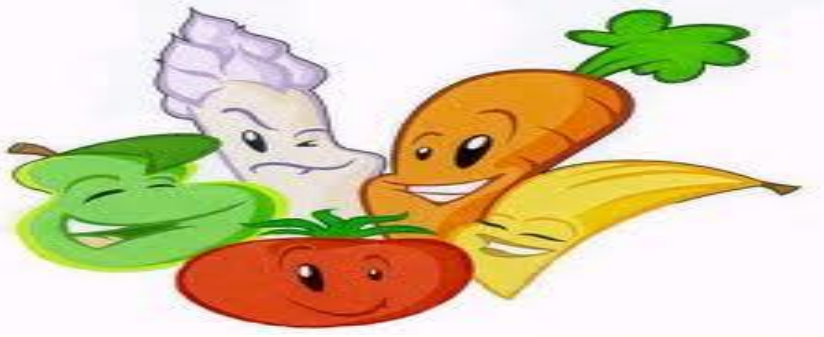
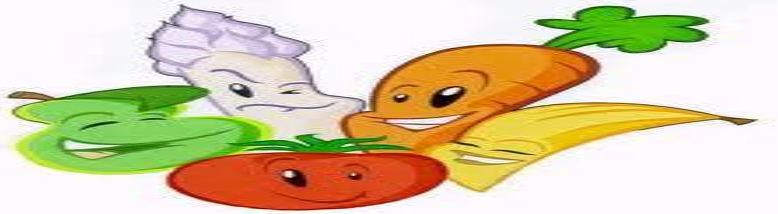


Application of Nutrient Risk Assessment in Indian Context

Dr.K.Bhaskarachary
Former Dy.Director and Head Dietetics, NIN, Hyderabad



Eating food is a RISKY process

There are more than 350 000 currently described plant species (Antonelli et al., 2020), perhaps up to 30 000 plants in total (Wilson, 1992) may be considered edible by humans, with at least 7 000 having been cultivated to some degree for food and agricultural purposes (Leibniz Institute of Plant Genetics and Crop Plant Research, 2022).

The human diet worldwide – is recorded for approximately 255 plants. These include around 26 cereals, 17 roots and tubers, 26 pulses, 44 vegetables, 69 fruits, 14 nuts, 28 oils, 24 herbs and spices, 3 sugars, and 4 stimulant crops.

More extreme calculations of the same data, generally focused on contribution to calories, lead to assertions that as few as a handful of staple crops provide the bulk of the world's food (FAO, 2019).

3,50,000/30,000/7000/255/4

But majority are with RICE,WHEAT,MAIZE and POTATO

IS THERE ANY EVIDENCE THAT TODAY'S FOOD IS LESS NUTRITIOUS THAN THAT EATEN BY PEOPLE SOME TIME AGO?

A report in the Journal of Complimentary Medicine in 2001 pointed out that US and **UK Government statistics show a decline in trace minerals of up to 76% in fruit and vegetables over the period 1940 to 1991.**

In 2003 News Canada reported that today's fruit and vegetables **contain far fewer** nutrients **than they did 50 years ago.**

In an analysis of milk it was concluded that the **iron content had fallen 62%, magnesium (another commonly deficient element) was down 21% and the copper in traces.**

