Protecting you, what you eat and the world in which we live

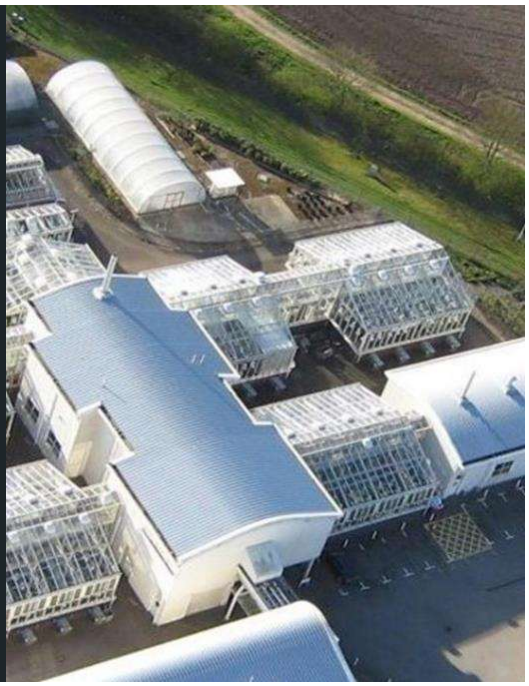
fera
Original thinking... applied

1

fera
Original thinking... applied

Our Vision

To be the global provider of leading-edge scientific solutions, evidence and advice across the agri-food chain.



2

Joint venture between Bridgepoint (75%) and Defra (25%) to:

- Delivering better outcomes through expert scientific services for public goods and competitive advantage
- National resilience for food & environmental incidents
- Transforming food production
- Investing ca 10% of revenues in R&D
- UK National Reference Laboratory for chemical residues and contaminants in food and feed
- Recognized by EFSA; Article 36 as competent organisation Food Safety Regulation and Standards
- Lead partner in Crop Health and Protection Centre
- 100 years of Regulatory, Safety & Expert Support to Government




3

Facilities, Partners and Operations

- **400** staff including **375** scientists across **17** disciplines
- The Fera entomology collection contains over **150,000** specimens and is a nationally important reference resource
- **95** acres secure site with specialist wildlife unit
- Containment Level [CL] **3** laboratories
- **75%/25%** ownership by Bridgepoint / Defra
- Fapas proficiency testing scheme has more than **4,500** participants in over **120** countries
- Over **100** procedures covered by the UKAS accreditation to the ISO/IEC 17025 Standard
- Fera is a founding member of CHAP, one of the Government's Centres for Agricultural Innovation
- Fera acts as National Reference Laboratory; Regulation (EU) 2017/625 in **7** areas
- **100** years heritage

Department for Environment Food & Rural Affairs · Food Standards Agency · Natural England · Environment Agency · Animal & Plant Health Agency · efsa European Food Safety Authority

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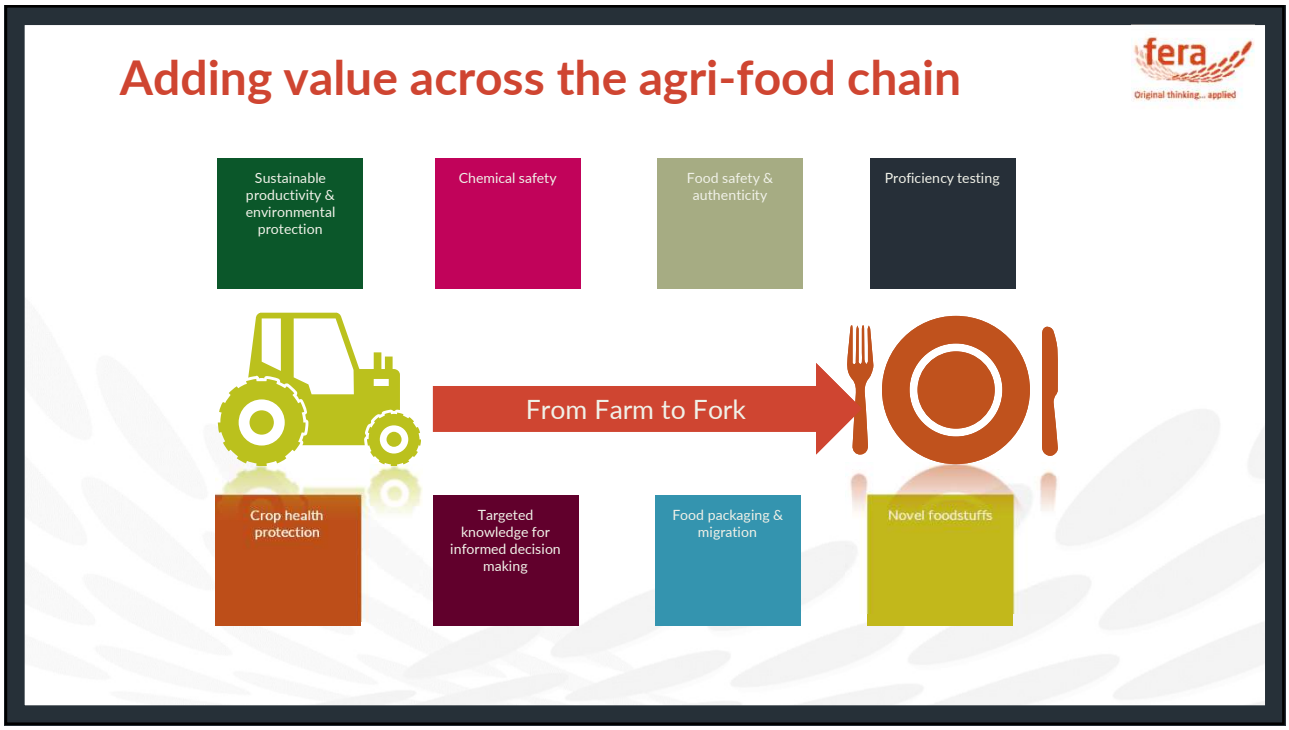
Original thinking... applied
Mesocosm
Thomson Suite
MTU
Elate Facilities
Bee Ecotoxicology
Glasshouses
Aquatic Facilities
Industrial Insect Products
Field Trials
420 scientists across 17 different disciplines
100 years heritage | 94 acre secure site
NRL in 7 areas specific + specific domain expertise in industrialization of insect products.

