The Evolution and Continuing Importance of Risk-Based Decisions and the Increasing Influence of Hazard-Based Approaches

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I am employed by Ramboll, an international scientific and engineering consultancy.

My presentation is entirely of my own creation and no funding of any kind has been used to create it.

ARE WE ALL SPEAKING THE SAME LANGUAGE?

- **AGENT:** A chemical, biological, or physical substance

  - **HAZARD:** The *type of harm to health* exposure to an agent can cause.

    - **RISK:** The likelihood (or probability) that the hazardous properties of an agent will be expressed under specified exposure conditions.

      - **SAFETY:** Conditions of exposure to a hazardous agent at which its risk is considered to be negligible.

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ARE WE ALL SPEAKING THE SAME LANGUAGE? (CONTD.)

- **RISK-BASED DECISION:** Any decision having the purpose of avoiding or minimizing risks to public health.

- **RISK ASSESSMENT:** The integration and evaluation of evidence concerning an agent's hazards, their relation to exposure, and the exposures experienced by human populations.
  - To estimate the health risks to those populations
  - *Scientific uncertainties* are explicitly described.

- **RISK MANAGEMENT:** Policy-based actions needed to achieve public health goals. Scientific uncertainties are taken into account.

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RISK MANAGEMENT

DEPENDS UPON

1 Legal and other policy-based criteria.

2 Decision models appropriate for the risk management context.

3 Risk assessments that are scientifically reliable and useful for the decision model.

4 Adequate consideration of scientific and other technical uncertainties.

5 Complete transparency regarding the basis for the decisions and actions to be taken.

UNCERTAINTY   COMMUNICATION

HAZARD-BASED DECISIONS

Exposure to agents should be controlled or eliminated based upon their hazardous properties…..

…….irrespective of the health risks they pose.

(we shall return to this topic later in the presentation)

UNCERTAINTY IS INHERENT IN SCIENCE

1 It can be reduced but not eliminated.

2 Its existence is not a valid excuse for indecision.

3 Models for incorporating uncertainties into decisions are available from decision science.

4 Risk communication is deficient if uncertainties and their influence on decisions are not discussed

> To ignore or minimize acknowledging the existence of uncertainty is to ignore science.

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RISK COMMUNICATION
EXPLAINING RISK-BASED DECISIONS TO THE GENERAL PUBLIC

- Much scholarly research on this topic, and guidance is available…
  - It is a risky undertaking unless it is well-informed by this research.

A FEW KEY LESSONS

- People's understanding of probabilities is poor.
- They are suspicious of absolute, unqualified statements.
- Perceptions of risk differ from expert understanding.

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A brief historical tour of the origin and evolution of risk-based decision making for chemical risk management, and of the persisting (growing?) appeal of hazard-based approaches

WITH A FOCUS ON FOOD SUBSTANCES

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THE FIRST SYSTEMATIC & EXPLICITLY DESCRIBED METHODS FOR EVALUATING THE SAFETY OF CHEMICALS

Introduced in the 1950s by FDA scientists
Intended for decisions about:

1. Substances intentionally introduced into foods
   - Food additives
   - GRAS substances

2. Substances, the intentional use of which, leads to their presence in food
   - Pesticides
   - Veterinary drugs for food-producing animals
   - Components of food contact materials

New Food Safety Laws 1954-1962

"SAFETY ASSESSMENT"

ORIGINAL GUIDING PRINCIPLES FOR SAFETY ASSESSMENT (1950s)

- Empirical data on toxicity reveals the existence of threshold doses for toxicity.
  - The observed threshold dose (e.g., from animal studies) was labelled a NOEL (later, the NOAEL*)
  - The NOEL should be divided by various "safety factors" to derive:

Allowable Daily (Human) Intakes (ADI)
An estimated threshold for a large, diverse human population

*No Observed Adverse Effect Level

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11

SOME CHARACTERISTICS OF ADIs AND RELATED MEASURES

1. The Risk of Toxicity at the ADI, or at intakes greater than or less than the ADI, are not quantified.

2. The ADI and its relatives are used as **"Bright-Line" Decision Models.**

   1. Intakes < ADI are acceptable (safe)

   2. Intakes > ADI are not acceptable

3. Although the ADI and its relatives are widely used, they provide no understanding of the sizes of the risk being accepted or not accepted

4. The uncertainty associated with the use of the ADI is generally unknown.

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AND YET...

ADIs have a long history of use and there is no evidence their use has jeopardized public health

(not easy to evaluate this)

_____

Efforts are underway to move towards quantifying risks for threshold agents..

