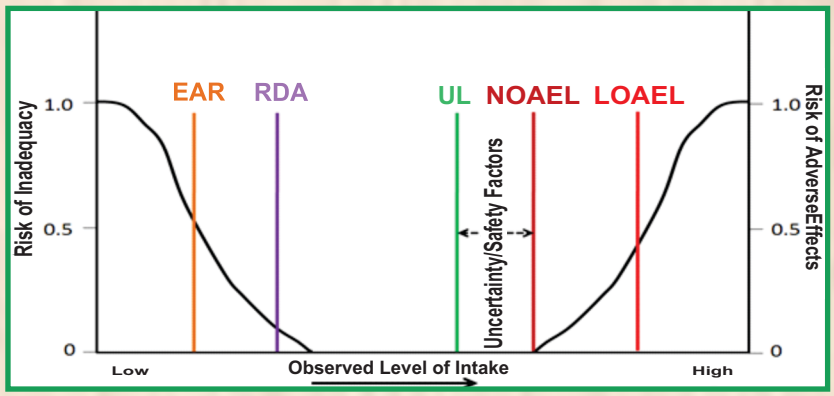
Risk Assessment of Vitamins, Minerals & Bioactive Compounds

An Executive Summary of the Monograph



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Foreword

Nutrients come from various sources in our daily diets. While it is recommended to obtain them from natural foods, it is practically not possible to do so and quite a bit comes from pre-packaged foods, fortified foods as well as supplements. The recommended daily allowances for each of these is derived considering the need for a healthy reference for man or woman to stay healthy all through the life. But all individuals are not the same and hence there can be no single level which will be sufficient for all. RDA therefore is a convenience figure which should be sufficient for 97.5% of the population so that none will fall into deficiency.

With this there is always a debate if the persons at the lower percentile of the population distribution curve whose daily needs are likely to be the Estimated Average Requirement or even less than that are likely to consume more than their individual requirement and thus likely to have adverse effect due to excess.

The risk assessment process addresses this potential safety issue based on available lab animal experimental data and reported human adverse events. The lowest level at which adverse effect is documented is the Lowest Observed Adverse Effect Level (LOAEL). Often several nutrients may not have any reported adverse effect even at many times higher intakes both in humans and in lab studies. They are the safest with no concern of excess. Those which do have a LOAEL offer a reference point for risk assessors to identify the nature of the hazard which may sometimes be just a change in a biochemical parameter or a clinically defined symptom or sign. Using this reference point, we go down several fold to arrive at a No Observed Adverse Effect Level or NOAEL, a safe intake or Tolerable Upper Limit (UL), an Acceptable Daily Intake (ADI) etc.

This process of risk assessment is fairly scientific method that is an assurance that despite the same nutrient coming from several sources and at the highest centile of intake would still not be expected to cause any adverse effect nor put the population at risk. This document is intended to create better understanding and informs about the methods and scientific basis of calculating the risk objectively. International experts also keep updating these as and when scientific publication of any adverse event is brought to light.

Finally, we should remember that risk is not only due to excess intake, risk is more often due to inadequate intakes leading to under nutrition. Even if there were to be a minimal risk, the benefits associated with adequate consumption of the nutrient versus the risk should be estimated to provide the healthy options to the consumer.

This is the Executive Summary of the Monograph provides which information on risk assessment methodology for a number of Vitamins, Minerals and Bioactives and can be a good guidance document.

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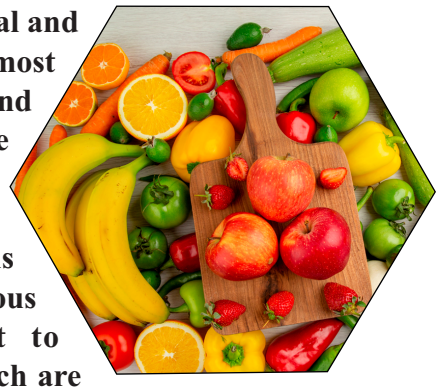


Vitamins and minerals are essential for a wide range of physiological and biochemical processes, including regulating and coordinating most bodily functions, tissue maintenance, bone and tooth development, and overall health. All essential nutrients needed to stay healthy cannot be synthesized in our bodies. Therefore, these compounds must be taken through our diet or obtained in other ways like fortified foods or supplementation. Throughout life, humans and other organisms require micronutrients in varying amounts to coordinate various physiological functions and maintain health. In contrast to macronutrient requirements (Protein, carbohydrate, and fat), which are measured in grams per day, micronutrient (vitamins and minerals) requirements in humans are typically less than 100 mg per day.

