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'Case Study: Risk Assessment of Food Additives'

Paul Hepburn, Adam Wood and Richard Cubberley

FICCI/FSSAI "Codex Masterclass on Risk Analysis Principles" (December 2025)

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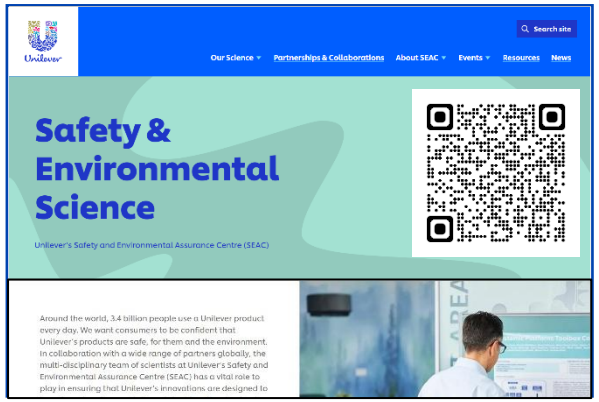
Please contact paul.hepburn@unilever.com or adam.wood@unilever.com with any questions



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2 **Enable** product Innovation, De-risking & Compliance

3 **Pioneer** industry & regulatory application of New Approaches, in partnership with other change leaders

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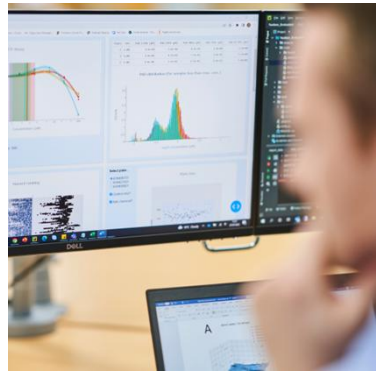

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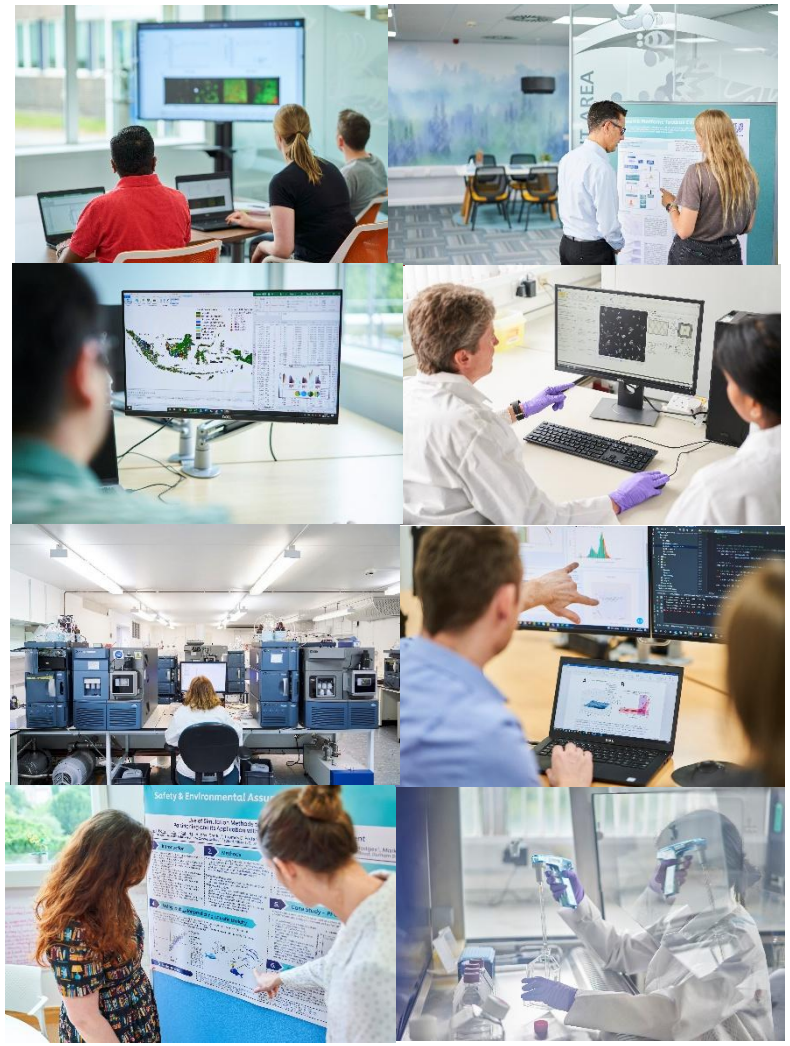
SERS Expertise



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- Industry
- Government

Safety Risk Assessments
- Consumers, Workers, Environment

Life Cycle Assessments
- Environmental Impacts

Product Compliance
- Regulatory Data & Dossiers

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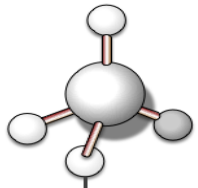
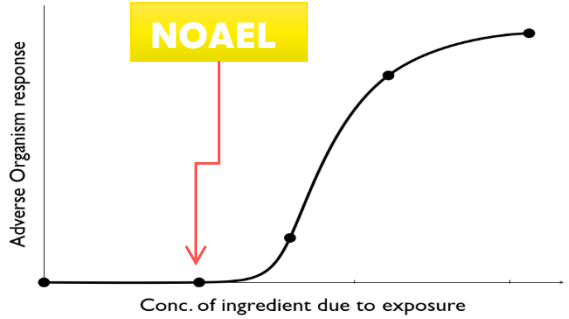
Traditional Risk Assessment for Food Additive Safety Assessment



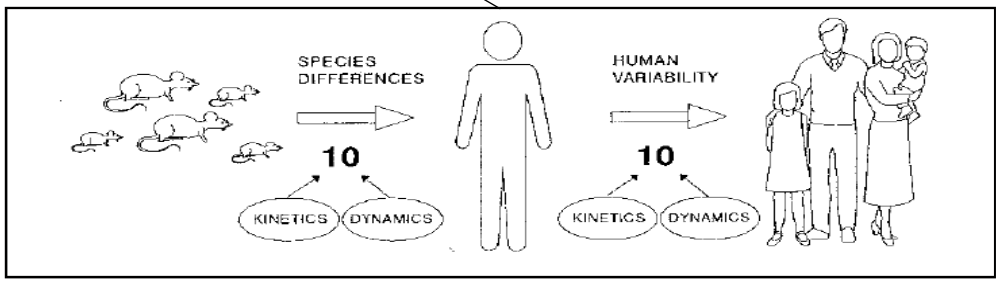


Amount/Conc. of ingredient due to exposure → Hazard Characterisation → Adverse Organism Reponse → Species Extrapolation → Safe Dose in Humans

Safety/ Uncertainty factors

- 90-day subchronic toxicology
- Chronic toxicology
- Reproductive and developmental toxicology (DART)
- Others (neurotoxicity, endocrine studies etc)

Targeted Testing



ADI/TDI* = NOAEL ÷ 100

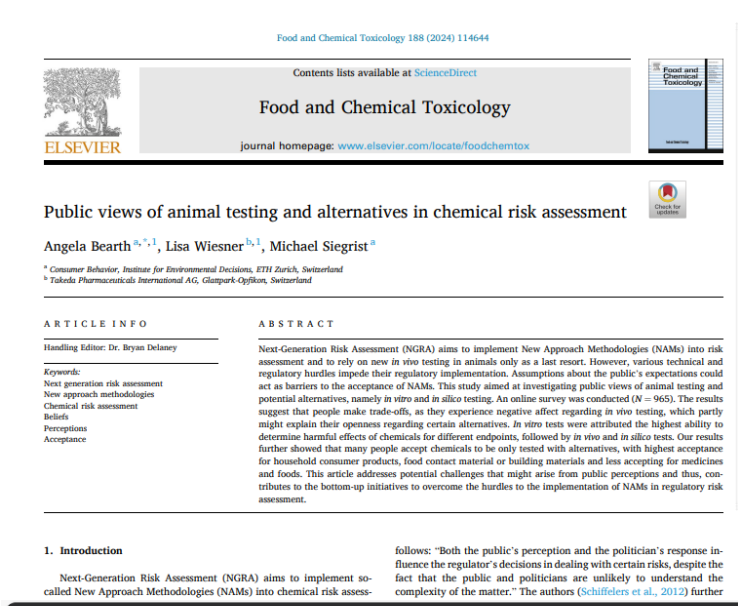
Exposure < ADI/TDI ☺

Exposure > ADI/TDI ☹

- **Acceptable Daily Intake**
- **Tolerable Daily Intake**

Reasons for change...

- **Human relevance** – Various pathological findings in animals are not human-relevant – e.g. some hepatic tumours in mice (aspartame/sweetener) – consequence can be detrimental to consumer trust in food/safety and lack of approval – US Delaney clause etc
- **Mechanistic** -possibility for more informative risk assessments – sensitive populations, mixture effects etc.
- **Changing consumer attitudes** – growing consumer dissatisfaction with animal testing (no longer a cosmetics only issue!)
- **Vegan claims** – compliance relies upon consideration of animal testing (e.g. ISO)
- **Speed/resource** – dramatic uptake in novel food innovation to meet e.g. sustainability targets – traditional paradigm too lengthy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journal homepage: www.elsevier.com/locate/foodchemtox

Public views of animal testing and alternatives in chemical risk assessment

Angela Bearth [a,*,1], Lisa Wiesner [b,1], Michael Siegrist [a]

[a] Consumer Behavior, Institute for Environmental Decisions, ETH Zurich, Switzerland
[b] Takeda Pharmaceuticals International AG, Glampark-Opfikon, Switzerland