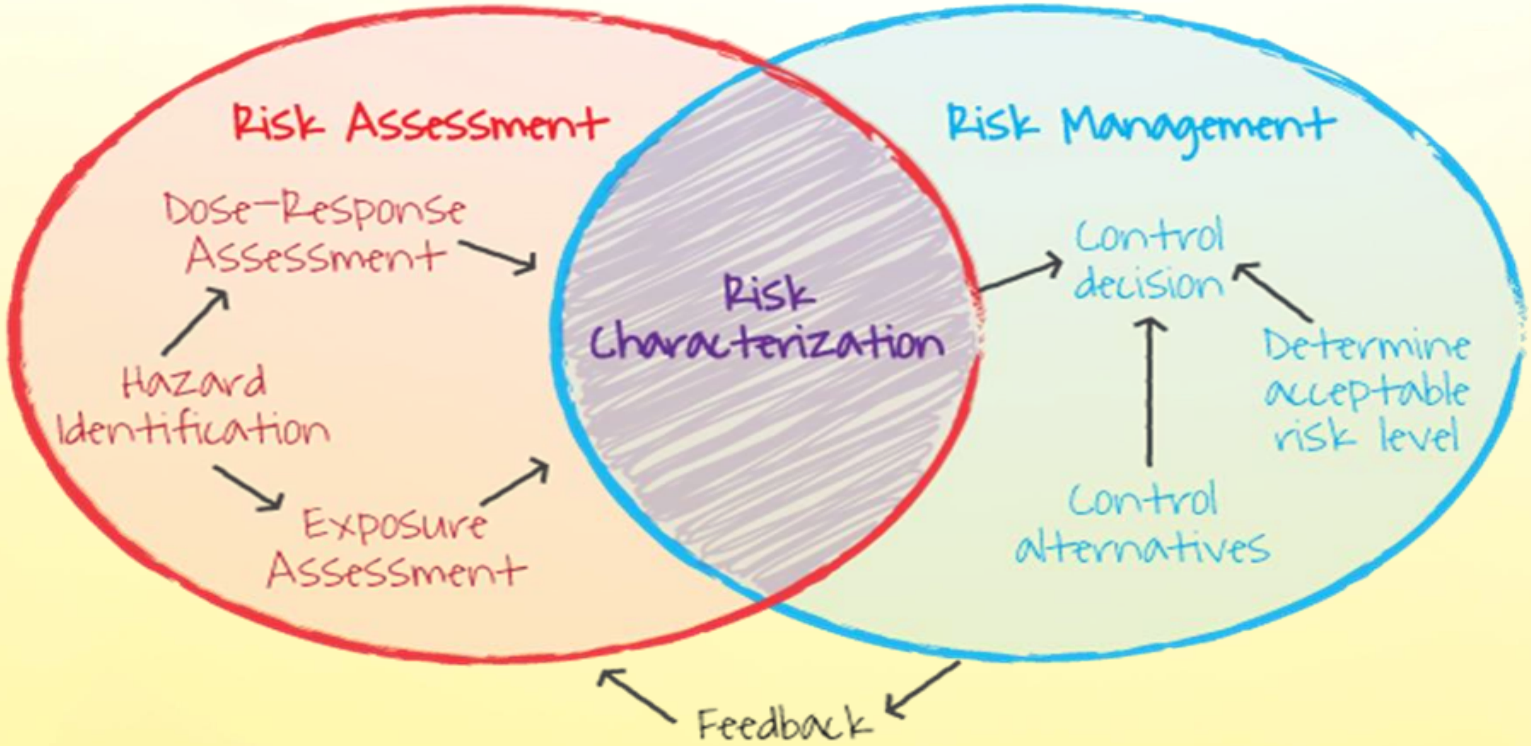
Transition down the lane

1937-2017

RICE RAW MILLED-Indian data

	1937	1951	1971	1989	2017
Moisture (g/100g)	12.96	13.0	13.7	13.7	9.93
Protein (g/100g)	6.85	6.9	6.8	6.8	7.94
Fat(g/100g)	0.55	0.4	0.5	0.5	0.56
Fibre(g/100g)	---	---	0.2	0.2	2.81
Carbohydrate (g/100g)	79.14	79.2	78.2	78.2	78.24
Energy (Kcal)	348.9	348	345	345	351

	1937	1951	1971	1989	2017
Minerals(g/100g)	0.50	0.50	0.6	0.6	0.52
Calcium (mg/100g)	7	10	10	10	7.49
Phosphorus (mg/100g)	108	110	110	160	95.62
Iron (mg/100g)	1.02	1.0	3.1	0.7	0.65
Carotene	0	0	0	0	0
Vitamin-B1 (mg/100g)	0.026	0.06	0.06	0.06	0.05



- **Virtually every aspect of life involves risk. How we deal with risk depends largely on how well we understand it.**
- **Risk assessment is an important public-policy tool for informing regulatory and technologic decisions, setting priorities among research needs, and developing approaches for considering the costs and benefits of regulatory policies.**

PHASE I: PROBLEM FORMULATION AND SCOPING

- What problems are associated with existing environmental conditions?
- If existing conditions appear to pose a threat to human or environmental health, what options exist for altering those conditions?
- Under the given decision context, what risk and other technical assessments are necessary to evaluate the possible risk-management options?

PHASE II: PLANNING AND CONDUCT OF RISK ASSESSMENT

Stage 1: Planning

- For the given decision context, what are the attributes of assessments necessary to characterize risks of existing conditions and the effects on risk of proposed options? What level of uncertainty and variability analysis is appropriate?

Stage 2: Risk Assessment

- *Hazard Identification*

  What adverse health or environmental effects are associated with the agents of concern?

- *Dose-Response Assessment*

  For each determining adverse effect, what is the relationship between dose and the probability of the occurrence of the adverse effect in the range of doses identified in the exposure assessment?

- *Exposure Assessment*

  What exposures/doses are incurred by each population of interest under existing conditions?

  How does each option affect existing conditions and resulting exposures/doses?

- *Risk Characterization*

  What is the nature and magnitude of risk associated with existing conditions?

  What risk decreases (benefits) are associated with each of the options?

  Are any risks increased? What are the significant uncertainties?

Stage 3: Confirmation of Utility

NO

- Does the assessment have the attributes called for in planning?
- Does the assessment provide sufficient information to discriminate among risk-management options?
- Has the assessment been satisfactorily peer reviewed?

YES

PHASE III: RISK MANAGEMENT

- What are the relative health or environmental benefits of the proposed options?
- How are other decision-making factors (technologies, costs) affected by the proposed options?
- What is the decision, and its justification, in light of benefits, costs, and uncertainties in each option?
- How should the decision be communicated?
- Is it necessary to evaluate the effectiveness of the decision?
- If so, how should this be done?

FORMAL PROVISIONS FOR INTERNAL AND EXTERNAL STAKEHOLDER INVOLVEMENT AT ALL STAGES

- The involvement of decision-makers, technical specialists, and other stakeholders in all phases of the processes leading to decisions should in no way compromise the technical assessment of risk, which is carried out under its own standards and guidelines.

Polar bear liver toxicity was first reported by Europeans in 1597 when the Dutch explorer Gerrit de Veer wrote in his diary that while taking refuge during the winter in Nova Zemlya (an archipelago in the Arctic Sea in northern Russia) that he and his men became seriously ill after eating polar bear liver. Since that early report, other similar reports of arctic explorers becoming ill and even dying after consuming polar bear liver have appeared.
A single polar bear liver (about 500 g) has an astonishing 9 million IU of vitamin A, and acute human toxicity occurs.

In India Vitamin A supplementation_Assam case

Arlappa, N. Vitamin A supplementation policy: A shift from universal to geographical targeted approach in India considered detrimental to health and nutritional status of under 5 years children. *Eur J Clin Nutr* **77**, 1–6 (2023).

"We are living in the midst of plenty but with serious public health concerns for Vitamin A, Iron and iodine"-Dr.C.Gopalan, NIN 1989.
Long term sustainable approach-Dietary diversity
Short term approach-Supplementation

Vitamin A

TUL for vitamin A in **infants**, a dose of 6000µg/day based on symptoms like **fontanelle dilation**, vomiting, higher intracranial pressure, was considered.

$$\text{UL} = \frac{\text{LOAEL}}{\text{UF}} \qquad \frac{6000\mu g/day}{10} = 600\ \mu g/day$$

A dose of 4500 µg/day was used to derive a TUL for vitamin A in **women of childbearing age** based on causality, quality and completeness with **teratogenicity** chosen as the critical adverse effect.

$$\frac{4500\mu g/day}{1.5} = 3000\ \mu g/day$$

At a 14000 µg/day dose, the most significant adverse effect for **all adults** (excluding women of childbearing age) was **liver abnormalities**.

$$\frac{14000\mu g/day}{5} = 3000\ \mu g/day$$

β-carotene

Hazard Identification

A critical review of the literature demonstrates that high doses of β-carotene supplementation induces **carotenoderma, which is harmless.**

- ATBC Cancer Prevention Study reported that supplementation with 20 mg/day β-carotene (with or without 50 mg of alpha tocopherol) in current smokers for 5 to 8 years resulted in a higher incidence of lung cancer and total mortality.
- However, β-carotene supplementation **did not induce any other primary cancers** (prostate, bladder, colon or rectum, stomach) in the study population.
- A multi-centred lung cancer prevention trial (CARET)-supplemental β-carotene (30mg/day) plus retinol (25,000 international units [I.U.]/day) versus placebo and observed a greater number of lung cancer cases.
- Physicians' Health Study, supplemental β-carotene, 50mg every other day versus placebo in 22,071 male U.S. physicians for 12 years did not show any significant effect on cancer incidence(including lung cancer and smokers) or mortality (Hennekens et al.,1996).

