2015 Expert Consultation on Nutrienet Risk Assessment
for Determination of Safe Upper Levels for Nutrients

Nutrient Risk Assessment & Upper Levels: Korean Experience

2015. 12.4

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Nutrient deficiency

Controlling vitamin and mineral deficiency is an affordable opportunity to improve the lives of two billion people and strengthen the pulse of economic development

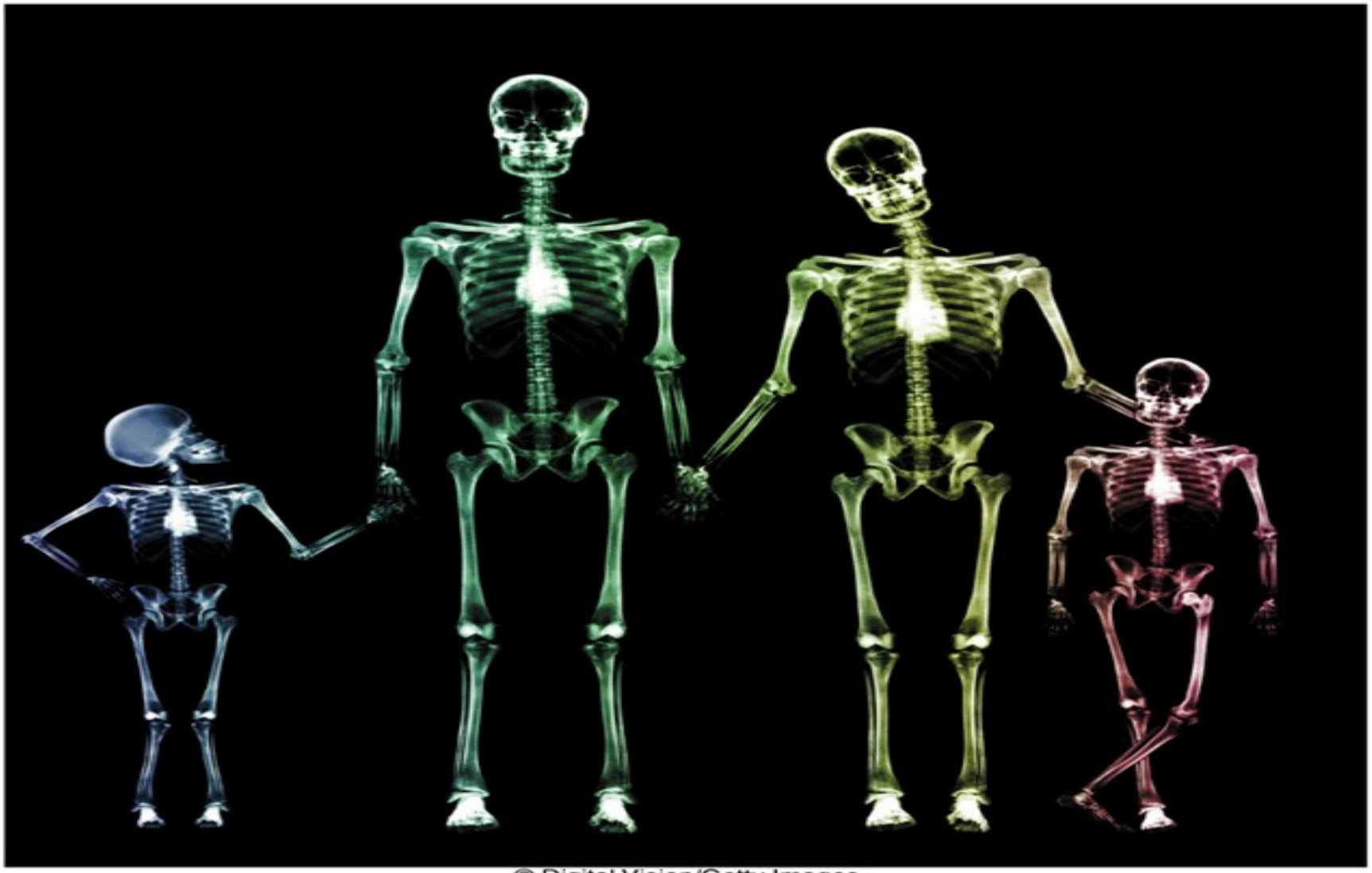
Vitamin & Mineral Deficiency, a global progress report, UNICEF, 2004

Nutrition in transition

Important shift in the burden from problems of dietary deficiency to problems of dietary excess

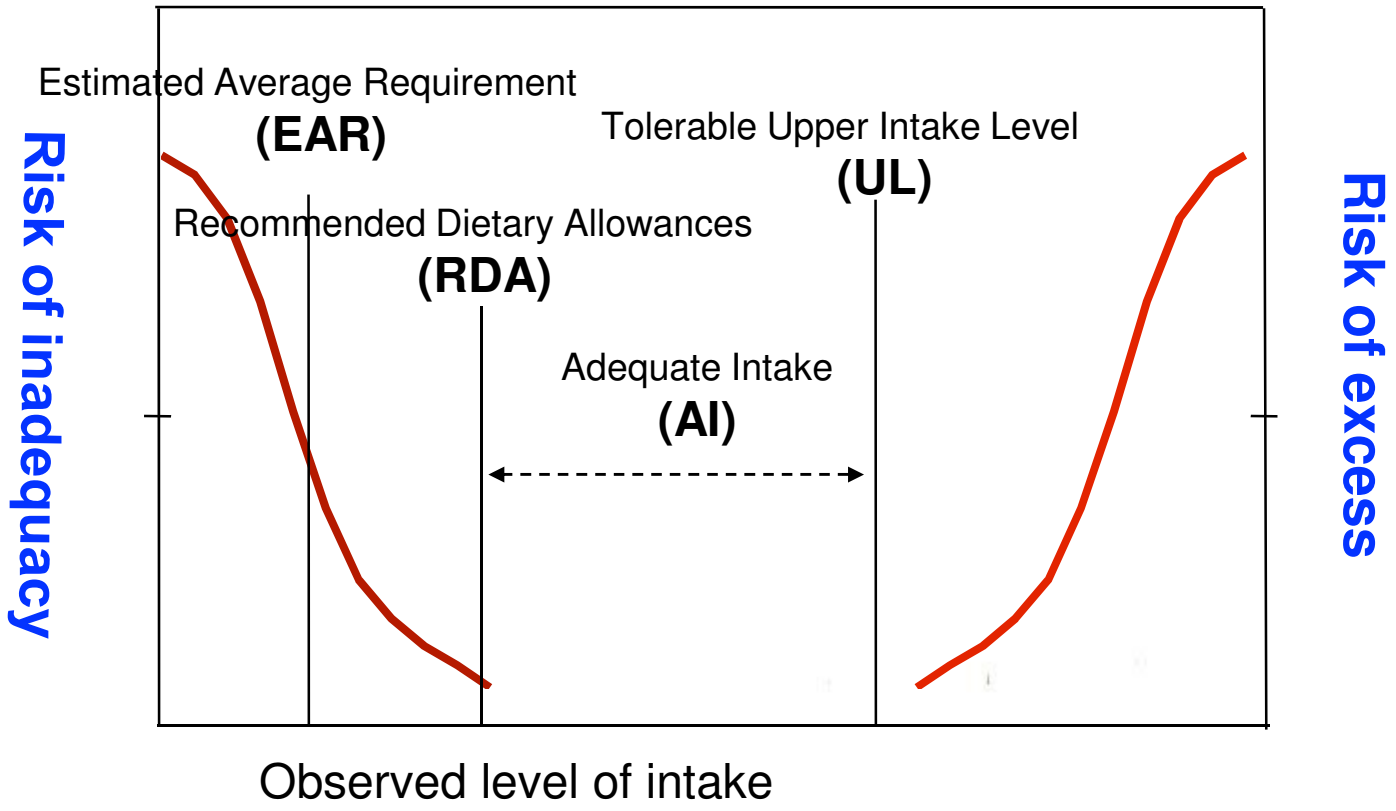
Hopkin et al., Nutrition Reviews 2001

Ensuring adequacy & safety throughout the life cycle

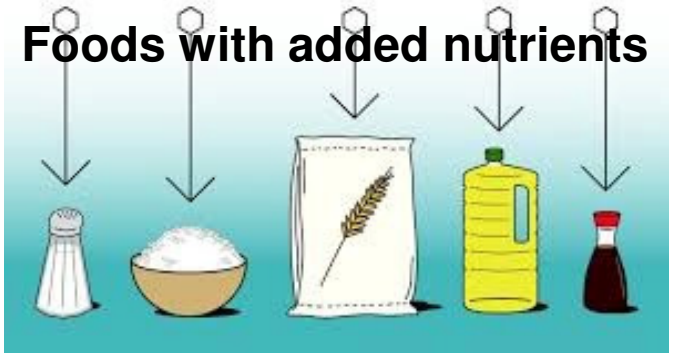


Reference intake levels for micronutrients

- Key challenge is to balance the risk of deficiency in some individuals with the risk of overconsumption in others in the same population.



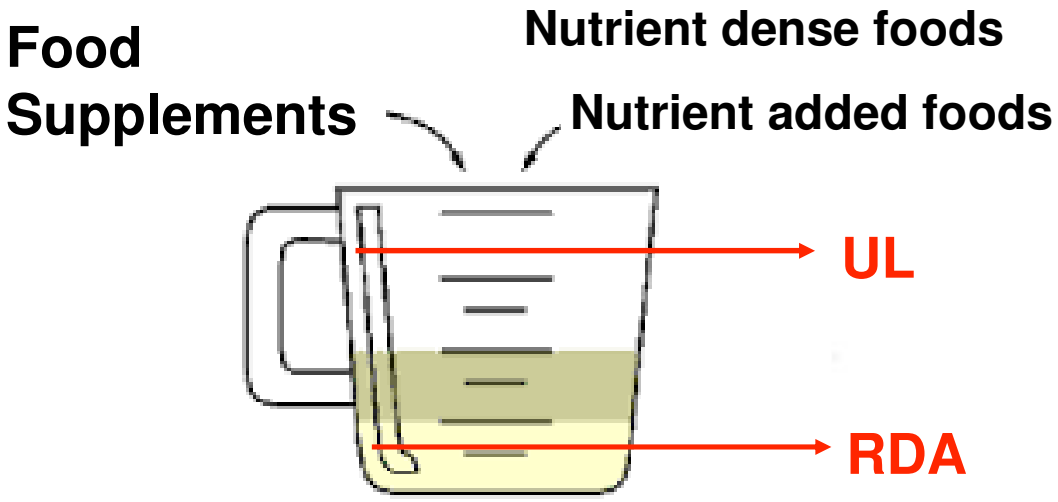
Three major ways of delivering micronutrients



The use of diversified diets can undoubtedly improve healthy,

but

Provide concerns that **the sum of intakes from all sources could reach levels that could cause adverse effects**.



