Current Status of Developing Harmonized Nutrient Reference Values - for Global Application

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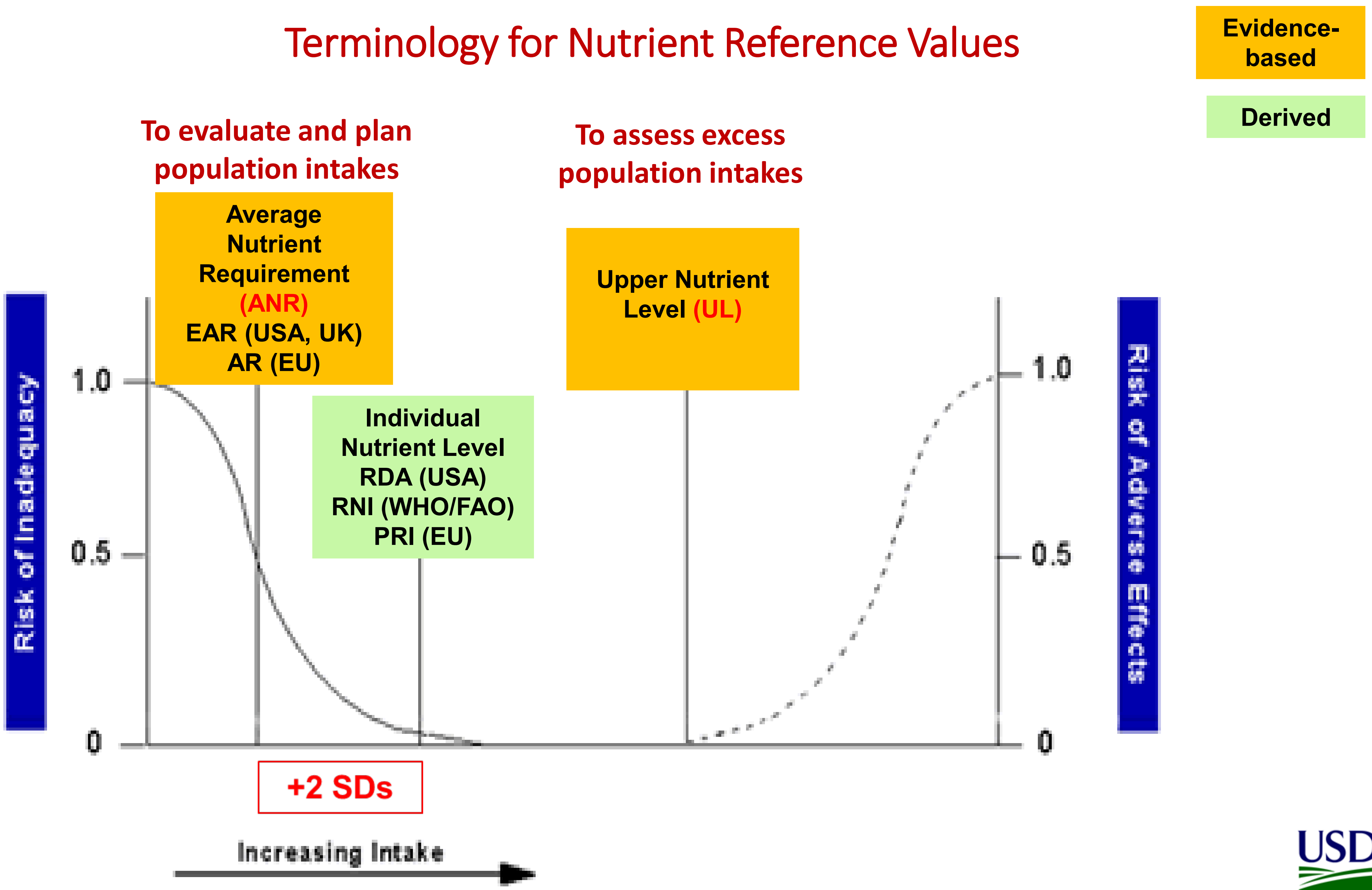
Lindsay H. Allen: Disclosures

- Grant support: Bill & Melinda Gates Foundation, Wellcome Trust
- Board of Directors: American Society for Nutrition (President)
- Scientific Advisory Committees: Micronutrient Forum, Access to Nutrition Index (ATNI), Arla Foods, USAID, NIH.

Overview

- Which DRI/NRV values are needed
- NASEM process to harmonize the APPROACH to setting NRVs (2019)
- NASEM Tool Kit (2020)
- Proposed harmonized VALUES for NRVs (2019)
- Future plans

Terminology for Nutrient Reference Values



Which NRV to use for what purpose

	Individuals	Populations
Assessing Adequacy	Estimated Average Requirement (EAR)	Estimated Average Requirement (EAR)
Planning Diets	Recommended Dietary Allowance (RDA)	Distribute intakes between EAR and UL

Target Median Intake

Planning Nutritionally Adequate Diets for Groups: Methods Used to Develop Recommendations for a Child and Adult Care Food Program

Suzanne P Murphy, Ann L Yaktine, Alicia L Carriquiry

Advances in Nutrition, Volume 12, Issue 2, March 2021, Pages 452–460,

Limitations of available Nutrient Reference Values

- NRVs used for many purposes: assessment and education, nutrition planning and monitoring, food based dietary guidelines, food programs, fortification, research, labeling.
- But, many countries/agencies have no or few ARs or ULs, including WHO/FAO.
- Instead, they use RDAs/RNIs, which meet requirements of 98.5% of people in a sex/age group and substantially overestimates the prevalence of nutrient inadequacy.
- Having ARs and ULs to enable assessment of intake adequacy and safety is probably much more important than "fine-tuning" existing RDAs/NRIs every 5-10 years.
- It's unlikely current gaps will be filled by more science (cost, difficulty especially for perinatal period and young children, lack of biomarkers). Cost of (re)doing Systema Reviews is prohibitive.