Hazard Characterization

The evidence on whether high doses of β-carotene could increase the risk of lung cancer in smokers is contradictory and **insufficient to assess** the dose-response relationship and determine a **tolerable upper intake level.**

Conclusions made by different organizations concerning β-carotene safety :

- JECFA (2002) evaluates β-carotene as a food additive and derives ADI (Acceptable Daily Intake)-Estimate of acceptable daily intake for man 0-5 mg/kg B.W.
- Institute of Medicine (IOM) (2000)- No UL
- European Commission, Scientific Committee on Food (EC SCF) (2006)- No UL
- Expert Group on Vitamins and Minerals (EVM) (2003)- 20/3- 7mg SafeUpper Limit (SUL)
- European Food Safety Authority (EFSA) (2012)- 15 mg/day, from its use as a food additive and as a food supplement.
- Norwegian Scientific Committee for Food Safety (VKM-2015)-20/5-It proposed a provisional U.L. of 4 mg/day for β-carotene supplementation.
- Council for Responsible Nutrition(CRN) US Recommendations-Supplemental intake of 25 mg/day for non-smokers;smokers should not use β-carotene supplements.
- US Preventive Services Task Force (USPSTF-2022)-USPSTF does not recommend β-carotene or alpha-tocopherol (vitamin E) supplements to prevent cancer or cardiovascular disease.

RISK Assessment-Communication-Risk manager

Spirulina_Vitamin A- **Content Claim**

Spirulina_Content Claim_**Risk communication**

Exogenous Oxytocin(OT) injections do not influence its content in milk. Further, OT present in milk is rapidly degraded during intestinal digestion, ruling out its intestinal absorption and associated adverse health consequences

On **nutrient sweeteners** ,**WHO's International Agency for Research on Cancer (IARC) classified aspartame as "possibly carcinogenic to humans," (Group 2B)**

But FAO/WHO's expert JECFA committee still says it can be safely consumed, Citing "limited evidence" for carcinogenicity in humans, and JECFA reaffirmed the acceptable daily intake of 40 mg/kg body weight.,

FDA is conducting a detailed inspection of the arsenic level in rice being sold in the American market, including those of basmati variety imported from India(2023).

While an analytical study of more than 1,300 samples of rice and rice products, including basmati from India, did not show any alarming levels of arsenic presence, the FDA will now conduct a "comprehensive risk assessment" study to determine the long-term impact of the arsenic found in rice.

Results showed that, based on associated exposure to selenium, cadmium, and **i-As in rice**, the current consumption of **rice does not pose a risk** to adult men **in China**. Also, a lower (50 g/day) or higher (200 g/day) rice consumption will not bring larger beneficial effects. (**Frontiers in Nutrition, July 2021, Volume 8)**

- The lung cancer and bladder cancer risk attributable to lifetime exposure to all rice and rice products is a small portion of all cases of these cancers, at **39 cases per million people** (10 cases/million bladder cancer and 29 cases/million lung cancer) (FDA-2016)

ALARA- As low as reasonably achievable

IRON

Hazard Identification

- By weighing the advantages and disadvantages of iron overdose, it appears that none of the consequences (CNS,CVD, interaction with other nutrients, and cancer) studied by different researchers have been proven to be harmful.
- However, iron overdose/toxicity consequences with some acceptance of the severity of gastrointestinal (GI) effects (Frykman et al., 1994) will be considered for hazard identification (IOM, 2001).

Hazard Characterization

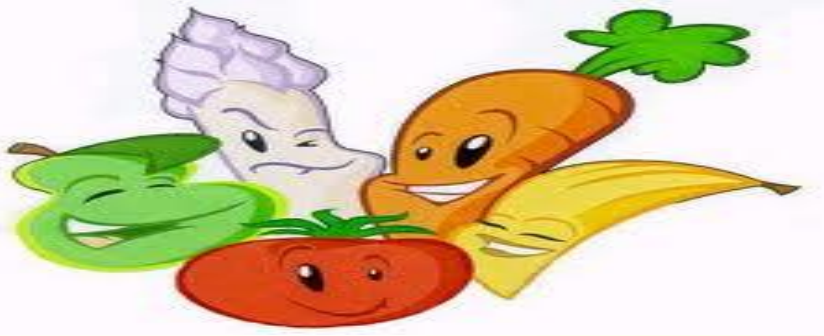
- **Ninety-seven (97) Swedish adult males and females participated in a double blind, placebo-controlled study-60 mg of elemental iron as iron fumarate daily for one month.**
- **Taking into account the average daily iron intake from food in women from six European countries (Van de Vijver et al., 1999) and men from Denmark (Bro et al., 1990), 11 mg/day has been added to the LOAEL (60 mg/day).**

Uncertainty Evaluation

To account for the extrapolation of a LOAEL to a UL, an uncertainty factor (UF) of 1.5 was selected. A higher UF is not warranted because the observed GI effects are self-limiting.