5


Adding value across the agri-food chain
fera
Original thinking... applied
Sustainable productivity & environmental protection
Chemical safety
Food safety & authenticity
Proficiency testing
From Farm to Fork
Crop health protection
Targeted knowledge for informed decision making
Food packaging & migration
Novel foodstuffs

6

Food at Fera

Food Safety
- Residues
  - Vet meds
  - Pesticides
- Chemical contaminants
- Food contact materials
- Microbiology
  - WGS - Origen
  - CL3
  - Shelf-life
- Allergens

Food Fraud
- Speciation
  - DNA
  - Proteins/peptides
- Adulteration
- Profiling

Novel Foods
- CBD
- Alternative proteins, insects as food and feed
- Gene editing

Information systems
HorizonScan – Food Safety at your fingertips

Early warning systems – supply chain controls

Standards and quality
fapas

UK National Reference Laboratory
Supporting the UK FSA and Official Laboratories
- Mycotoxins and emerging plant toxins
- Dioxins and PCB's
- PAH's and processing contaminants
- Trace elements
- Pesticides
- Veterinary medicines
- Food contact materials

Collaboration with and supporting EFSA and the European Commission
- Method development
- Building UK capability
- Surveillance

7

World class analytical capability

State-of-the-Art facilities: The Thomson Suite

Mass spec capability:
- 19 Triple-Quad LCMS
- 14 GCMS
- 3 Time of Flight (TOF) LCMS
- 1 High Resolution Orbitrap LCMS
- 3 High Resolution GCMS
- 2 Ion Ratio MS
- 3 Inductively Coupled Plasma MS

NMR capability:
- 2 500MHz, one equipped with a cryo-probe

UK NRL; ISO 17025 accreditation

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Safety

Surveillance and due diligence

- Trusted research services, advice, training, and testing services to the food and drink industry for over 30 years
- State-of-the-art analytical equipment and facilities, and detailed knowledge of current and emerging EU food safety regulations
  - Analysis and related interpretation of (bio)chemical constituents and contaminants in food
  - Compliance with legislation
- UKAS accredited
- Proficiency testing

State-of-the-Art facilities: The Thomson Suite

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Brand protection

Smart Surveillance

- World class research & development expertise and facilities
- Extensive scope of UKAS (ISO17025) accredited tests
- Multiplex testing to provide more analysis for reduced cost

Custom Made – Non-Targeted Analysis

- Early warning of emerging risks and prevention of food fraud
- Non targeted chemical and biochemical profiling – next generation sequencing, high resolution LC-MS mass spec & NMR spectroscopy
- Breadth of scientific skills delivers the routine safety assessments along with the more challenging
- Innovators of industry, breaking new ground with latest technology

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Food authenticity

- Manuka honey (methylglyoxal, dihydroxyacetone, Leptosperin)
- Illegal Dyes (Sudan, Rhodamine, Auramine, etc)
- Milk / skim milk powder (melamine)
- Use of Polyphosphates in Fish
- Wine (synthetic glycerol)
- Gelatine (GelSpec)
- Speciation (DNA / proteomics – peptides for processed meat products)

GelSpec
The science of trust

THE SUNDAY TIMES

Bee careful: that £45 honey may be fake

Jonathan Leake, Science Editor

Food Additives & Contaminants: Part A

Identification of novel peptides for horse meat speciation in highly processed foodstuffs

Amy J. Claydon, Helen H. Grundy, Adrian J. Charlton & M. Rosario Romero

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Chemical analysis

HS-GC-MS

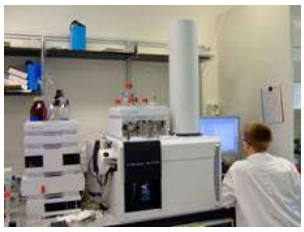
- **Volatile substances**
- Identification carried out by comparison to NIST database

GC-MS

- **Semi-volatile substances**
- Identification carried out by comparison to NIST database

GC-HR-MS

- **Semi-volatile substances**
- High resolution accurate mass data
- Identification carried out by comparison to NIST database



LC-HR-MS

- **Non-volatile and polar substances**
- Reversed phase – typically used
- HILIC – smaller, very polar and / or basic analytes
- Positive and negative ionisation modes
- High resolution accurate mass data
- Identification carried out by comparison to commercial and / or in-house databases