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AN IMPORTANT EXCEPTION TO EARLY RISK-BASED REGULATION

The safety assessment model was not to be applied to <u>carcinogens</u>:

Many leading scientists held the view that chemical carcinogenesis occurred through biological processes distinctly different from those leading to all other types of toxicity.

"NO SAFE LEVEL"

This view led to the introduction into federal food laws of the **DELANEY CLAUSE (1958):**

No carcinogen could be intentionally introduced into food, directly or indirectly.

A HAZARD-BASED DECISION MODEL

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THE INTRODUCTION OF CARCINOGEN RISK ASSESSMENT QUANTITATIVE RISK ASSESSMENT (QRA)

1970s

- EPA and FDA began adopting methods to estimate low-dose cancer risks.

  - The **no-threshold** assumption was adopted.

  - A **linear dose-response** model was adopted.

  - **Upper bounds** on low-dose cancer risk were developed.

- Carcinogens would be regulated based on quantitative measures of risk.*

- No fixed definition of safety, although 10-6 lifetime risk is often treated as a "Bright-Line."

*e.g., "There is a 10-5 probability of cancer in populations exposed to 10 ppb aflatoxin in the diet."

BENZENE

VINYL CHLORIDE

AFLATOXIN

DIMETHYLNITROSAMINES

DES

ASBESTOS

PAHs

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MOVING AWAY FROM "BRIGHT LINE" SAFETY CRITERIA FOR THRESHOLD EFFECTS

Move to Margin-of-Exposure (MOE) for non-carcinogen endpoints

$$MOE = \frac{NOAEL}{Human\ Exposure}$$

- Allows analysis of increases in MOE (decreases in risk) achieved with different interventions.

- The MOE is not a quantitative risk measure.

  » **MOE more useful for many decisions, but reveals nothing about the magnitude of risk reduction achieved with an intervention.**

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RISK MANAGEMENT FOR FOOD CONSTITUENTS & CONTAMINANTS

DECISION CONTEXTS SHOULD GUIDE SELECTION OF APPROACHES TO RISK ASSESSMENT

CURRENTLY AVAILABLE APPROACHES

1) Bright-Line Models - - threshold agents

2) Margin-of-Exposure (MOE) Models - - threshold agents

3) QRA Models - - non-threshold agents

SCIENCE AND DECISIONS
Advancing Risk Assessment

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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DECISION CONTEXTS FOR FOOD SUBSTANCES VARY ACCORDING TO HOW THEY COME BE PRESENT IN FOOD AND THE METHODS AVAILABLE TO REDUCE EXPOSURES TO THEM

A) NECESSARY AND UNAVOIDABLE

- Nutrients
- Natural Constituents

B) NOT READILY AVOIDABLE

- Compounds formed during processing and cooking
- Industrial chemical contaminants
- Naturally occurring contaminants

C) INTENTIONALLY INTRODUCED AND READILY AVOIDABLE*

- Food and color additives
- GRAS substances
- Animal drug residues
- Pesticides
- Substances migrating from packaging and other food contact materials

*If unsafe, uses can be stopped (although alternatives not always readily available)

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SAFETY DECISIONS FOR CATEGORY C SUBSTANCES
"READILY AVOIDABLE"

1) "Bright-Line" Decision Model (Safe/Not safe).

2) Estimated Daily Human Intake < ADI.

3) Substances that do not meet the safety criterion can be readily avoided, in the technical sense.

Appropriate for all substances in Category C

CONSIDER CATEGORY B SUBSTANCES
"NOT READILY AVOIDABLE"

Process-formed Compounds
Industrial & Natural Contaminants

Risk Models – Getting to the best approach to mitigation
- Bright-line models not very useful

Rather … models useful to describe how risks are changed with different mitigation strategies (*different interventions*) are needed

Decisions – select practicable intervention strategy that achieves adequate risk reduction.

SCIENCE AND DECISIONS

Advancing Risk Assessment

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CATEGORY B SUBSTANCES (CONT.)

The Problem with Bright-Line Models.

For both process-formed chemicals and industrial and natural contaminants, there is no way to eliminate exposures that exceed the "bright line" except to sample and analyze foods, and not allow into commerce foods that are "*unsafe*" (according to the bright-line criterion)

Because the risk associated with exposures at the "bright-line" is unknown, there is no clear way to ascertain whether the benefit achieved by eliminating foods from commerce is significant…

OR whether more serious actions are needed.

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CATEGORY B SUBSTANCES (CONT.)

