Risk Assessment of Food packaging and Contact Materials

6th Asian Conference on Food and Nutrition Safety
Singapore November 26th-28th, 2012

Dr. Forrest Bayer
Fellow Packaging, Scientific and Regulatory Affairs
Today’s Topics

◆ Reason for Packaging
◆ Packaging Migration
◆ Packaging Types and Materials
◆ Packaging Materials Risk Assessment
◆ The Threshold of Toxicological Concern
◆ The Threshold of Regulation
◆ Packaging migrant issue - Bis-Phenol A
Packaging Delivers
Safe and Quality Food

◆ Extends the shelf life of food products
  ❖ Preserves the compositional integrity of food
  ❖ Prevents microbial contamination
  ❖ Offers physical protection during food handling and storage

◆ Without packaging we would loose a tremendous amount of our food due to spoilage

◆ Meets consumer’s convenience requirements

◆ Provides a tool to communicate with consumers
  ❖ Nutrition information
  ❖ Customer engagement tool
  ❖ Promotion display
No material is inert. When a material is put in contact with a foodstuffs, there is always a release of substances from the material into the foodstuffs.
This release will depend on:

a) Type of material
   - Diffusion coefficients
   - Molecular weight of migrants

b) Type of foodstuffs
   - Partition factors

c) Contact conditions
   - continuous or discontinuous
   - time
   - temperature
The presence of trace packaging migrants in a food does not automatically imply that the food is unsafe.

Migration is taken into account by regulators when approving new food contact substances.

Toxicology studies are required by regulators prior to approval of a new food contact substance.

The toxicological testing required incorporates the level of migration / dietary exposure from the food contact substance.
Risk Perception of FC Materials

- Risk perception for food contact materials may differ from scientific reality.
- Press releases and media headlines may help create a perceived risk.
- Social and cultural factors can outweigh the scientific evidence.
- As analytical techniques improve, ultra-trace levels of food contact substances are being detected and presented sometimes out of context.
- Lower consumer trust overall in science, industry and regulators.
- Opportunities exist for proactive communication and education programs.
The Science News Cycle

Start Here

Your Research

Conclusion: A is correlated with B (p=0.56), given C, assuming D and under E conditions.

Your Grandma

I'm wearing this to ward off "A"... eventually making it to...

What You Don't Know About "A"... More at 11...

Local Eyewitness News

4

Local Eyewitness News

Local Eyewitness News

Cable News

CNC

We saw it on a Blog!

A causes B all the time

What will this mean for Obama?

Scientists out to kill us again

Posting by Random Dude

Comments (377)

OMG I know it!!!

 WTF??????

THE INTERNETS

Local Eyewitness News

University PR Office (YES, YOU HAVE ONE)

FOR IMMEDIATE RELEASE: SCIENTISTS FIND POTENTIAL LINK BETWEEN A AND B (UNDER CERTAIN CONDITIONS).

News Wire Organizations

A CAUSES B, SAY SCIENTISTS.

...which is then picked up by...

...who are read by...

The Coca-Cola Company
Packaging Types and Materials
Package Types

- Rigid and Flexible Plastics 38%
- Metal Containers 19%
- Glass 8%
- Paper/Paper Board 30%
- Other 5%
  - Film
  - Blister

Source: Pira International 2008
Typical Polymeric Packaging Materials

- Polyolefins
  - PP
  - HDPE
  - LDPE
  - LLDPE
- PET
- Styrene
- PVC
- Nylon
- EVA
- ABS
- PU
Typical Additives to Polymeric Packaging

- **Antioxidants**
- Anti-statics
- Antifogging agents
- Anti blocks
- **Plasticizers**
- Slip agents
- Thermal stabilizers
- Light (UV) stabilizers
- Colorants
- Carriers
Packaging Migrants
Packaging Migrants

- Monomers
- Oligomers
- Decomposition Products
  - Thermal
  - Oxidative
  - Photochemical
  - Ionizable
- Solvents
- Reaction Products
- Impurities (non-intentionally added substances (NIAS))
Regulation of Food Contact Materials
Regulatory Approaches

- General safety requirements – common to every country
- General safety only – Mexico, some Asian and South American countries, South Africa
- Mandatory positive lists – EU, MERCOSUR
- Voluntary positive lists – Japan, Germany
- No objection or opinion letters – Canada, U.S. (for recycled plastics)
- Combination approach – U.S.
- Pre-market registration – Argentina, Brazil, some Eastern European countries
Principal of “inertness” of the material and “purity” of the foodstuffs:

