

# APPENDIX 3

## Evidence review protocol overview

### Research aims:

Our focus will be on studies that provide primary empirical data, with robust methodologies, which provide evidence on one or more of the research questions. We will synthesise the evidence from relevant literature on food hypersensitivities (FHS) to support the FSA in answering priority research questions identified during a priority setting exercise on research into food hypersensitivity. In particular, evidence around appropriate and effective actions to ensure food safety and consumer choice, as per the project specification. Food hypersensitivities (FSH) encompass:

- **Food allergy:** sufferers experience immune system responses after ingesting certain foods (also referred to as IgE mediated reactions);
- **Food intolerance:** sufferers experience difficulty in digesting certain foods and experience negative physical reactions after ingesting certain foods (also referred to as non-IgE mediated food hypersensitivity/ non-allergic food hypersensitivity); and
- **Coeliac disease:** a condition where the immune system attacks the body after ingesting gluten.

### Primary research questions

Indicative uncertainty	Research Question	Relevant examples
<b>Risks posed to people with FHS by new/novel foods and/or processes</b>	<p>In individuals with FHS, what measures are needed to monitor for FHS reactions due to:</p> <ul style="list-style-type: none"> <li>• new uses of known allergens?</li> <li>• novel proteins which might induce sensitisation and thus clinical reactivity?</li> </ul> <p>What protocols should the FSA have when assessing</p>	<p>eg. The use of pea protein in protein concentrates, which is often declared only as “vegetable protein” in ingredients listing.</p> <p>eg. Wheat-based starch in packaging, or latex-based binders in packaging and sustainable cutlery. Does not refer</p>

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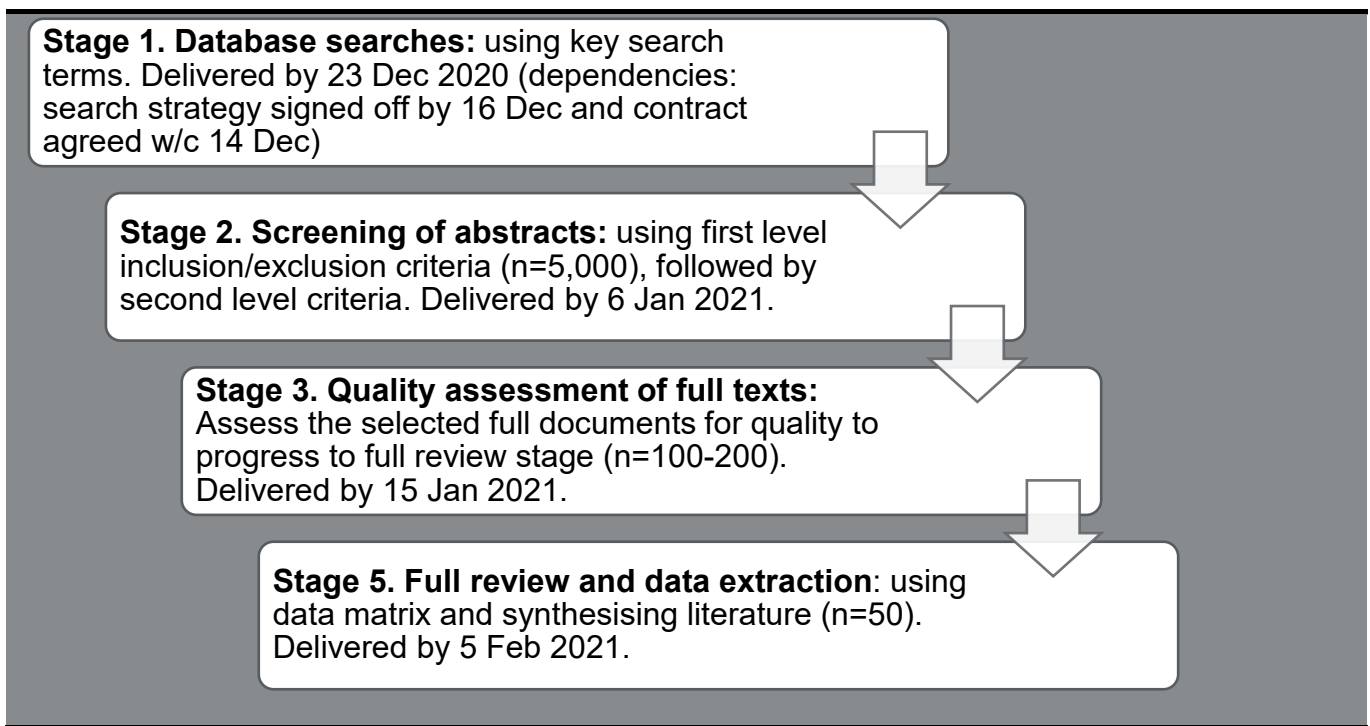
	<p>the risk to consumers with FHS posed by novel foods/ processes/ packaging?</p> <p>What data exist as to the likelihood of allergenic proteins in biobased food contact materials migrating into foods?</p>	<p>to risk of occupational allergy due to biobased food contact materials.</p>
<p><b>Improving traceability of allergens in the food supply chain</b></p>	<p>How should allergen information be communicated to consumers with FHS, in order to:</p> <ul style="list-style-type: none"> <li>• Improve consumer confidence in terms of possible allergen content?</li> <li>• Reduce the incidence of unintended allergen exposure?</li> </ul>	
<p><b>Risks posed due to shared production of foods, and how can these be mitigated</b></p>	<p>What are the health risks to consumers with FHS due to allergen cross-contact during food production?</p> <p>How effective are different control options in reducing these health risks?</p>	<p>eg. Shared production in small kitchens. Use of shared ovens (eg. gluten-free foods cooked in the same oven as gluten-containing foods).</p> <p>eg. Different cleaning strategies.</p>
<p><b>Communicating risk, so that consumers with FHS can be confident that the food they are provided is safe</b></p>	<p>What are the most effective ways for food business operators (FBOs) to communicate a level of competence (with respect to allergen risk management) to consumers?</p>	
<p><b>Allergen labelling, including Precautionary Allergen (“may</b></p>	<p>What forms of allergen labelling are effective for consumers to make informed decisions as to</p>	<p>Labelling to inform both what is present, what might be present (through cross-contact), and what is not present (whether or not a “free-from” claim is made).</p>

