Rapid projects support government departments to understand the scientific evidence underpinning a policy issue or area by convening academic, industry and government experts at a single roundtable. These summary meeting notes seek to provide accessible science advice for policymakers. They represent the combined views of roundtable participants at the time of the discussion and are not statements of government policy.

"What is the evidence base for plausible biological mechanisms for health impacts of ultra-processed foods (UPF)?"
Meeting notes from roundtable chaired by Robin May, Chief Scientific Adviser at the Food Standards Agency, facilitated by the Government Office for Science
20th November 2023, 11:00-12:30

Key points

- Plausible mechanisms for UPF health impacts include impacts on appetite, energy bioavailability, micronutrient intake and absorption, gut permeability, microbiome composition and others, but evidence varies for the degree of impact they can have.
- UPF classifications are broad, which is useful for flexibility in research methodology but challenging for 'stratifying' data. Breaking them down into sub-types of processing would enable research to draw and communicate better conclusions about outcomes of interest, and therefore mechanisms.
- Different types of processing, in the absence of any changes in composition, are known to impact on energy/nutrient availability; for instance, by impacting on molecular stability.
- Setting up infrastructure and methodology for domiciled feeding studies should be a research priority. These are the most robust way to measure biological impacts of food. However, they require significant resource, particularly when comparing UPF and non-UPF versions of the same foods.
- Innovative research methodologies to isolate causal biological mechanisms include stem-cell based micro gut models/organoid systems, examining localised gastro-intestinal systems and using camera technologies coupled with AI to identify 'real-life' food habits.

1. Plausible mechanisms

1.1 Importance of definitions and labelling in establishing mechanisms

- In this roundtable, UPFs were defined loosely as products that typically contain large numbers of ingredients produced commercially, rather than domestically, and involving production methods that are not achievable during home preparation.
- The Nova system of food classification uses descriptive criteria to assign foods to four groups based on processing-related criteria (Petrus et al., 2021). Within the UPF classification, recent studies show that some food groups have positive effects on health outcomes while others have negative effects on the same outcomes (Chen et al., 2023).
- This system has problems as it is broad, but changing it substantially would invalidate research to date. Instead, the four groups need to be further broken up to enable better defined research hypotheses around mechanisms and health outcomes.

- The UPF impact mechanisms that researchers seek to measure will depend on the outcome of interest, such as energy imbalance or chronic inflammation. Mechanisms could be divided into two broad sub-topics: those which drive overconsumption of calories, leading to obesity, and those through which UPFs, once consumed, could cause harm to biological systems, with outcomes such as enhanced cancer risk (noting that obesity itself can also have such biological impacts).
- An important mechanism is the sheer availability of UPFs compared to non-UPFs (in terms of market provision and affordability) that will impact health beyond purely biological terms.

1.2 Appetite and levels of consumption

- The energy availability of UPFs is higher when food is processed in certain ways. For example, as the absorption rate, glycaemic index and rate of energy uptake is modified in a product, a consumer may need to eat more to reach satiety. There is also evidence that UPF foods are consumed faster than non-UPF equivalents, leading to overeating (Forde et al., 2020).
- Cohort studies show that HFSS (High in saturated Fat, Salt and Sugar) foods are often UPFs, so it is difficult to empirically control for processing in respect to appetite.
- In controlled studies using calorie-labelled foods, some study participants may consume 400-700 more calories per day than their usual diet. As such, their overconsumption relative to their baseline levels may affect study results. It was also noted that these studies currently require residential lab facilities, so participants may not be carrying out their usual day-to-day activities.
- There is evidence that people who consume higher levels of UPFs have lower micronutrient status. This status is particularly important in mother and infant nutrition, and in later life (Antoniazzi et al., 2022; Garcia-Blanco et al., 2023). One possible explanation is that UPFs replace micronutrient rich foods in people's diets.
- The addiction potential of different foods was discussed, but the consensus was that there is little evidence of foods themselves being addictive. The 'addiction' comes more from the addictive style of eating palatable foods, where the hedonic effect of eating is the driver. Choice and preference are different from physiological or psychological addiction (Hall, 2020).