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Keywords:
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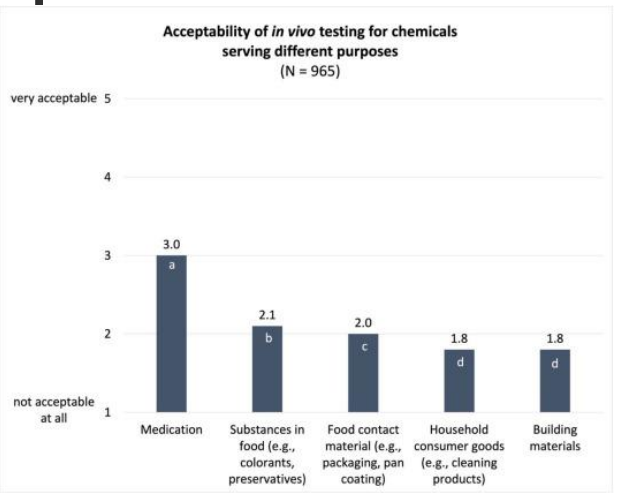
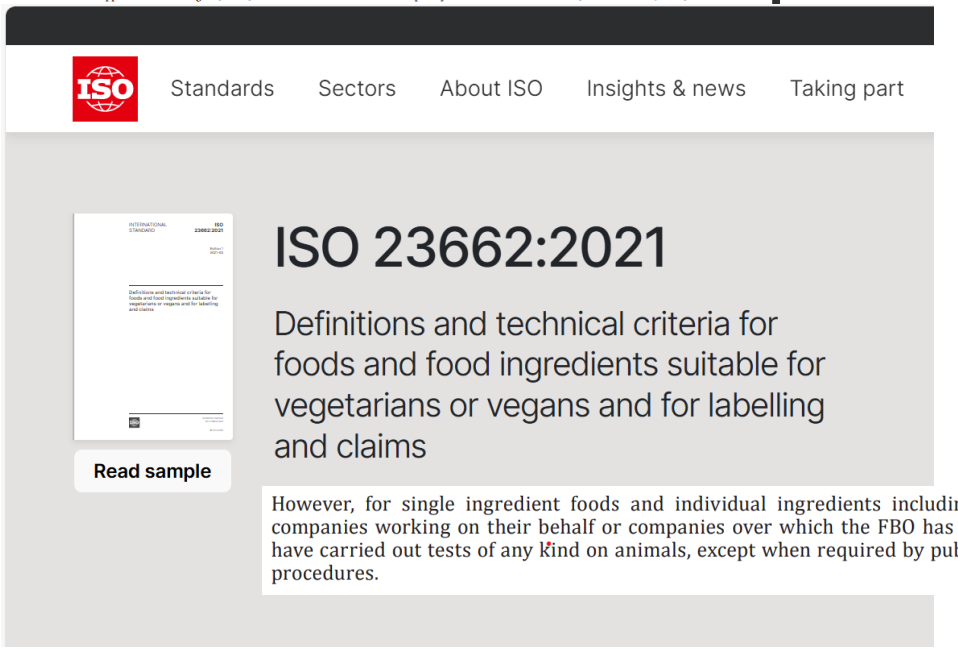
ABSTRACT

Next-Generation Risk Assessment (NGRA) aims to implement New Approach Methodologies (NAMs) into risk assessment and to rely on new *in vivo* testing in animals only as a last resort. However, various technical and regulatory hurdles impede their regulatory implementation. Assumptions about the public's expectations could act as barriers to the acceptance of NAMs. This study aimed at investigating public views of animal testing and potential alternatives, namely *in vitro* and *in silico* testing. An online survey was conducted ($N = 965$). The results suggest that people make trade-offs, as they experience negative affect regarding *in vivo* testing, which partly might explain their openness regarding certain alternatives. *In vitro* tests were attributed the highest ability to determine harmful effects of chemicals for different endpoints, followed by *in vivo* and *in silico* tests. Our results further showed that many people accept chemicals to be only tested with alternatives, with highest acceptance for household consumer products, food contact material or building materials and less accepting for medicines and foods. This article addresses potential challenges that might arise from public perceptions and thus, contributes to the bottom-up initiatives to overcome the hurdles to the implementation of NAMs in regulatory risk assessment.

1. Introduction

Next-Generation Risk Assessment (NGRA) aims to implement so-called New Approach Methodologies (NAMs) into chemical risk assessment follows: "Both the public's perception and the politician's response influence the regulator's decisions in dealing with certain risks, despite the fact that the public and politicians are unlikely to understand the complexity of the matter." The authors (Schiffelers et al., 2012) further





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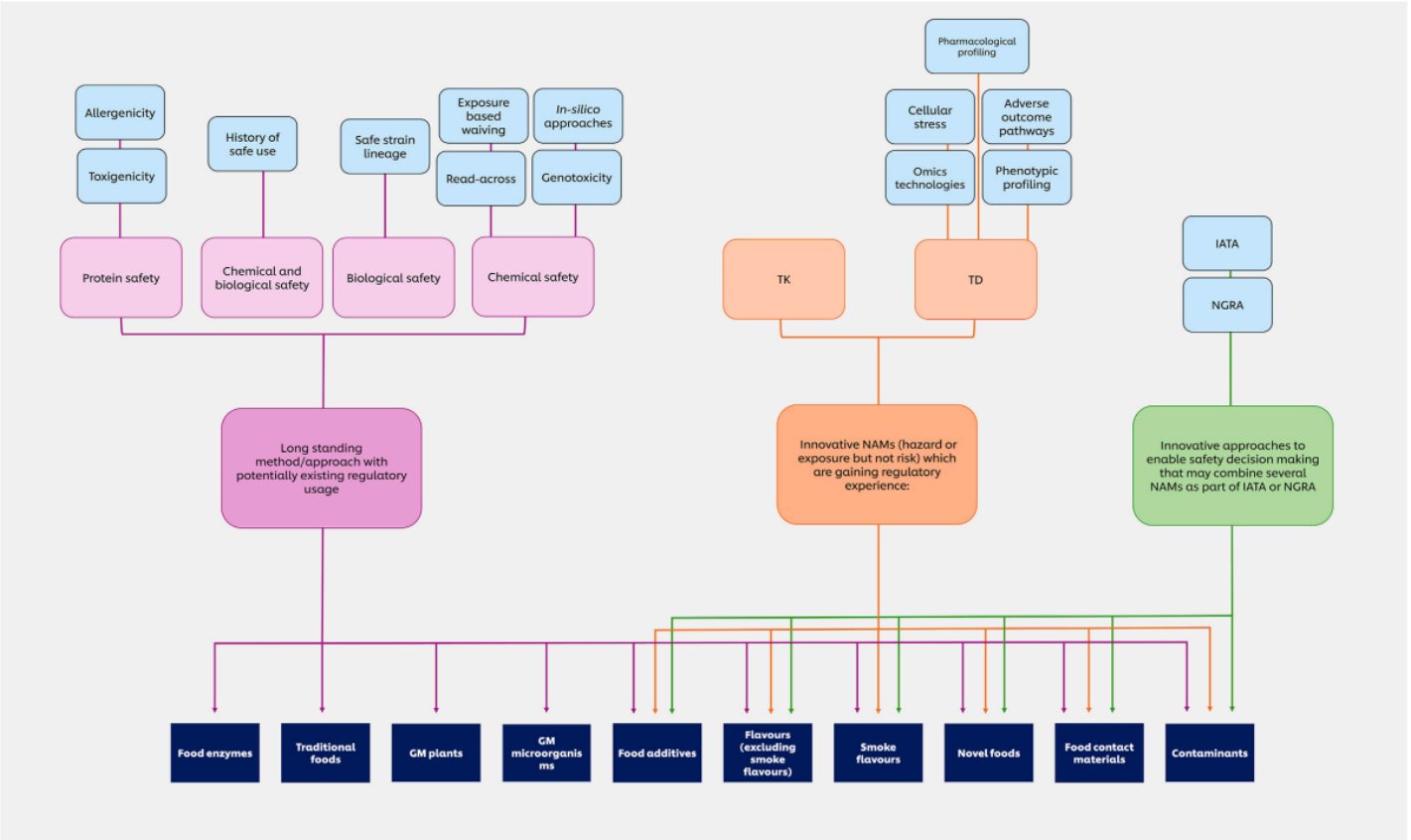
NGRA and New Approach Methodologies (NAMs)

- NAMs - Approaches that do not rely on generating new experimental animal data (though including those which use historical animal data) and comprising:
  In vitro, *in silico*, *in chemico* and *ex vivo* human models
- Such approaches may be used to provide information on hazard or exposure or used in combination.
- Some NAMs are long-standing (history of use), others are more-recent (transcriptomics).

Their use in risk assessment is considered the next generation of risk assessment (NGRA)



Wood et al., (2025). Regulatory Toxicology and Pharmacology, Volume 162, November 2025

Many NAMs of relevance to food safety exist and many could find use across multiple types of 'regulated products' (additives, flavours etc).

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CASE STUDIES

History of use

- A long-standing method (chemical and biological safety) that has played a role in numerous 'whole food' assessments, such as GM-crops and other novel foods, but also e.g. botanical extracts.

- Most often involves building an argument that a food is *'substantially equivalent'* to a reference food and that reference food has a substantial and well characterised history of consumption.

- Relies on considering factors such as 1.) compositional similarity between proposed/reference food, 2.) evidence of adverse effects from reference food and 3.) data on how the comparator is prepared, consumed etc.

Available online at www.sciencedirect.com
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www.elsevier.com/locate/foodchemtox

History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms

A. Constable [a], D. Jonas [b], A. Cockburn [c], A. Davi [d], G. Edwards [e], P. Hepburn [f], C. Herouet-Guicheney [g], M. Knowles [h], B. Moseley [i], R. Oberdörfer [j], F. Samuels [k,*]

Received 29 January 2007; accepted 29 May 2007

Abstract

Very few traditional foods that are consumed have been subjected to systematic toxicological and nutritional assessment, yet because of their long history and customary preparation and use and absence of evidence of harm, they are generally regarded as safe to eat. This 'history of safe use' of traditional foods forms the benchmark for the comparative safety assessment of novel foods, and of foods derived from genetically modified organisms. However, the concept is hard to define, since it relates to an existing body of information which describes the safety profile of a food, rather than a precise checklist of criteria. The term should be regarded as a working concept used to assist the safety assessment of a food product. Important factors in establishing a history of safe use include: the period over which the traditional food has been consumed; the way in which it has been prepared and used and at what intake levels; its composition and the results of animal studies and observations from human exposure. This paper is aimed to assist food safety professionals in the safety evaluation and regulation of novel foods and foods derived from genetically modified organisms, by describing the practical application and use of the concept of 'history of safe use'.

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Keywords: Safety assessment; Novel foods; Genetically modified foods; History of safe use

1. Introduction

Few foods have been subject to toxicological studies, however, foods generally are considered as safe to eat. An internationally accepted criterion for a safe food is a reasonable certainty of no harm resulting from consumption (CAC, 2001). It is, however, generally recognised that, while industry and national bodies strive for production, processing and labelling systems to ensure that food is 'safe and wholesome', complete freedom from risks is an unattainable goal (FAO, 1997). Many traditional foods are considered safe even though the food may contain anti-nutrients, toxins and/or allergens. Some foods require special preparation or processing to minimize the associated

Corresponding author. Tel.: +32 2771 0014; fax: +32 2762 0044.
E-mail address: fsamuels@ilsieurope.be (F. Samuels).

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doi:10.1016/j.fct.2007.05.028

Constable et al., 2007, Food and Chemical Toxicology, Volume 45, Issue 12

Research Article

A Multi-Criteria Decision Analysis Model to Assess the Safety of Botanicals Utilizing Data on History of Use

T. Neely, B. Walsh-Mason, P. Russell, A. Van Der Horst, S. O'Hagan, P. Lahorkar

Safety and Environmental Assurance Center, Unilever, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ, UK; Unilever R&D, 64 Main Road, Whitefield, Bangalore 560066, India

ABSTRACT

Botanicals (herbal materials and extracts) are widely used in traditional medicines throughout the world. Many have an extensive history of safe use over several hundreds of years. There is now a growing consumer interest in food and cosmetic products, which contain botanicals. There are many publications describing the safety assessment approaches for botanicals, based on the history of safe use. However, they do not define what constitutes a history of safe use, a decision that is ultimately a subjective one. The multi-criteria decision analysis (MCDA), is a model that has been developed, which assesses the safety of botanical ingredients using a history of use approach. The model evaluates the similarity of the botanical ingredient of interest to its historic counterpart – the comparator, the evidence supporting the history of use, and any evidence of concern. The assessment made is whether a botanical ingredient is as safe as its comparator botanical, which has a history of use. In order to establish compositional similarity between the botanical ingredient and its comparator, an analytical 'similarity scoring' approach has been developed. Applicability of the model is discussed with an example, *Brahmi* (*Bacopa monnieri*).

