Safety and Efficacy of Nutraceauticals

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Basic Requirements

It should be safe

It should serve the purpose

Definition of Food Safety

(FAO/WHO, 2003)

It is the degree of confidence that food will not cause sickness or harm to the consumer when it is prepared, served and eaten according to its intended use

Paracelsus
(16th Century alchemist

"All things are poisons; nothing is without poison; only the dose makes a thing not a poison".

Food Safety And Standards (Health Supplements, Nutraceuticals, Food For Special Dietary Use, Food For Special Medical Purpose, Functional Food And Novel Food) Regulations, 2016

I to VI schedules provide the list of nutraceauticals/ingredients whose safety has been established. For some minimum to maximum dose range is given. For some safe limits have not been given.

Any nutraceutical other than those listed in regulations, prior approval of FSSAI is required.

Safety Evaluation

Acute toxicity

Short term toxicity

Long term toxicity

Mutagenicity,

Carcinogenicity

Tertogenecity

Multigeneration studies

LOAEL, NOAEL, UL

Increase or Decrease the risk of

Chronic or other diseases

Hazard identification

known or potential adverse health effects of a given nutrient. It involves the collection, organisation and evaluation of all information pertaining to the adverse effects of a given nutrient. It concludes with a summary of the evidence concerning the capacity of the nutrient to cause one or more types of adverse effect in humans

Hazard characterization

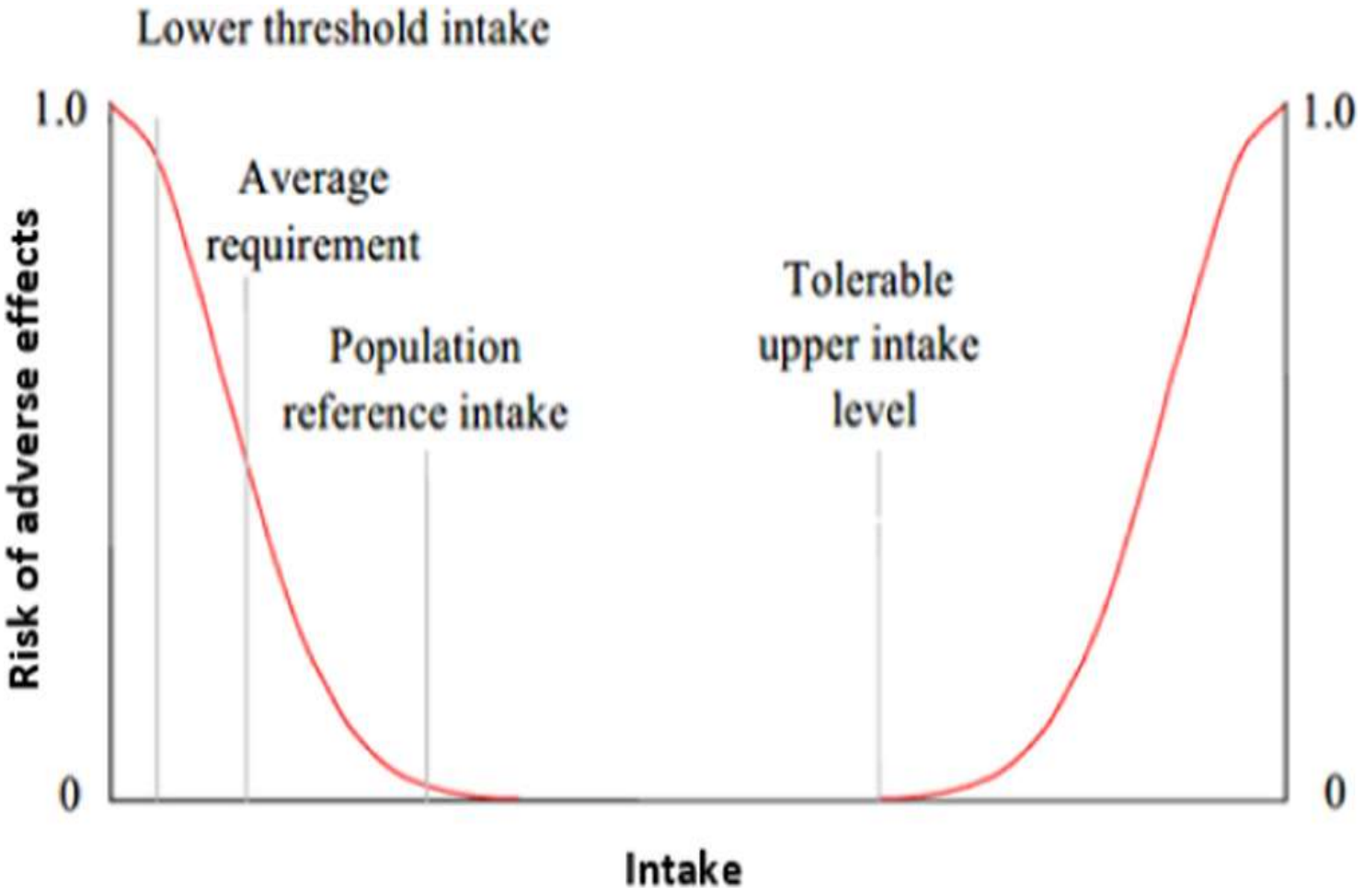
The qualitative and quantitative evaluation of the nature of the adverse effects associated with a nutrient; this includes a dose response assessment
, i.e. determining the relationship between nutrient intake (dose) and adverse effect (in terms of frequency and severity).
Based on these evaluations, an UL is derived taking into account the scientific uncertainties in the data.
ULs may be derived for various life-stage groups within the population.
LOAEL, NOAEL, Uncertainty Factor and UL

