CANTOX
HEALTH SCIENCES INTERNATIONAL

Consultants in Human Health, Toxicology & Regulatory Affairs

CONCEPTUAL FRAMEWORK FOR A TIERED APPROACH TO RISK RANKING AND PRIORITIZATION

Ian C. Munro, Ph.D., F.A.T.S., FRCPath

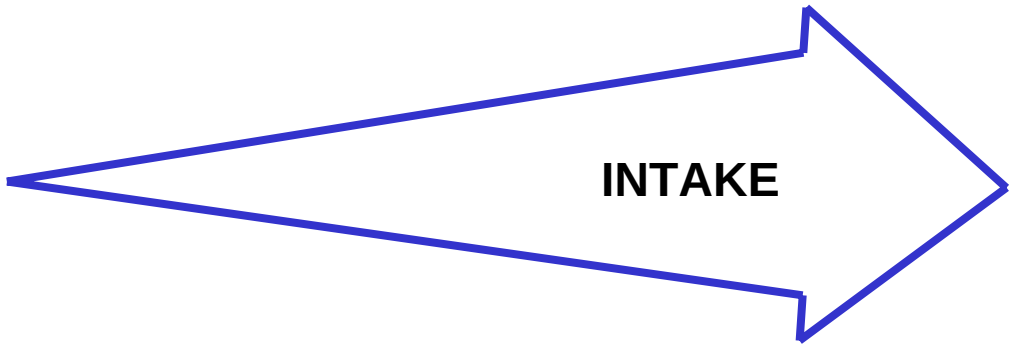
Workshop: Tools for Prioritizing Food Safety Concerns
Greenbelt Marriott Hotel, Greenbelt, MD
June 4-6, 2007

www.cantox.com

CANTOX
HEALTH SCIENCES INTERNATIONAL

CATEGORIES OF FOOD SAFETY CONCERNS

Single Chemical Entities	Complex Mixtures	Major Ingredients/ Whole Foods
Food and color additives	Botanicals	Starches
Packaging materials	Natural flavour complexes	Proteins
Processing aids	Processing reaction products	Fats & Oils
Bioactive substances		Fibres
Flavors		Whole foods (GMO's)
Contaminants		
Pesticide residues		



CANTOX
HEALTH SCIENCES INTERNATIONAL

PRESENTATION OUTLINE

- **Prioritization Elements**
- **Key Data Requirements**
- **Approaches to Evaluation**

The
SCIENCE
of
SUCCESS

PRIORITIZATION ELEMENT – SINGLE CHEMICAL ENTITIES

- Intake
- Structure and presumed metabolic fate
- Structure activity relationships (SAR) (*e.g.*, Redbook)
- Existing toxicity data and data on related structures

PRIORITIZATION ELEMENTS – COMPLEX MIXTURES

- Compositional data
- Intake of total mixture and individual components
- Toxicity and metabolic data on major components
- Toxicity data on the mixture where compositional data does not exist

CANTOX
HEALTH SCIENCES INTERNATIONAL

PRIORITIZATION ELEMENTS – MAJOR INGREDIENTS AND WHOLE FOODS

- Compositional data
- Intake
- History of use
- Substantial equivalence
- Toxicity and metabolic data