Regulatory categories in Korea

[Ministry of Health & Welfare]

Korean Dietary Reference Intakes (RDA & UL)

[Ministry of Food & Drug Safety]

Food Sanitation Act (since 1962)

- ★**Nutrient dense foods**
- ★**Nutrient added foods**

- Nutrition labelling
- No min & max limits

Health/Functional Food Act (since 2004)

- ★**Food supplements**

- Nutrition labelling
- **Min. & max. limits (2006)**

Topics to be presented

- **Principles** of risk management for setting maximum safe level for vitamin and mineral supplements
- **Process** for the categorization of micronutrients according to the risk of exceeding the UL
- **Current market practices** in Korea

1 PRINCIPLES OF RISK MANAGEMENT FOR SETTING MAXIMUM SAFE LEVEL FOR VITAMIN & MINERAL SUPPLEMENTS

CODEX guidelines for vit/min food supplements

GUIDELINES FOR VITAMIN AND MINERAL FOOD SUPPLEMENTS

CAC/GL 55 - 2005

3.2 Contents of vitamins and minerals

3.2.1 The minimum level of each vitamin and/or mineral contained in a vitamin and mineral food supplement per daily portion of consumption as suggested by the manufacturer should be 15% of the recommended daily intake as determined by FAO/WHO.

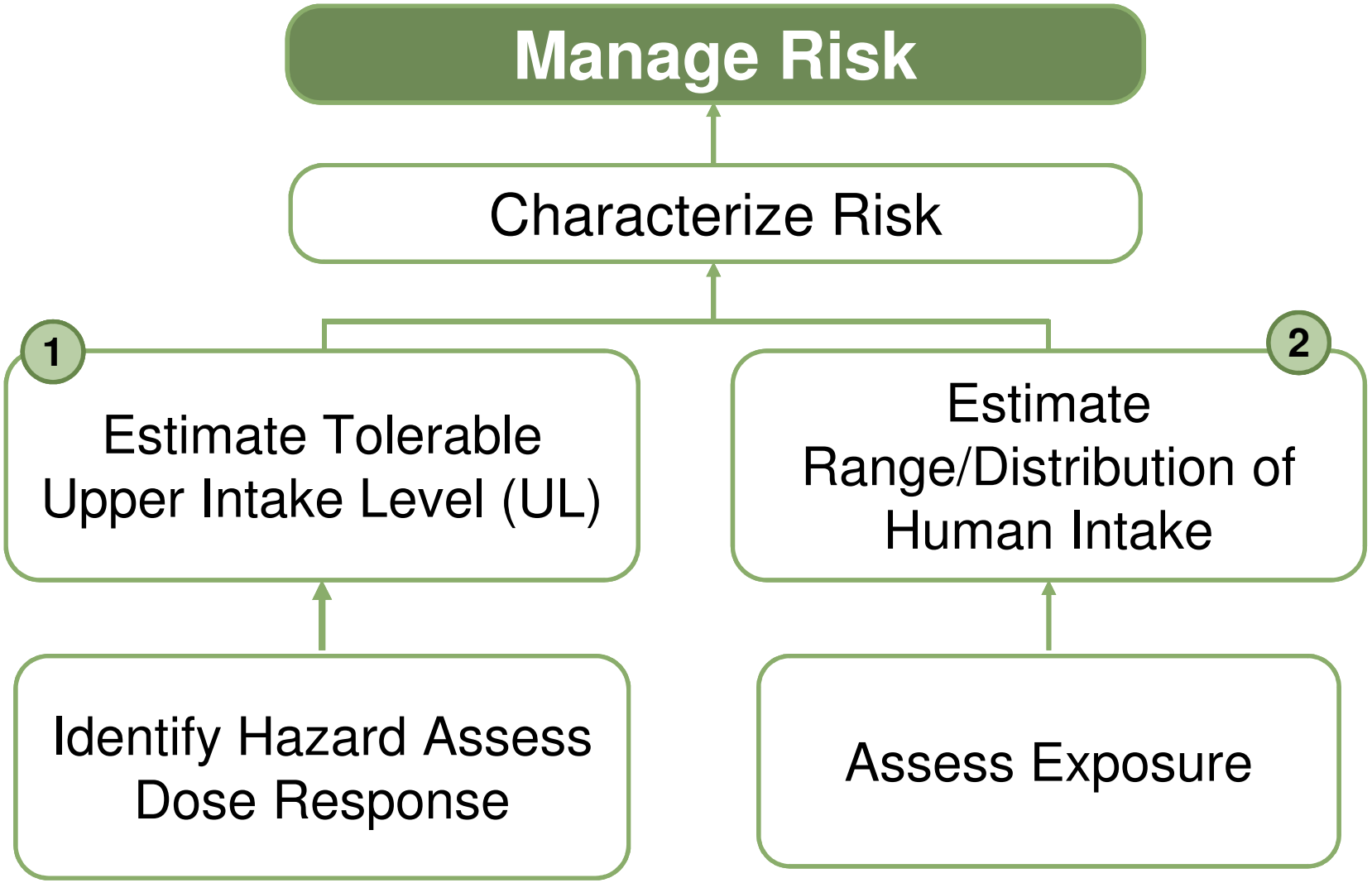
3.2.2 Maximum amounts of vitamins and minerals in vitamin and mineral food supplements per daily portion of consumption as recommended by the manufacturer shall be set, taking the following criteria into account:

1 upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into consideration, as appropriate, the varying degrees of sensitivity of different consumer groups;

2 the daily intake of vitamins and minerals from other dietary sources.

When the maximum levels are set, due account may be taken of the reference intake values of vitamins and minerals for the population. This provision should not lead to setting of maximum levels that are solely based on recommended nutrient intakes (e. g. Population Reference Intake or Recommended Daily Allowance values).

MSL for micronutrients: risk management

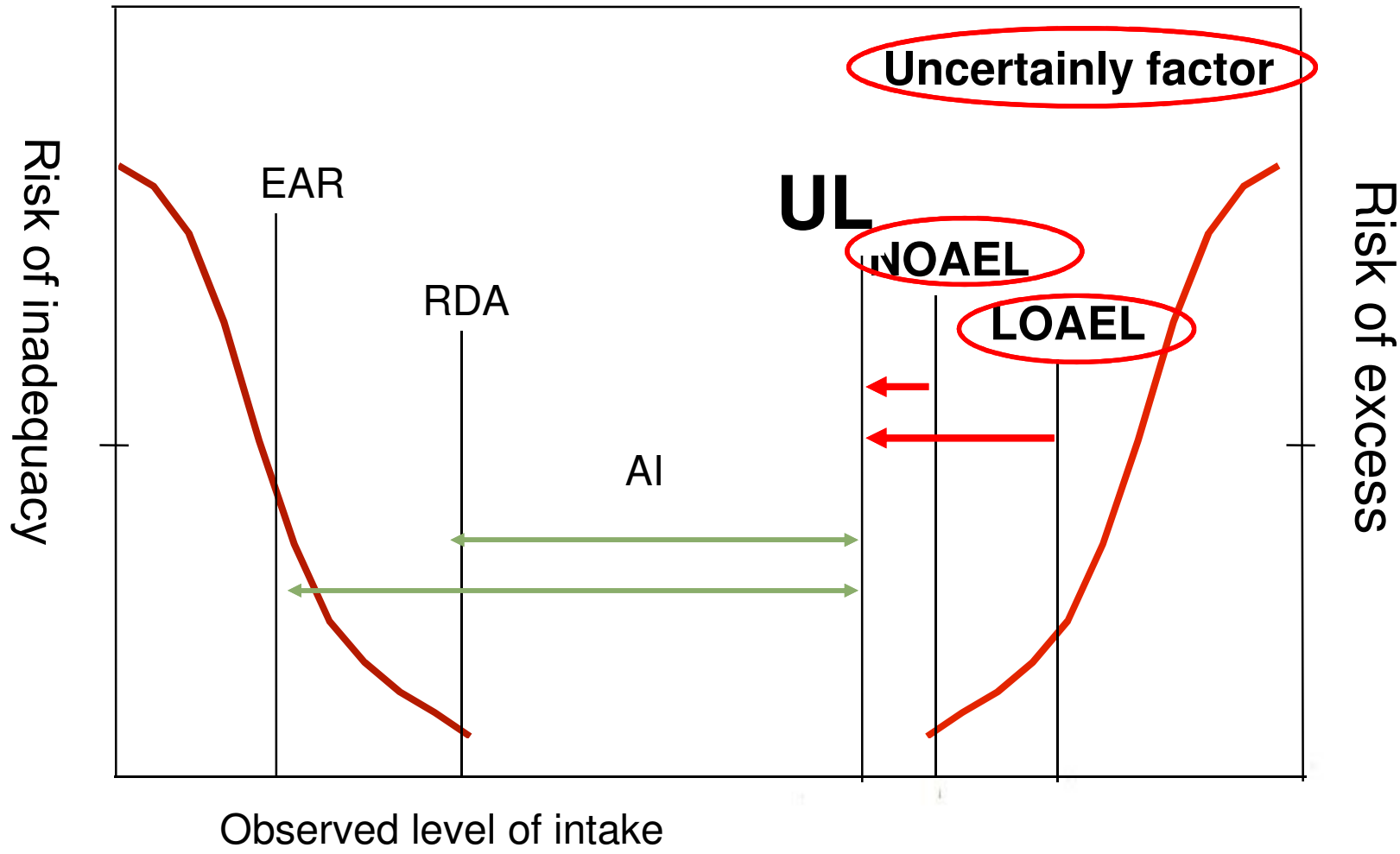


Key legal criteria for setting MSL

- **Objective basis for regulatory maximums for manufactured products**
- **Objective Codex standards, supportive of trade requirements under WTO**

1. Upper safe levels (**UL**) of vitamins and minerals by scientific risk assessment
2. Reference intakes of vitamins and minerals for the population (**Nutrient Reference Value, NRV**)
3. Intake of vitamins and minerals from all dietary sources

1 Upper safe levels of micronutrients



Numerical ULs for 14 nutrients

	Toxicologic end points	NOAEL	UF	UL
Vit A (ug RE)	Terotogenic/hepato-toxicity	4,500/14,000	1.5/5.0	3,000/3,000
Vit D (ug)	Hypercalcemia	60	1.0	60
Vit E (mg a-TE)	Bleeding	540	1.0	540
Vit C (mg)	Gastrointestinal intolerance	3,000	1.5	2,000
Niacin (mg NE)	Flushing (nicotinic acid) Hepatotoxicity (nicotinamide)	50/1,525	1.5/1.5	35/1,000
Vit B6 (mg)	Neuropathy	200	2.0	100
Folate (ug DFE)	Neurological injury	5,000	5.0	1,000
Ca (mg)	Milk alkali syndrome	5,000	2.0	2,500
Fe (mg)	Stomach pain	70	1.5	45
Zn (mg)	Copper deficiency	50	1.5	35
Cu (ug)	Damage in the liver	10,000	1.0	10,000
Mn (mg)	Neurological symptoms	11	1.0	11
I (ug)	Increase in TSH level	3,000	1.0	3,000
Se (ug)	Selenosis	850	2.0	400

2 Daily intake of nutrients in Korean population

- Assessment of the **current and potential intakes** of vitamins and minerals from the various dietary sources is required.
- Acquiring up-to-date composition and intake data and estimating usual intake are the major challenges.
- National nutrition surveys are the best sources of information: Korean National Health and Nutrition Examination Survey (**KNAHES**)
  - National Health Promotion Act
  - Cross-sectional study (>1 y; 24-hour recalls; dietary frequency)
  - Macronutrients, dietary fiber, Ca, P, Fe, Na, K, Vitamin A, carotene, retinol, thioamine, riboflavin, niacin, and vitamin C from food and beverages.
- **KFDA database** for food supplement registration and **other survey data** for supplement intake

Daily intake: 2001 KNHANES (n=2,201)

	Mean	Median	Mean highest Intake (MHI)
Vit A (ug RE)	788	616	2,239
Retinol (ug)	89.7	49	344
b-carotene (ug)	3,957	3,060	10,863
Vit C	139	107	434
Niacinamide (mg)	22.1	19.5	50.6
Vit B1 (mg)	1.6	1.4	3.8
Vit B2 (mg)	1.4	1.3	3.2
Ca (mg)	565	486	1,339
P (mg)	1,459	1,369	2,840
Fe (mg)	15.2	13.1	35.9

3 Nutrient Reference Values for labeling

Vit A (ug RE)	750
Vit D (ug)	10
Vit E (mg a-TE)	10
Vit C (mg)	100
Nicotinamide (mg NE)	16
Vit B6 (mg)	1.5
Folate (ug DFE)	400
Ca (mg)	800
Fe (mg)	14
Zn (mg)	10
Cu (ug)	800
Se (ug)	50
Mn (ug)	3.5
I (ug)	150

2 PROCESS FOR THE RISK CATEGORISATION OF MICRONUTRIENTS ACCORDING TO THE RISK OF EXCEEDING THE UL

Step 1. Group A micronutrients

- The ULs have not been established (**no adverse effects in healthy individuals with high intakes**)
- No further risk management measures are required.