Risk models

- Margin-of-Exposure (MOE) approaches are available – as MOEs increase, risk decreases.
- Quantitative risk models for carcinogens are well developed and are becoming available for other types of toxicity.

$*$

The best approach to mitigation:

- What risk reduction is achieved with each proposed intervention?

RISK-RISK TRADE OFFS

- Are there indirect effects of the intervention that might increase risk?

- What technically achievable intervention achieves the greatest benefit (perhaps also considering cost)?

CATEGORY A SUBSTANCES: THE GREATEST CHALLENGE!
("NECESSARY AND UNAVOIDABLE")

A model has been developed for substances in this category that are *nutritionally necessary.*

It is used to develop Dietary Reference Intakes (DRIs) designed to avoid nutritional deficiency, and to toxicity due to excessive intake.

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FIGURE 1: RELATIONSHIPS OF INTAKES AND ADVERSE EFFECTS OF SUBSTANCES THAT ARE NUTRITIONALLY NECESSARY
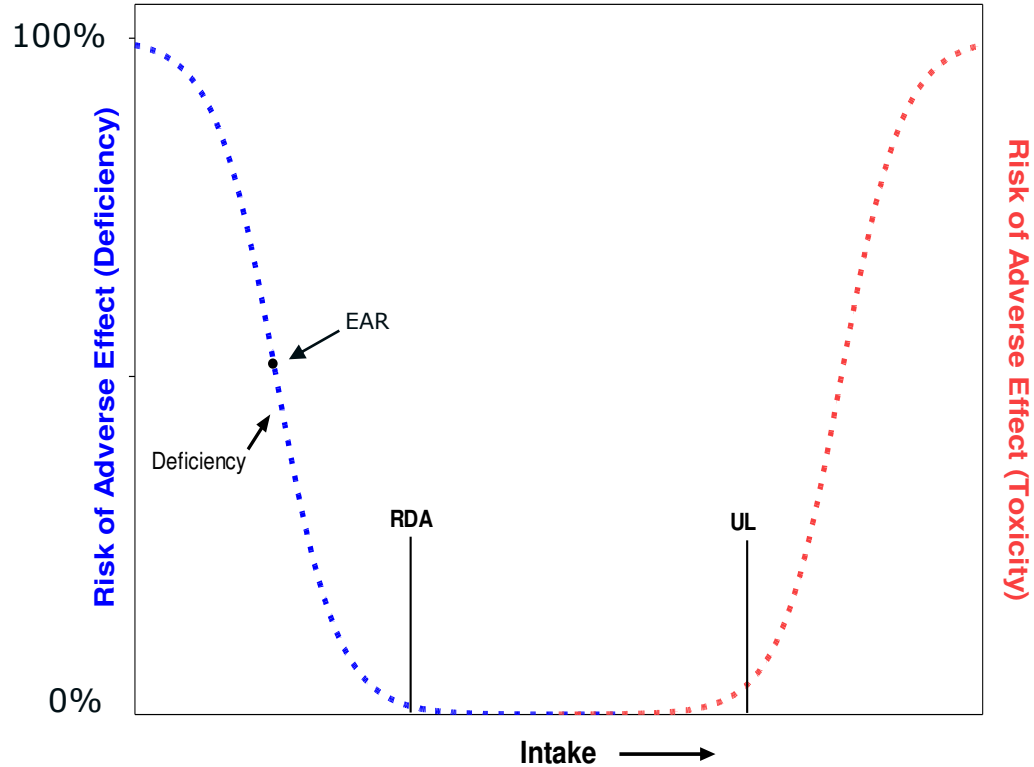
CHARACTERISTICS OF SUBSTANCES IN CATEGORY A THAT EXHIBIT INTAKE-RESPONSE RELATIONSHIPS AS DESCRIBED IN FIGURE 1

1. They are nutritionally necessary
2. The are, by themselves, necessary & sufficient to completely avoid deficiency disease
3. They are, if completely absent, capable of causing disease in 100% of the population

CHARACTERISTICS OF SUBSTANCES DESCRIBED IN FIGURE 1 (CONT.)