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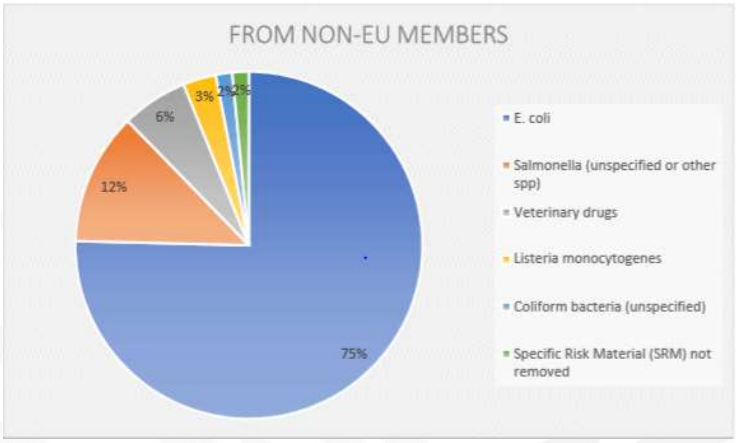
Food and feed safety risks – monitoring plans



HorizonScan
Food Safety at Your Fingertips

- Identify risks per region
- Identify risks per commodity
- Risk based sampling programmes
- Imported food analysis
- Regulatory restrictions

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Supporting government

- Food Safety and Authenticity
  - Method development
  - Building UK capability
  - National Reference Laboratory
  - Surveillance – NRCP, vet meds, pesticides, chemical contaminants, food contact materials
  - Antimicrobial resistance
  - Consultancy & Literature reviews
  - Joint Expert Groups
- Environmental
  - Method development
  - Building UK capability
  - Data generation – residues and contaminants

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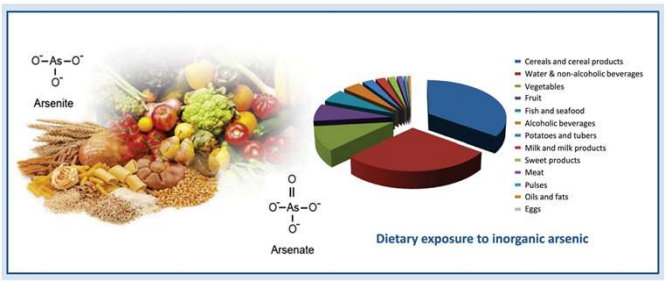
NRL Activities - FSA

Method development, e.g.

- MOSH/MOAH
- PFAS
- Inorganic arsenic
- Tropane alkaloids
- Hydrocyanic acid
- Pyrrolizidine alkaloids
- Methyl mercury



Other activities

- Incident preparedness
- Supported testing for Official Control Laboratories

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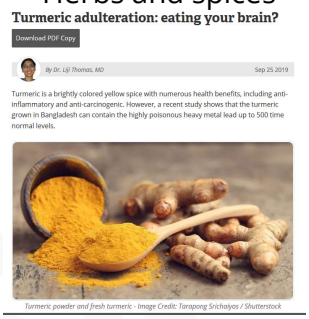
Surveys

- Herbs and spices



- Supplements

- CBD

Report Says 70% of CBD Products Are Contaminated with Heavy Metals or Pesticides

- Plant based drinks

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Overarching paper on consumption of plant-based drinks in children aged 6 months to 5 years of age.

Food Standards Agency

- Imported food survey

– analysis of imported foods for chemical and micro hazards, up to 2800 samples each year

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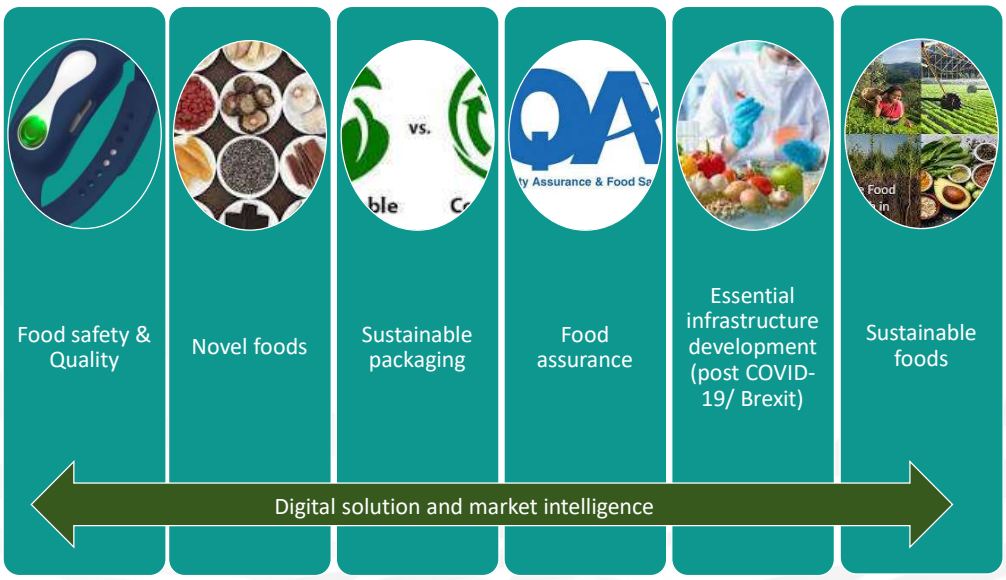
Science Strategic Direction



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Proficiency testing from Fera

Why participate in Proficiency testing?

