

CASE STUDY:
**Precaution in Risk Management of
Dietary Supplements**

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DISCUSSION POINTS

- **Concepts and definitions**
 - “Precaution” vs “precautionary principle”
 - “Precaution” vs “uncertainty”
 - “Intentional” vs “unintentional” exposures
- **Examples**
 - Nutrients in supplements
 - Nutrients added to conventional foods
 - Food contaminants



Coming to Terms

- **Definitions**
 - **Precaution (OED):**
 - **Precautionary Principle**
 - **Not defined but described by EC**
- **Sources**
 - **Rio 15 often seen as origin of precautionary principle**
- **Concept of Rio 15**
 - **Protection of environment while allowing development**



DEFINITIONS

- **Caution** – Prudent forethought to minimize risk
- **Precaution**
 - Care taken in advance
 - Measures taken in advance to prevent harm or secure good



Rio 15

- **Protect environment but allow development**
- **Gives governments authority to act without waiting for “full scientific certainty” of harm to the environment**

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- **Harm is *presence* of adverse effects**



SPS 5.7

- **WTO Sanitary and Phytosanitary Standards**
- **Paragraph 5.7 allows governments to not approve the safety of a new food product, ingredient or process where “the scientific evidence is insufficient”**

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- **Safety is *absence* of adverse effect**
 - **Sufficient evidence may, or may not, be available**
 - **“Full scientific certainty” of safety is impossible**



FALSE EQUIVALENCE

- Rio Declaration Principle 15 and SPS 5.7 are NOT equal
- *Rio 15* allows regulatory measures without “full scientific certainty” of harm
- *SPS 5.7* allows regulatory measures where “scientific evidence is considered insufficient” to demonstrate safety
- Proof of safety and proof of harm are opposites
- Proof of safety is proof of a negative—the *absence* of harm—and can never be proven with “full scientific certainty”
- Therefore:
 - If Rio 15 is the PP, the PP is NOT included in SPS
 - Rio 15 suggests impossible scientific standard for new food ingredients



Precaution in Risk Management for Supplements

Appropriate

- **Vitamin A (Prop 65)**
- **Nicotinic acid limit (CRN) to avoid hepatotoxicity**

Excessive

- **L-tryptophan (post-EMS epidemic)**
- **Iron packaging**
- **Chromium picolinate**
- **Delay of folic acid health claim for “safety” reasons**
- **Nicotinic acid limits based on flushing reaction**



Appropriate Precaution--California

Vitamin A (retinol, not carotenes)

- **Risk of hepatic disease with $> 8,300 \mu\text{g}$**
- **Risk of birth defects with use of supplements at “above $3,000 \mu\text{g}$ ”**
 - actual median intake was $6,500 \mu\text{g}$
- **No significant increase at $< 3,000 \mu\text{g}$**
- **CRN ULS = $10,000 \text{ IU}$ ($3,000 \mu\text{g}$); warning $> 1,500 \mu\text{g}$**
- **California Prop 65 DART limit of $3,000 \mu\text{g}$ (recognizing essential nutrient status and avoiding the 100,000 factor require by law)**



Appropriate Precaution--CRN

Nicotinic acid

- **Liver/GI tract toxicity:**
 - **LOAEL = 1,000 mg**
 - **NOAEL = 500 mg**
- **Slow-release (SR) = 2x potency = 50% limit**
- **Skin flushing LOAEL 50 mg (or less)**
- **NAS UL of 35 mg, based on flushing for both nicotinic acid (and nicotinamide!)**
- **CRN limit of 500 mg (250 mg SR), with flush warning > 35 mg**



Excessive Precaution--FDA

L-tryptophan and EMS

- **Appropriate chemistry and epidemiology tracing to contaminated source (Showa-Denko)**
- **Contaminant was derivative of a dimer of LT**
- **All credibly causal cases related to this LT source**
- **Animal studies by FDA—contaminant produced similar syndrome, but “clean” LT did not**
- **Clean LT at 4,000x dosage produced “slight” histological changes**
- **FDA was “not sure that LT itself could not” cause EMS**
 - **Apparently looking for absolute proof of a negative**
- **LT prohibited as supplement, but permitted as food additive**



