Webinar | 14 November 2024

EFSA'S ACTIVITIES ON TOLERABLE UPPER INTAKE LEVELS FOR VITAMINS AND ESSENTIAL MINERALS

STARTING AT 14:30

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(listen only mode)

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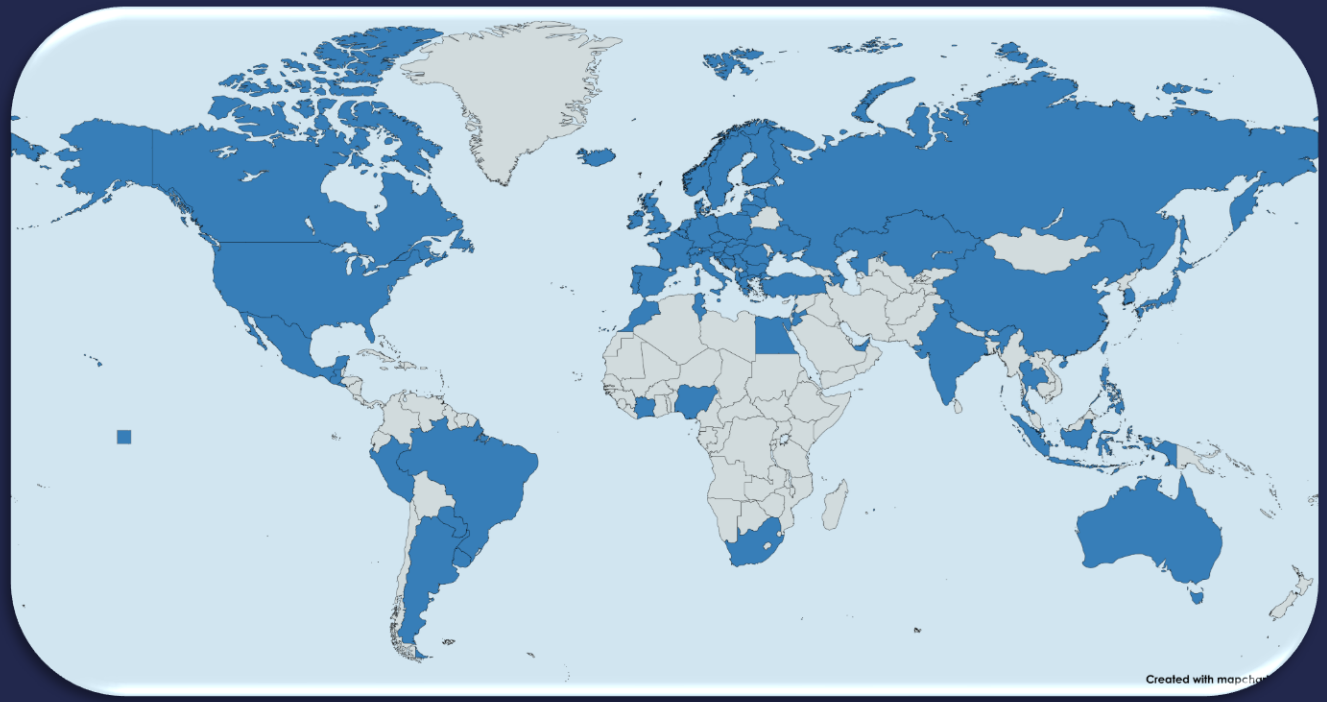
EFSA'S ACTIVITIES ON TOLERABLE UPPER INTAKE LEVELS FOR VITAMINS AND ESSENTIAL MINERALS

- **1564** registrants from **72** countries
- **33** questions received
  - Those directly **linked to the content of the presentations** will be addressed **by the speakers**
  - The **remaining questions** will be addressed during a **dedicated session**



TODAY'S MODERATOR AND SPEAKERS

Androniki Naska

National and Kapodistrian University of Athens

Chair of EFSA WG on ULs

Vice-chair of EFSA NDA Panel

Agnès de Sesmaisons

Senior Scientific Officer

NIF Unit, EFSA

Ionut Craciun

Scientific Officer

NIF Unit, EFSA

Nena Karavasiloglou

Scientific Officer

NIF Unit, EFSA

Leonard Matijević

Scientific Officer

NIF Unit, EFSA

Lucia Fabiani

Scientific Officer

NIF Unit, EFSA

AGENDA

Starting time
14:30

Introductory remarks
Androniki Naska

EFSA's UL assessment framework
Agnès de Sesmaisons

Fat soluble vitamins: vitamins A including β-carotene, D, E
Ionut Craciun

Break
15:45 – 15:55

B-vitamins: vitamin B6, folate
Nena Karavasiloglou

Essential minerals: selenium, manganese, iron
Leonard Matijević

Estimating intakes of vitamins and minerals & identification of 'at risk' populations in the EU
Lucia Fabiani

Answers to pre-submitted questions & concluding remarks
Androniki Naska

Ending time
17:00

Introductory remarks

ANDRONIKI NASKA

OBJECTIVES OF THE MEETING

- To provide stakeholders with **insights on the principles and methods applied** for the evaluations of Tolerable Upper Intake Levels (ULs) for micronutrients
- To summarise the **conclusions reached on each of the micronutrients** recently evaluated

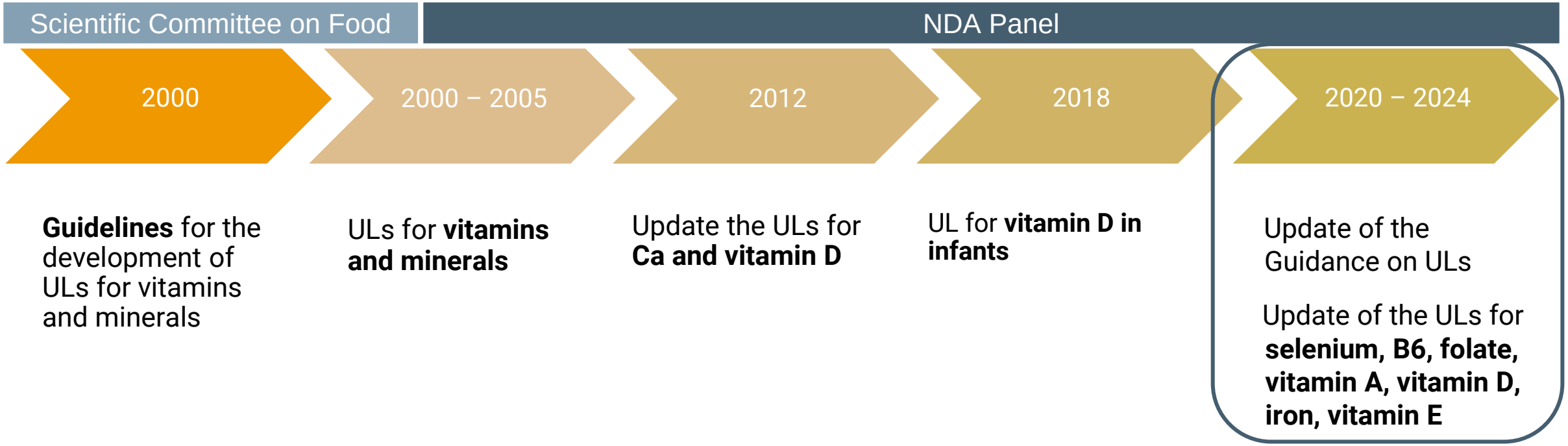
- **UL: Maximum amount of a nutrient that can be consumed safely over a long period of time**
- Science based value established by EFSA

Risk Assessment

- **MA: Maximum amount of a nutrient that can be added to foods (fortified foods) or used in food supplements**
- Legal values established by regulators

Risk Management

TOLERABLE UPPER INTAKE LEVELS FOR VITAMINS AND ESSENTIAL MINERALS AT EFSA



European Commission shall set **maximum amounts of vitamins and minerals added to foods**(1) **and in food supplements**(2)

(1) Regulation (EC) No 1924/2006
(2) Directive 2002/46/EC

EFSA was requested to

Update the methodological guidelines of the SCF (2000)

Review scientific evidence and provide advice **on ULs for selected vitamins and essential minerals**

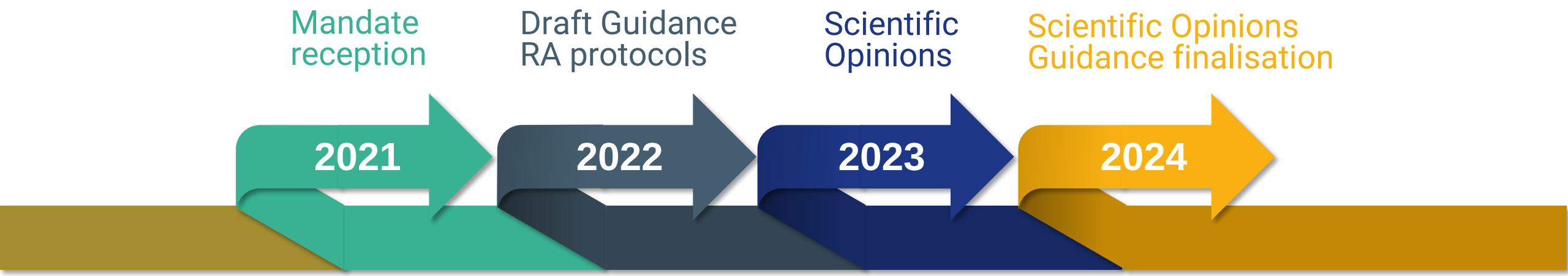
Advice in case **no UL can be established**

- **Folic acid/folate**
- **Vitamin B6**
- **Vitamin A & β-carotene**
- **Vitamin D**
- **Vitamin E**
- **Iron**
- **Manganese**
- **Selenium**

EFSA’s Tolerable Upper Intake Levels assessment framework

AGNES DE SESMAISONS

TIMELINE



Resource planning, preparatory work and expert consultations

Data collection (systematic reviews) and evaluation

Selenium
Vitamin B6
Folate
Manganese
Vitamin D

Vitamin A & β-carotene
Iron
Vitamin E

Public consultations

Adopted: 24 September 2024

DOI: 10.2903/j.efsa.2024.9052

SCIENTIFIC OPINION

efsa JOURNAL

Guidance for establishing and applying tolerable upper intake levels for vitamins and essential minerals

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) | Dominique Turck | Torsten Bohn | Montaña Cámara | Jacqueline Castenmiller | Stefaan de Henauw | Karen-Ildico Hirsch-Ernst | Angeles Jos | Alexandre Maciuk | Inge Mangelsdorf | Breige McNulty | Kristina Pentieva | Alfonso Siani | Frank Thies | Peter Aggett | Marta Crous-Bou | Francesco Cubadda | Aymeric Dopter | Susan Fairweather-Tait | Georg Lietz | Harry J. McArdle | Giovanni Passeri | Marco Vinceti | Misha Vrolijk | Ionut Craciun | Agnès de Sesmaisons Lecarré | Zsuzsanna Horvath | Laura Martino | Silvia Valtueña Martinez | Androniki Naska

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The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch

Abstract

Vitamins and essential minerals are micronutrients that are required for the normal functioning of the human body. However, they may lead to adverse health effects if consumed in excess. A tolerable upper intake level (UL) is a science-based reference value that supports policy-makers and other relevant actors in managing the risks of excess nutrient intake. EFSA's principles for establishing ULs for vitamins and minerals were originally developed by the Scientific Committee on Food in 2000. This guidance from the EFSA Panel on Nutrition, Novel Foods and Food Allergens provides an updated framework for UL assessments. A draft was published in 2022 and underwent a 2-year piloting period. The present document incorporates revisions based on the experience gained through its practical implementation. It covers aspects related to the planning of the risk assessment (problem formulation and definition of methods) and its implementation (evidence retrieval, appraisal, synthesis, integration, uncertainty analysis). As in the previous framework, the general principles developed for the risk assessment of chemicals in food are applied, i.e. hazard identification, hazard characterisation, intake assessment, risk characterisation. Specific to nutrients are their biochemical and physiological roles and the specific and selective mechanisms that maintain the systemic homeostasis and accumulation of the nutrient in the body. Such considerations must also be taken into account when conducting risk assessments of nutrients.

KEYWORDS

dietary reference value, mineral, tolerable upper intake level, UL, vitamin

NDA Panel Guidance for establishing and applying tolerable upper intake levels for vitamins and essential minerals

EFSA Journal. 06 November 2024.

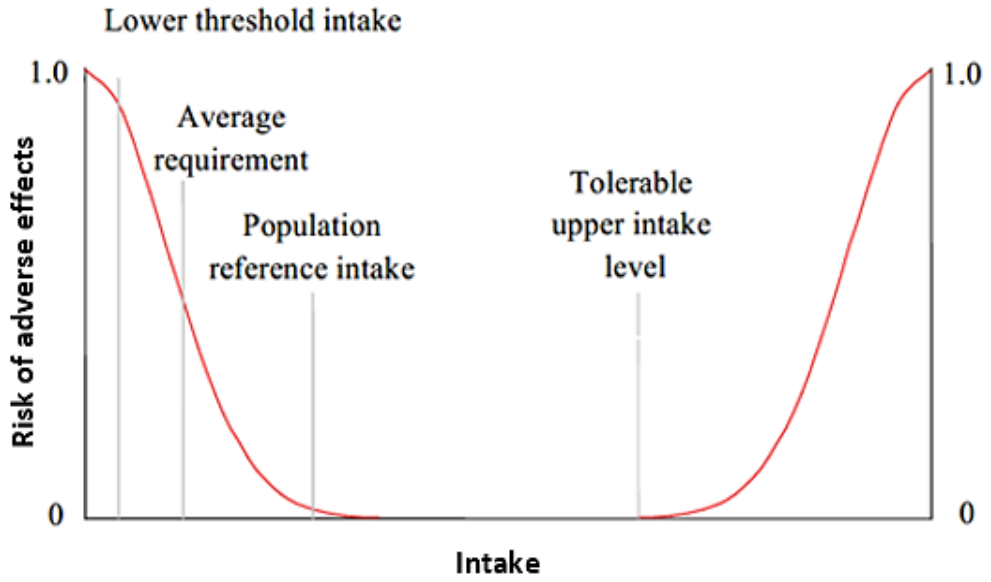
DOI: 10.2903/j.efsa.2024.9052

DEFINITION OF A TOLERABLE UPPER INTAKE LEVEL

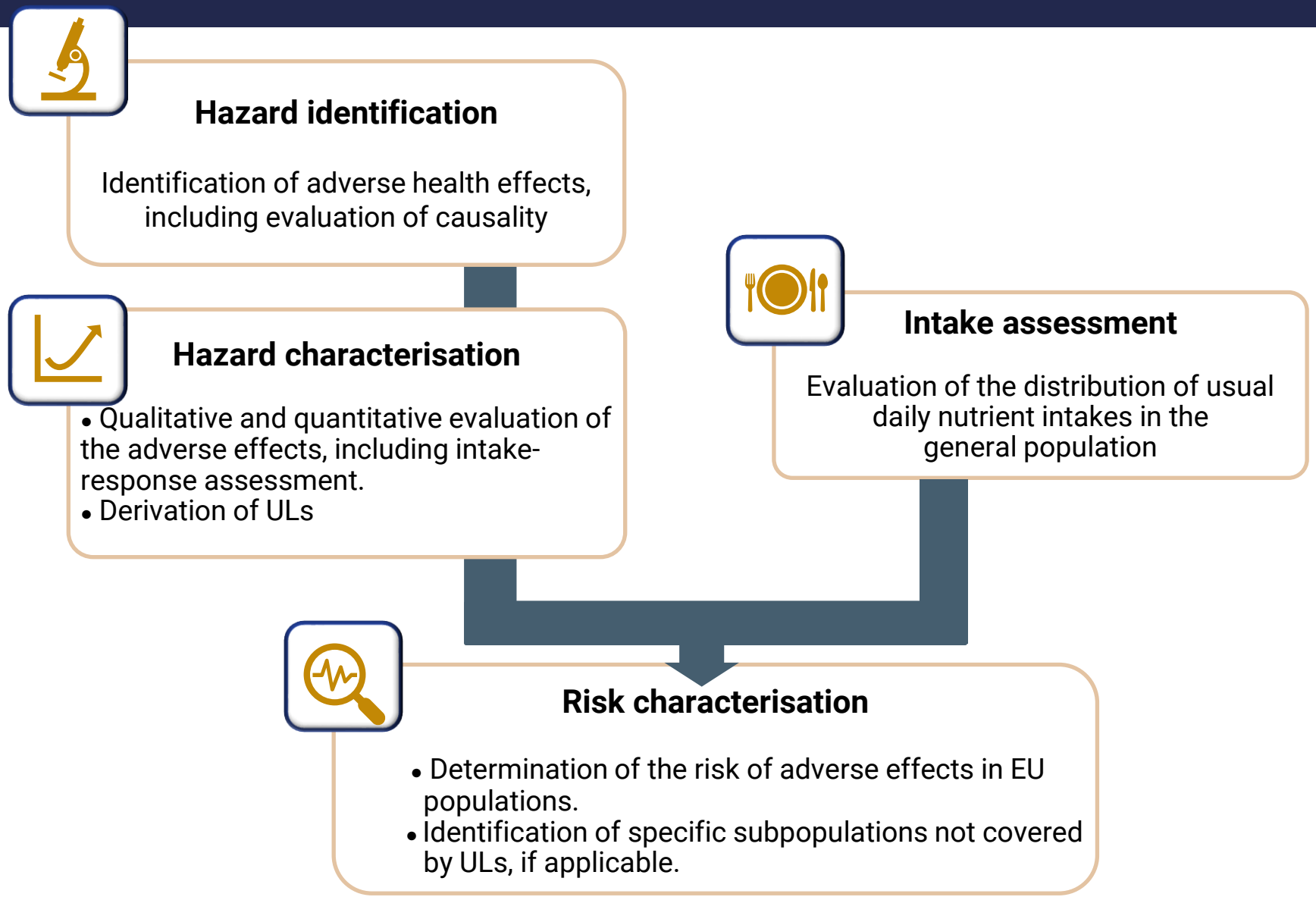
Tolerable upper intake level (UL): the maximum level of total chronic daily intake of a nutrient (from all sources) which is not expected to pose a risk of adverse health effects to humans.

