SAFETY OF FUNCTIONAL FOODS

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Example of Functional ingredients In Indian Diet

- Grains - Source of fibre (minor millets)
- Legumes (soya) – Isoflavones (Genistein, Diadezin)
- Probiotics - curds, butter milk, Fermented foods
- Fruits and vegetables- phytochemicals

Definition of Functional Foods

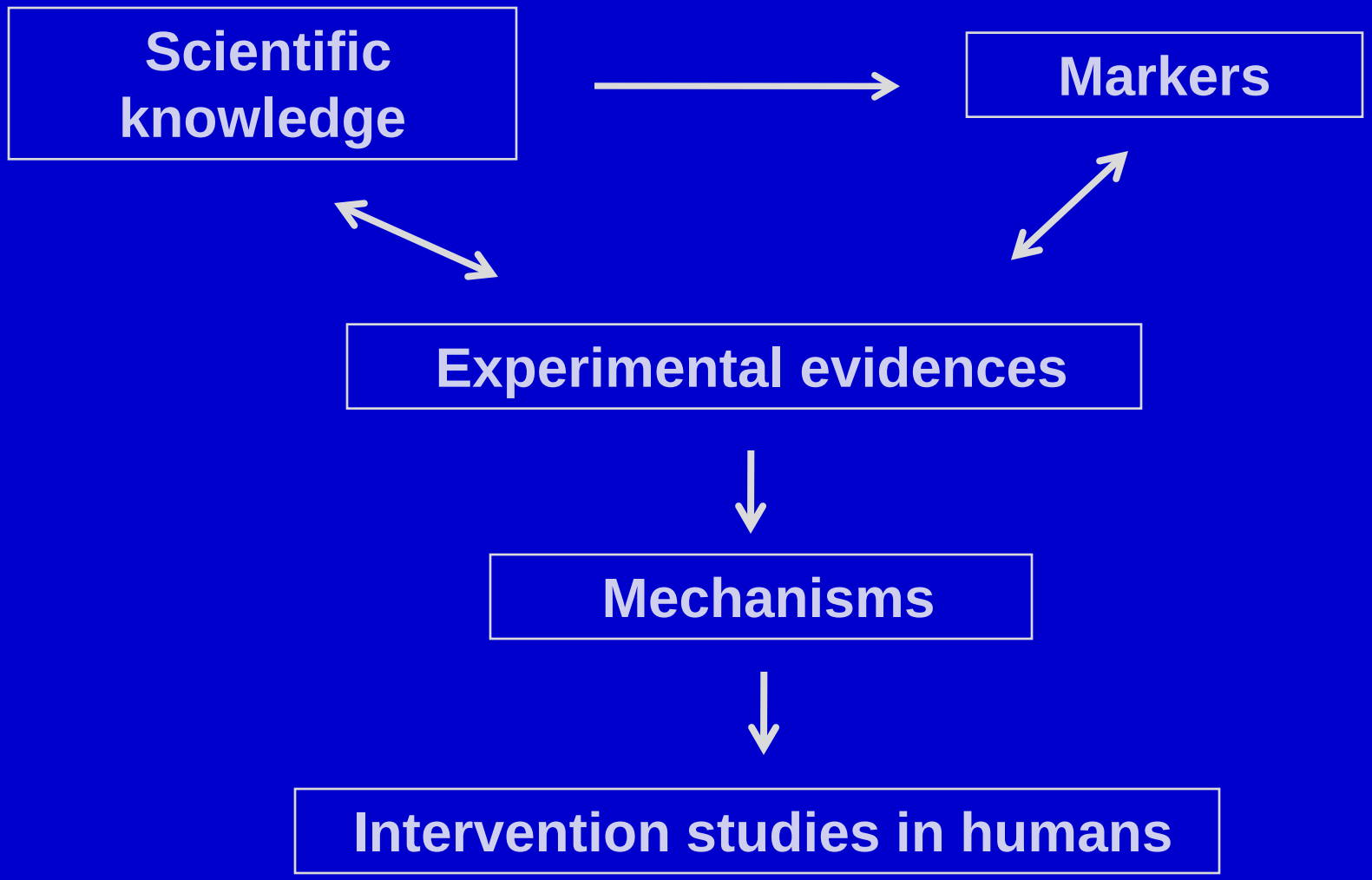
- Foods that provide additional physiological or health-promoting benefits beyond the well-established functions of nutrients contained in foods.

