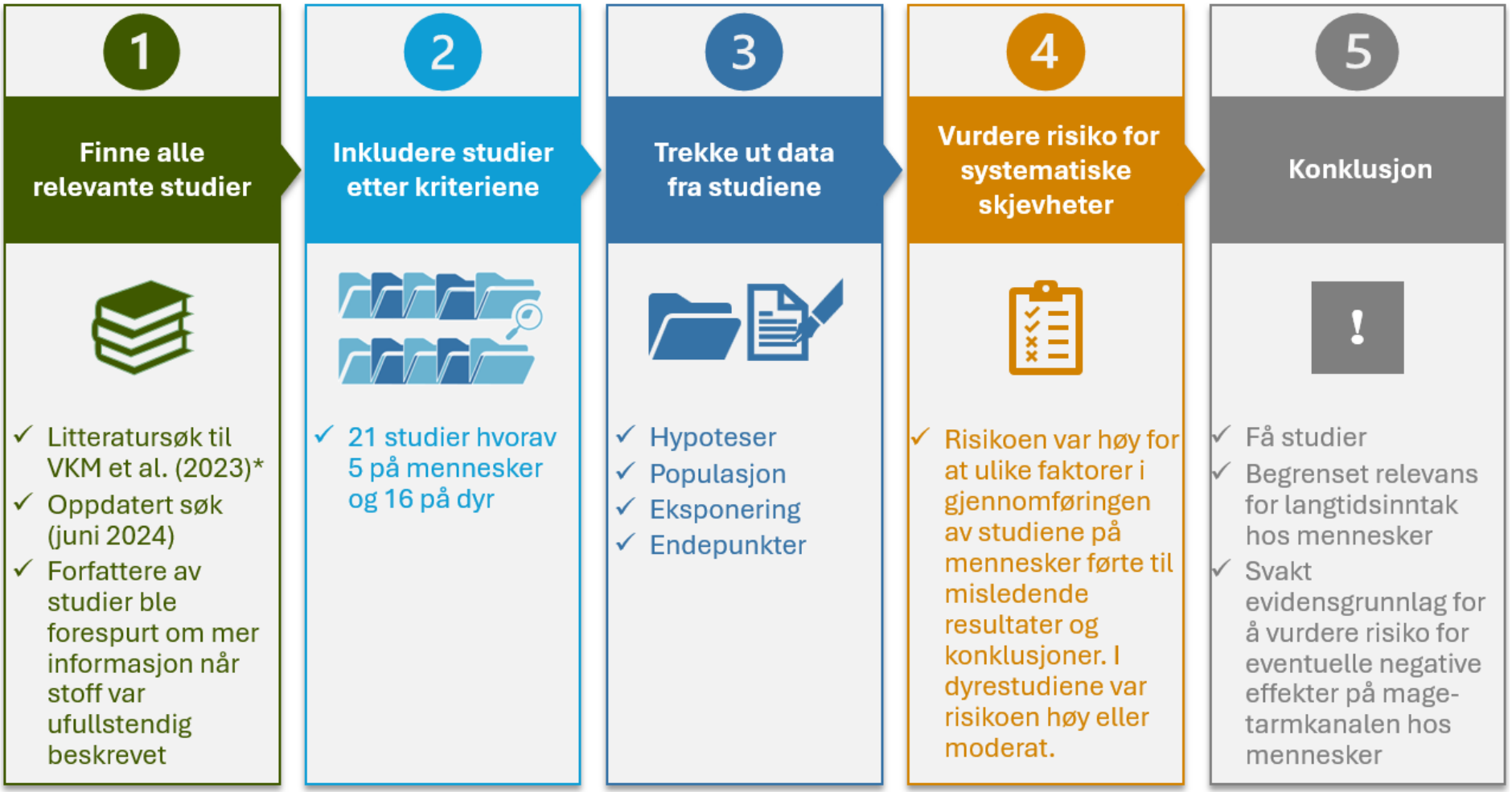
The risk of bias was assessed as high in the human studies and as high and moderate in the animal studies. High risk of bias means that there is high likelihood that the features of the study design or conduct of the study will give misleading results and thus, conclusions.

Conclusion

There were few eligible studies on the effects of agar (E 406), sodium alginate (E 401), carrageenan (E 407), processed Eucheuma seaweed (E 407a), sodium carboxymethyl cellulose (E 466), guar gum (E 412) and xanthan gum (E 415) on the gastrointestinal tract. In most of the studies the potential was high for systematic errors in the results or findings. None of the studies lasted long enough to evaluate long-term exposure in humans. Thus, the evidence base will be weak for assessment of the risk for negative effects on the gastrointestinal tract in humans. The conclusion in the present updated scoping review, after inclusion of six additional studies, remains the same as in the previous scoping review (VKM, 2023).

Key words: Colon, mapping review, eligibility criteria, EU regulation, food additives, gut microbiota, intestine, risk of bias.

Grafisk sammendrag



**VKM et al. (2023). Scoping review of research on gastrointestinal effects of selected emulsifiers, stabilisers, and thickeners*

Sammendrag på norsk

Denne kartleggingen er gjort på oppdrag fra Mattilsynet. Målet var å oppdatere en tidligere kartlegging av forskningslitteratur på effekter av følgende konsistensmidler, dvs. emulgatorer, stabilisatorer og fortykningsmidler, på mage-tarmkanalen: agar (E 406), natriumalginat (E 401), karragenan (E 407), bearbeidet Eucheuma-tang (E 407a), natriumkarboksymetylcellulose (E 466), gellangummi (E 418), guarkjernemel (E 412), og xantangummi (E 415). Effektene kunne være positive, negative eller nøytrale. En kartlegging er ikke det samme som en risikovurdering, som inkluderer vurdering av biologiske og kjemiske egenskaper, mulig toksisitet i ethvert organ og beregning av eksponering fra kosten. Den gir ikke noe mål på styrken av sammenhengen mellom inntak av konsistensmidler og effekter på mage-tarmkanalen.

Litteratursøket dekket tidsperioden fra 1. mars 2023 (da søket i den forrige kartleggingen ble avsluttet) til 11. juni 2024. Søkestrategi og kvalifikasjonskriterier var like i den oppdaterte kartleggingen som i den opprinnelige. I den opprinnelige kartleggingen (VKM, 2023) oppfylte 15 studier kvalifikasjonskriteriene. I tillegg oppfylte 214 studier alle kriteriene med unntak av kriteriet om at stoffet som ble testet må være i henhold til forskriften for tilsetningsstoffer i EU og Norge. Disse studiene ga utilstrekkelig informasjon om stoffene som ble testet. For å innhente den manglende informasjonen, sendte VKM forespørsler via e-post til forfatterne av de publikasjonene som hadde oppgitt en slik adresse. I de tilfellene det kom feilmelding, ble forespørselen sendt til en annen e-postadresse. Tilbakemeldinger fra forfattere førte til at seks nye studier fra totalt fem publikasjoner ble inkludert i den oppdaterte kartleggingen. Ingen studier ble inkludert fra det oppdaterte litteratursøket. I fire av de inkluderte studiene var effekter av natriumalginat (E 401) og guarkjernemel (E 412) undersøkt hos mennesker, mens i to studier var effekten av guarkjernemel (E 412) og karboksymetylcellulose (E 466) undersøkt hos griser.

Totalt oppfylte 21 kontrollerte studier kvalifikasjonskriteriene i den forrige (VKM, 2023) og den oppdaterte kartleggingen: fem studier utført på mennesker og 16 på dyr. På tvers av alle de inkluderte konsistensmidlene var dosene i studier utført på mennesker fra 36 til 214 mg/kg kroppsvekt per dag. Dosene i dyrestudiene (fire forskjellige arter) var fra 51 til 6000 mg/kg kroppsvekt per dag. Studiene som ble utført på mennesker varte mellom 1 dag og 1 uke (dvs. kun akutt eksponering). Fire av dyrestudiene var subkroniske (eksponering ≥13 uker), og de resterende studiene var subakutte (≤12 uker).

I studiene utført på mennesker ble følgende endepunkter undersøkt:
- Vekt og konsistens av avføring
- Tid og frekvensen av tømming av mageinnhold
- Regulering av glukose og insulin
- Metthet og appetitt

I studiene på dyr ble det sett på følgende endepunkter:
- Endringer i sammensetningen av tarmens mikrobiota eller antall bakterier

- Enzymaktivitet (fordøyelse, mikrobielt, celleproliferasjon, betennelse)
- Tarmens utnyttelse og gjæring av næringsstoffer
- Makroskopiske endringer (mage, tynntarm og tykktarm)
- Mikroskopiske endringer (mage-tarmkanalen) inkludert betennelse
- Vekt og forekomst av slimhinner i tykktarm
- Forekomst av blod eller slim i avføringen
- Tumorpromosjon hos kreftinduserte mus (genetisk eller kjemisk)

Risikoen for systematiske skjevheter ble vurdert som høy i studiene utført på mennesker og som høy og moderat i dyrestudiene. Høy risiko for systematiske skjevheter betyr at det er høy sannsynlighet for at faktorer som har med studiedesign eller gjennomføringen av studiene å gjøre vil føre til i misledende resultater og dermed konklusjoner.

Konklusjon

Det var få kvalifiserte studier som undersøkte effekter av agar (E 406), natriumalginat (E 401), karragenan (E 407), bearbeidet Eucheuma-tang (E 407a), natriumkarboksymetylcellulose (E 466), guarkjernemel (E 412) og xantangummi (E 415) på mage-tarmkanalen. De fleste studiene hadde høy risiko for systematiske feil i resultatene eller funnene. Ingen av studiene var egnet til å vurdere langtidseksponering hos mennesker. Dermed vil evidensgrunnlaget være svakt for å vurdere risiko for eventuelle negative effekter på mage-tarmkanalen hos mennesker. Konklusjonen i denne oppdaterte kartleggingen, med tillegg av seks studier, forblir den samme som i forrige kartlegging (VKM, 2023).

Abbreviations and glossary

Abbreviations

EST emulsifiers, stabilisers, and thickeners

EU European Union

GI gastrointestinal

IBS irritable bowel syndrome

PECO population, exposure, comparator, outcome

RoB Risk of Bias

Glossary

Digestive system
The gastrointestinal tract and 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).

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

Emulsifier
Food additives which prevent liquids that normally do not mix, such as water and oil, from separating. Compounds used as emulsifiers are amphiphilic in nature, i.e. they are molecules having both hydrophobic (nonpolar) and hydrophilic (polar) regions. 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.

Ex vivo
Experiments on living primary organs, tissues and cells isolated from an organism, where the experiment is executed outside the organism. Artificially created organs, tissues or fluids are not regarded as *ex vivo*, rather as experimental in vitro models.

Gastrointestinal tract
[In the human body] A tube and organ system specialised 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).

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).

Publication
A publication refers to a single article supplying information about one or more studies.