Dietary minerals are elements required in small amounts for normal health and function. They can be classified according to the amount required; macrominerals are defined as minerals that adults require in amounts ranging from milligrams to grams. In contrast, trace minerals/elements are required in micrograms to milligrams. The major macrominerals include calcium, phosphorus, potassium, sulfur, sodium, chlorine, and magnesium. Iron, copper, zinc, manganese, molybdenum, iodine, bromine, cobalt, and selenium are essential trace minerals.

Benefits of Bioactive Compounds

The definition of bioactive compounds (BCs) in the scientific literature is not universally agreed upon, one of the well-accepted definitions is that BCs are "natural or synthetic compounds that can interact with one or more components of living tissue and exert a wide range of effects". Bioactive compounds are also known as nutraceuticals, a term coined in 1979 by Stephan De Felice that refers to their presence in the human diet and their biological activity.

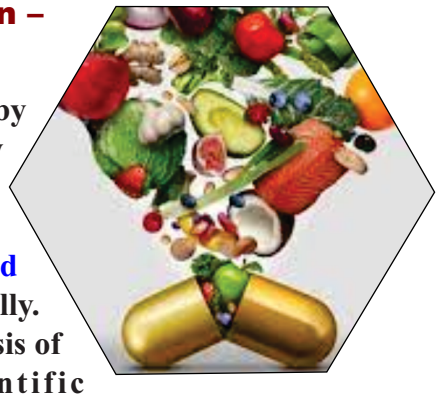
Bioactive substances present as natural constituents in food provide health benefits beyond the basic nutritional value of the product. Accumulated studies have revealed that bioactive compounds like Beta carotene, lutein, lycopene, glucosinolates, indoles, isothiocyanates, phytoestrogens, isoflavones, limonene, monoterpenes, allicin, allyl sulfides, organ sulfur compounds, flavonoids, catechins possess various health functions, such as antioxidant, antimicrobial, anti-inflammatory, antiobesity, antidiabetic, anticancer, cardiovascular protective, neuroprotective, hepatorenal protective, respiratory protective, digestive system protective, reproductive protective, and immunomodulatory properties.

Epidemiological and prospective studies have demonstrated the importance of bioactive compounds in fruits, vegetables, and nuts in lowering the risk of cancer and cardiovascular disease. In recent years, multiple meta-analyses have strongly suggested that adding one serving of fruits and vegetables

to the daily diet reduces the risk of cardiovascular diseases by as much as 7 percent.

Foods provide an array of nutrients and other bioactive components that have benefits for health. Nutritional needs should be met primarily through foods. However, in some cases, fortified foods and dietary supplements are useful when it is not possible to meet the needs for one or more nutrients (e.g., during specific life stages such as pregnancy, adolescence, and old age).

Reference Values for Nutrient Intakes for Population – Terminologies Used Internationally



A healthy person can get almost all vitamins in sufficient quantities by having a balanced and varied diet. In this regard worldwide many organizations/regions/countries have come up with the Dietary Reference Intakes (DRIs). DRIs are a set of scientifically based nutrient reference values for healthy populations. Recommended Dietary Allowances (RDA) had been the recognized standard globally. RDAs are the levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged by various Scientific organizations/countries to be adequate to meet the known nutrient needs of practically all healthy persons. The Estimated Average Requirements (EAR) is the daily intake value of a nutrient that is estimated to meet the nutrient requirement of half the healthy individuals in a life stage and gender group. Adequate Intake (AI) is a value based on observed or experimentally determined approximations of nutrient intake by a group (or groups) of healthy people—used when an RDA cannot be determined.

> **Tolerable Upper Limits (UL)** are the maximum daily nutrient intake that are unlikely to have a negative impact on nearly all members of the general population. **Tolerable Upper Intake Level (UL),** are expressed as part of the dietary reference intakes.