- Japan is the only country that has formulated a specific regulatory approval process for functional foods known as Foods for Specified Health Use (FOSHU).

FUNCTIONAL FOODS

- Natural food- Fiber in millets
- Food to which a component has been added- probiotic icecream
- Food from which a component has been removed- Processed Soya
- Food where the nature of one or more components has been modified- High Oleic sunflower oil
- Food in which the bioavailability of one or more components has been modified
- or any combination of these possibilities.

Strategy for functional food discovery and development



SAFETY OF FUNCTIONAL FOODS

- Needs to be assessed according to established regulations
- Proof of Concept
- Preclinical test – Efficacy and safety
- Pharmacokinetics
- ADI / Safe upper limits
- Biomarkers
- Clinical – Randomised Clinical Trials

Identification of Biomarkers

- Identified and validated for their predictive value.
- Markers correlated to events are indicator markers directly involved in the process of assessment are effect biomarkers.
- If the markers are related to risk of disease they are known as susceptibility markers. These are based on genetic polymorphism controlling the metabolism and / or the effect of a particular food component.

Identification of Biomarkers (Contd.)

- Intake biomarkers identified and validated to assess exposure to food component

- Biomarkers may be used to measure biological responses by measuring a specific protein, enzyme or hormone in response to consumption of a food.

Safe Limits for Nutrients

There is no evidence that essential micronutrients should be regarded as inherently safe at high doses and much evidence, that excessive intakes can cause harm