The
SCIENCE
of
SUCCESS

CANTOX
HEALTH SCIENCES INTERNATIONAL

SINGLE CHEMICAL ENTITIES – ESTABLISHING PRIORITIES FOR TESTING

- WHO, EHC-70
- FDA, Redbook

The SCIENCE of SUCCESS

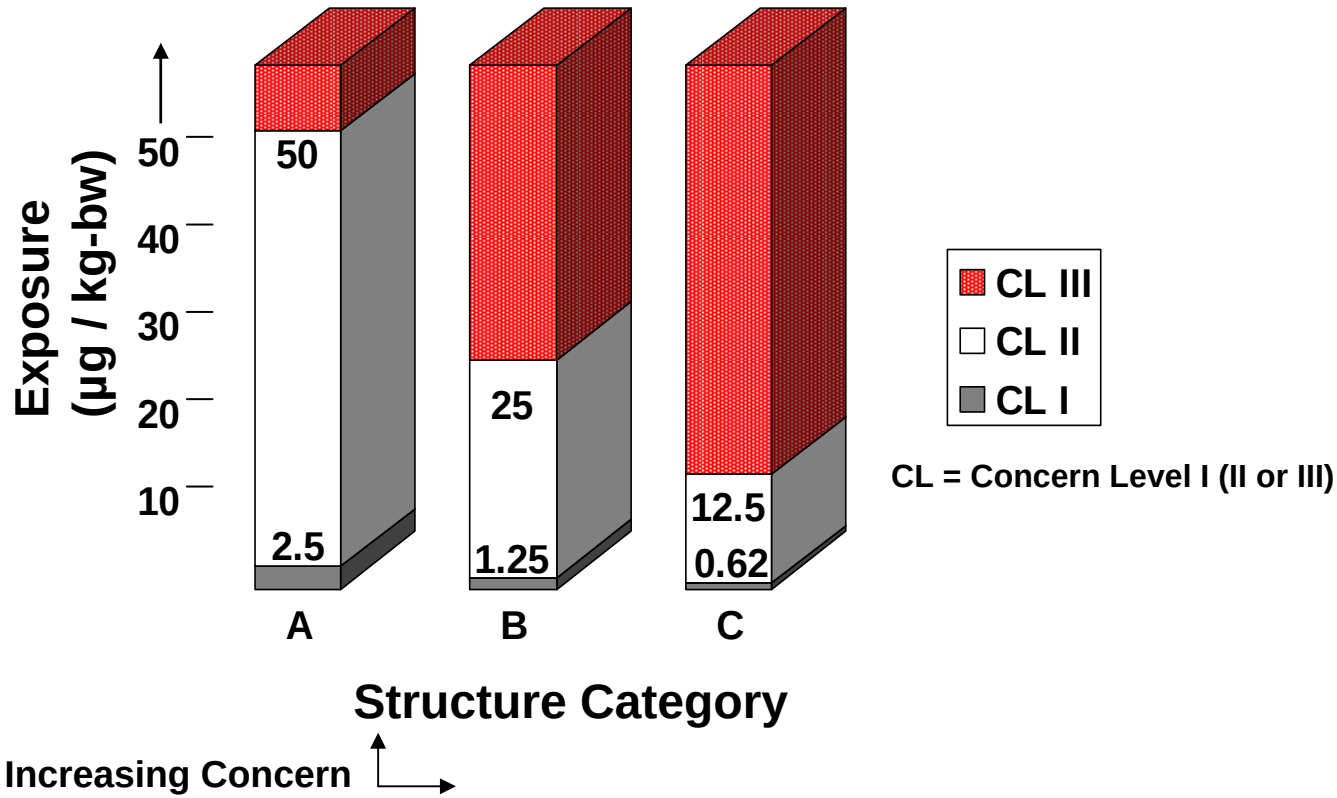
ENVIRONMENTAL HEALTH CRITERIA – 70 GENERAL PRINCIPLES AND APPROACH TO EVALUATION

- Data on composition and specifications
- Fate of the substances in food matrices including residues
- Estimated intake
- Metabolic disposition and fate in biological system
- Toxicity data

FDA CONCERN LEVELS

- **Based on intake, structural/molecular features**
- **Three structure categories A, B, C**
- **FDA developed Concern Levels I, II and III**