<b>contain”) Labels</b>	whether a food is “safe” for purchase/ consumption?	
<b>Informing the FSA as to incidents involving food hypersensitivity</b>	<p>What evidence is there for different reporting systems (eg. mandatory hospital reporting, reporting by FBOs) to deliver useful data to regulators that can impact on reducing the risk of unintended allergen consumption?</p> <p>What are the barriers that prevent reporting of near misses and other incidents to official bodies?</p>	<p>Reporting systems might include:</p> <ul style="list-style-type: none"> <li>• Mandatory/ voluntary reporting by healthcare professionals.</li> <li>• Direct reporting by food businesses</li> <li>• Strategies to overcome fear of enforcement such as no-blame approaches to increase reporting</li> <li>• Direct reporting by members of the public (and how to mitigate against the risk of “noise” in the signal)</li> <li>• Surveillance of serious incidents eg. deaths via the coronial system</li> </ul>
<b>Impact of co-factors on reaction severity</b>	<p>In consumers with FHS, what are the factors which can increase the risk of a severe reaction?</p> <p>How should risk posed by co-factors be communicated to those affected by FHS?</p>	<p>Incorporates both general advice to all FHS consumers, and individualised advice with respect to patient-specific co-factors.</p>
<b>Impact of socioeconomic factors (including race/ethnicity) on FHS</b>	<p>What are the socioeconomic factors which impact on risk in consumers with FHS?</p> <p>How do cultural attitudes impact on the management of FHS?</p>	<p>Includes:</p> <ul style="list-style-type: none"> <li>• understanding the impact of ethnicity/ race as a potential confounder</li> <li>• language difficulties in getting effective advice and communicating consumer needs</li> <li>• impact on affordability/ accessibility/ availability to appropriate foods for those with FHS</li> </ul>
<b>Impact of environmental exposures on the risk of developing FHS</b>	<p>What are the factors that drive a loss of immune-tolerance to food allergens?</p>	<p>Applies to both adults and children A priority question once FSA better understands how common loss of prior tolerance is as a presenting symptom.</p>