Record
The title or abstract (or both) of a report indexed in a database or website (such as a title or abstract for an article indexed in Medline).

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 identifies main concepts, theories, sources, and knowledge gaps (Tricco et al., 2018).

Stabiliser
Food additives that maintain 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 forming 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.

Background as provided by the Norwegian Food Safety Authority

In 2023, the Norwegian Scientific Committee for Food and Environment (VKM) conducted a scoping review of research on the effects of emulsifiers and thickeners on the gastrointestinal tract (vkm.no). The background for the assignment was concerns related to effects on the gastrointestinal tract of some emulsifiers, stabilisers and thickeners. Effects of the following additives were mapped: carrageenan (E 407), processed Eucheuma seaweed (E 407a), sodium carboxymethylcellulose (E 466), sodium alginate (E 401), agar (E 406), guar gum (E 412), xanthan gum (E 415) and gellan gum (E 418).

The scoping review revealed that information about the substances in question were inadequate in most of the studies. Thus, it was uncertain whether the substances met the EU regulative criteria for the included additives. As a result, only 14 studies were included, while 214 studies were excluded.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority asks VKM to do the following:

- Obtain information about the substances that were inadequately described in the studies that were excluded from the original scoping review (VKM et al., 2023) due to lack of information about the substance.
- Update the literature search to identify relevant studies published after the literature search was conducted in connection with the review published in 2023.
- Update the scoping review from 2023 with data from new included studies.

1 Introduction

Emulsifiers, stabilisers, and thickeners are food additives that affect the consistency of food and are used in several food products on the Norwegian market.

The present report is an update of the systematic scoping review published by the Norwegian Scientific Committee for Food and Environment (VKM) on research literature examining effects on the gastrointestinal (GI) tract after separate exposure to the following eight EST (VKM et al., 2023):

- agar (E 406)
- sodium alginate (E 401)
- carrageenan (E 407)
- processed Eucheuma seaweed (E 407a)
- sodium carboxymethyl cellulose (E 466)
- gellan gum (E 418)
- guar gum (E 412)
- xanthan gum (E 415)

Scientific publications reporting effects in humans and mammals, as well as *ex vivo* studies, were included in the previous scoping review (VKM et al., 2023).

This scoping review presents reported endpoints in eligible studies and does not aim to measure effect estimates or undertake a risk analysis of the association between intake of EST and effects on the GI tract in humans. A scoping review contrasts with a safety evaluation that consists of assessment of biological and chemical properties, potential toxicity of any organ, and dietary exposure estimates (https://www.efsa.europa.eu/en/topics/topic/food-additives).

1.1 Background

The EU regulation (EC) No 1333/2008 harmonises the use of food additives and includes a positive list of approved food additives (Annex II, part E). The EU regulation No 231/2012 contains specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008, which must be met for authorised use of the food additives. Examples of specifications are maximum concentrations of impurities or heavy metals, molecular weight limits, degree of substitution, and percentage loss on drying. The specifications are crucial since deviations from these may alter the chemical properties and/or potential toxicological properties of the substance in question. For example, specifications apply to carrageenan where the molecular size is an important property as low molecular weight (weight-average of 20–40 kDa) carrageenan may cause cancer in animals (EFSA et al., 2018). Therefore, the EU regulations specify that the carrageenan molecular weight fraction below 50 kDa must not be more than 5%. Some of the specifications listed in Regulation No 231/2012 are thus included as eligibility criteria for the different EST in this scoping review (see Table 2.2-2). In the previous scoping review (VKM, 2023), 214 studies (in 186 publications) fulfilled all eligibility criteria except the criterion that was specifically formulated to ensure that the EST tested would comply with food additive regulations

in Norway/EU (see Table 2.2-2). The information about the substance tested in these studies was insufficient. In this update of the scoping review (VKM et al., 2023), we have attempted to request the missing information from the corresponding authors of the 214 studies.

1.2 Aim

The aim of the current scoping review is to update the scoping review conducted by VKM in 2023 on gastrointestinal effects of selected emulsifiers, stabilisers, and thickeners, i.e. agar (E 406), sodium alginate (E 401), carrageenan (E 407), processed Eucheuma seaweed (E 407a), carboxymethyl cellulose (E 466), gellan gum (E 418), guar gum (E 412), and xanthan gum (E 415) (VKM, 2023).

The update will include:

i) A new literature search [1st March 2023 to 11th June 2024]
ii) Replies from requests for additional information on
    a. the 214 studies that were excluded in the previous scoping review based on insufficiently reported characteristics of the examined EST, and
    b. the studies from the new literature search with insufficiently reported characteristics of the examined EST.

The following elements will be addressed:

- The extent and characteristics of the research literature on gastrointestinal tract effects of the selected EST regarding e.g.
    - populations and gastrointestinal tract endpoints and outcomes
    - study designs
    - data on exposures
- Study hypotheses
- The extent to which the design and conduct of the studies is likely to have prevented bias (the degree of systematic errors).

2 Methods

We have adhered to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist" (Tricco et al., 2018). Figure 2-1 gives an overview of the methods used in the previous scoping review (VKM, 2023) and in the present update.

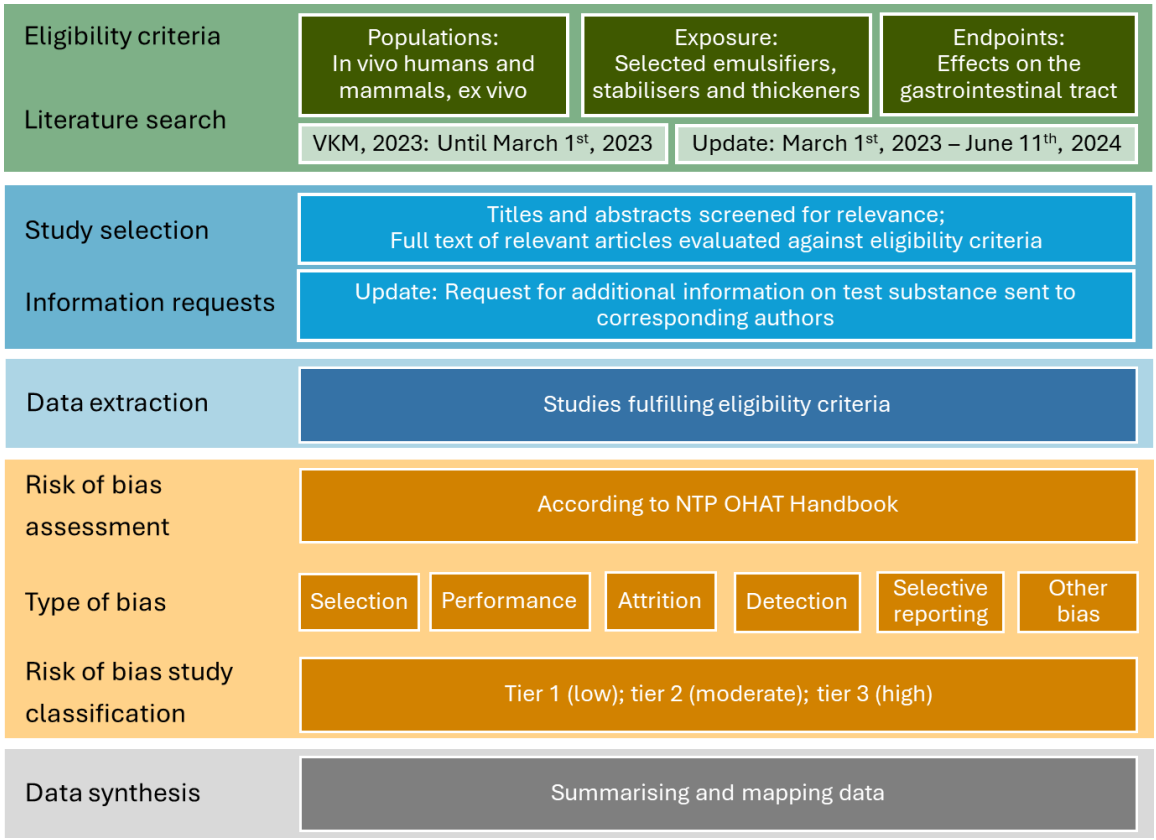


Figure 2-1. Schematic overview over the methods used in the previous (VKM, 2023) and updated scoping reviews. NTP OHAT: National Toxicology Program, Office of Health Assessment and Translation (NTP, 2019).

2.1 Information requests

To obtain information ensuring that the examined EST described in publications fulfilled requirements for approval for use as food additive in Norway/EU, the VKM sent information requests by email (see Appendix 1 for the request), including a 3-week reminder, to the corresponding authors of the publications identified in the previous scoping review wherever such contact information was available. If delivery failed, an effort was made to identify a new email address to which the request was re-sent. A reminder was sent to all who did not reply within three weeks. When an email address to the corresponding author was not reported in the publication, no request was sent. An overview of the information requests as well as inclusion of the studies in question and reason for exclusion is included in Supplementary materials 1 (sheet 3 "Requests for information").

2.2 Literature search

A senior research librarian performed literature searches in the electronic databases from MEDLINE (Ovid), Embase (Ovid), and Web of Science from March 1, 2023, to search date (June 11, 2024). The search terms and strategy are included in Appendix 2.

The identified records were imported into EndNote (Thomson Reuters, version X9), duplicates were removed, and the records were imported into Rayyan (Ouzzani et al., 2016) for screening of title and abstracts. Screening of records for relevance was performed independently by two reviewers. The between-reviewer calibration undertaken during the preparation of the previous scoping review was considered sufficient and was not repeated. Records selected for full text assessment were evaluated independently using the software EPPI-Reviewer (Thomas et al., 2022) by pairs of reviewers.

The study selection was based on the predefined eligibility criteria as stated in the protocol for the updated scoping review (VKM et al., 2024) covering population, exposure, comparison, outcomes, study design, publication year, country and language (Table 2.2-1). A sub-set of criteria based on the regulatory specifications for food additives (Regulation (EU) No 231/2012) was specified for the criterion "*The substance tested must be approved for use as food additive in certain foods in Norway/EU*" (Table 2.2-2).

Table 2.2-1. Eligibility criteria for studies on gastrointestinal effects.