CONCERN LEVELS AS RELATED TO CHEMICAL STRUCTURE AND EXPOSURE



CANTOX
HEALTH SCIENCES INTERNATIONAL

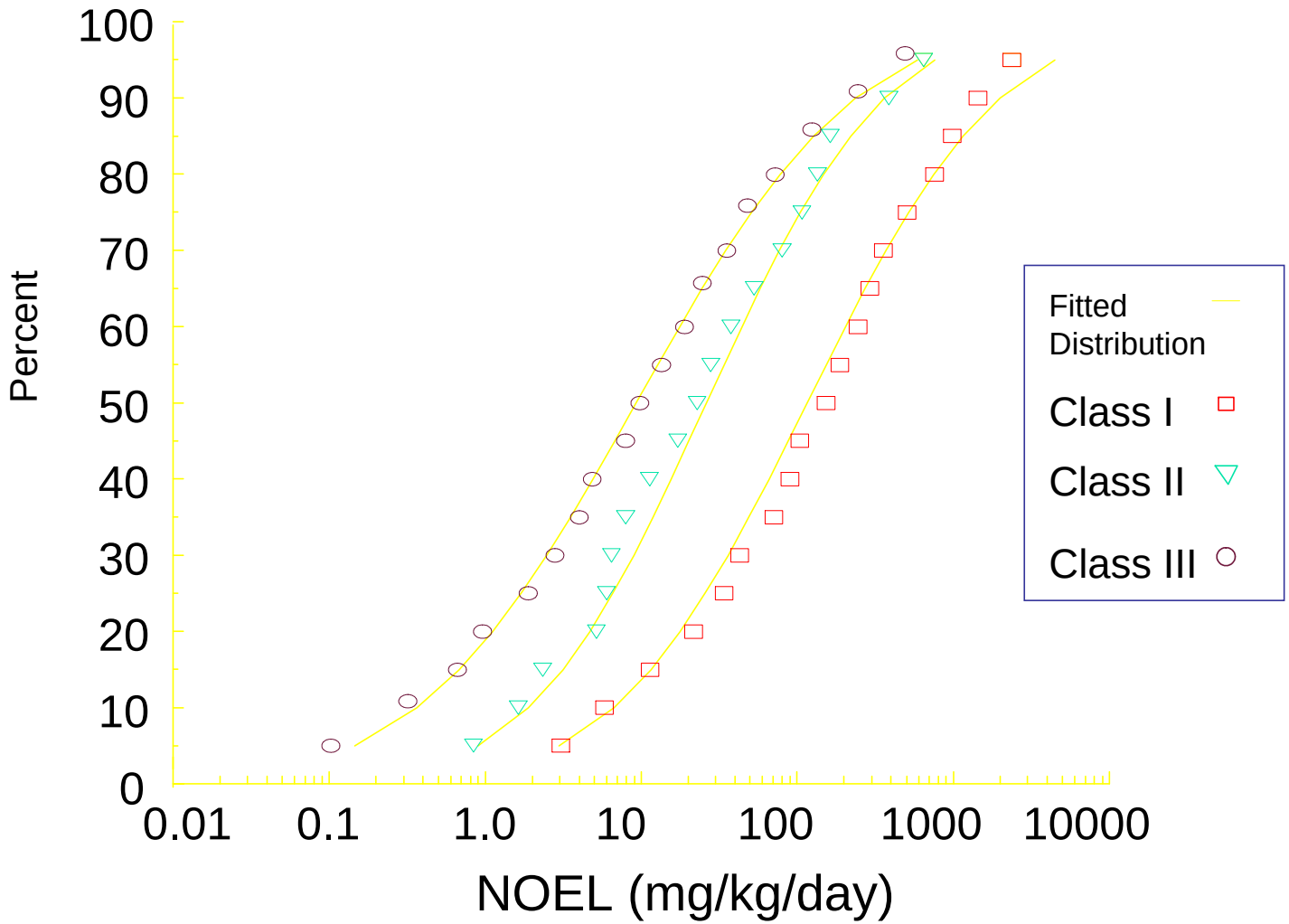
DEVELOPMENT OF A REFERENCE DATABASE

- Total of 2,944 NOELs entered into database for >612 substances
- Included food additives and pesticides
- Substances were grouped into Cramer *et al.* (1978) structural class in order to correlate structure with toxicity
- Most sensitive species, sex and endpoint for each substance were selected
- Cumulative distribution of NOELs for each structural class was plotted

NUMBER OF SUBSTANCES IN THE DATABASE

Cramer *et. al.* Structural Class	No. of Substances
I	137
II	28
III	447

CUMULATIVE DISTRIBUTIONS OF NOELs



DEVELOPMENT OF HUMAN EXPOSURE THRESHOLDS

- For each structural class, the 5th percentile NOEL was estimated
- The 5th percentile NOEL provides 95% probability that any other substance in the same structural class as those comprising the reference database would have a NOEL greater than the 5th percentile for that particular structural class

DEVELOPMENT OF HUMAN EXPOSURE THRESHOLDS (CONT'D)

Human exposure thresholds were derived by dividing the 5th percentile NOEL for each structural class by a 100-fold safety factor

- 100-fold safety factor is inherently applied in establishing safe intake levels

DEVELOPMENT OF HUMAN EXPOSURE THRESHOLDS (CONT'D)

- **Use of 5th percentile NOEL is more conservative than arithmetic mean**
- **Substantive margin of safety since human exposure thresholds are based on approximately 612 compounds with good supporting toxicity data**