Vitamin B1, B2, B12, biotin, panthothenic acid, K, & Cr

NO maximum safe level

Group A micronutrients

- No UL due to **lack of scientific evidence**
- Qualitative risk characterization.

Mo

Guidance level

Step 2: Group B & C

- Direct method
  - Maximum in products on basis of risk assessment of supplemental amounts of the ingredients.
  - **B-carotene (7 mg), nicotinic acid (17 mg), and magnesium (350 mg)**

- Difference method
  - Maximum by difference between UL and expected dietary intake from other sources

Step 3. Estimation of relative risk for each nutrient

	NRV	UL	Relative risk (UL/NRV)
Vit A (ug RE)	750	3,000	4.3
Vit D (ug)	10	60	6.0
Vit E (mg a-TE)	10	540	54.0
Vit C	100	2,000	20.0
Nicotinamide (mg NE)	16	1,000	62.5
Vit B6 (mg)	1.5	100	66.7
Folate (ug DFE)	400	1,000	2.5
Ca (mg)	800	2,500	3.1
Fe (mg)	14	45	3.2
Zn (mg)	10	35	3.5
Cu (ug)	800	10,000	12.5
Se (ug)	50	400	8.0
Mn (ug)	3.5	11	3.1
I (ug)	150	3,000	20

Group B

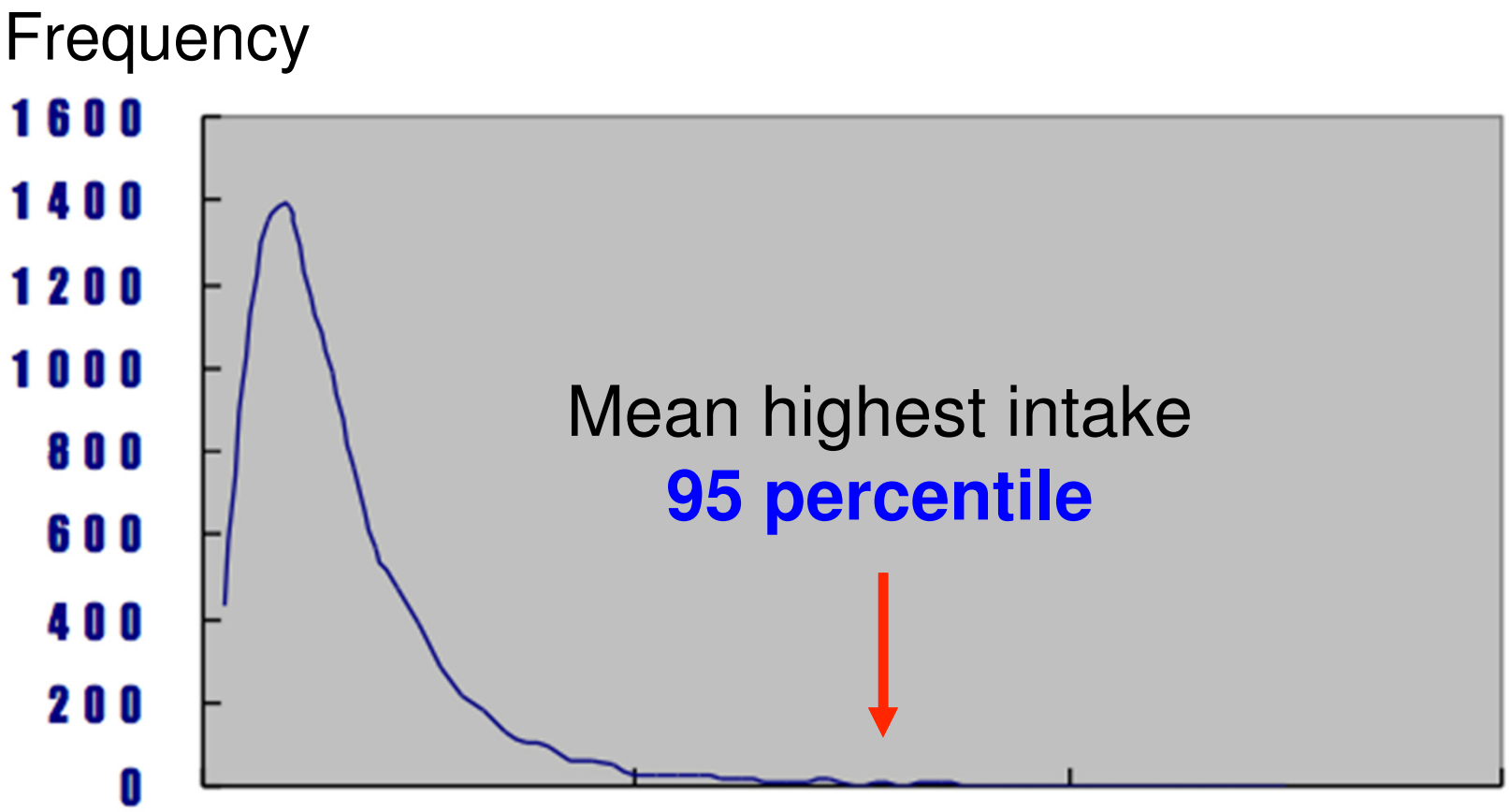
Group B

Step 4. Mean highest intake from foods

- To assure whether the potential intakes of vitamins and minerals from the various dietary sources are safe.
- Mean highest intake (MHI) from foods and fortified foods has been defined as the **95 percentile intake** (highest risk group).

Vitamin A intake

Example



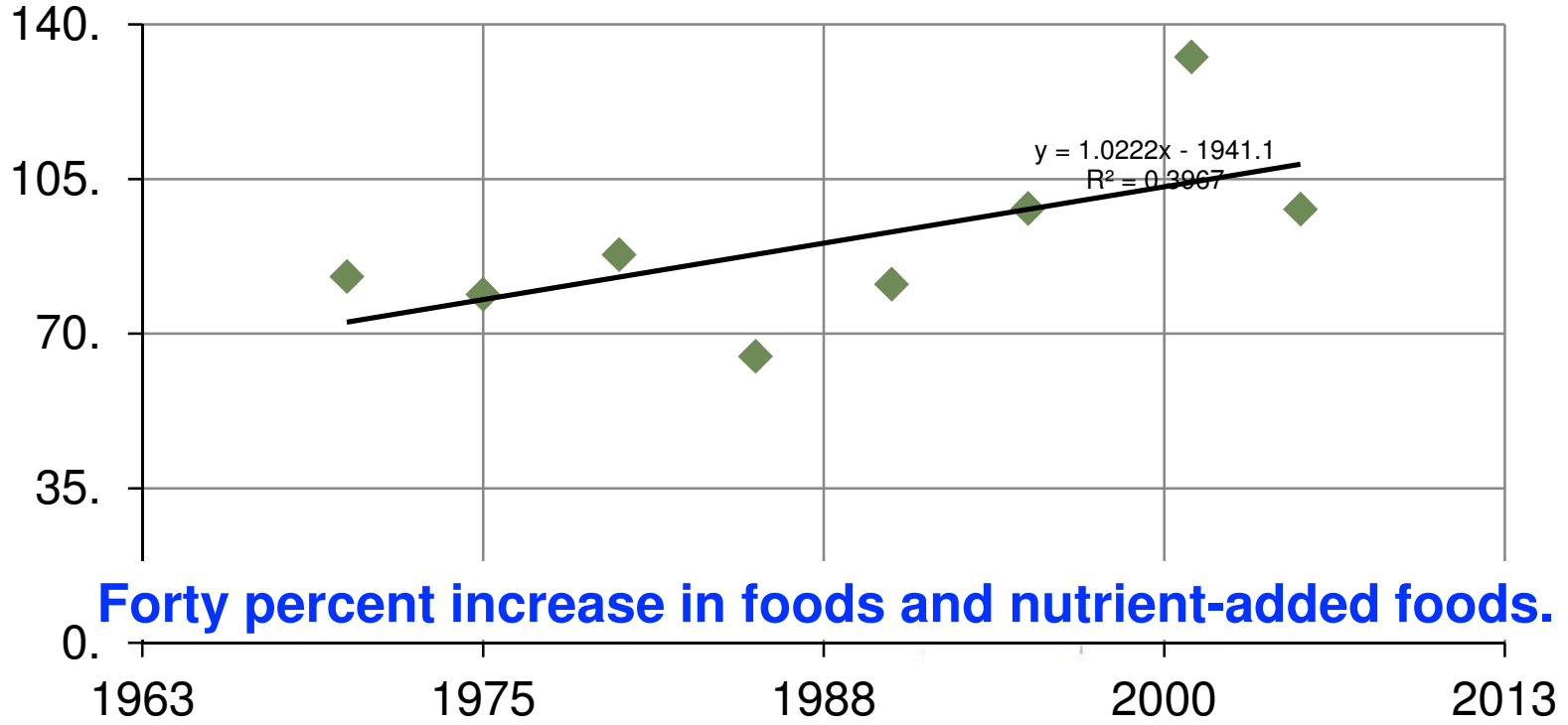
Step 5. Potential future intakes

- Future intake levels may change due to many reasons such as changes in consumer preferences, food supplement use, and the increased fortification of food products.

Step 4. Estimation of potential changes in dietary patterns

Year	1970	1975	1980	1985	1990	1995	2001	2005
Intake	82.9	78.9	87.9	64.9	81.2	98.3	132.6	98.2

KNHANES



Forty percent increase in foods and nutrient-added foods.

Group B

- Relative risk (UL/NRV) > 10
- Estimation of higher theoretical intakes to account for potential changes in dietary patterns

Vitamin E, B6, C, nicotinamide, & Cu

MSL = UL – (MHI X 1.4)

Group C

- Relative risk (UL/NRV) < 10
- Not only the risk of excessive intake but also the risk of insufficient intake need to take account.
- **Case-by-case consideration** for risk of deficiency, skewed distribution of intake, serious adverse effects, risk groups, and repeated intakes.