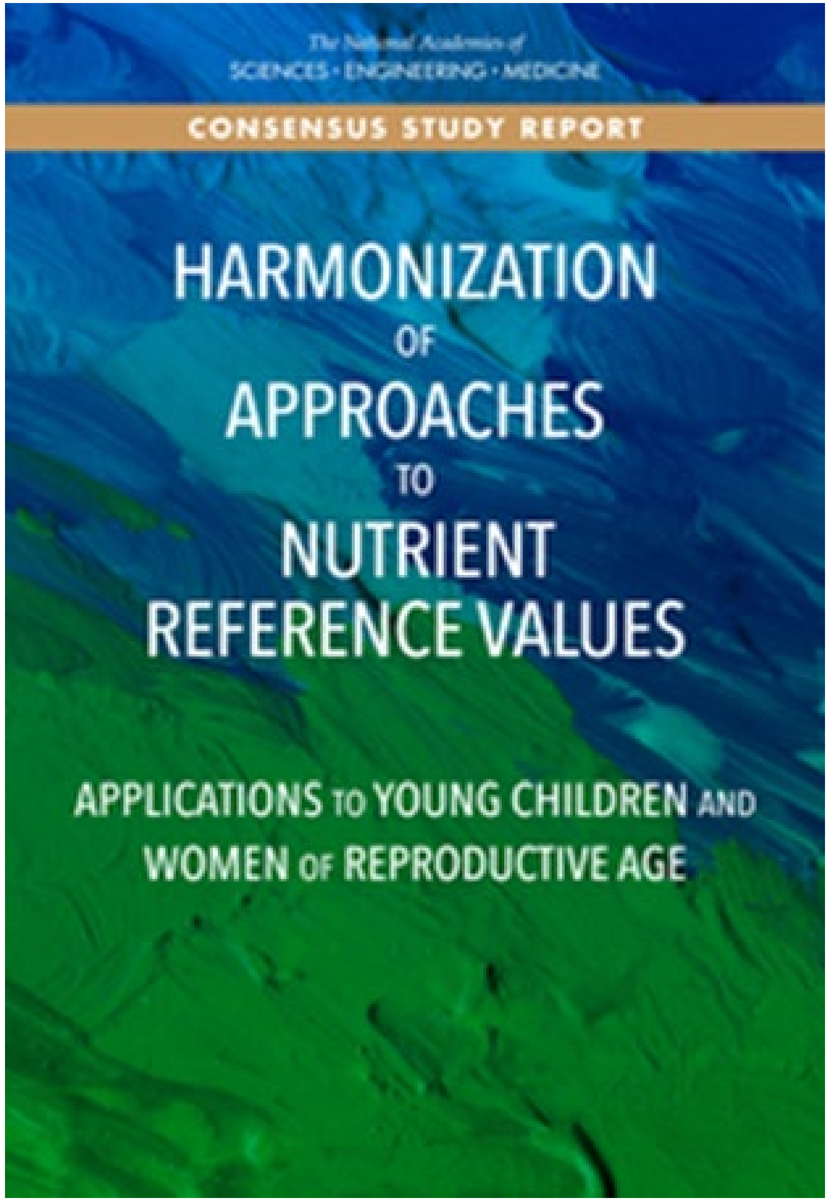
USDA

Why the Derivation of Nutrient Reference Values Should be Harmonized and How It Can be Accomplished

Ann L Yaktine, Janet C King, Lindsay H Allen

Advances in Nutrition, Volume 11, Issue 5, September 2020, Pages 1102–1107,

- Improve objectivity and transparency of values
- Provide common basis for nutrient review panels
- Improve access to resources for LMICs to adapt existing DRIs to their population.
- Evaluation of nutrient intake inadequacy across populations.
- Common basis for establishing nutrition policies e.g. feeding programs, food fortification, dietary guidance, product formulation, regulation and trade.



2019

Purpose: to describe a generic method for developing NRVs

Focus is on how to set an **AR and a UL,** and improve access to tools and data for setting intake recommendations.

Tool Kit describes generic resources needed: available systematic reviews and data bases, how local or regional factors affect requirements (genetics, bioavailability from food, infections).

Choices when setting recommendations:

- Derive new set of NRVs? or
- modify some existing "local" NRVs? or
- use existing NRVs published by e.g. IOM, EFSA