Underdeveloped and developing countries are at one end of the spectrum when it comes to not getting enough essential nutrients, such as vitamins and minerals. The other end of the spectrum is where developed countries consume too many nutrients through food supplements and fortification. The addition of multivitamins and multimineral supplements to the standard fortification reinforces the need for accurate, nutrient-specific, scientific risk assessments of nutrient safety. In this context, a safe limit for the nutrient, i.e. UL must be determined. *As exposure exceeds the UL, the risk of adverse effects increases.* The term "tolerable" was chosen because it implies a level of intake that can, with a high probability, be tolerated biologically by individuals. It does not imply acceptability in any other way. Over the past several decades, the UL has become internationally recognized as the most effective method for evaluating nutrient safety. Therefore, several international organizations and government agencies have developed or accepted UL value recommendations. These tolerable upper intake level values may be expressed in terms of total dietary intake, additional quantities, or both.

Low population intakes are evaluated against an EAR. The market for vitamins in the form of food supplements is growing continuously. The diverse range of tablets, capsules, and liquids gives the impression that sufficient vitamins and mineral intake are not possible from diet alone. Taking high-dose food supplements in addition to a balanced diet increases the risk of an oversupply of the respective vitamins and minerals. Given this scenario, regulators worldwide are paying attention to the process of establishing the upper level of intake for nutrient substances.

How ULs are Set

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 of the NOAEL or LOAEL. The UL is set at a level where it is believed that people will not experience the selected adverse effect.

Risk Analysis for Nutrients

Risk assessment and risk management for nutrients differ from other substances in foods because vitamins and minerals are essential for human life, and consequently, adverse effects can result from suboptimal intakes and deficiencies as well as from excessive intakes. In this context, the FAO/WHO has developed a model for setting upper levels of intake for nutrients and related substances, and the Codex Alimentarius Commission has developed the Principles and Guidelines for Nutritional Risk Analysis based on Scientific Risk Assessment.

The risk analysis framework was originally developed for the purposes of managing potential hazards of population (sub)groups to chemicals in foods and the environment. Its use has now expanded to other types of hazards (e.g., microbial pathogens in foods) and more recently to potential hazards associated with consumption of excessive intakes of nutrients and related food substances. In recent years, several expert committees have adapted the following risk assessment steps to derive upper levels of intake for nutrients. **Hazard identification, Hazard characterization, Exposure assessment, and Risk characterization are the four steps of the risk assessment model.**

Different countries and regions of the world have come up with Tolerable Upper Level (UL) for various nutrients.

The present monograph documents the information on the following:

1. **Terminologies used to express the safe limits for nutrients.**
2. Basis for deriving safe limits for nutrients.
3. **Risk analysis framework for some of the bioactive compounds.**
4. Identification of the gaps for further improvement in nutrient risk assessment.

Methodology for Risk Assessment of Vitamins and Minerals

Risk assessment is a method for systematically evaluating the likelihood of adverse human health effects from excessive exposure to an environmental agent (in this case, a nutrient or food component). International agencies like the United States Institute of Medicine (IOM), the Food and Nutrition Board (FNB), the European Commission scientific committee on food (ECSCF)of the European Food Safety and Standards Authority (EFSA), and the United Kingdom Expert Group on Vitamins and Minerals (UKEVM) started attempting to set limits for vitamins and minerals using scientific risk assessment methodology.

Vitamins and minerals are non-carcinogens and can be separated into two main types:

1. **Those depending on the threshold dose response concept (threshold approach).** Typically, studies of vitamin and mineral safety based on animal data employ the threshold method Risk assessments that use no observed adverse effect level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) identify intakes either below (NOAEL) or just above (LOAEL) the threshold for adverse effects.
2. **Those for which probability estimates have been constructed using the benchmark dose approach.** Studies of the safety of drugs, pesticides, and environmental contaminants frequently employ the benchmark dose approach to identify an intake that causes adverse effects in a population's specified percentage (10%). This method generates a probability basis for assessing the safety of the tested substance. However, it necessitates a comprehensive database that includes administration of a range of test substance concentrations, (or exposure to) at least up to those with adverse effects in 10% of the population. Such data are rarely available to human subjects and obtaining it would be unethical.

The methodology adopted for Nutrient Risk Assessment is the same as that used for Risk Assessment of Chemicals (Pesticide/Veterinary drug residues, environmental contaminants, and Food Additives), i.e., Hazard identification, Hazard characterization, Exposure Assessment, and Risk characterization. This process is used by the Food and Nutrition Board (FNB) of the Institute of Medicine (IOM), now under the National Academies of Sciences, Engineering, and Medicine (NASEM), to develop dietary reference intake (DRI) values includes Tolerable Upper Levels for nutrients.