- Normally established for the nutrient **from all dietary sources**; may be restricted to specific sources in some cases
- Does not consider adverse effects of **acute bolus dosages**
- Refers to an **average daily intake** (substantial day-to-day variation within an individual's intake of micronutrients)

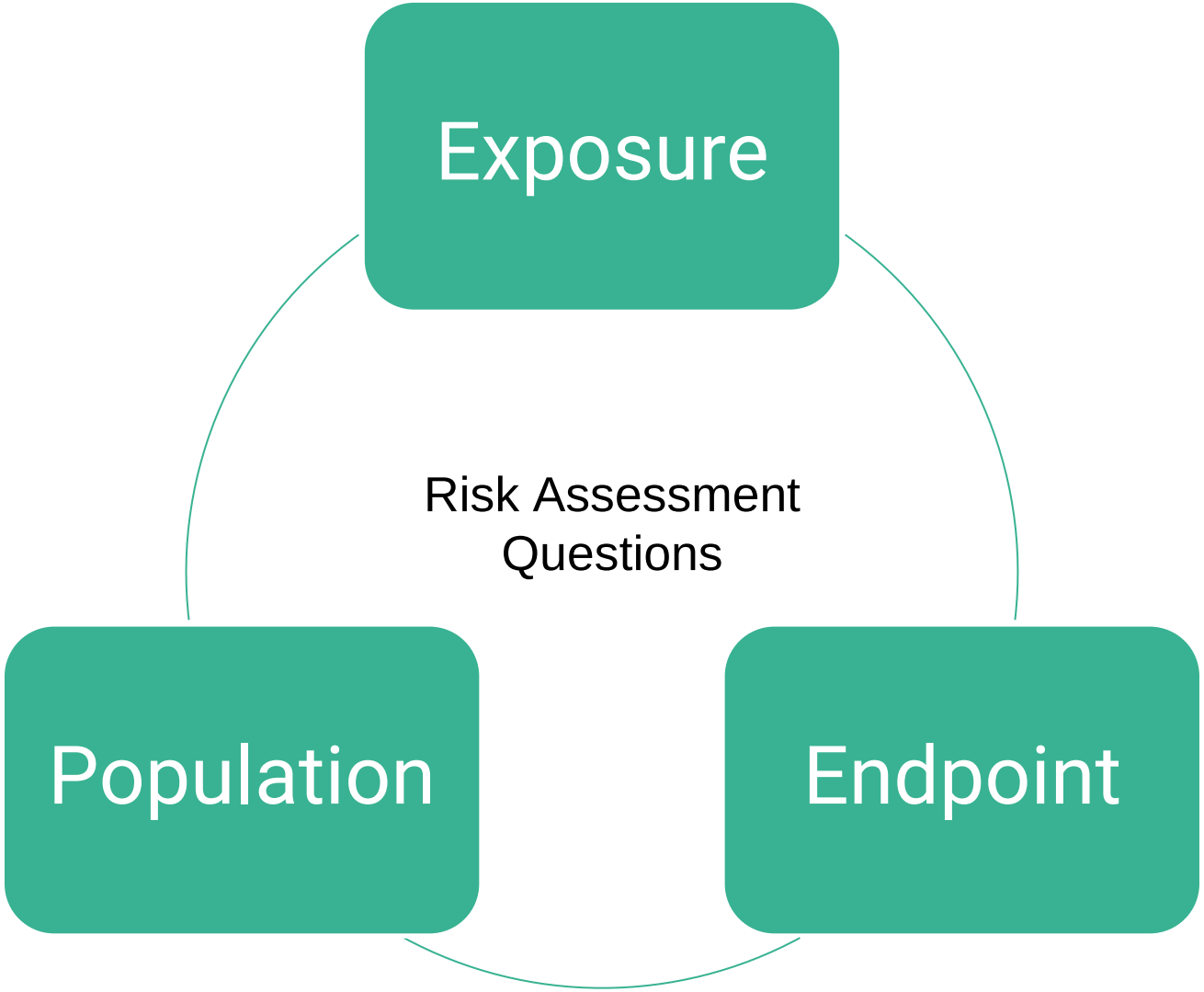
Dietary Reference Values



FOUR-STEP PROCESS OF NUTRIENT RISK ASSESSMENT



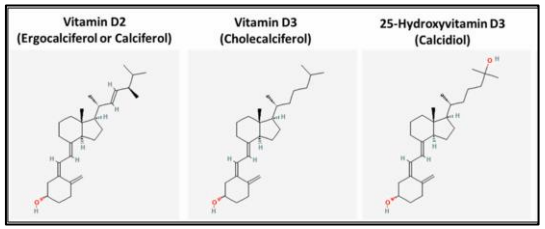
FORMULATION OF THE RISK ASSESSMENT QUESTIONS



DETERMINATION OF THE EXPOSURE OF INTEREST

Sources

(all dietary)

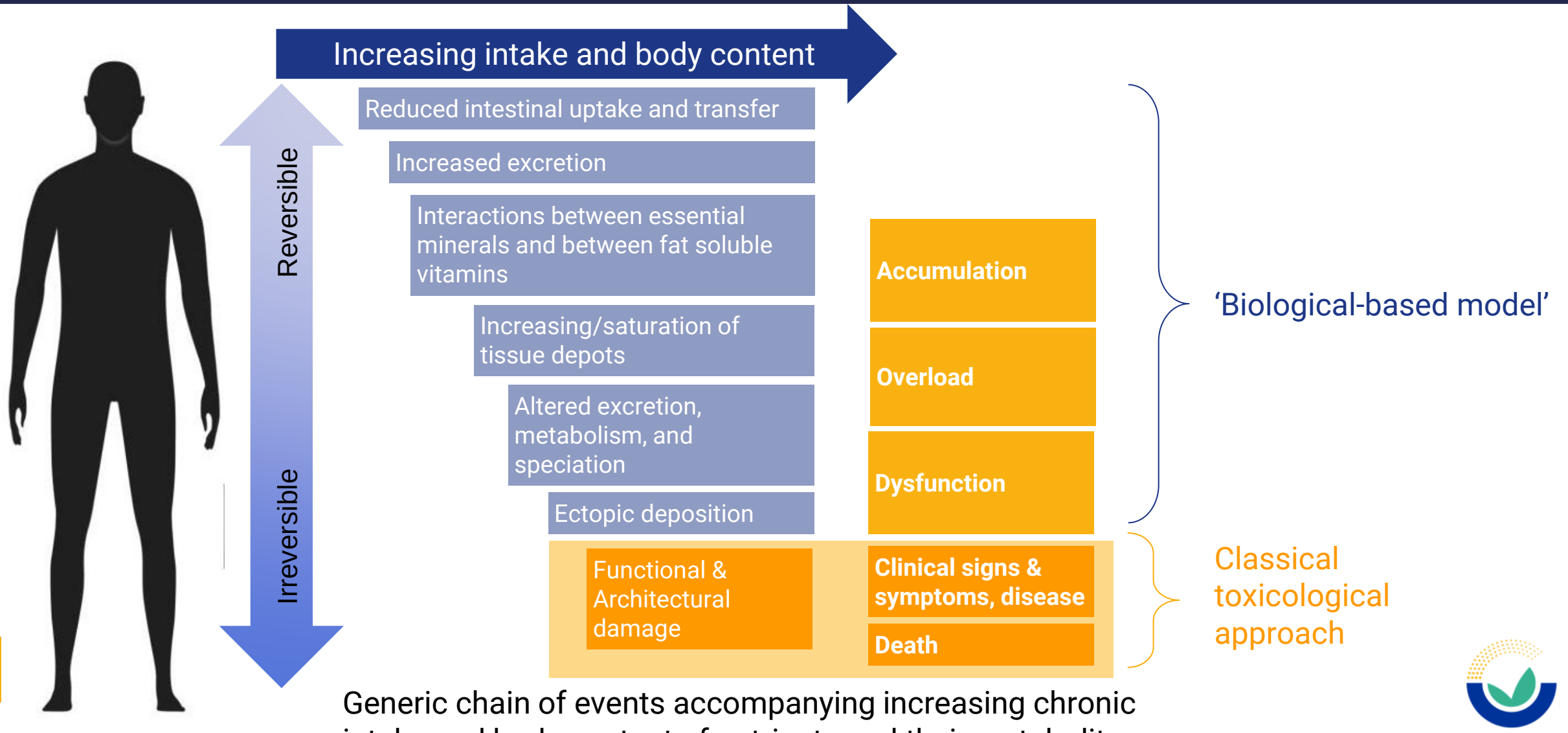


Chemical forms (naturally occurring and authorised)

Consumption patterns

- Absorption, distribution, metabolism, excretion
- Nature and severity of adverse effects

IDENTIFICATION OF RELEVANT ENDPOINTS



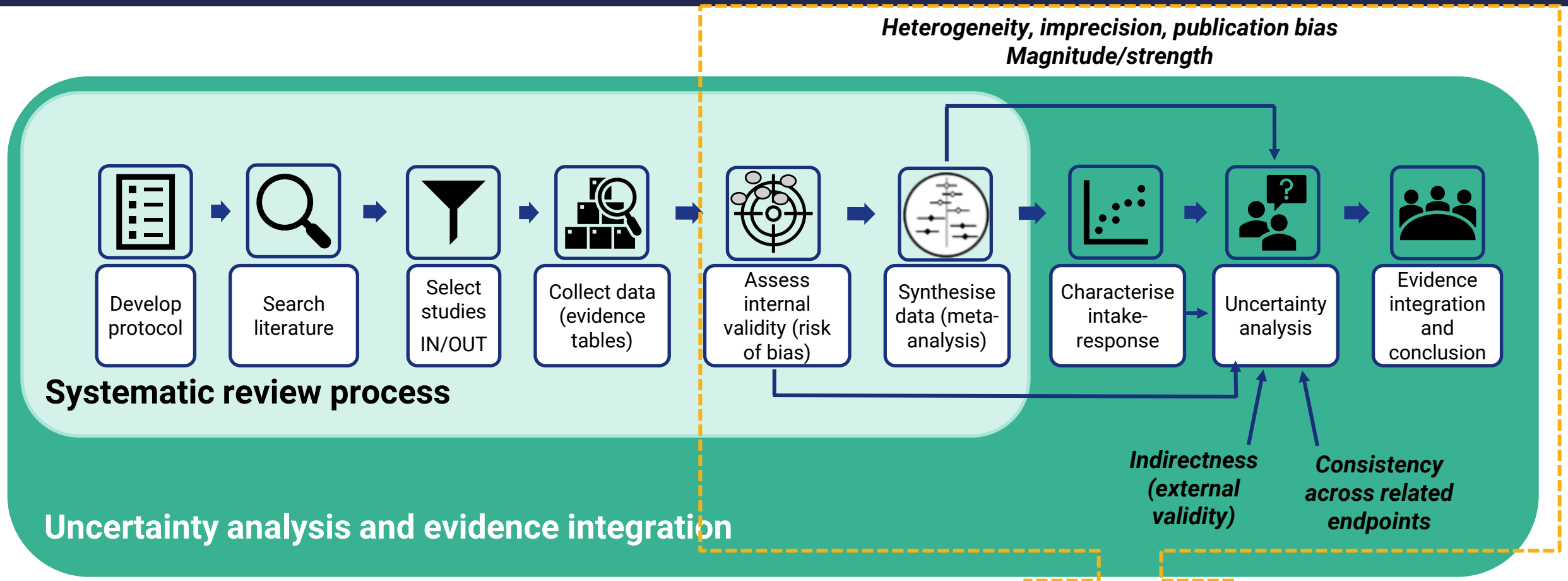
Generic chain of events accompanying increasing chronic intake and body content of nutrients and their metabolites

IDENTIFICATION OF RELEVANT SUB-POPULATIONS

- ULs should be protective for **all members of the general population**, throughout their lifetime
  - specific considerations for **particular lifestages** may be required (e.g. pregnancy, infants, children)

- A UL **may exclude sub-populations with distinct vulnerabilities** due to genetic predisposition or other factors (e.g. specific medical conditions or use of certain medications).

HAZARD IDENTIFICATION: EVIDENCE COLLECTION AND EVALUATION



HAZARD CHARACTERISATION AND ESTABLISHING AN UL

- Selection of critical effect
- Characterise intake-response relationship
- Identify a reference point
- Apply an uncertainty factor
- Establish UL

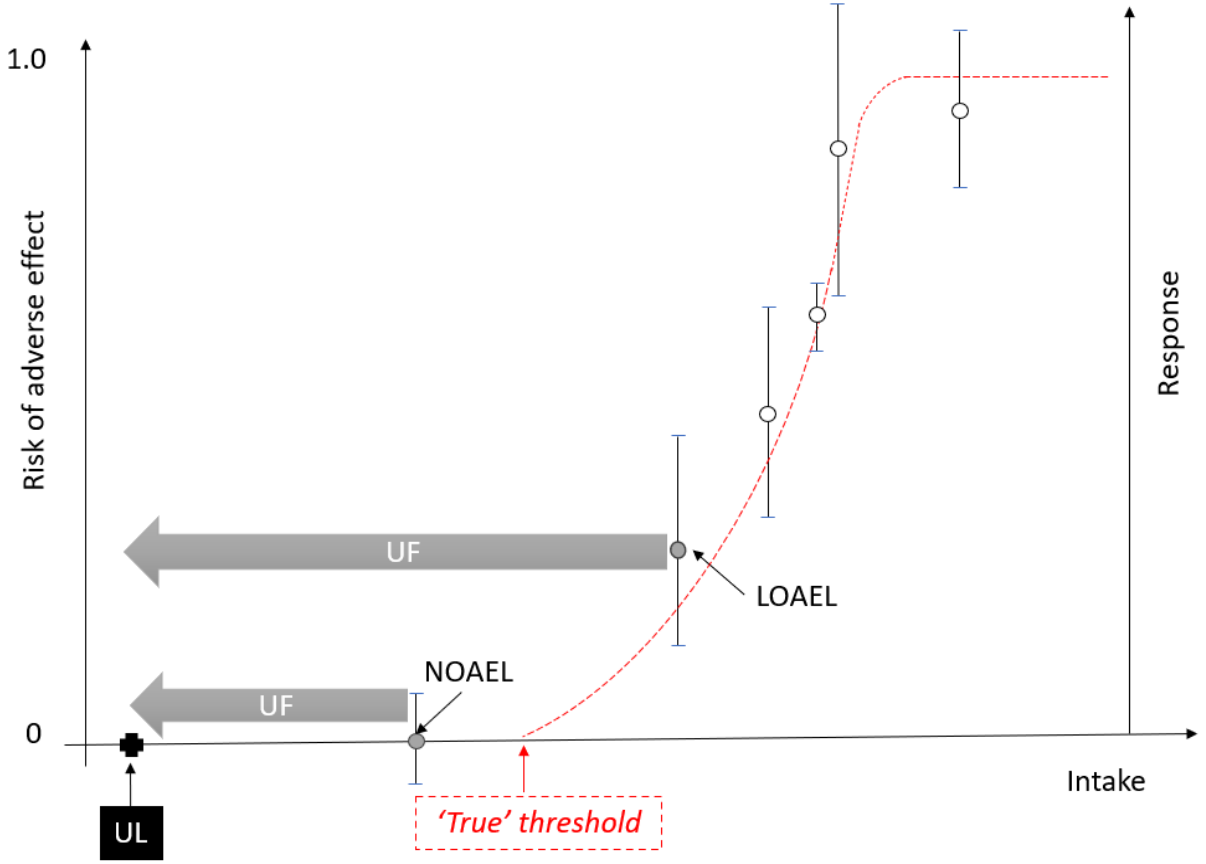
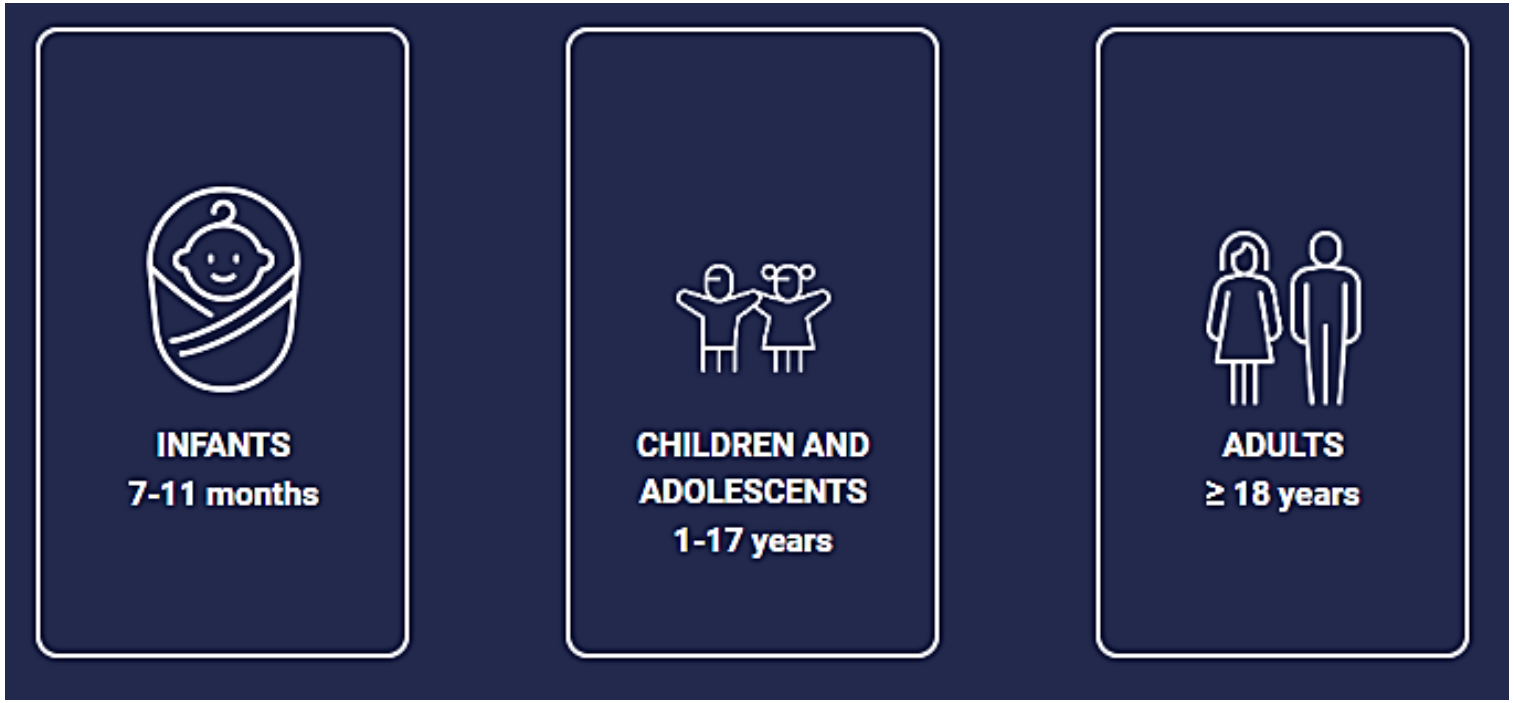


Illustration of the derivation of an UL based on a NOAEL or a LOAEL as a reference point

The dashed line represents the unknown 'true' intake–effect relationship. Dots represent the empirical data collected. Data are used to identify a reference point (NOAEL or LOAEL) to approximate the 'true' threshold dose. Either the NOAEL or LOAEL is divided by an uncertainty factor (UF) to establish the UL.