This evolution of the risk assessment of botanicals gives an objective, transparent, and transferable safety assessment approach.

Key words: Botanicals, *Brahmi*, history of safe use, multi multi-criteria decision analysis, safety assessment, similarity score

INTRODUCTION

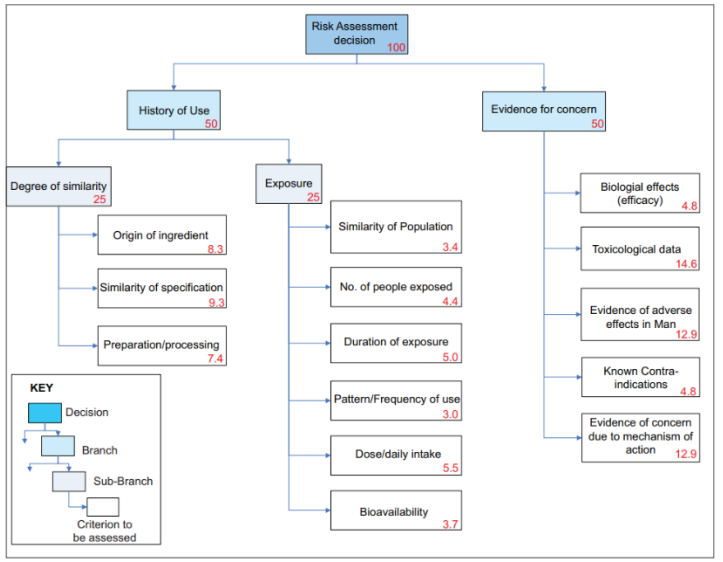
Herbal materials and extracts (botanicals) form a major component in indigenous peoples' traditional medicine and are a fundamental element in Ayurvedic, naturopathic, traditional oriental, and Native American Indian medicine. In Africa and Asia, 80% of the population use traditional medicine routinely.[1] In India over 70% of the population relies on some form of traditional medicine, mainly Ayurveda, Unani, and Siddha.[2] These materials, which are either a single herb or a synergistic mix, are complex and contain hundreds of different chemical constituents that may be responsible for any therapeutic effects observed.[3]

Over the last decade there has been a significant increase in the number of foods and cosmetic products that contain botanicals, many of which are marketed with a health benefit claim, but which are not intended to be marketed as medicines. Previously reported safety assessment approaches for botanicals in foods and food supplements have used a decision flow diagram approach, to capture the history of safe use with an appropriate comparator.[4–6] This approach has also been described as presumed safety.[7,8] The output of such an approach does not define what constitutes sufficient evidence to demonstrate a history of safe use. Ultimately, a

Address for correspondence: Dr T. Neely, Safety & Environmental Assurance Centre, Unilever, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ, UK. E-mail: theresa.neely@unilever.com

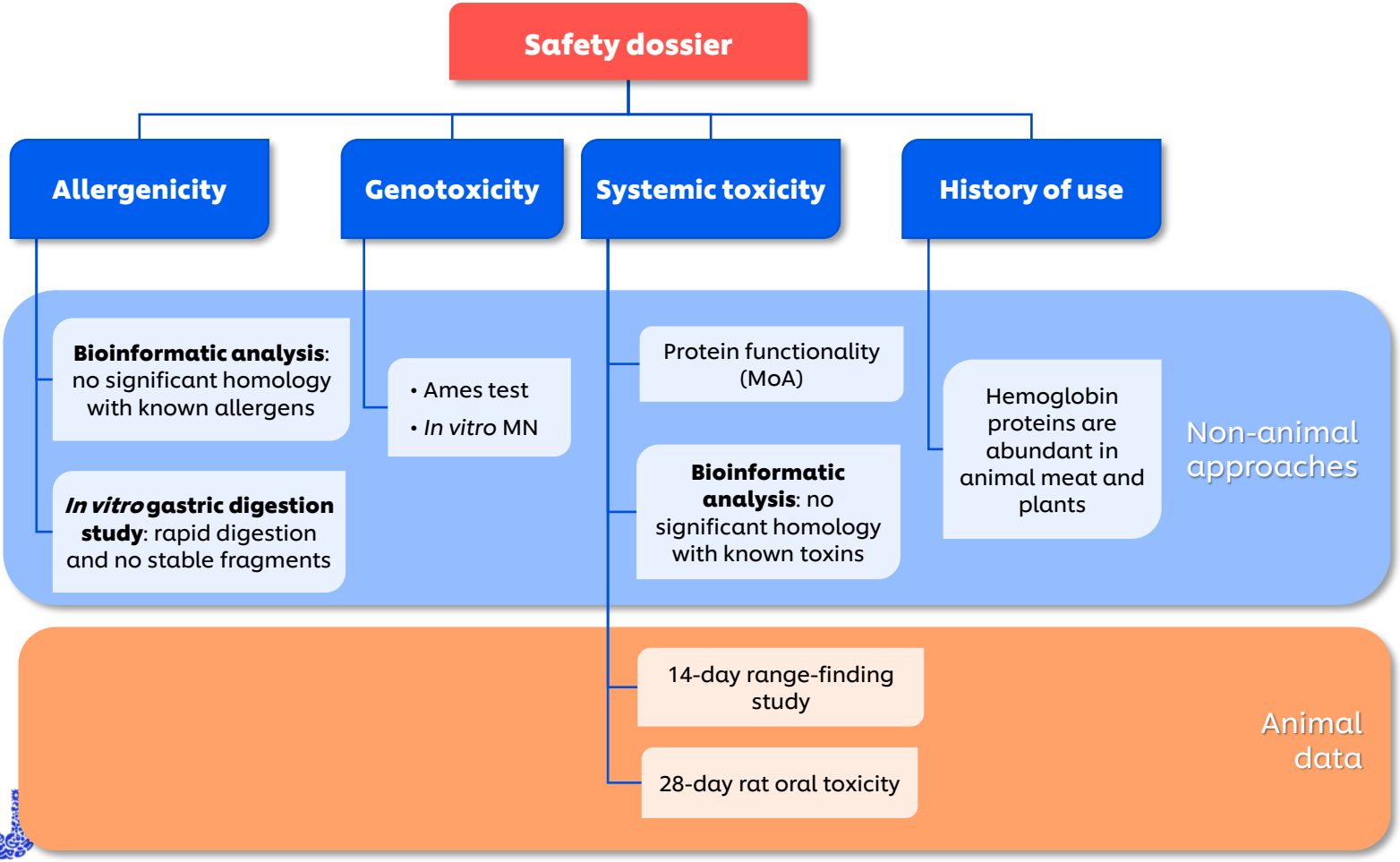
Toxicology International, Supplement, August 2011 | S20

Neely et al., 2011, Toxicology International, 18 (Suppl1)

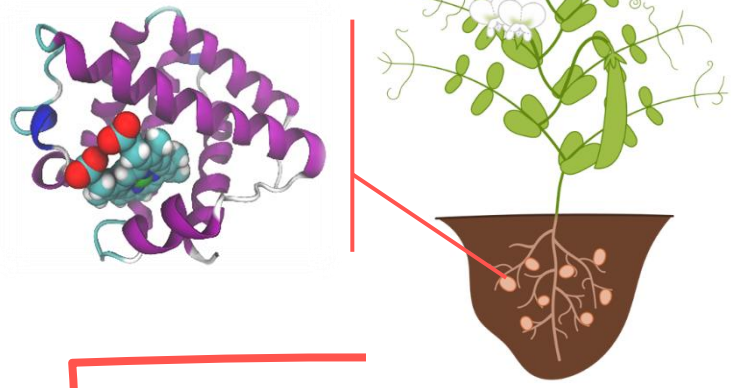


Soy leghemoglobin

- **Identity of the food:** leghemoglobin from soy (*Glycine max*) expressed in yeast (*Pichia pastoris*).
- **Proposed use:** food ingredient in meat-replacement products as iron source.



GRAS Notification (2017)



Key points

- The history of consumption of hemoglobin proteins in food together with the NAM data provided clear evidence to make a determination of safety.

Conclusion could have been based on comparison with other haemoglobin/overall protein intake rather than NOAEL from in vivo tox study.

Threshold of toxicological concern (TTC)

- The ability to waive toxicological testing for a substance without data if exposure falls below a threshold under which there is no appreciable health risk.
- Vast amount of guidance and best practice available externally.
- Significant work still underway externally to further develop approach – e.g. new rules, database harmonisation, new categories etc – e.g. FDA expanded decision tree.
- Work underway to develop an internal TTC (iTTC) value that could represent a higher tier method to waive exposures for substances without data.

GUIDANCE DOCUMENT

EFSA Journal

ADOPTED: 24 April 2019

doi: 10.2903/j.efsa.2019.5708

Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment

EFSA Scientific Committee, Simon J More, Vasileios Bampidis, Diane Benford, Claude Bragard, Thorhallur I Halldorsson, Antonio F Hernández-Jerez, Susanne Hougaard Bennekou, Kostas P Koutsoumanis, Kyriaki Machera, Hanspeter Naegeli, Søren S Nielsen, Josef R Schlatter, Dieter Schrenk, Vittorio Silano, Dominique Turck, Maged Younes, Ursula Gundert-Remy, George E N Kass, Juliane Kleiner, Anna Maria Rossi, Rositsa Serafimova, Linda Reilly and Heather M Wallace

Abstract

The Scientific Committee confirms that the Threshold of Toxicological Concern (TTC) is a pragmatic screening and prioritisation tool for use in food safety assessment. This Guidance provides clear step-by-step instructions for use of the TTC approach. The inclusion and exclusion criteria are defined and the use of the TTC decision tree is explained. The approach can be used when the chemical structure of the substance is known, there are limited chemical-specific toxicity data and the exposure can be estimated. The TTC approach should not be used for substances for which EU food/feed legislation requires the submission of toxicity data or when sufficient data are available for a risk assessment or if the substance under consideration falls into one of the exclusion categories. For substances that have the potential to be DNA-reactive mutagens and/or carcinogens based on the weight of evidence, the relevant TTC value is 0.0025 μg/kg body weight (bw) per day. For organophosphates or carbamates, the relevant TTC value is 0.3 μg/kg bw per day. All other substances are grouped according to the Cramer classification. The TTC values for Cramer Classes I, II and III are 30 μg/kg bw per day, 9 μg/kg bw per day and 1.5 μg/kg bw per day, respectively. For substances with exposures below the TTC values, the probability that they would cause adverse health effects is low. If the estimated exposure to a substance is higher than the relevant TTC value, a non-TTC approach is required to reach a conclusion on potential adverse health effects.