1.3 Gut permeability & microbiome

- Research into emulsifiers has demonstrated varying effects. A high emulsifier dosage study in mouse models investigated changes in the microbiome and epithelial cells (Bancil et al., 2020). It showed an increase in inflammation in the gut, although the effect differs between emulsifiers. Gut permeability is theorised to increase due to microbiome disruption, as there is a decreased mucosal gut barrier.
- While UPF components will always influence the microbiome to some degree, it is difficult to interpret studies that show associations rather than causal effects, because there is no 'ideal' or baseline microbiome, and because the consequences of changes in the microbiome for health are not understood.
- There is some evidence that emulsifiers can impact an individual's microbiome, with dietary emulsifiers contributing to a pro-inflammatory gut microbiota. There is also a decrease in diversity within the gut microbiome caused by certain emulsifiers (Bancil et al., 2020).

1.4 Food structure (mechanical vs chemical changes)

- Currently, there is inadequate understanding of how the combination of chemical and mechanical changes occurring during food processing affects the digestion, absorption and utilisation of nutrients in foods.
- Some mechanical processes, such as cooking, may not involve the addition of other components to food, yet by changing the fundamental matrix structure of the raw material they will affect the bioavailability of nutrition within the food for a given quantity consumed.
- The effects of mechanical changes in food have been investigated using almonds undergoing varying levels of mechanical processing (grinding, roasting or blanching) (Grundy et al., 2016). The results suggest that the bioavailability of the nutrition changes depending on the portion of the gut associated with nutritional absorption. However, the largest overall change in effect was due to the amount people consumed, not the make-up of the food, highlighting availability as a basic but important factor for health impacts.

2. Outstanding research priorities

2.1 Domiciled diet experiment infrastructure

- It was agreed that the most robust way to study biological impact of food consumption is to design controlled feeding studies with no variation between study participants' food intake (Hall, 2020).
- There are US research studies using caloric restriction, calorie balance or measured *ad libitum* feeding (where researchers measure the food not consumed) to analyse intake.
- The consequence of not adequately controlling feeding environments is not being able to guarantee adherence to diets, and therefore potentially skewing scientific results.
- Data for non-mass market foods, such as homemade bread, are hard to generate without a systematic approach. This makes experimental comparison between mass market and non-UPF foods very difficult.

2.2 Exploring cumulative and interacting components

- The current regulatory science approach is to assess and test each additive, ingredient or process at a time, but this is not always the most appropriate method due to the clusters of ingredients usually present and consumed in UPFs. There is also a question of whether current regulatory approaches can account adequately for the cumulative and interactive effects of food additives.
- Research should be conducted along the spectrum of, at one end, measuring single variables in isolation, repeating them with each variable of interest, through to the other end of embracing the diversity of variables in UPFs and therefore looking at population studies.
- New methodologies are being, and should continue to be, developed to conduct detailed studies on different organs, such as through stem cell-based micro gut models or other organoid systems. These methods have developed substantially in the last decade, including advances in metabolomic studies using urine, which allow researchers to confirm what participants ate during a 'real-world' trial.

2.3 Capturing 'real-world' food behaviour

- There is promising use of camera technology coupled with AI to identify food behaviours in real life, as there is often substantial variation within meal-to-meal food consumption. However, validating the use of these technologies may be challenging (Hall, 2020).

- Accessing data on real-world purchasing decisions by consumers would allow a better understanding of what people are choosing to eat.
- Allowing participants to choose foods from menus or manipulating food 'prices' within a study could enable study of factors affecting food choice.
- Retailers and the wider industry hold substantial data not publicly available on the consumption habits of wider groups, including how socio-economic factors interact with consumption patterns of UPFs. Access to such data would be a powerful research tool.