- External Quality Assessment
- Independent
- Global
- Demonstrate Competency
- Identify Training Needs
- Method Development

 Food Chemistry

 Food Microbiology

 GMO in Food

 Water and Environment

 Bespoke

 Reference Materials

Global Leader | 25 Year History | UKAS Accredited 0009 | 100 year Heritage | Over 400 PTs per year

Take confidence in your products, supply chain, analytical methods and people;
Mitigate your business risks

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Safety
- Overall migration
- Specific migration
- Non-intentionally added substances

Shelf life
- Food waste
- Active packaging

Fraud
- Material type?
- Reyclable and/or compostable and/or biodegradable?

UK National Reference Laboratory

EFSA
- Working group on Bisphenol A
- Provision of data to support EFSA evaluations

European Commission
- Technical guidance
- Evaluation of the Framework Regulation

Standards and quality

fapas, cen, bsi.

Food contact materials at Fera

Information systems

HorizonScan
Food Safety at your fingertips

Early warning systems – supply chain controls

Environmental impact
- Degradation in the environment
- Impact of chemical release

Pack integrity
- Protection from pests

State-of-the-Art facilities: The Thomson Suite

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Food Standard Agency
Science Advisory Committees

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Science Advisory Committees

- Science Council
- Advisory Committee on Novel Foods and Processes
- Advisory Committee on the Microbiological Safety of Food
- Advisory Committee on Animal Feedingstuffs
- Advisory Committee for Social Science
- Committee on Toxicity
  - **Joint Expert Group for Food Contact Materials (FCMJEG)**

https://cot.food.gov.uk/JEGFCM

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FCMJEG

- "…assesses and provides advice to the FSA on applications for the authorisation of new food contact materials including the materials, their chemical components, active and intelligent packaging and related recycling processes and on other topics relevant to the assessment of such applications as requested.

  The group coordinates with and considers the opinions of other relevant bodies concerned with the assessment of food contact materials and provides advice on general principles or new scientific discoveries in connection with food contact materials risks."

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Authorisations in progress

Register of regulated product applications

This worksheet contains one table. You can find what different phases of assessment mean in the Phase of assessment key worksheet.

RP ID nr	Product Type	Organisation	Product name	Summary	Phase of assessme
45	Food contact materials (recycled processes)	Polymer Extrusion Technologies (UK) Ltd	PETUK SSP Process	PETUK SSP Process is a 2 stage process incorporating single screw vented extrusion technology, followed by Solid-State Polymerisation operated within batch reactors.	Risk assessment
53	Food contact materials (recycled processes)	Wellman Neufchateau Recyclage	SOREPET GR+	SOREPET GR+ uses re-collected post consumer PET containers of previous food grade quality as input material (kerbside and deposit collection systems). The process involves washing and processing the input material to produce rPET pellets.	Risk assessment
94	Food contact materials (recycled processes)	Klockner Pentaplast	PET food trays	Process using re-collected post consumer PET containers and a small fraction of non-food consumer applications.	Risk assessment
262	Food contact materials (recycled processes)	Viridor Waste Limited	Starlinger iV+ Process	Recycling process using re-collected post consumer polyethylene terephthalate (PET) containers of original food grade quality as input material. This input material will be from specific collections systems. Output material is expected to be used for direct contact with food.	Risk assessment
1190	Food contact materials (plastic additives)	Keller and Heckman LLP	Phosphoric acid, mixed esters with 2-hydroxyethyl methacrylate	Application for the authorisation of phosphoric acid, mixed esters with 2-hydroxyethyl methacrylate (CAS Reg. No. 52628-03-2) for use as a monomer in the manufacture of plastic food contact materials and articles.	Risk assessment
1415	Food contact materials (recycled processes)	Esterpet Limited	Starlinger iV+	Recycling process using re-collected post consumer polyethylene terephthalate (PET) converting into food grade pellets through drying, extrusion, crystallistion and SSP.	Risk assessment
1642	Food contact materials (plastic additives)	Clariant Produkte (Deutschland) GmbH	Partially oxidized rice bran wax and its calcium salts (wax, rice bran, oxidized, partially saponified)	LICOCARE RBW 101-106 VITA and LICOCARE RBW 300-360 VITA is submitted as a food contact material (plastic additives) which is intended for use as a processing aid, lubricant, release agent, and/or slip agent in food-contact polymers. It is proposed for use levels up to 0.3% in finished polymers. This is an application for modification of authorisation and is intended for use in contact with all types of food under all conditions.	Risk assessment
1702	Food contact materials (plastic additives)	Milliken Chemical, Division of Milliken & Co.	Calcium tert-butylphosphonate	Calcium tert-butylphosphonate is submitted as a food contact material (plastic additive) which is intended for use as a nucleating agent in the manufacture of polyolefin food contact materials and articles. The calcium tert-butylphosphonate is intended to be used at a maximum level of 0.15 weight percent in all polyolefins in contact with all food types, including infant formula and human milk, without limitation on temperature.	Risk assessment
1741	Food contact materials (recycled processes)	Greiner Packaging Ltd	Starlinger viscotec Decon	Plastic recycling process intended to recycle food grade PET containers using Decon technology. The recycled PET is being used at up to 100% for the manufacture of materials and articles for direct contact for all types of foodstuffs for long-term storage at room temperature, with or without hotfill.	Risk assessment

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Non-routine work - position papers

- FSA sought the opinion of the FCMJEG
- *"Based on the information/evidence available to the FCM JEG at the time of the interim assessment, the FCM JEG considered it would not be possible to demonstrate that levels of CMR substances in ocean bound plastic would be sufficiently low to allow its use in food contact material applications, directly or behind a functional barrier."*
- Call for evidence underway