- Or, use Harmonized (combined) NRVs……………………

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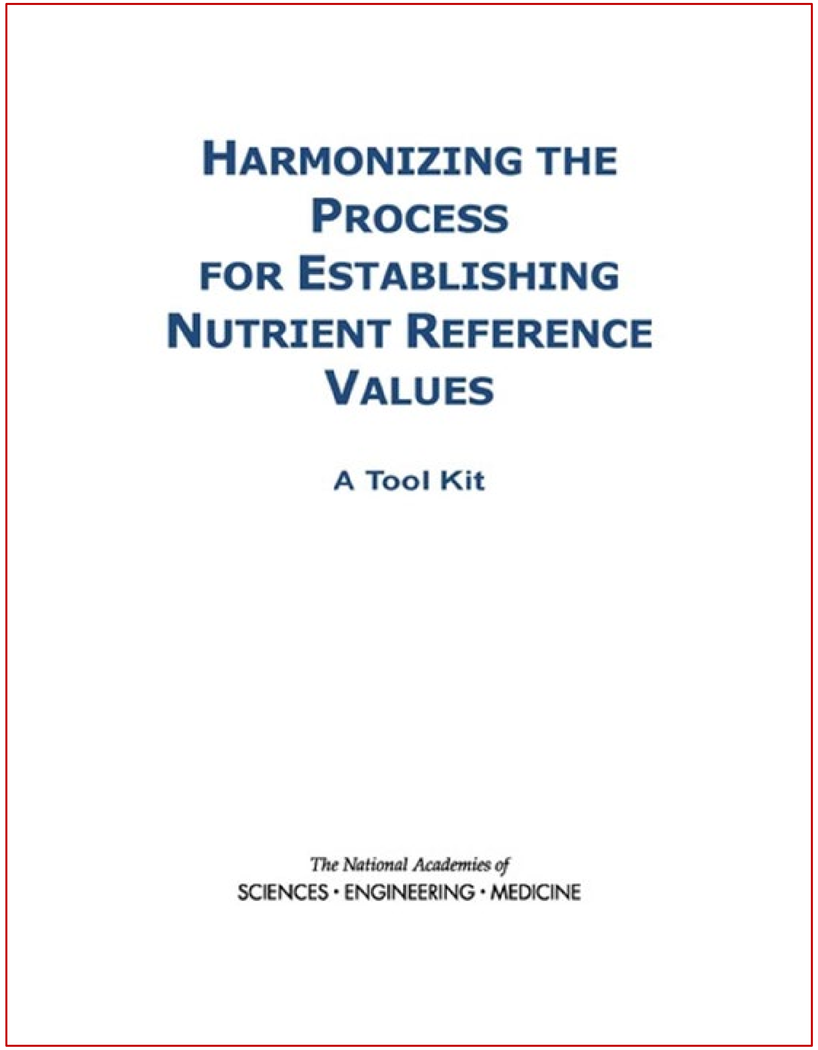
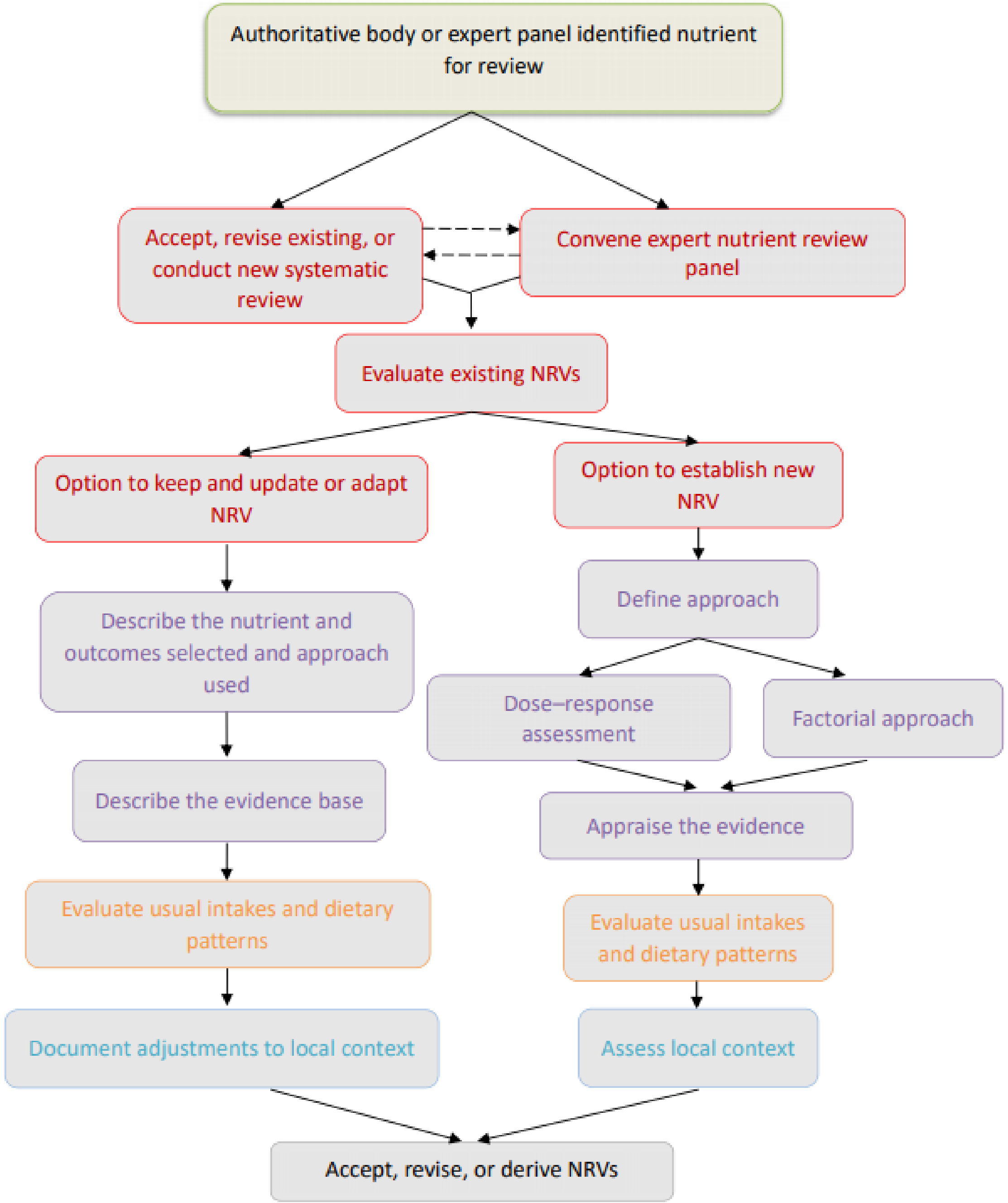
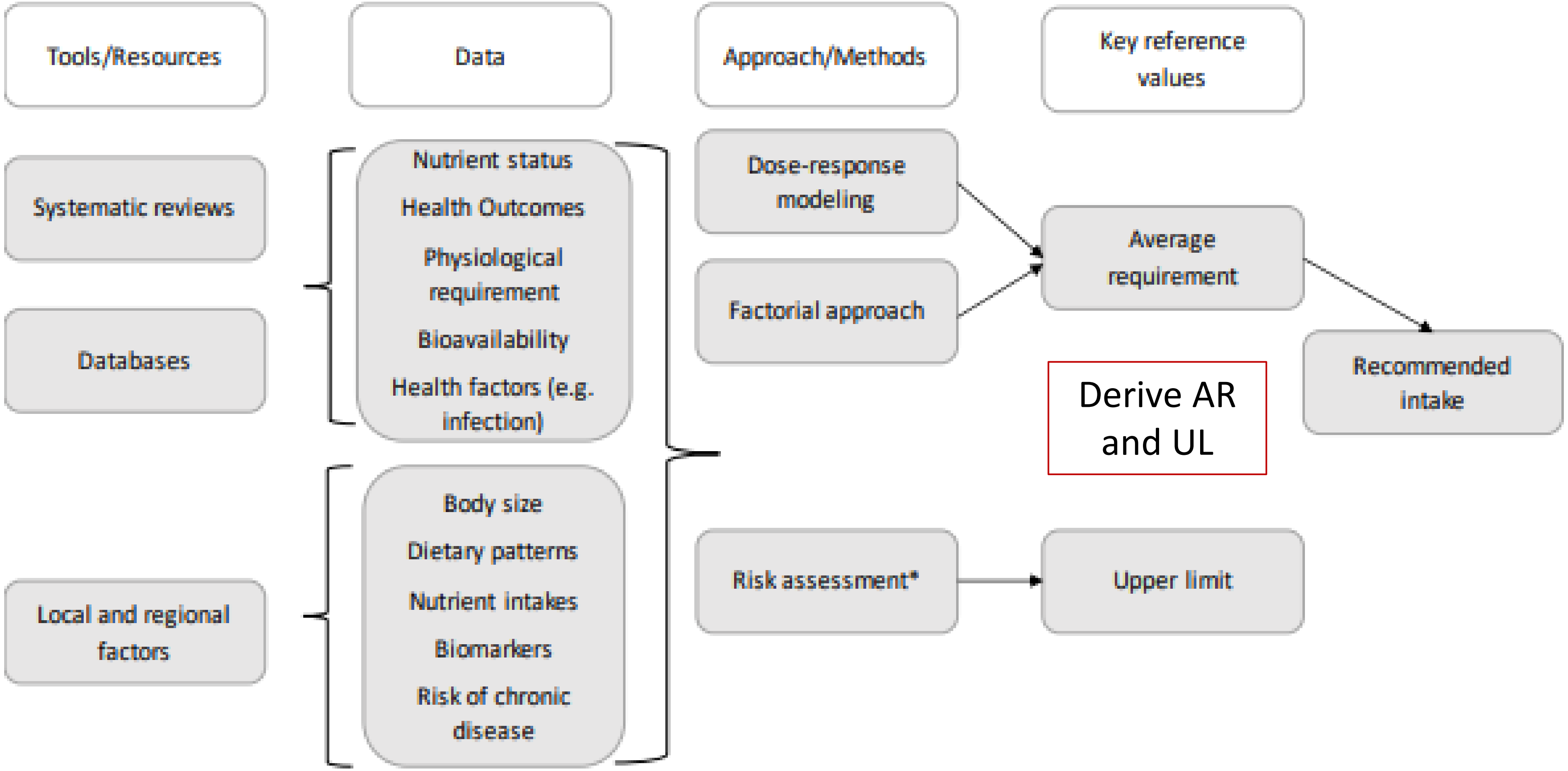