Population	Humans of all age groups, males, and females Mammals Ex vivo gastrointestinal tract model systems (human faecal samples)
Exposure	• Oral intake of agar (E 406), sodium alginate (E 401), gellan gum (E 418, 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 418), 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 (see Table 2.2-2).
Comparison	Placebo, no treatment, dose comparison
Endpoints	Any gastrointestinal tract effects including, but not restricted to: *Human studies* • 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

	• Gastrointestinal 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 (IBS) • (Non-symptomatic) gastrointestinal alterations such as changes in the microbiota, mechanical barriers, immunity, or faecal biochemical composition *Animal studies* • Changes in the gut microbiota composition and/or the microbiota numbers • Enzymatic activity (microbial or colonic mucosa) • Faecal or caecal content, weight, colour, consistency, and/or viscosity • Gastric transit time and stool frequency • Inflammation (colon or markers measured in faeces) • Intestinal permeability (markers measured in serum) • Intestinal utilisation and fermentation of nutrients • Macroscopic changes • Microscopic changes • Mucosal weight and/or protein content • Presence of mucus or blood in the faeces • Tumour development • Weight and/or length of intestines
Study design	• Human controlled studies • Animal experimental studies • Ex vivo gastrointestinal tract model studies • Systematic reviews. 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).
Publication year	From 1st of March 2023 to search date
Country	No restriction
Language	Danish, English, Norwegian and Swedish

Table 2.2-2. The sub-set of eligibility criteria for the criterion "The substance tested must be approved for use as food additive in certain foods in Norway/EU".

Food additive	**Information required to evaluate whether the examined substances are approved for use as food additive in Norway/EU**
Agar (E 406)	1) E number

Food additive	Information required to evaluate whether the examined substances are approved for use as food additive in Norway/EU
Gellan gum (E 418) Sodium alginate (E 401) Xanthan gum (E 415) Guar gum (E 412)*	OR 2) Either of the terms "food additive" or "food grade" are used in the description of the substance in the method section
Sodium carboxymethyl cellulose (E 466)	1) E number OR 2) Either of the terms "food additive" or "food grade" are used in the description of the substance in the method section AND Substitution is described, and the degree of substitution is ≥0.2 and ≤1.5 carboxymethyl groups (CH_2COOH) per anhydroglucose unit
Carrageenan (E 407) Eucheuma seaweed (E 407a)	1) E number OR 2) Either of the terms "food additive" or "food grade" are used in the description of the substance in the method section AND The substance is not hydrolysed or chemically degraded AND MW is described and the MW fraction below 50 kDa is < 5%

*"Partially hydrolysed guar gum" is an acceptable term and is included.
MW: molecular weight.

2.3 Data extraction

One reviewer extracted the data, and a second reviewer independently checked the data extraction for accuracy and completeness. Data were extracted for the same categories as in the previous scoping review. The reviewers who performed the data extraction were also involved in the data extraction of the previous scoping review. The between-reviewer calibration undertaken during the preparation of the previous scoping review (VKM et al., 2023) was considered sufficient and was not repeated.

2.4 Evaluation of risk of bias

Risk of bias (RoB) in the included studies was evaluated using the Handbook for conducting a literature-based health assessment using the National Toxicology Program (NTP), Office of Health Assessment and Translation (OHAT) approach for systematic review and evidence integration (NTP OHAT, 2015; NTP OHAT, 2019). The questions used to evaluate RoB and the determination of key questions was the same as in the original scoping review (Table 2.4-1). Two reviewers independently evaluated RoB. Disagreements were be resolved through discussions and by consulting a third author. A between-reviewer calibration was undertaken. A calibration was also performed to ensure that the RoB evaluations in the original scoping review (VKM et al., 2023) and the current update of this review were performed similarly.

Table 2.4-1. Types of bias distributed between eight and nine RoB questions applied to human and animal studies, respectively. X: RoB-question asked for the study type indicated; *: key question; N.A.: not applicable.

Type of bias	RoB question	Human study	Animal study
Selection	Was administered dose or exposure level adequately randomised?	X*	X*
	Was allocation to study groups adequately concealed?	X*	X
Performance	Were experimental conditions identical across study groups?	X*	X
	Were the research personnel (and human subjects) blinded to the study group during the study?	N.A.	X*
Attrition	Were outcome data complete without attrition or exclusion from analysis?	X	X
Detection	Can we be confident in the exposure characterisation?	X*	X*
	Can we be confident in the outcome assessment?	X*	X*
Selective reporting	Were all measured outcomes reported?	X*	X
Other bias	Were there no other potential threats to internal validity?	X	X

The rating of questions was integrated to classify the studies into tiers of overall RoB for each outcome in a study (Table 2.4-2) amended from an example in OHAT Handbook (NTP OHAT, 2015; NTP OHAT, 2019). Tiers 1, 2 and 3 represent low, moderate, and high RoB, respectively (the written expressions are not explicitly defined by OHAT).

Table 2.4-2. Classification of studies into tiers according to overall RoB for each outcome/study. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

	Tier 1 Low RoB	Tier 2 Moderate RoB	Tier 3 High RoB
Criteria for classification	All key questions are scored +/++ AND No more than one non-key question is scored – AND No non-key question is scored – –	All combinations not falling under tier 1 or 3	Any key or non-key question is scored – – OR More than one key question is scored –

2.5 Data synthesis

The extracted data were summarised in text, tables, and figures:

- The aims and hypotheses in each study, as stated by the authors (Table 3.3.1-1).
- The characteristics of the studies, including populations, exposures, comparisons, and endpoints studied within each study design (Table 3.3.2-1).
- RoB assessed in the included studies (Tables 3.3.3-1 and 3.3.3-2).
- The distribution of studies investigating gastrointestinal tract effects of EST across publication years (Figure 3.3.4-1).
- The endpoints addressed in the human (Figure 3.3.4-2) and the animal studies (3.3.4-3).

2.6 Deviations from the protocol

A protocol (VKM, 2024) was developed and made publicly available prior to commencement of the updated scoping review. The scoping review was prepared according to the protocol, except for the following deviations:

Excel was used instead of the software EPPI-Reviewer (Thomas et al., 2022) for the study selection, data extraction, RoB evaluation, and the synthesis of findings.

3 Results

3.1 Request for substance information

An overview of the information request procedure is presented in Figure 3.1-1. Of the 186 publications (214 studies), requests for information were sent to corresponding authors of 67 publications (74 studies). For the remaining 119 publications (140 studies), e-mail addresses of corresponding authors were not available.

Answers were received from 31 corresponding authors. Following an evaluation of the information received, five publications (six studies) were considered to fulfill the eligibility criteria for the substances tested (Supplementary materials 1, sheet 3 "Requests for information").

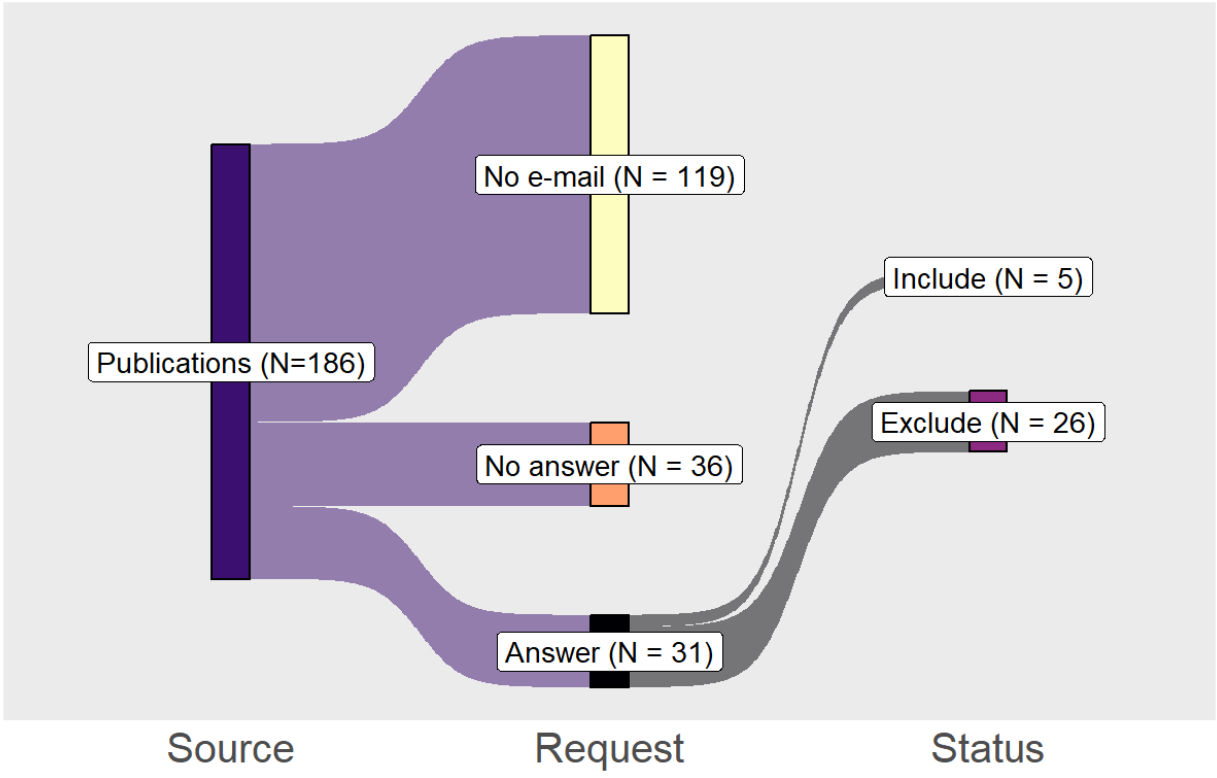


Figure 3.1-1. An overview of the information requests process. N: number of publications. No e-mail: e-mail addresses of corresponding authors were not available. Include: fulfils eligibility criteria. Exclude: does not fulfil eligibility criteria.

3.2 Literature search

An overview of the outcome of the literature search and the study selection process is presented in Figure 3.2-1. No primary studies were included (Supplementary materials 1, sheet 2 "Literature search"). Two records fulfilled all eligibility criteria except the substance specific requirements (Table 2.2-2). VKM contacted the corresponding

authors with a request to provide the required information, but this information was not received.