Step 1. Hazard identification

This step involves identifying the known or potential adverse health effects of a given nutrient. It involves collecting, organizing, and evaluating all information about a given nutrient's adverse effects. This section concludes with a summary of the evidence regarding the nutrient's potential to cause adverse effects in humans.

Step 2. Hazard characterization

This step is the qualitative and quantitative evaluation of the nature of the adverse effects associated with a nutrient; this includes a dose-response assessment, i.e., determining the relationship between nutrient intake (dose) and identification of adverse effects (in frequency and severity). A UL is derived from these evaluations, taking into account the scientific uncertainties in the data, with different ULs that may be derived for various life stage groups.

Step 3. Exposure assessment

This step evaluates the normal daily nutrient intakes of the general population.

Step 4. Risk characterization

This step analyses the conclusions from steps 1 through 3 and characterizes the risk. Generally, the risk is considered the probability of an adverse effect (and its severity). Risk will be proportional to the proportion of the population that exceeds the UL and the magnitude and duration of the excessive consumption. The scientific uncertainties associated with the UL and intake estimates are described during risk characterization so that risk managers know the level of scientific assurance they can place in the risk assessment.

Derivation of Tolerable Upper Limit

In general, the following procedure is adopted in deriving the UL.

1. Identification of critical hazard for each nutrient for each Adult general population/ women of reproductive age / adolescents / children / infants.
2. Identification of appropriate dose for critical hazard (Ideally from Human data. In the absence of human data, the animal data can also be considered) .
3. Identification of No Observed Adverse Effect Level (NOAEL) for Critical Hazard.
4. Identification of Lowest Observed Adverse Effect Level (LOAEL) in the absence of NOAEL.
5. Identification of appropriate Uncertainty Factor .
6. UL is a value derived by dividing the NOAEL/LOAEL with Uncertainty factor.

$$UL = \frac{NOAEL/LOAEL}{UF}$$

In addition to the above methodology a recently proposed Chronic Disease Risk Reduction Intake Model was also applied for sodium and potassium risk assessment.

Chronic Disease Risk Reduction Intake Model

Historically, undernutrition and nutritional deficiencies were prevalent in the population, contributing to high rates of diet-related disease. Although the standardization of food fortification and enrichment, along with dietary guidance to the public, contributed to reducing the prevalence of nutritional deficiencies, there was a subsequent rise in the prevalence of obesity and related chronic diseases. As the public health burden in the United States and Canada shifted toward the risk of chronic disease, and nutrition science has increasingly focused on the effect of dietary determinants, including nutrients and other food components, as potential modifiers of chronic disease risk. The public health significance of chronic disease warrants concerted efforts to understand the relationships between diet and chronic disease risk, but such efforts must navigate methodological challenges.

Understanding dietary determinants of chronic disease often requires different kinds of conceptual approaches and evidence than needed for evaluating nutrient deficiencies and toxicities. Dietary intake patterns are multidimensional and dynamic and change over the course of a lifespan. Chronic diseases are complex and multifaceted and develop over time. These complexities make identifying the relationship between nutrient intake and chronic disease difficult, especially when longitudinal data are limited or unavailable. Additionally, the extended time between exposure and outcome often precludes the use of randomized controlled trials to establish a causal relationship. Since its inception, the DRIs were intended to consider chronic disease risk, but available evidence on chronic disease outcomes was typically too limited to inform the

derivation of specific reference values. Further more, the DRI process lacked a mechanism for evaluating the evidence for causal and intake–response relationships between nutrient intake and chronic disease risk—two components of the DRI organizing framework. To overcome these challenges ultimately led to the Guiding Principles Report with nine recommendations by NASEM in 2017, which expanded the DRI model to include a new DRI category based on chronic disease.

A total of 14 Vitamins ***(Vitamin A, Vitamin D, Vitamin E, Vitamin K: B1, B2, B3, B4, B5,B6, B7,B9, B12,Vitamin C and Choline) 20 Minerals (Fe, Zn, Ca, mg, Mn, I, Cu, Cr, Mo, Se, F, P, K, Na, As, B. Ni, Si, Cl, Sulfate and Vanadium)*** **and 5 Bioactive compounds (β-Carotene, Lutein, Lycopene, EGCG and trypsin inhibitors) have been reviewed in the monograph.**

The information for each nutrient is presented in the following order:

1. **Nature and Importance of the nutrient in Human Nutrition.**
2. **Dietary Sources of nutrients**
3. **Metabolism**
4. **Other uses of nutrients**
5. **Toxicity**
6. **Hazard Identification**
7. **Hazard characterization and Derivation of UL.**

The Exposure Assessment and Risk characterization have been dealt holistically.