Tolerable Upper Intake Level

The Tolerable Upper Intake Level refers to the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases. The term tolerable is chosen because it connotes a level of Intake that can, with high probability, be tolerated biologically by individuals; it does not imply acceptability of that level in any other sense

Observed Safe Level

Shao and Hathcock (2006) developed a he Highest Observed Intake (HOI) as established by FAO/WHO (2006) as well as an Observed Safe Level (OSL) as proposed by Hathcock (2004) these would appear to be appropriate assessment methods to set safety.The Highest Observed Intake is derived only when no adverse health effects have been identified. It is the highest level of intake observed or administered as reported in studies of acceptable quality. The basic concepts of the HOI and OSL are identical. Due to the sanction of the HOI term by the FAO/WHO and further adoption in the Codex guideline on nutrient risk analysis (Codex Alimentarius Commission 2010)


Lower threshold intake
1.0
Average
requirement
Population
reference intake
Tolerable
upper intake
level
1.0
Risk of adverse effects
0
0
Intake

The health claims may include the following types, but not limited to.-

i) ingredients (nutrient or nutritional) function claims
(ii) enhanced function claims
(iii) disease risk reduction claims (Deleted.1st April,2022)
(iv) health maintenance claims
(v) immunity claims – increased resistance (excluding vaccines
(vi) anti-ageing claims.

Disease Risk reduction claims permitted (FSSAI)

Calcium or calcium & Vitamin D –Osteoporosis
Sodium – Hypertension
Dietary saturated fat - Blood Cholesterol
Potassium – Risk of high blood pressure
Alpha Linolenic acid- Blood cholesterol
Soluble dietary fibre - Lipid profile
Phytosterols and stanols- Lipid profile
Betaglucons and blood Glucose

Established functions of Vitamins

1.Vitamin A Vitamin A helps against night blindness.
2. Vitamin D Vitamin D supports strong bones.
3. Vitamin B12 Vitamin B12 is important for maintaining normal functioning of Nervous system and blood formation.
4. Folate & Folic acid Folate & Folic acid is important for foetal development and blood formation.
5. Iron Iron fights Anemia.
6. Iodine Iodine is required for normal growth, thyroid and brain function.
7. Zinc Zinc supports a healthy immune system.
8. Thiamine Thiamine is required for normal nerve and heart function
. 9. Riboflavin Riboflavin is necessary to release the energy from food.
10. Niacin Niacin is necessary to release the energy from food.
11. Pyridoxine Pyridoxine is necessary to release the energy from food

10 Benefits of Vitamin D

1.Healthy bones

2.Healthy teeth

3.Suuports immune system

4.Improves brain function

5.Supports healthy nervous systems

6.Supports lung function

7. Improves heart health

8. Reduces the risk of flu

9. Regulates insulin levels

10 Healthy infants

Vitamin D- Hazard characterization

Hyper calcimea was the only adverse effect found in toxicity studies of Vitamin D

Hazard characterization

NOAEL 10000IU
UF of 2.5
UL for adults 4000IU/Day

RDA for Vitamin D 400IU/Day

Lycopene –A bioactive compound

Lycopene – Caroteniod –Most potent Antioxidant

Major source Tomato, Carrot, watermelon, papaya etc

High intake of Lycopene Athero protective effect

Reduces LDL Cholesterol
Inhibits Several cancer cells

6mg /day reduces the risk of postrate cancer
6.5 mg/day risk of lung cancer in Non smoking women
12.5 mg/day reduces risk of lung cancer in non-smoking men
30mg/day decreases the growth of prostrate cancer
60mg/day reduces theLDL cholesterol