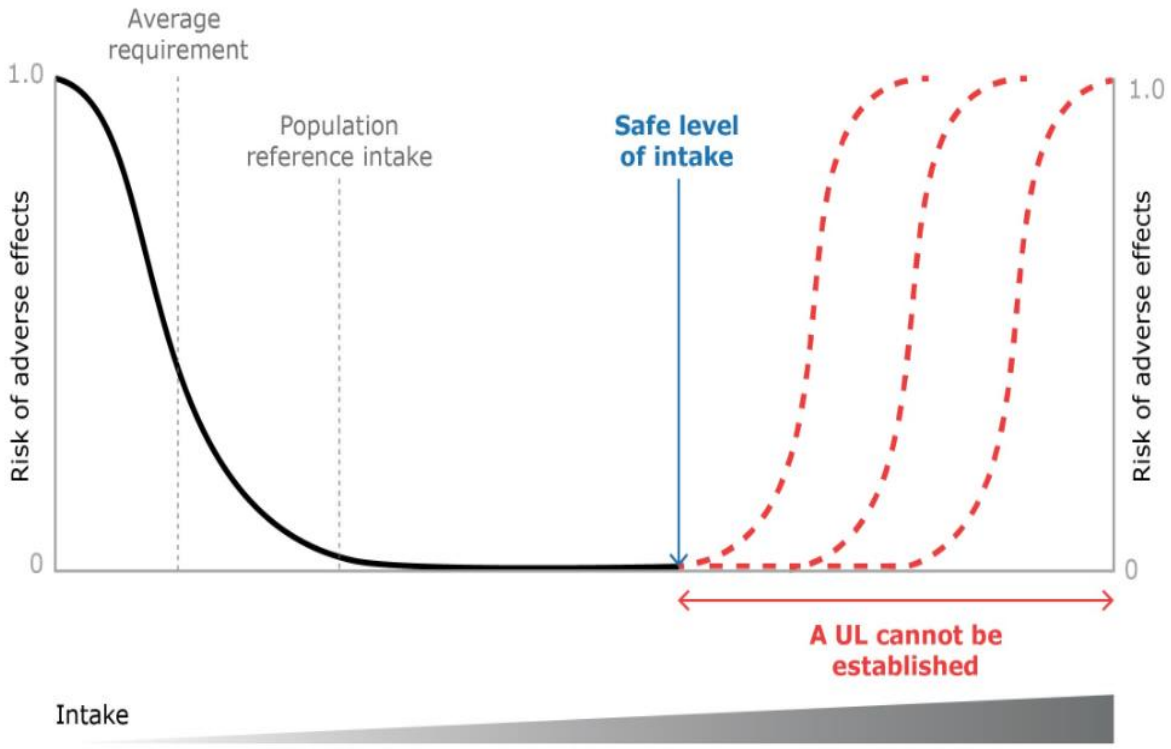
SCALING



Allometric scaling: proportional to a power of body weight (e.g. $BW^{0.75}$)
Isometric scaling: proportional to body weight

SAFE LEVEL OF INTAKE

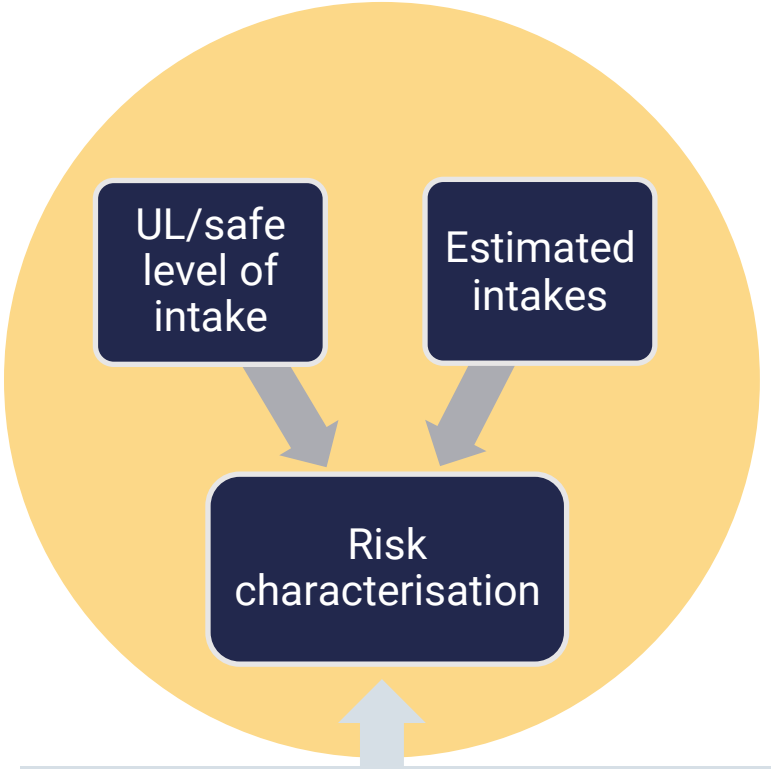
- "An indication […] on the **highest level of intake** for which there is reasonable confidence on the **absence of adverse effects**"
- Based on data which **characterise levels of intake *up to* which no adverse effects have been observed**
- Indicates that **more research is needed to determine a threshold** for the adverse effect(s)



Theoretical representation of a safe level of intake

RISK CHARACTERISATION

- Determination of the **risk of adverse effects in EU populations**
  - **Groups with intakes < UL**: no risk identified
  - **Groups with intakes ≥ UL**: proportion of the population at risk
  - **Groups with intakes < safe level of intake** : no risk identified
  - **Groups with intakes ≥ safe level of intake**: potential risk but proportion of the population at risk *cannot* be estimated
- Sub-populations with distinct sensitivities to the adverse effects of the nutrient excluded (not covered by ULs), if applicable.



- Accuracy of the intake estimates
- Magnitude and duration of the exceedance
- Nature and severity of the adverse effect

Highlights from EFSA’s latest opinions on fat-soluble vitamins: vitamin A including b-carotene, vitamin D and vitamin E

IONUT CRACIUN

VITAMIN A – PREVIOUS ASSESSMENTS

β-carotene

SCF (2000)

*"Supplemental β-carotene (**20 mg/day or more**) is contraindicated for use in current, heavy smokers."*

- Insufficient scientific basis to set a precise figure for an UL → lack of dose-response relationship
- Based on evidence from human intervention trials (lung cancer incidence/mortality)

EFSA ANS Panel (2012)

"β-carotene from its use as food additive and as food supplement at a level below 15 mg/day do not give rise to concerns about adverse health effects in the general population, including heavy smokers."

Preformed Vitamin A

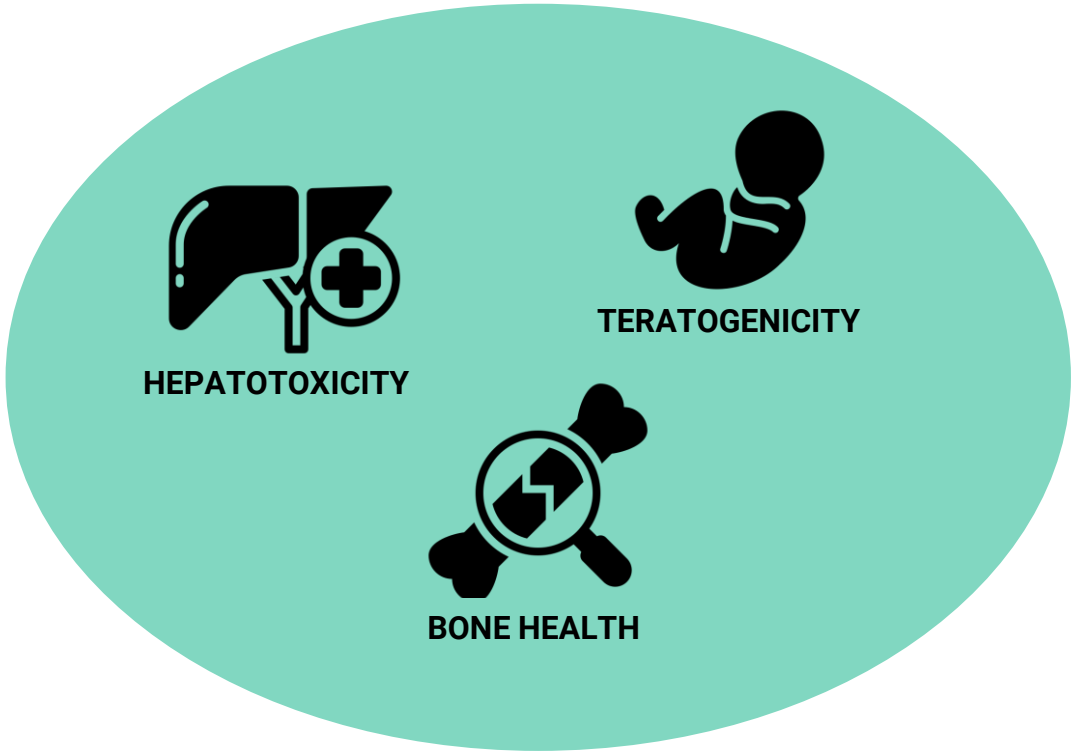
SCF (2002)

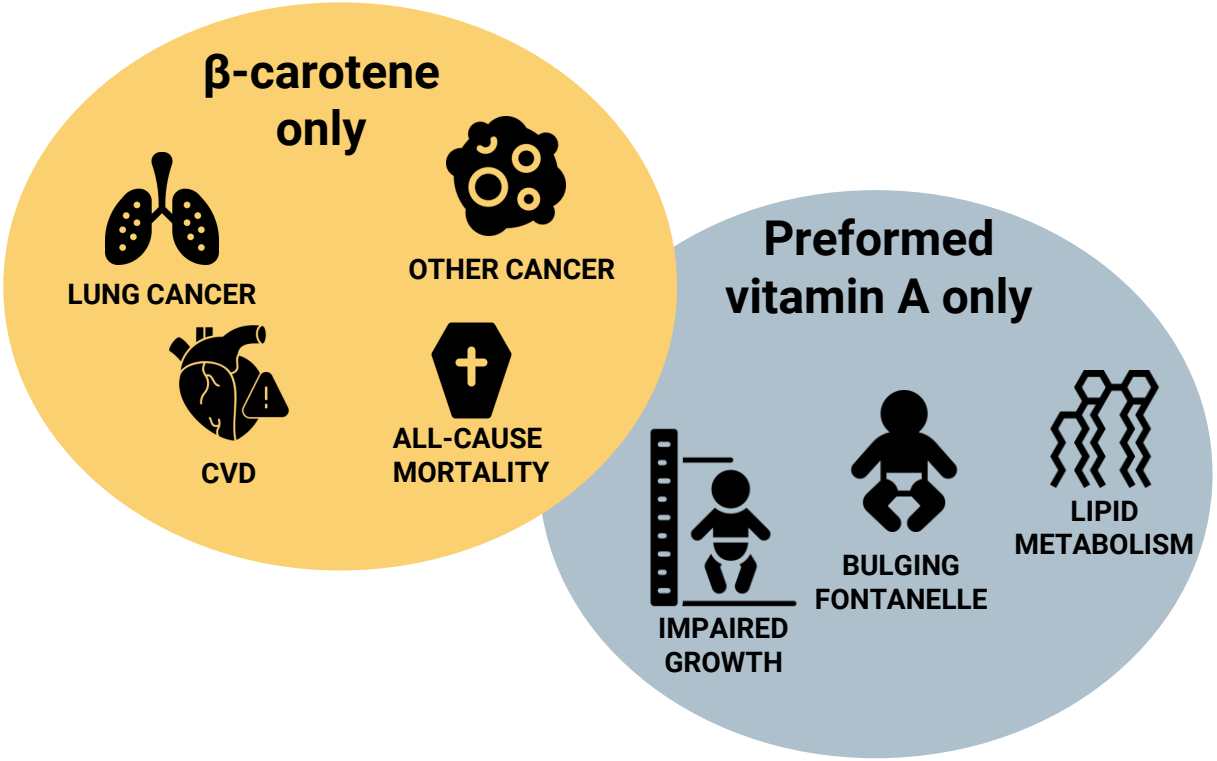
→ **UL of 3,000 µg RE/day** for women of childbearing age

- Critical effect: teratogenicity
- UL also appropriate for other population groups
- UL does not apply to post-menopausal women – may not provide an adequate margin of safety in relation to the possible decrease in bone density and the risk of bone fracture

  → restrict their intake to 1,500 µg RE/day

VITAMIN A – HAZARD IDENTIFICATION



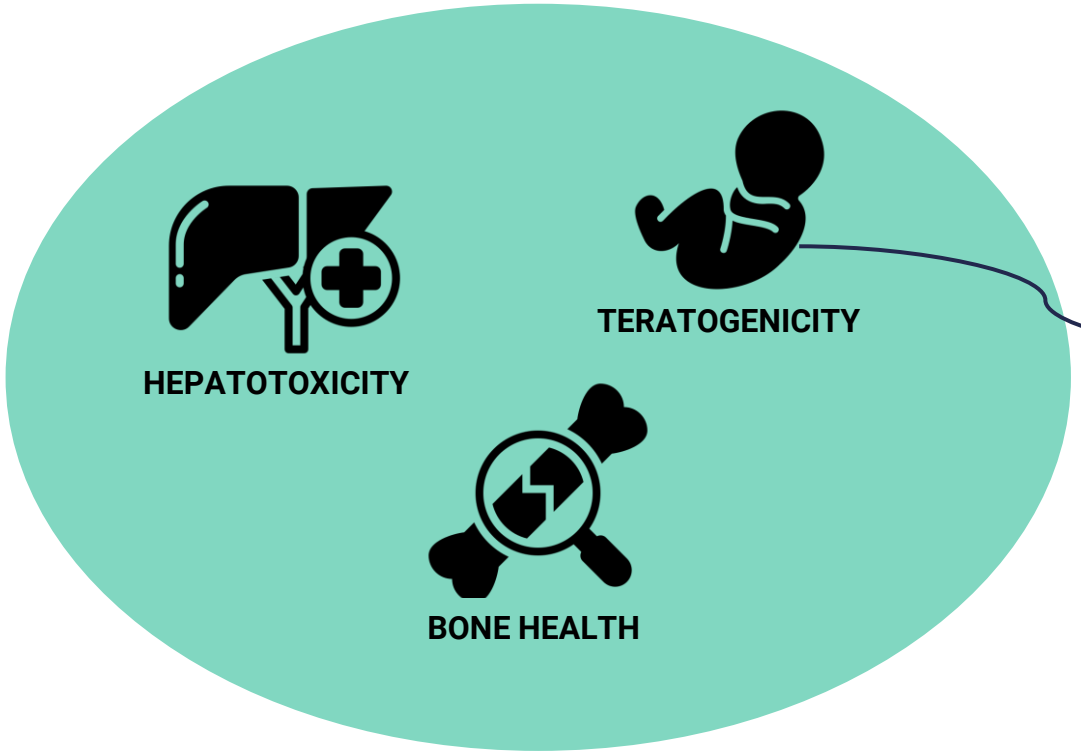


PRIORITY ADVERSE HEALTH EFFECTS

Preformed vitamin A (with or without β-carotene)
→ supplemental β-carotene to be primarily assessed as a source of vitamin A, and therefore for its potential to increase preformed vitamin A toxicity

OTHER ADVERSE HEALTH EFFECTS

VITAMIN A – HAZARD IDENTIFICATION



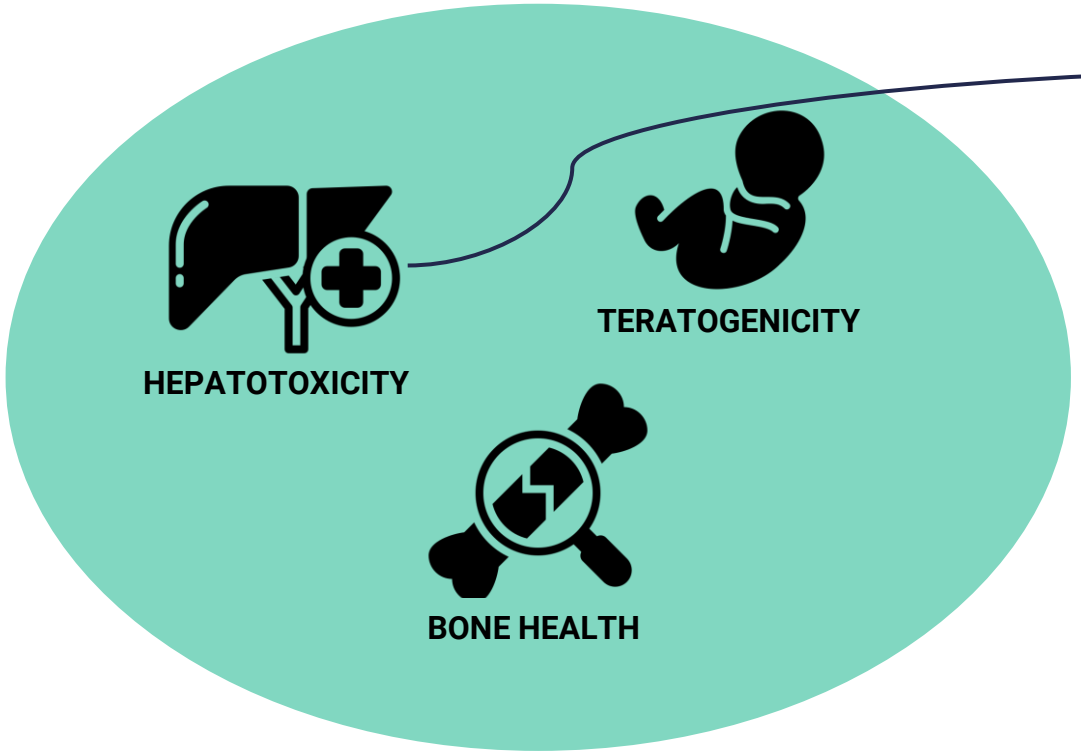
PRIORITY ADVERSE HEALTH EFFECTS

Preformed vitamin A (with or without β-carotene)
→ supplemental β-carotene to be primarily assessed as a source of vitamin A, and therefore for its potential to increase preformed vitamin A toxicity