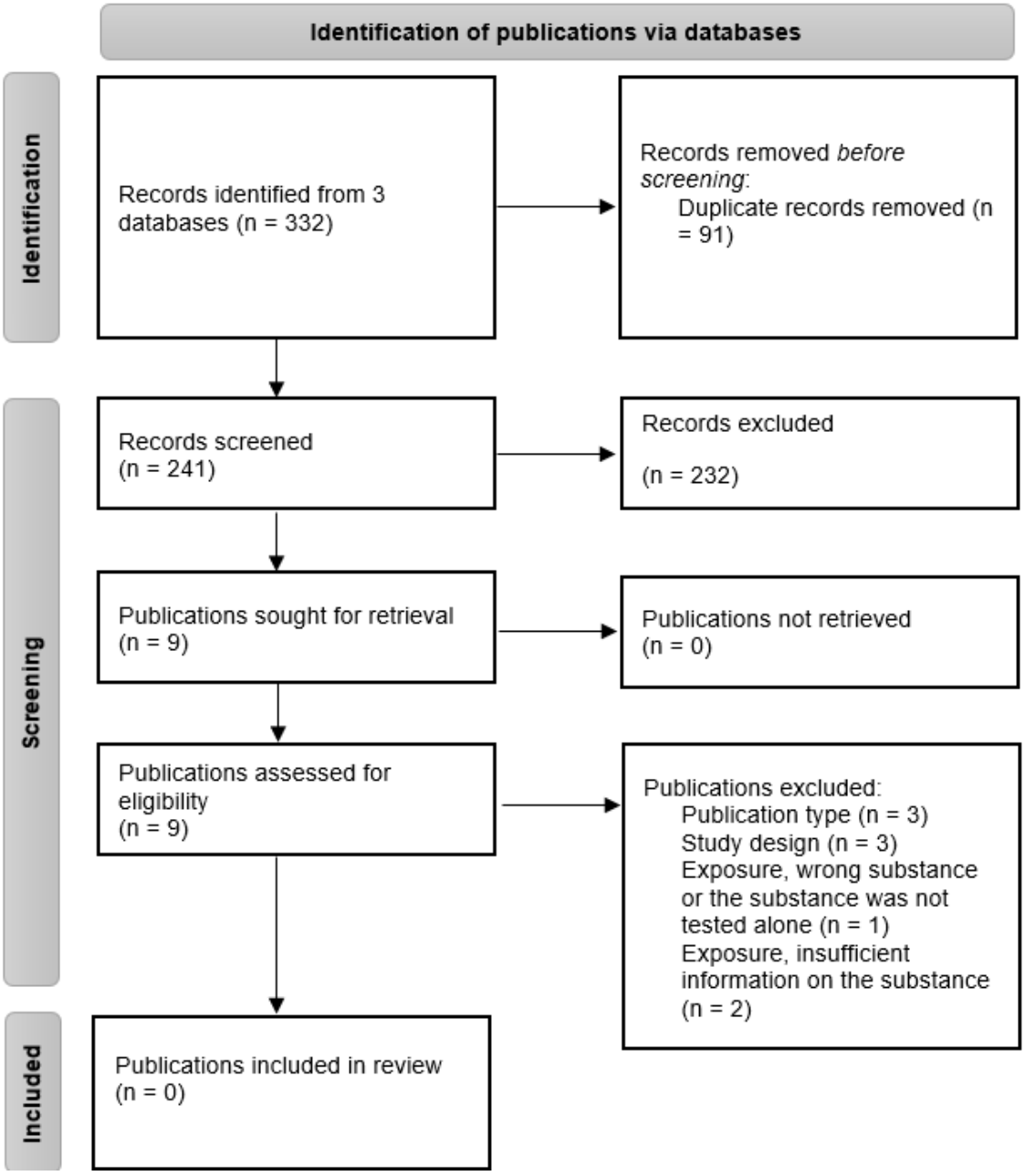


Figure 3.2-1. PRISMA Flowchart for the selection of human and animal experimental studies and *ex vivo* gastrointestinal tract model system studies (modified from Moher et al. (2009)) for the literature search covering the period from March 1, 2023 to June 11, 2024.

3.3 Results and data synthesis

In total, from the previous scoping review (VKM, 2023) and the present update, five human studies and 16 experimental animal studies fulfilling the eligibility criteria were identified. An overview of the studies fulfilling the eligibility criteria, including test species and substances tested, is presented in Table 3.3-1. No *ex vivo* studies that fulfilled the eligibility criteria were identified.

Table 3.3-1. Publications with studies fulfilling the eligibility criteria (from the previous scoping review (VKM, 2023) and the present update). *Publications included after receiving additional information about the substance from the corresponding author.

Reference	Species (number of participants or animals)	Substance tested
Human studies (n=5)		
Hoad et al. (2004)*	Human (12)	Alginate Guar gum
Mariotti et al. (2001)*	Human (7)	Guar gum
Tomlin and Read (1988)	Human (7)	Xanthan gum
Wanders et al. (2013)* Study 1	Human (121)	Guar gum and sodium alginate
Wanders et al. (2013)*Study 2	Human (10)	Guar gum and sodium alginate
Animal studies (n=16)		
Calvert and Reicks (1988)	Rat (32)	Carrageenan
Calvert and Satchithanandam (1992)	Rat (28)	Carrageenan
Cameron-Smith et al. (1994)	Rat (20)	Guar gum Xanthan gum
Chi-Moreno et al. (2005)*	Pig (6)	Guar gum
Gao et al. (2022)	Mouse (40)	Carrageenan
Hung et al. (2022)*	Pig (36)	Carboxymethyl cellulose
Mallett et al. (1984)	Rat (48)	Agar Guar gum
McGill et al. (1977)	Baboon (24)	Carrageenan
Pogozhykh et al. (2021)	Rat (16)	Eucheuma seaweed
Rideout et al. (2008)	Pig (36)	Guar gum
Viennois et al. (2017) Study 1	Mouse (total number not reported, number per group ranged from 5 to 10)	Sodium carboxymethyl cellulose
Viennois et al. (2017) Study 2	Mouse (number not reported)	Sodium carboxymethyl cellulose
Viennois and Chassaing (2021)	Mouse (total number not reported, number per group ranged from 3 to 13)	Sodium carboxymethyl cellulose
Weiner et al. (2007)	Rat (120)	Carrageenan
Weiner et al. (2015)	Pig (72)	Carrageenan
Wilcox et al. (1992)	Rat (144)	Guar gum

3.3.1 Reports of aims and hypotheses

The aims and hypotheses reported in the 21 included studies, 15 from the previous scoping review (VKM, 2023) and six included in the present update, are presented in

Table 3.3.1-1. Five studies presented a hypothesis to be tested in addition to the aim of the study.

Table 3.3.1-1. Aims and hypotheses of the studies fulfilling the eligibility criteria (from the previous scoping (VKM, 2023) and the present update) as stated by the study authors.

Reference	Aim of the study	Hypothesis tested
Human studies (n=5)		
Hoad et al. (2004)	Investigate the satiating effects of two types of alginates, which gel weakly or strongly on exposure to acid.	Not reported
Mariotti et al. (2001)	Determine whether guar gum could acutely affect the absorption and utilization of dietary nitrogen and whether these luminal effects could also perturb the kinetics of urea.	Not reported
Tomlin and Read (1988)	To investigate whether the degradation of viscous polysaccharides by colonic bacteria determines their effects on colonic function.	Not reported
Wanders et al. (2013) (study 1)	Determine the effects of dietary fibre with bulking, viscous and gel-forming properties on satiation, and to identify the underlying mechanisms.	Not reported
Wanders et al. (2013) (study 2)		
Animal studies (n=16)		
Calvert and Reicks (1988)	To examine the relationship between colonic thymidine kinase enzyme activity and mucin histochemistry and the reported effects of various dietary fibers on chemically induced colon carcinogenesis.	Not reported
Calvert and Satchithanandam (1992)	To examine the effect on colonic cell proliferation of feeding high-molecular-weight carrageenan.	No reported
Cameron-Smith et al. (1994)	The aims were to determine the effect that the gastrointestinal tract has on the viscosity of meals containing different soluble fibers, and to determine whether the glycaemic response of a meal (containing the soluble fiber) was predicted by the viscosity of the digesta in the small intestine.	Not reported
Chi-Moreno et al. (2005)	Evaluate the effect of diet viscosity, provoked by the addition of Guar gum, on the loss of endogenous amino acids recovered at the end of the small intestine.	Not reported
Gao et al. (2022)	To explore the risk of κ-carrageenan induced colitis under high-sucrose or high-salt diet in mice.	Not reported

Reference	Aim of the study	Hypothesis tested
Hung et al. (2022)	Evaluating the roles of dietary fibre content and viscosity on changes in nutrient digestibility and intestinal responses.	We hypothesised that increased viscosity would cause greater effects on nutrient digestibility and changes on intestinal physiology than the dietary fibre content
Mallett et al. (1984)	To study the effect of feeding a number of hydrocolloid materials (agar, carboxymethylcellulose, carrageenan, guar gum, gum acacia, locust-bean gum and pectin) on a range of caecal microbial enzyme activities that are of toxicological importance to the host animal.	Not reported
McGill et al. (1977)	To test infant formulas made with and without carrageenan in a nonhuman primate infant. To detect deleterious effects of native carrageenan on overall growth and development as well as on the alimentary tract and other tissues.	Not reported
Pogozhykh et al. (2021)	To assess the local and systemic toxic effects of the common food additive E 407a in rats orally exposed to it for two weeks.	Not reported
Rideout et al. (2008)	To examine the influence of different resistant starch varieties and conventional fibers on the efficiency of nutrient utilisation and intestinal fermentation in pigs.	Not reported
Viennois et al. (2017) (study 1)	To test whether regular consumption of dietary emulsifiers carboxymethylcellulose or polysorbate-80 exacerbate tumor development.	In the present study, we hypothesized that emulsifiers could be involved in colorectal cancer development through the promotion of low-grade intestinal inflammation and alterations of the intestinal microbiota.
Viennois et al. (2017) (study 2)		
Viennois and Chassaing (2021)	To investigate the impact of dietary emulsifiers consumption on cancer initiation and progression in a genetical model of intestinal adenomas.	In the present study, we hypothesized that dietary emulsifier consumption could aggravate initiation and development of genetically driven colorectal cancer.

Reference	Aim of the study	Hypothesis tested
Weiner et al. (2007)	To evaluate food-grade carrageenan that has been characterized for the low molecular weight fraction.	The present subchronic dietary toxicity study was conducted in rats to test the hypothesis that kappa carrageenan containing a high percentage of the Low Molecular Weight Tail below 50 kDa is safe for food use.
Weiner et al. (2015)	To evaluate (1) the potential absorption of carrageenan in the gastrointestinal tract, (2) the presence of carrageenan in serum following ingestion of swine-adapted infant formula containing carrageenan via toxicokinetic analysis and (3) to assess the impact of carrageenan on the developing immune system.	Not reported
Wilcox et al. (1992)	The effect on colonic cell proliferation of poligeenan, a nongenotoxic polysaccharide that induces colon tumors in rats, was compared with guar gum and carrageenan.	Not reported

3.3.2 Study characteristics

An overview of selected study characteristics of the included publications is shown in Table 3.3.2-1. Wanders et al. (2013) contains two studies that fulfilled the eligibility criteria, whereas for the remaining publications, one study in each fulfilled the eligibility criteria.

Two human studies had a latin-square design and three were cross-over studies. The number of participants ranged from seven (in two studies) to 121 (one study). The EST tested in the human studies were guar gum (n=4), sodium alginate (n=2), alginate (n=1) and xanthan gum (n=1). The study duration per EST lasted between 1 day to 1 week (acute).

The animal species used in the studies were baboons (n=1), pigs (n=4), mice (n=3), and rats (n=7). The EST tested in animal studies were agar (n=1), carrageenan (n=6), Eucheuma seaweed (n=1), guar gum (n=5), sodium carboxymethyl cellulose (n=2), carboxymethyl cellulose (n=1), and xanthan gum (n=1). The substances were administered either in the feed, drinking water, or as infant formula. Four of the animal experiments were subchronic studies (exposure ≥13 weeks) and the remaining studies were subacute studies (≤12 weeks).

