THEMATIC WORKSHOP

DERIVATION OF CONVERSION FACTORS FOR NEW SOURCES AND FORMS OF NUTRIENTS

Nutrition and Food Innovation Unit

9 March 2023

EUROPEAN FOOD SAFETY AUTHORITY

WELCOME AND PRACTICAL INFORMATION

WELCOME TO THE WORKSHOP PARTICIPANTS

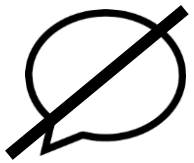
- Members of EFSA Panel on Nutrition, Novel Foods and Food Allergens
- Members of EFSA Working Groups on Novel Foods & Upper Levels
- Hearing experts from industry and other organisations
- Representatives from public organisations
- EFSA Staff

DURING THE MEETING REMEMBER TO:

- Mute your microphone

- Switch off your video

- Raise your hand to take the floor



- Don’t post questions or comments through the chat, except to request **technical or practical help**

BACKGROUND AND OBJECTIVE

BACKGROUND

- **Context**: The EC requested EFSA to **update its Guidance on safety evaluation of sources of nutrients and bioavailability of nutrient from the sources** (EFSA ANS Panel, 2021) regarding the scientific principles and data requirements for applicants in order to derive a conversion factor (CF) for proposed new sources or forms of nutrients.
- EFSA held **an open consultation through an Expert Survey** on key points to consider for derivation of conversion factors (15 Dec 2022 - 20 Jan 2023). The outcome was used to prepare a Discussion paper to shape and optimise the workshop discussion.

OBJECTIVE OF THE WORKSHOP

- To share and exchange views regarding the scientific principles and data requirements for deriving conversion factors for proposed new sources or forms of nutrients.
- To collect the views of the participants and possible orientations (in a workshop report)

➢The outcome will inform EFSA’s update of its guidance.

AGENDA OF THE WORKSHOP – ONE-DAY WORKSHOP

Part 1		
14.00	**Welcome and opening remarks**	Ana Afonso (Head of EFSA NIF Unit)
14.05	**Introduction**	Dominique Turck (Chair of the NDA Panel)
14:10	**Setting the scene: Outcome of the Expert Survey**	Albert Flynn (Rapporteur)
14.20	**Nutrient sources** - reference source (Q1) - nutrient metabolites (Q2)	Discussion for All
15.00	**Human studies to derive CF** - study designs (Q7) - acute/short term studies (Q8) - chronic studies (Q9)	Discussion for All
16:00	***BREAK***	
Part 2		
16:20	**Chemical/*in vitro* data to derive CF** - chemical data (Q4) - *in vitro* data (Q5)	Discussion for All
17:00	**Implications of CF for DRVs & UL** - DRVs for adequacy (Q10) - UL (Q11)	Discussion for All
17:30	**Wrap up and conclusions**	Albert Flynn (Rapporteur) & Dominique Turck (Chair of the NDA Panel)
18:00	***End***	

WORKSHOP ON CONVERSION FACTORS

Prof. Albert Flynn

efsa
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CONVERSION FACTORS (CF)

- To indicate the extent to which the proposed new sources or forms of nutrients are bioavailable:
  - as compared to native forms of the nutrient naturally present in foods

  OR

  - as compared to an authorised nutrient form/source for which the relative bioavailability versus one or more forms of the nutrient naturally present in foods is known

- CF used to express the contribution of nutrient sources to the reference intakes of those nutrients on labelling
- Also to specify composition of foods for specific groups (FSG), for assessing the adequacy and safety of nutrient intakes
- Example: CF for folic acid = 1.7 (vs food folate)

BIOAVAILABILITY

- Bioavailability (in legislation): ‘available to be used by the body’ [to exert its function as a nutrient]
- Does the novel form have the same physiological effect(s) as the reference form of the nutrient?
  - nutrient function at physiological intake levels?
  - is it covered by existing endpoints for nutrient adequacy?
  - equivalence of different chemical forms - capacity to meet the requirement for the nutrient
  - adverse effects at high intakes?
  - is it covered by existing endpoints for UL?
- understanding of the absorption, distribution, metabolism and excretion (ADME) properties of the novel and reference forms of the nutrient is needed

GENERAL APPROACH TO DERIVE CF

- CF derived from relative bioavailability of the nutrient from the novel form/source vs a reference form/source
- Comparative studies on bioavailability of the nutrient from novel form/source vs a similar amount (equimolar) of the nutrient from reference form/source under identical experimental conditions
- may be based on studies in humans, animals, *in vitro* gastro-intestinal models (bioaccessibility or cellular uptake/absorption studies), or dissociation under conditions of human GIT
- Methodologies and data requirements may reflect the chemical similarity of the sources
  - Salts of same chemical form vs different chemical forms
  - Vitamins may have chemically related compounds ('vitamers') with different relative vitamin activity ('equivalence')
- Approach to be adopted case by case