Vitamin A, folate, Ca, Fe, Zn, Cu, Mn, Se, & I

MSL = (UL-MHI)/2

Group C: vitamin A

Example

- The 97.5 percentile intake for Korean adults is less than 3,000 ug RE/day, while RDA is 700 ug RE/day.
- The distribution of intake is great, especially in relation to consumption of liver and liver products.
- Current intakes may exceed the UL, careful consideration should be given.

Group C: calcium

Example

- High dietary calcium levels can influence the bioavailability and absorption of many trace elements in individuals with low intakes. (magnesium, iron, manganese, and zinc)
- Acute adverse effects relate to constipation, abdominal pain, and diarrhea.
- Subpopulations known to be susceptible to high levels of calcium include individuals with renal insufficiency, alkalosis, and dehydration due to vomiting and anorexia, and those using thiazide diuretics.
- A supplemental level up to 2,500 mg/day would not be expected to result in any adverse effect.

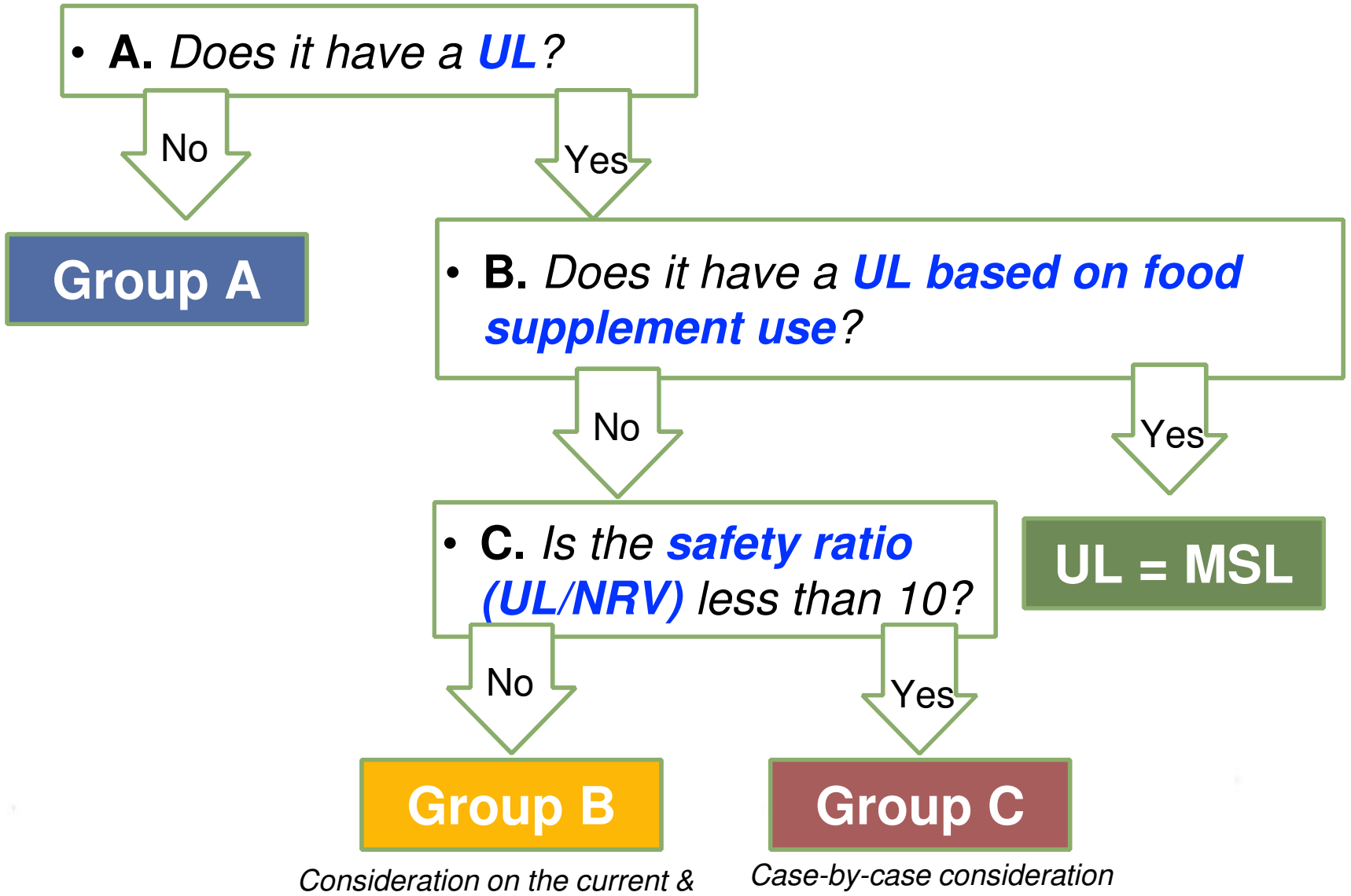
Step 5. Final adjustment

- Possible problems that could be faced by new MSL of vitamins and minerals were critically elaborated.
  - e.g. **Overages** (the amounts over the declared values on product labels).

- The opinions from academia and industry were translated into the proposed regulation.

- **Group A**: Nutrients that do not represent a risk to human health (No UL established by MHW)
- **Group B**: Low risk of exceeding the UL
- **Group C**: Potential risk at excessive intake

Summary of risk categorization



Categorisation of nutrients

Difference method			Direct method
Group A	Group B	Group C	
No UL set [No evidence of risk within ranges currently consumed]	Low risk of exceeding the UL (ratio>10)	Potential risk of exceeding the UL (ratio<10)	Direct risk assessment of supplemental amounts of the ingredients.
Vitamin B1 Vitamin B2 Vitamin B12 Vitamin K Biotin Pantothenic acid K Cr (trivalent) [Mo]	Vitamin E Vitamin B6 Vitamin C Nicotinamide Cu	Vitamin A Vitamin D Folate Ca Fe Zn Mn Se I	b-carotene Nicotinic acid Magnesium

MLs of vitamin/mineral supplements: Group B

Nutrients	MSL		KDRI	
	New	Old	RDA	UL
Vit E (mg a-TE)	400	150	10	540
Vit B6 (mg)	67	10	1.5	100
Vit C (mg)	1,000	1000	100	2,000
Nicotinamide (mg)	670	13	16	1,000
Cu (ug)	7,000	1,500	800	10,000

67~74% of UL

MLs of vitamin/mineral supplements: Group C

Nutrients	MSL		KDRI	
	New	Old	RDA	UL
Vit A (ug RE)	1,000	700	750	3,000
Vit D (ug)	24	5	10	60
Folate (ug DFE)	400	250	400	1,000
Ca (mg)	800	700	800	2,500
Fe (mg)	15	15	14	45
Zn (mg)	12	12	10	35
Mn (mg)	2	2	3.5	11
Se (ug)	150	50	50	400
I (ug)	150	75	150	3,000

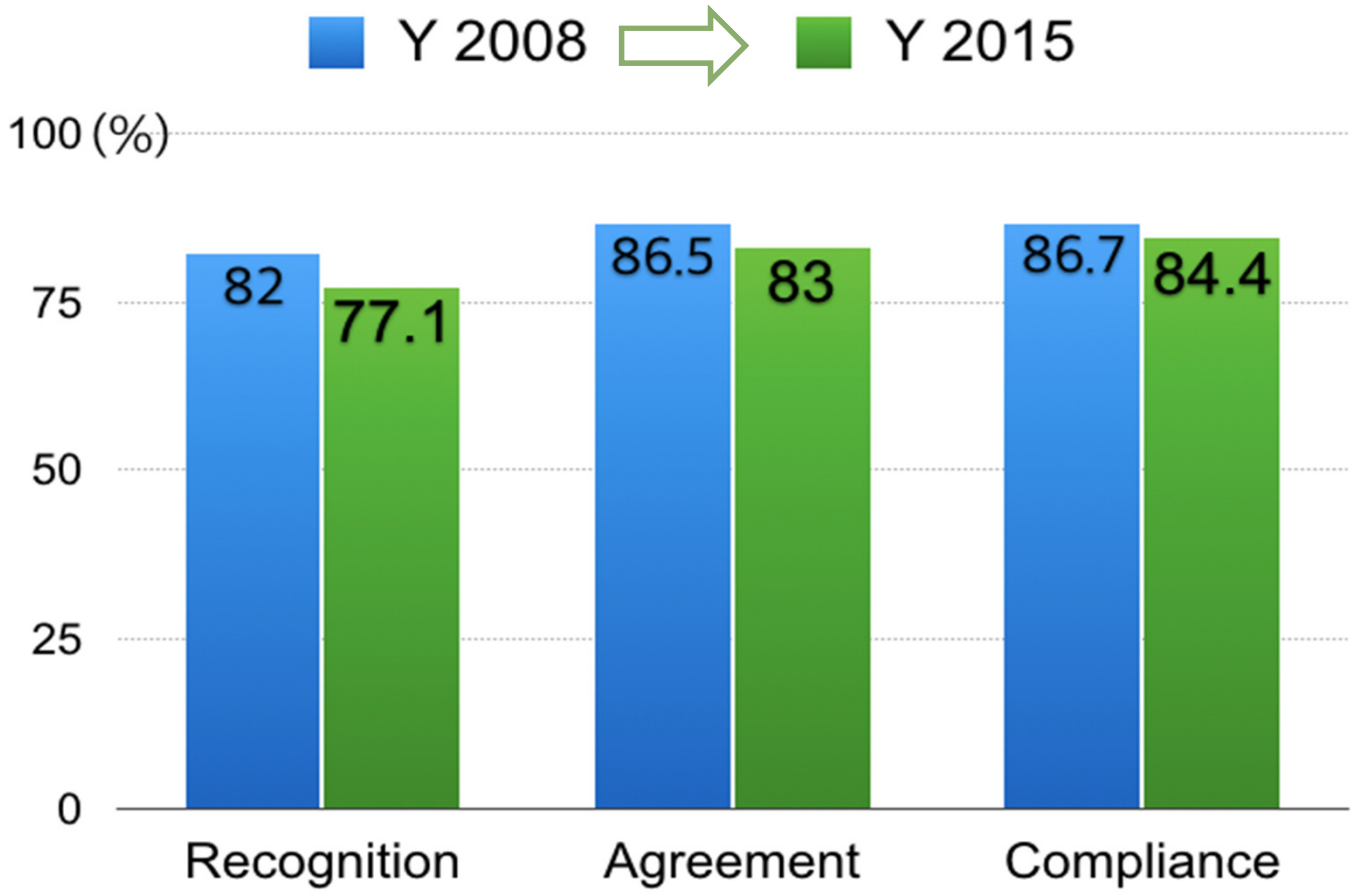
18~40% of UL

Exception

3 CURRENT MARKET PRACTICES IN KOREA

Regulation & compliance

- Maximum Safe Limits for food supplements are **voluntary**.