Additionally, the following points of discussion arising from the review of NRA, i.e., Risk assessment of Nutrients and Bioactive Compounds –Approaches and Challenges, Terminologies Used for Risk assessment of Nutrients and Bioactive Compounds, comparative Table of UL of different organizations/countries, and finally key recommendations have been included.

A list of ULs of various regions and countries have been compiled in the following Table. As can be seen from the Table, most of the tools are the same as IOM ULs, but countries have adopted them as their country ULs. However, there are minor differences among various regions/countries.

Table 1: A Comparative Account of TULs of Various Regions and Countries

Serial No.	Country/ Nutrient	IOM(USA)	EFSA(EU)	Australia	Canada	India	Ireland	Japan	Malaysia
1	Vitamin A	3000µg	3000µg	3000 µg	3000 µg	3000µg	3000 µg	2700µg	3000 µg
2	Vitamin D	100µg(4000IU)	100µg	80 µg	100 µg	100µg(4000IU)	100µg	100µg	100 µg
3	Vitamin E	1000 mg	300 mg	300mg	1000 mg	NO TUL	300mg	850mg	1000mg
4	Vitamin K	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NOTUL	NO TUL
5	Thiamine (B1)	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NOTUL	NO TUL
6	Riboflavin (B2)	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NOTUL	NOTUL	NO TUL
7	Niacin (B3)	35 mg	900(10mg)	900(35mg)	35mg	35 mg	900(ND)	300(80 mg)	35mg
8	Pantothenic acid (B5)	NO TUL	NO TUL	NO TUL	NO TUL	ND	NO TUL	NOTUL	NO TUL
9	Pyridoxine (B6)	100 mg	25 mg	50mg	100mg	100 mg	25mg	55mg	100mg
10	Biotin (B7)	NO TUL	NO TUL	NO TUL	NO TUL	ND	NO TUL	NOTUL	ND
11	Folic acid (B9)	1000 µg	1000 µg	1000 µg	1000µg	1000 µg	1000 µg	900 µg	1000 µg

Contd.....

12	Cyanocobalamin (B12)	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL	NO TUL
13	Vitamin C	2000mg	NO TUL	NO TUL	2000mg	2000mg	2000mg	NOTUL	2000mg
14	Choline	3500mg	NO TUL	3500mg	3500mg	ND	ND	ND	ND
15	Iron (Fe)	45 mg	NO TUL	45mg	45mg	45 mg	45mg	50 mg	45mg
16	Zinc (Zn)	40 mg	25 mg	40mg	40mg	40 mg	25mg	40mg	45mg
17	Calcium (Ca)	2500mg	2500mg	2500mg	2500µg	2500mg	2500mg	2500mg	2500mg
18	Magnesium (Mg)	350 mg	250 mg	350mg	350mg	350mg	250mg	350mg	350mg
19	Manganese (Mn)	11mg	NO TUL	NO TUL	11mg	ND	11mg	11mg	11mg
20	Iodine (I)	1100 µg	600 µg	1100 µg	1100ug	1100 ug	600ug	3000ug	1100ug
21	Copper (Cu)	10 mg	5 mg	10mg	10mg	ND	5mg	7mg	10mg
22	Chromium (Cr)	NO TUL	NO TUL	NO TUL	NO TUL	ND	250µg	500µg	NO TUL
23	Molybdenum (Mo)	2 mg	0.6mg	2mg	2mg	ND	700 µg	600 µg	2mg
24	Selenium (Se)	400 µg	300 µg	400 µg	400µg	ND	300 µg	450 µg	400 µg
25	Fluoride	10mg	7mg	10mg	10mg	ND	ND	ND	10mg
26	Phosphorus	4ooomg	NO TUL	4000mg	4000mg	ND	NOTUL	3000mg	3500mg
27	Potassium	NO TUL	NO TUL	NO TUL	NO TUL	ND	NO TUL	ND	ND
28	Sodium	2300mg	NO TUL	2300mg	2300mg	ND	2300mg	ND	2300mg
29	Arsenic	NOTUL	ND	ND	NO TUL	ND	ND	NOTUL	ND
30	Boron	20mg	10mg	ND	20mg	ND	11mg	ND	ND
31	Nickel	1mg	NO TUL	ND	1mg	ND	ND	ND	ND
32	Silicon	NO TUL	NO TUL	ND	NO TUL	ND	NO TUL	ND	ND
33	Chloride	3600mg	NO TUL	ND	3600mg	ND	3600mg	ND	ND
34	Sulphate	NO TUL	ND	ND	NOTUL	ND	ND	ND	ND
35	Vanadium	1.8mg	NO TUL	ND	1.8mg	ND	ND	ND	ND
36	Beta Carotene	25 mg*							
37	Lutein	20 mg*							
38	Lycopene	20 mg*							
39	Epigalo catechin gallate	704 mg*							
40	Trypsin Inhibitors	5 mg*							