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Divergence

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Divergence

- 31st January 2020 - all EU Regulations were implemented as GB Law
- Assimilated Law
- No changes in GB Regulations since EU exit

- EU
  - updates to 10/2011
  - Commission Regulation (EU) 2022/1616 of 15 September 2022 on recycled plastic materials and articles intended to come into contact with foods

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Divergence - recycling

Commission Regulation (EU) 2022/1616 of 15 September 2022 on recycled plastic materials and articles intended to come into contact with foods, and repealing Regulation (EC) No 282/2008 (Text with EEA relevance)

C/2022/6146

OJ L 243, 20.9.2022, p. 3–46 (BG, ES, CS, DA, DE, ET, EL, EN, FR, GA, HR, IT, LV, LT, HU, MT, NL, PL, PT, RO, SK, SL, FI, SV)

In force: This act has been changed. Current consolidated version: 20/09/2022

ELI: http://data.europa.eu/eli/reg/2022/1616/oj

20.9.2022 EN Official Journal of the European Union L 243/3

COMMISSION REGULATION (EU) 2022/1616

of 15 September 2022

on recycled plastic materials and articles intended to come into contact with foods, and repealing Regulation (EC) No 282/2008

(Text with EEA relevance)

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European evaluation of FCMs

European Commission | Log in | English | Search on Europa | Search

Law

Evaluation of Food Contact Materials (FCM)

Have your say > Published initiatives > Evaluation of Food Contact Materials (FCM)

Roadmap
Feedback period
28 November 2017 - 26 December 2017
FEEDBACK: CLOSED

Public consultation
Consultation period
11 February 2019 - 06 May 2019
FEEDBACK: CLOSED

Final version
09 June 2022

About this initiative

Summary	The purpose of this evaluation is to assess whether the current EU legislative framework for of Food Contact Materials (FCM) is fit for purpose and delivers as expected. The evaluation will cover the functioning of the FCM Regulation in its entirety and the rules and tools provided for by this legislation, such as specific implementing measures. It will also examine the situation concerning materials for which there are no EU measures and which are subject to permitted national measures.
Topic	Food safety
Type of act	Staff working document
Category	Evaluation

Roadmap

FEEDBACK: CLOSED

EUROPEAN COMMISSION

Brussels, 9.6.2022
SWD(2022) 164 final

COMMISSION STAFF WORKING DOCUMENT

EXECUTIVE SUMMARY OF THE EVALUATION

of the

legislation on Food Contact Materials - Regulation (EC) No 1935/2004

{SEC(2022) 251 final} - {SWD(2022) 163 final}

https://food.ec.europa.eu/safety/chemical-safety/food-contact-materials/revision-eu-rules_en

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European evaluation of FCMs

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52022SC0164&from=EN

- Key findings:
  - "FCM Regulation and its implementation are broadly effective in terms of the scope, definitions and traceability rules to achieve the set objectives"
  - "….rules for plastic FCMs largely ensure the safety of starting substances used in their manufacture…."
  - "However the rules for plastics are technically complex and resource intensive…."
- Potential weaknesses
  - identification and measures to control non-intentionally added substances (NIAS)
  - deficiencies in the exchange and availability of compliance documentation in the supply chain
  - scope of the mandatory risk assessment, which does not sufficiently address vulnerable populations or potential exposure to combinations of substance
  - non-plastics – Member States have introduced specific measures for other material types – rules differ

Collectively, these issues highlight a need to better ensure the safety of the final FCM article brought into contact with food consumed by all EU citizens

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European evaluation of FCMs

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52022SC0164&from=EN

- Non-plastics:
  - "Article 3 of the Framework Regulation does not define the level of safety or quality expected for FCMs. Further, it does not state how safety should be achieved nor how it can be demonstrated."
  - Risk assessments that make better use of all available information on substances and extend beyond only plastic could lead to efficiency gains.
- Novel materials:
  - The approach to regulating plastic FCMs is insufficient to address new and potentially more innovative materials.
  - Ongoing changes in the design of materials and their composition including bio-based and biodegradable materials present increasing challenges within the constraints of the current approach.
  - Other novel developments, such as those that incorporate nano-technology and chemical recycling, are presently insufficiently addressed.

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Revision of EU FCM rules: Main policy themes and pillars

Safety and sustainability of food contact materials (FCMs)

A + B together to become the core of the future risk management approach + new material categories to apply that approach

A. Redress focus onto final material

- Better define the level of safety required, addressing the full characteristics of all final FCM articles and migrating substances, including NIAS
- Cluster into broader material types (synthetic, natural, inorganic; recycled, composite, active)

B. Prioritisation of substances

- Define rules for the risk assessment of all substances that migrate from FCMs
- Tiered approach:
  - Tier 1: generic risk (hazard) based (CMRs, EDs, PBTs and vPvBs)
  - Tier 2: risk assessment by public authorities
  - Tier 3: Self-assessment by business operators of more benign substances

C. Supporting more sustainable alternatives

- Ensure fewer hazardous chemicals
- Prioritise more sustainable use of FCMs
- Coherence and support to other EU rules on sustainability, including packaging and food

Information exchange, compliance and enforcement of FCMs

To verify safety, sustainability and ensure smooth functioning of the internal market

D. Improving quality and accessibility of supply chain information

- Clear and consistent rules on data requirements and information transfer throughout the supply chain, including a DoC for all FCMs
- Digitalisation to help businesses, including SMEs to ensure compliance and for Member States to enforce

E. System for verifying compliance and undertaking of official controls

- Delegated bodies under Official Control Regulation 2017/625
- Notified Bodies tasked with conformity assessment