Derivation of UL

$$UL = \frac{LOAEL}{UF} = \frac{70mg}{1.5} = 45 \text{ mg/day}$$



❖ **2019-**The Journal of Nutrition

Revisiting Dietary Iron Requirement and Deficiency in Indian Women: Implications for Food Iron Fortification and Supplementation

Santu Ghosh,[1] Srishti Sinha,[3] Tinku Thomas,[1] Harshpal S Sachdev,[4] and Anura V Kurpad[2]

❖ **2022-**Indian J Public Health

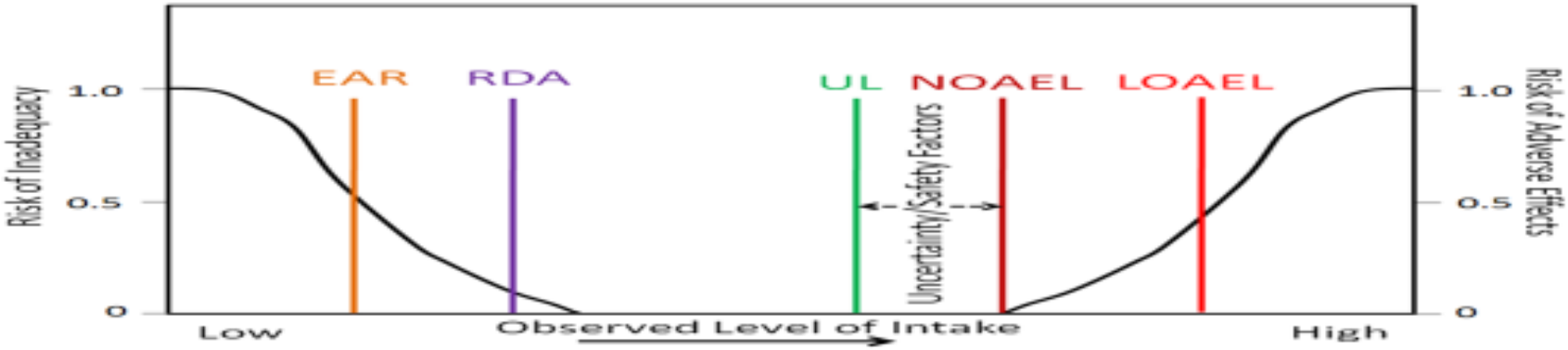
Large-scale Staple Food Fortification as a Complementary Strategy to Address Vitamin and Mineral Vulnerabilities in India: A Critical Review

Mona Duggal[a], B. Sesikeran[b], N. Arlappa[a], Sirimavo Nair[a], Vedeika Shekhar[a], Vandana Sabharwal[a]

❖ **2023-Nutrients**

Women in Selected Communities of Punjab, India Have a High Prevalence of Iron, Zinc, Vitamin B12, and Folate Deficiencies: Implications for a Multiply-Fortified Salt Intervention (1.3mg/g) (Nutrients 2023, 15, 3024).

Iron intake from usual diet, mg/d	18.8	(EAR)15	(-%) 46.0	(+%) 2.2
Projected iron intake from usual diet and MFS, mg/day	25.2	15	16.9	**4.9**

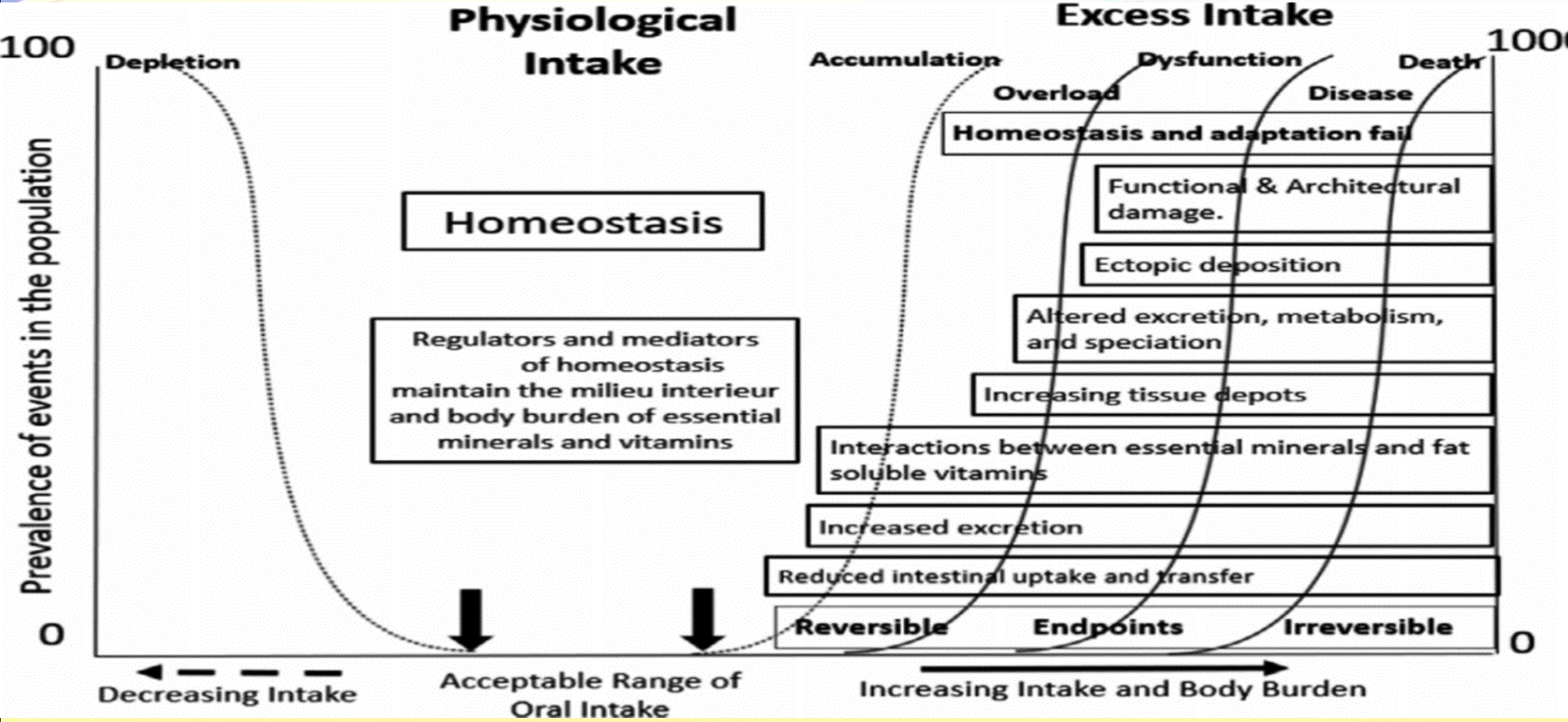


UL, is the highest level of daily nutrient intake that is unlikely to pose risk of adverse health effects to almost all individuals in the population. To set this, the committee (Either IOM, EFSA, VKM or other agencies) first sets a no observed adverse effect level (NOAEL) and/or the lowest observed adverse effect level (LOAEL).