Dose-response relationship observed between preformed vitamin A and birth defects
Threshold of 3,000 µg RE/day supplemental retinol for cranial NCD
- Supported by findings from other studies above and below this threshold

β-Carotene per se is **not considered to be teratogenic** – in vitamin A-repleted states, it is unlikely that maternal β-carotene intake would enhance the teratogenic effects of preformed vitamin A
→ However, the available data in humans does not allow to address this question

VITAMIN A – HAZARD IDENTIFICATION



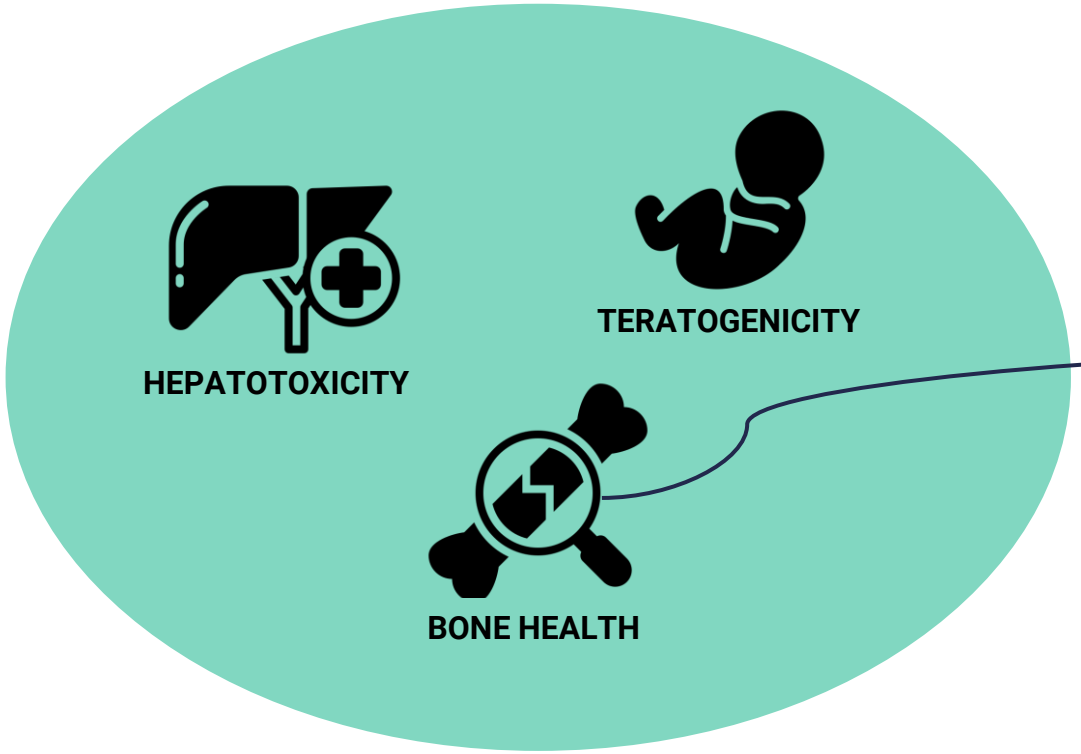
Available RCTs **do not report an adverse effect** on liver enzymes
→ No RCTs testing doses below the LOAEL for liver damage (i.e., <7,500 µg RE/day)
→ No data with high intakes of β-carotene

The available evidence **does not allow characterising the dose-response relationship**

PRIORITY ADVERSE HEALTH EFFECTS

Preformed vitamin A (with or without β-carotene)
→ supplemental β-carotene to be primarily assessed as a source of vitamin A, and therefore for its potential to increase preformed vitamin A toxicity

VITAMIN A – HAZARD IDENTIFICATION



The evidence that has become available since the assessment of the SCF (2002) **does not support** the association between preformed vitamin A **at intakes ≤ 3000 µg RE/day and impaired bone health**

The **causality** of the relationship between the intake of preformed vitamin A **at levels that are below the current UL** (i.e. in the range 1000–3000 µg RE/day) and an increased risk of bone fractures **cannot be established**.

No evidence that dietary **β-carotene** could contribute to preformed vitamin A toxicity on bone

PRIORITY ADVERSE HEALTH EFFECTS

Preformed vitamin A (with or without β-carotene)
→ supplemental β-carotene to be primarily assessed as a source of vitamin A, and therefore for its potential to increase preformed vitamin A toxicity

PREFORMED VITAMIN A – DERIVATION OF THE UL

Selection of critical effect

TERATOGENICITY

No consistent evidence of adverse effects on other endpoints below the UL of 3000 µg RE/day

Lowest doses reported to produce the different effects:

- Bulging fontanelle: 7500 µg RE
- Hepatotoxicity: 7500 µg RE/day
- Bone density/fracture: causality cannot be established at levels below the current UL
- Lipid metabolism: 7500 µg RE/day

β-carotene per se is not considered to be teratogenic

↓

UL based on teratogenicity should apply to preformed vitamin A only

Preformed vitamin A

Retain the **UL of 3,000 µg RE/day** for adults, based on a **NOAEL**

No UF necessary

Applies to all adults, including **post-menopausal women**

Allometric scaling for other population groups

PREFORMED VITAMIN A – UL VALUES

	UL (µg RE/day)
4-6 months	600
7-11 months	600
1-3 years	800
4-6 years	1,100
7-10 years	1,500
11-14 years	2,000
15-17 years	2,600
≥18 years	3,000
Pregnancy	3,000
Lactation	3,000

Newly set

No change compared to SCF, 2002

β-CAROTENE – HAZARD CHARACTERIZATION

β-CAROTENE

LUNG CANCER

Selection of critical effect

LUNG CANCER RISK

Available data are **not sufficient and suitable** to characterise a dose–response relationship and/or identify a reference point for supplemental β-carotene

No UL can be established

Smokers should avoid supplements containing β-carotene

Supplemental β-carotene by the **general population** should be limited to the purpose of **meeting vitamin A requirements**

VITAMIN D – PREVIOUS ASSESSMENTS

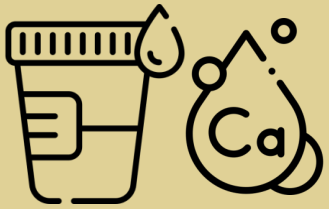
EFSA NDA Panel (2012)

→ **UL for adults of 100 µg/day**

- Based on a NOAEL for hypercalcaemia of 250 µg/day
- Uncertainty factor of 2.5 – to account for the low number and short duration of the studies, the limited sample size and the characteristics of the subjects (young males only).

VITAMIN D – HAZARD IDENTIFICATION

PRIORITY ADVERSE HEALTH EFFECTS



PERSISTENT HYPERCALCAEMIA AND HYPERCALCIURIA

MUSCULOSKELETAL HEALTH

OTHER ADVERSE HEALTH EFFECTS

KIDNEY STONES

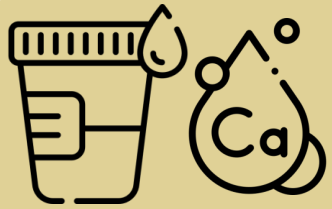
CANCER

CVD

ALL-CAUSE MORTALITY

VITAMIN D – HAZARD IDENTIFICATION

PRIORITY ADVERSE HEALTH EFFECTS



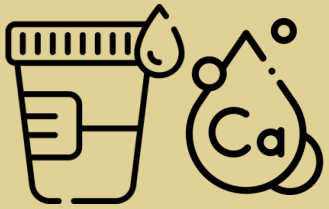
PERSISTENT HYPERCALCAEMIA AND HYPERCALCIURIA

MUSCULOSKELETAL HEALTH

- Vitamin D (up to 250 µg/day) for 5-6 months: No risk of persistent hypercalcemia.
- Vitamin D (250 µg/day) + calcium for 1-3 years: 3x risk of persistent hypercalciuria.
- No persistent hypercalcemia/hypercalciuria with:
  - Vitamin D alone (up to 100 µg/day).
  - Lower doses + calcium (up to 125 µg/day).
    - Shorter periods (3-6 months).
- Limited RCTs → No dose-response analysis

VITAMIN D – HAZARD IDENTIFICATION

PRIORITY ADVERSE HEALTH EFFECTS

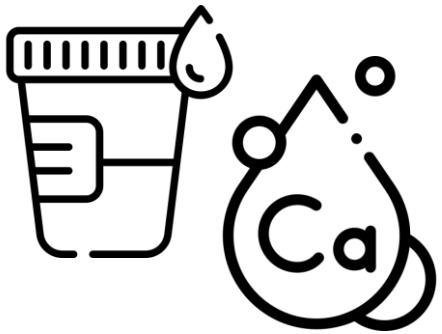


PERSISTENT HYPERCALCAEMIA AND HYPERCALCIURIA

MUSCULOSKELETAL HEALTH

- Vitamin D (up to 250 µg/day) for 1-5 years: No increased risk of falls or fractures.
- No adverse effect on areal BMD (or BMC in children) with:
  - High vitamin D (up to 50 µg/day in children, up to 250 µg/day in adults) for ≥ 1 year.
- High doses (up to 250 µg/day) + calcium for 3 years in older adults: Negative dose-response with volumetric BMD, no impact on bone strength.

VITAMIN D – DERIVATION OF THE UL



Selection of critical effect

PERSISTENT HYPERCALCAEMIA/HYPERCALCIURIA

↓

LOAEL = 250 µg/day (Hypercalciuria)

↓

UF = 2.5 to account for LOAEL as RP

↓

UL = 100 µg VDE/day

VDE = Vitamin D Equivalents
1 µg VDE = 1 µg vitamin D3
1 µg VDE = 1 µg vitamin D2
1 µg VDE = 0.4 µg calcidiol monohydrate*

*applies up to 10 µg/day of calcidiol monohydrate

Children aged 1-10 y
UL = 50 µg VDE/day
based on their lower body weight

VITAMIN D – UL VALUES

	UL (µg VDE/day)
4-6 months*	25
7-11 months*	35
1-3 years	50
4-6 years	50
7-10 years	50
11-14 years	100
15-17 years	100
≥18 years	100
Pregnancy	100
Lactation	100

VDE, Vitamin D equivalents
*Values established by the NDA Panel in 2018 (EFSA NDA Panel, 2018)

No change compared to NDA Panel, 2012

VITAMIN E – PREVIOUS ASSESSMENTS

SCF (2003)

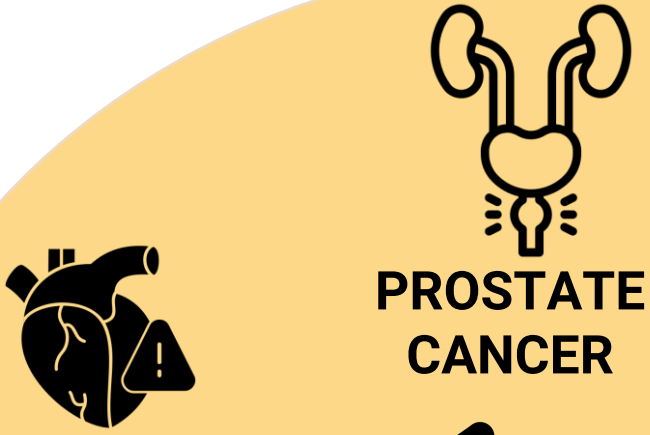
→ **UL for adults of 300 mg/day***

- Based on a NOAEL for blood clotting of 540 mg/day
- Uncertainty factor of 2 – to cover interindividual differences in sensitivity

*α-tocopherol and other tocochromanols

VITAMIN E – HAZARD IDENTIFICATION

PRIORITY ADVERSE HEALTH EFFECTS



CVD

PROSTATE CANCER

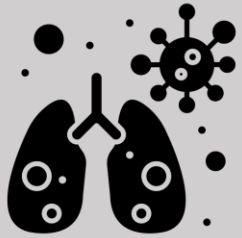
IMPAIRED BLOOD COAGULATION AND RISK OF BLEEDING

OTHER ADVERSE HEALTH EFFECTS

ALL-CAUSE MORTALITY

PREGNANCY RELATED OUTCOMES

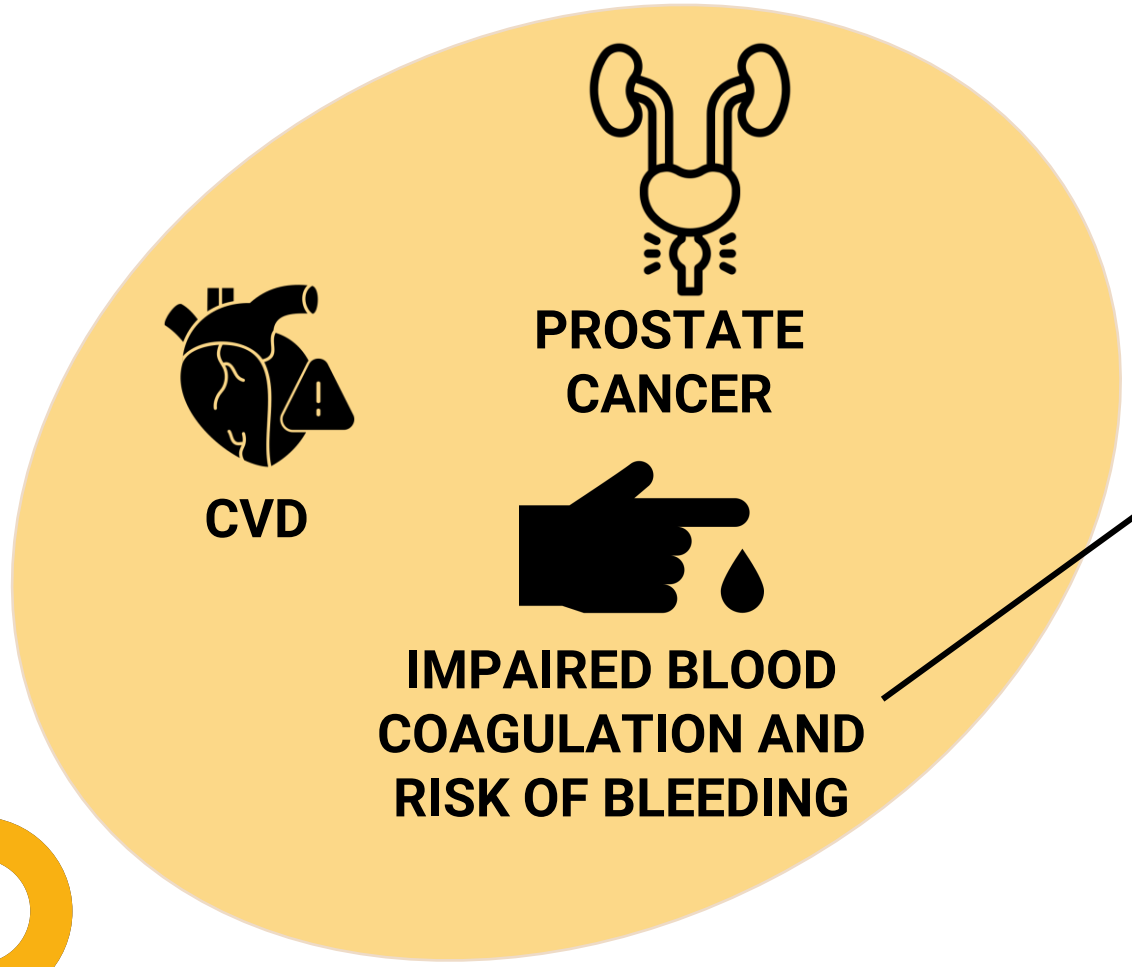
CATARACTS



RESPIRATORY INFECTIONS

VITAMIN E – HAZARD IDENTIFICATION

PRIORITY ADVERSE HEALTH EFFECTS

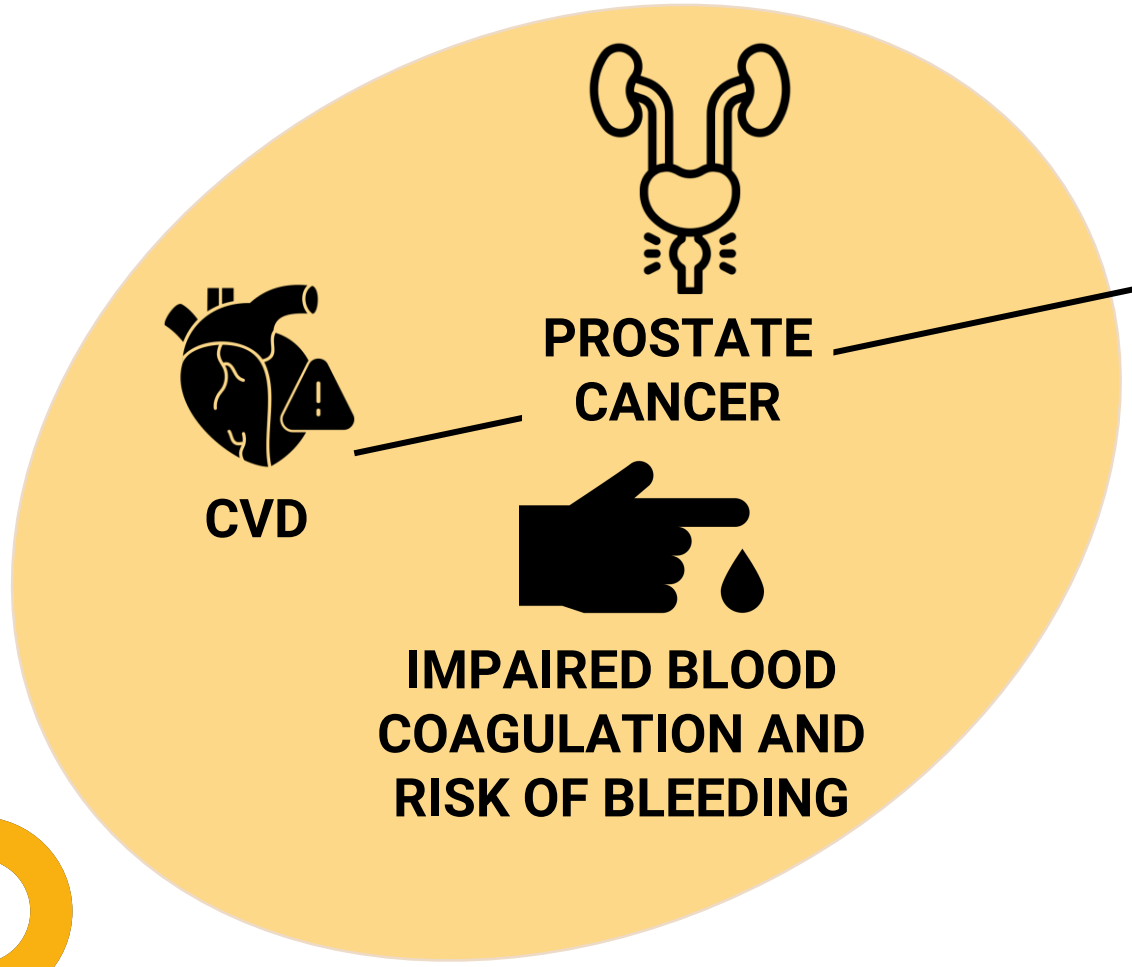


- **No relevant data on risk of bleeding events**
- **Prothrombin time (PT) and activated partial thromboplastin time (aPTT) (aPTT) unaffected by α-tocopherol**
- **Platelet function changes did not affect bleeding time**