F. Analytical methods

- Migration testing rules
- Analytical methods (i.e. for official controls)
- Further development of test methods and technical standards as required

https://food.ec.europa.eu/document/download/2e1b1eb0-66fe-45e6-bf6d-ffd64a735fca_en?filename=cs_fcm_revision_policy-pillars_202305.pdf

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Substances of interest

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PFAS – UK

- High resolution mass spectrometry database developed to include those PFAS previously detected in / related to FCM
  - Chromatographic properties of > 50 PFAs determined
  - Packaging materials screened for the presence of PFAS
- Targeted analysis
  - Dedicated laboratory space – Fera experienced in low level analysis of organic environmental contaminants
  - Dedicated instrumentation – UPLC-MS/MS with ElectroSpray Ionisation (ESI) in negative polarity operated in Multiple Reaction Monitoring (MRM) mode.
    A novel ionisation mechanism needed to achieve the EU regulatory limits for foods

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Bispheno

- Bisphenol A, F
  - Dedicated la
  - Specific mea
  - LC-MS/MS
  - Target LOD?

Conclusions and Next Steps

19. The Committee noted that the current UK TDI is substantially above the new TDI established by EFSA. However, while the Committee considered it possible that the TDI would need to be revised to account for new evidence and ensure it was sufficiently protective, on balance the weight of evidence did not support the conclusions drawn by EFSA, or a TDI as low as that derived by EFSA. The Committee had concerns about the endpoint selected and noted that there were effects apparent in other endpoints, which would need to be considered.

20. The COT considered the endpoint and approach applied by the BfR to be more reasonable than EFSA's assessment, albeit still with a significant level of conservatism.

21. The COT acknowledges that given the size of the database, undertaking their own weight of evidence approach, with a transparent data integration, would not be a short undertaking. Hence, after assessment of the scientific evidence and approaches taken to establish a health based guidance value, the Committee agreed to adopt the TDI of 0.2 ug/kg bw per day derived by the BfR.

22. The Committee will be publishing a supplementary statement in due course, providing detail on their discussions of the EFSA opinion and BfR assessment, their evaluation of the evidence base, and deliberations to adopt the TDI derived by the BfR.

23. In line with EFSA and the BfR, the Committee highlighted that the most current exposure data predates the 2015 EFSA opinion. To undertake a full risk assessment, and to fully assess realistic exposures in and potential risks to the UK population, up to date exposure data will be required.

itous substances

Print this page

https://cot.food.gov
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Mineral oils - UK

- Meeting held in March 2023
- Discussion paper on the EFSA Draft Opinion for Public Consultation on “Update of the risk assessment of mineral oil hydrocarbons (MOH) in food”
- “Overall, the Committee agreed that the 2023 EFSA draft opinion was a good compilation and discussion of the available data and agreed with the EFSA’s approach and conclusions”

https://cot.food.gov.uk/Discussion%20paper%20on%20the%20EFSA%20Draft%20Opinion%20for%20Public%20Consultation%20on%20Update%20of%20the%20risk%20assessment%20of%20mineral%20oil%20hydrocarbons%20%28MOH%29%20in%20food

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Reporting

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Test reports

- Confidential but typically cover
  - Sample details
  - Method overview
  - Results – concentrations measured for targeted analysis
  - Discussion – interpretation of results in line with any regulatory restrictions if requested by the client
  - NIAS reporting in the format requested by the client but suitable to support FCM dossier submissions / safety assessments

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Migration testing

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FCM Testing – What?

Thousands of substances used in the manufacture of food contact materials

Intentionally Added Substances (IAS)

- Known ingredients such as monomers, catalysts, solvents, suspension media, additives etc.

Non-Intentionally Added Substances (NIAS)

- Known or unknown isomers, impurities, reaction products and breakdown products of these ingredients
- Possible contaminants from manufacturing process
  - Recycled materials
  - Irradiated products
- Contamination from indirect sources such as printing inks, coatings, adhesives, secondary packaging

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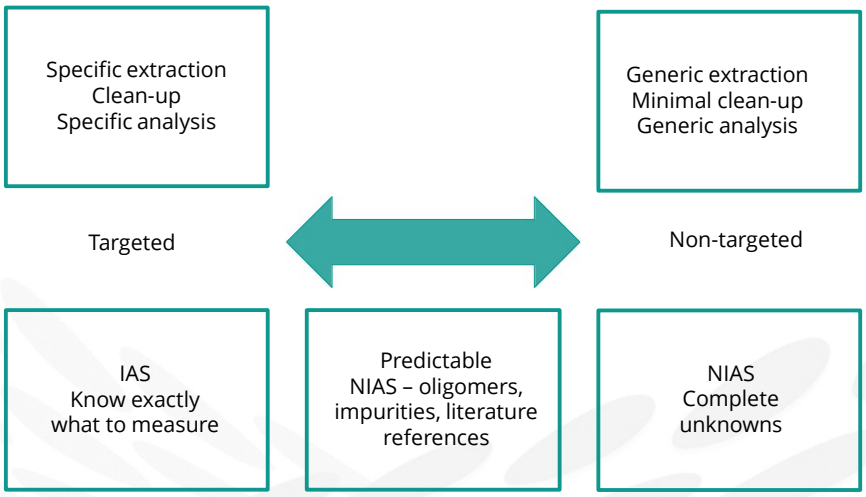
FCM Testing – How?