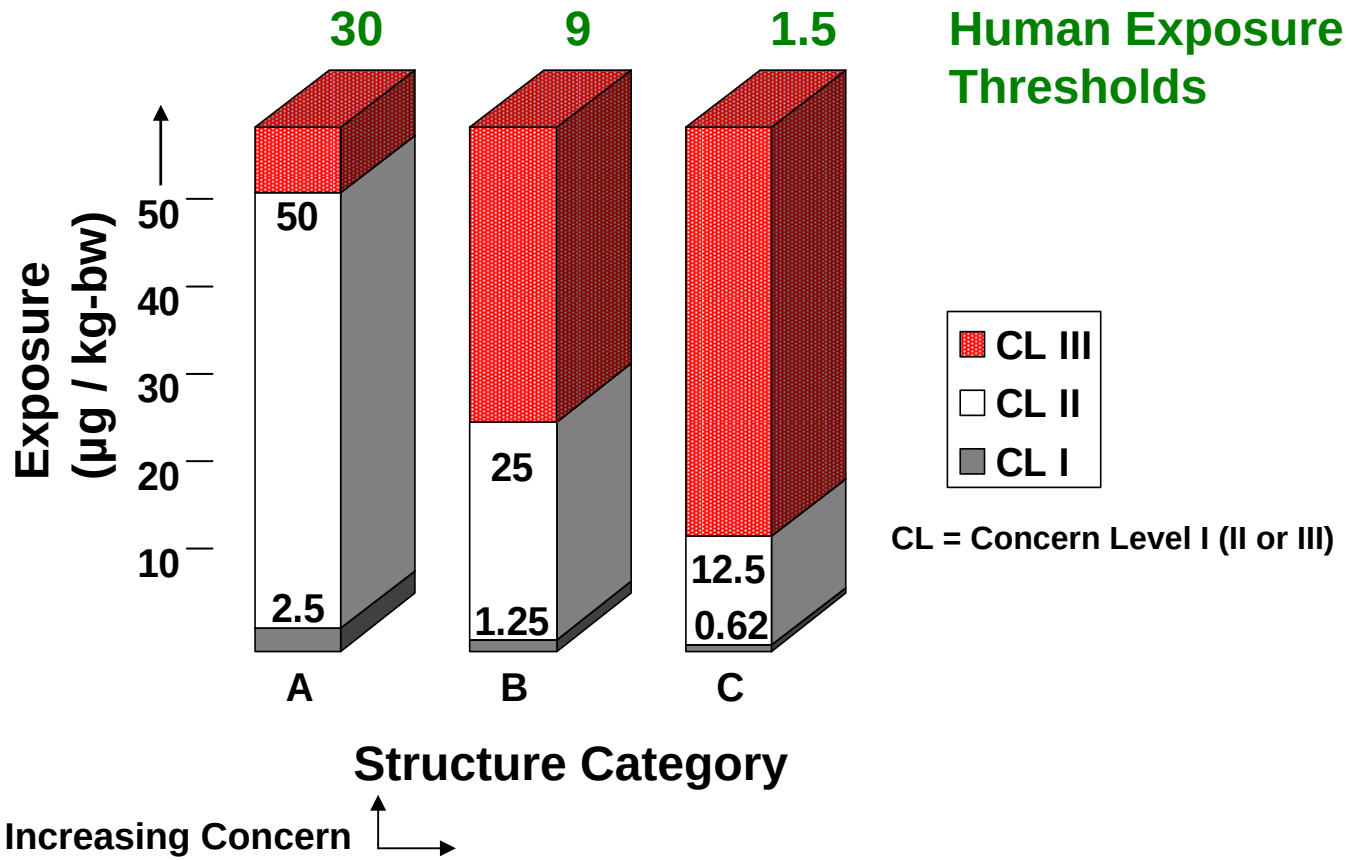
CANTOX
HEALTH SCIENCES INTERNATIONAL

HUMAN EXPOSURE THRESHOLDS FOR CRAMER *ET AL.* STRUCTURAL CLASSES

Structural Class	No. of Chemicals	5th Percentile NOEL (µg/kg/day)	Human Exposure Threshold (µg/kg/day)
I	137	2,993	30
II	28	906	9
III	447	147	1.5

The SCIENCE of SUCCESS

CONCERN LEVELS AS RELATED TO CHEMICAL STRUCTURE AND EXPOSURE



CANTOX
HEALTH SCIENCES INTERNATIONAL

TOXICITY TESTS RECOMMENDED FOR DIFFERENT CONCERN LEVELS BY FDA

	Concern Levels		
	I	II	III
Short-term Tests for Genetic Toxicity	X	X	X
Metabolism and Pharmacokinetic Studies		X	X
Short-term Toxicity Tests with Rodents	X		
Subchronic Toxicity Tests with Rodents		X	X
Subchronic Toxicity Tests with Non-Rodents		X	
Reproduction Study with Teratology Phase		X	X
One-year Toxicity Test with Non-Rodents			X
Carcinogenicity Study with Rodent			X
Chronic Toxicity/Carcinogenicity Study with Rodents			X

COMPLEX MIXTURES

- **Food additive preparations**
- **Herbs, botanicals, spices and extracts**
- **Natural flavor complexes – essential oils and oleoresins**

SOME GENERAL PRINCIPLES

- Source, specifications and manufacture
- Composition, identification of principal constituents
- Intended conditions of use
- Level of intake
- Toxicological evaluation

