

Safety and Efficacy of Natural/Herbal Ingredients in Health Supplements

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Presentation Outline

Safety:

- Role of the manufacturer to ensure the safety of their product
- Safety assessment process
- Sources of safety information
- Evaluating ingredients
- Evaluating multi-ingredient products



Presentation Outline

Efficacy:

- Efficacy VS Effectiveness
- Clinical study for Health Supplements
- Example of Clinical study for Health Supplements

Discussion, Question and Answer



SAFETY OF NATURAL/HERBAL INGREDIENTS IN HEALTH SUPPLEMENTS



Role of the Manufacturer

- The Manufacturer has the responsibility to ensure the safety of their product.
- Safety of the product is assured by having a
 - defined and integrated safety program
 - company-wide awareness of safety as a priority
 - system to monitor and respond to adverse health events



Importance of a Safety Program

- ❑ A Safety Program is required to:
 - Protect consumer health
 - Meet regulatory requirements
 - Enhance company reputation

- ❑ Manufacturer must make safety a priority.
 - Invest in trained and experienced scientists
 - Safety is a shared responsibility among all company functions: R&D, QA, TR, Sales and Marketing, etc
 - Needs resources/costs \$



Safety Program Responsibilities

A Safety Program should be implemented early and throughout the products' lifetime.

- Pre-market: Safety Assessment of ingredients and finished products
- Product development: Support development, and clinical and consumer use tests
- Manufacturing: GMP and QA
- Post-market: Monitor and respond to adverse events and safety-related questions



Safety Assessment

Conducting a Safety Assessment of Health Supplements ingredients follows the same scientific principles as evaluating the safety of any kind of substance.

- Identification of the nature of the substance
- Summary of the available data on relevant exposures
- Identification of any safety concern
- Determination of safe usage conditions and safe levels of exposure in humans



Safety Assessment

Guidance on how to conduct Safety Assessments and examples (references provided at end of presentation)

- ❑ Scientific organizations provide guidance documents on how to conduct a safety assessment on botanical or food ingredients
 - International Life Sciences Institute (ILSI)
- ❑ Regulatory agencies have procedures on how to assess safety of ingredients
 - Canada NHPD, European Food Safety Authority (EFSA)
- ❑ There are government agencies that conduct safety assessments
 - US National Toxicology Program (US NTP), Joint European Committee on Food Additives (JECFA)



Health Supplement Ingredients

Ingredients used in Health Supplements can be complex.

- Wide variety of sources
- Complex Compositions
- Naturally Derived
- Innovative



Sources of Safety Information

❑ Raw Material Supplier

- Identification, feedstock, processing methods, characteristics
- Non-published studies

❑ Publicly available literature

- Web-based search
- Research studies in scientific journals, reports from scientific organizations and government agencies
- Reference books
- Lay-person sources

❑ Manufacturer generated information

- Analytical chemistry, assays
- Research and Development- *in vitro* studies, clinical studies, consumer-use studies



Evaluating Ingredients:

I. Information relevant to determining ingredient identification, characterization and standardization as available

Source of Ingredient:

- Identity, Scientific name, common names
- Part(s) of plant used
- Geographic origin

Growth conditions:

- Wild or cultivated, harvesting process

Methods of preparation:

- extraction, solvents
- Purity criteria (micro, heavy metals, residual solvents, etc)
- Level and nature of excipients



Evaluating Ingredients:

I. Information relevant to determining ingredient identification, characterization and standardization as available

☐ Specifications:

- Standard reference (pharmacopeia)
- Identity tests
- Tests to determine constituents and quantity relevant for beneficial effects
- Tests to determine inherent constituents of toxicological relevance

☐ Standardization criteria:

- Plant-extract ratio
- Chemical/Active/Marker identification and level/range



Evaluating Ingredients- Example

RED RASPBERRY with x % ELLAGIC ACID

Description:

- Extract obtained from rasp leaf.
- Botanical name: *Rubus spp.*
- Extraction solvent:
ethanol x%/water y%
- Extraction ratio: z/1

Composition:

- Natural extract, excipients, etc....