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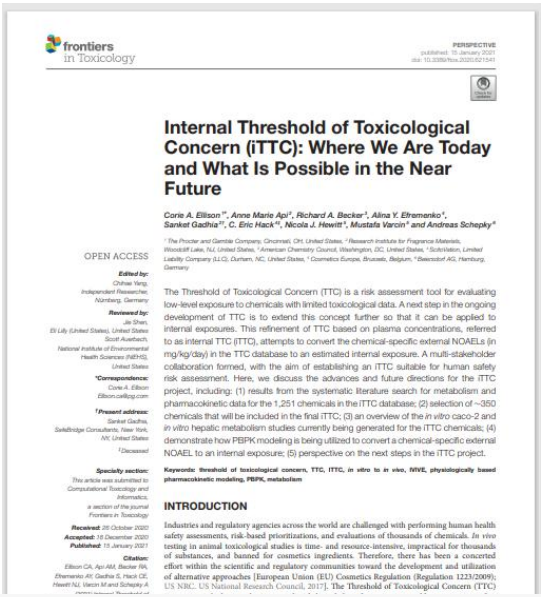
Keywords: Threshold of toxicological concern, risk assessment, Cramer classification scheme

Requestor: European Food Safety Authority

Question number: EFSA-Q-2017-00468

Correspondence: sc.secretariat@efsa.europa.eu



frontiers in Toxicology

PERSPECTIVE

Internal Threshold of Toxicological Concern (iTTC): Where We Are Today and What Is Possible in the Near Future

OPEN ACCESS

The Threshold of Toxicological Concern (TTC) is a risk assessment tool for evaluating low-level exposure to chemicals with limited toxicological data. A next step in the ongoing development of TTC is to extend this concept further so that it can be applied to internal exposures. This refinement of TTC based on plasma concentrations, referred to as internal TTC (iTTC), attempts to convert the chemical-specific external NOAELs (in mg/kg/day) in the TTC database to an estimated internal exposure. A multi-stakeholder collaboration formed, with the aim of establishing an iTTC suitable for human safety risk assessment. Here, we discuss the advances and future directions for the iTTC project, including: (1) results from the systematic literature search for metabolism and pharmacokinetic data for the 1,251 chemicals in the iTTC database; (2) selection of ~350 chemicals that will be included in the final iTTC; (3) an overview of the *in vitro* caco-2 and *in vitro* hepatic metabolism studies currently being generated for the iTTC chemicals; (4) demonstrate how PBPK modeling is being utilized to convert a chemical-specific external NOAEL to an internal exposure; (5) perspective on the next steps in the iTTC project.

Keywords: threshold of toxicological concern, TTC, iTTC, *in vitro* to *in vivo*, IVIVE, physiologically based pharmacokinetic modeling, PBPK, metabolism

INTRODUCTION

Industries and regulatory agencies across the world are challenged with performing human health safety assessments, risk-based prioritizations, and evaluations of thousands of chemicals. *In vivo* testing in animal toxicological studies is time- and resource-intensive, impractical for thousands of substances, and banned for cosmetics ingredients. Therefore, there has been a concerted effort within the scientific and regulatory communities toward the development and utilization of alternative approaches [European Union (EU) Cosmetics Regulation (Regulation 1223/2009); US NRC, US National Research Council, 2017]. The Threshold of Toxicological Concern (TTC)

https://www.fda.gov/food/food-chemical-safety/expanded-decision-tree-fdas-food-chemical-toxicity-screening-tool

An official website of the United States government Here's how you know

FDA U.S. FOOD & DRUG ADMINISTRATION

Home / Food / Food Ingredients & Packaging / Food Chemical Safety / Expanded Decision Tree: FDA's Food Chemical Toxicity Screening Tool

Expanded Decision Tree: FDA's Food Chemical Toxicity Screening Tool

Food Chemical Safety

List of Select Chemicals in the Food Supply Under FDA Review

Examples – TTC Approach in Practice

SCIENTIFIC OPINION

EFSA JOURNAL

Flavouring group evaluation 419 (FGE.419): 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one

EFSA Panel on Food Additives and Flavourings (FAF) | Maged Younes | Gabriele Aquilina | Laurence Castle | Gisela Degen | Karl-Heinz Engel | Paul J. Fowler | Maria Jose Frutos Fernandez | Peter Fürst | Ursula Gundert-Remy | Rainer Gürtler | Trine Husøy | Melania Manco | Peter Moldeus | Sabina Passamonti | Romina Shah | Ine Waalkens-Berendsen | Matthew Wright | Romualdo Benigni | Claudia Bolognesi | Kevin Chipman | Eugenia Cordelli | Karin Nerby | Camilla Svendsen | Maria Carfi | Gabriele Gagliardi | Carla Martino | Salvatore Multari | Wim Mennes

Abstract

The EFSA Panel on Food Additives and Flavourings (FAF) was requested to evaluate the safety of 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one [FL-no: 16.134] as a new flavouring substance, in accordance with Regulation (EC) No 1331/2008. The substance has not been reported to occur naturally and is chemically synthesised. In food, it is intended to be used as a flavouring substance only in chewing gum. The chronic dietary exposure to [FL-no: 16.134] was estimated to be 45 µg/person per day for a 60-kg adult and 28.4 µg/person per day for a 15-kg 3-year-old child. [FL-no: 16.134] did not show genotoxicity in a bacterial reverse mutation test and an in vitro mammalian cell micronucleus assay. Based on the submitted toxicokinetic and metabolism data, it can be predicted that the flavouring substance is metabolised to innocuous products only. The Panel derived a lower confidence limit of the benchmark dose (BMDL) of 0.71 mg/kg bw per day for a 20% increase in the relative thyroid (including parathyroid) weight observed in a 90-day toxicity study in rats. Based on this BMDL, adequate margins of exposure of 887 and 374 could be calculated for adults and children, respectively. The Panel concluded that there is no safety concern for [FL-no: 16.134], when used as a flavouring substance at the estimated level of dietary exposure, based on the intended use and use levels as specified in Appendix B. The Panel further concluded that the combined exposure to [FL-no: 16.134] from its use as a food flavouring substance and from its presence in toothpaste and mouthwash is also not of safety concern.

KEYWORDS

SCIENTIFIC OPINION

EFSA Journal

Scientific Opinion of Flavouring Group Evaluation 411 (FGE.411): 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide from chemical group 30 (miscellaneous substances)

EFSA Panel on Food Additives and Flavourings (FAF), Maged Younes, Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Ursula Gundert-Remy, Rainer Gürtler, Trine Husøy, Peter Moldeus, Agneta Oskarsson, Sandra Rainieri, Romina Shah, Ine Waalkens-Berendsen, Detlef Wölfle, Romualdo Benigni, Mona-Lise Binderup, Claudia Bolognesi, Leon Brimer, Kevin Chipman, Francesca Marcon, Daniel Marzin, Pasquale Mosesso, Gerard Mulder, Camilla Svendsen, Jan van Benthem, Maria Anastassiadou, Maria Carfi and Wim Mennes

Abstract

EFSA was requested to deliver a scientific opinion on the implications for human health of the flavouring substance 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide [FL-no: 16.133], in the Flavouring Group Evaluation 411 (FGE.411), according to Regulation (EC) No 1331/2008 of the European Parliament and of the Council. The substance has not been reported to occur in natural source materials of botanical or animal origin. It is intended to be used as a flavouring substance in specific categories of food but not intended to be used in beverages, except for milk and dairy based beverages that are opaque. The chronic dietary exposure to the substance estimated using the added portions exposure technique (APET), is calculated to be 225 µg/person per day for a 60-kg adult and 142 µg/person per day for a 15-kg 3-year-old child. A 90-day oral gavage study in rats showed no adverse effects at doses up to 100 mg/kg body weight (bw) per day, providing an adequate margin of safety. Developmental toxicity was not observed in a study with rats at the dose levels up to 1,000 mg/kg bw per day. The Panel concluded that there is no safety concern for [FL-no: 16.133], when used as a flavouring substance at the estimated level of dietary exposure calculated using the APET approach and based on the recommended uses and use levels as specified in Appendix B. This conclusion does not apply for use in beverages where the substance can be subject to phototransformation.

Keywords: flavouring, 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide, FGE.411, [FL-no: 16.133]

Requestor: European Commission

Question number: EFSA-Q-2015-00820

Correspondence: FIP@efsa.europa.eu

Example 1: 2-methyl-1-(2-(5-(ptolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-on (substanc

Cramer Class III: 90 µg/person/day

Exposure: Adults 45 µg/day | Children 28.4 µg/day

Outcome: Below TTC → **No animal data needed, HOWEVER,** applicant did perform a 90-day study (BMDL = 0.71 mg/kg; MoE 887 & 374)

Animal testing unnecessary

Example 2: 2-(4-methylphenoxy)-N-(1H-pyrazol-3-yl)-N- (thiophen-2-ylmethyl)acetamide (substance B)

- Cramer Class III (90µg/person per day)
- Dietary exposure: 225 µg/day (adults) and 142 µg/day (children).
- Exposures were hence ~2-fold above TTC and animal studies performed (90-day and developmental toxicity study). No effects in either study (up to 100 mg/kg) and MoE (min) was 10,500
- **In the future, possibly an internal TTC could be used to address safety for cases like this.**

Unilever

Examples – TTC Approach in Practice

A

B

SCIENTIFIC OPINION

JOURNAL

Flavouring group evaluation 419 (FGE.419): 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one

EFSA Panel on Food Additives and Flavourings (FAF) | Maged Younes | Gabriele Aquilina | Laurence Castle | Gisela Degen | Karl-Heinz Engel | Paul J. Fowler | Maria Jose Frutos Fernandez | Peter Fürst | Ursula Gundert-Remy | Rainer Gürtler | Trine Husøy | Melania Manco | Peter Moldeus | Sabina Passamonti | Romina Shah | Ine Waalkens-Berendsen | Matthew Wright | Romualdo Benigni | Claudia Bolognesi | Kevin Chipman | Eugenia Cordelli | Karin Nørby | Camilla Svendsen | Maria Carfì | Gabriele Gagliardi | Carla Martino | Salvatore Multari | Wim Mennes

Abstract

The EFSA Panel on Food Additives and Flavourings (FAF) was requested to evaluate the safety of 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one [FL-no: 16.134] as a new flavouring substance, in accordance with Regulation (EC) No 1331/2008. The substance has not been reported to occur naturally and is chemically synthesised. In food, it is intended to be used as a flavouring substance only in chewing gum. The chronic dietary exposure to [FL-no: 16.134] was estimated to be 45 µg/person per day for a 60-kg adult and 28.4 µg/person per day for a 15-kg 3-year-old child. [FL-no: 16.134] did not show genotoxicity in a bacterial reverse mutation test and an in vitro mammalian cell micronucleus assay. Based on the submitted toxicokinetic and metabolism data, it can be predicted that the flavouring substance is metabolised to innocuous products only. The Panel derived a lower confidence limit of the benchmark dose (BMDL) of 0.71 mg/kg bw per day for a 20% increase in the relative thyroid (including parathyroid) weight observed in a 90-day toxicity study in rats. Based on this BMDL, adequate margins of exposure of 887 and 374 could be calculated for adults and children, respectively. The Panel concluded that there is no safety concern for [FL-no: 16.134], when used as a flavouring substance at the estimated level of dietary exposure, based on the intended use and use levels as specified in Appendix B. The Panel further concluded that the combined exposure to [FL-no: 16.134] from its use as a food flavouring substance and from its presence in toothpaste and mouthwash is also not of safety concern.