CANTOX
HEALTH SCIENCES INTERNATIONAL

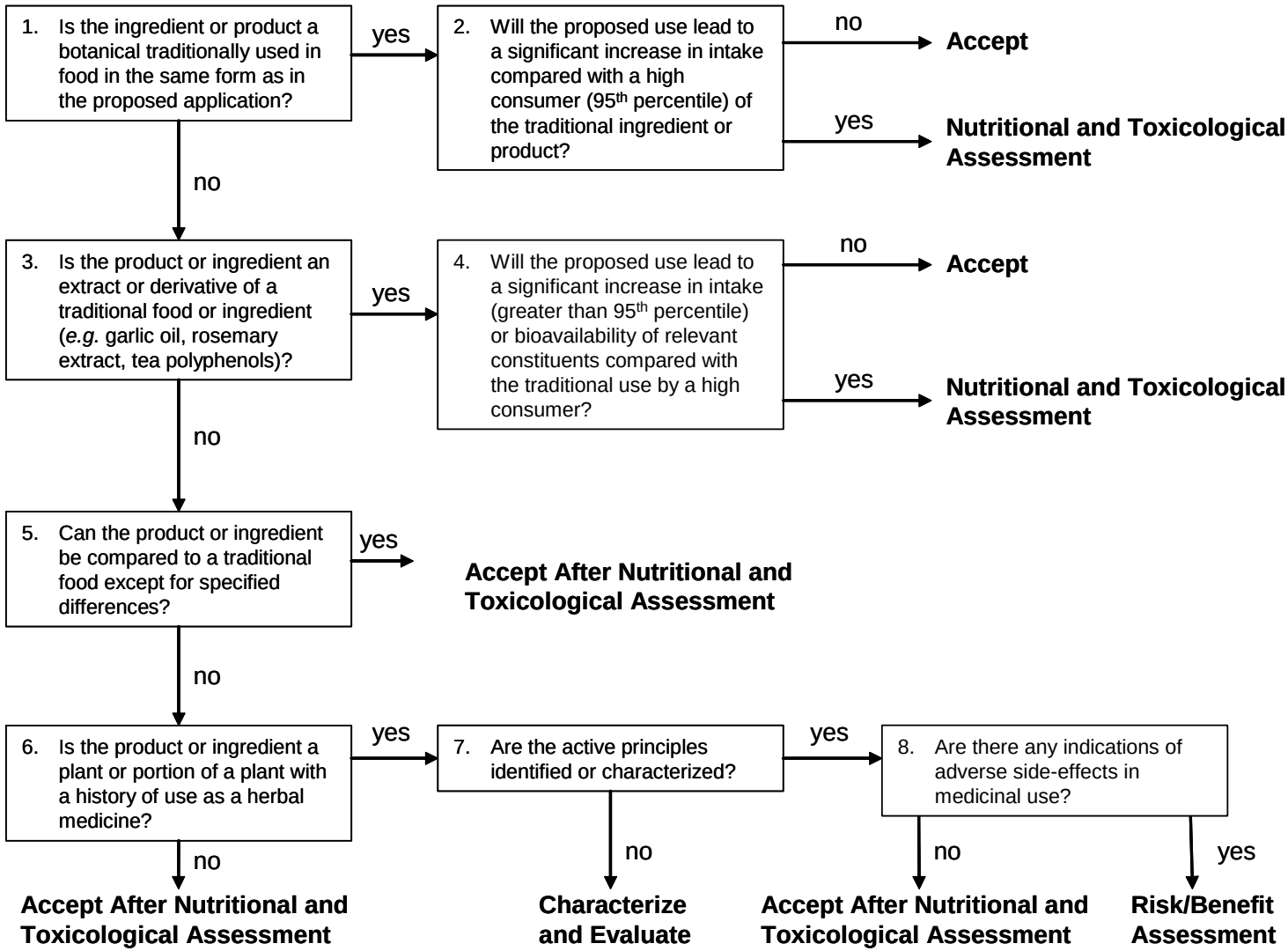
SUGGESTED EVALUATION SCHEMES

- **Botanicals**
- **Natural flavor complexes**

The
SCIENCE
of
SUCCESS

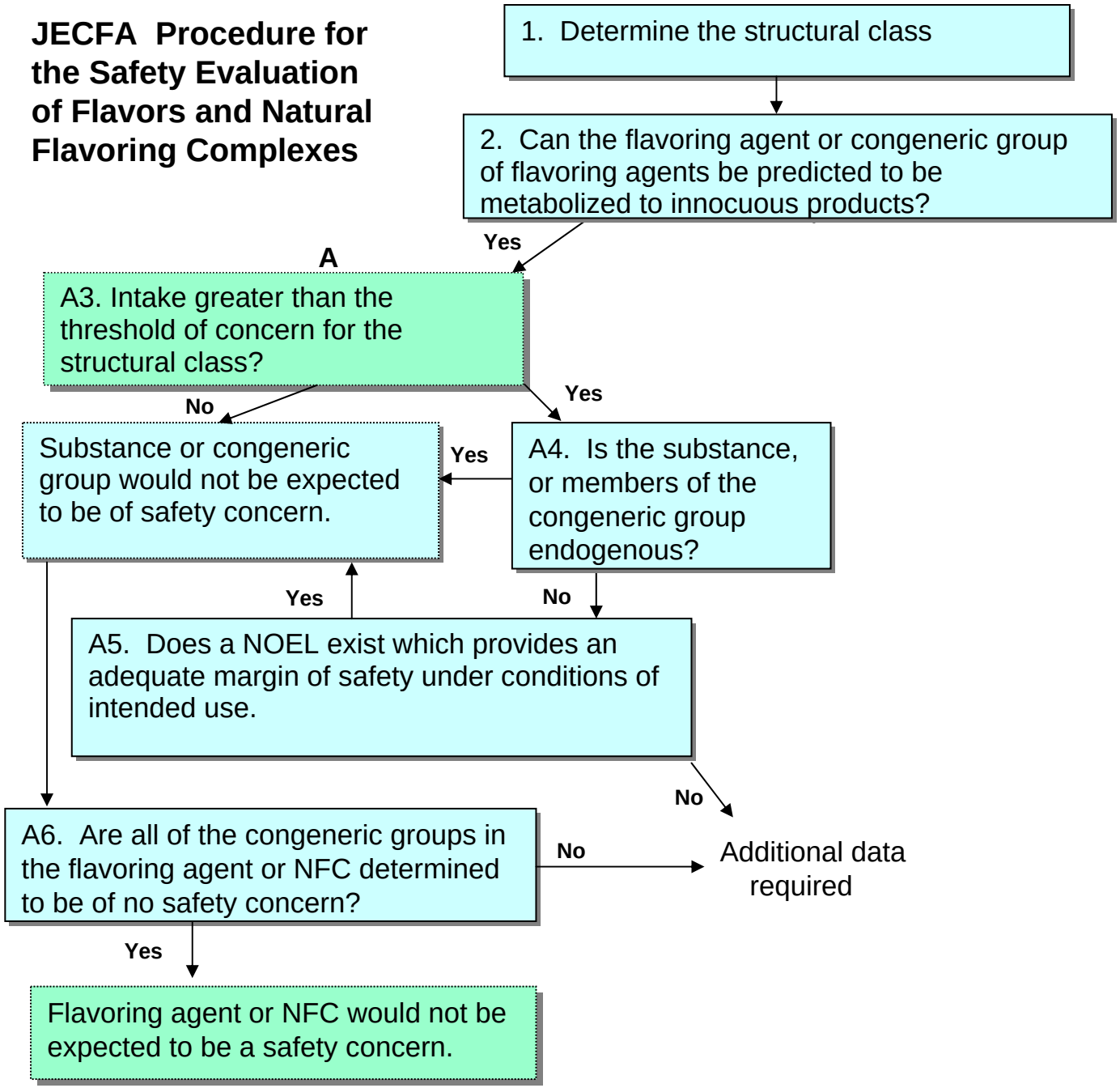
CANTOX
HEALTH SCIENCES INTERNATIONAL

BOTANICALS – ILSI EUROPE DECISION TREE

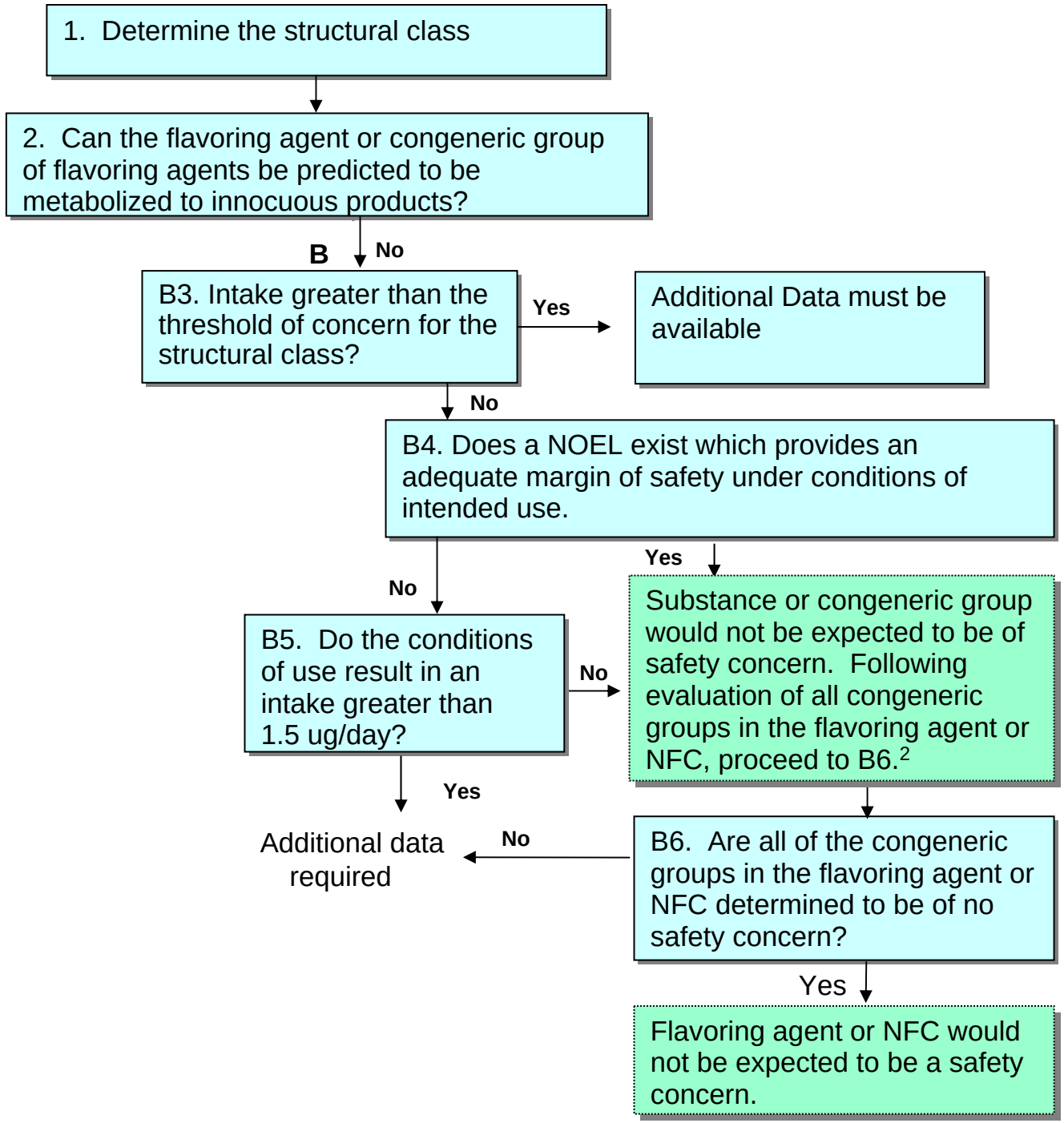


The SCIENCE of SUCCESS

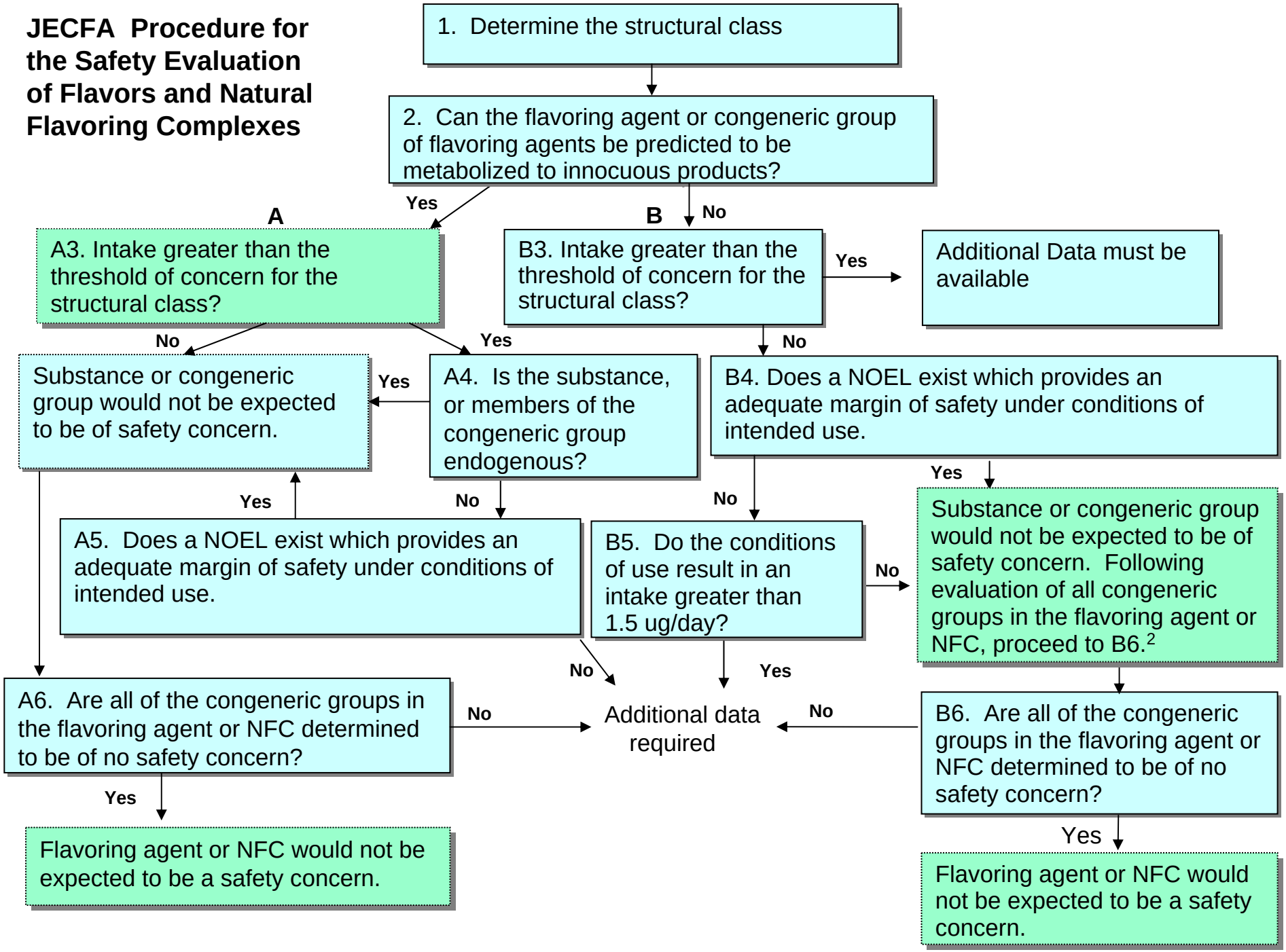
JECFA Procedure for the Safety Evaluation of Flavors and Natural Flavoring Complexes



JECFA Procedure for the Safety Evaluation of Flavors and Natural Flavoring Complexes



JECFA Procedure for the Safety Evaluation of Flavors and Natural Flavoring Complexes



CANTOX