Specification:

.....

Sensory quality:

- Aspect: powder/liquid, etc...
- Color: white/brown, etc...
- Flavor: characteristic

Analytical quality:

- Identification: TLC conform
- Ellagic acid content: > a%
- Loss on drying: < b%
- Particle size: 100% through c mesh
- Residual ethanol content: < d%

Microbiological quality:

- Total plate count: < e cfu/g
- Yeasts and molds: < f cfu/g



Evaluating Ingredients

II. Information for evaluating safety

History of Use:

- How has it been used- food, medicine, other?
- How long has it been in use historically?
- If used as food, what is the estimated dietary exposure of the ingredient?
- Potential/reported pharmacological activity
- What has been the serving size/daily intake/doses
- Preparation, target population(s)
- Information on health/adverse effects
- Known warnings (precautions, contraindications, interactions)



Evaluating Ingredients

II. Information for evaluating safety

Regulatory allowed intakes:

- Information regarding allowed levels of ingredient may be obtained from positive lists or monographs
- Countries may also have guidance on ingredients' daily dose, duration and required cautionary statements



Evaluating Ingredients

II. Information for evaluating safety

Human Studies:

- Clinical studies
- Epidemiology studies
- Case reports
- In most cases, these studies are *not specifically used* to test safety in humans. They are designed instead for clinical/effectiveness outcomes. These studies may be useful sources of safety information if they document identity of **exposure, dose-response, whether any adverse effects occurred, highest observed safe dose, duration of intake, etc.**



Evaluating Ingredients

II. Information for evaluating safety

Toxicology Studies:

- A safe intake level for human consumption may be estimated through extrapolation from the animal data.
- Both human data on observed safe use and the animal data on extrapolated safe levels should be reported and compared for relevance.
- Protocol and design for the conduct of toxicological studies are standardized.
- International guidelines have been developed to achieve consistency in experimental techniques.



US FDA Redbook- Tox Protocols

Redbook 2000

July 2000; Revised July 2007

<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm>

Guidance for Industry and Other Stakeholders Toxicological Principles for the Safety Assessment of Food Ingredients

Redbook 2000 <http://www.cfsan.fda.gov/guidance.html>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
July 2000; Updated July 2007

Table of Contents

[I. Introduction](#) (July 2007)

[II. Agency Review of Toxicology Information Submitted in Support of the Safety Assessment of Food Ingredients](#) (available in [1993 Draft "Redbook II"](#))

[III. Recommended Toxicity Studies](#) (July 2007)

[IV. Guidelines for Toxicity Studies](#)

- A. [Introduction](#) (November 2003)
- B. General Recommendations for Toxicity Studies
 1. [General Guidelines for Designing and Conducting Toxicity Studies](#) (November 2003)
 2. [Guidelines for Reporting Results of Toxicity Studies](#) (November 2003)
 3. [Pathology Considerations in Toxicity Studies](#) (July 2000)
 4. [Statistical Considerations in Toxicity Studies](#) (July 2000)
 5. [Diets for Toxicity Studies](#) (available in [1993 Draft "Redbook II"](#))
- C. Guidelines for Specific Toxicity Studies
 1. [Short-Term Tests for Genetic Toxicity](#) (July 2000)
 - a. [Bacterial Reverse Mutation Test](#) (July 2000)
 - b. [In vitro Mammalian Chromosomal Aberration Test](#) (November 2003)
 - c. [In vitro Mouse Lymphoma TK⁺ Gene Mutation Assay](#) (April 2006)
 - d. [In vitro Mammalian Erythrocyte Micronucleus Test](#) (July 2000)
 2. Acute Oral Toxicity Tests (available in [1993 Draft "Redbook II"](#))
 3. Short-Term Toxicity Studies
 - a. [Short-Term Toxicity Studies with Rodents](#) (November 2003)
 - b. [Short-Term Toxicity Studies with Non-Rodents](#) (November 2003)