Regulation & compliance

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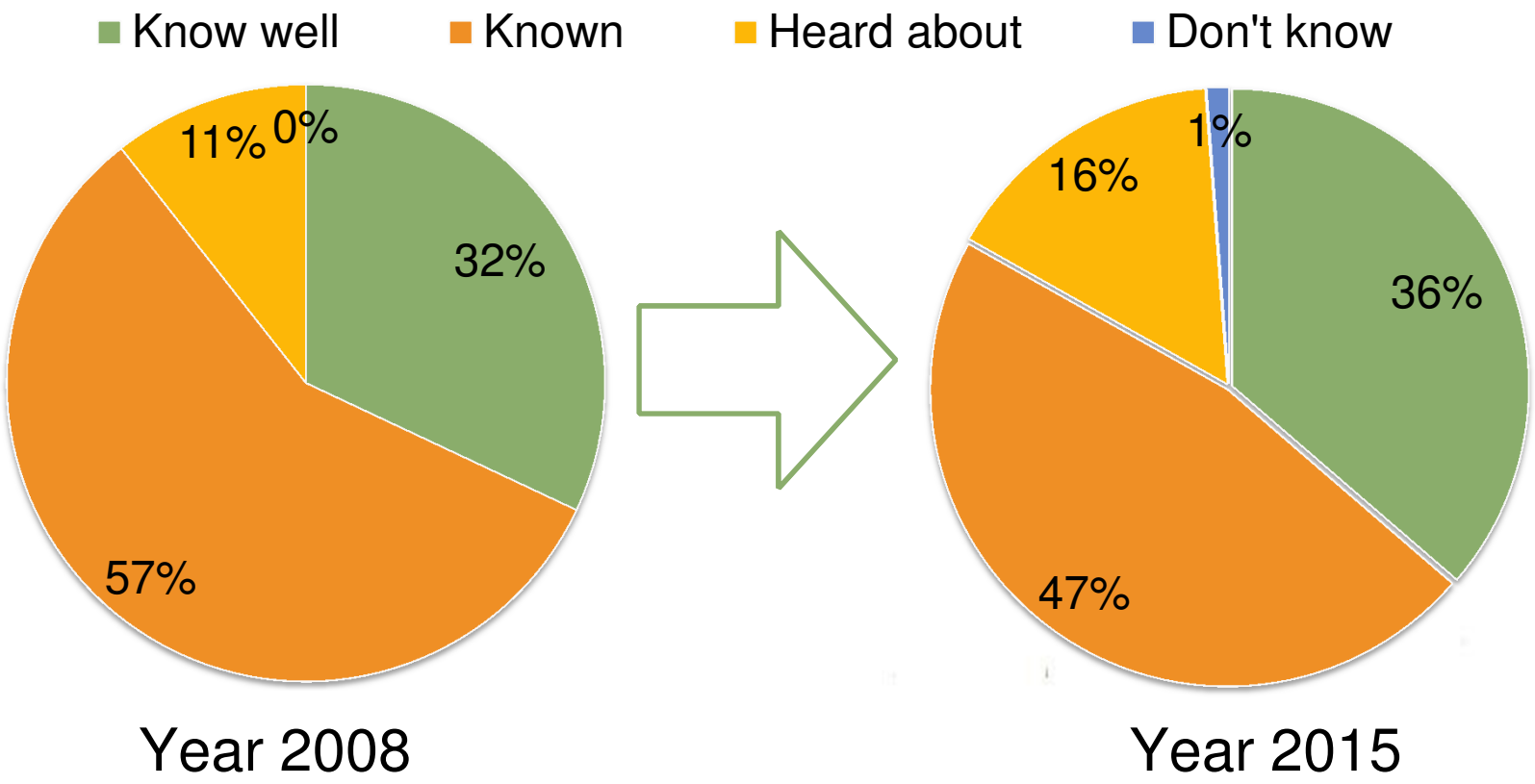
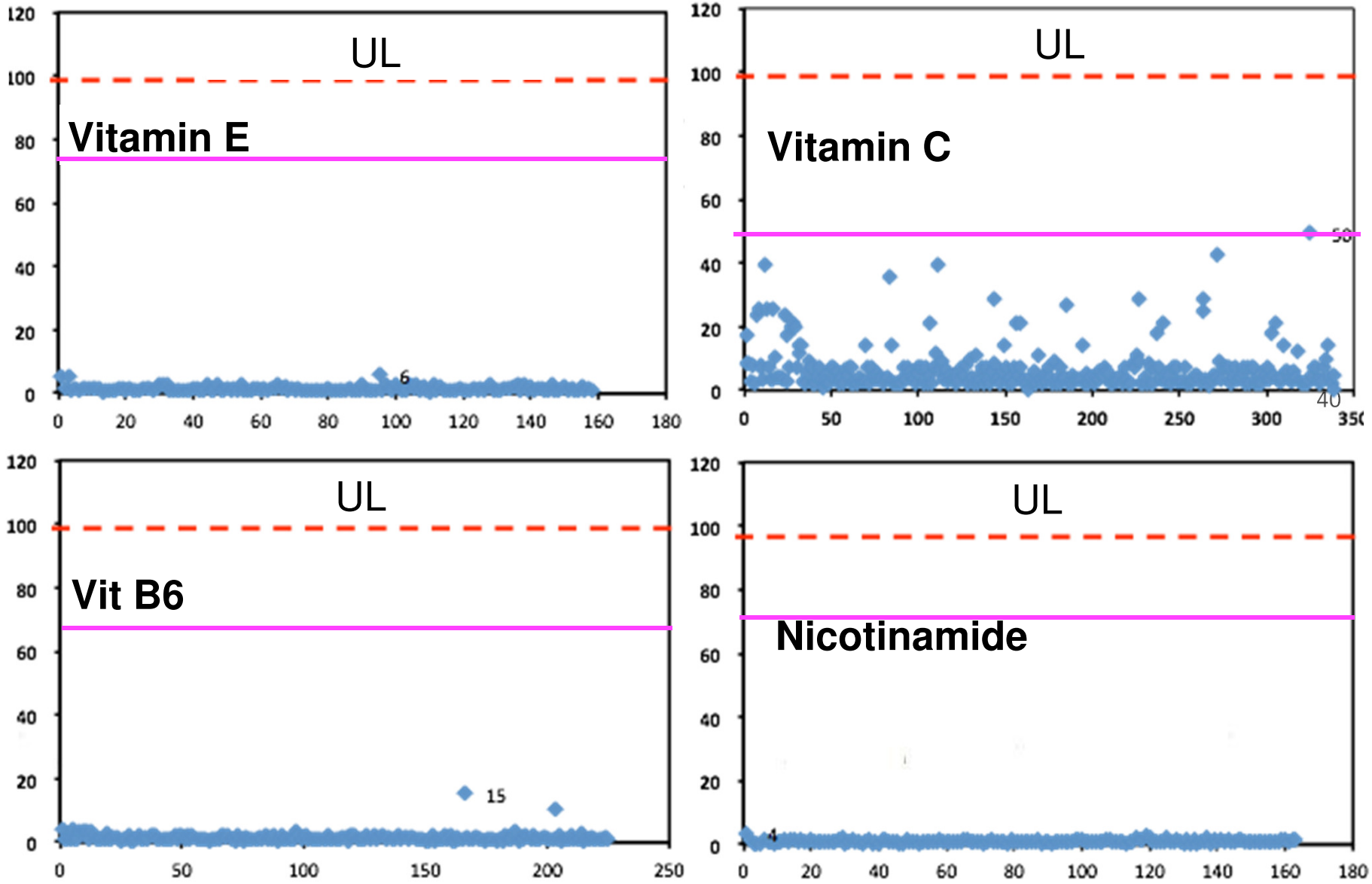


Product compliance (2012~2014)



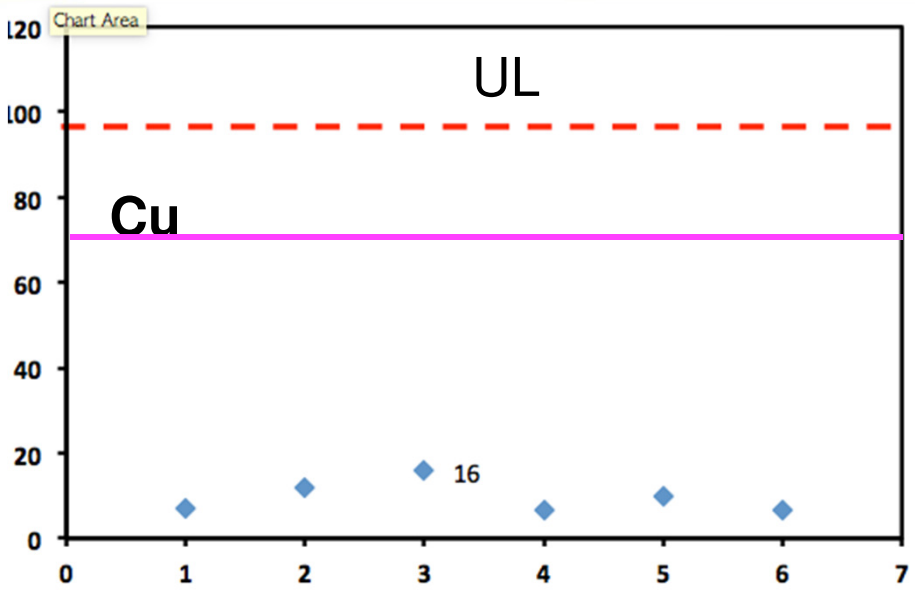


Chart Area
UL
Cu
16
0
20
40
60
80
100
120
0
1
2
3
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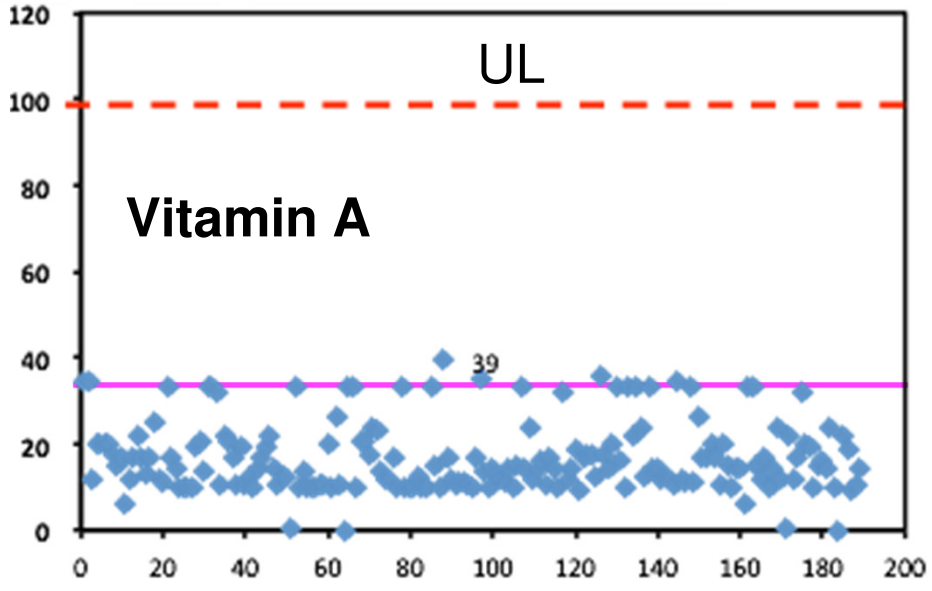
5
6
7