HEALTH SCIENCES INTERNATIONAL

INGREDIENTS AND WHOLE FOODS – KEY ISSUES

- Often impossible to achieve 100x fold safety factor (LSRO)
- Nutritional status may be altered in test animals resulting in pseudotoxicity
- A different approach is required with less emphasis on toxicity testing and more emphasis on compositional and metabolic data
- Clinical trials can play a key role in macro ingredient safety evaluation

APPROACHES TO SAFETY EVALUATION

- Compositional data are essential
- Because of high exposure impurities and contaminants need to be emphasized
- Analytical comparison of the new product with a suitable naturally occurring counterpart is a key element of the safety assessment
- Animal toxicity tests need to be designed in a thoughtful manner. Standard Redbook procedures often cannot be used

COMPOSITIONAL STUDIES GUIDE THE SAFETY EVALUATION

- **Key to developing a credible approach to safety evaluation relies on having detailed compositional data**
- **These data can be used to predict metabolic fate (*e.g.,* resistant starches, chemically or enzymatically modified carbohydrates, fats and oils)**
- ***In vitro* metabolic and fermentation techniques can be used to evaluate potential *in vivo* metabolic fate**
- **Limited toxicity testing may be used to confirm safety**

ADDITIONAL FACTORS TO CONSIDER IN SAFETY EVALUATON OF WHOLE FOODS AND INGREDIENTS

- **Changes in food consumption patterns**
  - Potential for nutritional effects
  - High intakes by certain sub-groups
- **New foods/ingredients being introduced**
  - Potential for allergenic reactions
- **Post-market monitoring**
  - Confirm expected consumption patterns
  - Assess potential shifts in nutrient intake
    e.g. How much EPA/DHA is actually being consumed?

CONCLUSIONS RE FRAMEWORKS

- **Three separate categories of concern**
  - Single chemical entities
  - Complex mixtures
  - Whole foods and major ingredients
- **Each category requires a unique approach; no single approach can be used across the entire spectrum of potential risks**