Studies conducted in populations not taking anticoagulant or antiplatelet drugs

VITAMIN E – HAZARD IDENTIFICATION

PRIORITY ADVERSE HEALTH EFFECTS



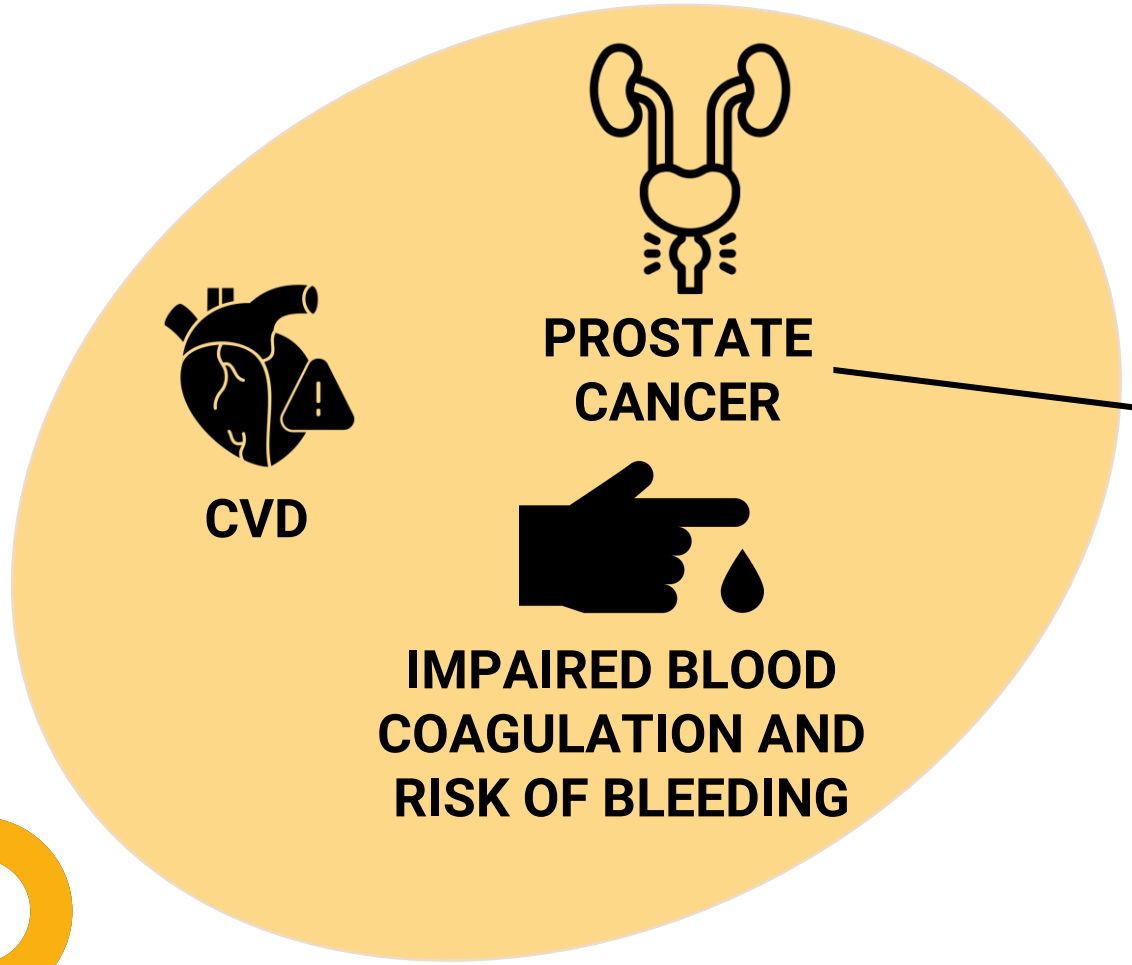
No positive relationship between α-tocopherol intake and increased risk of:

CVD, myocardial infarction, angina, CHD, total stroke, or ischemic stroke.

→ Evidence for increased risk of **haemorrhagic stroke** and **congestive heart failure**: cannot be used for establishing a UL for vitamin E.

VITAMIN E – HAZARD IDENTIFICATION

PRIORITY ADVERSE HEALTH EFFECTS



Increased risk of prostate cancer reported in **SELECT** study (364 mg α-tocopherol/day)

Three other RCTs (up to 268 mg α-tocopherol/day) **do not support** this finding.

Heterogeneity: α-tocopherol form, dose, participant characteristics, and other factors.

Observational studies and animal data **do not provide supportive evidence**.

→ Available body of evidence is **insufficient to conclude** on a relationship between α-tocopherol intake and prostate cancer risk.

VITAMIN E – DERIVATION OF THE UL

Selection of critical effect

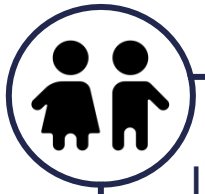
IMPAIRED BLOOD COAGULATION AND RISK OF BLEEDING

No relevant new evidence on the risk of bleeding events

No basis to change the UL previously established by the SCF

NDA Panel retains the UL previously established by the SCF

300 mg α-tocopherol/day for adults



Allometric scaling

Infants, children and adolescents

VITAMIN E – UL VALUES

	UL (mg/day)
4-6 months	50
7-11 months	60
1-3 years	100
4-6 years	120
7-10 years	160
11-14 years	220
15-17 years	260
≥18 years	300
Pregnancy	300
Lactation	300

ULs apply to all stereoisomeric forms of α-tocopherol.

Newly set

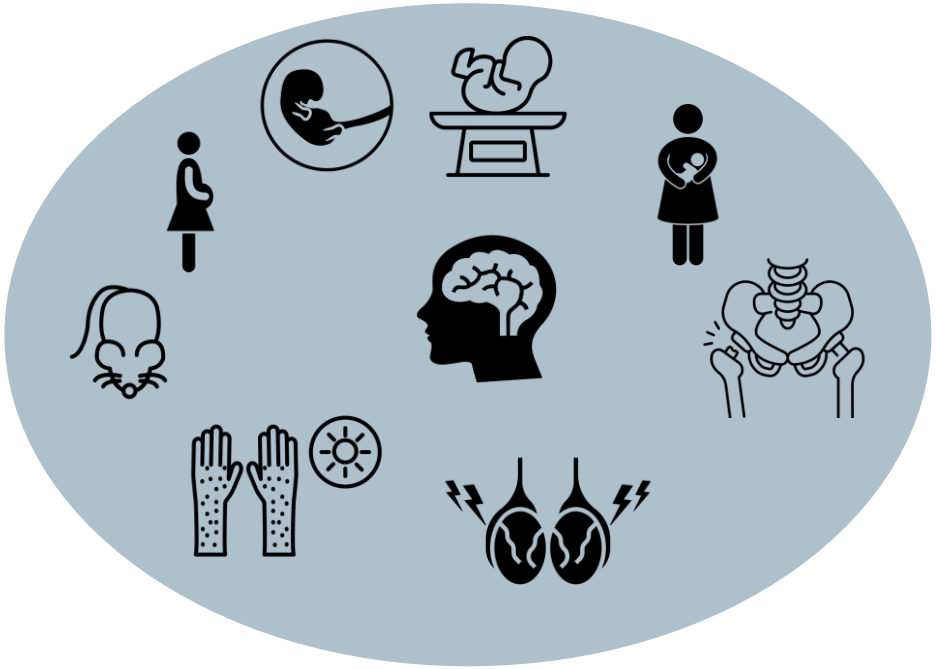
No change compared to SCF, 2003

Highlights from EFSA’s latest opinions on B-vitamins: vitamin B6 and folate

NENA KARAVASILOGLOU

Image shutterstock_79146808

VITAMIN B6 - HAZARD IDENTIFICATION



Experimental animal data show that vitamin B6 causes peripheral neuropathy in a **dose related manner**.
A similar relationship has been shown in humans

Images created by Claire Jones, Muhammad Shabraiz, Hafiz Nur Lutfianto, koi, Noura Mbarki, Rahul, Gan Khoon Lay, Andrew Doane, Svelte UX and Usama Zahoor from Noun project

VITAMIN B6 - BASIS FOR THE DERIVATION OF THE UL

Critical endpoint selection

Case-control, Dalton and Dalton, 1987*

- RP 100 mg/day

SCF, 2000

- RP 50 mg/day
- Supported by case-reports and Member States' vigilance data
- LOAEL based on a study on

NDA, 2023

Images created by Usama Zahoor and Cuputo from Noun project and shutterstock_1081671080

* Dalton K and Dalton MJ, 1987. Characteristics of pyridoxine overdose neuropathy syndrome. Acta Neurologica Scandinavica, 76, 8–11. https://doi.org/10.1111/j.1600-0404.1987.tb03536.x

VITAMIN B6 - DERIVATION OF THE UL

Critical endpoint selection

LOAEL: 50 mg/kg body weight

Uncertainty factor : 300

Value: 11.7 mg/day

RP: 50 mg/day

Uncertainty factor : 4

Value: 12.5 mg/day

UL: 12 mg/day

- No indication of increased susceptibility of children or infants to vitamin B6 toxicity
- Allometric scaling

Images created by Usama Zahoor, Gan Khoon Lay, Andrew Doane, Musmellow, Icon Island and Cuputo from Noun project, and shutterstock_1081671080

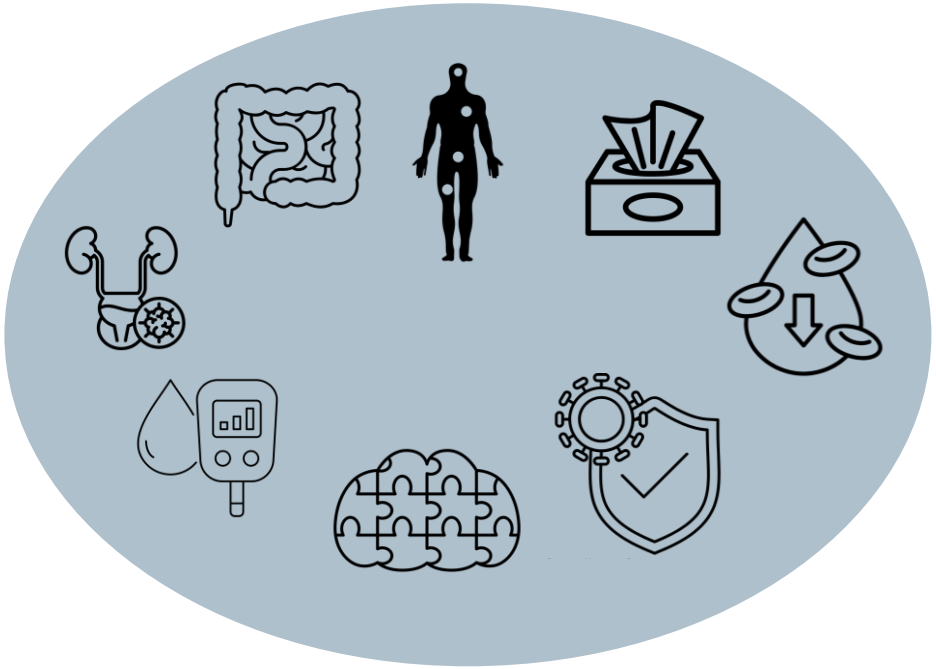
VITAMIN B6 – UL VALUES

	UL (mg/day)
4-6 months	2.2
7-11 months	2.5
1-3 years	3.2
4-6 years	4.5
7-10 years	6.1
11-14 years	8.6
15-17 years	10.7
≥18 years	12
Pregnancy	12
Lactation	12

Newly set

Decreased compared to SCF, 2000

FOLATE (VITAMIN B9) - HAZARD IDENTIFICATION



Dietary intake of folate and impaired cognitive function in individuals with **low cobalamin** (vitamin B12) **status**

Images created by Wes Breazell, Dahlia nur aini, Arif Hariyanto, Amethyst Studio, Ferifrey, Vectors Market, zaenul yahya, slamet and Muhammad Owais from Noun project

FOLATE - DERIVATION OF THE UL

- Critical endpoint selection
- SCF: UL 1000 µg folic acid, adults
- No new evidence since 2000

- NDA retains the ULs set in 2000
- No data for infants

- No indication of increased susceptibility of infants to folate toxicity
- Mean/median folate concentration of mature breast milk is in the range of 45-99 µg/L, approximate average of 80 µg/L
- Allometric scaling

Images created by Wes Breazell, Gan Khoon Lay, Andrew Doane, Musmellow and Cuputo from Noun project

FOLATE – UL VALUES

	UL (µg/day)
4-6 months	200
7-11 months	200
1-3 years	200
4-6 years	200
7-10 years	400
11-14 years	600
15-17 years	800
≥18 years	1000
Pregnancy	1000
Lactation	1000

Newly set

- No statement can be made about the safety of 5-MTHF-glucosamine or l-5-MTHF-Ca above the UL for folic acid
- The UL applies to the combined intake of folic acid and 5-MTHF salts under their authorized conditions of use

NDA Panel considerations

Coffee/tea break

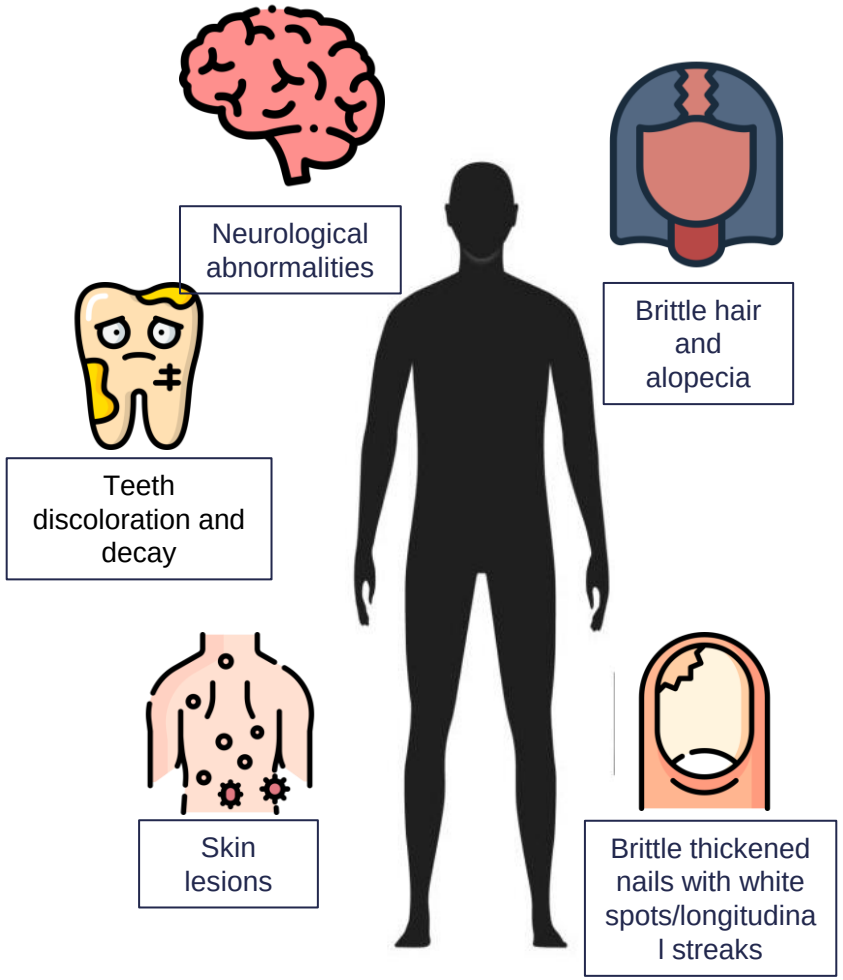
The session will start again at 15:55

Highlights from EFSA’s latest opinions on essential minerals: selenium, iron, manganese

LEONARD MATIJEVIĆ

SELENIUM – HAZARD IDENTIFICATION

Well-established effects



Signs and symptoms of chronic selenosis

Since SCF (2000) assessment:
+ 5 RCTs (**SELECT trial**) and 3 observational studies

Effects observed at intakes below the previously identified **NOAEL** (850 µg/day)

SELENIUM – HAZARD IDENTIFICATION

No Positive relationship / Insufficient Evidence

- Hypertension ✓
- Alzheimer's disease ✓
- Thyroid diseases ✓
- Prostate cancer ✓
- All-cause mortality ✓
- Amyotrophic lateral sclerosis ?
- Skin cancer ?
- Neuropsychological development in children ?