4. [Subchronic Toxicity Studies](#)
 - a. [Subchronic Toxicity Studies with Rodents](#) (November 2003)
 - b. [Subchronic Toxicity Studies with Non-Rodents](#) (November 2003)
5. Chronic Toxicity Studies
 - a. [Chronic Toxicity Studies with Rodents](#) (July 2007)
 - b. [One-Year Toxicity Studies with Non-Rodents](#) (November 2003)
6. [Carcinogenicity Studies with Rodents](#) (January 2006)
7. [Combined Chronic Toxicity/Carcinogenicity Studies with Rodents](#) (July 2007)
8. [In Vivo Exposure Phase for Addition to Carcinogenicity Studies with Rodents](#) (July 2007)
9. Reproduction and Developmental Toxicity Studies
 - a. [Guidelines for Reproduction Studies](#) (July 2000)
 - b. [Guidelines for Developmental Toxicity Studies](#) (July 2000)
10. [Neurotoxicity Studies](#) (July 2000)

[V. Additional Studies](#) (available in [1993 Draft "Redbook II"](#))

- A. Introduction
- B. Metabolism and Pharmacokinetic Studies
- C. [Immunotoxicity Studies](#)

[VI. Human Studies](#)

- A. Clinical Evaluation of Food Ingredients (available in [1993 Draft "Redbook II"](#))
- B. [Epidemiology Studies](#) (October 2001)

[VII. Glossary: Acronyms and Definitions](#) (April 2004)

¹This guidance has been prepared by the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

²*Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food* (also known as Redbook I), U.S. Food and Drug Administration, Bureau of Foods (now CFSAN), 1982. May be purchased from: National Technical Information Services (NTIS), 5285 Port Royal Road, Springfield, VA 22161, Telephone (703) 605-6000, NTIS Order Number PB83-170696.

³*Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food 1993 Draft "Redbook II" Table of Contents*

HOME

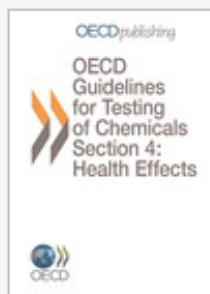
NUTRITION

OECD Testing Guidelines

http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

OECD Guidelines for the Testing of Chemicals, Section 4

Health Effects



ISSN: 2074-5788 (online)

DOI: 10.1787/20745788

The OECD *Guidelines for the Testing of Chemicals* is a collection of about 100 of the most relevant internationally agreed testing methods used by government, industry and independent laboratories to identify and characterise potential hazards of new and existing chemical substances, chemical preparations and chemical mixtures. They are a set of tools for professionals, used primarily in regulatory safety testing and subsequent chemical and chemical product notification and chemical registration. They can also be used for the selection and ranking of candidate chemicals during the development of new chemicals and products and in toxicology research. This group of tests covers health effects.

Also available in: [French](#)

OECD Guidelines for the Testing of Chemicals

6

[Hide](#) / [Show Abstract](#)

| Mark | Date | Title |
|--------------------------|--------------|----------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 28 July 2011 | Test No. 443: Extended One-Generation Reproductive Toxicity Study OECD |
| <input type="checkbox"/> | 28 July 2011 | Test No. 456: H295R Steroidogenesis Assay OECD |
| <input type="checkbox"/> | 28 July 2011 | Test No. 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays OECD |

Evaluating Ingredients

II. Information for evaluating safety

Analytical:

- Chemical identification may be undertaken to characterize botanicals.
- Scientific evidence for risk can be obtained by considering if the plant constituents are compounds with established toxicity or are closely related in structure to compounds with established toxicity.

In-vitro:

- Validated *in-vitro* studies (proven to predict a specific effect in animals and/or humans with reasonable certainty) can be indicators of risk to human health.
- There needs to be comparable exposure in humans and the *in-vitro* effects must correlate with a specific adverse health effect in humans or animals.