- These characteristics do <u>not</u> apply to non-nutritive constituents of Category A

- They do not apply to constituents of Category A that may increase or decrease the risk of *chronic diseases.*

  - No single substance would be necessary and sufficient to cause or to avoid disease in 100% of the population
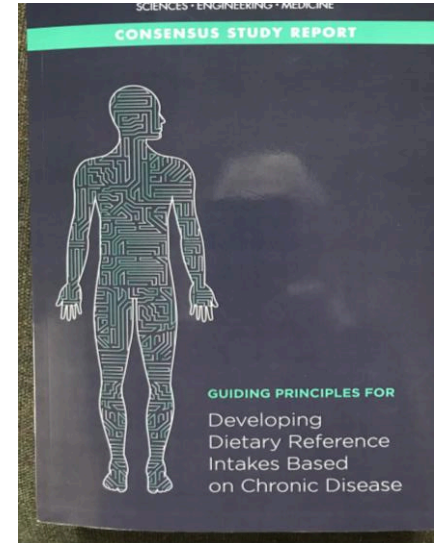
LIKELY DOSE-RESPONSE RELATIONSHIPS (CONCEPTUAL) FOR NATURAL FOOD SUBSTANCES THAT DECREASE CHRONIC DISEASE RISKS
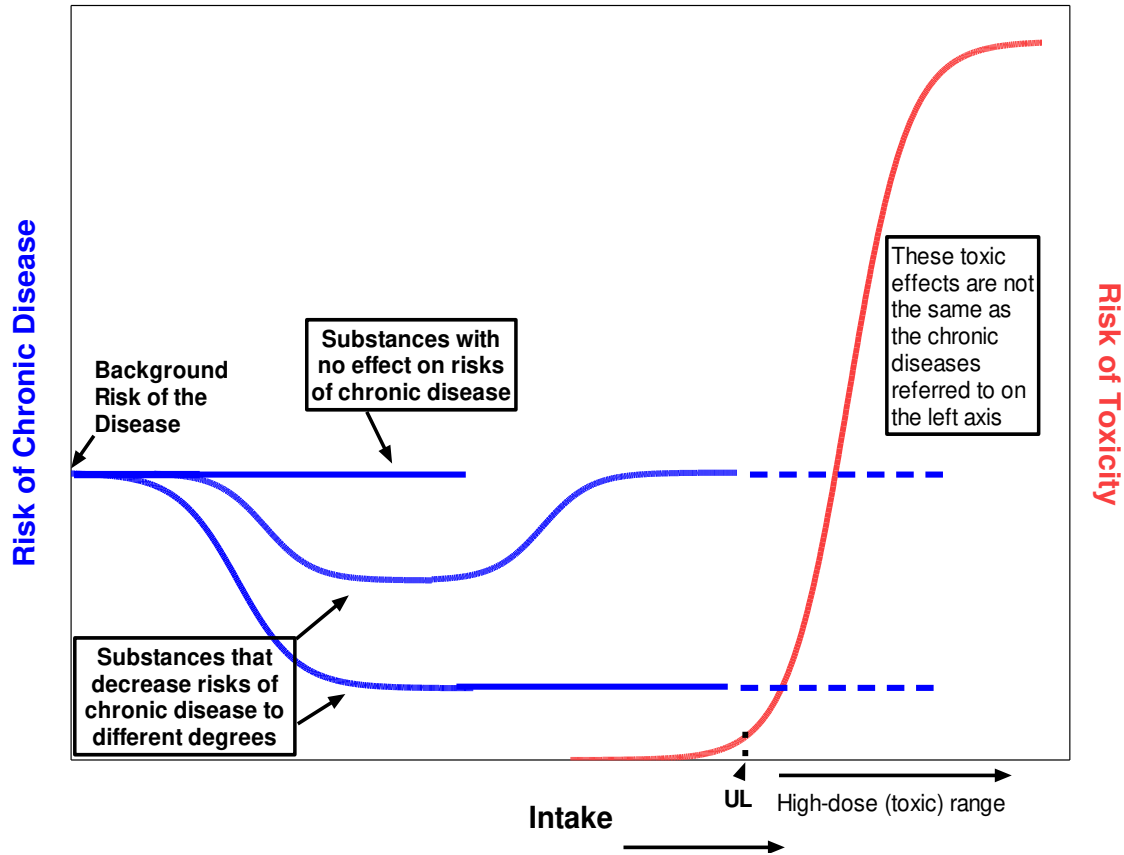
ONE OPTION: A RANGE OF BENEFICIAL INTAKES (RBI)

If it were possible to develop from available evidence dose-response relationships of the type shown in the previous figure, then a basis for dietary recommendations might exist.

The RBI would begin at levels of intake at which risk begins to decline, and the upper end would extend as far as the available evidence permitted, but would end before any risk of high dose toxicity were to set in (UL).

Other options are available…

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RISK ASSESSMENT/RISK MANAGEMENT

- Risk assessment should provide a characterization of the strength of the evidence for the effect, the strength of the effect (magnitude of risk reduction), and the uncertainties associated with these characterizations.