Positive relationship

Type 2 Diabetes ⚠

Evidence from 10 **observational studies**

Low level of certainty

Evidence from 5 **RCTs**
Pooled mean effect: RR (95% CI) = 1.11 (1.00, 1.24)

Moderate level of certainty

Very low: 0–15%	Low: >15–50%	Moderate: >15–75%	High: >75–100%

No indication for a specific risk or increased susceptibility to adverse effects of excessive selenium intake **during pregnancy or lactation** from populations living in seleniferous areas

SELENIUM – HAZARD CHARACTERISATION AND DERIVATION OF THE UL

Selection of critical endpoint
Alopecia: Early sign of selenium toxicity

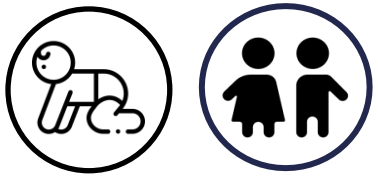
LOAEL of 330 µg/day from the SELECT trial

Uncertainty factor of 1.3 applied
- LOAEL as the reference point
- Lack of data in women
- Alopecia mild and reversible

UL of 255 µg/day for adults

No data to support the derivation of a UL for **infants** and **children**

UL extrapolated from adults based on **allometric scaling**



SELENIUM – UL VALUES

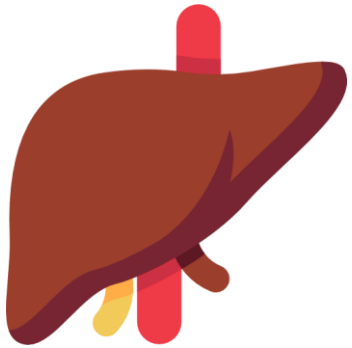
	UL (µg/day)
4-6 months	45
7-11 months	55
1-3 years	70
4-6 years	95
7-10 years	130
11-14 years	180
15-17 years	230
18 years +	255
Pregnancy	255
Lactation	255

Increased compared to SCF, 2000

Decreased compared to SCF, 2000

IRON – HAZARD IDENTIFICATION

Well-established effects



Systemic iron overload

Accumulation of iron in organs, especially the liver
May lead to organ and liver damage

Well described in patients with impaired downregulation of iron absorption

Also **reported in individuals without disorders of iron metabolism (case reports)**

Adverse GI effects

Acute effects include: nausea, constipation, vomiting, bloating, flatulence, mucositis and loss of appetite

58 RCTs identified → evidence differed according to the study population, iron forms administered, the doses (ranging from 3 to 150 mg/day) and the study duration (ranging from 1 to 72 weeks)

Plausible threshold below which adverse GI effects are less likely to occur between 20 and 50 mg/d of supplemental iron intake

IRON – HAZARD IDENTIFICATION

No Positive relationship / Insufficient Evidence

- Zinc absorption
- Pregnancy outcomes
- Infections in infants and children
- Cognitive development in infants and children
- Gestational diabetes
- T2DM

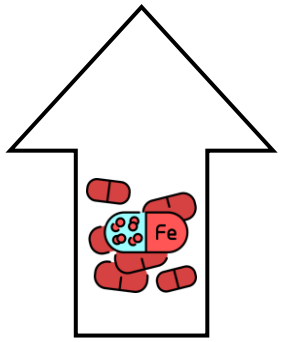
Positive relationship

Impaired growth
(iron-replete infants and toddlers)

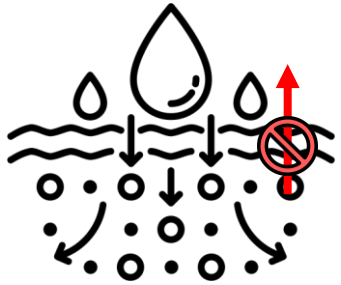
Evidence from 5 **RCTs**
Low level of certainty

Very low: 0–15%	Low: >15–50%	Moderate: >15–75%	High: >75–100%

IRON – HAZARD CHARACTERISATION

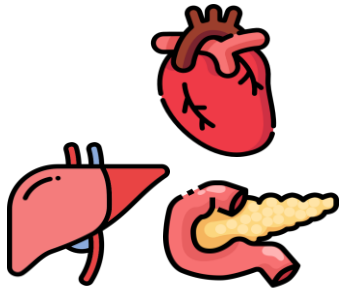


Dietary iron intake

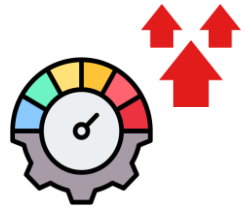


Iron supply to the body regulated via iron absorption

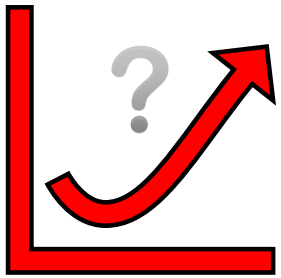
No active excretion pathway



Accumulation in organs, especially the **liver**



IRON TOXICITY



No adequate data to characterise a dose–response relationship and identify a reference point

→ **No UL for iron intake can be established** for any population group

IRON – HAZARD CHARACTERISATION AND SAFE LEVEL OF INTAKE

- **Black stools** – reflects the presence of large amounts of unabsorbed iron in the gut

  → only indicator for which sufficiently reliable and consistent data are available to characterise a dose–response
- Presence of black stools is **not an adverse event** *per se*
- A **conservative endpoint** among the chain of undesirable events that **may lead to systemic iron overload and iron toxicity**
- Occurrence of black stools can be used as a basis to derive a **safe level of intake**, i.e. the highest level of intake where there is **reasonable confidence** in data on the absence of adverse effects

Safe level of intake = 40 mg/day

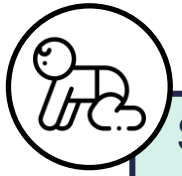
Total intake of iron from diet and supplements not expected to lead to adverse effects, in the **general adult population**

IRON – HAZARD CHARACTERISATION AND SAFE LEVEL OF INTAKE

Data in infants, children and adolescents

- No **reliable data** on the occurrence of black stools upon iron supplementation are available in infants, children and adolescents.
- Mechanisms of iron homeostasis may only be fully developed by the age of **9 months of age**
- From 7 to 11 months, infants have **higher** dietary iron requirements than young children (1-3 years)

Safe levels of intake for **total iron intakes** from all sources for **children** (from 1 year of age) are scaled down from adult levels using allometric scaling **to account for growth and physiological differences**



Safe levels of **supplemental*** intake for **infants** (4–11 months of age) are scaled down from the highest adult supplemental intake which has not led to the occurrence of black stools, using allometric scaling **to account for infants' elevated iron requirements and rapid physiological changes**

* Fortified foods and food supplements (not from infant and follow-on formulae)

IRON – UL VALUES

	Safe level of intake** (mg/day)
Supplemental* intake	
4-6 months	5
7-11 months	5
Total intake	
1-3 years	10
4-6 years	15
7-10 years	20
11-14 years	30
15-17 years	35
18 years +	40
Pregnancy	40
Lactation	40

* Fortified foods and food supplements (not from infant and follow-on formulae)
** Not applicable to individuals who receive iron under medical supervision

Newly set,
No values previously set by the NDA Panel (2004)

MANGANESE – HAZARD IDENTIFICATION

Well-established effects

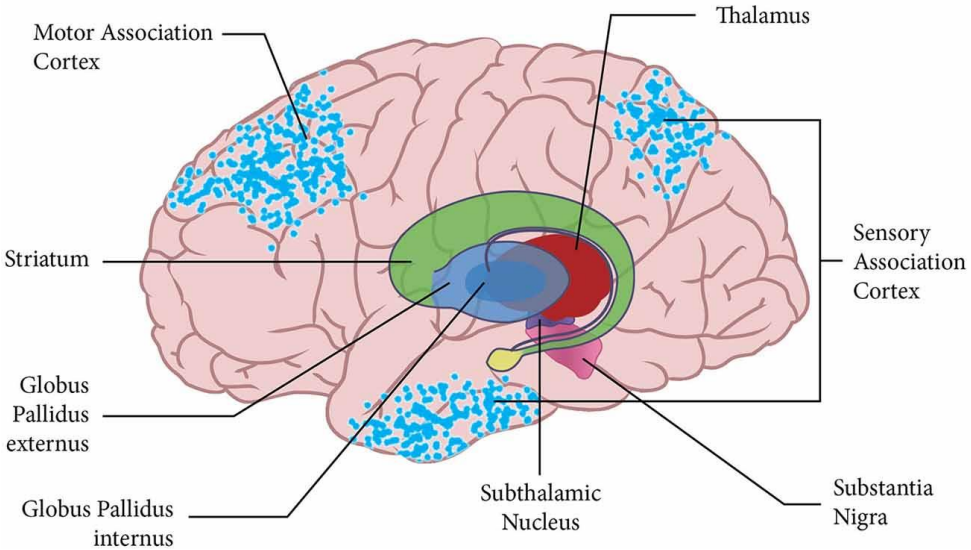
Manganese neurotoxicity (manganism)

Neurological disorder – shares some similarities with idiopathic Parkinson's disease

→ neuropsychological abnormalities and motor symptoms:

- Impaired motor skills
- Tremors
- Facial muscle spasms
- Difficulty walking

The neurotoxic effects in humans of chronic exposure to high manganese concentrations *by inhalation* are **well documented**



MANGANESE – HAZARD IDENTIFICATION & CHARACTERISATION

HUMAN DATA

→Cognitive impairment
→Impairment of motor function
→Impairment of behaviour
→ADHD
→Impaired neurodevelopment
→Impaired neurological functions

Available BoE is **insufficient** to conclude on a relationship

Case reports of manganese dietary intoxication show **symptoms of manganism**, with MRI evidence of brain manganese accumulation

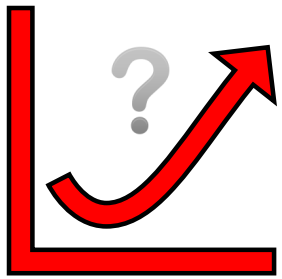
ANIMAL DATA

→Neurotoxicity

BoE indicates that **oral exposure to manganese can affect neurological functions in rodents** (motor and learning abilities)

Little evidence for a higher susceptibility to the neurotoxic effects of manganese in early life (few studies)

Data do not allow to derive a reference point (**large uncertainties regarding critical dose**)



Available human and animal studies support **neurotoxicity as a critical effect**

Data are **not sufficient and suitable** to characterise a dose–response relationship and identify a reference point

→ **No UL can be established**

MANGANESE – DERIVING A SAFE LEVEL OF INTAKE

Children, Adolescents & Adults

No indication of adverse effects, including neurotoxicological effects, **at the levels of background dietary intake**

High Consumers: Safety indicated at **P95**

Safe level of intake: Mean of 4 highest available P95

Infants

Data are insufficient to determine when manganese homeostatic processes become fully mature **during infancy**

Safe level of intake: A more **conservative** approach
Mean of all available P95

MANGANESE – SAFE LEVEL OF INTAKE

	Safe level of intake (mg/day)
4-11 months	2
1-2 years	4
3-6 years	5
7-13 years	6
14-17 years	7
18 years +	8
Pregnancy	8
Lactation	8

Newly set, no values previously set by the SCF (2000)

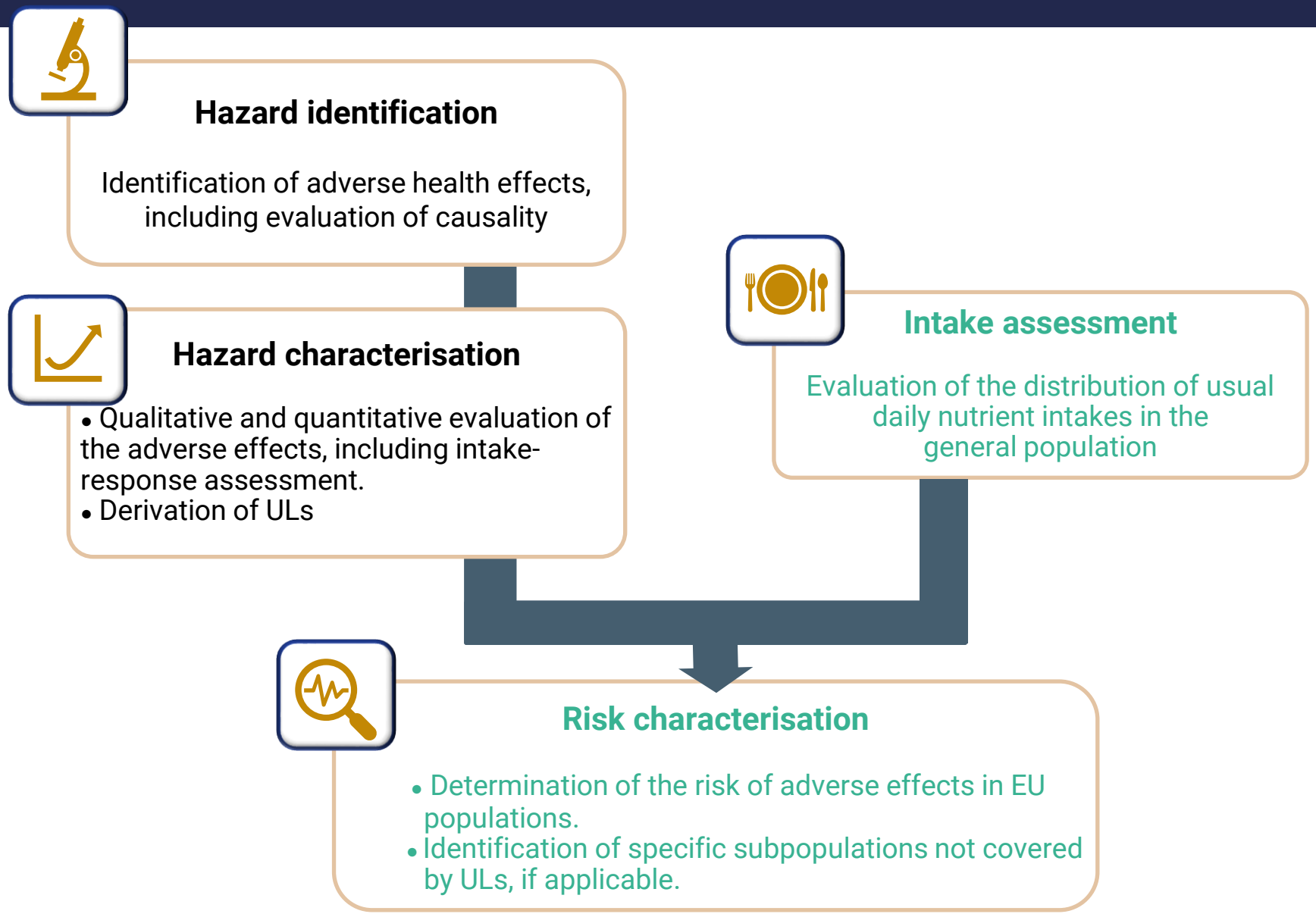
"Given the findings on neurotoxicity and the potentially higher susceptibility of some subgroups in the general population, oral exposure to manganese beyond the normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit'"

SCF 2000 considerations

Estimating intakes of vitamins and minerals and identification of ‘at risk’ populations in the EU

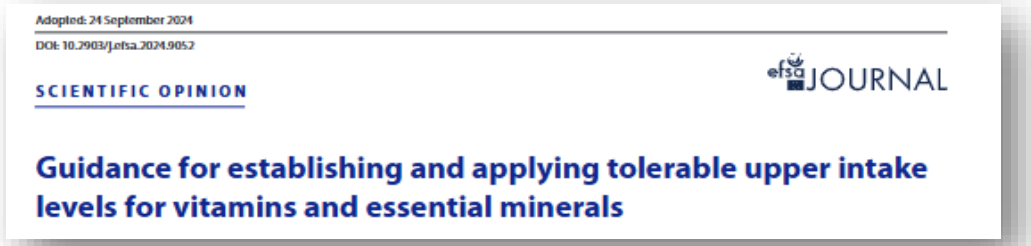
LUCIA FABIANI

FOUR-STEP PROCESS OF NUTRIENT RISK ASSESSMENT



Estimating nutrient intakes from different dietary sources

DATA NEEDS



Adopted: 24 September 2024

DOI: 10.2903/j.efsa.2024.9052

SCIENTIFIC OPINION

efsa JOURNAL

Guidance for establishing and applying tolerable upper intake levels for vitamins and essential minerals

*…"a comprehensive characterisation of the risks associated with the dietary intake of a nutrient requires a **complete intake assessment from all dietary sources**…"*

Estimates of the nutrient intake from its **natural sources** in the diet, including water

Estimates of the nutrient intake from its addition to foods ('**fortified foods**') under the provisions of Regulation (EC) No 1925/2006

Estimates of the nutrient intake from its use in **food supplements** under the provisions of Directive 2002/46/EC.