<b>Current knowledge of FHS amongst the general public</b>	What are the current gaps/ inaccuracies in knowledge with respect to FHS amongst the general public?	Focus on general public, but also applies to specific stakeholders eg. FBOs, healthcare.
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### Protocol for searching, screening and reviewing the literature

The flow chart below explains the four stage process for our rapid evidence review, culminating in data extraction and synthesis of literature. Please note, a 10% sample of literature will be completed by two reviewers for the purposes of validation.



#### Stage 1. Database searches:

We will be reviewing relevant literature from two types of sources: published studies in scientific journals and grey literature from government and other public agency sources. UCC Library Services (led by Donna Ó Doibhlin) will conduct the search for published/academic literature based on agreed search terms and RSM will search the grey literature.

Alongside the formal search strategy, the academic advisors will identify key sources, including those not yet published, based on their own knowledge and networks. RSM will also issue a call for evidence and ask the FSA, our advisors and three key charities who we are working with on our existing project with the FSA (Allergy UK, The Anaphylaxis Campaign, Coeliac UK) to disseminate this call for evidence. We will pay particular attention to any studies underway since

the Covid-19 pandemic began, given the potential impact on food production, consumption and experience for people with FHS.

We propose to use the following search criteria and databases, but these may need to be further refined depending on the number of 'hits' returned from the database searches.

<b>Search terms and criteria</b>	
<b>Language:</b>	English
<b>Time period:</b>	January 1996 – Present (as per the specification) Particular attention to be paid to literature published since January 2020 which considers impact (or potential impact) of covid-19 May need to include studies before 1996 if seminal studies are identified
<b>Countries:</b>	OECD Countries
<b>Search strings:</b>	(food hypersensitivities OR food hypersensitivity OR food allergy OR food allergies OR food intolerance OR celiac OR coeliac OR food allergen OR food allergens OR food sensitivities OR food anaphylaxis) <b>AND</b> (Risk OR New/Novel OR Packaging OR Communication/Messaging OR Management OR Cross-contact/Cross-contamination/Shared OR Labelling/Label/Labels OR Reporting OR Socioeconomic OR Cultural OR Tolerance OR Knowledge/Opinion OR Public OR Exposure OR Incidents OR Supply Chain/Production/Processes OR Precautions OR Covid-19)
<b>Databases:</b>	<b>Published/Academic Literature:</b> Medline/PubMed, Embase, ScienceDirect (Elsevier), Google Scholar, Web of Science, Scopus, CINAHL  <b>Grey Literature:</b> <ul style="list-style-type: none"> <li>Government sources (UK sources including FSA, HSE, Defra, PHE; and international sources e.g. EU (particularly EFSA) or US</li> </ul>

	<p>(particularly FDA) data, and international organisations like the WHO)</p> <ul style="list-style-type: none"> <li>• Relevant third sector organisations (Allergy UK, the Anaphylaxis Campaign, National Allergy Strategy Group and Coeliac UK)</li> <li>• Internet search engine searches</li> </ul>
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## Stage 2. Screening of abstracts:

We will review the longlist of c.5,000 abstracts or introductions of published and unpublished studies, articles and reports ('grey literature') pertaining to the research questions on FHS as specified above. We will use an online proforma to ensure a standardised and systematic process.

Stage 2a) The table below sets out the first level inclusion/ exclusion criteria which we will apply to each abstract. We anticipate excluding at 25% to 50% at this point either because they are not of central relevance to FHS or they are duplicate studies in our sample.