UL
Vitamin A
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40
60
80
100
120
0
20
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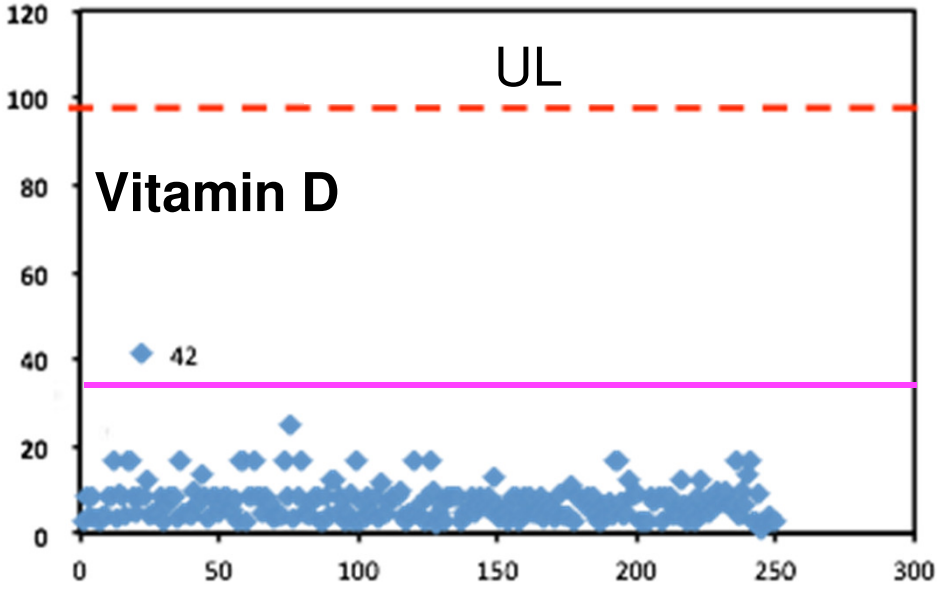
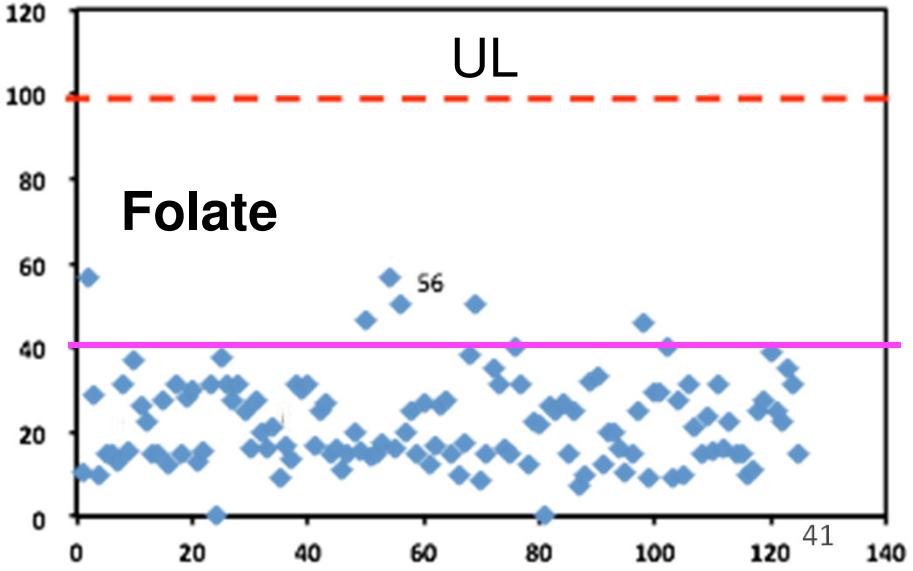
60
80
100
120
140
160
180
200


UL
Vitamin D
42
0
20
40
60
80
100
120
0
50
100
150
200
250
300


UL
Folate
56
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20
40
60
80
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120
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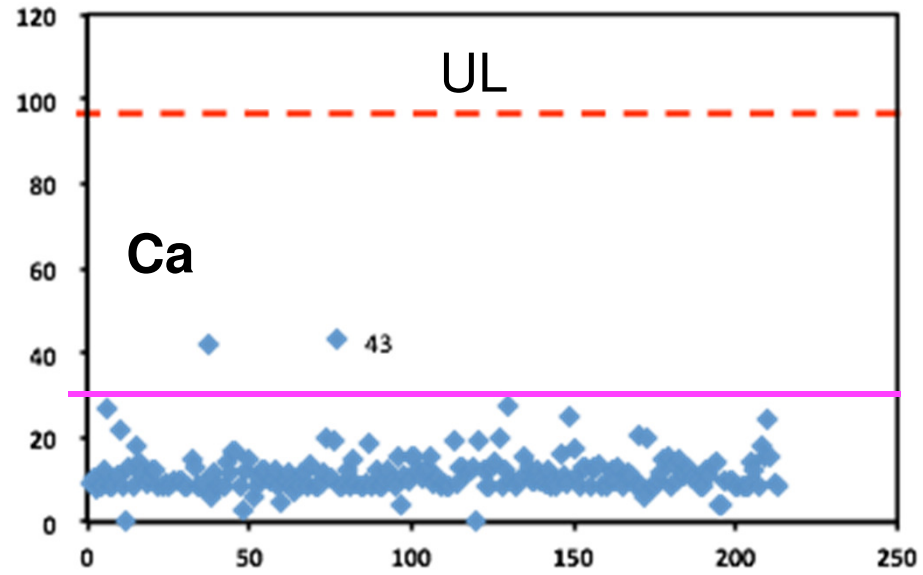
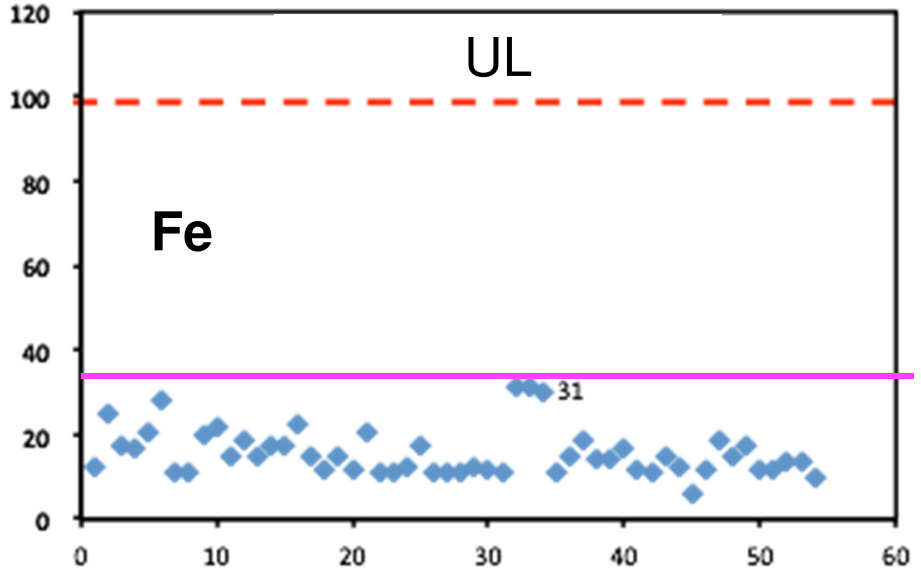
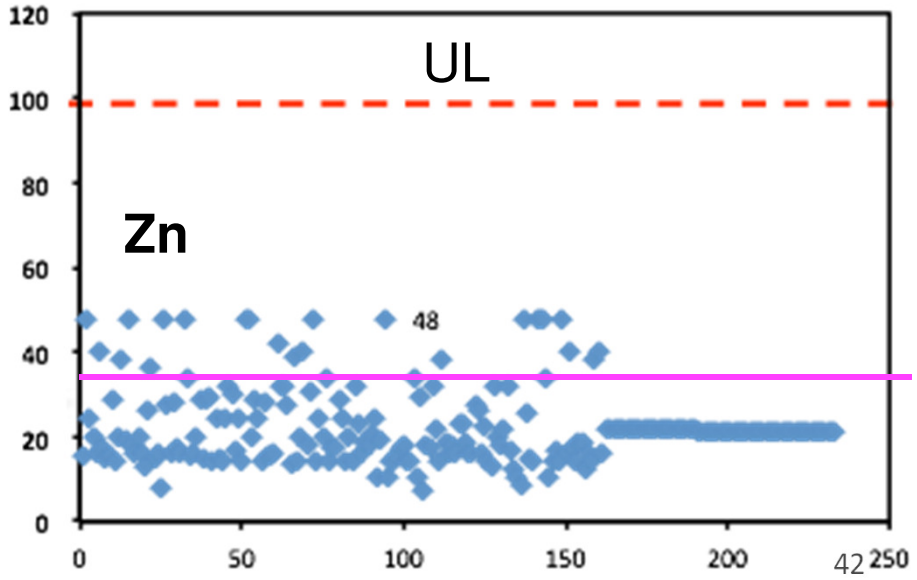
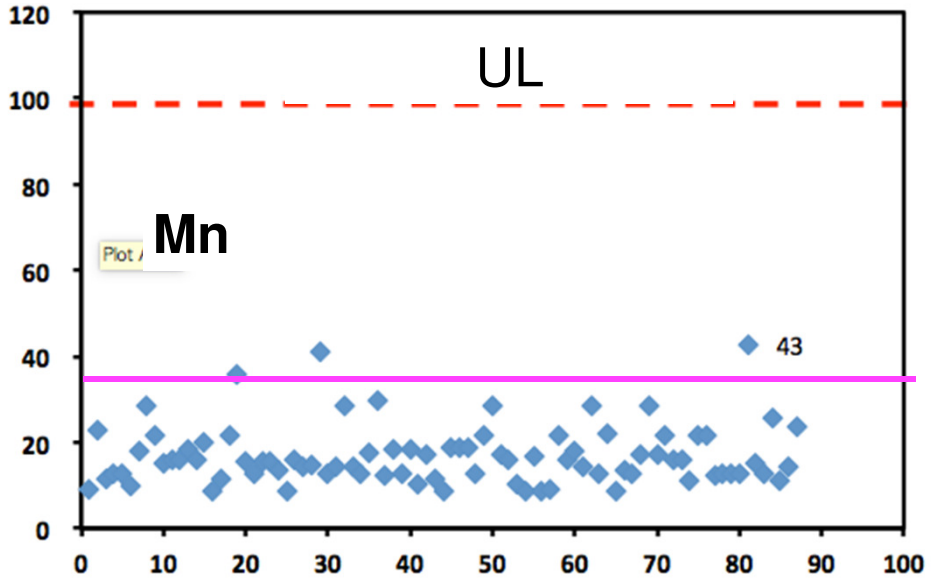
140

Product compliance (2012~2014)