The UL is then set lower based on a number of uncertainty/safety factors off the NOAEL or LOAEL as shown in the figure. The right vertical axis is used to represent the risk of an adverse event. Notice the NOAEL at the point where no adverse effects have been reported. The LOAEL is somewhere above the NOAEL. The UL is set at a level where it is believed that people will not experience the selected adverse effect.

As it can be seen from the graph that there is relatively small gap between the Estimated Average Requirement (EAR) and Recommended Daily Allowance of nutrients of the population, but the gap between RDA and Tolerable Upper Level (TUL)is very wide. That means the risk of adverse effects associated with the consumption of nutrients starts at much higher intakes of nutrients.

In practice, the UL can be used as an upper bound for the maximum tolerable level of usual intake for individuals. The UL is not a recommended intake.
Occasional, short-term and limited excursions above the UL are possible without adverse effects.



EFSA Journal 2022;20(1):e200102

IRON-UL

WHO(1983). Set the provisional maximal tolerable intake for iron at 0.8 mg/kg BW, excluding the use of iron oxide colorants, iron supplements for pregnancy and lactation, and medicinal iron.

IOM(2000). IOM based on Frykman et al., 1994 data, concluded though mid GI effects- **45mg/day**.(With food no problem)

Japan(2015). Set UL based on 0.8mg/kg/B.W- 55mg/day

EFSA (2004). EFSA reviewed and evaluated iron safety but concluded that the data were **not sufficient** to identify a UL value.

EVM (2003). The UK's EVM concluded that the evidence was **insufficient** to set an SUL value for iron. Instead, it set a guidance level based on some clinical reports of gastrointestinal effects from doses of soluble iron salts containing iron levels as low as 50 mg.**50/3= 17mg/day GL.**

CRN(Council for responsible nutrition-2013). A substantial body of evidence supports a NOAEL value for longer-term iron supplementation of 18 to 65 mg per day for ferrous and ferric compounds. This frequency of mild effects represents a **nuisance rather than a hazard**, and 60 mg of iron qualifies as a supplemental NOAEL if the product label makes the consumer aware of the potential gastrointestinal effects. **60/1= 60 mg/day UL.**

India(2020). 45mg/day

First author, year (reference)	Study design[1]	Participants[2]	Age (mean)	Duration (weeks)	Iron dose[3] (mg/day)	$FeSO_4$ n	$FeSO_4$ GISEs n (%)	placebo n	placebo GISEs n (%)	Baseline Hb (g/dL) ($FeSO_4$)
Baykam, 2006 [57]	Parallel	F	27.8	17.3	80	82	19 (23)	86	16 (19)	12.9
Cook, 1990 [63]	Parallel	F	18–48	2	50	67	31 (46)	66	14 (21)	NR
Davis, 2000 [64]	Parallel	RLS	58.6	12	130	14	5 (36)	14	0 (0)	14.3
Fouad, 2013 [65]	Parallel	F	35	1	25	20	8 (40)	20	4 (20)	NR
Ganzoni, 1974 [66]	Cross-over	M+F	27M, 33F	2	111	90	49 (54)	90	19 (21)	15.25
Gordeuk, 1987 [67]	Parallel	F, blood donors	NR	1	180	24	18 (75)	23	8 (35)	12.7
Hallberg, 1966_1 [24]	Parallel	Blood donors	NR	NR	222	175	40 (23)	169	23 (14)	NR
Hallberg, 1966_2 [24]	Parallel	Blood donors	NR	NR	222	111	31 (28)	115	16 (14)	NR
Hallberg, 1966_3 [24]	Parallel	Blood donors	NR	NR	180	170	45 (26)	177	22 (12)	NR
Levy, 1978 [68]	Cross-over	M+F	19–55	4.3	200	107	57 (53)	107	22 (21)	NR
Maghsudlu, 2006 [69]	Parallel	F, blood donors	28.7	4	150	185	19 (10)	182	8 (4)	13.52
Mirrezaie, 2006 [54]	Parallel	F, blood donors	34.2	6	50	49	17 (35)	46	9 (20)	NR
Meier, 2003 [70][4]	Parallel	Pregnancy	25.2	NR	60	38	24 (63)	36	19 (53)	13
Makrides, 2003 [71]	Parallel	Pregnancy	28.5	20	20	200	136 (68)	193	133 (69)	13.1
Pereira, [40]	Parallel	M+F	32	1	130	10	9 (90)	10	4 (40)	NR
Sutton, 2004 [45]	Parallel	Hip and knee-replacement	70	6	195	35	8 (23)	37	8 (22)	10.4
Tuomainen, 1999 [72][21]	Parallel	M	45–64	26	180	15	3 (20)	15	0 (0)	14.53
Voucher, 2012 [60]	Parallel	F	36.5	12	80 slow-Fe	102	12 (12)	96	10 (10)	13.5
Yalcin, 2009 [73]	Parallel	Post-partum	27.7	16.3	80	24	8 (33)	23	6 (26)	13.1
Waldvogel, 2012 [59]	Parallel	F, blood donors	31.8	4	80 slow-Fe	74	25 (34)	71	8 (11)	12.6

Meta-analysis confirms that ferrous sulfate is associated with a significant increase in gastrointestinal-specific side-effects but does not find a relationship with dose. **PLoS one, Feb,2015**

Dietary Iron Absorption Rate

- 16.6% from the normal American diet
- 16% from the normal French diet
- 15% from the normal Japan diet
- 14% from the normal Swedish diet
- 15%-WHO/FAO
- 8%-India

Hemochromotosis:The homeostatic iron regulator (HFE) gene C282Y mutation, a common cause for hemochromatosis in Europe, is considered almost nonexistent in India.

Hemoglobinopathies are the commonest genetic disorders worldwide. They include thalassemia's(α and β) and Sickle cell anemia(β).

It has been shown that patients with Thalassemia have reduced intake of key nutrients (Fung et al 2012). Furthermore, intake of some essential nutrients appears to worsen with age. Optimizing dietary intake through nutrient dense food and appropriate use supplementation/fortification where necessary may improve in these patients.

There is evidence from epidemiological studies that high **dietary heme intake** via meat consumption increases the risk for adverse health effects , particularly T2DM, GDM, coronary heart disease, CVD, and some cancers (such as colorectal, esophageal, and breast cancer). These effects can be at least partially attributed to excessive iron accumulation due to the increased bioavailability of heme iron.