Hazard Identification

No adverse effects except Carotenemia

Lycopene dipostion in Liver, but no hepatic dysfunction

Hazard Characterization

Many studies to identify NOAEL at different doses
NOAEL 3000mg/kgbw/day
Another study 1% diet
IOM Due to lack of data NO TUL derived
EFSA 50mg/kgbw/day
JECFA NO ADI specified
Highest observed Intake 20mg/day

Efficacy of Nutracueaticals

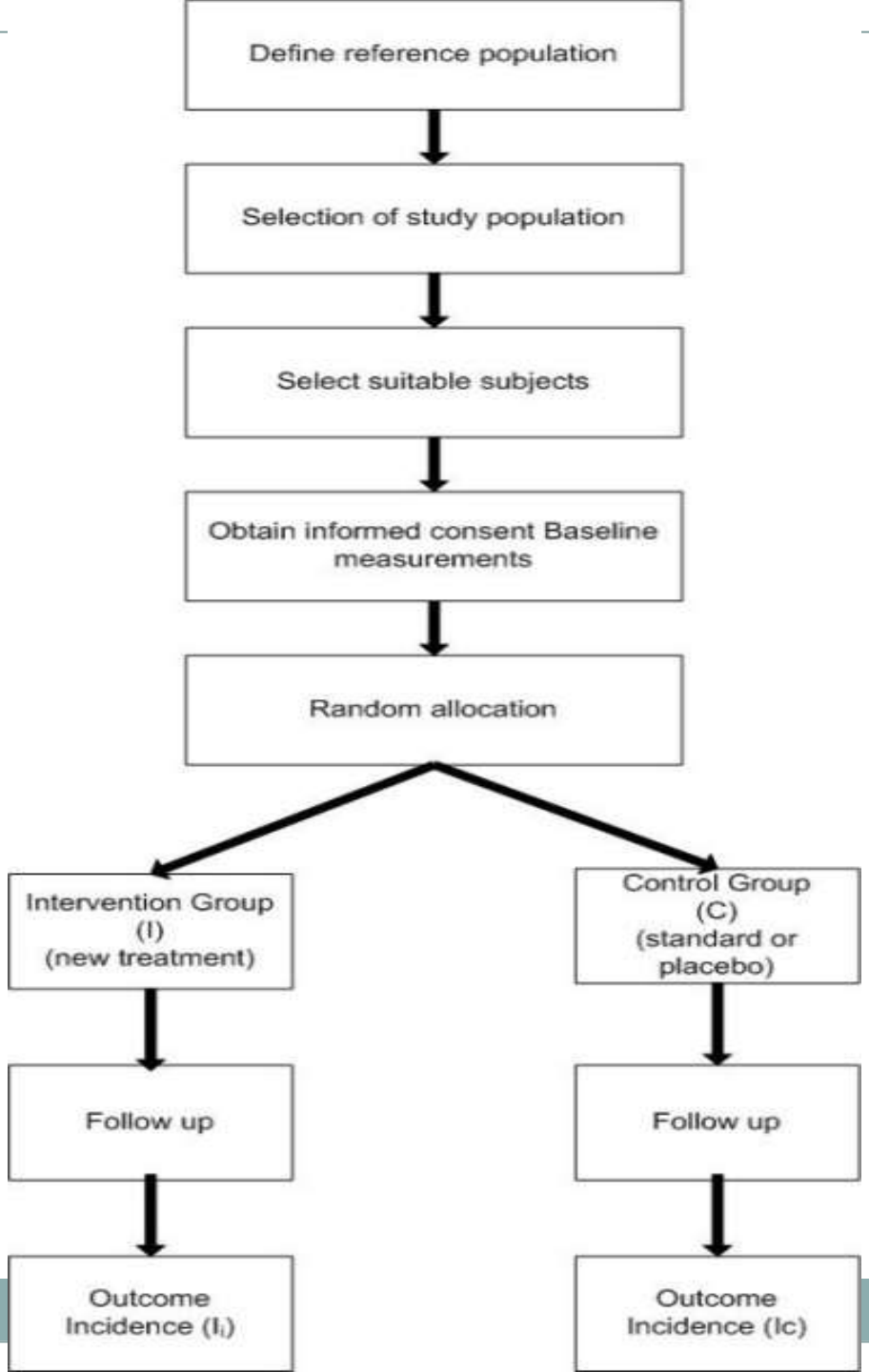
1.Well Designed human clinical trails

2. Observational studies are not sufficient

3. Ex vivo, In vitro animal studies can support but not sufficient

What is well designed Human intervention trial ?