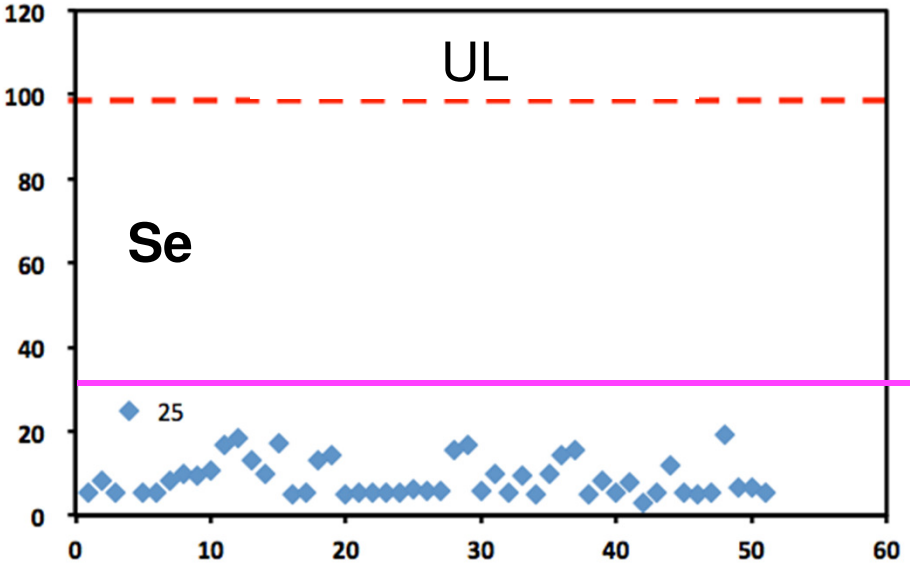


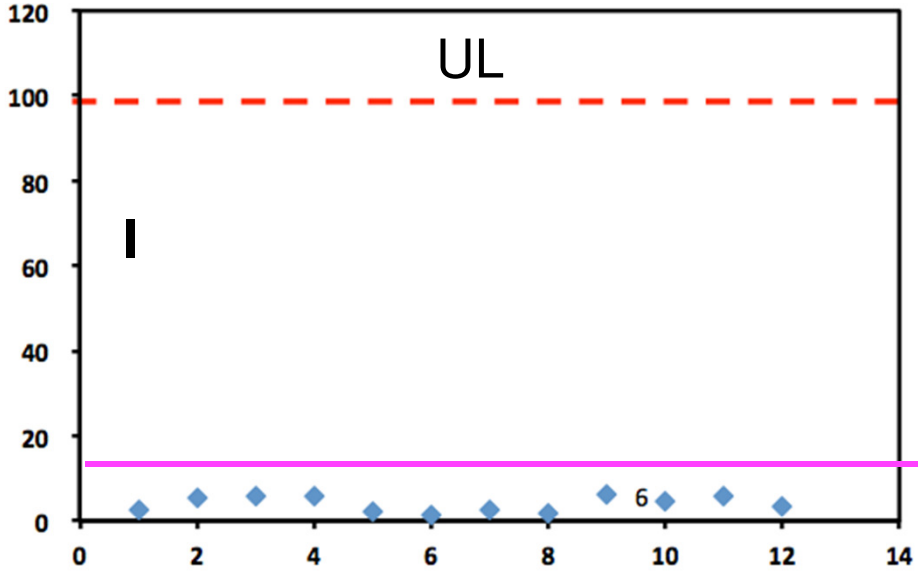


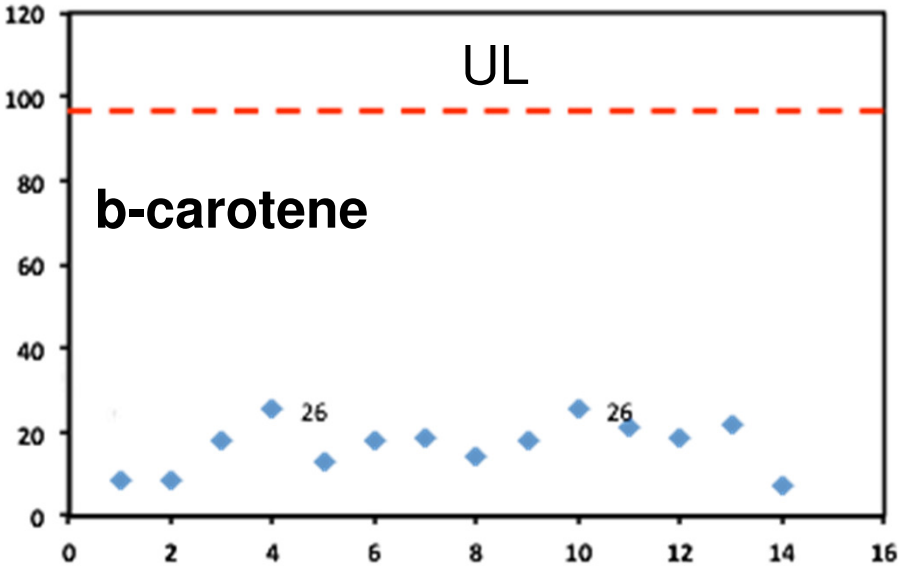


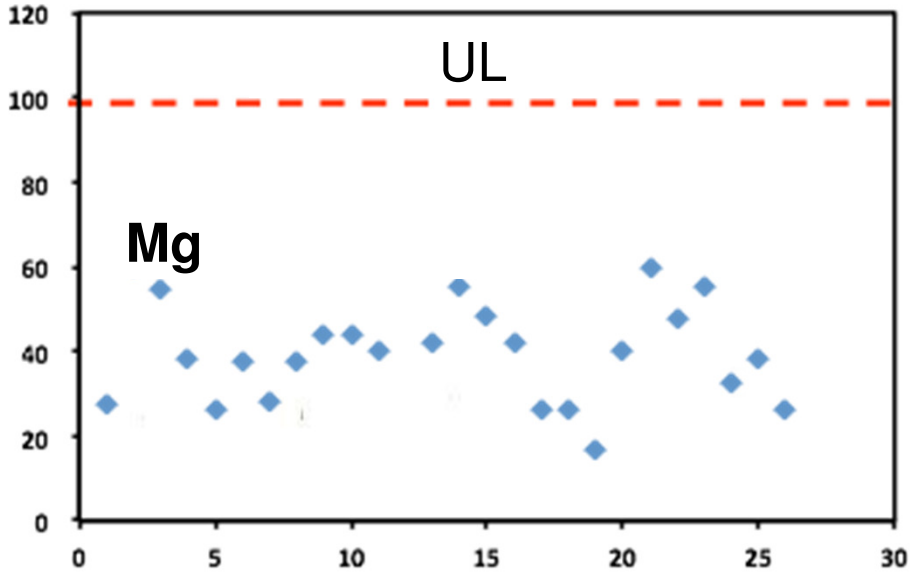


Product compliance (2012~2014)