(* Safe levels not UL)

Source: Compiled by Authors

Note : In Table 1, column about India includes ICMR-NIN published RDA with Tolerable Upper Limits for Vitamins (like Niacin, Pyridoxine, Folic acid, Vitamin C, Vitamin A and Vitamin D) and in Minerals and Trace Elements (like Calcium, Iron, Zinc, and Iodine). All the data (except Calcium) on the Tolerable Upper Limits were examined and adopted from IOM. In case of Calcium, ICMR –NIN has relied on report of expert committee of 2018 on Safe Upper Limits of Vitamins/ Minerals. Rest (24/35) of the Vitamins, Minerals and Trace Elements may be adopted from IOM till ICMR-NIN comes out ULs for these nutrients.

Relation between RDA and Upper Tolerable Limit

An attempt has been made to identify the relation between RDA and UL in order to derive a safety factor with which the severity of the hazard of the given Vitamin or Mineral can be identified. The following Table 2 indicates the RDA vs. UL for their ratios. The UL as a percentage of RDA ranges from 153% for Sodium to 6666% For vitamin E. It is a challenging task to derive a factor that can uniformly describe the severity of the toxicity, as the severity of hazards on which ULs are derived are not uniform. Contrary to popular belief, that nutrients with lower UL values are necessarily more toxic than nutrients with higher UL values , there is no such relationship. This is because the criteria need more consistency for identifying the critical hazard or uncertainty factor for determining ULs.

Table 2: A Relation between RDA and TUL for Various Nutrients

Serial No.	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	Gastrointestinaleffects
6	Flouride	10mg	4mg	250	NOAEL	Skeletal fluorosis
7	Folate	1000 µg	400 µg	250	LOAEL	Neuropathy
8	Vitamin A	3000 µg	900 µg	333	LOAEL	Tertogenicity
9	Vitamin D	50 µg	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	55 µg	727	NOAEL	Hair brittleness
15	Iodine	1100 µg	150 µg	733	LOAEL	Elevated Serum Thyroid harmone
16	Copper	10000 µg	900 µg	1111	NOAEL	Liver damage
17	Vitamin C	2000mg	90mg	2222	LOAEL	Osmatic diarrhea
18	Molybdenum	2000 µg	45 µg	4444	NOAEL	Impaired reproduction in rats

Source: Compiled by Authors

Note:

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 .

Conclusions

A Tolerable Upper Intake Level (UL) is the highest level of continuing daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the life-stage group for which it has been designed. The need for UL has increased because of an increase in the regular intake of fortified foods and nutritional supplements by significant proportions of the population. Few nutrients are consumed from the natural foods that could cause toxicity for example, polar bear liver consumption and Vitamin A toxicity. Hence, it helps the people to understand the adverse effects of nutrients if consumed beyond such a limit. Tolerable Upper Limits for normal individuals of all age groups, physiological groups have been determined for each nutrient and few Bioactive compounds have been documented in this monograph. For some nutrients, the data are not sufficient currently to establish a UL. This indicates the need for caution in consuming high intakes of those nutrients. It should not be interpreted as meaning that high intakes pose no risk of adverse effects. For example, Arsenic is known to be toxic in high doses, but it has no UL because not enough data exist on chronic intake of lower doses to set a UL. Similarly for other nutrients like Thiamine, Riboflavin, Chromium, Molybdenum, Vanadium etc., When a UL cannot be determined, it is important to be careful about consuming levels above the RDA or AI.