However, a contribution of confounding factors present in meat products is also possible, while in most cases the HR or OR values were relatively low (below 2), indicating weak correlations.

(Charlebois, E.; Pantopoulos, K. Nutritional Aspects of Iron in Health and Disease. Nutrients **2023,** 15, 2441)

Extruded rice fortified with MGFP has excellent sensory characteristics. Fed in a school lunch meal, it increases iron stores and **reduces the prevalence of iron deficiency in Indian children**. **Am J Clin Nutr 2006; 84:822–9.**

In vitro dialysability of iron from fortified rice (NIN,2020)

Nutrient	Iron (mg/100 g ± SD)	Dialyzable iron (mg/100 g ± SD)	Dialyzability (% ± SD)
Fortified Rice	12.4 ± 0.84	0.55 ± 0.06	4.54 ± 0.28
Unfortified Rice	0.27 ± 0.03	0.045 ± 0.006	16.66 ± 1.0

The Potential Contribution of Fortified Maize Flour, Oil, Rice,Salt, and Wheat Flour to Estimated Average Requirements and Tolerable Upper Intake Levels for 15 Nutrients in **153 Countries**. Nutrients,**2021**, 13, 579.

In both scenarios, the median Tolerable Upper Intake Levels (ULs) met were <55% for all nutrients. **Under the realistic scenario, no country exceeded 100% of the UL for any nutrient.** Current fortification practices of the five foods of interest have the global potential to contribute up to 15 nutrients to the diets of people, with minimal risk of exceeding Uls.

Cytotoxicity was enhanced when the Fenton reaction occurred inside cells. Instead of enhancing cytotoxicity, extracellular iron ions exerted protective effects against the cytotoxicity of extracellular hydrogen peroxide in an ion concentration-dependent manner.

Distance had a negative impact on the reactivity of extracellular _OH and biologically effective targets.

Furthermore, an assessment of plasmid DNA breakage showed that the **Fenton reaction system did not effectively induce DNA breakage**.

(Igarashi, K.; Shoji, Y.;Sekine-Suzuki, E.; Ueno, M.;Matsumoto, K.-i.; Nakanishi, I.;Fukui, K. Importance of Locations of Iron Ions to Elicit Cytotoxicity Induced by a Fenton-Type Reaction.Cancers **2022,** 14, 3642.

A relation between RDA and TUL for various nutrients.

	Name of the nutrient	UL	RDA US	UL as percentage of RDA	Basis of UL	Critical hazard Considered for UL	
1	Sodium	2300 mg	1500mg	153	LOAEL	All cause deaths	
2	Chloride	3600mg	2300mg	156	NE	Based on Sodium	
3	Calcium	2500mg	1200mg	208	LOAEL	Kidney stone Milk-Alkali syndrome	
4	Niacin	35 mg	16mg	218	LOAEL	Flushing	
5	Iron	45mg	18mg	250	LOAEL	Gastrointestinal effects	
6	Flouride	10mg	4mg	250	NOAEL	Skeletal fluorosis	
7	Folate	1000µg	400µg	250	LOAEL	Neuropathy	
8	Vitamin A	3000µg	900µg	333	LOAEL	Tertogenicity	
9	Vitamin D	50µg	15µg	333	NOAEL	Hypercalcemia	
10	Zinc	40mg	11mg	363	LOAEL	Copper metabolism	
11	Manganese	11mg	2.3mg	478	NOAEL	Nuerotoxicity	
12	Phosphorus	4000mg	700mg	571	NOAEL	Hyperphospatemia	
13	Choline	3500mg	550mg	636	LOAEL	Hypotension	
14	Selenium	400µg	55µg	727	NOAEL	Hair brittleness	
15	Iodine	1100 mg	150mg	733	LOAEL	Elevated Serum Thyroid harmone	
16	Copper	10000mg	900mg	1111	NOAEL	Liver damage	
17	Vitamin C	2000mg	90mg	2222	LOAEL	Osmatic diarrhea	
18	Molybdenum	2000mg	45mg	4444	NOAEL	Impaired reproduction in rats	
19	Vitamin B6	100mg	1.7mg	5882	NOAEL	Neuropathy	
20	Vitamin E	1000mg	15mg	6666	LOAEL	Increased tendency to hemorrhage	

1. Majority of Uls (11/20) are derived based on LOAELs
2. One nutrient ie Chloride Uls is based on Sodium, as it is present inequimolar concentraion with Sodium
3. Ul of Molybdenum is derived based on animal experiment, no human toxicity is reported
4. The critical hazards associated with Iron and Vitamin C to derive Uls are transitory in nature .

Factors to consider when assessing the risk of high intakes:

- the accuracy of the intake data
- the percentage of the population consistently consuming the nutrient at intake levels in excess of the UL
- the seriousness of the adverse effect
- the extent to which the adverse effect is reversible when intakes are reduced to levels less than the UL.

Dietary Supplements ingredients include micronutrients, macronutrients, herbals, botanicals, phytochemicals, zoo chemicals, as well as many other concentrates, metabolites, constituents, extracts, or combinations (e.g., probiotics, glucosamine, and melatonin).

Multivitamin-mineral (MVM) DS are the product that is most commonly used; however, no legal or regulatory definition of the term "micronutrient supplement" or MVM exists.

Currently no standardized methods are available to assess the prevalence of use and nutrient exposures from DS.