- Migration of substances shall not endanger human health
- Migration cannot bring an unacceptable change in the composition of foodstuffs
- Migration cannot deteriorate the organoleptic characteristics of foodstuffs
US Food Contact Regulations

- Reflects an approach based on exposure assessment
- Various options exist to obtain authorization
- The **Food Contact Notification** program is beneficial for both the FDA and industry – efficient, proprietary and it works
- ‘Threshold of Regulation’ and ‘No Migration’ principles are very useful in determining regulatory compliance of substances with little or no migration
- **Food Additive Master File**
European Food Contact Regulations

- Incomplete harmonization of regulations
- Positive lists only exist for plastics, regenerated cellulose and ceramics
- Harmonization of plastics regulations is complete
- Other substances like paper, colorants and coatings are regulated at member state level
- Materials like printing inks and adhesives are not covered by specific regulations
- Mutual recognition exists in principle, but interpretation can be challenging
- Authorization process for a new food contact substance can take 2-3 years
MERCOSUR
Food Contact Regulations

Brazil, Argentina, Paraguay, Uruguay

- **Plastics** are regulated through a combined approach of the FDA and EU

- **Positive list of monomers** is controlled through SMLs (similar to EU) and a partial positive list of additives is controlled through maximum use rates (similar to FDA)

- **Resolutions** exist for regenerated cellulose, plastics and paper.

- **Pre-registration** requirements exist in some of the countries
Asia/Russia Food Contact Regulations

◆ A very active region for rapidly evolving food contact regulations

◆ **Challenge** for global companies is to monitor and ensure compliance with the emerging regulations

◆ **China’s** food contact regulations are rapidly developing: (updating GB-9685-2008, *Hygienic Standard for Adjuvants and Processing Aids in Food Containers and Packing Materials*). This went into effect June 2009.

◆ **India** is developing new food contact regulations

◆ **Russia** is developing new food contact regulations
Two governing regulations governed by
- Ministry of Health, Labor and Welfare (MHLW) & Industrial hygienic Associations
- Food Sanitation Law (1947)
- Food Safety Basic Law (2003)
  - Article 4 Definitions
  - Utensils
  - Containers/Packages
- Specifications by material
  - 15 polymer materials have “end use specifications”
  - Does not include a list of permitted additives
Industry groups (Hygienic Associations) have established voluntary standards for various polymers & additives

- Japan Hygienic Olefin and Styrene Plastics Association (JHOSPA)

Positive lists include permitted monomers, end tests and list of acceptable additives

- 800 members: Resin & additive Mfgs, fabricators, converters, distributors and food companies
  - Set Voluntary Standards, certifications, registrations
  - Conduct research & communicate with regulatory authorities
Types of Regulatory Data Requirements for Approval
Data Provided for Safety Evaluation

◆ **Chemistry data** – for confirming identity of a food contact substance and for assessing potential consumer exposure to the substance and its impurities

◆ **Toxicology data** – for use as basis for establishing a safe level of consumer exposure to the substance and its impurities
  
  ❖ (Chemistry and toxicology data should be on substances expected to migrate to food under the intended conditions of uses)

◆ **Environment data** – for consideration of impact on human environment
Chemistry Information

- Identity
- Manufacturing process
- Specifications
- Intended use and technical effect
- Stability
- Migration
- Exposure assessment
Migration Testing
GENERAL FOOD SIMULANTS
For Migration Testing

◆ 3% (w/v) acetic in aqueous solution
◆ 10% (v/v) ethanol in aqueous solution
◆ 50% (v/v) ethanol in aqueous solution
◆ Rectified olive oil
  ❖ HB 307
  ❖ Sunflower oil
  ❖ Other fatty food simulants

Details in Chemistry Guidance:
http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081818.htm
# MIGRATION TESTING CONDITIONS

## CONDITIONS OF CONTACT IN ACTUAL USE

<table>
<thead>
<tr>
<th>Contact Time</th>
<th>Test Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t \leq 0.5$ hours</td>
<td>0.5 hours</td>
</tr>
<tr>
<td>$0.5 &lt; t \leq 1$ hour</td>
<td>1 hour</td>
</tr>
<tr>
<td>$1.0 &lt; t \leq 2$ hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>$2.0 &lt; t \leq 24$ hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>$t &gt; 24$ hours</td>
<td>10-30 days</td>
</tr>
</tbody>
</table>