The extracted endpoints are presented in supplementary materials 1 (sheet 5 "DataExtraction_HumanStudies" and sheet 6 "DataExtraction_AnimalStudies"). An overview of the doses tested is given in supplementary materials 1 (sheet 7 "Dose_HumanStudies" and sheet 8 "Dose_AnimalStudies"). The dose ranges reported or estimated, across all EST in the human and animal studies (four different species)

were 36-214 mg/kg bw per day and 51-6000 mg/kg bw per day, respectively (Table 3.3.2-1).

Table 3.3.2-1. Characteristics of the included studies (see Supplementary Material 1, for details in dose calculations and estimations).

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
Human studies (n=5)					
Tomlin et al (1988)	Latin-square design Cross-over	Human 6 males, 1 female Age not reported Healthy	**Xanthan gum** Given as drink together with self-selected diet restricted in fibre 3 times daily for 1 week Dose: 15 g/day Dose [estimated average]: 214 mg/kg bw per day	No treatment	Faecal weight; Gastric transit time; Stool frequency
Mariotti (2001)	Randomised controlled study	Human 5 males and 2 females Mean age = 23, range = 20-36 years Healthy	**Guar gum** One exposure per meal (every participant had both meals, one time) Both meals Dose: 4.75 g/day Dose [estimated]: 68 mg/kg bw per day	Two test meals; with and without guar gum	Gastric emptying and the appearance of dietary plasma; Plasma glucose and insulin; Total, dietary, and endogenous plasma urea kinetics; Urinary excretion of total, dietary, and endogenous nitrogen amino acids

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
Hoad (2004)	Randomised controlled study Latin-square design Cross-over	Human 3 males and 9 females Mean age = 24 years, range = 19–29 years Healthy	**Guar gum and alginate** Given as a meal A single exposure of each study substance (one meal per participant per substance) Dose [estimated] for sodium alginate: 93 mg/kg bw per day Dose [estimated average] for guar gum: 46 mg/kg bw per day	Four test meals; a control meal, two alginate meals (one weak-gelling alginate meal and one strong-gelling alginate meal), and a guar gum meal	Gastric emptying; Satiety
Wanders (2013) (study 1)	Randomised controlled study, crossover	Human 44 males and 76 females Mean age = 25 years, range = 18–50 years Healthy	**Guar gum and sodium alginate** Given as cookies 6 sessions, one per product, separated by at least 2 days Dose: The intake of each test product was ad libitum Dose [estimated] for sodium alginate: 107 mg/kg bw per day Dose [estimated] for guar gum: 64 mg/kg bw per day	Six test products a control without added fibre, three products with added fibre (cellulose/ guar gum in 2 concentrations / alginate in 2 concentrations	Palatability; Satiation and oral exposure time

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
Wanders (2013) (study 2)	Randomised controlled study, crossover	Human 6 males and 4 females Mean age = 21 years, range = 18–50 years Healthy	**Guar gum and sodium alginate** Given as a cookies 6 sessions, one per product, separated by at least 7 days Dose [estimated] for sodium alginate: 71 mg/kg bw per day Dose [estimated] for guar gum: 36 mg/kg bw per day	Six test products: a control without added fibre, three products with added fibre (cellulose/ guar gum in 2 concentrations / alginate in 2 concentrations)	4 h gastric emptying rate; Appetite sensation
Animal studies (n=16)					
McGill et al (1977)	Randomised experimental study	Baboon N=24, 3 groups, 3 males/group, 5 females/group Newborn	**Carrageenan** 0; 300; 1500 mg/L in infant formula 5 times/day first 14 days 4 times/day next 14 days 3 times/day next 56 days 2 times/day next 28 days until 112 days old	No treatment	Faecal colour, weight, and consistency; Microscopic changes (gastrointestinal tract); Macroscopic changes (small intestine and colon); Presence of mucus or blood in faeces

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
			Total formula consumed (g, mean) for concentration levels (mg/L): 0: 35 949 g 300: 34 252 g 1500: 38 899 g Mean daily doses (mg/kg bw per day) for each sex [estimated]: Males (mean): 0; 67; 353 Females (mean): 0; 71; 400		
Mallett et al (1984)	Randomised experimental study	Rat: Sprague-Dawley N=48, 8 groups, 6 males/group 3 weeks old at arrival (age at start of exposure: not reported)	**Agar and guar gum** 0; 50 g/kg in feed, ad libitum Subacute, 4 weeks Dose [estimated]: 6000 mg/kg bw/day	No treatment	Changes in gut microbiota number (caecum); Microbial enzyme activity (caecum); Caecal content weight; Concentration of ammonia (caecum)
Calvert et al (1988)	Non-randomised experimental study	Rat: Fischer 344 N=32, 4 groups, 8 males/group	**Carrageenan** 0; 5% in feed, ad libitum Subacute, 4 weeks	No treatment	Enzymatic activity (colonic mucosa); Macroscopic changes (stomach, colon); Microscopic changes (colon); Mucosal weight (colon); Mucosal protein content (colon)

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
		9-10 weeks at start of exposure	Dose [estimated]: 6000 mg/kg bw/day		
Calvert et al (1992)	Non-randomised experimental study	Rat: Fischer 344 N=28, 4 groups, 7 males/group Age not reported	**Carrageenan** 0; 0.65; 1.31; 2.61% in feed, ad libitum Subacute, 4 weeks Doses, week 1 (mg/kg bw/day, ±SE in parentheses): 0.65%: 467.8 (11.3) 1.31%: 947.5 (22.8) 2.61%: 1943.9 (106.2)	No treatment	Enzymatic activity (colonic mucosa); Faecal weight; Microscopic changes (colon); Mucosal protein content (colon)
Wilcox et al (1992)	Non-randomised experimental study	Rat: Fischer 344 N=144, 4 diets, 9 timepoint groups/diet, 4 males/timepoint group, 11 weeks at start of exposure	**Guar gum** 0; 5% in feed Subchronic, up to 91 days Dose [estimated]: 4500 mg/kg bw/day	No treatment	Enzymatic activity (colon); Cell proliferation (colon))

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
Cameron-Smith et al (1994)	Randomised experimental study	Rat: Sprague-Dawley N=20, 4 groups, 5 males/group Age not reported	**Guar gum and xanthan gum** 0; 70 g/kg in feed, ad libitum Subacute, 2 weeks Dose [estimated]: 8400 mg/kg bw/day	No treatment	Faecal viscosity (stomach and small intestine)
Chi-Moreno (2005)	Randomised experimental study (3×3 Latin Square design)	Pig; Duroc × Yorkshire × Landrace N=6 Age not reported	**Guar gum** The treatments were assigned randomly (two pigs per treatment) in each experimental period. Each period had a 7-days duration, 5 days of adaptation to the diet and 2 days to collect samples of ileal content. The pigs were fed equal amounts at 07:00 and 19:00 h. Dose [estimated]: 624 mg/kg bw/day	Three diets. 1) basal diet with corn starch, crystalline cellulose, saccharose and soybean oil; 2) basal diet plus 0.5% Guar gum; 3) basal diet plus 1.0% Guar gum.	Endogenous ileal flow; Composition of amino acids from endogenous protein
Weiner et al (2007)	Randomised experimental study	Rat: Fischer 344 N=120, 3 groups/sex 20/sex/group 50 days at start of exposure	**Carrageenan** 0; 25 000; 50 000 ppm in feed, ad libitum Subchronic, 90 days	No treatment	Faeces consistency; Microscopic changes (gastrointestinal tract)

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
			Doses (mg/kg bw/day): 25 000 ppm: males 1656; females, 1872 50 000 ppm: males, 3394; females, 3867		
Rideout et al (2008)	Randomised experimental study	Pig: Yorkshire N=36, 6 groups, 4-6 pigs/group (guar gum n=5), sex not reported Age not reported	**Guar gum** 0; 10% in feed, ad libitum Subacute, 30 days Dose [estimated]: 5200 mg/kg bw/day	No treatment	Intestinal utilisation and fermentation of nutrients
Weiner et al (2015)	Randomised experimental study	Pig: Yorkshire N=72, 4 groups/sex, 9/sex/group 4 days at start of exposure	**Carrageenan** 0; 0.5; 3.0; 10.0 g/L/day in infant formula 6 times/day (~83.33 mL/kg bw per dose) Subacute, 28 days Doses (mg/kg bw/day, SD in parentheses): 0.5: males 51.71 (4.06); females 55.57 (6.88)	No treatment	Microscopic changes (stomach, small intestine and large intestine); Immunohistochemical changes, TNF-alpha and IL-8 (colon); Weight of stomach, small intestine and large intestine

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
			3.0: males 192.86 (18.38); females 202.53 (12.72) 10.0: males 430.27 (67.33); females 448.25 (59.98)		
Viennois et al. (2017) (study 1)	Non-randomised experimental study	Mouse: C57BL/6; colitis-induced colorectal cancer model N varies depending on endpoint, 5-10/group, male 4 weeks at start of exposure	**Sodium carboxymethyl cellulose** 0; 1% (w/v) in drinking water Dose [estimated]: 1500 mg/kg bw/day Subchronic, 127 days over a period of 141 days ~ 18 weeks	No treatment	Colon length and weight; Tumour development (colon); Myeloperioxidase activity (colonic tissue); Changes in gut microbiota composition; Cell proliferation (colon); Faecal lipcalin-2; Lipopolysaccharide and D-lactic acid (serum)
Viennois et al. (2017) (study 2)	Non-randomised experimental study	Germ-free and conventional Swiss Webster mice (number, sex and age not reported)	**Sodium carboxymethyl cellulose** 0; 1% (w/v) in drinking water Dose [estimated]: 1500 mg/kg bw/day Subchronic, 3 months	No treatment	Effect of changes in gut microbiota composition on the expression levels of genes that control proliferation (Cyclin D1, D2, Ki67), apoptosis (BCL2 and BAD), and angiogenesis (VEGFA)

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
Pogozhykh et al (2021)	Randomised experimental study	Rat: WAG N=16, 2 groups, 8/group, sex not reported Adults	**Eucheuma seaweed** 0; 1% PES solution in drinking water Dose: 140 mg/kg bw/day Subacute, 2 weeks	No treatment	Microscopic changes (small intestine and large intestine)
Viennois et al (2021)	Randomised experimental study	Mouse: C57BL/6J wild-type and APC^{min} N varies depending on endpoint 3-13/group Both males and females 7 weeks at start of exposure	**Sodium carboxymethyl cellulose** 0; 1% (w/v) in drinking water Dose [estimated]: 1500 mg/kg bw/day Subchronic, 15 weeks	No treatment	Changes in gut microbiota composition; Colon length and weight; Faecal lipcalin-2 and macroscopic examination of inflammation parameters; Tumour development (small intestine and colon)
Gao et al (2022)	Randomised experimental study	Mouse: C57BL/6J N=40, 4 groups, 10 mice/group, sex not reported 11 weeks at start of exposure	**Carrageenan** 0; 0.5% in drinking water Subacute, 9 weeks Dose [estimated]: 900 mg/kg bw/day	No treatment	Changes in gut microbiota composition; Microscopic changes (colon); Lipopolysaccharide and D-lactic acid (serum); Myeloperoxidase activity (colonic tissue); Colon length

Reference	Study design	Population	Substance and dose(s) tested	Comparison	Endpoint(s)
Hung (2022)	Experimental study	Pigs: Topigs females (Landrace × Yorkshire) sired by Duroc boars N=36	**Carboxymethyl cellulose** Pigs were assigned to one of six dietary treatments in a 2 × 3 factorial arrangement with two basal diets – maize–soyabean meal (MSBM) and MSBM þ 30 % DDGS diets, and three levels of viscosity: non-viscous cellulose (CEL) at 5 % inclusion, medium-viscous CMC (MCMC) at 6.5 % inclusion and high viscous CMC (HCMC) at 6.5 % inclusion. Dose [estimated]: 3826 mg/kg bw/day	Two basal diets; three levels of viscosity (non-viscous cellulose; medium viscous carboxymethylcellulose; high viscous carboxymethylcellulose)	Viscosity of ileal digesta; Growth performance; Ileal digestibility; Intestinal epithelial responses to dietary fibre and viscosity; Digestive enzymes activities

3.3.3 Risk of bias assessment

The risk of bias (RoB) rating for the included studies is shown in Tables 3.3.3-1 (human studies) and 3.3.3-2 (animal studies). An overview of the reasonings for the RoB rating is available in the Supplementary Materials 2.