Supplement use has been measured by methods that focus solely on supplements, such as frequency-based questionnaires (FBQ), supplement inventories, and short screening tools. Little is known about the accuracy, reliability, and measurement error structure of DS assessment methods

Caveats with dietary supplements (DS)

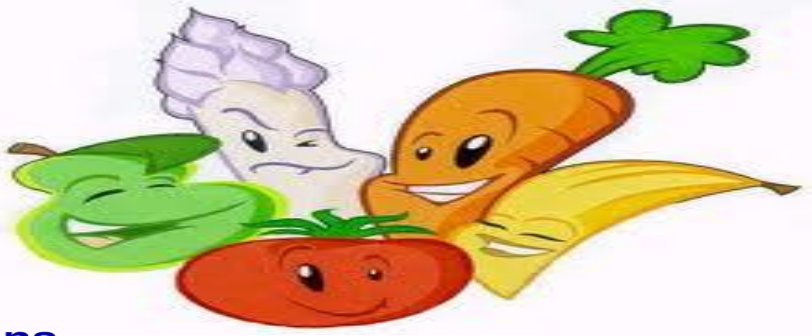
- There is tremendous variation in the dietary assessment methods used for DS.
- Assessments for DS may query usage over a time period different from those for foods.
- No single comprehensive analytical database exists; this is an ever-evolving marketplace.
- Nutrient amounts in DS databases rely on label declarations, which have varying accuracy and tend toward overages.
- Default product types are typically assigned (depending on assessment method), which may or may not accurately reflect the nutrient content estimates.
- Dissolution and dissolvability are not equivalent to bioavailability, which can bias exposure estimates.
- The form (unit) on the DS label can differ from those of foods.
- Limited database values are available for botanical and herbal DS.
- DS can be consumed daily, episodically, or seasonally.
- Some users take multiple DS with varying frequencies.

For most nutrients, the UL is likely to represent a low quantile in the distribution of the sensitivity threshold for an adverse effect, much as the RDA represents a high quantile in the distribution of requirements.

It was argued in the DRI reports on assessment that using the RDA as the cut-point to estimate the prevalence of low intake in a group led to overestimating the proportion of persons with intakes below their requirements. **Similarly, it is likely that using the proportion of individuals with usual intakes above the UL overestimates the proportion of individuals who may be at risk of adverse effects.**

However, rather than using ULs, the risk of excess may be approached in the same way as the risk of inadequacy, that is, by estimating an average tolerance for population subgroups for each nutrient and formulating a distribution of tolerances (estimated average tolerance) in the group, with a variance that reflects between-person differences.

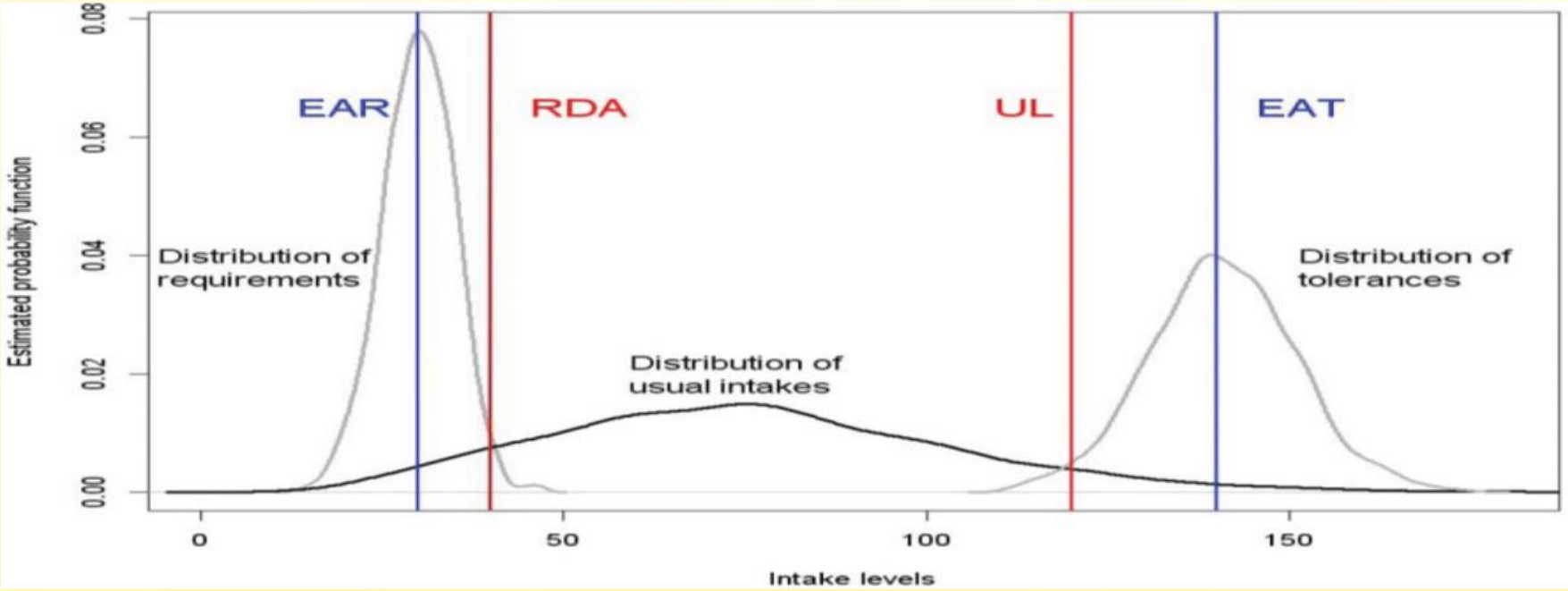
The estimated average tolerance would be analogous to the EAR cut-point method at the high end that would estimate the percentage of individuals whose intakes would fall above their tolerances.



Fortification: new findings and implications

Johanna T Dwyer and others

Nutrition Reviews, Volume 72, Issue 2, 1 February 2014, Pages 127–141,



Proposed new approach for determining risk of excess nutrient intake. Abbreviations: EAR, estimated average requirement; **EAT, estimated average tolerance**; RDA, recommended dietary allowance; UL, upper limit.

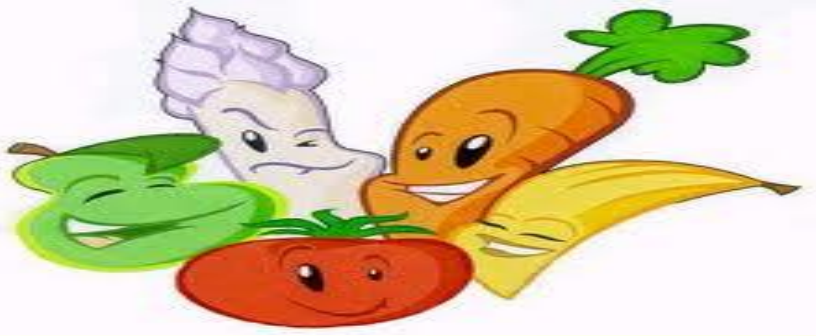
- **Risk-benefit analysis of foods including a formal public health assessment followed by management and communication has been establishing itself as a scientific discipline.**