Safety Assessment

- ❑ After review of the information, the safety assessment can be conducted.
- ❑ Information on the ingredients and doses must be related to those used in the final product, i.e. ingredient identity and any quantitative/qualitative differences between the ingredient described in the information and the ingredient used in product must be taken into account.
- ❑ Any assumptions or limits to evaluating the data should be stated.
- ❑ The safety assessment should identify:
 - If there are any risks associated with intake/exposure
 - If there are any contraindications
 - If there are any interactions
 - What is the Acceptable Daily Intake (ADI) for the intended use population



Safety Assessment

If the ingredient is important or commonly used, there may be existing evaluations by an authoritative group of scientists, such as the Joint Expert Committee on Food Additives (JECFA) or a GRAS Panel (a panel of experts convened to examine whether the substance is “Generally Recognized as Safe” under national or international guidelines).



JECFA

<http://www.inchem.org/pages/jecfa.html>

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

WORLD HEALTH ORGANIZATION

**TOXICOLOGICAL EVALUATION OF SOME
FOOD COLOURS, EMULSIFIERS, STABILIZERS,
ANTI-CAKING AGENTS AND CERTAIN
OTHER SUBSTANCES**

FAO Nutrition Meetings Report Series
No. 46A WHO/FOOD ADD/70.36

The content of this document is the result of the deliberations of the Joint FAO/WHO Expert Committee on Food Additives which met in Rome, 27 May - 4 June 1969¹

Food and Agriculture Organization of the United Nations

World Health Organization

¹ Thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives, FAO Nutrition Meetings Report Series, in press; Wld Hlth Org. techn. Rep. Ser., in press.

TURMERIC

Biological Data

Biochemical aspects

Safety Assessment

“How data is evaluated is dependent on what information is available.”

Common scenarios:

- Scenario 1:** For ingredients that have been commonly consumed by humans, a compelling pattern of history of safe intake as components of foods is used as the acceptable daily intake (ADI)
 - ADI is an estimate of the amount of a [substance] that can be ingested daily over a lifetime without appreciable health risk
- Scenario 2:** Information supports use with no adverse effects in humans
 - The highest observed intake level (HOI) with sufficient scientific evidence of safety becomes the ADI
- Scenario 3:** Animal studies/toxicity studies provide data about dose-response relationship.
 - No Observed Adverse Effect Level (NOAEL) with appropriate Margin of Safety (MOS) can be used to estimate ADI



Data from Humans- food equivalent

Scenario 1: For ingredients that have been commonly consumed by humans, a compelling pattern of history of safe intake as components of foods is used as the acceptable daily intake (ADI)

- Food Equivalent method
- The chemical identity of the supplemental form is the same, or less than, as that found in foods.
- The intake level, frequency of intake and duration of use are similar to that that occurred through food consumption.
- The population on which the history of use is based had sufficient health care to provide a good chance of observing any adverse effects.
- No established pattern of adverse effects is credibly related to intake of the substance.
- Example: blueberry extract



Data from Humans- HOI

Scenario 2: Information supports use with no adverse effects in humans

- The highest observed intake level (HOI) with sufficient scientific evidence of safety becomes the ADI

- The January 2006 FAO-WHO report on risk assessment defined a Highest Observed Intake (HOI) as estimate of safe level when no toxicity has been observed.
- Very similar to CRN/IADSA Observed Safe Level (OSL) method and UK EVM's unnamed method for some nutrients
- Example: Glucosamine; review of the daily levels in supplements



Data from Animals*- NOAEL

Scenario 3: Animal studies/toxicity studies provide data about dose-response relationship.