## TEST CONDITIONS

<table>
<thead>
<tr>
<th>Test Temperature</th>
<th>Contact Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T \leq 5^\circ$ C</td>
<td>$T \leq 5^\circ$ C</td>
</tr>
<tr>
<td>$5^\circ &lt; T \leq 20^\circ$ C</td>
<td>$5^\circ &lt; T \leq 20^\circ$ C</td>
</tr>
<tr>
<td>$20^\circ &lt; T \leq 40^\circ$ C</td>
<td>$20^\circ &lt; T \leq 40^\circ$ C</td>
</tr>
<tr>
<td>$40^\circ &lt; T \leq 70^\circ$ C</td>
<td>$40^\circ &lt; T \leq 70^\circ$ C</td>
</tr>
<tr>
<td>$70^\circ &lt; T \leq 100^\circ$ C</td>
<td>$70^\circ &lt; T \leq 100^\circ$ C</td>
</tr>
<tr>
<td>$100^\circ &lt; T \leq 121^\circ$ C</td>
<td>$100^\circ &lt; T \leq 121^\circ$ C</td>
</tr>
<tr>
<td>$121^\circ &lt; T \leq 130^\circ$ C</td>
<td>$121^\circ &lt; T \leq 130^\circ$ C</td>
</tr>
<tr>
<td>$130^\circ &lt; T \leq 150^\circ$ C</td>
<td>$130^\circ &lt; T \leq 150^\circ$ C</td>
</tr>
<tr>
<td>$T &gt; 150^\circ$ C</td>
<td>$T &gt; 150^\circ$ C</td>
</tr>
</tbody>
</table>

* *Use simulant C at reflux temperature*

** *Use simulant D at 150° C or 175° C, in addition to simulants A, B & C used as appropriate at 100° C or at reflux temperature***
TOXICOLOGICAL TEST REQUIREMENTS
Toxicology Data Recommendations

- Toxicology data is needed for establishing a safe level of consumer exposure to an FCS.
- The greater the expected exposure, the more toxicity information required to support safety.
- Exposure-driven tiered approach recommended by FDA for safety testing.
- Toxicology guideline is available on FDA’s website:
  http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081825.htm
US FDA Toxicology Data Recommendations

< 0.5 PPB dietary exposure
   No testing needed
   Potential carcinogenicity should be discussed

0.5 - 50 PPB  Two genotoxicity tests:
   Bacterial gene mutation test
   \textit{in vitro} mouse lymphoma \text{tk}^\pm test

50 PPB – 1 PPM  Above plus:
   \textit{in vivo} chromosomal damage rodent cells
   90-day subchronic rodent
   90-day subchronic non-rodent

> 1 PPM
   Chronic (2 yr) rodent studies
   1-yr feeding study in dogs
   Multigenerational studies in rats
EU Toxicology Data Requirements

< 50 PPB migration Three *in vitro* mutagenicity tests:

- Ames test
- *in vitro* gene mutation in mammalian cells
- *in vitro* chromosomal aberration in mammalian cells

50 PPB – 5 PPM Above plus:

- 90-day oral toxicity study
- Data on potential for accumulation in man

> 5 PPM Above plus:

- 90-day oral toxicity study in 2\textsuperscript{nd} species
- Absorption/distribution/metabolism/excretion study
- Reproductive toxicity in one species
- Developmental toxicity in two species
- Chronic toxicity / carcinogenicity in two species
THRESHOLD OF TOXICOLOGICAL CONCERN
“All things are poison, and nothing is without poison, only the dose permits something not to be poisonous”

Paracelsus: 1493-1541

*It’s the dose that makes the poison*
What does "TTC" Mean?

"The Threshold of Toxicological Concern (TTC) concept is a principle that, through a probabilistic approach, refers to the possibility of establishing human exposure levels for chemicals below which there would be no appreciable risk to human health."

-- ILSI, 2003
What is the TTC Concept Based On?

- **TTC concept** was proposed in 1967 by Frawley, et al.

- **Reliance** on existing data on various chemical classes of substances to predict the toxicological potential of substances of undetermined toxicity.

- **Acceptance** of the concept that the chemical structure defines potential for toxicity and that structural features can be used to group substances into various categories of toxicological concern.