Safe Upper Levels for Vitamins and Minerals

May 2003

Expert Group on Vitamins and Minerals

MICHAEL LANGMAN

Figure 1. Theoretical dose-response relationships in humans

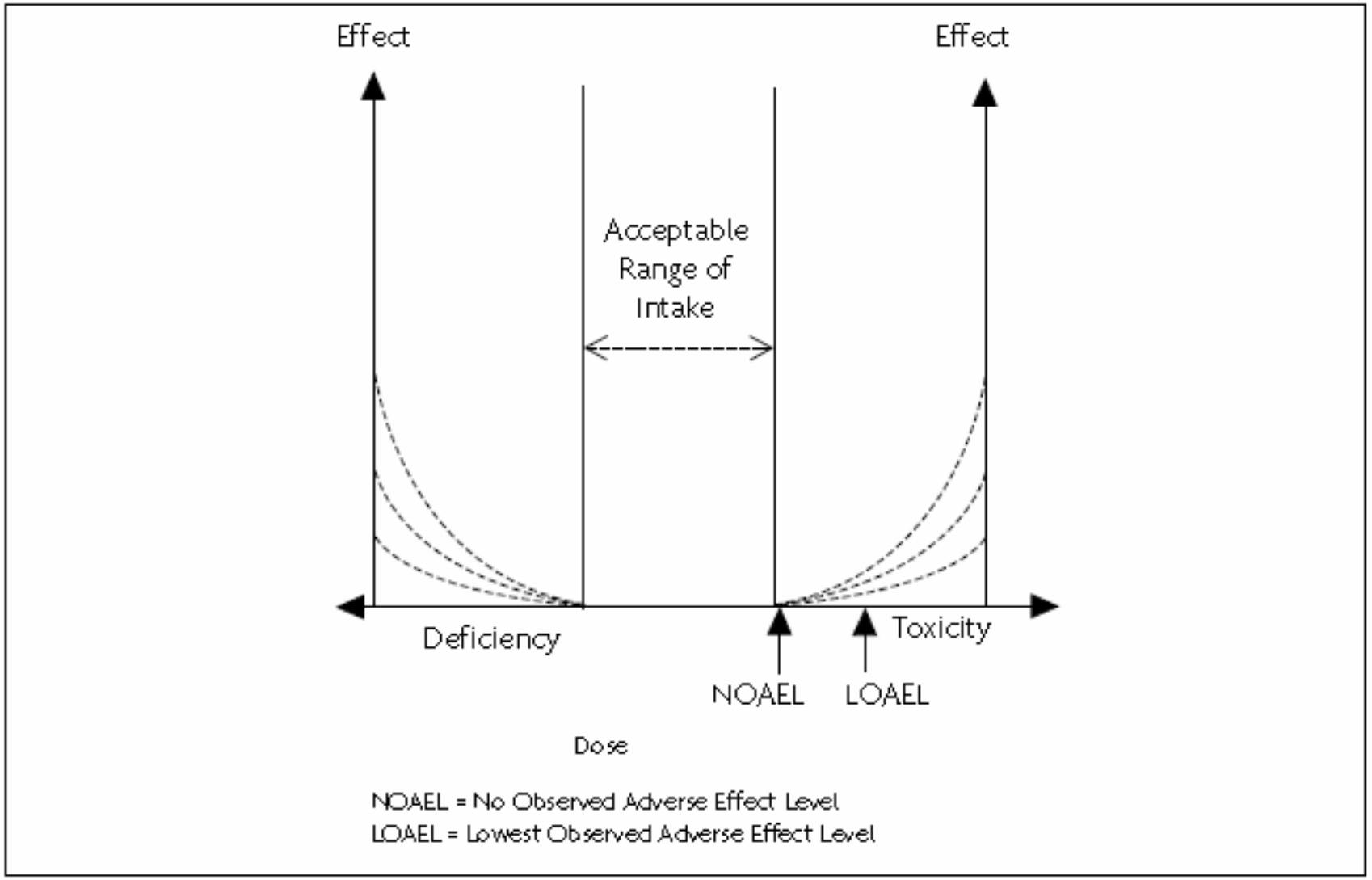
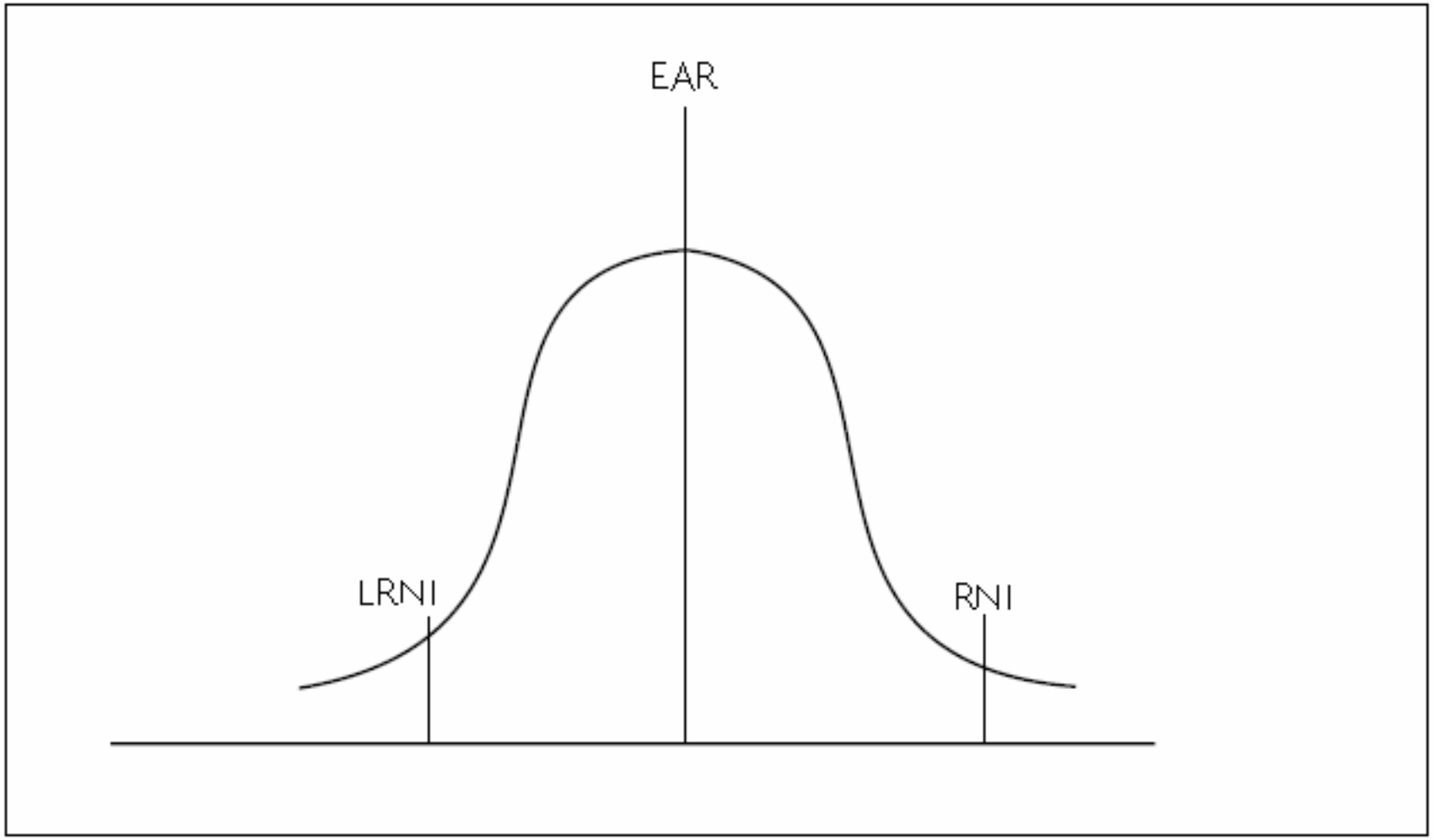