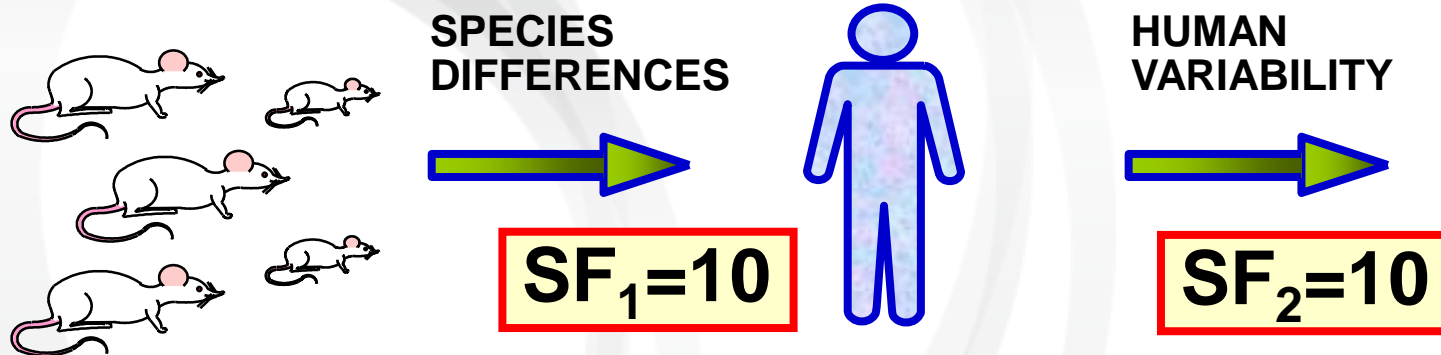
- No Observed Adverse Effect Level (NOAEL) with appropriate Margin of Safety (MOS) can be used to estimate ADI.

- The NOAEL is the greatest dose of an agent that causes no detectable adverse alteration of morphology, function, growth, development or lifespan of the target.
- NOAEL obtained from animal/toxicity studies.
- To extrapolate NOAEL to humans, safety factors are used to give a margin of safety to estimate the ADI for humans.
- Consider if animal study is relevant to human mechanism of action.
- * Animal testing bans due to animal welfare and costs.
- Example: Spanish Needles (*Bidens pilosa*).



Use of Safety Factors

Safety factors are used to extrapolate from animals to an average human and from average humans to potentially sensitive sub-populations (example: SFs=10 for each extrapolation)



$$\boxed{SF_1} \times \boxed{SF_2} = \boxed{\text{Margin of Safety (MOS)}}$$

$$\boxed{10} \times \boxed{10} = \boxed{100}$$

Margin of Safety

MOS Examples:

- MOS < 100 if there is a substantial number of clinical studies or human population studies that examined safety outcomes;
- MOS = 100 if NOAEL has been determined from repeat dose study
- MOS > 100 ingredient is intended for “at-risk” population, sensitive population, or data is incomplete

$$\text{ADI} = \frac{\text{NOAEL}}{\text{SAFETY FACTOR}}$$



When data indicates safety risk

- Safety risk is a genuine toxicological risk. It is not a nuisance such as gastrointestinal distress.
- When information has indicated a safety risk, the Safety Assessment should examine the dose-response relationship, consider any uncertainties in the data related to human exposure, and determine the ADI and any restrictions on usage.

Example: EGCG

Determine the upper limit of safety

Determine the ADI for health population

Contraindications: Do not use if have liver disease

Warning Statements: Stop using if develop signs of liver problems



Limited data

- Ingredients are often food based/derived or region specific traditionally used herbs that are not well-known in other parts of the world so that safety data is limited; e.g. if historically used as herbal in humans, there will not be animal/toxicity studies conducted. Example: Echinacea.
- Ingredients must be evaluated on a case-by-case basis; e.g. cannot use a checklist of studies or data because it will depend on the history of the ingredient.
- Dealing with uncertainty: There will always be some level of uncertainty to manage. Some decisions: How critical are the data gaps? Are new studies necessary? Can controls be in place to reduce risk? Is there sufficient information?
- Evaluation requires judgement by experienced, scientifically trained person.