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Migration

Migration = the mass transfer of chemical constituents, from an external source, into food by sub-microscopic processes

Migration occurs from

- Food packaging
- Materials and articles used in food manufacture, transport and storage
- Materials and articles used in food preparation and consumption

Migration may impact food in two ways

- Food safety – migration of harmful substances
- Food quality – migration of substances which impart taint or odour, or bring about a change in the composition of the food

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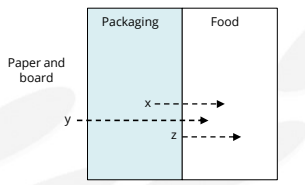
Factors affecting migration

Migration is a diffusion and partitioning process that is dependent on:

- The nature of the food contact material
- The nature and concentration of the migrating substance
- The nature of the foodstuff
- The nature, extent and type of contact between the food contact material and the foodstuff
  - The temperature of the contact
  - The duration of the contact

Depiction of chemical migration from and through a **porous material**



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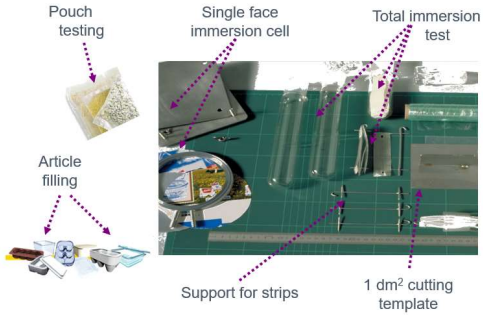
Migration testing

Typically…

Migration testing
- Food simulants / foodstuffs
- Exposure type
- Exposure time and temperature
- Representative of intended final use of FCM
- IAS

NIAS analysis
- Extraction into solvents
  - Polar and non-polar
- Represents worst case



Not mutually exclusive

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NIAS

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What is the aim of a NIAS assessment?

To determine the substances present in a food contact material and to assess the risk of exposure to these substances

How?

- **No definitive (legal) guidance**
- Regulation (EU) No 10/2011 (for plastics)
- Regulation (EC) 1935/2004 (for all food contact materials and articles)
  - Article 3

Typical approach

- Extract all migratable substance – solvent(s) selected based on material type
- Analyse the extracts using a suite of analytical techniques capable of detecting a range of substances (polar, non-polar, volatile, non-volatile, ionic)
- Identify the substances detected
- Quantify the substances detected
- Determine the migration
- Determine the exposure

Could the substances detected be associated with the monomer/additive for which approval is sought?

(20) During the manufacture and use of plastic materials and articles reaction and degradation products can be formed. These reaction and degradation products are non-intentionally present in the plastic material (NIAS). As far as they are relevant for the risk assessment the main reaction and degradation products of the intended application of a substance should be considered and included in the restrictions of the substance. However it is not possible to list and consider all reaction and degradation products in the authorisation. Therefore they should not be listed as single entries in the Union list. Any potential health risk in the final material or article arising from reaction and degradation products should be assessed by the manufacturer in accordance with internationally recognised scientific principles on risk a

Nerin et al. (2022) "The initial approach was to attempt to prepare a prescriptive methodology but as this proved impossible...."

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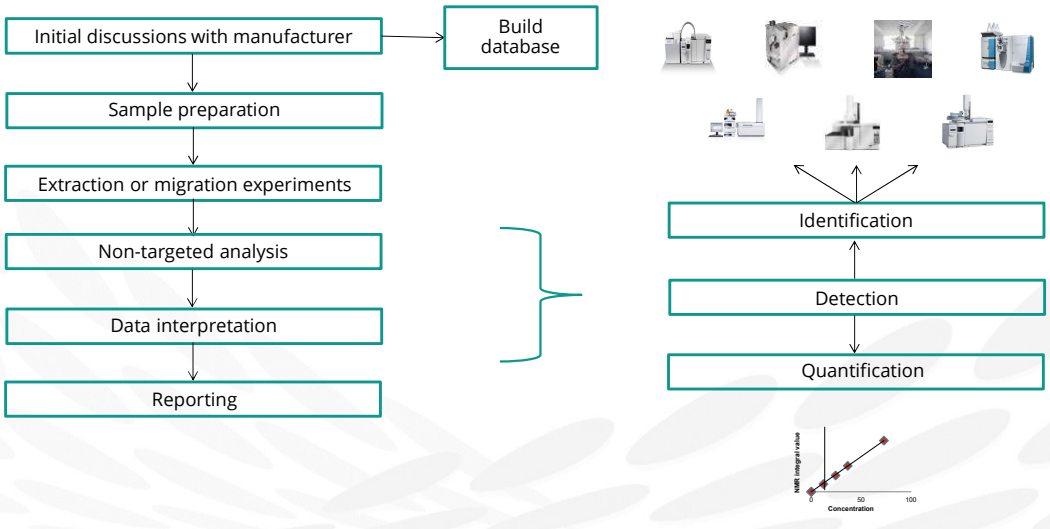
Typical NIAS workflow



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Non-targeted analysis for NIAS

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Analysis

HS-GC-MS

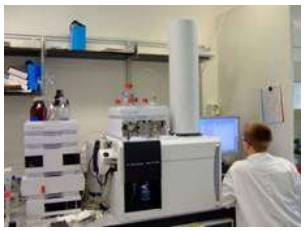
- **Volatile substances**
- Identification carried out by comparison to NIST database

GC-MS

- **Semi-volatile substances**
- Identification carried out by comparison to NIST database