1st level criteria	Inclusion criteria	Exclusion criteria
<b>Type of allergies:</b>	Food hypersensitivities/ allergies/ coeliac/ anaphylaxis are the focus of the study	Hypersensitivities/ allergies/ anaphylaxis mentioned, but not related to food
<b>Other</b>		Duplicates (UCC to remove most during search stage, but some duplicates are likely to remain)

Stage 2b) The second level inclusion/ exclusion criteria will then be applied to each abstract that passes the first level criteria. The second level criteria are listed below and relate to the detailed research questions. These may need to be refined depending on the number of studies retrieved during stage 1 search. Abstracts which do not meet any second level inclusion criteria will be discarded and the remaining abstracts will form the shortlist of relevant literature for further screening and quality assessment at stage 3.

2 <sup>nd</sup> level criteria	Inclusion criteria	Exclusion criteria
<b>Topics based on research questions:</b>	<p>Related to one or more these topics:</p> <ul style="list-style-type: none"> <li>• Risk to consumers with FHS posed by new/ novel types of foods/ processes/ packaging (eg. Biobased packaging)</li> </ul>	Not related to any of the topics related to the research questions

	<ul style="list-style-type: none"> <li>• Traceability of allergens in the food supply chain</li> <li>• Communication of allergen information</li> <li>• Cross-contamination/ cross-contact of allergens during food production and ways to reduce this risk</li> <li>• Communication of allergen risk management</li> <li>• Allergen labelling</li> <li>• Reporting systems on incidents involving food hypersensitivity and obstacles that hinder reporting</li> <li>• Other factors which increase risk of severe reaction</li> <li>• Socioeconomic/ cultural factors related to FHS</li> <li>• Environmental exposures on the risk of developing FHS</li> <li>• Current knowledge of FHS amongst general public (only recent studies in last 5 years as emphasis is on current)</li> </ul>	
<p><b>Outcome:</b></p>	<p>Outcomes/Impact on the health and risks faced by consumers with FHS caused by:</p> <ul style="list-style-type: none"> <li>• new foods/processes/packaging and cross-contamination</li> <li>• socioeconomic/cultural factors</li> <li>• environmental exposures</li> <li>• level of awareness of FHS amongst general public</li> </ul> <p>Effectiveness of the methods/systems in terms of reducing risks associated with FHS:</p> <ul style="list-style-type: none"> <li>• communication methods on allergen information/management (including effective labelling) and factors increasing risk of severe reactions</li> </ul>	<p>Does not have any of the outcomes/impacts/effectiveness of methods associated with the research questions</p>

	<ul style="list-style-type: none"> <li>reporting systems on incidents and 'near misses'</li> </ul>	
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**Stage 3. Quality assessment of full texts:**

From stage 3, we expect to generate a shortlist of c.100-200 studies and we will obtain and screen the full texts to identify the final list of the most relevant and pertinent studies to undergo full review at stage 4. We will work with the FSA and our advisors to agree this final list. The selection will be based on tighter inclusion criteria including quality measures ie. the extent to which methodologies/ evidence bases are robust using the AMSTAR checklist (source: [https://amstar.ca/Amstar\\_Checklist.php](https://amstar.ca/Amstar_Checklist.php)) together with GRADE criteria.

**Stage 4. Full review and data extraction:**

We will complete a full review of c.50 studies and extract data into separate spreadsheets for each research question, using the headings suggested below. The final list of studies will be further interrogated for quality. The process for data extraction will be to start with systematic reviews, thus getting an overview of the evidence and then proceeding to individual studies.

For data extraction, we will specify the headings used to extract information into the data extraction spreadsheet (effectively a coding framework). Headings will likely include title, author, date, country, study type, study aims, methods/ evidence base, findings, strengths and limitations reported in study, key themes/topics, relevant outcomes and a quality appraisal:

**Table for each research question:**

URN	Authors/ Year/ Title	Country	Study type and aims	Methods and quality appraisal	Findings	Key themes/ topics	Strengths/limitations reported in study	Relevant outcomes associated with research questions

Quality appraisals will be completed concurrently with the extraction process. Given the breadth of research likely to be picked up in this review, we suggest using the Mixed Methods Appraisal Tool which has 19 screening questions to assess qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies, and mixed methods studies (source: <https://www.nccmt.ca/knowledge-repositories/search/232>).

Findings will be synthesised according to the research questions and written up into separate report sections.