KEYWORDS

2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one, FGE.419, FL-no: 16.134

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 12 September 2018

Scientific Opinion of Flavouring Group Evaluation 411 (FGE.411): 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide from chemical group 30 (miscellaneous substances)

EFSA Panel on Food Additives and Flavourings (FAF), Maged Younes, Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Ursula Gundert-Remy, Rainer Gürtler, Trine Husøy, Peter Moldeus, Agneta Oskarsson, Sandra Rainieri, Romina Shah, Ine Waalkens-Berendsen, Detlef Wölfle, Romualdo Benigni, Mona-Lise Binderup, Claudia Bolognesi, Leon Brimer, Kevin Chipman, Francesca Marcon, Daniel Marzin, Pasquale Mosesso, Gerard Mulder, Camilla Svendsen, Jan van Benthem, Maria Anastassiadou, Maria Carfì and Wim Mennes

Abstract

EFSA was requested to deliver a scientific opinion on the implications for human health of the flavouring substance 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide [FL-no: 16.133], in the Flavouring Group Evaluation 411 (FGE.411), according to Regulation (EC) No 1331/2008 of the European Parliament and of the Council. The substance has not been reported to occur in natural source materials of botanical or animal origin. It is intended to be used as a flavouring substance in specific categories of food but not intended to be used in beverages, except for milk and dairy based beverages that are opaque. The chronic dietary exposure to the substance estimated using the added portions exposure technique (APET), is calculated to be 225 µg/person per day for a 60-kg adult and 142 µg/person per day for a 15-kg 3-year-old child. A 90-day oral gavage study in rats showed no adverse effects at doses up to 100 mg/kg body weight (bw) per day, providing an adequate margin of safety. Developmental toxicity was not observed in a study with rats at the dose levels up to 1,000 mg/kg bw per day. The Panel concluded that there is no safety concern for [FL-no: 16.133], when used as a flavouring substance at the estimated level of dietary exposure calculated using the APET approach and based on the recommended uses and use levels as specified in Appendix B. This conclusion does not apply for use in beverages where the substance can be subject to phototransformation.

Keywords: flavouring, 2-(4-methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide, FGE.411, [FL-no: 16.133]

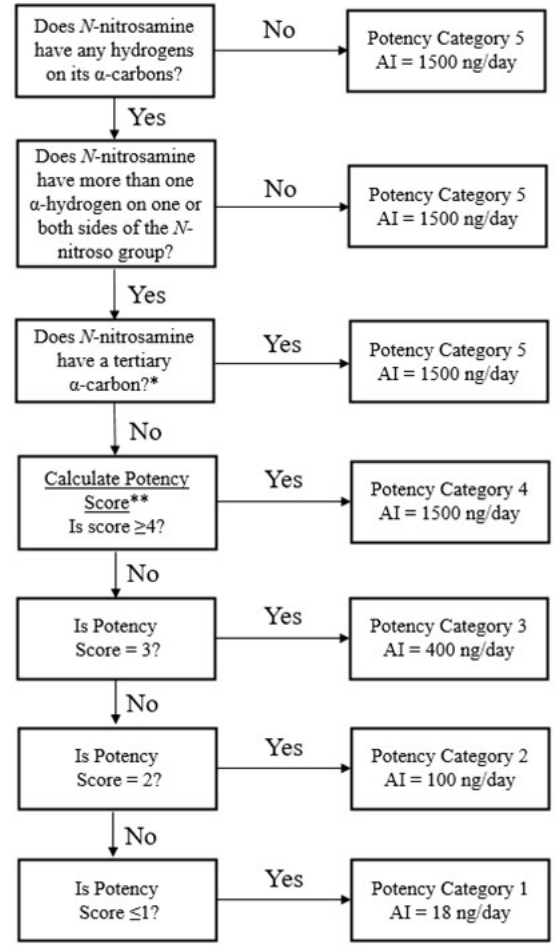
Requestor: European Commission
Question number: EFSA-Q-2015-00820
Correspondence: FIP@efsa.europa.eu

Parameter	Substance A	Substance B
Cramer Class	III (90 µg/person/day)	III (90 µg/person/day)
Exposure (Adults)	45 µg/day	225 µg/day
Exposure (Children)	28.4 µg/day	142 µg/day
TTC Comparison	Below TTC → **No animal data needed**	Above TTC → **Animal studies performed**
Study Details	90-day study (BMDL = 0.71 mg/kg; MoE 887 & 374)	90-day and PNDT - No effects in either (up to 100 mg/kg); MoE min = 10,500
Conclusion:	**Animal testing unnecessary**	**Future: Internal TTC could address cases**

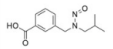
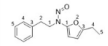
Key Takeaway: TTC can reduce unnecessary animal testing and guide safety decisions.

Assessing Nitrosamines with no Specific Toxicological Data (QSARs)

- Carcinogenic Potency Categorization Approach (CPCA)
- 5 potency categories set based on existing toxicological data (Read Across)
- Chemical similarities between the nitrosamines assigned to each category were used to set rules based on specific structural features
- Rules translated into the flow diagram on the right
- Deactivating and activating features described and assigned a score which when totalled up allows a potency category and corresponding Acceptable Intake (AI) value to be assigned
- Similar schemes used by US FDA, Health Canada and European Medicines Agency



Activating Feature	Example	Individual Activating Feature Score
Aryl group bonded to α-carbon (i.e., benzylic or pseudo-benzylic substituent on *N*-nitroso group)		-1
Methyl group bonded to β-carbon (cyclic or acyclic)		-1

Deactivating Feature	Example	Individual Deactivating Feature Score
Carboxylic acid group anywhere on molecule		+3
N-nitroso group in a pyrrolidine ring		+3
N-nitroso group in a 6-membered ring containing at least one sulfur atom		+3
N-nitroso group in a 5- or 6-membered ring *		+2
N-nitroso group in a morpholine ring		+1
N-nitroso group in a 7-membered ring		+1
Chains of ≥5 consecutive non-hydrogen atoms (cyclic or acyclic) on both side of acyclic *N*-nitroso group. Not more than 4 atoms in each chain may be in the same ring		+1

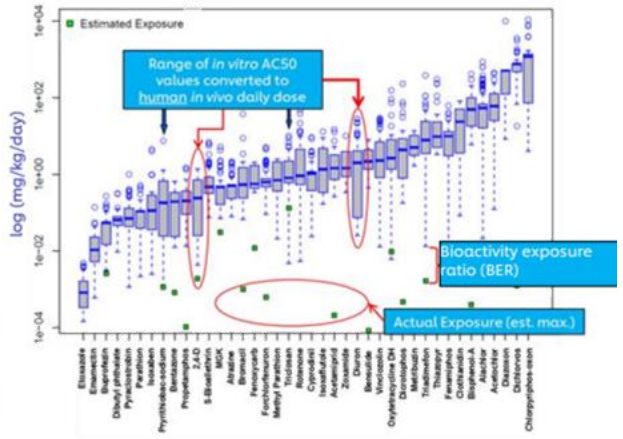
The need for innovative NAMs

Until recently, for, ingredients used at levels >TTC or ingredients where a history of use cannot be established…

Demonstrating safety without animal testing was challenging. However, in recent years, tremendous progress made in areas such as…

- High-throughput screening
- Computational sciences – bioinformatics, pharmacokinetic modelling, statistics etc

These scientific advancements have opened new possibilities that have collectively shifted the dial in terms of our ability to demonstrate safety using non-animal methods



Graph from Rusty Thomas EPA, with thanks. Rotroff et al (2010) Toxicological Sciences , **117**, 348-358

$$BER = \frac{Lowest\ bioactivity\ POD}{Internal\ in\ vivo\ exposure\ (Cmax)}(uM)$$

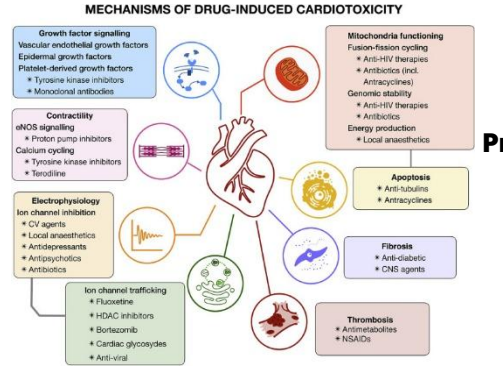
NAM development – protection vs prediction

Rapid development of NAMs for use in risk assessment. Two alternate philosophies:

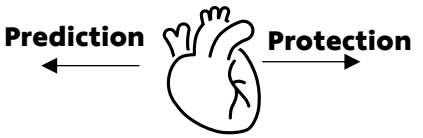
1.) NAMs developed to predict (possibly quantitatively) adverse effects

2.) NAMs developed to measure bioactivity (quantitatively) without classification as adversity or not.

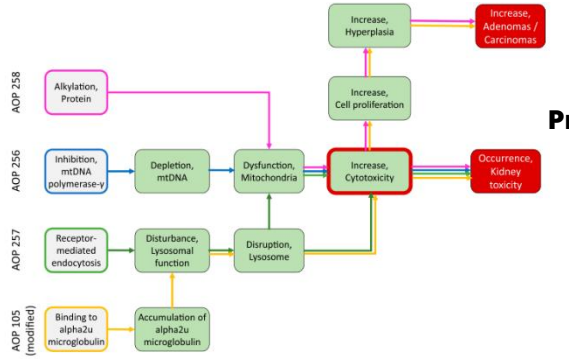
Both have a place in **future** risk assessment. **Unilever have invested significant resource into protective NAMs**



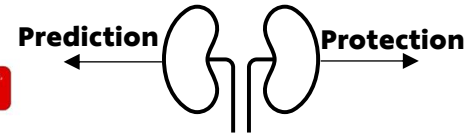
Manoshina et al., (2021). Cell Reports Medicine. 2:3 100216