When description of allocation was missing in the animal studies, the scoring of the RoB question "Was allocation to study groups adequately concealed?" was changed from "Probably high RoB" to "Probably low RoB". The reason for this change is that most experimental rodents are inbred, and that allocation has less impact than for human studies. Moreover, although lack of allocation concealment has been shown to reduce effect sizes, this is mostly an issue when outcomes are subjective (Hirst et al, 2014). Since this question is not a key-question, the change had no impact on the scoring of the tiers.

The scoring of the RoB question "Can we be confident in the exposure characterisation?" were re-evaluated for all the included studies to ensure harmonisation across the original and updated scoping review. The update had no impact on the scoring of the tiers.

The human studies were assessed to be tier 3. Six animal studies were assessed to be tier 2, and ten to be tier 3.

Table 3.3.3-1. RoB rating and classification into tiers for the human studies. *Key question. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	**1**.* Was administered dose or exposure level adequately randomised?	**2**.* Was allocation to study groups adequately concealed?	**3**.* Were the research personnel and human subjects blinded to the study group during the study?	**4**. Were outcome data complete without attrition or exclusion from analysis?	**5**.* Can we be confident in the exposure characterisation?	**6**.* Can we be confident in the outcome assessment?	**7**.* Were all measured outcomes reported?	**8**. Were there no other potential threats to internal validity?	**Tier**
Hoad et al. (2004) (all but one endpoint)	+	-	-	++	+	+	++	-	3
Hoad et al. (2004) Endpoint: solid lump volume	+	-	-	-	+	-	++	-	3

Reference	**1**.* Was administered dose or exposure level adequately randomised?	**2**.* Was allocation to study groups adequately concealed?	**3**.* Were the research personnel and human subjects blinded to the study group during the study?	**4**. Were outcome data complete without attrition or exclusion from analysis?	**5**.* Can we be confident in the exposure characterisation?	**6**.* Can we be confident in the outcome assessment?	**7**.* Were all measured outcomes reported?	**8**. Were there no other potential threats to internal validity?	**Tier**
Mariotti et al. (2014)	- -	- -	-	++	+	+	++	+	3
Tomlin and Read (1988)	-	-	-	++	-	++	++	-	3
Wanders et al. (2013) Study 1	+	-	-	++	+	-	++	++	3
Wanders et al. (2013) Study 2	+	-	-	++	+	-	++	++	3

Table 3.3.3-2. RoB rating and classification into tiers of animal studies. *Key question. Definitely low risk of bias (++); probably low risk of bias (+); probably high risk of bias (-); definitely high risk of bias (--).

Reference	**1**.* Was administered dose or exposure level adequately randomised?	**2.** Was allocation to study groups adequately concealed?	**3**.* Were experimental conditions identical across study groups?	**4**. Were the research personnel blinded to the study group during the study?	**5**. Were outcome data complete without attrition or exclusion from analysis?	**6**.* Can we be confident in the exposure characterisation?	**7**.* Can we be confident in the outcome assessment?	**8**. Were all measured outcomes reported?	**9**. Were there no other potential threats to internal validity?	**Tier**
Calvert and Reicks (1988)	- -	+	++	-	++	+	-	++	+	3
Calvert and Satchithanandam (1992)	-	+	++	-	++	-	+	++	+	3
Cameron-Smith et al. (1994)	-	+	+	-	+	-	+	++	-	3
Chi-Moreno et al. (2005)	+	+	+	-	++	-	+	++	-	2
Gao et al. (2022)	+	+	++	-	-	-	-	++	+	3
Hung et al. (2022)	-	+	+	-	++	+	+	++	++	2
Mallett et al. (1984)	+	+	+	-	++	- -	-	++	+	3
McGill et al. (1977)	+	+	+	-	+	+	+	+	-	2
Pogozhykh et al. (2021)	+	+	+	-	+	-	-	++	+	3
Rideout et al. (2008)	++	+	++	-	+	-	++	++	+	2

Reference	**1**.* Was administered dose or exposure level adequately randomised?	**2.** Was allocation to study groups adequately concealed?	**3**.* Were experimental conditions identical across study groups?	**4**. Were the research personnel blinded to the study group during the study?	**5**. Were outcome data complete without attrition or exclusion from analysis?	**6**.* Can we be confident in the exposure characterisation?	**7**.* Can we be confident in the outcome assessment?	**8**. Were all measured outcomes reported?	**9**. Were there no other potential threats to internal validity?	**Tier**
Viennois et al. (2017) Study 1	+	+	- -	-	-	-	-	++	-	3
Viennois et al. (2017) Study 2	-	+	- -	-	-	-	+	++	-	3
Viennois and Chassaing (2021)	-	+	-	+	-	-	+	+	-	3
Weiner et al. (2007)	++	+	++	-	+	++	-	++	-	2
Weiner et al. (2015)	+	+	+	-	+	++	-	++	-	2
Wilcox et al. (1992)	+	+	-	-	-	- -	-	++	-	3

3.3.4 Data synthesis

In total, 21 studies (in 19 publications) are included in the present scoping review (Table 3.3.1-1). In several of the included studies, more than one relevant endpoint and/or more than one of the EST included were studied. No studies on gellan gum (E 418) fulfilled the inclusion criteria.

The 21 studies were published in the period from 1977 to 2022 (Figure 3.3.4-1) of which six were published in the time period 1977-1992; two in 1994-2003; six in 2004-2013; and seven in 2014-2024.

Five controlled human studies and 16 experimental animal studies reported four and 12 gastrointestinal-related endpoints, respectively (Figure 3.3.4-2 and Figure 3.3.4-3).

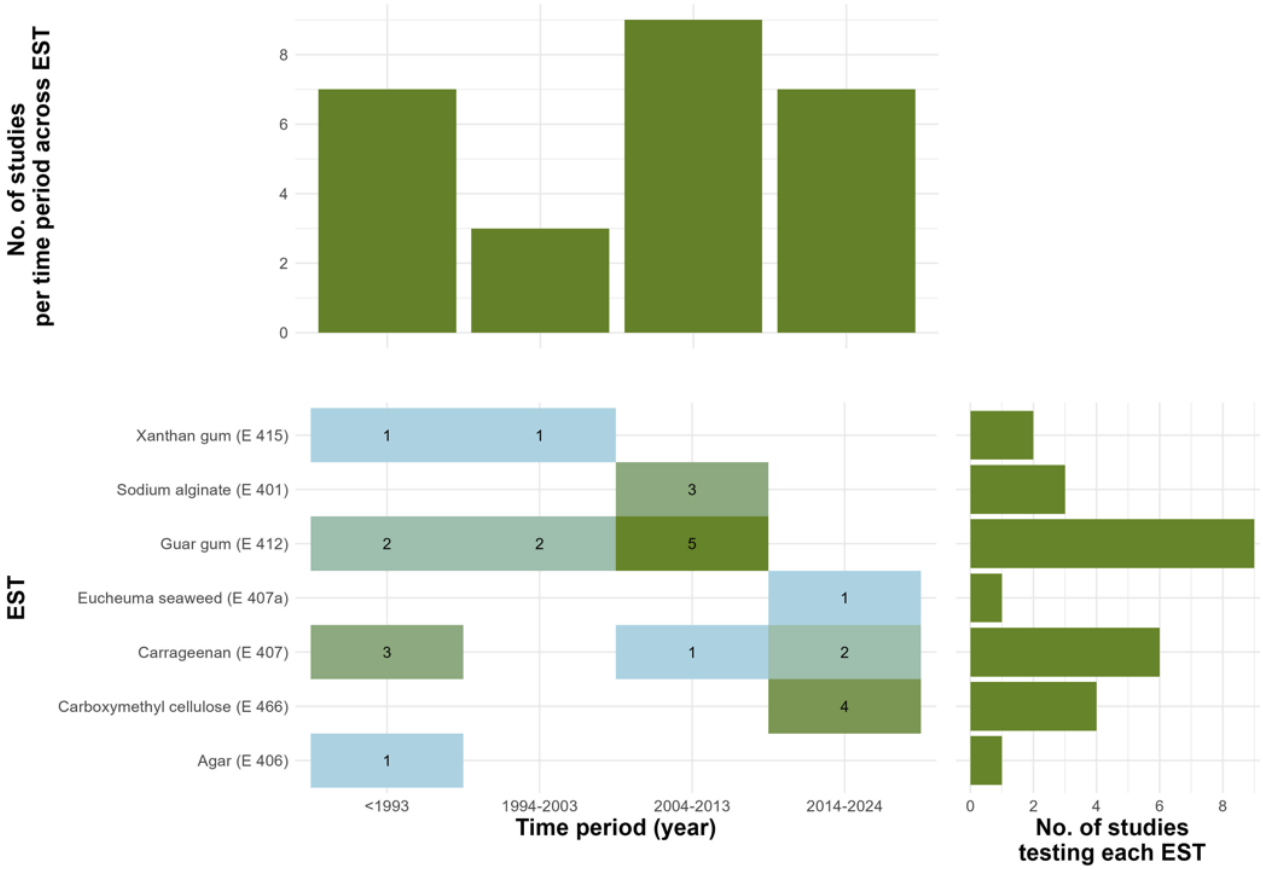


Figure 3.3.4-1. Studies on EST in different time periods. The number of studies testing an EST for a gastrointestinal endpoint for the different time periods (heat-map), number of studies across the EST for the time periods (top bar plot), and number of studies testing each EST (right bar plot). In several studies more than one of the EST were included. EST: Emulsifier, stabiliser, thickener.

