Countdown to 2027: maximising NAMs in food safety assessment: closing the gap for regulatory assessments in Europe

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Background

- Safety assessments of regulated food products in the European Union (EU) (and globally) largely rely on experimental animal studies.
- Non-animal/new approach methods (NAMs) offer possible benefits versus traditional animal studies [1]. However, the regulatory adoption of these methods remains limited and requests to conduct animal studies on regulated products continue.
- To address this, the European Commission (EC) is developing a roadmap to phase out animal testing for chemical safety assessment and the ambition of the European Food Safety Authority (EFSA) is that by 2027, new scientific developments (NAMs) will lead to *"the minimisation of animal testing"* [2].
- We reviewed several NAMs applicable to regulated food products and reflected on the current provisions in EU foods legislation and accompanying EFSA sectoral guidance for the use of such NAMs (phase 1). Based on these, we propose targeted changes to the EU foods regulatory system and research projects to advance the regulatory adoption of NAMs (phase 2) (Fig 1).

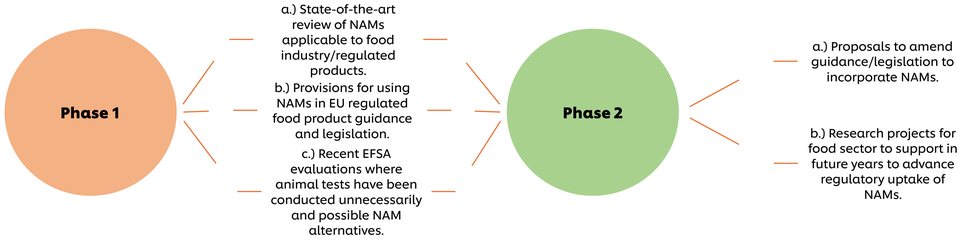

Fig. 1 Project strategy. *Reviewing sector relevant NAMs, reflection in legislation/corresponding guidance and potential applications in recent opinions were included in phase 1. Learnings informed phase 2, which consisted of proposing amendments to EU legislation/corresponding guidance to promote the use of NAMs, research activities the food sector could support.*

Phase 1 – state of the art on NAMs applicable to food sector/regulated products

- NAMs relevant for the food-sector were mapped to EU regulated food categories and classified depending on their regulatory familiarity, their assessment applicability domains (biological and/or chemical safety) and their use in in risk assessment stages, i.e. hazard identification, hazard characterisation, exposure assessment and risk characterisation (Fig 2).

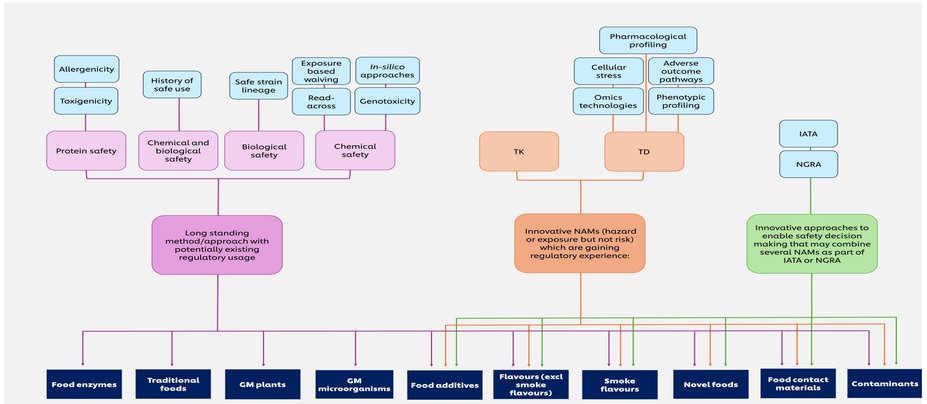

Fig. 2. NAMs identified as relevant to the safety assessment of different EU regulated food categories.

Phase 1 – Provisions for using NAMs in EU regulated food product guidance and legislation

- Legislation (n=10) and sectoral guidance (n=11) were reviewed to understand provisions made for conducting safety assessments with/using NAMs. NAMs were nearly entirely absent from legislation, and sectoral guidance was inconsistent with respect to the presence and usage conditions described (Fig 3).