HARMONIZING THE PROCESS FOR ESTABLISHING NUTRIENT REFERENCE VALUES
A Tool Kit
The National Academies of
SCIENCES · ENGINEERING · MEDICINE


Authoritative body or expert panel identified nutrient for review
Accept, revise existing, or conduct new systematic review
Convene expert nutrient review panel
Evaluate existing NRVs
Option to keep and update or adapt NRV
Option to establish new NRV
Describe the nutrient and outcomes selected and approach used
Define approach
Dose–response assessment
Factorial approach
Describe the evidence base
Appraise the evidence
Evaluate usual intakes and dietary patterns
Evaluate usual intakes and dietary patterns
Document adjustments to local context
Assess local context
Accept, revise, or derive NRVs

Framework for deriving key NRVs – 4 core elements

Collect data from SRs and databases

Main local factor = bioavailability



Examples of processes used by agencies developing DRVs

	FAO/WHO	EFSA	NASEM
Working group(s)	Global expert group	EFSA staff, external panel, & other European scientists	Federal steering committee & expert panel
Steps	Scoping review (available literature)	Problem formulation (population sub-groups, sources of intake, health outcomes, sub-questions, methods & eligible studies)	Literature scan to confirm sufficient evidence
	Problem formulation (key questions in PICO format) + public consultation	Study search, data extraction & evaluation	Systematic review
	Systematic reviews	Systematic review	Panel review and draft report
	Expert group review	Draft opinion	External review
	Draft document	Public consultation	NASEM approval
	External & public reviews	Final report	Final report
	Final report		
Timeline	12-36 months	6-9 months (10 yrs, 34 nutrients)	18 months
Cost	$10-100 K per review (multiple reviews) + staff & volunteer time	??	~$1M per nutrient

Perspective: Proposed Harmonized Nutrient Reference Values for Populations FREE

Lindsay H Allen ✉, Alicia L Carriquiry, Suzanne P Murphy

Advances in Nutrition, nmz096, https://doi.org/10.1093/advances/nmz096

Published: 08 November 2019 **Article history ▾**

2 core values needed for population assessment; AR and UL

Purpose: to **harmonize ARs and ULs** for as many nutrients as possible, combining best existing values and applying scientific judgement.

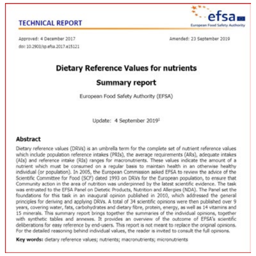
Perspective: Proposed Harmonized Nutrient Reference Values for Populations FREE

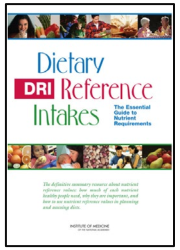
Lindsay H Allen ✉, Alicia L Carriquiry, Suzanne P Murphy

Advances in Nutrition, nmz096, https://doi.org/10.1093/advances/nmz096

Published: 08 November 2019 **Article history** ▾

Purpose: to **harmonize AR and UL values** for as many nutrients as possible, based on EFSA, IOM values and scientific judgement.





Justification

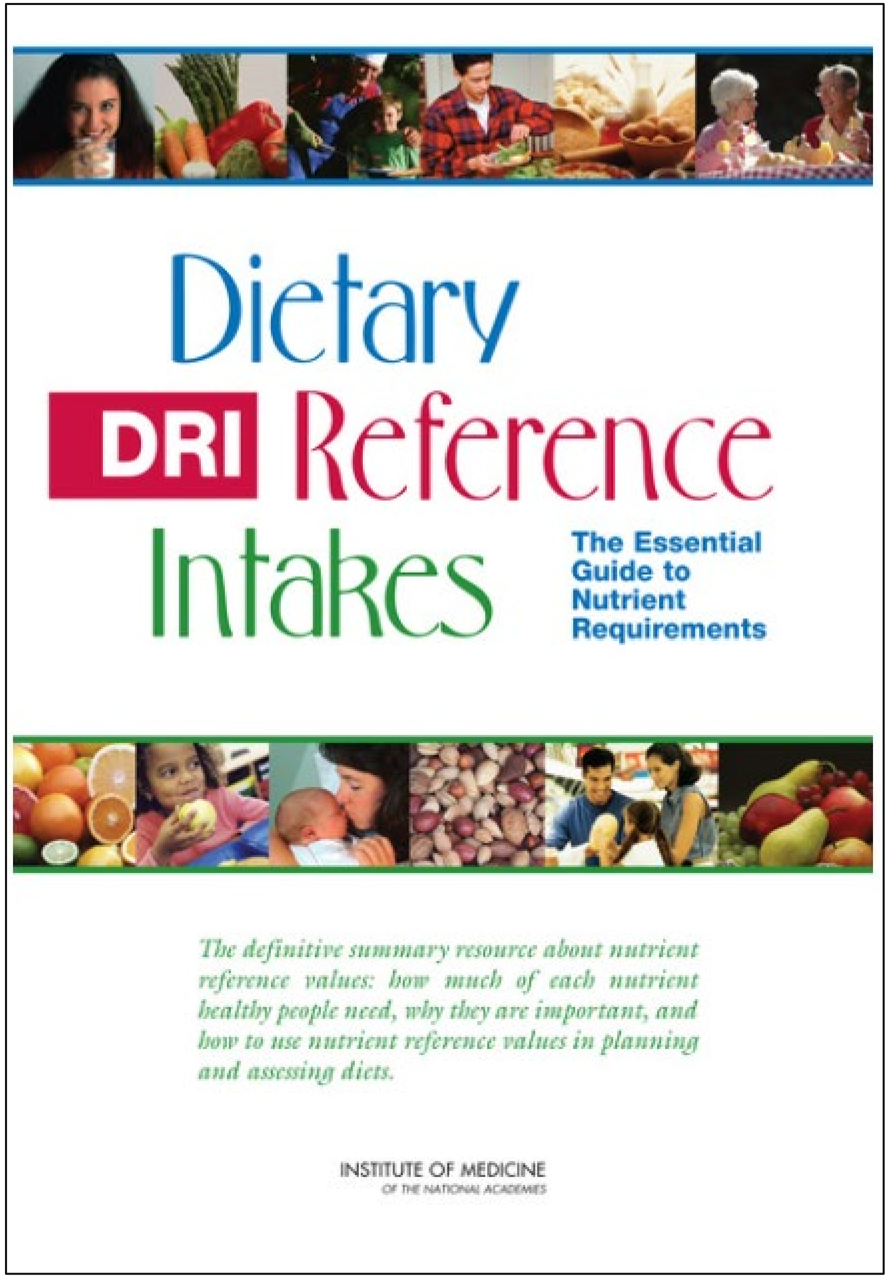
- All requirement recommendations are uncertain and vary among individuals.
- After correction for bioavailability from diet (Fe, Zn) unlikely that actual requirements vary much across population groups. A high prevalence of deficiency based on biomarkers does not mean requirements should be higher – rather they are not met.
- Using NRVs to assess or plan population intakes relies on variably accurate food composition data.
- Nutrition programs and population evaluations are ongoing and H-NRVs are needed.