NUTRIENT INTAKE ASSESSMENTS IN THE CONTEXT OF UL REVISION

FoodEx2 efsa

Harmonised intakes from **background diet*** estimated by EFSA, excluding food supplements

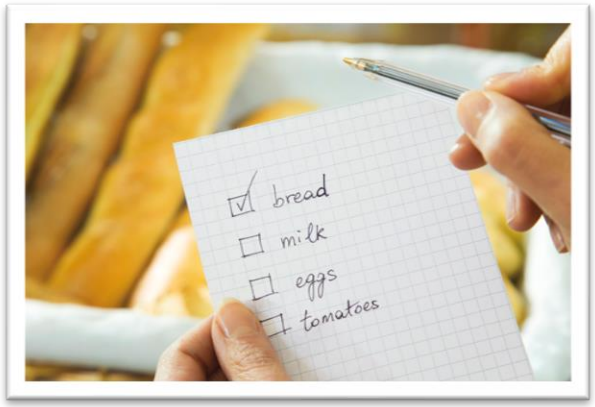
* For vit E, vit B6, vit D (infants), Fe, Se: fortified foods not excluded, but contribution likely to be minimal

Intake estimates **from all dietary sources, including fortified foods and/or food supplements** from national dietary consumption surveys and TDS in European Countries

MINTEL

Nutrient content in **fortified foods** and **food supplements** available in the EU market

DATA SOURCES: EFSA COMPREHENSIVE EUROPEAN FOOD CONSUMPTION DATABASE



- Most complete and detailed collection of food consumption data currently available in the EU.
- Compilation of existing national data on food consumption at individual level (49 surveys, 23 Member States). Since 2011 EFSA has funded 21 dietary surveys on children and/or adults from 21 countries under the **EU Menu project and methodology**
- Data collected through *24-hour recall* or *dietary record* surveys (2-7 days per subject);
- Random samples at national level
  - different age classes, from infants to elderly
  - special population groups (e.g., pregnant women, vegetarians)

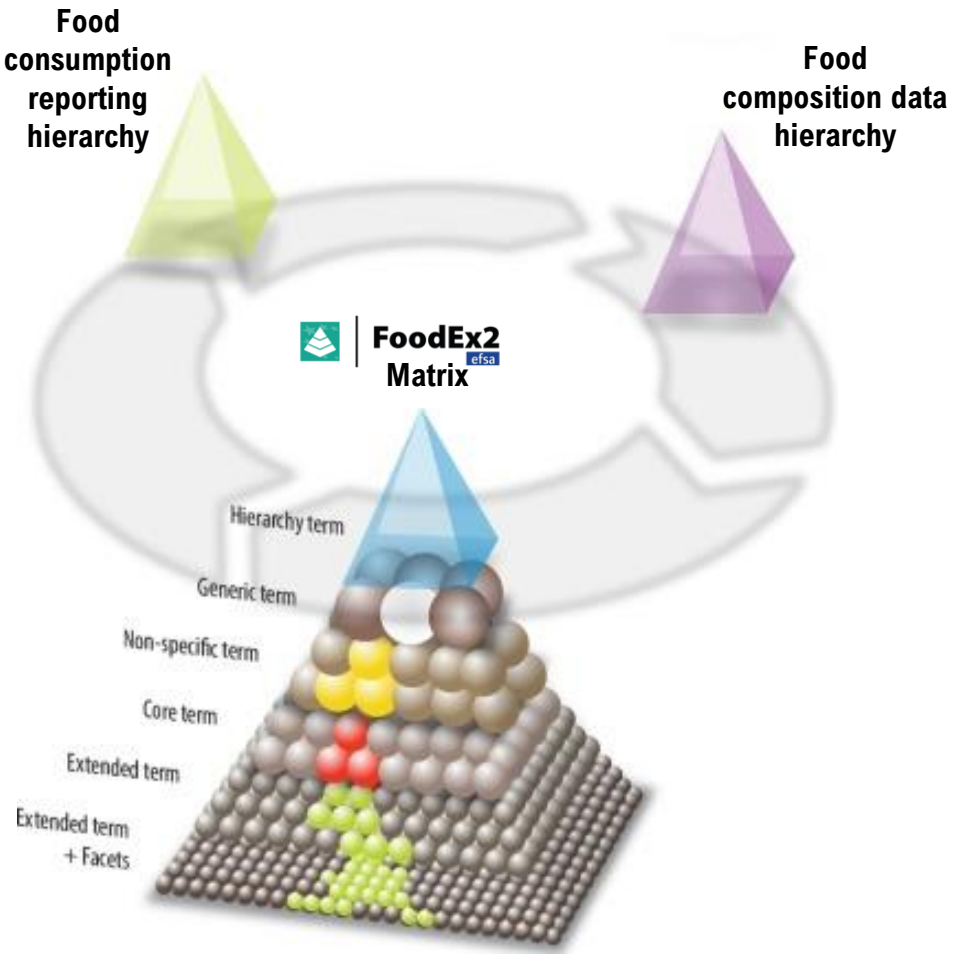
https://www.efsa.europa.eu/en/data-report/food-consumption-data

DATA SOURCES: EFSA FOOD COMPOSITION DATABASE

- Contains food content of vitamins and minerals coded in EFSA's FoodEx2 classification system
- Data provided by 14 national compilers, covering approximately 1,750 foods and composite dishes
- Data are derived from scientific literature, analytical results, other foods considered to have analogous content, calculated from recipes, borrowed from other countries

https://www.efsa.europa.eu/en/data-report/food-composition-data

EFSA INTAKE ESTIMATES

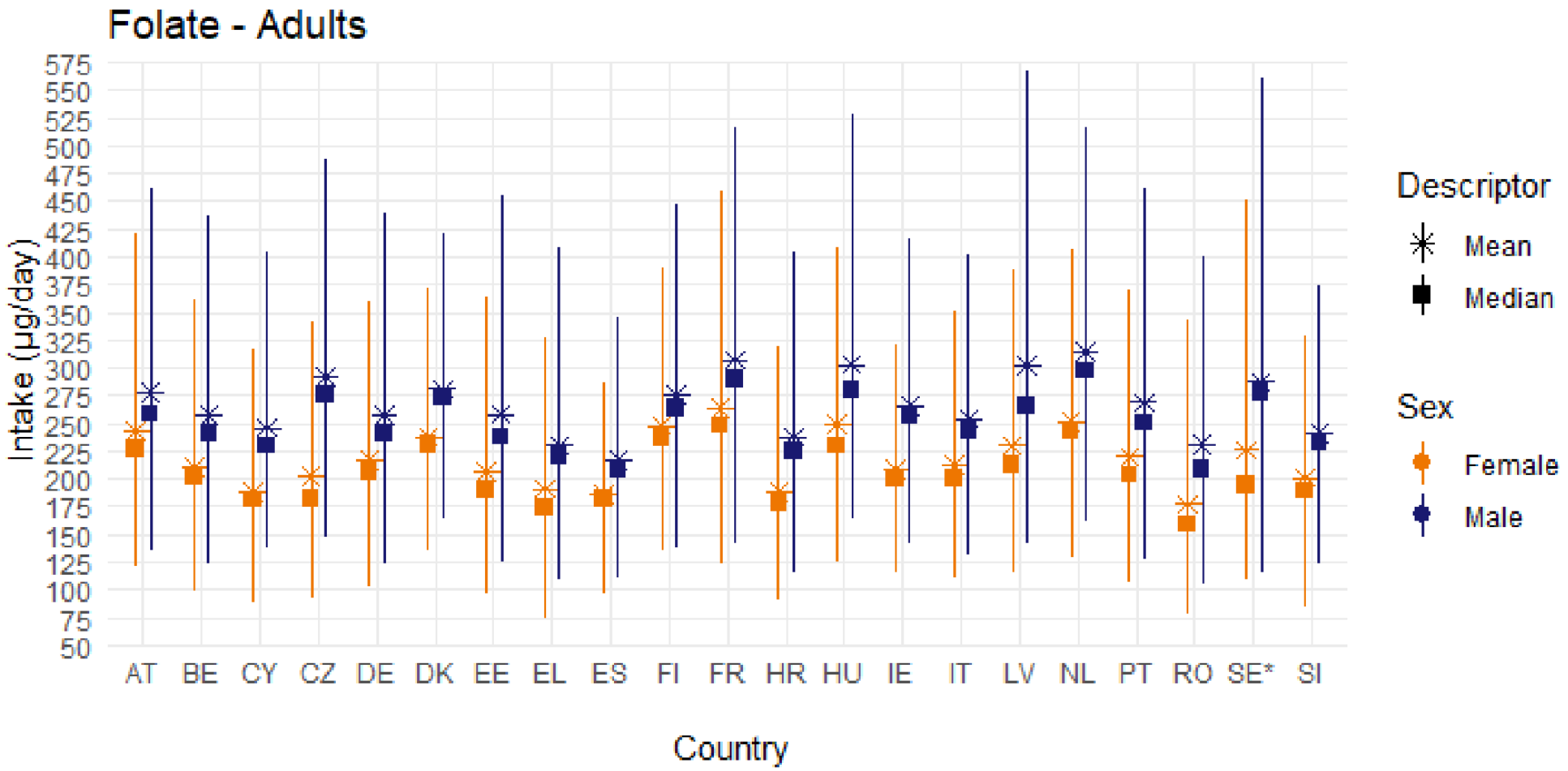


Nutrient intake estimates from background diet mean and high consumers (P95) - by sex and by country

• Infants	4 – 12 months
• Toddlers	1 – 2 years
• Young children	3 – 6 years
• Older children	7 – 9 years
• Young adolescents	10 – 13 years
• Older adolescents	14 – 17 years
• Adults	18 – 65 years
• Older adults	65 years +

- Pregnant women
- Lactating women
- Vegetarians

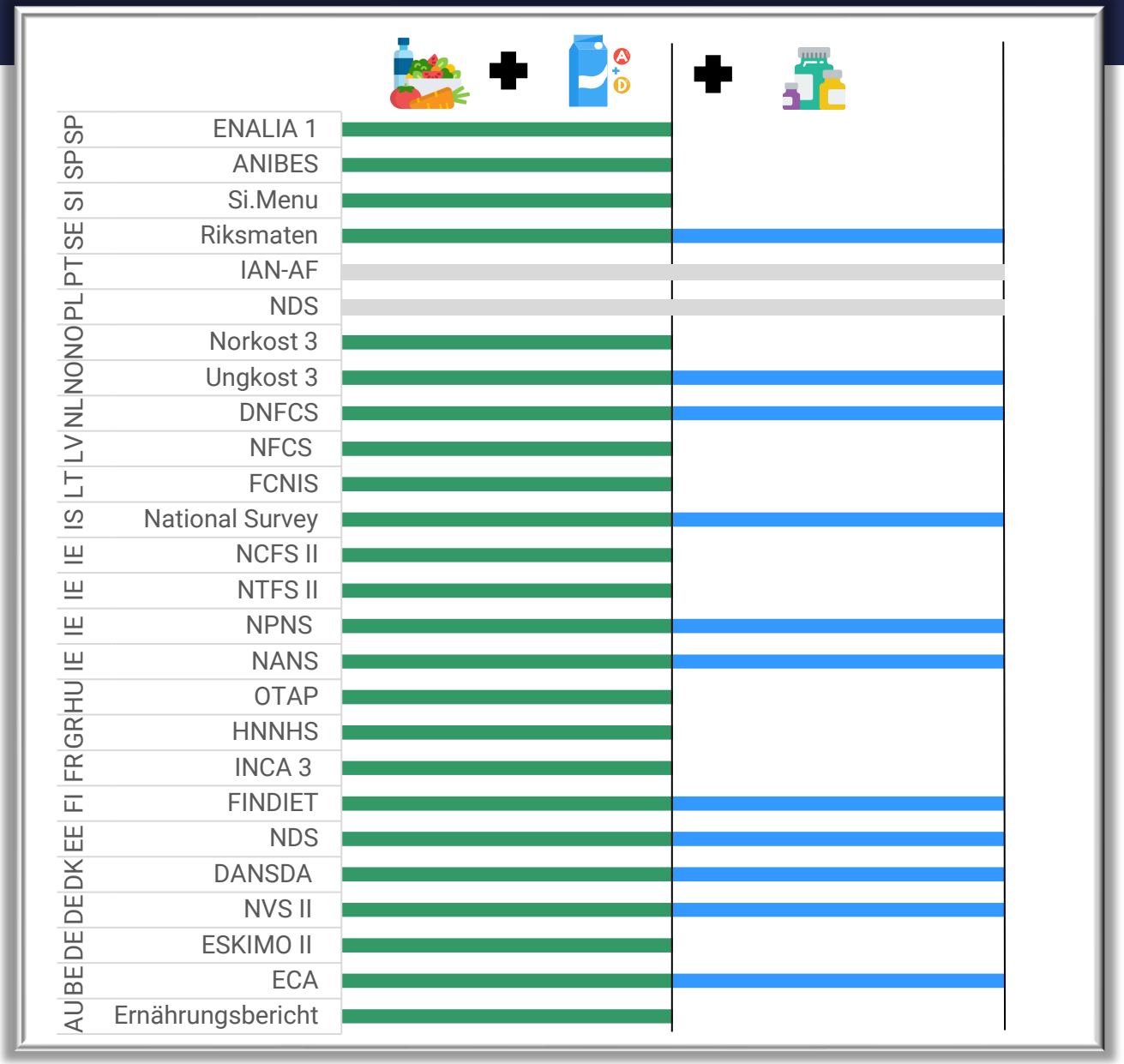
EFSA INTAKE ESTIMATES (FROM BACKGROUND DIET)



AT: Austria; BE: Belgium; CY: Cyprus; CZ: Czech Republic; DE: Germany; DK: Denmark; EE: Estonia; EL: Greece; ES: Spain; FI: Finland; FR: France; HR: Croatia; HU: Hungary; IE: Ireland; IT: Italy; LV: Latvia; NL: The Netherlands; PT: Portugal; RO: Romania; SE: Sweden; SI: Slovenia.

NATIONAL INTAKE ESTIMATES FROM FORTIFIED FOODS AND FOOD SUPPLEMENTS

- Heterogeneous **methods to estimate intake from fortified foods and food supplements** e.g. food propensity questionnaires, 24-h recalls, weighted food diaries
- Estimates of the **contribution of fortified foods and food supplements** to total nutrient intakes in EU populations are scarce (contribution was very much country-dependent)
- A few surveys report P95 for intakes from all sources among **users of food supplements** (NVS II, NANS, NPNS, Ungkost, Norkost)



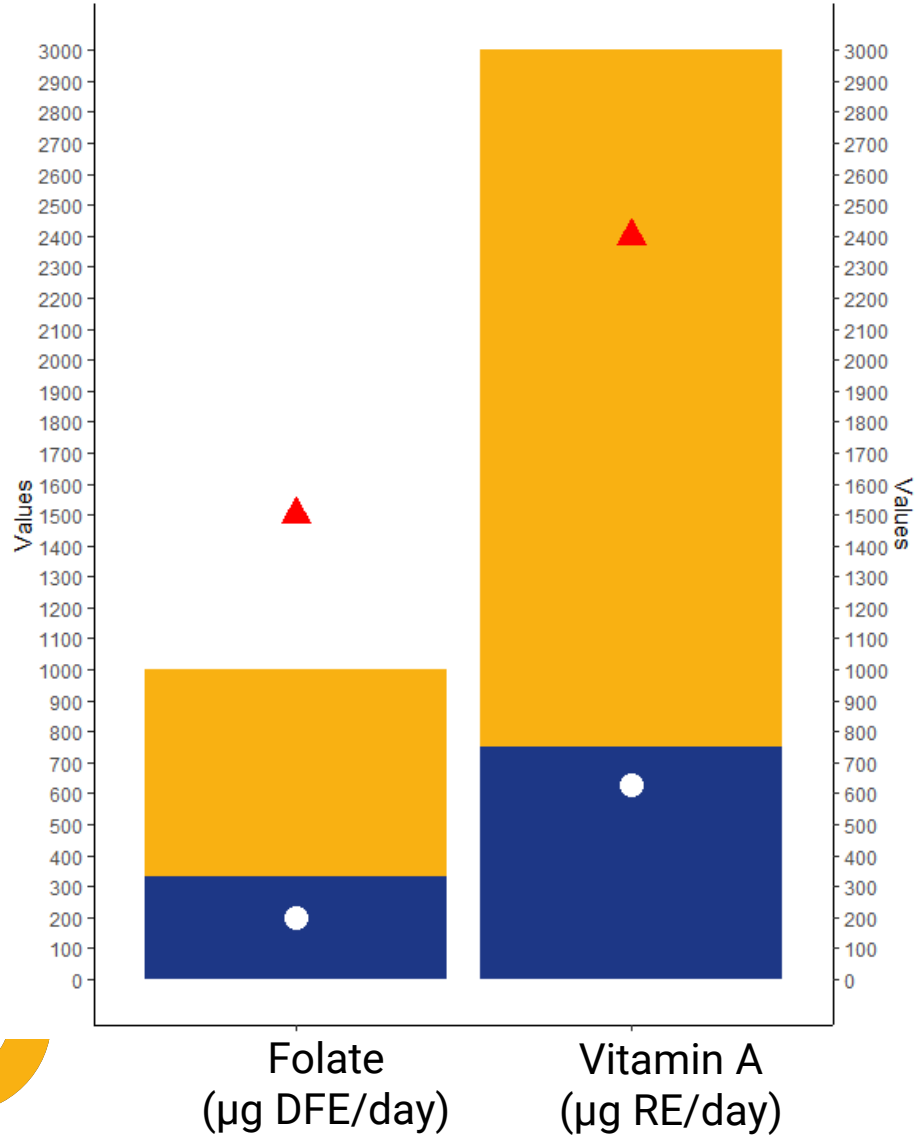
FORTIFIED FOODS AND FOOD SUPPLEMENTS ON THE EU MARKET

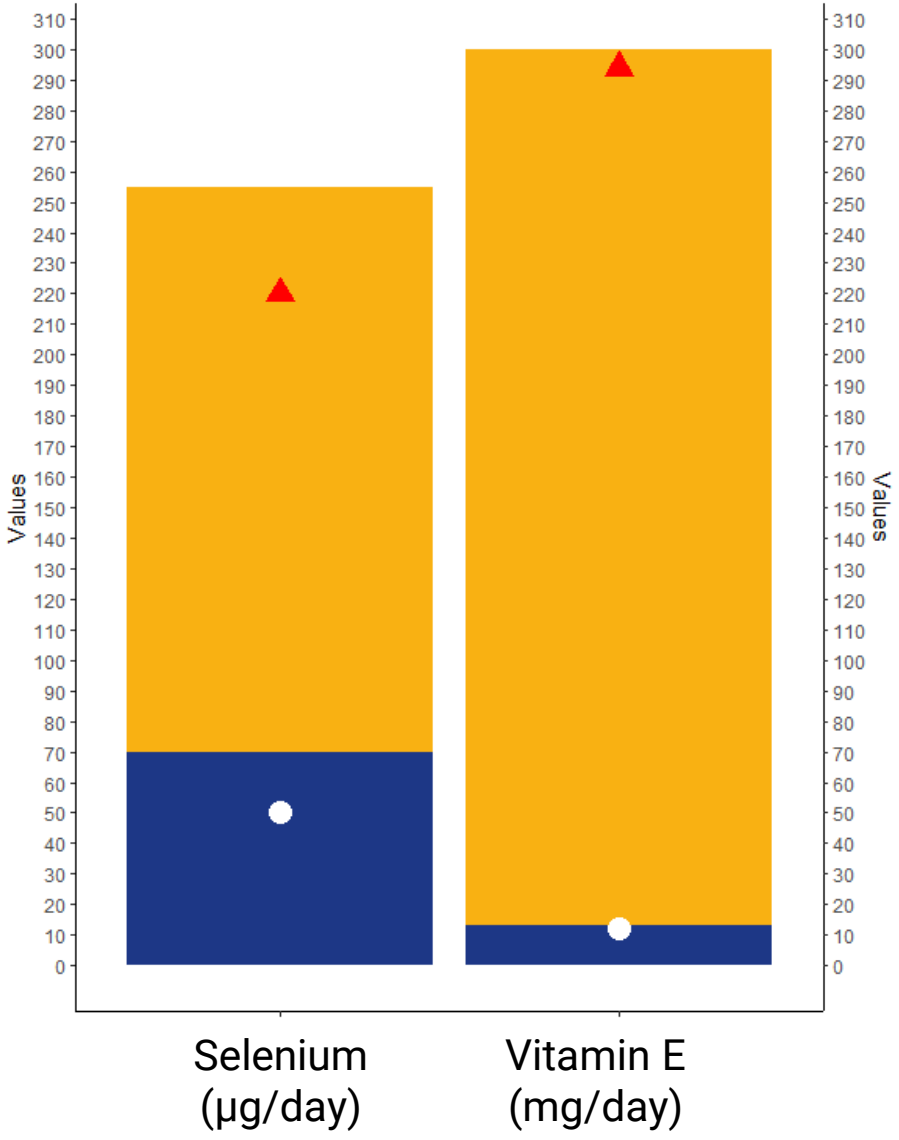
MINTEL

- Based on product labels and nutrition declarations
- Categories of products in the EU market over the last 5 years*
- Content per serving (as recommended by the manufacturers)
- Useful qualitative information, but data not useful to support estimation of actual consumption