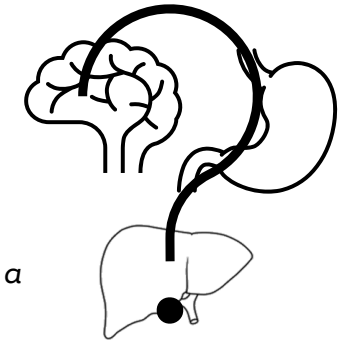


NAMs capturing early biological changes protective of apical effects



Mally and Jarzina (2022). Frontiers in Toxicology





Limited coverage approaches

Cell based/reporter assays

Data rich approaches

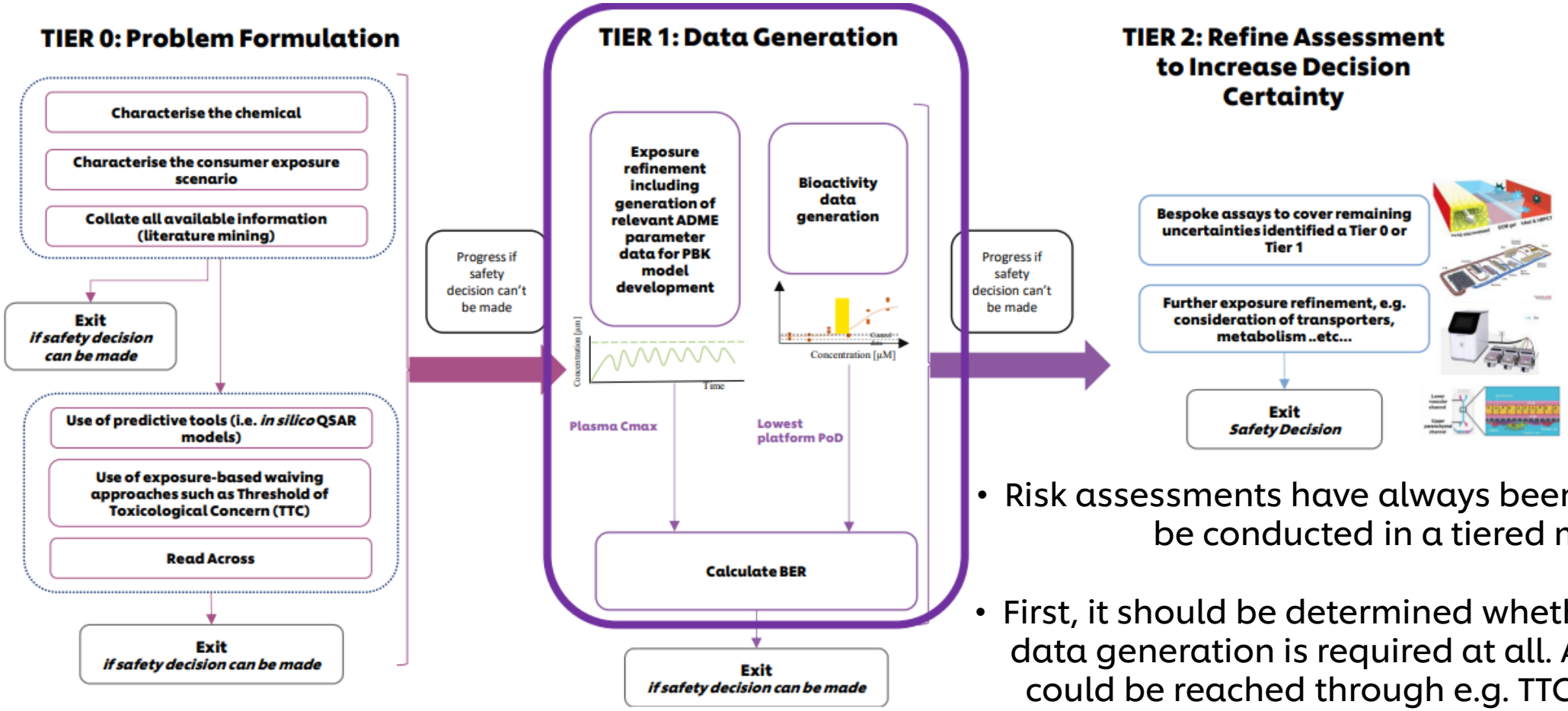
Transcriptomics

Cell painting

State of the art (>20-years)

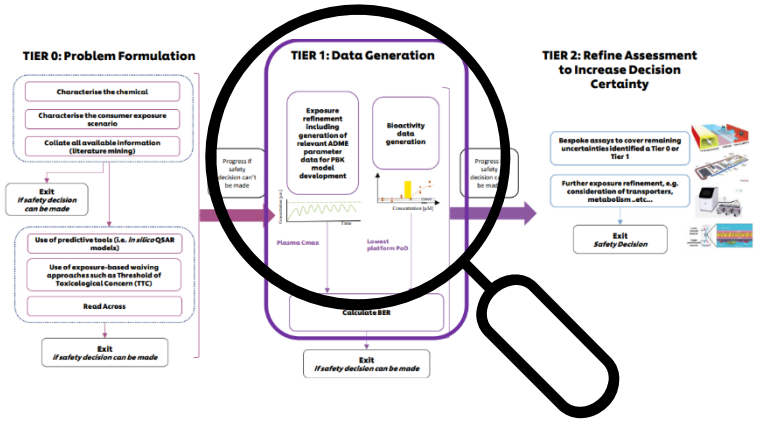
There are 78 major human organs; let's say there are five different ways in which chemicals could be toxic to each one (an underestimate); and let's say we need five key events (including a molecular initiating event) measured across each IATA with new in vitro tests. That's around 2000 assays conducted at just one dose and at one time point for complete human AOP-driven biological coverage. Carmichael et al., (2022). Altex, 39:3

Place of innovative NAMs in tiered risk assessment framework



- Risk assessments have always been and will always be conducted in a tiered manner.
- First, it should be determined whether experimental data generation is required at all. A safety decision could be reached through e.g. TTC or read-across without new studies being performed.
- If data generation is needed, **NAMs are used in a tiered way, starting with broad coverage (protective) NAMs progressing to specific (predictive) NAMs as needed.**

Unilever's NAM toolbox and NGRA tiered framework approach



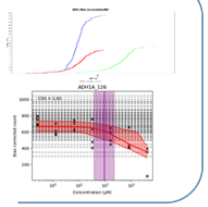
- Unilever's basic NAM toolbox uses **non-specific and specific NAMs.**
- Point of departures (PoDs) from these are compared with PBK model estimates of internal exposure to enable risk characterisation (through a **bioactivity exposure ratio/BER**).

Point of Departure (PoD) determination from Bioactivity assays

Non-specific effects

High-Throughput transcriptomics (HTTr)

- TempO-seq technology – full gene panel
- 24hr exposure
- 7 concentrations
- Various cell models (e.g. HepG2, MCF7, HepaRG)
- Dose-response analysis using BMDExpress2 and BIFROST model



Reynolds et al. 2020. Comp Tox 16: 100138
Baltazar et al. 2020. Toxicol Sci 176(1):236–252

Cell stress panel (CSP)

- 36 biomarkers covering 10 cell stress pathways
- HepG2
- 24hr exposure
- 8 concentrations
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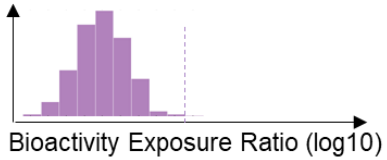
Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. Toxicol Sci 176(1): 11-33

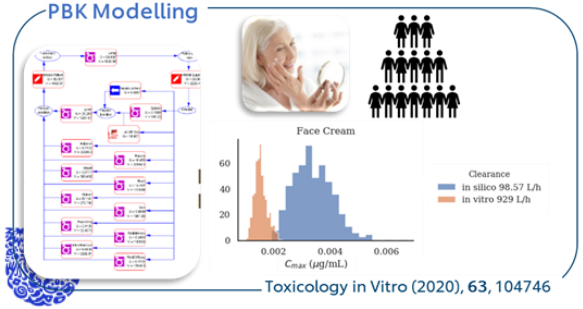
Specific effects

In vitro pharmacological profiling

Bioactivity Exposure Ratio (BER) Distribution



PBK Modelling



Toxicology in Vitro (2020), 63, 104746

Plasma C_{max} estimate → **C_{max} Error Distribution model (CMED)**

(Bayesian model)

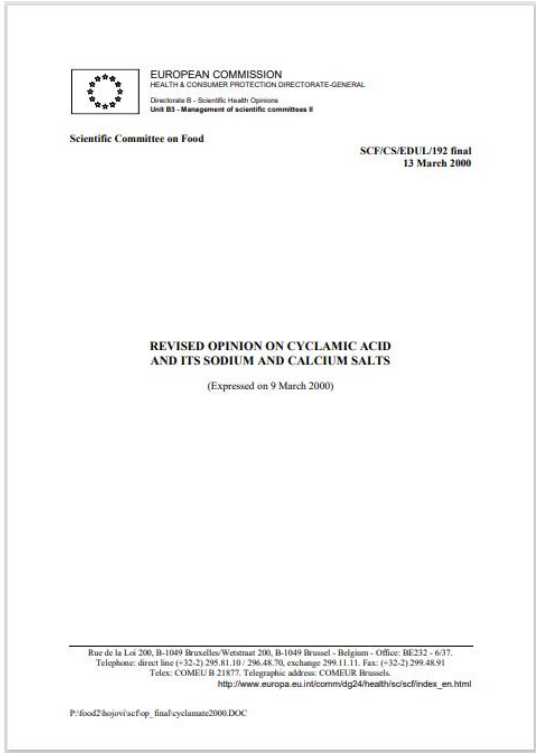
BIOACTIVITY EXPOSURE RATIO = $\frac{\text{BIOACTIVITY}}{\text{EXPOSURE}}$

The bigger the BER, the greater the confidence that bioactivity will not occur in exposed consumers

Unilever

Case study - cyclamate

- Sodium cyclamate, also called E952 (ii), is used as an artificial sweetener.
- Has been reviewed by JECFA (1982) and the SCF (2000) with ADIs established as 0-11 mg/kg (JECFA) and 0-7 mg/kg (SCF). Re-evaluation currently underway by EFSA.
- ADI is based on a NOAEL of 100 mg/kg derived from a 90-day rat study where the rats were administered cyclohexylamine (CHA: the major metabolite of cyclamate).



EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Directorate B - Scientific Health Opinions
Unit B3 - Management of scientific committees II

Scientific Committee on Food

SCF/CS/EDUL/192 final
13 March 2000

REVISED OPINION ON CYCLAMIC ACID AND ITS SODIUM AND CALCIUM SALTS

(Expressed on 9 March 2000)

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: BE232 - 6/37.
Telephone: direct line (+32-2) 295.81.10 / 296.48.70, exchange 299.11.11. Fax: (+32-2) 299.48.91
Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels.
http://www.europa.eu.int/comm/dg24/health/sc/scf/index_en.html

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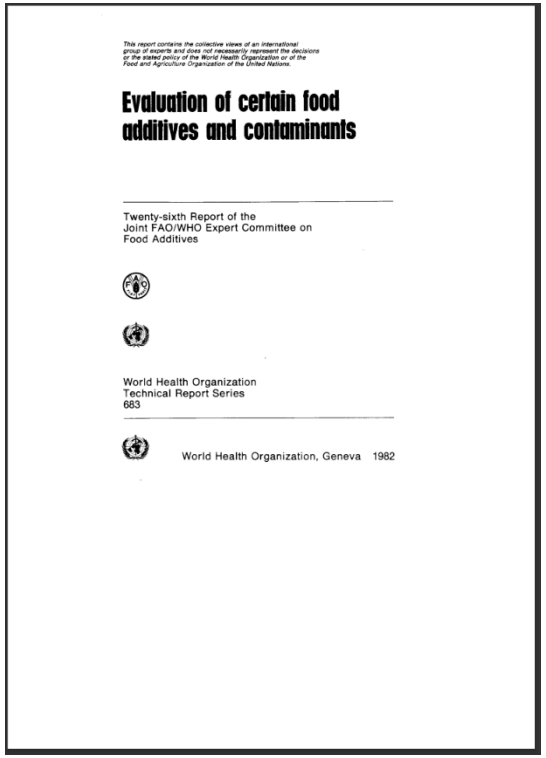


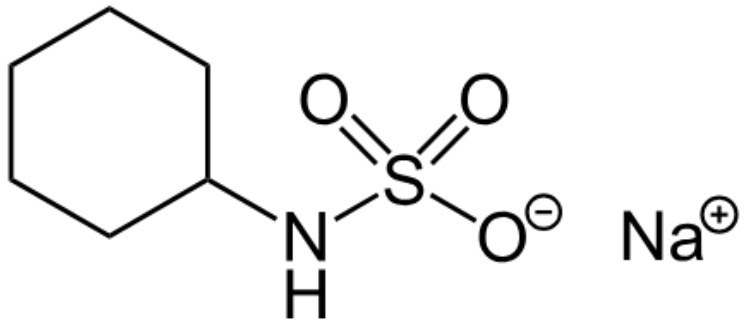
This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or of the Food and Agriculture Organization of the United Nations.