Why develop Harmonized Nutrient Reference Values?

- Unlikely that requirements for absorbed nutrients differ much across populations. (Use for setting Dietary Guidelines is what differs.)
- WHO/FAO has no ARs or ULs, except for B12 and folate.
- IOM and EFSA have no ARs for 6 nutrients (just AIs).
- Many IOM and EFSA values for infants/children extrapolated from infant AI, or adult AR or AI, causing implausible jumps in NRVs.
  - e.g. calcium AI 260 mg at 7-12 mo. → EAR 500 mg at 1-3 years.
- True requirements are variable and estimates of bioavailability and intakes always uncertain.
- Cost and time needed to develop/modify existing or additional NRVs prohibitive especially with systematic reviews (although Tool Kit will help). Missing values for e.g. infants/children a challenge.
- Programs and evaluations are ongoing and H-NRVs are needed.

Institute of Medicine (IOM)

(now National Academies of Science, Engineering and Medicine)



European Food Safety Authority

(EFSA)

TECHNICAL REPORT

efsa
European Food Safety Authority

Approved: 4 December 2017 Amended: 23 September 2019
doi: 10.2903/sp.efsa.2017.e15121

Dietary Reference Values for nutrients

Summary report

European Food Safety Authority (EFSA)

Update: 4 September 2019[1]

Abstract

Dietary reference values (DRVs) is an umbrella term for the complete set of nutrient reference values which include population reference intakes (PRIs), the average requirements (ARs), adequate intakes (AIs) and reference intake (RIs) ranges for macronutrients. These values indicate the amount of a nutrient which must be consumed on a regular basis to maintain health in an otherwise healthy individual (or population). In 2005, the European Commission asked EFSA to review the advice of the Scientific Committee for Food (SCF) dated 1993 on DRVs for the European population, to ensure that Community action in the area of nutrition was underpinned by the latest scientific evidence. The task was entrusted to the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). The Panel set the foundations for this task in an inaugural opinion published in 2010, which addressed the general principles for deriving and applying DRVs. A total of 34 scientific opinions were then published over 9 years, covering water, fats, carbohydrates and dietary fibre, protein, energy, as well as 14 vitamins and 15 minerals. This summary report brings together the summaries of the individual opinions, together with synthetic tables and annexes. It provides an overview of the outcome of EFSA's scientific deliberations for easy reference by end-users. This report is not meant to replace the original opinions. For the detailed reasoning behind individual values, the reader is invited to consult the full opinions.