Excessive Precaution--FDA

Iron Packaging Rule

- **Rule initiated to prevent pediatric poisonings by gram quantities of high-potency prenatal iron supplements containing ferrous sulfate taken accidentally**
- **Child-resistant packaging (blister packs) mandated**
- **No exemption for products containing “electrolytic iron”—fine particles of metallic iron**
- **Electrolytic iron is orders of magnitude less toxic than ferrous sulfate**
- **Rule over turned by Court due to lack of FDA’s sole jurisdiction on packaging for safety**
 - **Court ruled that Consumer Product Safety Commission has first responsibility**



Excessive Precaution--FDA

“Safety” based delay in folic acid Health Claim

- In 1993, FDA reviewed scientific literature relevant to health claim for folic acid reducing the risk of NTDs—and found no “significant scientific agreement”
- After publication in 1996 of a multinational randomized, double-blinded, placebo-controlled trial that showed protection by 800 μg folic acid, FDA delayed due to “safety concerns” related to masking of vitamin B12 deficiency
- FDA approved the health claim only after the FNB set a UL of 1,000 μg folic acid (not including food folates)
- FNB UL = human LOAEL/5 (an aggressively low LOAEL)



Excessive Precaution--UK

Chromium Picolinate

- *Separate issues: Chromium, and Picolinate*
- **Some uncertain but potentially adverse effects in cell cultures and invertebrates**
- **No adverse effects in rats at same Cr dose with chloride and picolinate (in same study)**
- **UK EVM guidance level set on data from chloride, but deemed picolinate unsafe**
- **Cr from picolinate form has higher bioavailability**
- **Discussion often implies need for proof of negative**
- **Recent issue not considered by UK is hypothetical conversion of Cr³⁺ to Cr⁶⁺ (very speculative)-authors seem to want certain proof that none whatever is converted, or Cr should be considered “unsafe”**



Excessive Precaution--UK

- **Rejected human data accepted by US and other human data accepted by EC**
- **Derived 10 mg limit from animal data**
- **Aggressive Uncertainty Factor selection (composite 300) led to same (10 mg) limit previously identified from human data now considered unreliable**
- **Previous justification by precautionary principle, but not now asserted**
- **Ignores long-term clinical uses at 25 mg and greater**



“Precautionary” Basis of Proposed Vitamin B-6 Limits

- UK COT
 - Ignored objective neurological evidence of human NOAEL of 200 mg/day
 - Improper extrapolation of credible animal data to propose human limit of 10 mg
 - Minister of Food Safety used PP to justify actions
- EC SCF
 - Ignored objective neurological evidence of human NOAEL of 200 mg/day
 - Based on telephone survey “scientific data” in a 3rd-tier journal
 - Applied unprecedented UF of 4 to median “adverse” intake to set UL at 25 mg



Selenium: *Precaution is built in*

- **RDA: 55 μg**
- **Benefits shown at 200 μg supplemental (300 total)**
- **Epidemiological NOAEL ~850 μg total**
- **Clinical NOAEL & CRN ULS: 200 μg supplement**
- **Official ULs: 300-450 μg total**
- **Dietary Range: 20 to >1,000 μg**
- **97.5 percentile intake in UK = 100 μg**
- **High intake areas very restricted geography, and supplement levels are small in comparison**



Conclusions

- **Precaution is already included in Risk Analysis for foods (PP would be redundant)**
- **Reversed burden of proof is a major problem**
 - Proof of safety vs proof of harm
- **Potentially impossible standards for new ingredients, products, or processes**
- **Non-scientific declaration that a product is “unsafe” (safety not proven with “full scientific certainty”)**
- **Speculation could provide “justification” for trade barriers**



THANK YOU

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