GC-HR-MS

- **Semi-volatile substances**
- High resolution accurate mass data
- Identification carried out by comparison to NIST database



LC-HR-MS

- **Non-volatile and polar substances**
- Reversed phase – typically used
- HILIC – smaller, very polar and / or basic analytes
- Positive and negative ionisation modes
- High resolution accurate mass data
- Identification carried out by comparison to commercial and / or in-house databases

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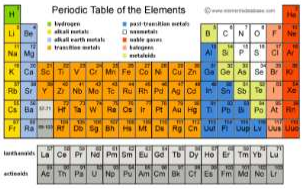
Inductively Coupled Plasma - Mass Spectrometry

- Highly sensitive quantitative data for 65+ **trace elements**
- Applicable to most sample types



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Identification of NIAS

- Step 1
  - Build a database of potential migrants associated with raw materials and other starting materials (including impurities if known) below 1000 Da
    - Specific to each study – sample information from supplier
  - Analysis of starting substances to determine impurities
  - Comparison of list of accurate masses generated through the analysis to theoretical database
- Step 2
  - Consider retention time, structures, MS/MS fragment data, isotopic fit

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Identification of NIAS

- Step 3
  - Confirmation of identity by analysis of an analytical standard – not always (rarely) available
- Our experience is we never identify every peak in every chromatogram – *couple analytical chemistry with tox testing?*

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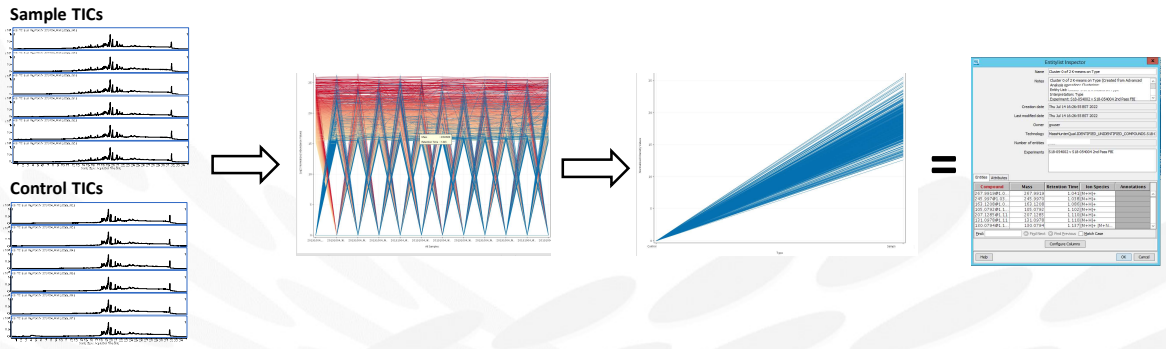
Data Analysis 1 – Finding Features of Interest

- Feature extraction using commercial software (e.g. MassHunter Qualitative Analysis Software Molecular Feature Extraction (MFE) algorithm (Agilent))
- Profiling v suitable control with e.g. Mass Profiler Professional software in conjunction with MassHunter Qualitative Analysis Software



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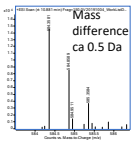
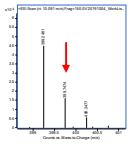
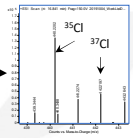
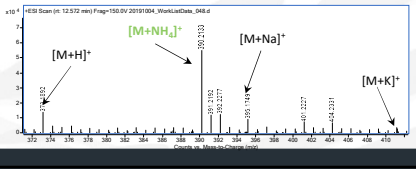
Data Analysis 2 – Authenticating the Data

- Algorithms are not perfect so data is checked for:
  - Duplicate features
  - Adduct and isotope pairs (including $^{35}Cl/^{37}Cl$ if required)
  - Presence/absence in control and procedural blanks
- Spectra are checked:
  - Multiply charged species with a neutral mass >1000 are rejected
  - Isotopic peaks rejected
  - Isotopic pattern (in particular $^{35}Cl/^{37}Cl$)
  - Adduct ion information









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Data Analysis 3 - Identification

- Compare experimental data with database
  - Process allows matching of different adduct ions (not restricted to $[M+H]^+$)
- Formula generation:
  - Formulae are generated where there is no database match or the match is thought to be unlikely (in consultation with client)
  - Element list and adducts for inclusion agreed with client

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Data Analysis 4 - Confirmation

Fragmentation carried out on LC-QTOF (MS/MS) or ion trap-Orbitrap (MS^n)

- Collision energy optimised and fragments obtained
- Comparison to reference standard (best, gives retention time and fragment data)

OR

- Comparison to *in silico* fragmentation performed using Mass Frontier software (HighChem)

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Quantification of NIAS

- How can we quantify if we don't know what we are looking for?
  - Internal standards
    - ^{2}H, ^{13}C analogues – not naturally occurring
    - Range of compounds to cover the mass range of interest?
    - IS that responds in positive and negative ionisation (for LC-MS)
  - External standards
    - Chemically similar to substances of interest – similar ionisation?
    - e.g. BADGE or BADGE hydrolysis products for epoxy-related coatings
    - e.g. Polyester diol urethane substance for polyester-related coatings
  - Synthesis of authentic standards to confirm identity
    - Retention time, accurate mass, fragmentation comparison
    - Expensive and time consuming

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Confidentiality

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Confidentiality

- All work is conducted in confidence
- Previous work carried out for associations involved reporting summary results to the association as well as individual results to the specific customers

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