Determining Maximum Levels of Vitamin and Minerals

- ASEAN TMHS ATSC developed a scientific method to assess the risk and then the manage potential risk of vitamins and minerals in Health Supplements.
- Using this method, a Maximum Level was determined for many Vitamins and Minerals.
- The method used risk assessment based on the WHO model (NOAEL and UF) and a risk management model based on ERNA (European Responsible Nutrition Alliance).



Risk Assessment Methodology

1. Decide on the most critical adverse effects of that nutrient reported in the literature.
2. Choose the most relevant and comprehensive reports as references for the NOAEL value.
3. Assign an appropriate UF if there are concerns on the credibility of data, severity of adverse effects, etc.
4. For nutrients with reported adverse effects, derive UL (upper limit of safety) using the formula $UL = NOAEL \div UF$.



Risk Management Methodology

1. Categorize risk groups:

i) Nutrients without reported adverse effects = Group A

ii) Nutrients with reported adverse effects

- derive their PSI using the formula

$$\text{PSI} = \frac{\text{UL} - \text{MHI}}{\text{RLV}}$$

- PSI > 1.5 to Group B
- PSI < 1.5 to Group C

PSI = Population Safety Index

MHI = Mean Highest Intakes

RLV = Reference Labeling Value, commonly known as Labeling RDA



Risk Management Methodology

2. Establish ASEAN Maximum Level (ML):

I. Group A

$$ML = (HOI \div UF) - MHI$$

II. Group B

$$ML = UL - MHI$$

III. Group C

$$ML = \text{lowest RLV}$$

or lowest existing maximum limit

HOI = Highest Observed Intake

MHI = Mean Highest Intakes

RLV = Reference Labeling Value, commonly known as Labeling RDA



WORKSHEETS USED BY ACCSQ TRADITIONAL MEDICINES AND HEALTH SUPPLEMENTS SCIENTIFIC COMMITTEE (ATSC) FOR THE ESTABLISHMENT OF THE ASEAN MAXIMUM LEVEL OF VITAMINS & MINERALS IN HEALTH SUPPLEMENTS

Worksheets Used in the Establishment of ASEAN Maximum Levels of Vitamins and Minerals in Health Supplements

LS-11-000018

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| Introduction | Methodologies | Page 03 – 06 | |
| Group A Vitamins & Minerals | Vitamin B1 | Page 07 – 08 | [ASEAN ML = 100 mg/day] |
| | Vitamin B2 | Page 09 – 10 | [ASEAN ML = 40 mg/day] |
| | Vitamin B12 | Page 11 – 12 | [ASEAN ML = 0.6 mg/day] |
| | Pantothenic Acid | Page 13 – 14 | [ASEAN ML = 200 mg/day] |
| | Biotin | Page 15 – 16 | [ASEAN ML = 0.9 mg/day] |
| | Chromium | Page 17 – 18 | [ASEAN ML = 0.5 mg/day] |
| Group B Vitamins & Minerals | Vitamin A (Retinol) | Page 19 – 22 | [ASEAN ML = 1.5 mg (5000 IU)/day] |
| | Vitamin D | Page 23 – 26 | [ASEAN ML = 0.025 mg (1000 IU)/day] |
| | Vitamin E | Page 27 – 30 | [ASEAN ML = 536 mg (800 IU)/day] |
| | Vitamin C | Page 31 – 34 | [ASEAN ML = 1000 mg/day] |
| | Vitamin B6 | Page 35 – 38 | [ASEAN ML = 100 mg/day] |
| | Folic Acid | Page 39 – 42 | [ASEAN ML = 0.9 mg/day] |
| | Nicotinamide | Page 43 – 45 | [ASEAN ML = 450 mg/day] |
| | Molybdenum | Page 46 – 48 | [ASEAN ML = 0.36 mg/day] |
| | Boron | Page 49 – 52 | [ASEAN ML = 6.4 mg/day] |
| | Selenium | Page 53 – 56 | [ASEAN ML = 0.2 mg/day] |
| Calcium | Page 57 – 59 | [ASEAN ML = 1200 mg/day] | |
| Group C Vitamins & Minerals | Copper | Page 60 – 63 | [ASEAN ML = 2 mg/day] |
| | Nicotinic Acid | Page 64 – 67 | [ASEAN ML = 15 mg/day] |
| | Iron | Page 68 – 71 | [ASEAN ML = 15 mg/day] |
| | Magnesium | Page 72 – 75 | [ASEAN ML = 350 mg/day] |
| | Phosphorous | Page 76 – 79 | [ASEAN ML = 800 mg/day] |
| | Manganese | Page 80 – 83 | [ASEAN ML = 3.5 mg/day] |
| | Zinc | Page 84 – 87 | [ASEAN ML = 15 mg/day] |
| | Iodine | Page 88 – 92 | [ASEAN ML = 0.15 mg/day] |
| | Vitamin K | Page 93 – 95 | [ASEAN ML = 0.12 mg/day] |
| Minerals excluded from the setting of ASEAN Max Levels | Potassium | Page 96 – 99 | |
| | Fluoride | Page 100 – 103 | |