2.4 R&D considerations to enable research

- It was suggested that by reframing research into UPFs as conferring both positive and negative effects (Chen et al., 2020), it may enable more collaboration between industry and regulators. This could take the form of improving nutritional benefits in foods or increasing how they create satiety in consumers. This would require considerable 'trust building' first, given widespread suspicion in the media around conflicts of interest.
- Animal studies are a useful model, but current and emerging methods for human research provide more applicable data. *In vitro* methods using organoids to model intestine or liver behaviour have shown promise in lowering the cost burden of this research.
- Greater transparency concerning the amounts (rather than just presence) of additives that companies use in products, such as emulsifiers, nanoparticles or colourings, would be beneficial. Currently, most studies can only differentiate foods by the presence or absence of certain additives, which may not reflect realistic exposure through 'normal' consumption.
- In the absence of specific data on the contents of particular foods, it was suggested that a metabolic study-based approach could be harnessed to show how individual foods are digested by consumers. This includes using intake biomarkers (from urine and blood) for more accurate quantification of exposure to UPFs.
- New technologies can enable studies of localised areas affected by UPFs, such as the gastrointestinal environment, rather than (or as well as) measuring systemic biomarkers.
- Bringing networks of labs/industries together to share and convene research on complex systems such as the gastrointestinal tract would be useful. These could join up small cohort studies focused on specific mechanisms and outcomes.

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Observers: FSA, DHSC and OHID Officials

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Epidemiology and clinical trials in relation to health impacts of ultra-processed food
Meeting notes from roundtable chaired by Ian Young, Chief Scientific Advisor, Department of Health Northern Ireland
27th November 2023, 13:00 – 14:30

Key points

- The Scientific Advisory Committee on Nutrition (SACN) statement review of evidence remains valid, although the amount of emerging evidence is substantial.
- A recent high quality Lancet report (Cordova et al., 2023) and a recent paper on diabetes risk (Chen et al., 2023) reinforce the concept that not all UPF, as defined by NOVA, are associated with adverse health outcomes.
- Establishing sub-categories of UPF foods with different nutritional characteristics and health effects within NOVA may be helpful in informing future policy.
- The main value of controlled clinical trials is likely to be the understanding of mechanisms by which UPF may have health effects.
- Epidemiological studies should be hypothesis driven, based on plausible mechanisms and exposures which are likely to be physiologically relevant.
- Consideration should be given to grouping additives and aspects of processing by potential mechanisms of action - for example, eating rate, palatability, appetite, digestion etc. This may help to address the very large number of processes, additives and mechanisms potentially involved, not all of which may be harmful or beneficial.

1. Is the existing basis of epidemiological and clinical data provided by the SACN report adequate and comprehensive?

- The SACN statement covers the majority of the high-quality evidence derived from epidemiological studies and clinical trials available at the time of its publication. However, it was pointed out that the area of UPF is a fast-moving space with an ever-increasing volume of evidence, including an important recent Lancet report (Cordova et al., 2023) and a paper on UPF and type 2 diabetes risk (Chen et al., 2023).
- The SACN statement considered lower quality (e.g. cross sectional) evidence as well as higher quality evidence (prospective epidemiological studies and clinical trials). However, given the increasing number of studies in the field it was suggested that future reports should include only the stronger evidence. Many observational studies published to date do not report on how foods were attributed to different processing categories or on how agreement was reached in the ways foods were coded, do not adequately correct for known covariates (such as dietary energy density, diet quality etc), and do not consider the role of specific food groups in driving observed associations.
- Along with study quality, the dietary assessment methods and tools employed also need to be considered. Dietary intake is primarily self-reported using assessment methods (such as FFQs) that were not designed with assessment of food processing in mind, which presents

difficulties when assessing the data. This also highlights the need to expand the available databases to include information about processing as well as nutritional content.

2. Are we using an appropriate classification system for UPF?

The previous workshop on mechanisms touched on the need to use an appropriate classification system. The SACN statement considered the range of classifications available. The NOVA system is currently the one predominately used but has limitations, in particular through not considering nutritional composition.

- While there were mixed views on this, developing a new classification system was generally considered difficult given that NOVA dominates existing and current literature in the field. However, the validity of NOVA as a system that characterises the level of processing of foods was questioned and its limitations were highlighted; for example, there is considerable inter-individual variation when researchers seek to classify foods.
- NOVA is currently not sufficiently nuanced and does not distinguish between foods with very different nutritional value which may be subject to similar degrees of processing. It also does not consider cost and sustainability, two important aspects that should be communicated to the public. Additionally, NOVA seems to be misaligned with public health priorities, as it does not distinguish between additives that are associated with potential adverse health effects and added nutrients for the purpose of fortification in the context of public health policy.
- Working with the existing NOVA system and developing subcategories within category 4, based on nutritional composition in addition to processing, was considered a better alternative when compared to developing a new system at present. Additionally, it would be useful to consider 'sustainability of processing' as a component of future approaches to food processing categorisation with a view to offering guidance to consumers.