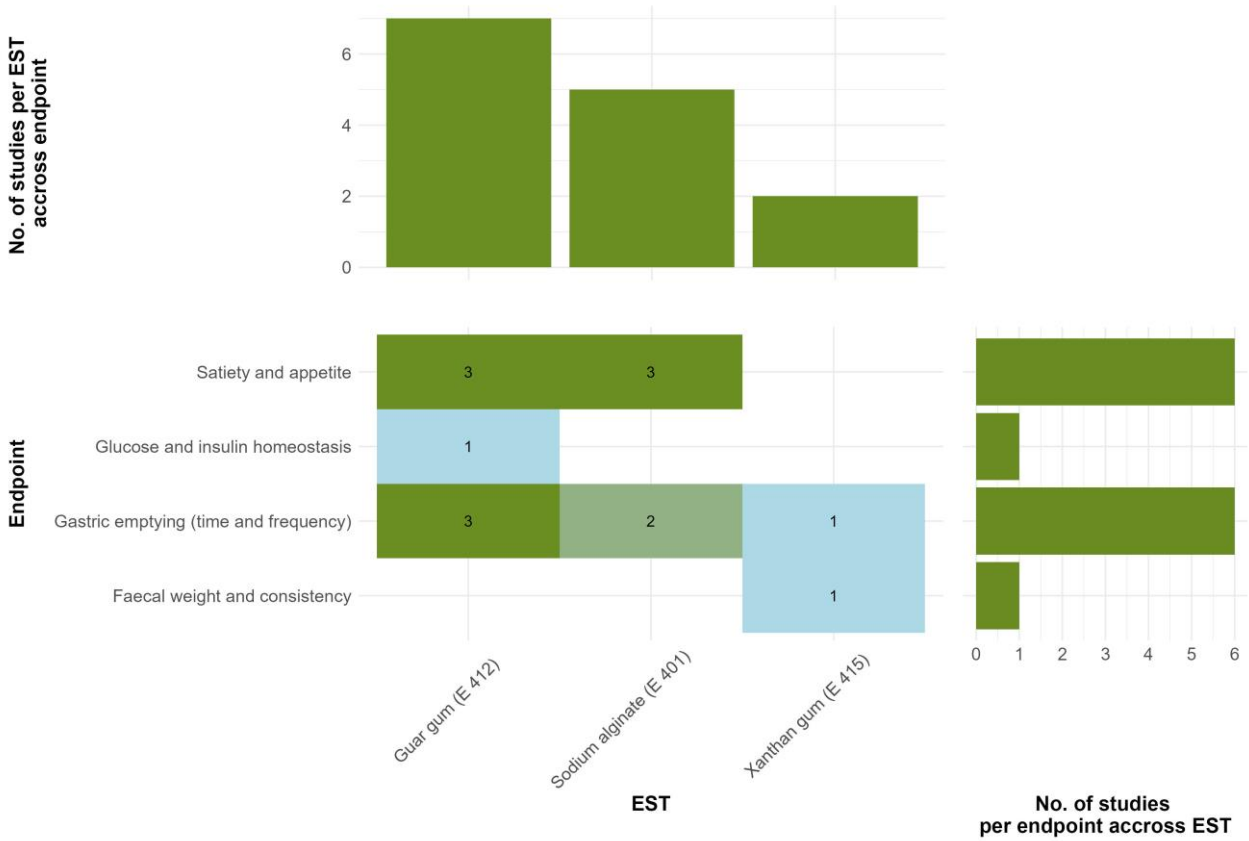


Figure 3.3.4-2. Gastrointestinal-related endpoints addressed in the human studies. The number of studies testing each EST for the different endpoints (heat map), the number of studies per EST across the endpoints (top bar plot), and the number of studies per endpoint across EST (right bar plot). In several of the included studies, more than one relevant endpoint and/or more than one of the EST included were studied. EST: Emulsifier, stabiliser, thickener.

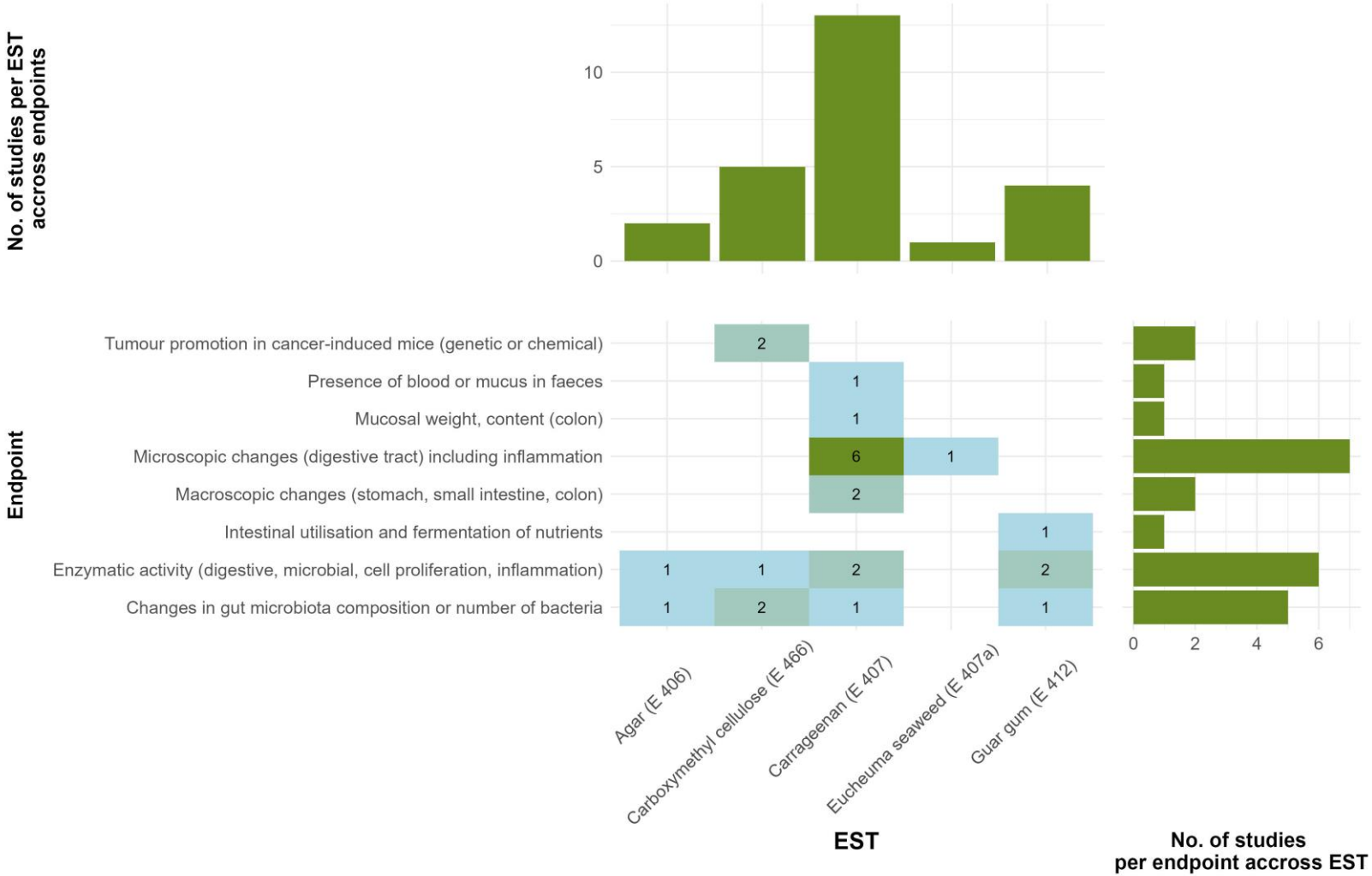


Figure 3.3.4-3. Gastrointestinal-related endpoints addressed in the animal studies. The number of studies testing each EST for the different endpoints (heat map), the number of studies per EST across the endpoints (top bar plot), and the number of studies per endpoint across EST (right bar plot) In several of the included studies, more than one relevant endpoint and/or more than one of the EST included were studied. EST: Emulsifier, stabiliser, thickener.

4 Discussion and conclusion

The previous and updated scoping reviews had the same aim, namely, to map and describe characteristics of the research literature investigating positive and negative effects on the gastrointestinal (GI) tract after intake of selected emulsifiers, stabilisers, and thickeners (EST). Thus, this scoping review is not a toxicological evaluation that can be used for regulatory purposes of the included EST. It should be noted that the gastrointestinal tract is only one of several organs and tissues that are assessed for adversity in a risk assessment of food additives.

In the previous scoping review, 214 studies fulfilled all eligibility criteria except the criterion that was specifically formulated to ensure that the EST tested would be approved for use as food additive in Norway/EU. Six studies were included following VKM's request for additional information on substance characteristics to the corresponding authors with known e-mail addresses (74/214 studies). The main reasons for the low number of eligible studies following the request were that 1) less than half of the corresponding authors replied, 2) corresponding authors could not provide the requested data, or 3) the documentation provided by the authors showed that the substance was not in accordance with our criteria. Corresponding authors of publications between 1977 and 2000 without email addresses were not contacted. since we considered it unlikely to find the address. It should be noted that 208 studies were not included due to insufficient information about the substance tested. The corresponding author of two of the publications retrieved in the updated literature search (Figure 3.2-1), were contacted to provide missing information on the test substances. However, the information we sought was not provided, and thus, the two publications were not included.

The importance of reporting the molecular weight of carrageenan was shown in a Round Robin test in which the molecular weight of batches of food grade carrageenan from several suppliers was analysed by 12 laboratories. In four out of five batches from one supplier, the analyses showed a higher content of low molecular weight carrageenan than the maximum 5% accepted according to the regulation in Norway/EU. Some of the analyses showed the presence of 10-12% carrageenan with molecular weight below 50 kDa (personal communication). Studies in which the substance investigated was not in compliance with the specifications of E 407, e.g. Bhattacharyya et al. (2017), or the molecular weight of carrageenan was missing, were not relevant for evaluation of health effects of carrageenan used as food additive in EU/Norway. Therefore, such studies were not included in either the previous or the updated scoping review. Contrary to the EU regulations, no molecular weight limitation is set for carrageenan in specifications defined by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Differences in food additive regulations between different countries and continents may explain why e.g. the molecular weight of carrageenan sometimes is not reported in studies performed outside Europe.