Figure 2. Nutritional requirements



Dietary Reference Intakes

Estimated Average Requirement (EAR): the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group.

Recommended Dietary Allowance (RDA): The average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group.

Adequate Intake (AI): The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate. Used when an RDA cannot be determined.

Tolerable Upper Intake Level (UL): The highest average daily intake level 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 potential risk of adverse effects may increase.

Source: Institute of Medicine, National Academy of Sciences, *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids,* p. 3. Washington, DC: National Academy Press, 2000.

Safe Upper Levels

an intake that can be consumed daily over a lifetime without significant risk to health on the basis of available evidence

Guidance Levels

an approximate indication of levels that would not be expected to cause adverse effects, but have been derived from limited data and are less secure than SULs.

SULs or Guidance Levels are the doses of vitamins and minerals that susceptible individuals could take daily on a life-long basis, without medical supervision

Supplemental intake + Dietary and other known exposures = Estimated SUL (total)

Risk assessments

- Risk assessment :
- Hazard identification (Adverse effects)
- Hazard characterisation (including dose-response assessment);
- Exposure assessment
- Risk characterisation.

- Risk-benefit analysis

Extrapolating LOAEL to derive NOAEL (based on human data)

- If adverse effect is a biochemical change with no clinical or organ correlation – factor is 3
- Eg Serum transaminase levels were elevated at 30mg dose i.e LOAEL
- Then NOAEL will be 30/3 = 10 mg
- If adverse effect was a serious toxic change then NOAEL will be 30/10= 3 mg

Extrapolating NOAEL to derive SUL (based on ANIMAL data)

- If NOAEL is 10 mg
- SUL = 10 / 10 x 10 = 0.1 mg
- Factor of 10 for inter species variation
- Factor of 10 for inter individual variation

Risk Assessment for Folic Acid

- Folic acid is generally considered as safe in therapeutic use.
- Few data from toxicological studies of folates in animals.
- ESTABLISHMENT OF GUIDANCE LEVEL
- Insufficient data to establish a Safe Upper Level for folic acid.
- Increased folate intake may increase the incidence of multiple births.
- Currently no substantive evidence for such an effect.