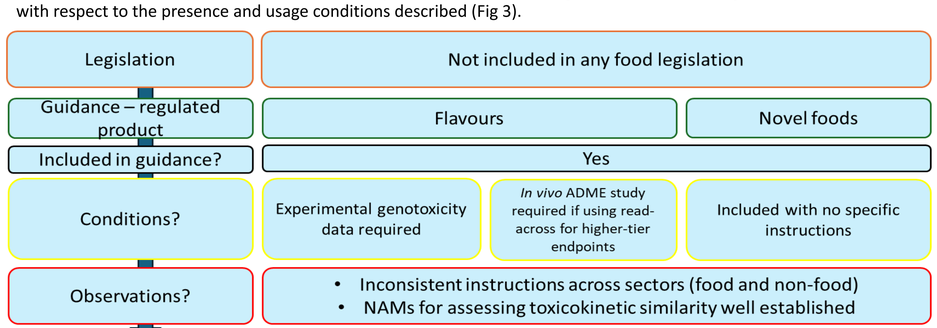

Fig. 3. Example of EU foods legislation and accompanying sectoral guidance provisions for usage of read-across

Phase 1 – Recent EFSA evaluations where animal tests have been conducted unnecessarily and possible NAM alternatives

- EFSA novel foods opinions (2003 and 2023) (n=153) were screened to identify cases where animal testing was conducted by the applicant on the novel food.
- No reduction was seen in the proportion of dossiers where animal testing was conducted by applicants (Fig 4). This is despite several historical attempts to reduce animal testing based on e.g. toxicokinetic properties.
- Next, opinions where animal testing was conducted unnecessarily were identified, and a possible NAM based alternate strategy was developed. Cases varied by regulated product, the type of animal study conducted and the possible NAM which could have been used instead (Table 1).

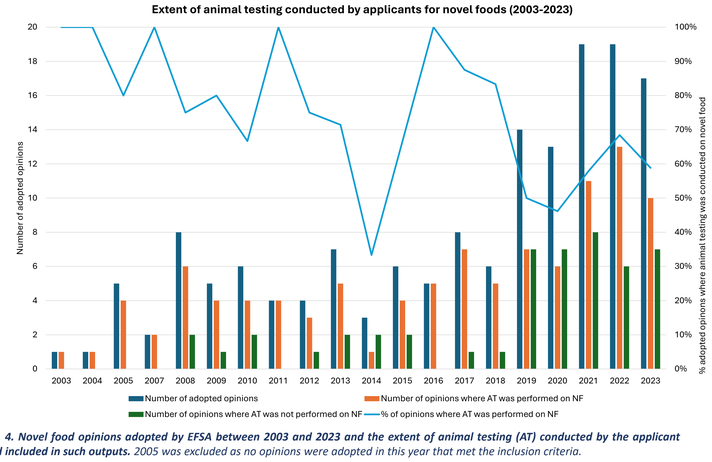

Fig. 4. Novel food opinions adopted by EFSA between 2003 and 2023 and the extent of animal testing (AT) conducted by the applicant and included in such outputs. *2005 was excluded as no opinions were adopted in this year that met the inclusion criteria.*

Table 1. EFSA opinions where animal testing has been conducted unnecessarily, including potential NAM alternatives. *Examples 1-4 refer to 1.) 2-(4-methylphenoxy)-N-(1H-pyrazol-3-yl)-N-(thiophen-2-ylmethyl)acetamide, 2.) (S)-1-(3-(((4-amino-2,2-dioxido-1H-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one, 3.) Soy leghemoglobin and 4.) N,N-bis(2-hydroxyethyl)stearylamine partially esterified with saturated C16/C18 fatty acids respectively.*