Animal studies accounted for 76% of the studies fulfilling the eligibility criteria in the previous and updated scoping review. Although many diseases are shared by animals

and humans, findings of gastrointestinal tract effects in animal studies cannot always be used to draw conclusions about human health (VKM, 2023), e.g.:

- Although the gastrointestinal tract in rodents and humans is similar, rodents have a forestomach that is absent in humans. Whether negative health effects observed in rodents can be expected to apply to humans must be evaluated on a case-by-case basis.
- Inflammation may play a role for certain endpoints in the included studies. Furthermore, inflammation is known to be affected by the microbiome. The microbiome in rodents and humans share only 4% of the genes, indicating that the microbiome is different in rodents and humans and that rodents may not be the most appropriate model for studies of inflammation and microbiome changes in humans (Hugenholtz and de Vos, 2018; Ward et al., 2020).

Due to the concern for an association between carrageenan and negative gastrointestinal tract effects, carrageenan has been replaced with other EST in some food products in Norway. This measure contrasts with the fact that only a few of the included studies in the current review addressed gastrointestinal tract effects of either carrageenan or relevant substitutions. Thus, the scientific basis for replacing carrageenan is weak. It is noteworthy that no studies of effects of carrageenan in humans met the inclusion criteria.

In this scoping review, VKM has not assessed whether the reported endpoints in the included studies may be beneficial or adverse or whether they are within normal physiological ranges. Neither do we report on additional findings that would be needed to determine whether a reported endpoint could lead to e.g. organ injury or adversity. Certain endpoints, such as detection of inflammatory responses may be involved in or induce several different effects, and such responses may also originate from other substances than EST or e.g. stress reactions. Most of the endpoints we report are not direct evidence of health outcomes in humans.

Conclusions

There were few eligible studies on the effects of agar (E 406), sodium alginate (E 401), carrageenan (E 407), processed Eucheuma seaweed (E 407a), sodium carboxymethyl cellulose (E 466), guar gum (E 412) and xanthan gum (E 415) on the gastrointestinal tract. In most of the studies the potential was high for systematic errors in the results or findings. None of the studies lasted long enough to evaluate long-term exposure in humans. Thus, the evidence base will be weak for assessment of the risk for negative effects on the gastrointestinal tract in humans. The conclusion in the present updated scoping review, after inclusion of six additional studies, remains the same as in the previous scoping review (VKM, 2023).

5 Data gaps

There is currently not enough data available to evaluate whether EST may induce any effect, negative or positive, on the gastrointestinal tract. Well-designed studies with sufficient study sizes are needed that include sufficient description of the substances to be tested to ensure that they fulfil the criteria for being used as a food additive in Norway/EU

Studies addressing effects related to long-term exposure are needed, because it is likely that most of the population are exposed to EST during their entire lifetime.

6 Supplementary materials

Supplementary materials 1: here

This Excel file includes:

- An information sheet providing guidance on the contents of Supplementary Materials 1.
- The references of studies identified in the updated literature search that were assessed in full text.
- The references of the studies where we have contacted the corresponding author to retrieve more information about the substance tested.
- An overview of the studies retrieved in the updated literature search where the full text was assessed against the eligibility criteria.
- An overview of the studies where we have contacted the corresponding author to retrieve more information about the substance tested.
- An overview of the studies fulfilling the eligibility criteria, including the studies from the original mapping.
- An overview of the extracted data from all human studies fulfilling the eligibility criteria, including the studies from the original mapping.
- An overview of the extracted data from all animal studies fulfilling the eligibility criteria, including the studies from the original mapping.
- An overview of the doses tested in the human studies fulfilling the eligibility criteria, including the studies from the original mapping.
- An overview of the doses tested in the animal studies fulfilling the eligibility criteria, including the studies from the original mapping.
- The data used for the creation of Figures 3.3.4-1, 3.3.4-2, and 3.3.4-3.

Supplementary materials 2: here.

This Excel file includes:

- References of the included studies.
- The risk of bias assessment of the human studies.
- The risk of bias assessment of the animal studies.

Scripts used for the creation of Figures 3.3.4-1, 3.3.4-2, and 3.3.4-3: here.

Data and the R script used to clean data files for making Figure 3.1-1., Figure 3.3.4-1, Figure 3.3.4-2, and Figure 3.3.4-3: here.

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Appendix 1: Request for information

Dear Dr. [name],

We are contacting you to enquire about specific chemical properties of [name of chemical substance] which was investigated in your study [title of the study] published in [title of the journal] [year of publication].

The Norwegian Scientific Committee for Food and Environment (VKM) has recently carried out a systematic scoping review to map the research literature investigating effects on the gastrointestinal tract after intake of emulsifiers, stabilisers, and thickeners (Scoping review of research on gastrointestinal effects of selected emulsifiers, stabilisers, and thickeners, ISBN: 978-82-8259-435-6). Your study was retrieved in the literature search; however, it could not be included in the scoping review because it had insufficient description of chemical properties.

We are currently updating the scoping review, and would appreciate the following documentation which will enable us to determine whether we can include your study in the update:

For guar gum, sodium alginate, and xanthan gum:

- Was the substance food grade? If yes, please describe how this was documented. We would also appreciate a copy of the documentation.

For carrageenan:

- Was the substance hydrolysed or chemically degraded? If yes, please describe how this was documented?
- Was the molecular weight fraction less than 50 kDa no more than 5%? If yes, please describe how this was documented.
- We would also appreciate a copy of the documentation.

For sodium carboxymethyl cellulose:

- Was substitution described and degree of substitution not less than 0.2 and not more than 1.5 carboxymethyl groups ($-CH_2COOH$) per anhydroglucose unit? If yes, please describe how this was documented. We would also appreciate a copy of the documentation.

Your response will be of high value to ensure that all relevant data are included in the updated scoping review. Please contact us if you have any questions.

Appendix 2: Literature search

Total number of records before deduplication = 332. Total number of records after deduplication = 241.

Database: **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <March 2023 to June 10, 2024>**

Date: 11.06.2024

Records: 111 (2 systematic reviews)

1	Agar/ or Carrageenan/ or Carboxymethylcellulose Sodium/ or Alginates/	38549
2	(agar or "9002-18-0" or "E406" or carr#g?e?n* or "9000-07-1" or "E407" or "carboxymethyl cellulose" or carboxymethylcellulose or K679OBS311 or "9004-32-4" or "E466" or "E407a" or processed Eucheuma seaweed? or sodium alginate? or "28961−37−7" or "E412" or gellan gum? or "E412" or guar gum? or xanthan gum? or "E415").tw,kf.	104030
3	or/1-2	121379
4	exp Gastrointestinal Tract/	702978
5	((GI or gastrointestinal or "gastro intestinal" or digestive or alimentary or aliment or gastrointestine or intestine) adj (tract? or tractus or canal?)).tw,kf.	112675
6	or/4-5	781646
7	3 and 6	4115
8	limit 7 to "therapy (maximizes sensitivity)"	1493
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.	3986770
10	8 or (7 and 9)	1729
11	exp Rodentia/ or Mice/ or Animals/ or Rats/ or Rabbits/ or Dogs/ or Haplorhini/ or Swine/ or Guinea Pigs/	7475030
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.	10904508
13	or/11-12	13299100
14	7 and 13	2897

15	10 or 14	3283
16	(202303* or 202304* or "202305" or 202306* or 202307* or 202308* or 202309* or 202310* or 202311* or 202312*).ep,ed,dt.	1429742
17	(202401* or 202402* or 202403* or 202404* or 202405* or 202406*).ep,ed,dt.	870397
18	or/16-17	2128607
19	15 and 18	111
20	limit 19 to "reviews (maximizes specificity)"	2
21	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.	570008
22	20 or (19 and 21)	2

Database: Embase <March 2023 to 2024 June 10>

Date: 11.06.2024

Records 146 (2 systematic reviews)

1	agar/ or carrageenan/ or carboxymethylcellulose/ or alginic acid/ or gellan/ or guar/ or guar gum/ or xanthan/	84537
2	(agar or "9002-18-0" or "E406" or carr#g?e?n* or "9000-07-1" or "E407" or "carboxymethyl cellulose" or carboxymethylcellulose or K679OBS311 or "9004-32-4" or "E466" or "E407a" or processed Eucheuma seaweed? or sodium alginate? or "28961−37−7" or "E412" or gellan gum? or "E412" or guar gum? or xanthan gum? or "E415").tw,kf.	125043
3	or/1-2	161613
4	exp gastrointestinal tract/	80425
5	((GI or gastrointestinal or "gastro intestinal" or digestive or alimentary or aliment or gastrointestine or intestine) adj (tract? or tractus or canal?)).tw,kf.	152695
6	or/4-5	195137
7	3 and 6	2042
8	limit 7 to "therapy (maximizes sensitivity)"	210

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.	5408039
10	8 or (7 and 9)	351
11	exp rodent/ or mouse/ or animal/ or rat/ or leporidae/ or dog/ or haplorhini/ or pig/ or guinea pig/	5553867
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.	13465390
13	or/11-12	14525753
14	7 and 13	1235
15	10 or 14	1373
16	(2023* or 2024*).yr,dd,dp,dc.	3227664
17	(202303* or 202304* or "202305" or 202306* or 202307* or 202308* or 202309* or 202310* or 202311* or 202312*).dd,dc.	1592955
18	(202401* or 202402* or 202403* or 202404* or 202405* or 202406*).dd,dc.	1060542
19	or/16-18	3227664
20	15 and 19	146
21	limit 20 to "reviews (maximizes specificity)"	2
22	exp Meta-Analysis/ or "systematic review"/ 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.	816757
23	21 or (20 and 22)	2

Database: Web of Science

Date: 11.06.2024

Records: 75 (0 systematic reviews)

#	Search Query	Results

1	TS=("Agar" or "9002-18-0" or "E406" or "carrageen*" or "carragen*" or "carrhagen*" or "carragheen*" or "carrogeen*" or "carboxymethyl cellulose" or "carboxymethylcellulose" or "K679OBS311" or "9004-32-4" or "E466" or "E407a" or "processed Eucheuma seaweed$" or "sodium alginate$" or "28961−37−7" or "E412" or "gellan gum$" or "E412" or "guar gum$" or "xanthan gum$" or "E415")	136768
2	TS=(("GI" or "gastrointestinal" or "gastro intestinal" or "digestive" or "alimentary" or "aliment" or "gastrointestine" or "intestine") NEAR/0 ("tract$" or "tractus" or "canal$"))	112861
3	#1 AND #2	1191
4	TS=("randomized" or "randomised" or "randomly" or "rct" or "placebo" or "trial" or "groups")	5038603
5	#3 AND #4	153
6	TS=("ex vivo" or "exvivo" or cell$ 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")	14020994
7	#3 AND #6	751
8	#5 OR #7	808
9	#5 OR #7 Timespan: 2023-03-01 to 2024-06-30	75
10	TS=(("systematic*" NEAR/1 "review*") or ("review" and (("structured" or "database*" or "systematic*") NEAR/1 "search*")) or "integrative review*" or ("evidence" NEAR/1 "review*")) OR TI=("metaanal*" or "meta anal*") OR AB=("metaanal*" or "meta anal*")	640191
11	#9 AND #10	0
12	#9 NOT #11	75