Key words: dietary reference values; nutrients; macronutrients; micronutrients

USDA

Harmonized Average Requirements and Harmonized Upper Levels

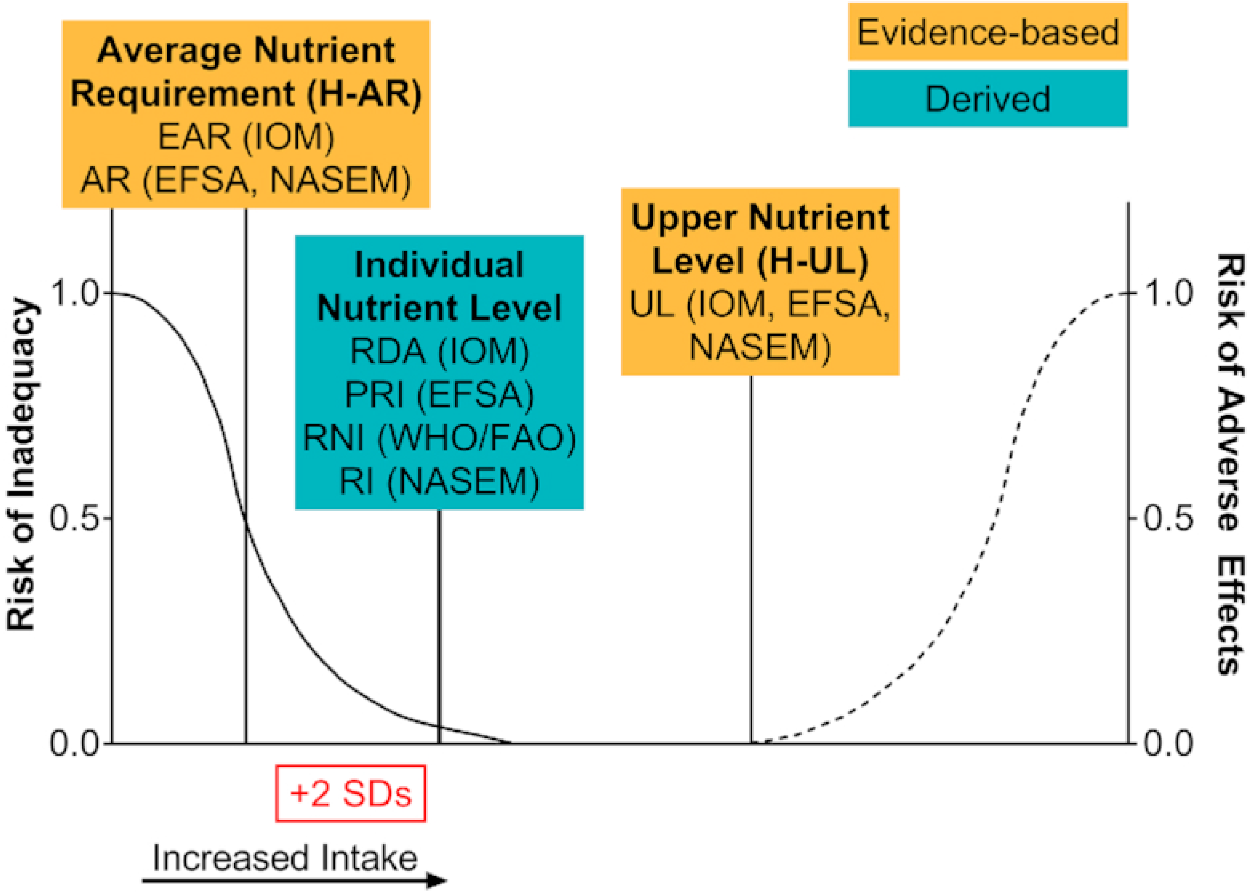
We propose

H-ARs

and

H-ULs

for global application



Advances in Nutrition, nmz096, https://doi.org/10.1093/advances/nmz096

How we developed H-ARs

- Used EFSA for most ARs because set in 2014-2017.
- (IOM set 1998-2001, except for vitamin D and Ca in 2011).
- EFSA did systematic reviews on some nutrients (IOM only on D and Ca).
- <u>BUT</u> EFSA has AR for only 7 vitamins and 3 minerals (similar to IOM's).

  IOM has AR for 10 vitamins and 9 minerals.
- So used IOM if no EFSA (P, Cu, Mo, I, Mg, Se).
- If large differences between EFSA and IOM values, reasons for our selection explained (e.g. used different studies or criteria).

Source of values for Harmonized Average Requirements (H-ARs) for vitamins and minerals: IOM vs. EFSA[1]

Nutrient	IOM EAR-Children[2]	IOM EAR – Adults[3]	EFSA AR – Children[2]	EFSA AR- Adults[3]	H-AR decision	H-AR functional outcome[4]
Vitamin A (µg RE/d)	210-630	500-625	205-580	490-570	Use EFSA	Adequate liver stores
Vitamin C (mg/d)	13-63	60-75	15-85	80-90	Use EFSA	Balance; adequate body pool
Vitamin D (µg/d)	10	10			Use IOM	Serum 25(OH) vitamin D
Vitamin E (mg/d)	5-12	12			Use IOM	Prevent peroxide-induced hemolysis
Thiamin (mg NE/d)	0.4-1.0	0.9-1.0	0.3[5]	0.6[5]	Use IOM	Normal erythrocyte transketolase activity
Riboflavin (mg/d)	0.4-1.1	0.9-1.1	0.5-1.4	1.3	Use EFSA	Urinary riboflavin excretion
Niacin (mg/d)	5-12	11-12	5.5[5]	11[5]	Use IOM	Excretion of niacin metabolites
Vitamin B6 (mg/d)	0.4-1.1	1.1-1.4	0.5-1.5	1.3-1.5	Use EFSA	Plasma pyridoxal 5-phosphate
Vitamin B12 (µg/d)	0.7-2.0	2.0			Use IOM	Maintain hematological status and normal serum B12
Folate (µg DFE/d)	120-330	320	90-250	250	Use EFSA	Serum and red blood cell folate
Calcium (g/d)	500-1100	800-1000	390-960	750-860	Use EFSA	Factorial approach
Phosphorus (g/d)	380-1055	580			Use IOM	Serum phosphate
Copper (mg/d)	2.60-6.85	7.0			Use IOM	Plasma copper, serum ceruloplasmin, platelet copper
Molybdenum (µg/d)	13-33	34			Use IOM	Balance studies
Iodine (µg/d)	65-95	95			Use IOM	Thyroid accumulation and turnover
Iron (mg/d)	3.0-7.7	5.0-8.1	5-8	6-7	Use EFSA	Factorial approach
Magnesium (mg/d)	65-340	255-350			Use IOM	Balance studies
Selenium (µg/d)	17-45	45			Use IOM	Plasma glutathione peroxidase activity
Zinc (mg/d)	2.5-8.5	6.8-9.4	3.6-11.8	6.2-12.7	Use EFSA	Null balance

Harmonized Average Requirements (H-ARs) for protein and vitamins (2a) and minerals (2b)[1]

2a	Protein	Vit A	Vit C[3]	Vit D	Vit E	Thiamin	Riboflavin	Niacin	Vit B_6	Folate[4]	Vit B12	*Pantothenic acid*	*Biotin*	*Choline*
	(g/kg/d)[2]	(µg RAE)	(mg)	(µg)	(mg α-tocopherol)	(mg)	(mg)	(mg)	(mg)	(µg DFE)	(µg)	*(mg)*	*(mg)*	*(mg)*
Source	EFSA	EFSA	EFSA	IOM	IOM	IOM	EFSA	IOM	EFSA	EFSA	IOM	*EFSA*	*EFSA*	*EFSA*
Life Stage[7]														
Infants														
7-11 mo	1.12	190												
Children														
1–3 y	0.79	205	15	10	5	0.4	0.5	5	0.5	90	0.7	*3.2*	*16*	*112*
4-6 y	0.69	245	25	10	6	0.5	0.6	6	0.6	110	1	*3.2*	*20*	*136*
7-10 y	0.75	320	40	10	6	0.5	0.8	6	0.9	160	1	*3.2*	*20*	*200*
Males														
11-14 y	0.73	480	60	10	9	0.7	1.1	9	1.2	210	1.5	*4*	*28*	*272*
15-17 y	0.71	580	85	10	12	1	1.4	12	1.5	250	2	*4*	*28*	*320*
18-24 y	0.66	570	90	10	12	1	1.3	12	1.5	250	2	*4*	*32*	*320*
25-50 y	0.66	570	90	10	12	1	1.3	12	1.5	250	2	*4*	*32*	*320*
51-70 y	0.66	570	90	10	12	1	1.3	12	1.5	250	2	*4*	*32*	*320*
>70 y	0.66	570	90	10	12	1	1.3	12	1.5	250	2	*4*	*32*	*320*
Females														
11-14 y	0.71	480	60	10	9	0.7	1.1	9	1.2	210	1.5	*4*	*28*	*272*
15-17 y	0.68	490	75	10	12	0.9	1.4	11	1.3	250	2	*4*	*28*	*320*
18-24 y	0.66	490	80	10	12	0.9	1.3	11	1.3	250	2	*4*	*32*	*320*
25-50 y	0.66	490	80	10	12	0.9	1.3	11	1.3	250	2	*4*	*32*	*320*
51-70 y	0.66	490	80	10	12	0.9	1.3	11	1.3	250	2	*4*	*32*	*320*
>70 y	0.66	490	80	10	12	0.9	1.3	11	1.3	250	2	4	32	320