Regulated product domain	NAM alternates	Example	Overview, studies conducted and results	Non-animal approach
Flavourings	TTC	1	1. Exposure >TTC, requiring a 90-day and developmental toxicity study. 2. No effects observed (NOAELs > highest tested dose) (100 and 1000 mg/kg bw/day respectively).	1. Possibility to use iTTC with internal exposure estimates obtained through use e.g. pharmacokinetic modelling.
Flavourings	*In vitro* ADME assays/PBK modelling	2	1. Application for acid and its salt. 90-day, dev tox and three *in vivo* TK studies conducted. 2. AUC of the salt was higher than the acid (as qualitatively anticipated).	1. Physico-chemical, e.g. water solubility or solubility in gastric fluids. 2. *In vitro* ADME (e.g. Caco-2) to estimates permeability through GI tract. 3. TK data from the 90-day study to validate a PBK model.
Food additives	HoSU/protein safety	3	1. Recombinant bovine haemoglobin (expressed in GM strain). 2. 14-day, two 28-day studies and a 90-day study conducted (no effects in any study).	1. Composition is largely protein - digested to small peptides, amino acids and haem B. 2. Recipient (non-GM) strain has qualified presumption of safety (QPS) status.
Food contact materials	Read-across and/or innovative TK/TD NAMs	4	28-day oral study submitted by the applicant as a bridging study to justify read-across for 90-day toxicity.	1. NAMs on target/source could have been used to substantiate read-across. 2. Integrating "last-resort" requirement into foods regulation. 3. Greater pre-application communication

Phase 2a - Amendments to guidance/legislation to incorporate NAMs

- Based on findings from phase 1, targeted proposals to specific EU foods legislation and accompanying sectoral guidance were made to promote further use of NAMs (Fig 4).

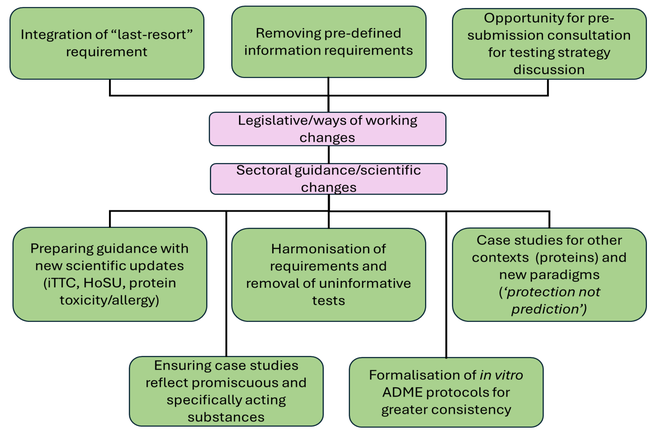

Fig. 4 . Possible legislative/changes to the ways of working in the EU foods regulatory system and to the EU food scientific evaluation processes to encourage use of NAMs

Phase 2b - Research projects for food sector to support in future years to advance regulatory uptake of NAMs

- Based on findings from phase 1 and 2a, targeted, potential research projects to advance the regulatory readiness of each NAM were proposed (fig 5).

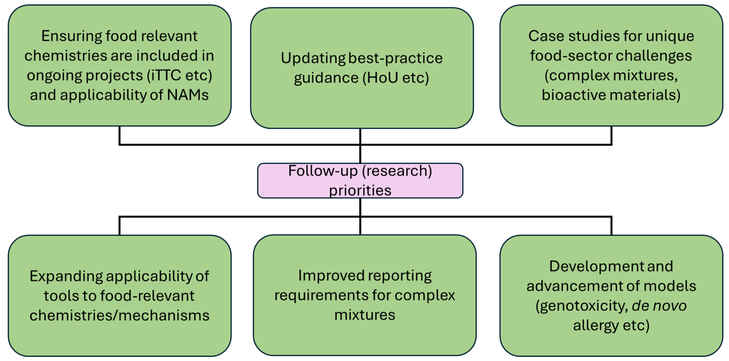

Fig . 5. Possible follow-up research activities the food-sector could co-ordinate to advance the scientific and regulatory adoption of NAMs.

Conclusions

- The food industry has played a key role in the historical development and application of NAMs.
- Regulatory uptake of NAMs remains limited and the proportions of dossiers reliant on animal testing has not appreciably changed over time (Fig 4), and several examples are clear where testing has been conducted unnecessarily (Table 1).
- Proposals made here to amend legislation, sectoral guidance and ways of working offer an opportunity to deliver a tangible reduction in animal testing in the foods, regulatory ecosystem.
- Many of these proposals are amenable to other geographies where a similar regulatory framework (to the EU) and/or reliance on animal testing exists.
- Proposed research activities pave the way for follow-up projects that could establish the food sector as a key force in the next phase of efforts to replace animal testing.

References:

1. FoodDrinkEurope, Joint Position, Integration of New Approach Methodologies (NAMs) in food safety risk assessment, 4 July 2023
2. EFSA Strategy 2027 (2021).