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Folic Acid (contd…)

- Main concern of excess folic acid is the masking of vitamin B12 deficiency.
- Data indicates supplementation with 1 mg/day folic acid does not mask vitamin B12-associated anaemia in the majority of subjects
- Supplementation with 5 mg/day folic acid masks B12 deficiency
- What happens between 1 and 5 mg/day - not known.
- For guidance purposes only, in the general population a supplemental dose of 1 mg/day would not be expected to cause adverse effects.

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Folic Acid (contd…)

- Assuming a maximum intake from food of approximately 0.49 mg/day, a total dose of 1.5 mg/day (equivalent to 0.025 mg/kg bw/day in a 60 kg adult) would not be expected to have any adverse effects.

Risk assesment for Pyridoxine

- Adverse effect, for vitamin B6 is neuropathy in humans and laboratory animals.
- Occurs after consumption of high doses and/or long duration.
- Mostly reversible but in some cases with high doses, the effects are irreversible.
- Progressive sensory ataxia , unstable gait and numb feet and hands, followed by profound impairment of position sense and vibration sense in the distal limbs.
- Animal studies also demonstrate neurotoxicity
- Doses as low as 50 mg/kg bw/day have been associated with demyelination

SUL for B6

- LOAEL: 50 mg/kg bw/day, based on the study by Phillips *et al*. (1978) in dogs
- Uncertainty factors: 3 for LOAEL to NOAEL extrapolation
- 10 for inter-species variation
- 10 for inter-individual variation
- Safe Upper Level 50/3 x 10x 10 = 50 / 300 =0.17 mg/kg bw/day supplemental pyridoxine- equivalent to 10 mg/day for a 60 kg adult over a lifetime

B6 Dose Range

- In humans, 10 mg/day represents a clear SUL, with no adverse effects
- Doses of 200 mg/day vitamin B6 or more taken for long periods are associated with neuropathy.
- The effect of taking vitamin B6 at doses between 10 and 200 mg is unclear.

Niacin[g] (nicotinic acid and nicotinamide)	35 mg	The UL for nicotinic acid is based on vasodilation (flushing). Nicotinamide appears not to be associated with the flushing effects.	LOAEL = 50 mg	16/14 mg-RDA Indian : 16 – 21 mg/d	20 mg DNI
Vitamin B_6	100 mg	The critical adverse effect from high intake is neuropathy.	NOAEL = 200 mg	1.3, 1.5, or 1.7 mg[k] Indian : 2 – 2.5 mg/d	2.0 mg
Folate[g]	1,000 mcg	Excess folate may precipitate or exacerbate neuropathy in vitamin B_{12}-deficient individuals.	LOAEL = 5 mg	400/400 mcg[l] Indian : 200 – 500 µg/d	400 mcg

STEPS IN RISK ASSESSMENT

- Hazard Identification- scientific review.
- Specify Dose response- establish upper level.
- Intake /Exposure assessment.
- Risk characterization- public health impact.
- Too little nutrients and too much nutrients – both are safety issues.
- Nutrient risk assessments have to be life stage specific eg. adolescents, lactating. Aging populations etc.,

FACTORS FOR SUBSTANTIATION OF NUTRITIONAL SAFETY

- Source and origin of food
- Nutrient composition
- Presence of anti-nutritional factors
- Methods of production and / or preparation
- Technical specification including preparation
- Purpose to indicate rationale behind the development of functional food
- Instruction for storage and use including frequency, dose and duration in relation to dietary recommendations

Thank You