Evaluation of certain food additives and contaminants

Twenty-sixth Report of the Joint FAO/WHO Expert Committee on Food Additives

World Health Organization
Technical Report Series
683

World Health Organization, Geneva 1982



E Number	Name	EFSA's Assessment
E 420	Sorbitols	Re-evaluation ongoing
E 421	Mannitol	Re-evaluation ongoing
E 950	Acesulfame K	Re-evaluation completed in 2025
E 951	Aspartame	Re-evaluation completed in 2013
E 952	Cyclamates	Re-evaluation ongoing
E 953	Isomalt	Re-evaluation ongoing
E 954	Saccharins	Re-evaluation completed in 2024
E 955	Sucralose	Re-evaluation ongoing
E 957	Thaumatin	Re-evaluation completed in 2021
E 959	Neohesperidine DC	Re-evaluation completed in 2022
E 960a	Steviol glycosides from Stevia	First evaluated in 2010
E 960c	Enzymatically produced steviol glycosides	Evaluated in 2019
E 960d	Glucosylated steviol glycosides	Evaluated in 2022
		First evaluated in 2007

Unilever

Unilever's NAM toolbox

Point of Departure (PoD) determination from Bioactivity assays

Non-specific effects

High-Throughput transcriptomics (HTTr)

- TempO-seq technology – full gene panel
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- 7 concentrations
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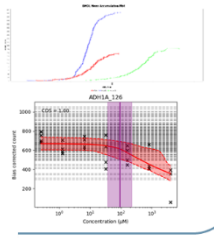

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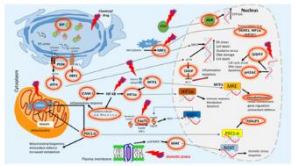
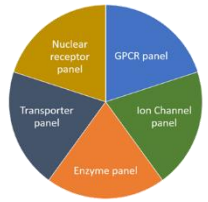


Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. Toxicol Sci 176(1): 11-33

Specific effects

In vitro pharmacological profiling



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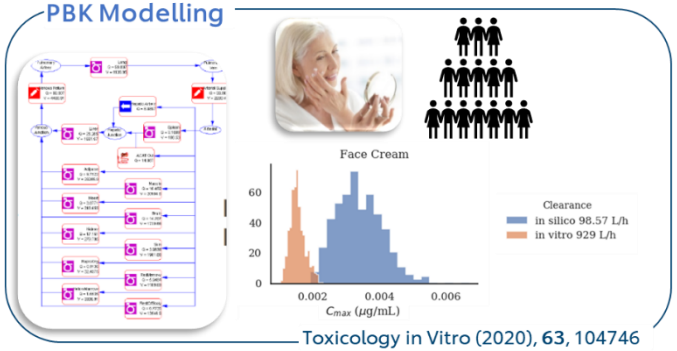
PBK Modelling

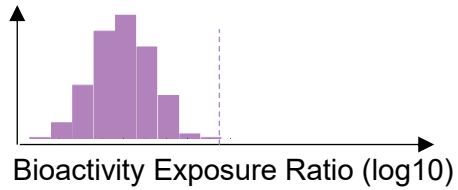


Toxicology in Vitro (2020), **63**, 104746

Plasma C_{max} estimate → **C_{max} Error Distribution model (CMED)**

(Bayesian model)

Bioactivity Exposure Ratio (BER) Distribution



BIOACTIVITY EXPOSURE RATIO = $\frac{\text{BIOACTIVITY}}{\text{EXPOSURE}}$

The bigger the BER, the greater the confidence that bioactivity will not occur in exposed consumers

Unilever

NGRA data - cyclamate

Exposure/PBK modelling:

PBK models need several building blocks!

An external dose

↓

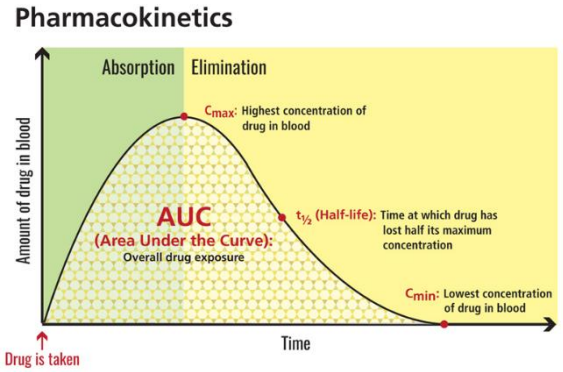
Physical-chemical properties

↓

Pharmacokinetic properties

The outcomes are estimates of internal exposure, such as the maximum concentration in plasma (Cmax)

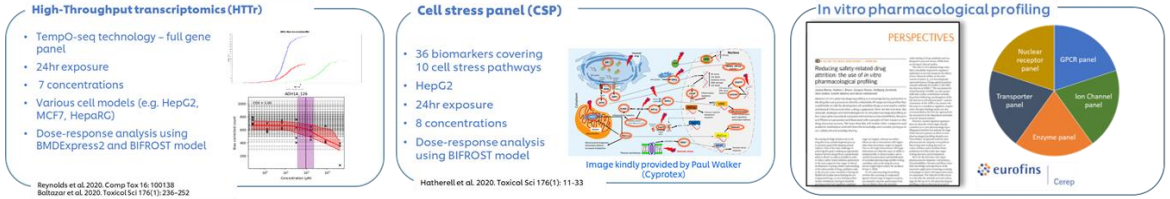
For cyclamate, our PBK modelling estimated a Cmax of **~69 µM** after consumption of the ADI

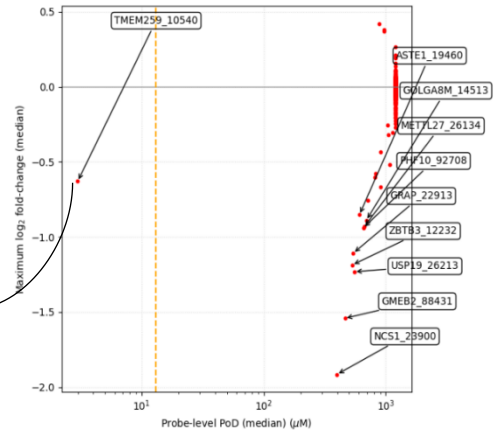


Point of departure estimation:

Sodium cyclamate tested in the Unilever NAM toolbox

- Result is a series of PoDs across various NAMs





For cyclamate, the lowest PoD across the NAMs was from the transcriptomics study

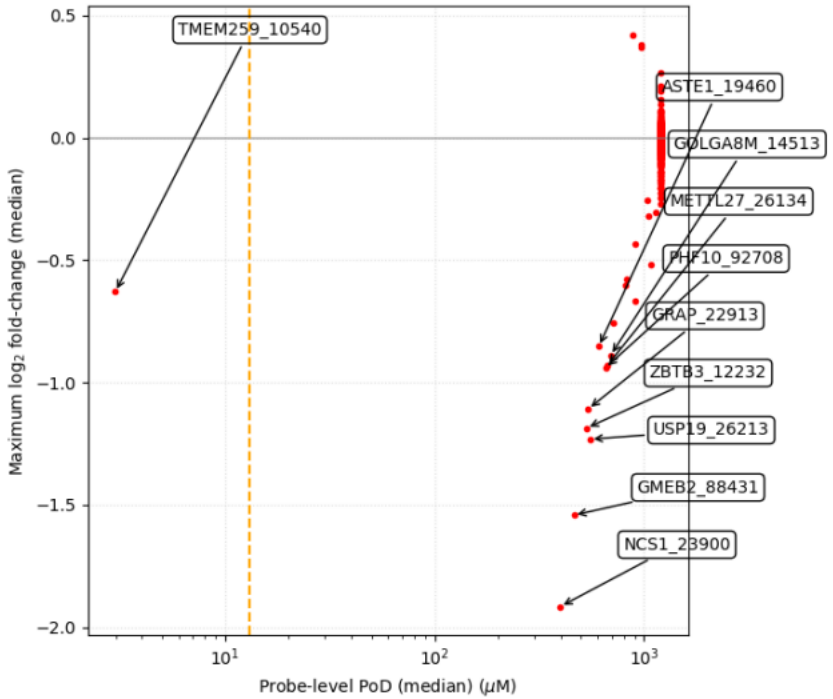
PoD (13) / Exposure (69) = 'Bioactivity : Exposure Ratio' (BER) (13/69 = 0.18)

For cyclamate, bioactivity occurs at a lower exposure than dietary intake of the ADI – **higher tier models needed!**

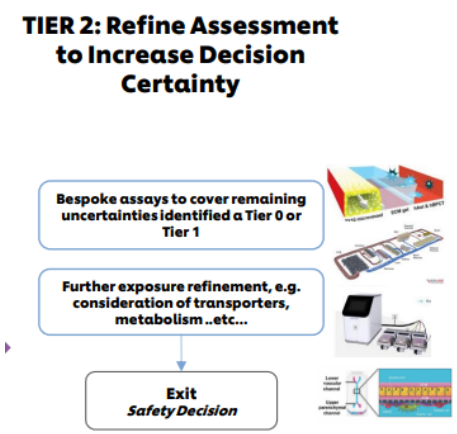
Unilever

Cyclamate - summary

- PBK estimates of internal exposure – at the ADI, Cmax = ~68 uM.
- Lowest PoD from the NAMs (~12 uM) came from the transcriptomics study - HepG2 cells when looking for the lowest responding genes – **highly conservative!**
- NAM PoDs less than Cmax - further experimental data generation would be required.
- **(Next generation) risk assessments require tiering!**
- Exciting developments underway externally with higher tier *in vitro* models e.g. organ on chip, alternative data analysis methods – key characteristics, gene signatures and computational sciences – AI etc.



Single gene level PoDs after Cyclamate treatment (HepG2 cells) – unlikely toxicological significance



Call to action: Evolution of dietary intake surveys to **always** include information on the time of intake as well as the amounts of consumed will be needed to support the shift to NGRA by the food sector

External developments

- In recent years, national and international food safety authorities have been working towards further integrating NAMs in risk assessment.
- Food industry have made positive steps towards building internal NGRA capability and working to achieve regulatory change.
- Progress is still needed to maximise the use of NAMs in food safety assessments!

