RISK ASSESSMENT CONSIDERATIONS FOR FOODS DERIVED FROM RNAi-BASED GM PLANTS

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TALK OUTLINE

GM FOOD SAFETY ASSESSMENT

BACKGROUND

- Approach to GM food safety assessment developed over many years – Codex guidelines adopted in 2003
- Assessment framework intended to be flexible enough to address a broad range of GM foods
- Consensus around the key safety assessment elements and the types of evidence necessary to inform the assessment - harmonisation

GM FOOD SAFETY ASSESSMENT

OBJECTIVE & PROCESS

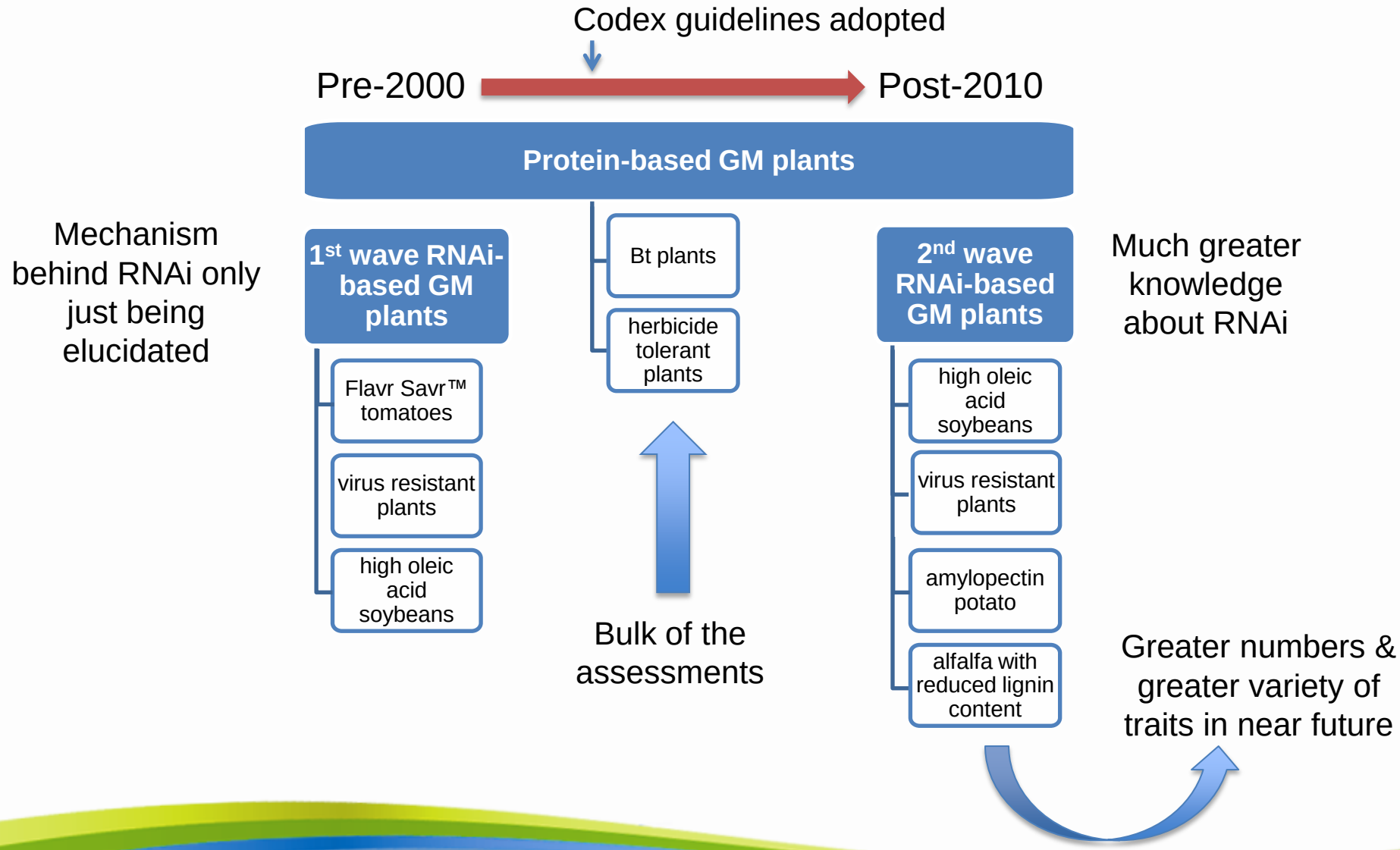
- Identification of new or altered hazards relative to a conventional counterpart – comparative approach
- The comparison is used to identify any differences (intended & unintended)
- Any differences are further assessed to determine if they raise food safety and/or nutritional concerns
- Appropriate risk management measures if food safety and/or nutritional concerns exist

"....as safe as....."