The randomized controlled trial is considered as the most rigorous method of determining whether a cause-effect relationship exists between an intervention and outcome
The strength of the RCT lies in the process of randomization that is unique


Define reference population
Selection of study population
Select suitable subjects
Obtain informed consent Baseline measurements
Random allocation
Intervention Group (I) (new treatment)
Control Group (C) (standard or placebo)
Follow up
Follow up
Outcome Incidence (I_i)
Outcome Incidence (Ic)

Strengths of a randomized controlled trial

- Strongest evidence of any epidemiological study design that a given intervention has a postulated effectiveness and is safe.
- A RCT provides the best type of epidemiological study from which to draw conclusions on causality.
- Randomisation provides a powerful tool for controlling for confounding, even by factors that may be unknown or difficult to measure. Therefore, if well designed and conducted, a RCT minimizes the possibility that any observed association is due to confounding.
- Clear temporal sequence - exposure clearly precedes outcome.
- Provides a strong basis for statistical inference.
- Enables blinding and therefore minimizes bias.
- Can measure disease incidence and multiple outcomes.

- Weaknesses of RCT

- Ethical constraints - for example, it is not always possible or ethical to manipulate exposure at random.
- Expensive and time consuming.

Measurement of claimed health effect

Direct measurement
Validated biomarker
(Plasma cholesterol for cardio vascular diseases)

Plasma cholesterol vs dietary cholesterol

Production condition, batch to batch variability
Analytical procedures, stability studies, storage conditions and shelf life

Study design
Statistical analysis

Key information in each included study

(a) Study Reference
(b) Study Design
(c) Objectives
(d) Sample Size In The Study Groups And Loss To Follow-up Or Non-response
(e) Participant Characteristics
(f) Method Used To Measure The Food Or Property Of Food Including Amount Consumed
(g) Confounders Measured
(h) Method Used To Measure The Health Effect
(i) Study Results, Including Effect Size And Statistical Significance
(j) Adverse Effects.

An assessment of the quality of each included study based on consideration of, as a minimum

(a) A clearly stated hypothesis
(b) Minimisation of bias
(c) Adequate control for confounding
(d) The study participants' background diets and other relevant lifestyle factors
(e) Study duration and follow-up adequate to demonstrate the health effect
(f) The statistical power to test the hypothesis.

Decision Tree approach for establishing Food Health Relationship

Formulate FRH

Formulate Literature Search Strategy

Identify & categorise studies (Y/N)

Are there any human studies (Y/N)

A well designed experimental, cohort, case control studies (Y/N)

Assess and interpret evidence Are the studies likely to be of sufficient quality to allow a subsequent assessment of the totality of evidence? (Y/N)

Assess totality of evidence Consistent association? Causal relationship independent of other factors? (Y/N)

Food-health relationship likely to be established under identified circumstances (Y/N)

Consider amount of food/property of food required to achieve the health effect in context of their respective populations

US FDA

Science based evaluation of the strength of evidence to support the claim statement

Methodology quality
Quality of evidence
Number of various types of studies-sample size
Overall consistency of the evidence

Significant Scientific Agreement

Extent of Agreement among qualified expert in the field – lies very close to consensus

1. Identifying studies to that evaluate the substance/disease relationship
2. Intervention studies
3 Observational studies
4 Research synthesis studies
5 Animal & invitro studies
6 Identifying surrogate endpoints of disease risk
7 Evaluating human studies
8 Assessing the methodological quality of studies
9 Evaluating the totality of scientific evidence

Oats

Coronary artery disease

Colorectal cancer

Blood Pressure

60 g Oats(un processed) /day has a beneficial effect on lowering the serum cholesterol (USFDA)

Help in reduction of rise in blood glucose after that meal (FSSAI)

Oryzanol

Helps in Lowering cholesterol

Effect On Hypertension

Anti-Diabetic effect

Protective Effect on Liver

Anti – carcinogenic effect + 11

Oryzanol content varies from 0.2-0.5% = 200-500 mg/100g

60-150mg/day at the rate of 30g/day oil

300mg/day 8 week RCT study

To Conclude

Safety and efficacy are basic requirements of nutraceuticals

Observational studies or studies in animal models or in vivo and intro studies can help the understanding the biochemical basis of efficacy, but Human clinical trail is must show the efficacy.


Thank you for your attention