- Whether the RBI or other measure becomes a dietary recommendation is a risk management decision.

- Risk management decisions are also needed to reduce risks associated with substances that increase disease risk.

AND

THE PROBLEM OF OVERLAPPING

RISKS AND BENEFITS

"NET RISK"

RISK-BASED DECISIONS FOR FOOD SUBSTANCES SUMMATION

The most well-developed approach for identifying adverse effects of food substances and identifying intakes at which such effects are likely to be avoided is that used for intentionally introduced substances (Category C).

The "Category C approach" has several significant limitations in its applicability to Category A and B substances. The latter categories typically involve different and more complex types of evidence to identify adverse effects and different models for describing risks.

For Category A and B substances, identifying intakes at which the occurrence of adverse effects can be best minimized often involves some type of trade-off analysis. Such analyses require improved methods for characterizing adverse effects, evidence integration, and risk modeling that allows risks at different levels of intake to be estimated.

The goal for Category A and B substances might best be described as minimizing "net risks" to health, taking into account technical limitations in available risk mitigation approaches.

Uncertainties should always influence risk management decisions.

DECISION-MODELS NEED CONTINUING IMPROVEMENT

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NOTWITHSTANDING THE FACT THAT RISK ASSESSMENT AND RISK-BASED DECISION-MAKING HAVE SUCH STRONG SCIENTIFIC STANDING

Hazard-based approaches remain appealing to many and appear to be gaining strength.

Two reasons:
1. The limitations of risk-based approaches
2. The marketplace appeal and apparent simplicity of hazard-based approaches.

"Endocrine disruption is worse than kidney toxicity!"

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THERE ARE SOME DISADVANTAGES TO RISK-BASED APPROACHES

- Require much more data and analysis and therefore more scientific resources and skills.

- Offer more opportunities for scientific disagreement and therefore delay.

- Depend on often limited or absent data on human exposure.

- Require elucidation of scientific uncertainties, which everybody hates to deal with.

- Are much more difficult to communicate, at all levels.

WHILE PURELY HAZARD-BASED APPROACHES ARE APPARENTLY MUCH SIMPLER AND HAVE GREAT MARKETPLACE APPEAL

Consider:

1. Eliminating or seriously restricting a chemical based on its toxic hazards does not necessarily mean the product in which it is present has been made safer in any scientifically meaningful way.

2. Although some types of hazards are more serious than others, or may confer greater low dose risks, risk assessment methods are fully capable of taking such differences into account.

3. Such approaches have little utility for natural and industrial contaminants and none for natural substance.

4. Such approaches often require the development of alternatives, an often difficult and uncertain undertaking that in many cases will not improve product safety.

5. Most legal requirements are risk-based.

SEVEN KEY MESSAGES

1. Risk-based decision models are necessary to identify intakes of food constituents and contaminants that are unlikely to pose risks to health, and that may in some cases reduce disease risks.

2. Available risk-based models are adequate for decisions regarding intentionally introduced substance, but could be improved by the introduction of quantitative risk measures.

3. Decision models for unavoidable food contaminants require improvement, and efforts to achieve consistency in approaches.

4. Models for decisions regarding nutrient inadequacy and excess are reasonably well developed. Models pertaining to the effects of nutrients and other natural food substances on chronic disease risks are now under active development.

5. Decision models useful for dealing with situations involving competing risks are available to develop estimates of "net risk", but have not seen much practical application.

6. Much improvement is needed in the treatment and communication of uncertainty in risk- based decisions.

7. Although most laws require risk - based decision-making for food substances, there is much advocacy for hazard- based decision; the ultimate consequences of this advocacy are not identifiable.

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RISK VS. HAZARD

AUDIENCE OPINIONS SOLICITED!

THANK YOU!

APPENDIX: PEOPLE'S TOLERANCE FOR RISK VARIES ACCORDING TO PERCEIVED ATTRIBUTES OF THOSE RISKS

TOLERATED RISKS

- VOLUNTARILY ASSUMED
- PERSONAL BENEFIT HIGH
- SCIENTISTS AGREE
- NOT CATASTROPHIC
- NATURAL
- HAZARD NOT FEARSOME
- COMMON EVENT
- EQUITABLY DISTRIBUTED

NON-TOLERATED RISKS

- IMPOSED BY OTHERS
- NO PERCEIVED PERSONAL BENEFIT
- SCIENTISTS DISAGREE
- CATASTROPHIC
- INDUSTRIAL
- HIGHLY DREADED HAZARD
- RARE EVENT
- DISTRIBUTION NOT EQUITABLE

These factors influence how people receive messages about risk.

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