Thus, this monograph will be useful reference material for students, researchers, public health policy makers, food regulators, national governments for addressing issues related to food fortification, dietary supplements, nutraceutical, and general health of the communities/regions/countries. This monograph essentially documents UL of various Vitamins and Minerals and Safe Limits for few Bioactive Compounds in addition to many gaps and flaws. It is impossible to estimate the actual risk (likely) of negative health effects for each member of the general population since the actual risk curve (probability of adverse effect at each level of consumption) is unknown. **The UL is intended to be used as a benchmark for potential negative effects until further study is done in this area, as well as to help ensure that individual intakes do not frequently or consistently exceed the safe intake.** However, in order to assess risk of each individual Nutrient and Bioactive Component, the dietary intakes including supplements in the specific populations groups is required.

The procedure for applying the UL in assessing the proportion of individuals in a group who are potentially at risk of adverse health effects from excess nutrient intake must keep following factors in mind:

- **ULs for nutrients are based on different sources of intake, one must be careful to use the appropriate usual intake distribution in the assessment. For some nutrients (e.g., Fluoride, Phosphorus, Vitamin C) the distribution of usual intake would need to include intake from all sources, while for others (e.g., Magnesium, Folate, Niacin, Vitamin E) only the distribution of usual supplement intake would be needed.**
- **The accuracy of the intake data.**
- **The percentage of the population consistently consuming the nutrient at intake levels in excess of the UL.**

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. A 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).

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About ILSI India and K-FFIG

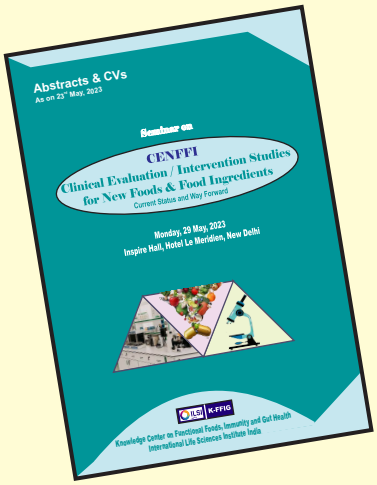
ILSI India is an entity of the International Life Sciences Institute (ILSI), headquartered in Washington DC., USA. ILSI India provides scientific inputs and secretariat assistance to the South Asian Region It has headquarters in New Delhi. It is a scientific, non-profit organization.

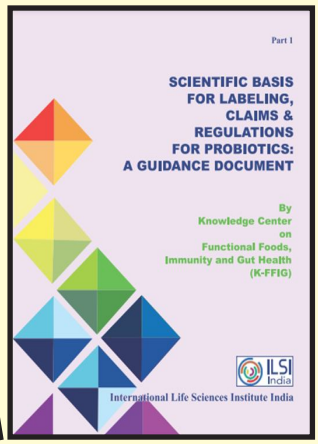
ILSI India designs programs to foster multi-sector collaboration for conducting, summarizing, and disseminating science related to most pressing health issues in the region. ILSI strategy encourages global action on identifying and then resolving outstanding scientific questions in the four thematic areas that capture the core of ILSI / ILSI India's work: Food Safety, Risk Science and Toxicology, Nutrition and Health, Sustainable Agriculture and Nutrition Security. They also help elucidate new opportunities for driving scientific progress. All activities follow Principles of Scientific Integrity which are part of ILSI Mandatory Policies. More information can be downloaded from: http://www.ilsi-india.org.

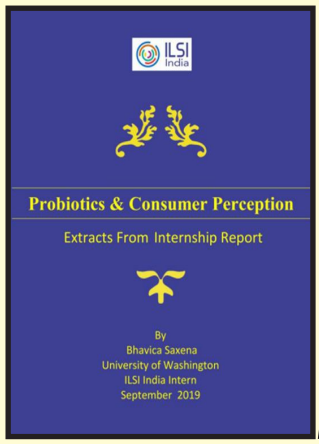
Gut Microbiome is an exciting new field of research. As the science of microbiome and the role of food based approaches in strengthening it over a lifetime is emerging ILSI-India launched **Knowledge Center on Functional Foods, Immunity and Gut Health (K-FFIG)** - a center of excellence - in New Delhi in October 2019. The Knowledge Center acts as a Think Tank, involving stakeholders from Government, Academia and Industry, that works towards sharing relevant research and technological developments in the area of human microbiome and functional foods. **K-FFIG** has undertaken several activities including: organization of **Scientific Meetings,** undertaking **Surveys,** sponsoring **Research,** publishing **Monographs** and articles in **journals,** creating **Resource Center** on latest studies on Microbiome and Gut Health and Functional Foods including Probiotics and Prebiotics. For more information visit: http://www.ilsi-india.org/kffig.htm.