World Health Organization

NANYANG TECHNOLOGICAL UNIVERSITY SINGAPORE

Agenda

New Approach Methodologies (NAMs) in Future Food Safety Risk Assessment

a Joint Workshop by World Health Organization (WHO) and Nanyang Technological University, Singapore (NTU Singapore)

Royal Plaza on Scotts, Singapore, 18 to 20 June 2025

mb210624-a2

EFSA Strategy 2027

Science

Safe food

Sustainability

future challenges. Within its risk assessment approaches, EFSA will develop and integrate new scientific developments focusing on NAM-based methods and the minimisation of animal testing, innovations in food systems, data, and technology, and strive to meet One health policy needs.

EXTERNAL SCIENTIFIC REPORT

APPROVED: 2 May 2022

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Development of a Roadmap for Action on

New Approach Methodologies in Risk Assessment

Sylvia E. Escher[1], Falko Partosch[1], Sebastian Konzok[1], Paul Jennings[2], Mirjam Luijten[3], Anne Kienhuis[3], Victoria de Leeuw[3], Rosmarie Reuss[4], Katrina-Magdalena Lindemann[4], Susanne Hougaard Bennekou[5]

[1] Fraunhofer ITEM, [2] Vrije Universiteit Amsterdam, [3] National Institute for Public Health and the Environment, [4] Eurai AG, [5] The National Food Institute Denmark

Abstract

While whole animal studies have their place in risk assessment of food and feed components, it is thought that more modern approaches such as human focused new approached methodologies (NAMs) would bring advantages including a greater focus to the human species, a focus on molecular mechanism and kinetics and the possibility of addressing susceptible populations. This report outlines the thinking from the authors and culminates in activity proposals in seven distinct but interacting scientific areas i.e. development of additional AOPs/AOP networks (AOPs), advanced cell culture models including Organ on a chip (OoC), toxicokinetic assessment with a focus on physiological based kinetic modelling (PBK), exposome, human susceptibility, data integration and new concepts in human risk assessment. Furthermore, the development of a Forum is proposed to facilitate the implementation of new approaches and concepts in risk assessment. The report was compiled by the project team, renowned experts in the various areas, and recommendations were discussed with EFSA and further refined following consultation with external experts via a dedicated workshop. The authors are convinced that if the recommendations are taken up, there will be a significant impact in the field, resulting in increasing the uptake and utilisation of these emerging technologies by all stakeholders involved.

Key words: Next Generation Risk Assessment, New Approach Methods, implementation, AOP, IATA

Question number: EFSA-Q-2022-00231

Correspondence: SPIDO@efsa.europa.eu

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

Adam Wood[a,*], Franck Atienzar[b], Danilo Basili[c], Myriam Coulet[c], Rebeca Fernandez[d], Melina Galano[e], Maricel Marín-Kuan[c], Gina Montoya[c], Przemyslaw Piechota[c], Ans Punt[a], Elena Reale[c], Si Wang[f], Paul Hepburn[a]

[a] Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, UK
[b] Coca-Cola Services SA/NV, Chaussée De Mons 1424, 1070, Anderlecht, Belgium
[c] Société des Produits Nestlé S.A. Nestlé Research, Rte du Jorat 57, 1000 Lausanne 26, Switzerland
[d] FoodDrinkEurope, Avenue des Nerviens 9-31, 1040, Brussels, Belgium
[e] dsm-firmenich, Alexander Fleminglaan 1, 2613 AX, Delft, the Netherlands
[f] PepsiCo International, Beaumont Park, 4 Leycroft Road, Leicester, LE4 1ET, UK

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ABSTRACT

Safety assessments of regulated food products in the European Union (EU) largely rely on experimental animal studies. Currently, the European Commission is developing a roadmap to phase out animal testing for chemical safety assessment across all relevant pieces of legislation, including foods, while the ambition of the European Food Safety Authority (EFSA) is that by 2027, new scientific developments, i.e., new approach/non-animal methods (NAMs), will be integrated into assessments leading to "*the minimisation of animal testing*". However, considering recent requests that have been made to conduct new animal studies for some regulated products, significant progress is required to minimise further and ultimately replace animal testing in the food safety environment. To advance this, we review several NAMs amenable for use in food safety assessment and reflect on their presence in EU food safety regulation and sectoral guidance. For many years, proposals to incorporate NAMs into food safety assessments have been made with questionable regulatory impact. Therefore, we present several amendments which could be made to the EU food regulatory system and current strategies towards phasing out animal testing which, if taken up, could lead to a tangible difference in the extent of animal testing within the food safety environment. Recognising that research may be required for some of these NAMs to enhance regulatory uptake, we propose potential follow-up projects that complement recent research & innovation (R&I) needs published by EFSA which food safety stakeholders could coordinate or participate in.

1. Introduction

The General Food Law Regulation establishes that only safe food can be placed on the EU market and sets basic criteria for establishing safety (Regulation (EC) No 178/2002). Many food related products, so called 'regulated products'[1] require an independent scientific assessment to evaluate their safety before market (Table 1). Regulated products include those consumed as food (such as genetically modified (GM) plants and certain novel and traditional foods)), substances intentionally added to foods for improvement purposes, such as additives, flavourings and nutrients, those used during production, such as enzymes and

* Corresponding author.
E-mail address: adam.wood@unilever.com (A. Wood).

[1] The General Food Law defines food/foodstuffs as a substance/product (irrespective of processing) intended/reasonably expected to be ingested (excluding residues/contaminants). Despite this, the assessment of food/foodstuffs and residues and contaminants follow similar methodologies, with many non-animal approaches applicable to the assessment of food/foodstuffs equally applicable to either. Given this, the scope of this review includes both food/foodstuffs and selected other food safety topics as listed in Table 1.

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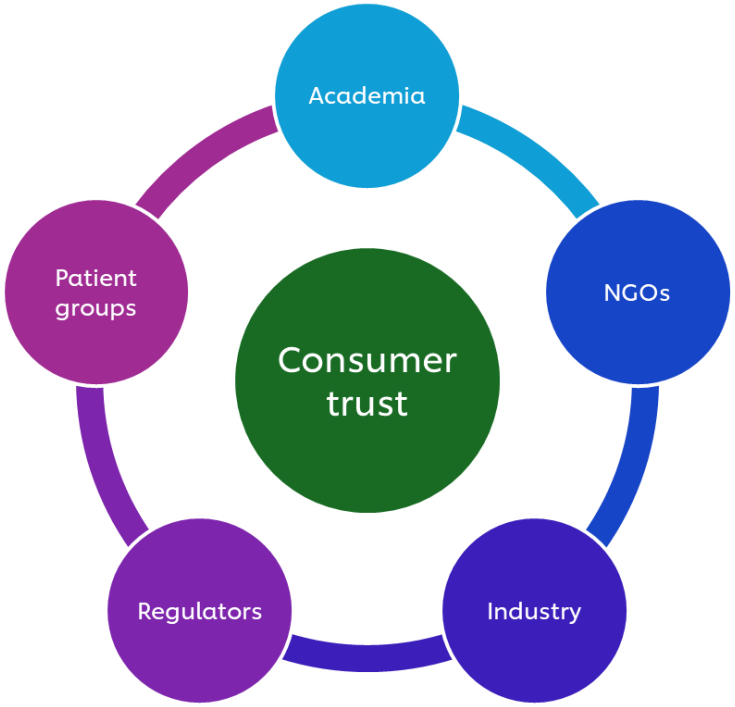
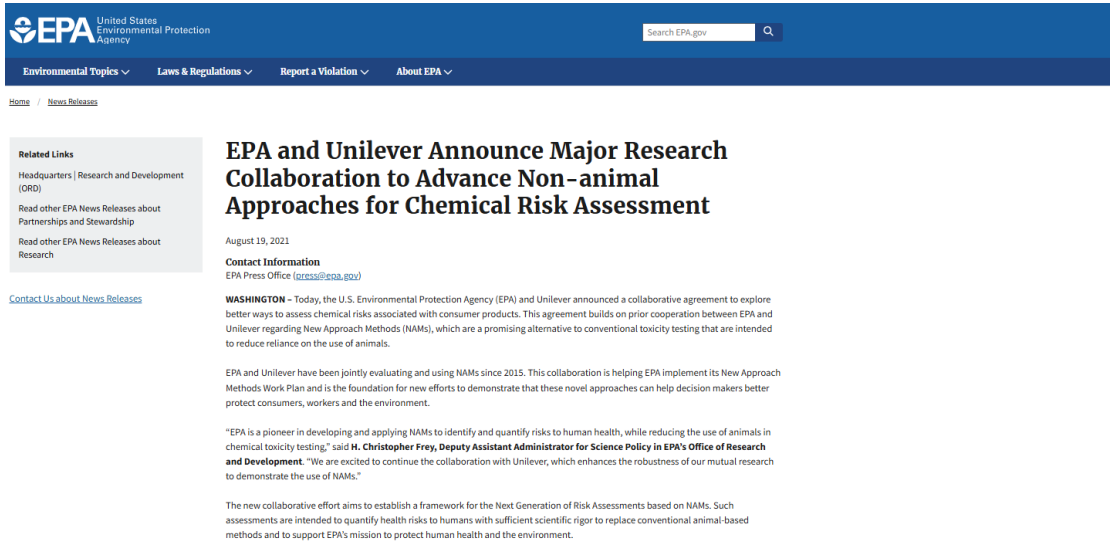
Unilever

Wrap-up

- Food safety is complex because food is complex! 'Food' comprises everything from single chemicals (flavours, additives) to complex mixtures with nutritionally relevant components.
- Multitude of different toxicological studies needed to deliver safe food given its complexity.
- The food safety ecosystem has played a key historical role in the development and application of NAMs.
- Paradigm shift is underway in risk assessment towards the use of innovative NAMs.
- **Multi-disciplinary, multi-stakeholder engagement and collaboration needed to fully achieve the vision of non-animal safety science.**





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EPA and Unilever Announce Major Research Collaboration to Advance Non-animal Approaches for Chemical Risk Assessment

August 19, 2021

Contact Information
EPA Press Office (press@epa.gov)

WASHINGTON – Today, the U.S. Environmental Protection Agency (EPA) and Unilever announced a collaborative agreement to explore better ways to assess chemical risks associated with consumer products. This agreement builds on prior cooperation between EPA and Unilever regarding New Approach Methods (NAMs), which are a promising alternative to conventional toxicity testing that are intended to reduce reliance on the use of animals.

EPA and Unilever have been jointly evaluating and using NAMs since 2015. This collaboration is helping EPA implement its New Approach Methods Work Plan and is the foundation for new efforts to demonstrate that these novel approaches can help decision makers better protect consumers, workers and the environment.

"EPA is a pioneer in developing and applying NAMs to identify and quantify risks to human health, while reducing the use of animals in chemical toxicity testing," said **H. Christopher Frey, Deputy Assistant Administrator for Science Policy in EPA's Office of Research and Development**. "We are excited to continue the collaboration with Unilever, which enhances the robustness of our mutual research to demonstrate the use of NAMs."

The new collaborative effort aims to establish a framework for the Next Generation of Risk Assessments based on NAMs. Such assessments are intended to quantify health risks to humans with sufficient scientific rigor to replace conventional animal-based methods and to support EPA's mission to protect human health and the environment.

Unilever