If no AR available, we estimated AR from AI

- 6 nutrients have no AR in either EFSA or IOM.
- So calculated H-AR as AI/1.25 (because 2x 12.5%CV added to AR to make RDA/PRI). AIs from EFSA (except chromium).
- Probably overestimates requirements, but is better than using AI or RDA/PRI for estimating prevalence of inadequate intakes.
- Also, AIs are based on usual intakes of well-fed populations (US, Canada, Europe).
- Italicized in tables to indicate lower uncertainty.
- Not done for infants 0-6 mo., or 6-11 mo. except Fe, Zn, protein.

Bioavailability corrections for iron and zinc

2b	Calcium	Phosphorus	*Chromium*	Copper	*Fluoride*	*Manganese*	Molybdenum	Iodine	Iron[5] High absorption	Iron[5] Moderate absorption	Iron[5] Low absorption	Magnesium	Selenium	Zinc[6] Refined diet	Zinc[6] Semi-refined	Zinc[6] Semi-unrefined	Zinc[6] Unrefined diet
	(mg)	(mg)	*(µg)*	(µg)	*(mg)*	*(mg)*	(µg)	(µg)	(mg)	(mg)	(mg)	(mg)	(µg)	(mg)	(mg)	(mg)	(mg)
Source	EFSA	IOM	*IOM*	IOM	*EFSA*	*EFSA*	IOM	IOM	EFSA	EFSA	EFSA	IOM	IOM	EFSA	EFSA	EFSA	ESFA
Life Stage[7]																	
Infants																	
7-11 mo										8	16					2.4	
Children																	
1–3 y	390	380	*8.8*	260	*0.48*	*0.4*	13	65		5	10	65	17			3.6	
4-6 y	680	405	*12*	340	*0.8*	*0.8*	17	65		5	10	110	23			4.6	
7-10 y	680	405	*12*	340	*1.2*	*1.2*	17	65		8	16	110	23			6.2	
Males																	
11-14 y	960	1055	*20*	540	*1.76*	*1.6*	26	73	8	12.8	25.6	200	35			8.9	
15-17 y	960	1055	*28*	685	*2.56*	*2.4*	33	95	8	12.8	25.6	340	45			11.8	
18-24 y	860	580	*28*	700	*2.72*	*2.4*	34	95	6	9.6	19.2	330	45	7.5	9.3	11	12.7
25-50 y	750	580	*28*	700	*2.72*	*2.4*	34	95	6	9.6	19.2	350	45	7.5	9.3	11	12.7
51-70 y	750	580	*24*	700	*2.72*	*2.4*	34	95	6	9.6	19.2	350	45	7.5	9.3	11	12.7
>70 y	750	580	*24*	700	*2.72*	*2.4*	34	95	6	9.6	19.2	350	45	7.5	9.3	11	12.7
Females																	
11-14 y	960	1055	*16.8*	540	*1.84*	*1.6*	26	73	7	11.2	22.4	200	35			8.9	
15-17 y	960	1055	*19.2*	685	*2.24*	*2.4*	33	95	7	11.2	22.4	300	45			9.9	
18-24 y	860	580	*20*	700	*2.32*	*2.4*	34	95	7	11.2	22.4	255	45	6.2	7.6	8.9	10.2
25-50 y	750	580	*20*	700	*2.32*	*2.4*	34	95	7	11.2	22.4	265	45	6.2	7.6	8.9	10.2
51-70 y	750	580	*16*	700	*2.32*	*2.4*	34	95	6	9.6	19.2	265	45	6.2	7.6	8.9	10.2
>70 y	750	580	*16*	700	*2.32*	*2.4*	34	95	6	9.6	19.2	265	45	6.2	7.6	8.9	10.2

Proposed Harmonized Upper Levels (H-Uls)

- EFSA values from 2000 - 2005, 8 minerals and 6 vitamins
- IOM values from 1997 – 2011, and better explained.
- FAO/WHO has a few, e.g. vitamin A in perinatal period.
- Inconsistent criteria for adverse effects, different supplements…
- Decisions carefully explained…………..