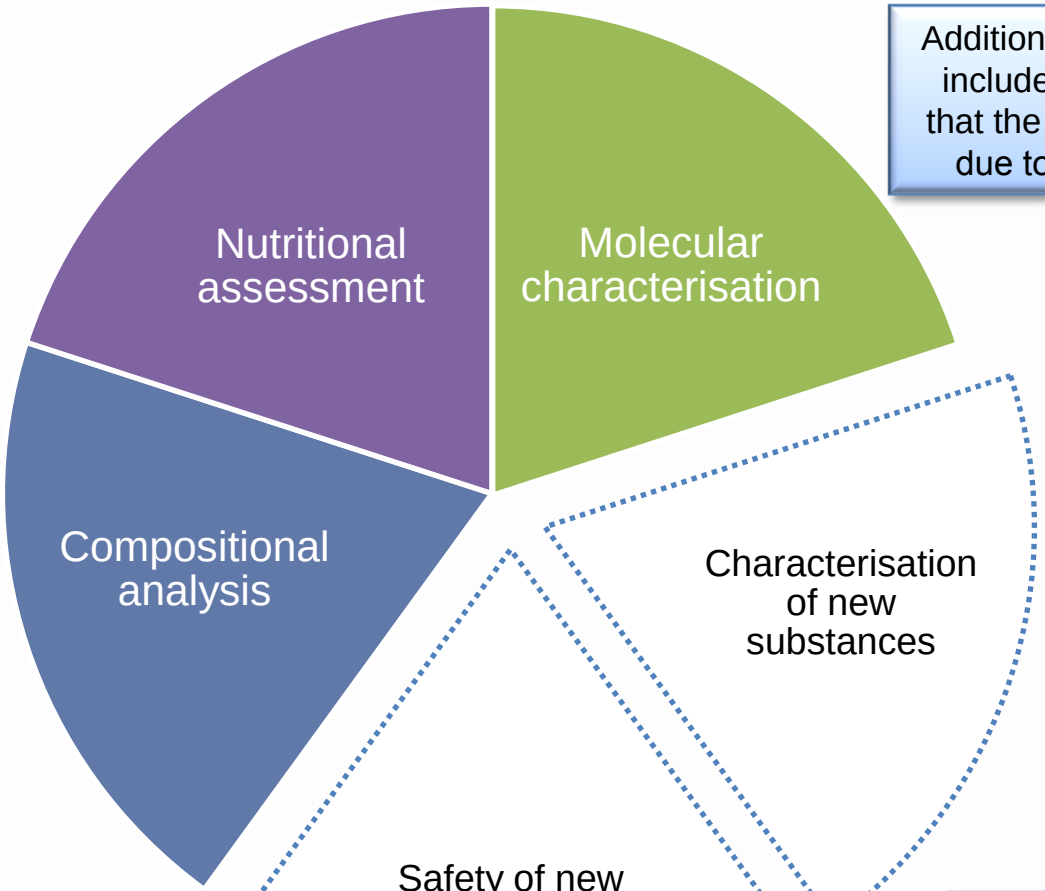
KEY SAFETY ASSESSMENT ELEMENTS

- Case-by-case assessment
- Emphasis on newly expressed proteins
- Conclusion about safety based on totality of the evidence

ASSESSMENT EXPERIENCE



PREVIOUS EXPERIENCE WITH ASSESSMENT OF RNAi-BASED GM PLANTS



Assessment of trait - same as for protein-based modifications

Additional information included to confirm that the phenotype is due to “silencing”

Omitted/reduced if no protein-based traits introduced

Cell Research (2011) :1-20.

www.nature.com/cr

ORIGINAL ARTICLE

Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA

Lin Zhang[1, *], Dongxia Hou[1, *], Xi Chen[1, *], Donghai Li[1, *], Lingyun Zhu[1, 2], Yujing Zhang[1], Jing Li[1], Zhen Bian[1], Xiangying Liang[1], Xing Cai[1], Yuan Yin[1], Cheng Wang[1], Tianfu Zhang[1], Dihan Zhu[1], Dianmu Zhang[1], Jie Xu[1], Qun Chen[1], Yi Ba[3], Jing Liu[1], Qiang Wang[1], Jianqun Chen[1], Jin Wang[1], Meng Wang[1], Qipeng Zhang[1], Junfeng Zhang[1], Ke Zen[1], Chen-Yu Zhang[1]

SOME COMMENTARY

"These results raise the question of whether food-derived small RNAs could play an active role in human/animal health." – Vaucheret & Chupeau 2011 *Cell Res*. 22: 3-5

Impact on human & animal health

"This profound discovery by Zhang et al. should make decision takers more cautious when considering the issues that may arise from the consumption of transgenic crops" – Jiang et al 2012 *Bioessays* 34: 280-284