-- ILSI, 2003
Structural Alerts

halogenated methanes
X=H, F, Cl, Br, I, in any combination
THRESHOLD OF REGULATION
Threshold of Regulation (TOR)

- Established in 1995
- Specifies a limit 0.5 ppb for projected dietary exposure of food contact materials,
- Translating into a daily exposure of 1.5 ug/day for chemical without structural alerts for carcinogenicity

A Tiered Approach to Threshold of Regulation – Cheeseman, et al, in 1999,

- Limit of 10 – 15 ppb possible:
- No structural alerts,
- Is negative in genotox tests
- And acute toxicity (LD50) above 1000 mg/kg bw
 Establishment of TOR Limit (1)

◆ First considered a level 1.0 ppb

◆ Required level to be low enough to ensure public health protection, should the substance be found to be a carcinogen

◆ Analysis of 18,000 acute feeding studies in rats and mice showed that all acute toxic effects occurred above 100 ppb
Establishment of TOR Limit (2)

- Of 220 chemicals subjected to 2+ year feeding studies, only 5 (pesticides) exhibited toxic effects below 1000 ppb, but none were toxic at dietary levels of 100 ppb.

- **Decided on 0.5 ppb**: This is 2000 times lower than the level likely to cause non-carcinogenic effects, and 200 times lower than chronic exposure levels at which toxic pesticides induce toxic effects.
Specifically addressed the application of TTC to potentially sensitive endpoints:

- Immunotoxicity
- Developmental toxicity
- Neurotoxicity / Developmental neurotoxicity
- Endocrine active compounds
- Allergenicity

With the exception of allergenicity, the TTC of 1.5 ug/d was found to be conservative for all non-cancer endpoints.
### Other TTC Exposure Limits

<table>
<thead>
<tr>
<th>Cramer Class*</th>
<th>Number of Chemicals</th>
<th>5th Percentile NOEL</th>
<th>TTC Exposure Limits**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramer Class III</td>
<td>137</td>
<td>0.15 mg/kg/d</td>
<td>90 ug/d</td>
</tr>
<tr>
<td>(most toxic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cramer Class II</td>
<td>28</td>
<td>0.91 mg/kg/d</td>
<td>540 ug/d</td>
</tr>
<tr>
<td>(intermediate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cramer Class I</td>
<td>447</td>
<td>3 mg/kg/d</td>
<td>1800 ug/d</td>
</tr>
<tr>
<td>(least toxic)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


** Munro, et al. 1996. Fd. Chem. Tox 34: 829
Regulatory Acceptance of TTC

- U.S. FDA - Threshold of Regulation accepted since 1995 for food packaging materials
- Genotoxic impurities in pharmaceuticals
  - EMEA
  - FDA-CDER
- JECFA (Joint Expert Committee on Food Additives)
- EFSA (European Food Safety Authority)
Draft opinion of EC Scientific Committees (SCCP/SCHER/SCENIHR*) on TTC

- Generally supports the use of TTC for low exposures to chemicals and outlines areas for additional work.
  - Expansion and validation of chemical databases to support application to broader use areas.
  - Evaluating thresholds for local effects.
- Draft opinion issued by EFSA 2011.

*SCCP – Scientific Committee on Consumer Products  
*SCHER – Scientific Committee on Health and Environmental Risks  
*SCENIHR - Scientific Committee on Emerging and Newly Identified Health Risks
BPA A CURRENT PACKAGING MIGRANT ISSUE
BPA: The Facts - Toxicology

◆ Not a carcinogen
  ❖ No evidence of cancer in NTP bioassays in two species

◆ Not mutagenic
  ❖ No *in vitro* or *in vivo* genetic or chromosomal effects in guideline studies

◆ Not a developmental toxicant
  ❖ Did not cause birth defects or malformations

◆ Not a selective reproductive toxicant
  ❖ Did not reduce fertility or impair ability to reproduce at doses not toxic to the mother
Global Regulatory Agencies Recently Reviewing BPA Toxicology

- World Health Organization (WHO): Nov. 2010
- European Commission’s Institute for Health and Consumer Protection: Feb 2010
- FSNAZ: Food Stds. Australia New Zealand: March 2009; April 2012
- California Developmental and Reproductive Toxicant Identification Committee (DARTIC): July 2009
- Japanese Ministry of Health: June 2011; March 2006
- UK Food Standards Authority: April 2001
Summary

◆ Packaging materials are complex
◆ Packaging migrants exists
◆ Global regulatory frameworks vary
  - EU focuses on potential levels of migration to foods and safety data to support those levels
  - U.S. and Canada focus on potential dietary exposures to substances and safety of those exposure
◆ Concepts such as the Threshold of Toxicological Concern can provide a conservative approach to risk assessment
◆ Detailed toxicological assessment insures the safety of packaging materials
THANK YOU