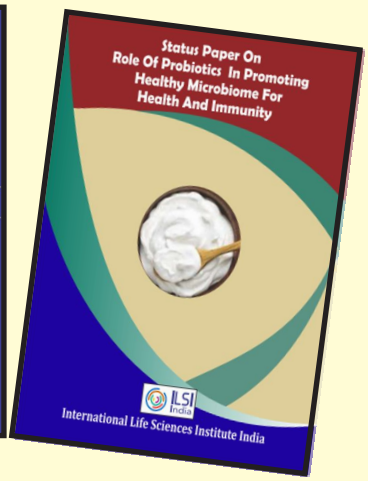
Monograph can be download from: http://www.ilsi-india.org / kffig

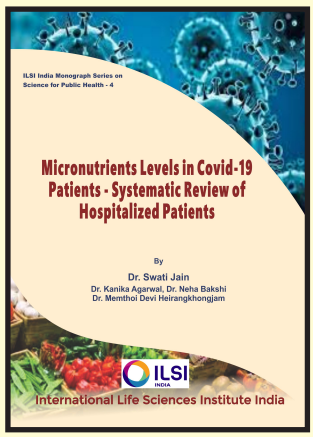
Latest Publications

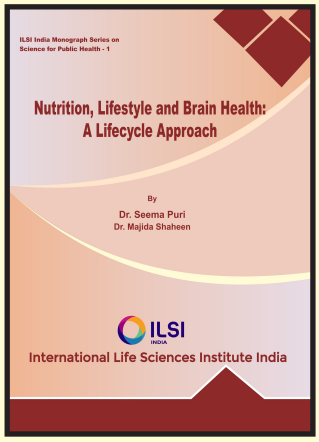


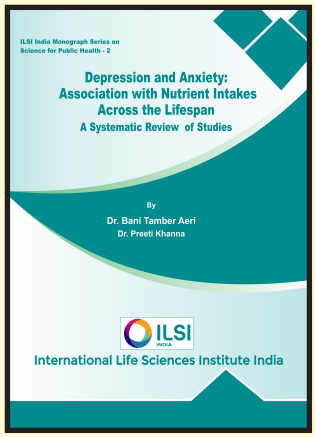


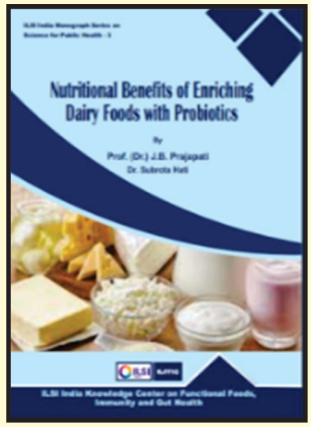


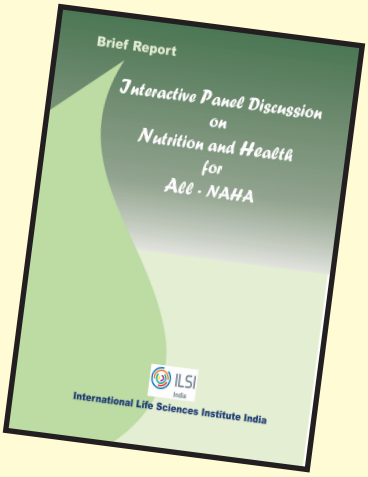


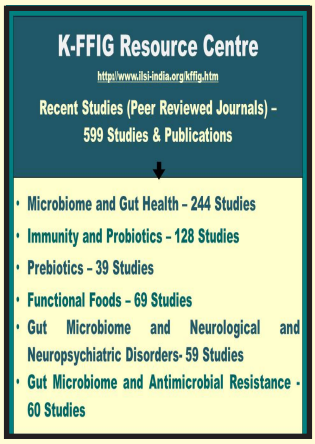


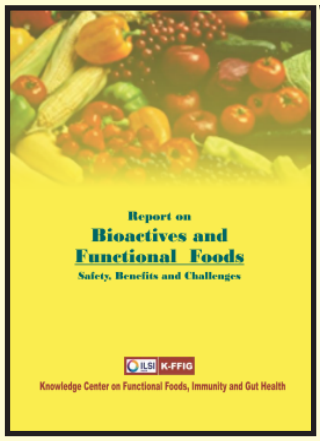












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New Delhi, India

Website: http://www.ilsi-india.org/kffig.htm