‘Scientific balance between hazard and risk: the application of TTC in food safety’

Richard W. Lane, Ph.D.
ILSI NA
Disclaimers

• I work for PepsiCo
• I have been associated with ILSI NA for a while
  – Including threshold of toxicologic concern (TTC) projects
• The subject of this presentation is vast
  – This is basic information with assumptions made about what preceding speakers have covered
• The views expressed in this presentation are mine and do not necessarily reflect the position or policy of PepsiCo Inc.
Preface
One of the many problems we face

- **Analytical chemists** can find almost any chemical, at incredibly low levels, in almost any food matrix.
- **Detection** often means problems because the mere presence of a substance, whether its hazards are known or unknown, is used to imply a health risk.
- Everyone wants safe foods, so detection is taken seriously.
- How can we properly address these low levels, especially when there are no toxicology data?
The Rise and Demise of Exposure
The central tenet of toxicology

“All substances are poison, and nothing is without poison; only the dose permits something not to be poisonous”

Paracelsus (1493-1541)
The central tenet of toxicology

• This concept allowed decisions to be made about what level of exposure is “safe” because the dose, as Paracelsus teaches us, unmakes the poison.
  – The introduction of the threshold
Applying the central tenet to additives

Here is where I invite each and everyone of you to sit down and define those uses which can be assumed to be safe. As I stated earlier this exercise sounds like fun, but it is just plain hard work. I am not certain that my solution is the best, but I assure you it is the result of many hours of reflection and analysis. In its briefest form, I believe that any chemical suitable for use in food-packaging is safe for man at a level of 0·1 ppm in the total diet. Extrapolating this dietary concentration to a practical and meaningful guideline for regulatory purposes, use of a chemical in a container at a level of 0·2% or less will contribute less than 0·1 ppm to man’s diet.

The central tenet disputed

- New research
  - Cancer from ionizing radiation
  - Chronic studies conducted on potent carcinogens

- New demands from society
  - Laws
  - Court decisions
  - Interested parties
  - Chemophobic public
The central tenet disputed

• Eventually, the view of chemical hazards split.
  – Carcinogens handled differently from noncarcinogens
    • Based on hazard alone
    • One-hit hypothesis
  – "There is no safe exposure to a carcinogen"
    • That is, no threshold

Two views of chemical risk

![Diagram showing two views of chemical risk: No-Threshold Toxicant and Threshold Toxicant. The x-axis represents increasing dose, and the y-axis represents increasing adverse effect. The NOAEL point is marked where the dose meets the threshold.]
As a society we moved

• From “safe” to “risk”
• From “the dose makes the poison” to “any amount of a chemical poses a finite possibility of harm”
  – Which spread to all chemicals with any hazard
• Only the “poison” was seen; the “dose” was forgotten
As a society

- This seemed sensible until it became known that carcinogens are not just industrial chemicals that could be banned, but are found in everyday life.
  - Formed by microorganisms and plants, home cooking, food processing, and in our bodies
- One-hit theory came under attack
  - Hormesis and other data implying thresholds
  - Allegations of ignoring/manipulating data
- But we have never been able to change our view
Dealing with two views of chemicals

- If there is no threshold:
  - VSD (Virtually Safe Dose)
  - Threshold: A level where no hazards appear
- If there is a threshold:
  - Dose-response curve
Back to our problem

• Given the dual view of chemicals, what happens when analytical chemists find very low levels substances in food for which there are no data?
  – Is it a carcinogen or not?
  – Is the detection important or not?

• What is needed is a general principle that is conservative enough so there is *de minimis* risk to consumers yet practical enough to allow commerce to continue when appropriate.
Toxicologically Insignificant Exposure

Better know as
Threshold of Toxicological Concern
The importance of exposure

• Using the risk assessment paradigm

\[ \text{Risk} = f(\text{hazard[toxicity]} \text{ and exposure}) \]

• we see that when exposure is low enough hazard is of less importance and risk can be \textit{de minimis}.

• That’s fine when one knows the a chemical’s toxicity, but can this approach be used to make a conclusion on insignificant exposure when one does not?
From rodent TD$_{50}$ to *de minimis* risk

---

**Fig. 3.** Distribution of TD$_{50}$s for 343 rodent carcinogens from the Gold *et al.* (1984) CPD and distribution of 1 x 10^-6 risks calculated by linear extrapolation from the TD$_{50}$s (modified from Rulis, 1989).

(modified from Rulis 1989 & Munro *et al.* 1999)
From rodent NOELs to acceptable risk

Fig. 2. Cumulative distribution of the most conservative NOELs for compounds in the reference database grouped into Cramer et al. (1978) structural classes I, II and III (Ο), class I percentiles; ○, class II percentiles; Δ, class III percentiles; — fitted lognormal distribution.

Table 2. Fifth percentile NOELs and human exposure thresholds for each Cramer (1978) structural class

<table>
<thead>
<tr>
<th>Structural class</th>
<th>Fifth percentile NOEL (mg/kg body weight/day)</th>
<th>Human exposure threshold (mg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.0</td>
<td>1.8</td>
</tr>
<tr>
<td>II</td>
<td>0.91</td>
<td>0.54</td>
</tr>
<tr>
<td>III</td>
<td>0.15</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*The human exposure threshold was calculated by multiplying the fifth percentile NOEL by 60 (assuming an individual weighs 60 kg) and dividing by a safety factor of 1000, as discussed in the text.

(Munro et al. FCT 1996)
Threshold of toxicological concern

• These constructs indicating toxicologically insignificant exposure are referred to as the “threshold of toxicological concern” (TTC).
• “Concern,” like beauty, is in the eye of the beholder, yet there is wide agreement that these exposures are toxicologically insignificant.
  – To be accepted as protective of public health by many scientists, regulatory authorities, and nongovernment agencies, they are very conservative
Threshold of toxicological concern

• Useful for
  – Prioritizing for testing or other forms of evaluation
  – Estimating virtually “safe” levels of exposure
  – Situation management when a detection occurs

• Must be used appropriately
  – Cannot be used in place of suitable data
  – Does not override regulatory requirements
  – Cannot be used to overcome poor GMPs or HACCP
  – Does not override religious requirements
Balance between hazard and risk
Balance between hazard and risk

• The TTC recognizes that not all hazards are equal and has balanced acceptable risk according to hazard and chemical structure.

• Toxicologically insignificant exposures are below
  – 0.15 µg/d: Chemicals with alerts for DNA reactivity
  – 1.5 µg/d: Threshold of Regulation
  – 18 µg/d: Organophosphates
  – 90 µg/d: Cramer structural class III substances
  – 540 µg/d: Cramer structural class II substances
  – 1800 µg/d: Cramer structural class I substances
Conclusion
Hazards and Risks: The Exposure Revolution

• By developing the TTC we are simply adapting the situation we created 50+ years ago to what Paracelsus taught us 500 years ago:

“All substances are poison, and nothing is without poison; only the dose permits something not to be poisonous”
Thank you