CF FOR VULNERABLE GROUPS

- If target population is a vulnerable group and/or the food may be the only source of nutrition
  - e.g. infant formula, FSMP, TDR

- need greater certainty on the relative bioavailability and CF of new forms/sources
- data in a relevant population essential for the assessment

- studies may not be possible in the target population due to ethical concerns
  - study population should be representative of the target population
  - or a population from which extrapolation of the results to the target population is biologically appropriate
  - justified by a scientific rationale

REFERENCE NUTRIENT SOURCE

Criteria for selection of the reference nutrient source for comparison with the novel source

- a naturally occurring form with a significant contribution to dietary intake is preferable
- should be covered by existing endpoints for DRVs for nutrient adequacy and UL
- ideally there should be a linear relationship between intake of the nutrient from the reference form/source and the relevant biomarkers of nutrient intake, status or effect
  - not true for nutrients with percentage absorption or activation that is dose-dependent
- A reference form/source with high bioavailability may be preferable
  - not a characteristic of some naturally occurring nutrients in foods

NUTRIENT METABOLITES AS NUTRIENT SOURCES

Requirements for nutrient metabolites (e.g. submitted as Novel Foods) to be considered also as nutrient sources

- Does the metabolite have the same physiological effect(s) as the reference form of the nutrient?
  - nutrient function at physiological intake levels?
  - is it covered by existing endpoints for nutrient adequacy?

- Does the metabolite have the same adverse effects at high intakes?
  - i.e. is it covered by existing endpoints for UL?

- An understanding of the ADME properties of the metabolite and reference form of the nutrient is needed

HUMAN STUDIES TO DERIVE CF (1)

- Studies in humans have the highest predictive value on relative bioavailability
- Designs for comparative bioavailability studies of novel vs reference forms/sources in relevant population and age groups representative of the target population include:
  - randomised, two-period crossover studies (with an adequate wash-out period)
  - randomised parallel studies
  - Depletion-repletion studies
- Relative bioavailability of the nutrient from the novel form/source may be dose-related
  - equivalent nutrient doses (ideally equimolar) from novel and reference sources
  - studies should cover the dose range that is proposed for use of the novel form/source
- Factors that may influence nutrient bioavailability should be controlled
  - e.g. food matrix, conditions of consumption (empty or full stomach) and frequency (e.g. once or twice daily), and the nutrient status of study subjects

HUMAN STUDIES TO DERIVE CF (2)

- Study design based on ADME properties of the novel & reference forms/sources of the nutrient (further definition of distribution – ref to storage)
- Acute/short term, single-dose studies may be suitable to assess relative bioavailability
  - e.g. measurement of the concentration - time profile of the nutrient/metabolite in blood
  - e.g. measurement of absorption and/or utilisation of the nutrient, or retention
  - e.g. Labelling with stable isotopes permits the use of lower doses of nutrient, and to differentiate between orally administered and endogenous forms
- Chronic repeated-dose studies of appropriate duration with relevant biomarkers of nutrient status or effect may be suitable to assess relative bioavailability

CHEMICAL/IN VITRO DATA TO DERIVE CF

- Chemical data and *in vitro* data are unsuitable to predict *in vivo* bioavailability
  - These types of studies measure bioaccessibility
  - ~~there may be limited circumstances where they may predict relative bioavailability of a nutrient from a novel source vs reference source (influencing food matrix factor)~~
- Example: different salts of the same chemical form of a nutrient with similar dissociation characteristics
  - if dissociation under gastrointestinal conditions is the key process for bioavailability
- Example: *in vitro* bioaccessibility coupled with uptake into/translocation across intestinal cell models under simulated gastrointestinal digestion conditions
  - when bioavailability critically depends on these steps
  - conditions for such assays should be standardised (dependent on substance) and validated, e.g. by use of the INFOGEST method (validated static model), dynamic tiny TIM system

IMPLICATIONS OF CF FOR DRV & UL

- If CF <1 for a novel source this may need to be considered when assessing adequacy of the novel source under proposed conditions of use, particularly for uses for vulnerable groups
- If CF >1 for a novel source this may need to be considered when assessing safety of the novel source under proposed conditions of use
  - If this CF applies at the high intakes near UL a lower UL may be needed for novel source
  - If the novel source is not covered by an existing endpoint for establishing UL it may be necessary to establish a different UL for the novel source