ASEAN Vitamin D ML

- **Find the UL**

ASEAN reviewed all published Vit D clinical studies. Highest NOAEL was in found in Heaney (2003) at 0.25 mg/day for 20 weeks in men. UF used by ASEAN is 3.

$$\begin{aligned} \text{UL} &= \text{NOAEL}/\text{UF} \\ &= (0.25/3) \text{ mg/day} \\ &= 0.0833 \text{ mg/day} \end{aligned}$$

- **Determine ML calculated using US MHI.**

$$\begin{aligned} \text{ML} &= \text{UL} - \text{MHI} \\ &= (0.0833 - 0.05) \text{ mg/day} \\ &= 0.0333 \text{ mg/day} \end{aligned}$$

rounded down to 0.025 mg/day.



ASEAN ML for Vit D = 0.025 mg/day

The method ensures safety in several ways:

- No Observed Adverse Effect level found from human studies.
- Included an Uncertainty Factor, even though human study.
- Maximum Highest Intake value was from the United States, a population with high supplementation and food intakes.
- The safety of this ML is supported by other clinical studies that found 0.05 mg/day for 1 year had no adverse effects.

The ML is conservative. The ML is based on factors that result in safe use for wide spectrum of the population.



Product Safety Assessment

Components of a Product Safety Assessment

- Description of the finished product.
- Safety summaries of all active ingredients. (all are at levels <ADI)
- Review acceptability of excipients.
- Relevant studies (clinical, consumer preference), if any, with the finished product.
- Describe any interactions, contraindications.
- Possible side effects.
- Cautionary statement.
- Previous marketing experience of the finished product.



Product Safety Assessment

SAFETY SUMMARY REPORT FOR

Template from
Amway modelled
after Canada NPHD
Safety Evidence
Guideline

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APPENDIX

Individual Safety Assessment Reports (if not monographed)



Mixtures of potential concern

A “filter” method considers the potential for a toxicologically significant synergistic effect such as:

- One or more components can significantly enhance the uptake of other components.
- One or more components can inhibit significantly the excretion/clearance of other components.
- One or more of the components can exert their toxic action via the formation of an active metabolite(s) and may one or more of the components induce the drug metabolising enzymes that may be involved in the formation of these active metabolites.
- Two or more components can act on different enzymes in an important metabolic pathway.
- Two or more components can act on different elements of cellular protection mechanisms or cellular repair mechanisms.

These questions are applicable to drugs. Ingredients used in HS usually do not act in these ways.