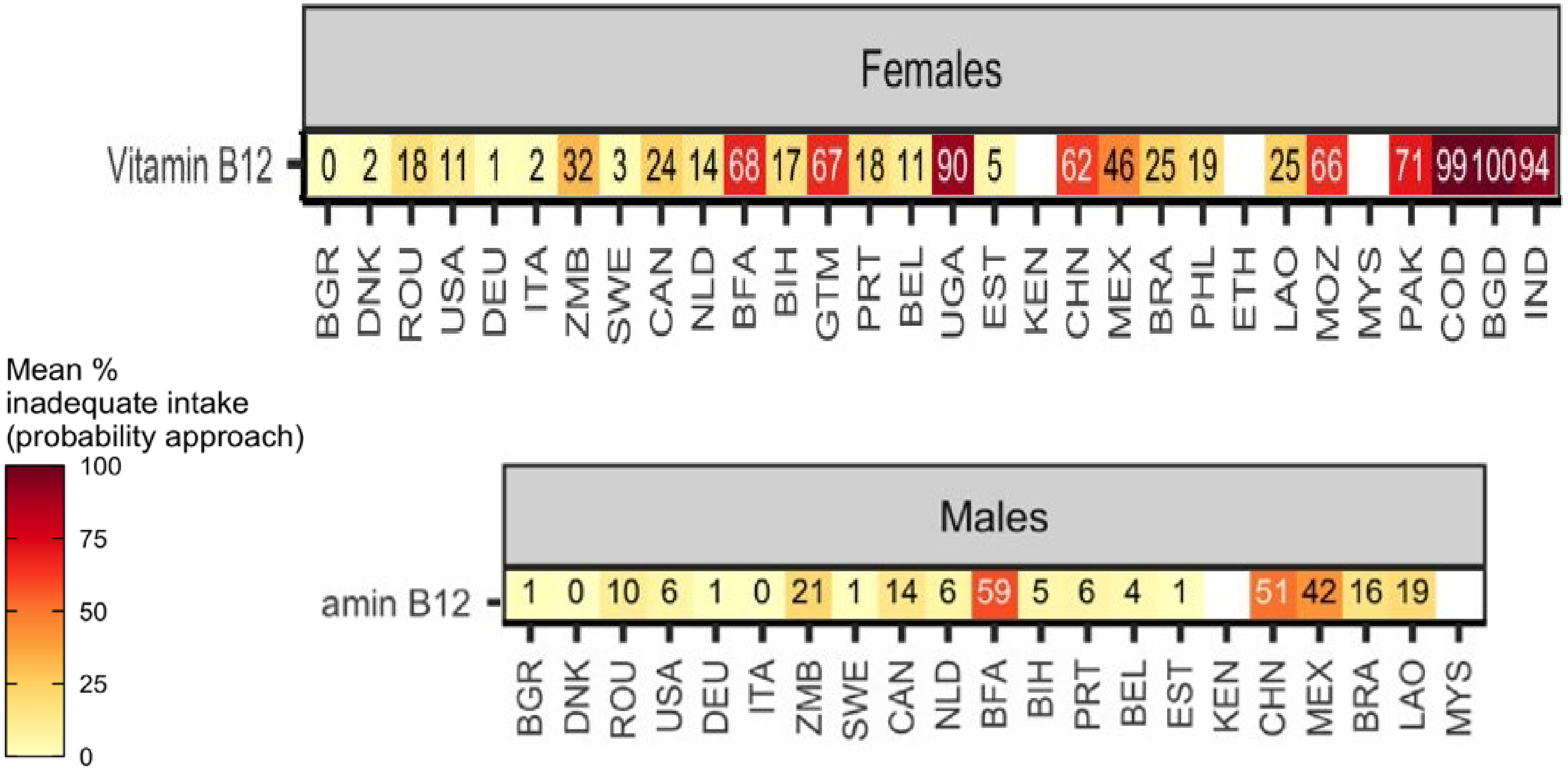
Source and criteria for H-ULs carefully explained

Nutrient	IOM UL-Children[2,4]	IOM UL – Adults[3,4]	EFSA UL – Children[2,5]	EFSA UL - Adults[3,5]	H-UL decision	H-UL adverse effect[6]
Vitamin A (µg/d)	600-2800	3000	800-2600	3000	Use EFSA	Teratogenicity
Vitamin C (mg/d)	400-1800	2000	No UL	No UL	Use IOM	GI effects
Vitamin D (µg/d)	63-100	100	50-100	100	Use IOM	High serum calcium
Vitamin E (mg/d)	200-800	1000	100-260	300	Use EFSA	Blood clotting
Niacin (mg/d)	10-30	35	2-8	10	Use EFSA	Flushing
Vitamin B6 (mg/d)	30-80	100	5-20	25	Use EFSA	Neurotoxicity
Folate (µg/d)	300-800	1000	200-800	1000	Use EFSA	Neuropathy if B12 deficient
Choline (g/d)	1.0-3.0	3.5	No UL	No UL	Use IOM	Hypotension, fishy body odor
Calcium (g/d)	2.5-3.0	2.0-2.5	No UL	2.5	Use IOM	Milk alkali syndrome
Phosphorus (g/d)	3.0-4.0	3.0-4.0	No UL	No UL	Use IOM	Elevated serum P
Copper (mg/d)	1.0-8.0	10.0	1.0-4.0	5.0	Use EFSA	Liver function
Fluoride (mg/d)	1.3-10.0	10.0	1.5-7.0	7.0	Use EFSA	Bone fractures
Manganese (mg/d)	2.0-9.0	11	No UL	No UL	Use IOM	Blood manganese, neurotoxicity
Molybdenum (µg/d)	300-1700	2000	100-500	600	Use EFSA	Reproductive toxicity
Iodine (µg/d)	200-900	1100	200-500	600	Use EFSA	Changes in thyroid hormones
Iron (mg/d)	40-45	45	No UL	No UL	Use IOM	GI distress
Magnesium (mg/d)	65-350	350	250	250	Use EFSA	Mild diarrhea
Selenium (µg/d)	90-400	400	60-250	300	Use EFSA	Selenosis (e.g., loss of hair and nails)
Zinc (mg/d)	7-34	40	7-22	25	Use EFSA	Copper status

Summary

- 25 H-AR and 19 H-UL values proposed.
- Based on combining extensive reviews in US/Canada/Europe and $$$$€€€€.
- Provides core set of very useful, harmonized values to estimate:
    - Prevalence of inadequate and excess intakes of specific nutrients
    - Intake gaps that need filling through programs
    - Risk of excess intake through fortification or supplementation
    - Differences in intake adequacy ACROSS countries and regions
- Countries may decide to set Dietary Guidelines based on own Target Median Intake (i.e. “x% <AR” - not “<RDA”), and adjust bioavailability of Fe, Zn.
- Provides values that countries/agencies can adopt/modify/revise, and avoid an expensive, long-term process.

Prevalence of inadequate intake (<EAR) using harmonized recommended intake values



Passarelli et al. Estimating national and subnational nutrient intake distributions of global diets. Am J Clin Nutr 2022.

What “local” adjustments to NRVs are really needed?

- Assume that all human share similar biology and requirements for absorbed nutrients.
- So there should be 1 set of biologically-based NRVs for the world.
- Then countries/regions should consider adjustments needed for their population;
    - Bioavailability (use algorithms for % iron and zinc absorption from diet)
    - Body size and activity? (For energy and protein – express per kg).
    - Infection?
    - Genetics?
    - (Not sunlight or skin color – recommend enough vitamin D for everyone).
- These potential adjustments need to be better defined and quantified.

Comments

- Need international body to review, update, monitor, and evaluate application.
- WHO/FAO is logical body to maintain systematic reviews and evidence-based data.
- Until they update NRVs and provide global ARs, what should countries/regions do?
- NOW we can improve understanding of NRV development and application, and determine and quantify local adjustments that might be needed.
- In contrast, translation of NRVs into Food-Based Dietary Guidelines must be a "local" process.
- The world, countries/regions need Harmonized Values NOW for global applications e.g. comparison of prevalence of inadequate intakes in surveys, food fortification levels, IMAPP software, complementary feeding, Codex, supplement formulation.
- World Food Program is using the Harmonized Values and is developing software to simulate adequacy or excessive intakes from program interventions.