*The Mintel GNPD contains information on over 3 million food and beverage products, of which more than 1 million are or have been available on the European food market. Twenty-five out of the twenty-seven EU Member States and Norway are present in the database. The database provides the compulsory ingredient information reported on product labels and the nutrition declaration when available http://www.mintel.com/globalnew-products-database

COMPARISON OF FS DOSES ON THE EU MARKET AND DRVS (ADULT MALES)





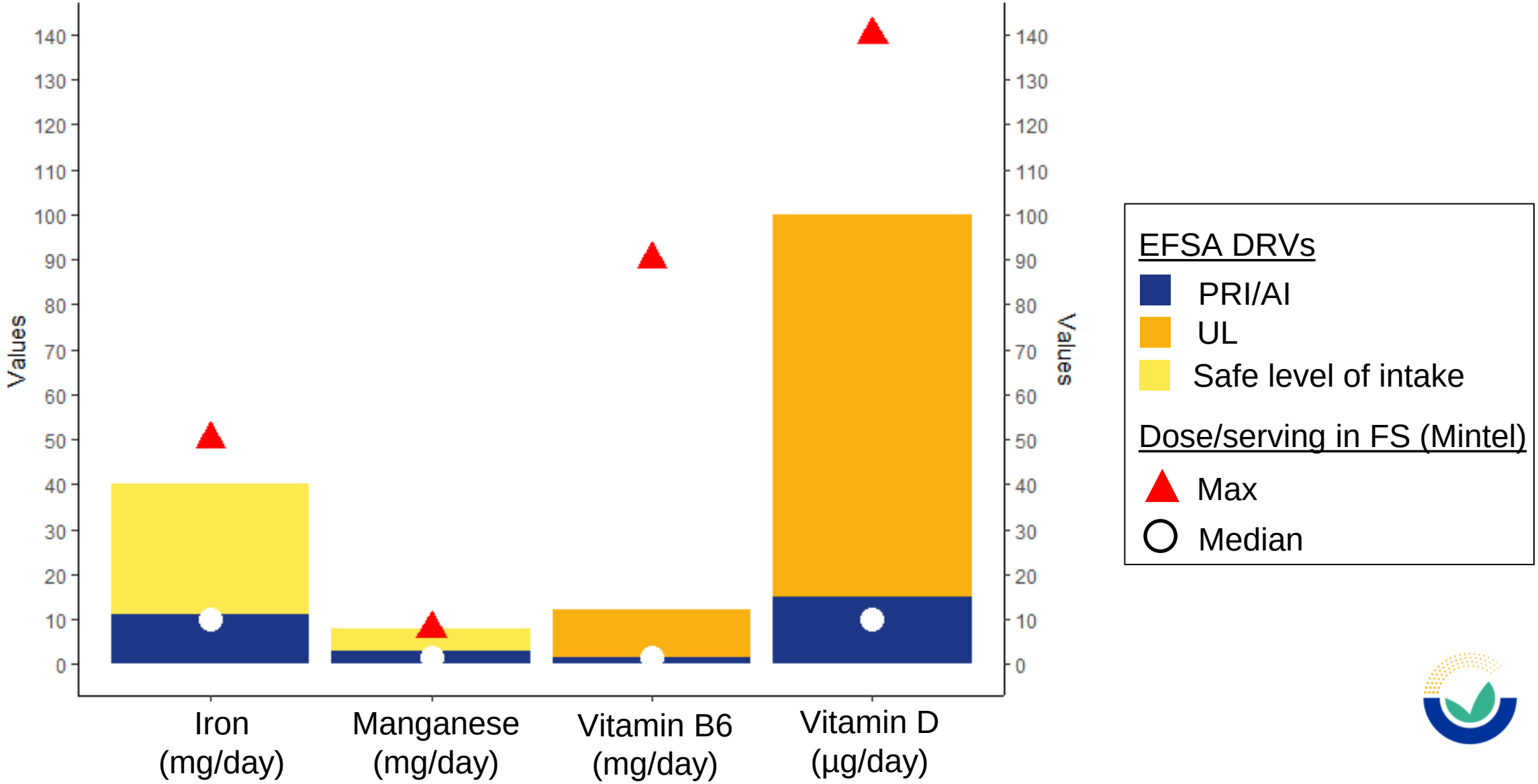
EFSA DRVs

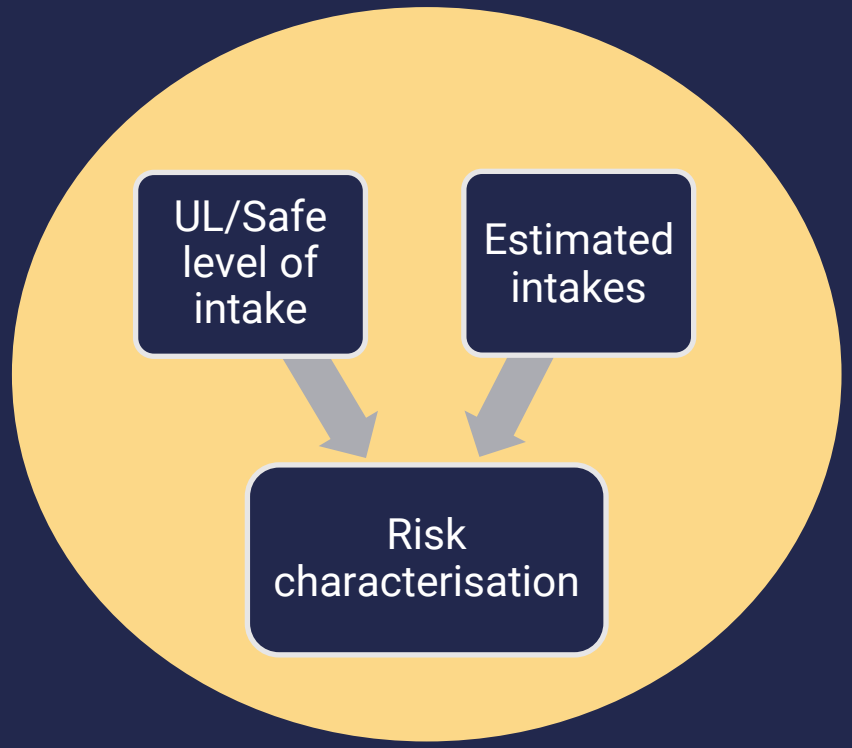
- PRI/AI
- UL

Dose/serving in FS (Mintel)

- Max
- Median

COMPARISON OF FS DOSES IN THE EU MARKET AND DRVS (ADULT MALES)





Identification of ‘at risk’ populations in the EU

RISK OF EXCESS INTAKE: MAIN FINDINGS

Intake estimates in high consumers (P95) from **all sources (including fortified foods and food supplements)** reported in national surveys were **below ULs/Safe Level of Intakes** (few exceptions)

SPECIFIC CONSIDERATIONS

All micronutrients: ULs/Safe Level of Intakes could be exceeded in **regular consumers of high-dose food supplements**

selenium: ULs could be exceeded in regular consumers of **Brazil nuts**

β-carotene: ●smokers should avoid **supplements** containing β-carotene ●**supplemental β-carotene** by the general population should be limited to the purpose of meeting vitamin A requirements

preformed vitamin A: ULs unlikely to be exceeded if consumption of **liver, offal** and products thereof is limited to once per month or less

CONCLUDING REMARKS

Need for **harmonised data collection methods** regarding consumption of **fortified foods and food supplements**

Need for **more complete food composition databases**

Preparatory activities for new phase of EU Menu surveys

EFSA projects to address these limitations

Ongoing project on the **update of the EFSA food composition database**

Submitted questions

ANDRONIKI NASKA

QUESTIONS (1/5)

1. In the context of the shifting to a more prominent plant-based diet, I would be happy to have some insights on the vitamins and mineral added to the so-called plant based food products and the potential risk of deficiency/excess of such micronutrients.

2. How will the ULs affect novel food applications?

3. I would like to discuss the harmonization of mineral addition across Europe. For instance, in the case of iodine, the permitted quantities and even the compounds that can be used vary from country to country. Are there scientific reasons that justify this lack of harmonization?

4. When an upper limit leaves room for food fortification and/or for supplements, which route does the EFSA prefer and why?

QUESTIONS (2/5)

5. What are the reasons for which EFSA recommended Upper Limits are different to those of FDA?

6. Upper level of magnesium

7. Is there a security risk for nutrients for which there is no upper limit such as Vitamins : C, B1, B2, B5, B8, B12, K and minerals : potassium, chromium, silicon ?

QUESTIONS (3/5)

9. Could upper limit be different for specific population such as vegans, athletes, etc ?

10. For food products intended for adults with cancer, do you recommend fortifying with vitamins and minerals, or do we not know enough about the interactions with the disease?
    - If yes, in which elements and at what level?
    - Are there any differences from one cancer to another?

11. Is it possible to give a very brief overview of the maximum levels of vitamins and minerals in each country of the European Union?
    Or present a table showing the variations between the regulations and the threshold values identified by EFSA?

QUESTIONS (4/5)

12. Propolis must be standarized to make it possible for beekeepers to put in on the market, because most of the people are using it without knowing what are they using. On of the analysis that has to be done before propolis make it on the market is mineral composition. What do you think of that?

13. Any update of the approved form of isomeres for vitamin and mineral?

14. Is there a study / research, regarding effectiveness of taking Vitamins via natural foods vs Vitamin pills ? Also, is there a difference due to timing(i.e. during morning, before or after meal etc) of consuming food with certain vitamins/taking pills ?

15. Are there any plans for an UL's review for other micronutrients?

18 QUESTIONS REGARDING MAXIMUM AMOUNTS IN FOODS AND FOOD SUPPLEMENTS

- Asking further information about
  - Timeline
  - Technical bases
  - Implementation
  - Plans for follow-up assessments
  - Standard analytical tolerances

- Outside of EFSA’s remit

Concluding remarks

ANDRONIKI NASKA

TO CONSOLIDATE….

- Engagement
- Comprehensive review
  - Toxicology
  - Epidemiology
- Transparency in describing inherent uncertainties, following standardised procedures
- Tolerable Upper Intake Level (UL) and Safe level of intake.

UL Opinion	DOI
Vitamin A/ β-carotene	10.2903/j.efsa.2024.8814
Vitamin D	10.2903/j.efsa.2023.8145
Vitamin E	10.2903/j.efsa.2024.8953
Vitamin B6	10.2903/j.efsa.2023.8006
Folate	10.2903/j.efsa.2023.8353
Selenium	10.2903/j.efsa.2023.7704
Iron	10.2903/j.efsa.2024.8819
Manganese	10.2903/j.efsa.2023.8413
UL Guidance	10.2903/j.efsa.2024.9052

DRV Finder

Dietary Reference Values for the EU

The DRV Finder* is an interactive tool that gives quick and easy access to EFSA's Dietary reference values (DRVs) for nutrients. It is intended for end users of these values, **such as nutrition and health professionals, risk managers, policy-makers, food manufacturers and scientists.**

DRVs are **science-based nutrient reference values for healthy populations**. They vary by life stage and gender. They have many purposes, such as assessing the nutritional quality of diets of individuals or groups, designing diets (e.g. school meals), creating nutrition guidelines, dietary counselling, setting reference values for food labelling, and for the development of nutrition and food policies.

*DRVs are not nutrient goals or recommendations for individuals.

Do you want to find DRVs per **"Population"** or per **"Nutrients"?**

TARGET POPULATIONS | NUTRIENTS

multimedia.efsa.europa.eu/drvs/index.htm

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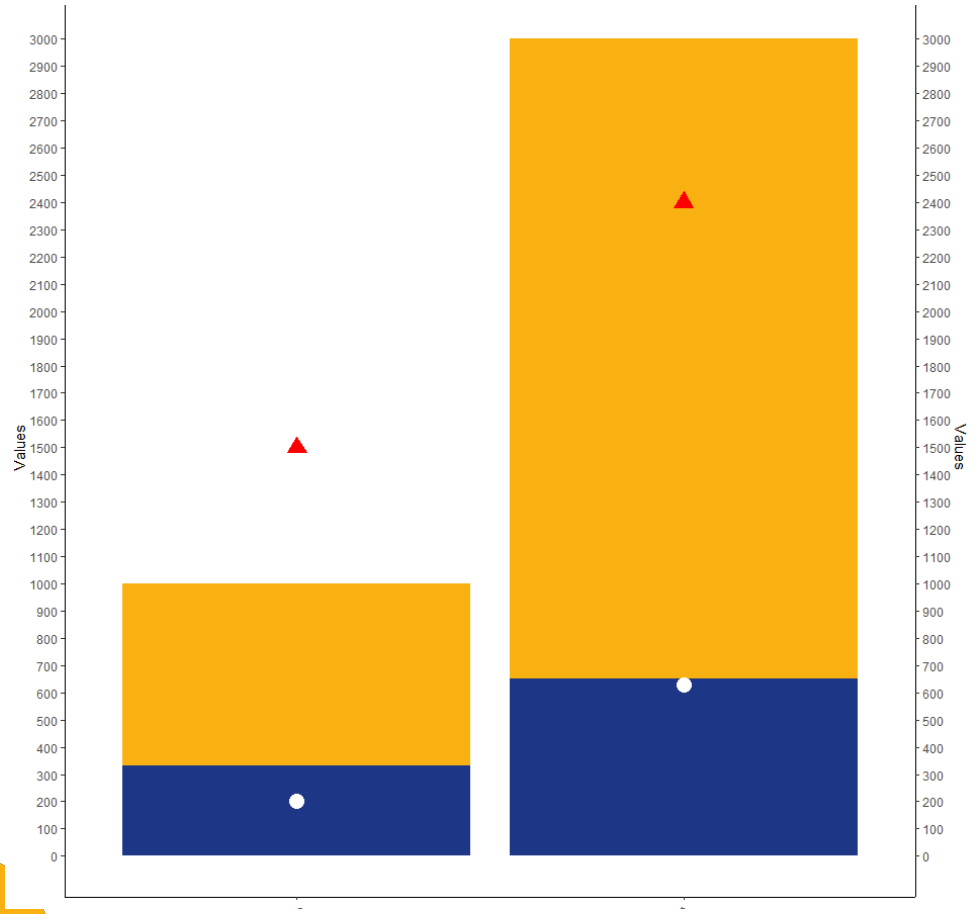
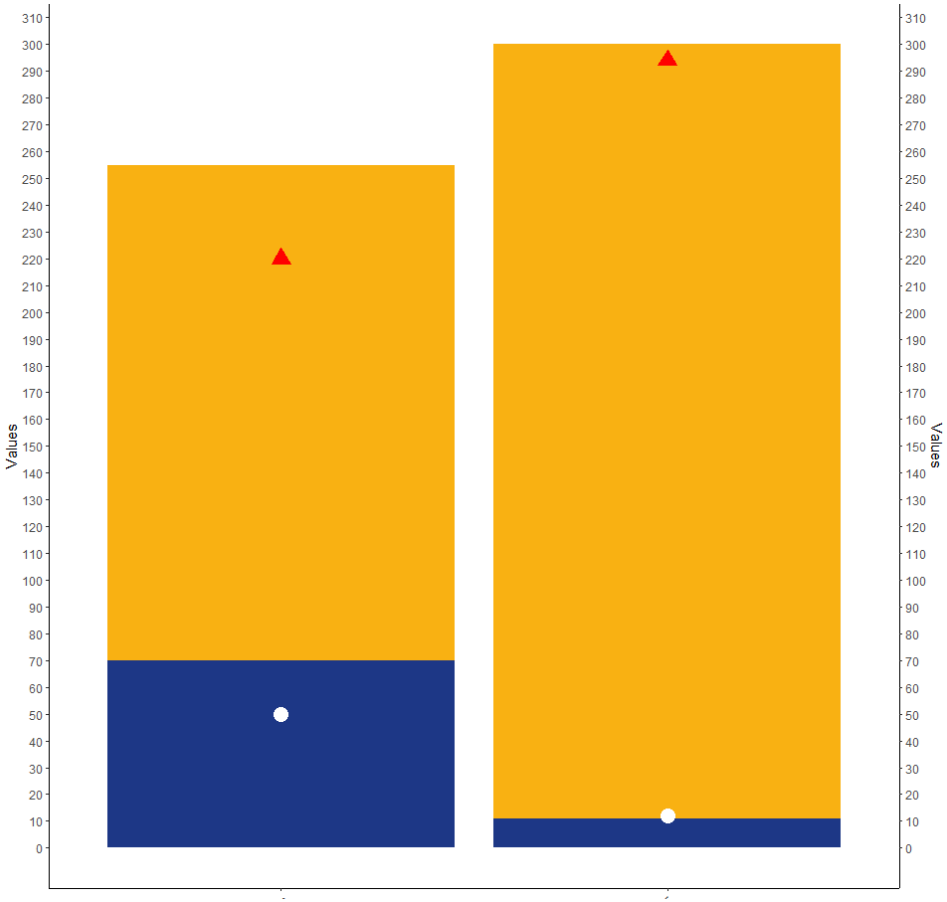


Folate (µg DFE/day)

Vitamin A (µg RE/day)



Selenium (µg/day)

Vitamin E (mg/day)

EFSA DRVs

- PRI/AI
- UL

Dose/serving in FS (Mintel)

- Max
- Median

COMPARISON OF FS DOSES ON THE EU MARKET AND DRVS (ADULT FEMALES)