Testing for Interactions

The state-of-the-art on testing for interactions:

- *In vivo* toxicity testing and clinical studies are inadequate for testing for interactions. Interactions are unlikely to be detected because they are rare, it is not known what targets to study and is dependent on test subject physiology.
- *In vitro* predictive models for drugs are still in development and it is not known whether they are applicable to health supplements.
- Methods exist to combine mechanistically based toxicology studies with statistical modelling to determine interactions.
- Studies to determine potential interactions may be investigated for new drugs, but are not typically conducted unless there is a known potential risk

“Therefore, testing for interactions at this stage is not effective and not feasible”



Safety of Multi-Ingredient HS

- ❑ History of use shows that risk from multi-ingredient health supplements is low.
- ❑ Post-market serious adverse effect reports with health supplements are rare.
- ❑ Explanation:
 - Ingredient amounts are below risk (ADI) levels or at food equivalent levels.
 - Adverse events are independent (not the same causal pathway).
- ❑ Evaluation of interactions is warranted under the following conditions:
 - When there are common mechanisms of toxicity.
 - When there are reports, such as in monographs, of potential interactions or contraindications.



Safety of Multi-Ingredient HS

Risk Management practices:

- Warning labels to reduce possible interactions with medicines

“Individuals taking medicine or under doctor supervision should seek medical advice before taking.”

- Monographs cite possible and theoretical interactions

The Natural Standard: “Most herbs and supplements have not been thoroughly tested for interactions with other herbs, supplements, drugs, or foods. The interactions listed below are based on reports in scientific publications, laboratory experiments, or traditional use. You should always read product labels. If you have a medical condition, or are taking other drugs, herbs, or supplements, you should speak with a qualified healthcare provider before starting a new therapy.”

- Monograph information regarding interactions

Canadian monographs, EFSA database

- Internet sites that have searchable databases: www.drugs.com, www.drugdigest.org, www.medscape.com



Health Canada

Monograph for Gingko biloba

http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-rod/monograph/mono_ginko_biloba-eng.php

Risk information: Statement(s) to the effect of:

Caution(s) and warning(s):

- ▶ Consult a health care practitioner prior to use if you are taking medications for diabetes, high blood pressure, or seizures (Brinker 2009).
- ▶ Consult a health care practitioner prior to use if you are pregnant or breastfeeding (Blumenthal et al. 2000; WHO 1999).

Contraindication(s): Do not use if you are taking health products that affect blood coagulation (e.g. blood thinners, clotting factor replacements, acetylsalicylic acid, ibuprofen, fish oils, vitamin E) as this may increase the risk of spontaneous bleeding (Brinker 2009; Bent 2005).

References- Guideline or Examples of Safety Assessments

ILSI publication

<http://www.ncbi.nlm.nih.gov/pubmed/14563389>

NHPD

<http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/tradit-eng.php#a2.7>

EFSA

<http://www.efsa.europa.eu/en/scdocs/doc/1249.pdf>

US NTP

<http://ntp-server.niehs.nih.gov/>

JECFA

<http://www.inchem.org/pages/jecfa.html>



Toxicity Testing Protocols

- **USA FDA “Redbook”**

<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/default.htm>

- **OECD Protocols**

http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788



Other relevant information

- **US FDA GRAS Generally Recognized as Safety database:**
<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/default.htm>
- **European Commission SCCP, SHER, SCENIHR comment on mixtures:**
http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_150.pdf
- **Canadian NHPD Monographs:**
<http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licenprod/monograph/index-eng.php>



EFFICACY OF NATURAL/HERBAL INGREDIENTS IN HEALTH SUPPLEMENTS



Efficacy VS Effectiveness

- ❑ **Efficacy:** The capacity for beneficial change or therapeutic effect of a given intervention (for example a drug, medical device, surgical procedure, or a public health intervention)
- ❑ **Effectiveness:** The capability of producing a desired result
 - Effectiveness relates to how well Health supplement works in practice
 - Measurement of health outcome



Clinical Study for Health Supplement

- ❑ **Goal:** To evaluate the effectiveness of Health Supplements
- ❑ **Population:** General population/Healthy population
- ❑ **Outcome:**
 - Elevate the blood level of certain nutrients
 - Enhance body normal function
 - Use marker of human health



Thank you