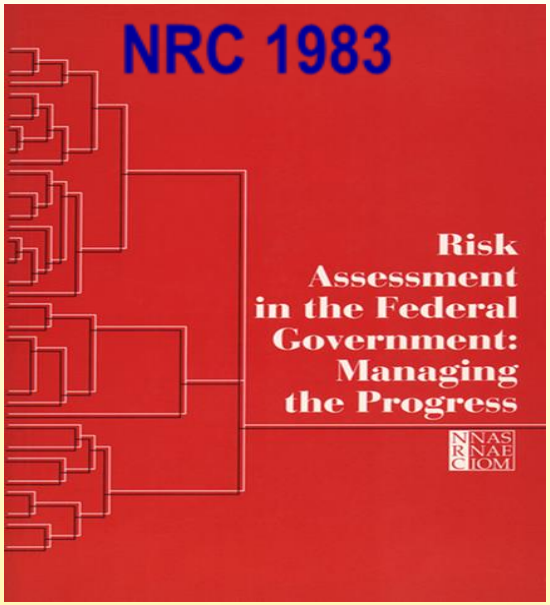
- **The iron inadequacy by nutrient gap analysis calculated by NIN, using the 2020 Nutrient requirement, showed high level of iron inadequacy (80% population). The lowest rate of iron inadequacy was among ≥18 year old male subjects, and the highest level of iron inadequacy was observed among adolescent girls and women.**

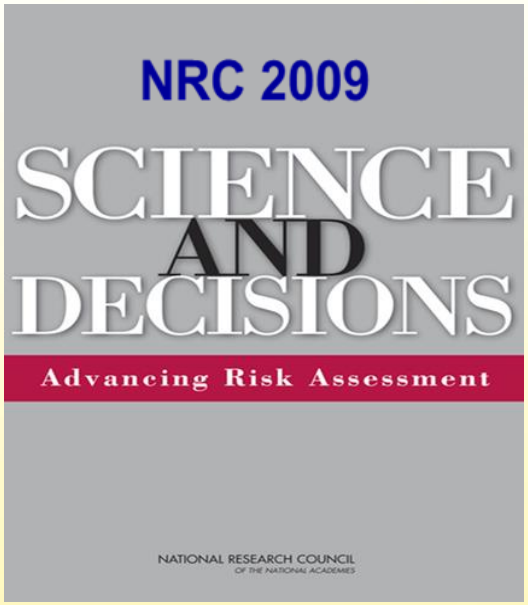
- **India's health is severely impacted by inadequate nutrition. Six out of the top 15 health risk factors in India are linked to poor nutrition, which accounts for more than 18% of all lost Disability Adjusted Life Years (DALYs), according to the WHO Global Burden of Disease study (GBD). With more than 3% of all DALYs lost in India, iron deficiency is the single most significant nutritional risk factor**

- **The cost of one DALY lost due to iron deficiency anemia (IDA) in India is approximately ₹30,000 and the cost incurred to avert IDA led one DALY is just ₹1,545, providing a cost-benefit ratio of 1:18. Amounting to only around 1 per cent of the food subsidy bill in 2018-19, rice fortification has the potential to avert a total of 94.1 million anaemia cases that can lead to savings of ₹8,098 crore over a period of five years. Iron deficiency-anemia is the biggest cause of disability for the past 10 years and contributed 20 per cent direct and 50 per cent associated maternal deaths in India. Its economic burden is equivalent to about 4 per cent of GDP.**

- **The risk associated with dietary intake of Iron seems to be negligible. Thus, arguing that Iron fortified food will harm by Iron over loading in all Traits need to be revisited and one should not deprive the Iron deficiency anemia children and adolescents (prevalent 1-3 %Thalassemia) verses iron deficiency anemia (More than 40%).**

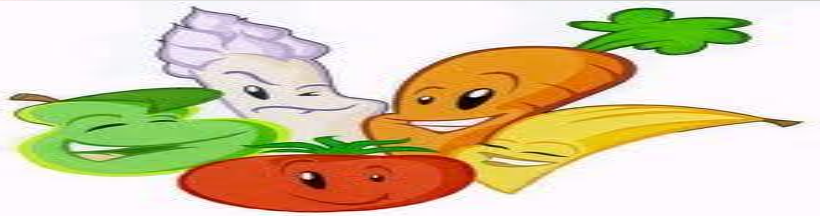






The Red book established a framework for the concepts and conduct of risk assessment that has been adopted by numerous expert committees, regulatory agencies, and public health institutions.

The Silver book embeds these concepts within a broader framework for risk-based decision-making. Together, these are essential references for those working in the regulatory and public health fields.



Thank you all

Key Recommendations

1)The Nutrient Risk Assessment methodology needs to be harmonized rather than the tolerable upper limits.

2) Human clinical trial data is best for the derivation of the UL However, in many cases it is not available and other data should also be consulted and developed, including epidemiological data, human case reports, and animal studies.

3) Without human clinical trial data, epidemiological evidence of nutrient toxicity should become a vital consideration for deriving the UL.

4)There is a need to develop country-specific ULs based on many factors including food consumption intakes and patterns, nutritional status, food environment, and lifestyles.

5) In identifying a hazard related to excessive nutrient consumption, care must be taken to distinguish between long lasting and serious and minor and merely transient effects. For example, minor gastrointestinal distress that can occur when supplements are taken on an empty stomach should not be considered equivalent to the risk of a serious consequence, such as liver toxicity. Similarly, dermal "flushing" that can be produced by nicotinic acid is transient but does not produce any known pathology. In both cases, transient symptoms can be reversed by withdrawing the particular nutrient.

6)The concept of using the Highest Observed Intake or guidance level should be determined for nutrients or bioactive compounds where there is no data on safety/toxicity.

7) There is a need to generate data at regular intervals on the population's nutrient intake (producing data by centiles, including at the median and the 5th and 97.5 percentile) to identify deficiencies and to assess excess intakes for risk assessment.

8) The exposure assessment methodology needs to be improved to capture the intake of vitamins, minerals, and bioactive substances.

9) special committee should monitor developed and developing countries where the nutrient deficiencies are high and excesses are less common (theoretically, adverse effects of any nutrient will start above the NOAEL and below the LOAEL)