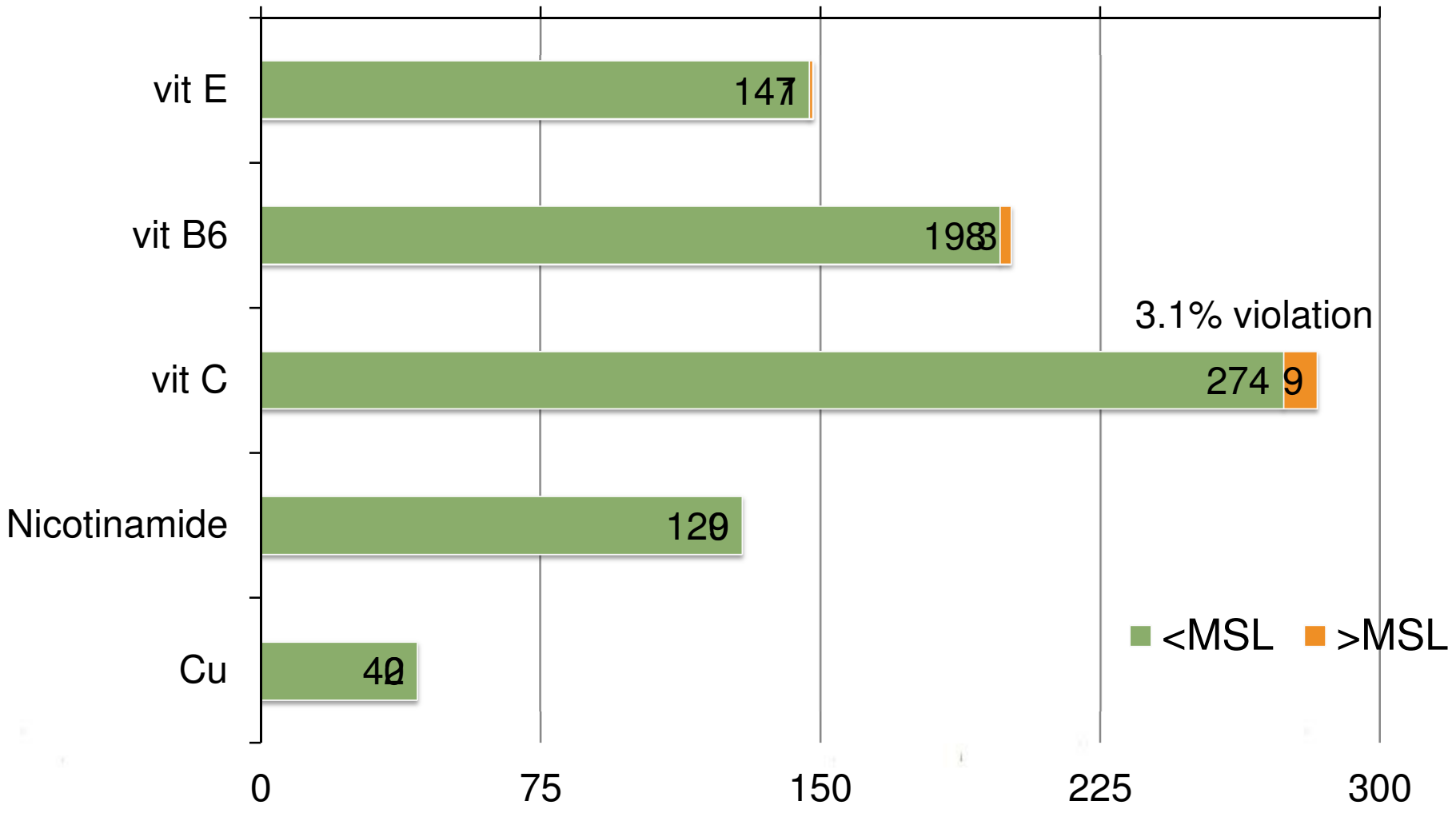




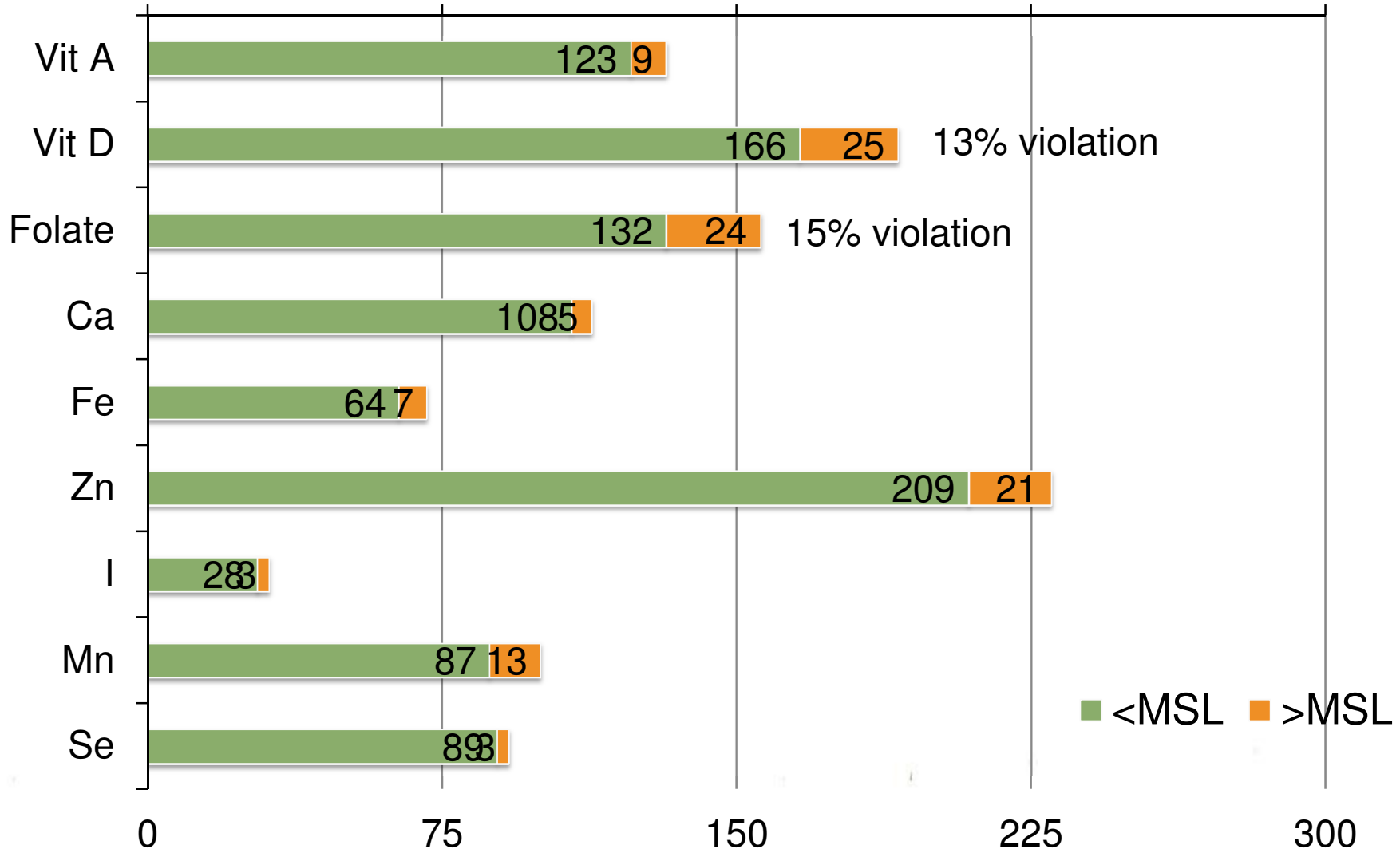




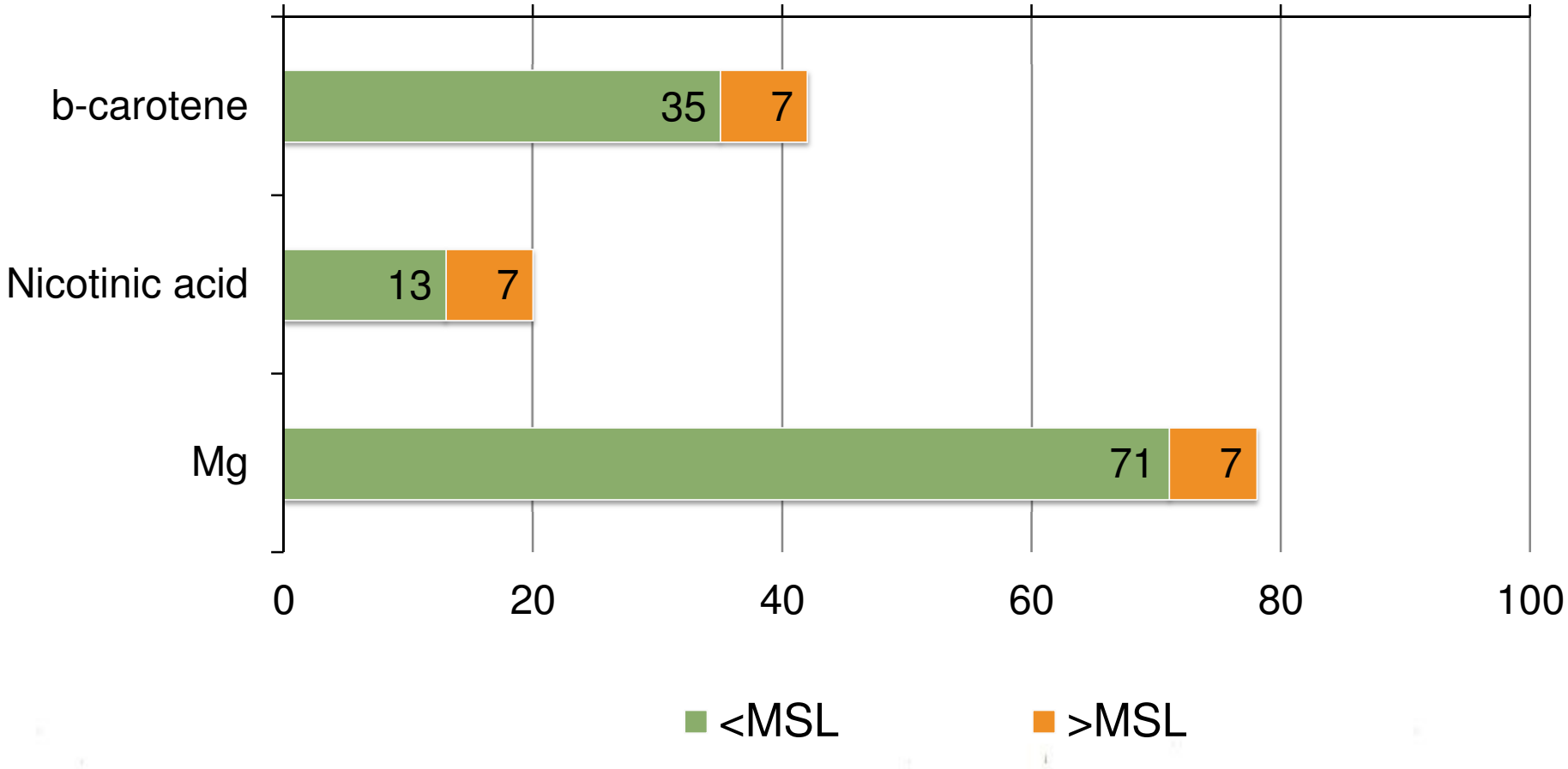
Compliance: Group B



Compliance: Group C

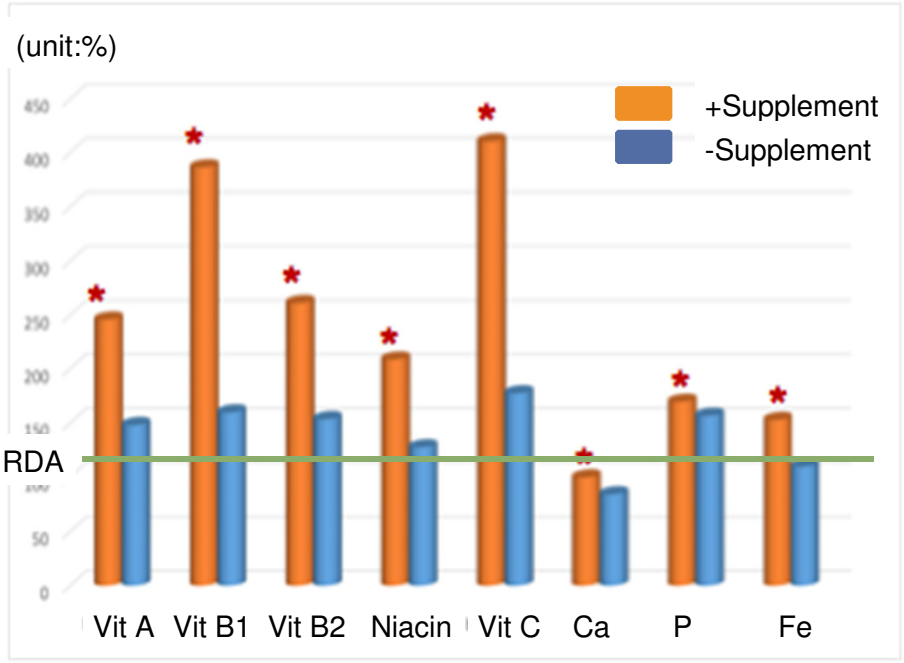


Compliance: Direct method

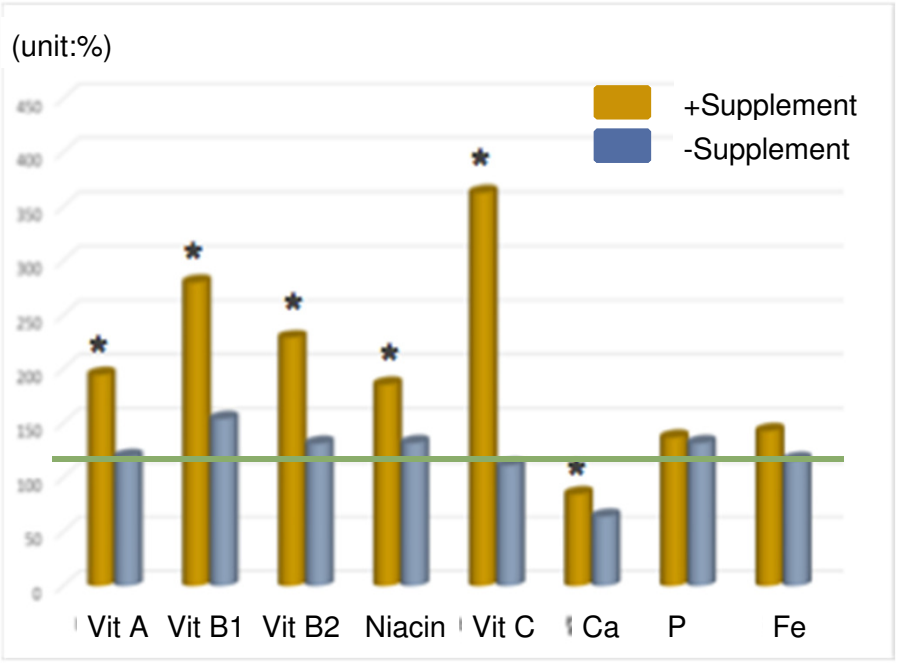


Current status of micronutrient intake for children

[1~6 y (n=1,356)]



[7-12 y (n=1,443)]



2010, 2011 KNHANES

Summary and take home message

- **Maximum level of vit/min in food supplements** is a necessary measures for safety precaution.
- **Risk assessment** provides a systematic means to evaluate the probability of the occurrence of adverse health effects due to excessive intake.
- The **ratio of UL and RDA (NRV)** can be used to help categories nutrients on the basis of the risk associated with exceeding ULs.
- Assessment of the **current and future intake** of vitamins and minerals from all dietary sources is required.
- Acquiring up-to-date composition and intake data and **estimating usual intake** are the **major challenges**.

Thank You!

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