Safety of GM crops where RNAi used

"….exposure to dsRNA …….could be the cause of off-target effects and adverse effects in non-target organisms" – Heinemann et al 2013 *Environment International* 55: 43-55

Exposure via food could lead to off-target and adverse effects in humans and other organisms

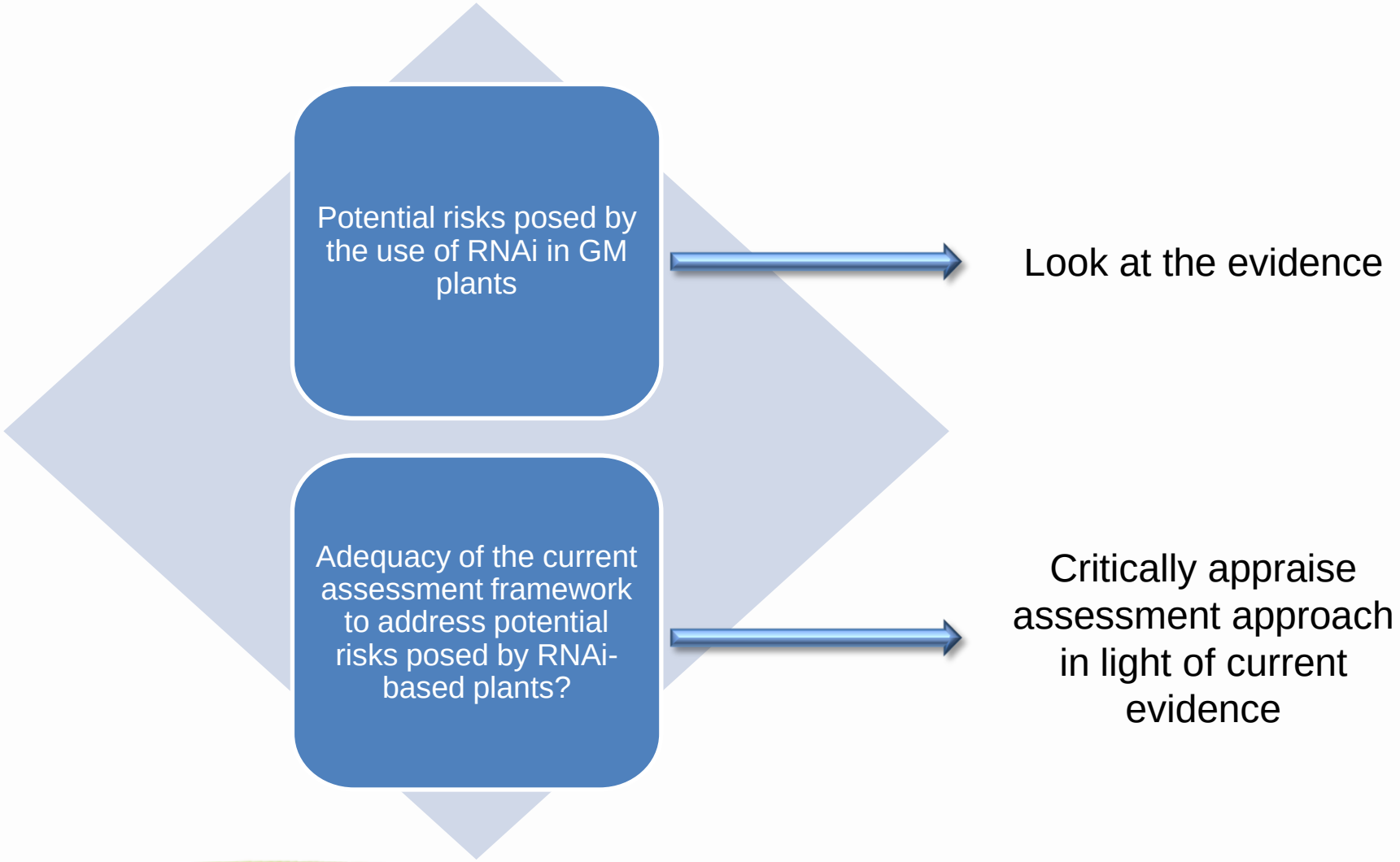
"Regulatory bodies are not adequately assessing the risks of dsRNA-producing GM products" – Heinemann et al 2013 *Environment International* 55: 43-55