3. Are there ongoing epidemiological studies and clinical trials that can improve the evidence?

- There are currently a limited number of randomised controlled trials that are ongoing and focus on UPFs. Their outcomes vary and include eating rate, palatability, reward value and changes in the microbiome; and therefore, their results will be informative mainly in relation to mechanisms. A critical appraisal of the studies' hypotheses, design and how their conclusions are drawn would be helpful.
- It was pointed out that it is likely to be difficult to draw conclusions on the association between UPFs and long-term health outcomes from the trials currently underway due to the difficulty of conducting trials across a sufficient duration. Good quality epidemiological studies may be better suited for this purpose.

4. When thinking about future work commissioned in this area, what should the key priorities be?

4.1 Epidemiological studies – what are the priorities for epidemiological research going forward?

- Epidemiological studies should be hypothesis driven, based on plausible mechanisms and exposures which are likely to be physiologically relevant. Further research is also needed to clearly establish the role of 'processing' on health outcomes independently of a food's nutrient composition.

- Consideration should be given to grouping additives and aspects of processing by potential mechanisms of action - for example, eating rate, palatability, appetite, digestion etc. This may help to address the very large number of processes, additives and mechanisms potentially involved, not all of which may be harmful or beneficial.
- Substitution analysis was also suggested, which acknowledges that UPFs replace other types of foods consumed within a dietary pattern. Examples of such studies were provided (Enget Jensen et al., 2024; Ibsen et al., 2021; Khan et al., 2023; Lee et al., 2022; Smith et al., 2015; Tomova et al., 2022)
- Considering the impact of UPFs on different ages, ethnic backgrounds and sex/gender would be useful, but should not be the primary focus in the first instance until mechanisms and impacts are clearer. It was noted that this is a separate issue to on-going data collections on food poverty and disadvantaged populations.
- Food processing should be reported in a more systematic way. Additionally, food processing that can have detrimental or beneficial effects based on the available evidence should be more closely examined.
- Information on amounts of additives in foods is currently lacking and often not publicly available. Alternative sources of this information, other than current surveys, should be considered.
- When classifying additives, it is important to draw on the theoretical background and current hypotheses on plausible mechanisms linking specific additives or groups of additives to health outcomes.
- There are opportunities to use metabolomic analyses of urine samples to quantify exposure to food additives and contaminants that would enhance the robustness of epidemiological studies, especially those with lower quality dietary data.
- Evaluations from countries that have included UPF recommendations or public health interventions as part of their dietary guidelines can also provide interesting insights on the efficacy of recommendations to avoid or reduce UPF. Guidelines have been in place for almost 10 years in Brazil, and although the term 'ultra-processed' is widely recognised, there seem to have been little change in population level intakes in the period since avoiding UPF became part of the national dietary guidelines.

4.2 Clinical trials – to what extent should they be part of a future research call and with what design?

- The main value of controlled clinical trials is likely to lie in exploring potential mechanisms underpinning health impacts of UPF.
- Given the lack of high-quality data demonstrating that food processing or specific aspects of processing have an independent association with or impact on health, there were mixed views on the value of real-world trials of the impact of advice to reduce UPF consumption (which might be beneficial or result in harms, or a combination of both). It was recognised that the impacts of such advice may differ in different population groups (for example, by age, ethnicity or socioeconomic deprivation).
- It will be difficult to design and run RCT's / clinical trials to test some mechanisms – for example, testing 'cocktails' of additives would be impractical given the number of additives available in the food supply, and defining an appropriate exposure period and endpoint would be challenging.
- It is currently difficult to design a behavioural trial that aims to mimic the effect of real-world intakes of UPFs, as there is limited confidence in what constitutes worthwhile advice around

UPF consumption in the absence of a clear understanding of which types of UPF are likely to be associated with health harms. The ubiquity of UPFs in the current food market also makes the design of such studies challenging. Additional difficulties in such trials include definition of appropriate end points and design of a control arm that can facilitate meaningful comparisons.

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Apologies from John Mathers, (Newcastle University) who provided input subsequently.

Observers**:** SACN and Government Office for Science Officials

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