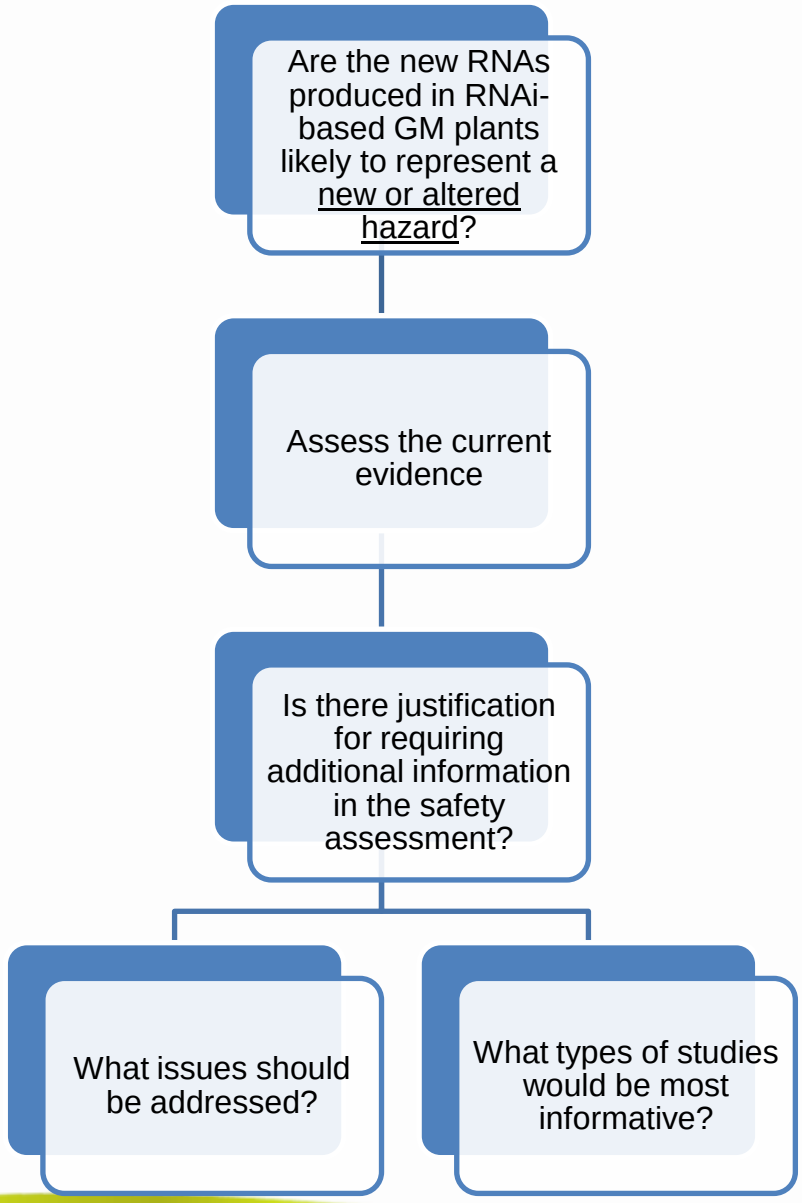
Question the adequacy of current risk assessment frameworks

"The molecular mediators of RNAi ……occur naturally in foods; therefore, there is an extensive history of safe consumption" – Petrick et al 2013 *Reg. Tox. Pharmacol*. 66: 167-176

Not a new hazard

KEY ISSUES


Potential risks posed by the use of RNAi in GM plants
Look at the evidence
Adequacy of the current assessment framework to address potential risks posed by RNAi-based plants?
Critically appraise assessment approach in light of current evidence



Challenges

- Active area of research
- Data gaps in the evidence base = uncertainty
- Weigh up evidence from disparate areas of research

SOME QUESTIONS – FOOD PERSPECTIVE

Examples	Comment
Human exposure via food?	- Naturally occurring versus new small RNAs produced in GM plants - Fresh versus processed food
Systemic uptake in humans following ingestion?	- Zhang et al 2011 - Other evidence for and against? - Biological barriers?
Likelihood of exerting an effect once taken up?	- Intake level required to get a sustained effect? - Other factors? - Experience with the oral delivery of small RNAs as therapeutics
How common are off-target effects?	- Clinical applications - Predictability?
Evidence of adverse effects in humans?	- Invertebrates versus humans and other mammals - Experience with clinical applications of RNAi

CURRENT ASSESSMENT FRAMEWORK

- Current framework includes capacity to assess other substances produced as a consequence of the genetic modification on a case-by-case basis
  - ➢ Small RNAs produced in RNAi-based GM plants could be assessed as a new/novel substance
  - ➢ Explicit guidance exists for the assessment of new proteins but only limited guidance for other types of new/novel substances

Recent data packages submitted for regulatory review have included additional information to address the safety of the RNAs

- History of safe use
- Site and level of expression (exposure)
- Mode of action and specificity
- No need for additional endpoints addressing potential toxicity because no evidence that ingested RNA can elicit toxicity in humans regardless of sequence

FSANZ PERSPECTIVE

- Not convinced the RNAs produced by RNAi-based GM plants represent a new or altered hazard for humans
- Will continue to assess food derived from RNAi-based GM plants using the current assessment framework
  - Decide on a case by case basis if additional information is required
- Continuing to monitor the literature and engage with experts in the field, developers and fellow regulators

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