TOXICOLOGY AND RISK ASSESSMENT OF CHEMICAL MIXTURES
M Krishan¹, A Kretser¹
1International Life Sciences Institute, North America, Washington D.C.

INTRODUCTION
Evaluation of potential health risk from simultaneous exposure to multiple chemicals has been one of the major challenges for toxicology research and risk assessment (RA). Current RA methods are largely based on evaluation of high dose toxicity data of individual chemicals. However, in most real world situations, exposures occur to a complex range of chemicals at low doses rather than to single chemical at a very high dose. Important factor in RA of chemical mixtures is the availability of reliable data on the identity, levels of exposure, and toxicological interactions for the whole mixture or its individual components. Terminology and problem formulation is complex and the framework for mixture RA varies greatly among different agencies.

OBJECTIVES
As part of the International Life Sciences Institute North America Technical Committee on Food and Chemical Safety, 2013 Summer Fellowship Program, current methods were analyzed to achieve the following:

- Describe the landscape of RA for chemical mixtures
- Characterize differences in RA frameworks
- Assess regulatory acceptance of these frameworks with a focus on food mixtures
- Employ a screening level approach that evaluates the effects from chemical mixtures
- Characterize differences in RA frameworks
- Select appropriate established mixture model

METHODS
- Literature was reviewed for mixture RA paradigms used by government agencies, nonprofit organizations and international agencies.

RESULTS

- Hazard index to characterize hazard
- Compare intake rates of individual contaminants to health reference values
- Hazard index to characterize hazard

SUMMARY
- Significant overlaps and differences between paradigms. There appears to be no single unified method.
- US EPA's original framework forms the basis of most of the globally accepted methods for mixtures RA.
- Whole mixture, sufficiently similar mixture or component-based approaches are used depending on data availability.
- ATSDR follows two separate frameworks for cancer and non-cancer effects and has developed interaction profiles for some metals.

Case Studies
- Tiered approach appears to be a useful way of rapidly screening the effects of chemical mixtures.
- For Tier 1 (Deltamethrin levels using biomonitoring data) and Tier 2, all HI values were less than 1.

Limitations of WVEA-FCID Database
- The food diaries (food consumption data) were collected for two non-consecutive days but the data was not consistent.
- The NHANES surveys (2003-2006) collected disproportionately more food diaries for children and Mexican American population.
- The statistical estimates are based on small number of survey respondents which may be less reliable than estimates based on larger number of respondents.

Research Needs:
- Availability of real measurement data on exposure to various contaminants can improve safety evaluation of chemical mixtures.

Acknowledgments:
Funding: ILSI North America Technical Committee on Food and Chemical Safety. We would like to thank Dr. Glenn Rice, National Center for Environmental Assessment, U.S. EPA, Cincinnati for his help and guidance throughout the project. We would also like to thank Dr. Andrew Maier, University of Cincinnati and Dr. Michelle Embry, ILSI HESI for their inputs in this project.

Hazard Index to characterize hazard

Dose-Response (Toxicology Assessment)

Health reference values used by different agencies and associated endpoints for the 4 contaminants

Exposure Assessment
- Levels of contaminants
- Distribution of consumption rates in US population (youth, adults and specific sub-populations)
- Exposure model (Exposure (Estimated Intake))

Deltamethrin Health Reference Value (CAS# 68359-53-2)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Male</td>
<td>Adult Female</td>
<td>Youth</td>
</tr>
<tr>
<td>RfD = 0.0001 mg/kg per day</td>
<td>RfD = 0.0001 mg/kg per day</td>
<td>RfD = 0.0001 mg/kg per day</td>
</tr>
<tr>
<td>NOAEL = 1 mg/kg/day</td>
<td>NOAEL = 1 mg/kg/day</td>
<td>NOAEL = 1 mg/kg/day</td>
</tr>
<tr>
<td>UF: 1000</td>
<td>UF: 100</td>
<td>UF: 100</td>
</tr>
</tbody>
</table>

Risk Characterization
- Identify health reference values for four contaminants
- Non-cancer health effects observed following chronic exposure
- Evaluate endpoints for each of the contaminants
- Select appropriate established mixture model, such as the hazard index

Risk Characterization
- Determine intake rates of individual contaminants to health reference values
- Group components (most relevant/common MDA/target organ/health effect)
- Hazard index to characterize hazard

Exposure model
- Exposure (Estimated Intake)
- Consumption rate of contaminants (mg/kg/day) per food item

Deltamethrin level in beans = 0.65 ppm

Deltamethrin level in beans = 0.0000015 mg/kg

Tier 1
- TIER 1: Using the most recent, relevant and most conservative health reference value
  - Cyfluthrin (FDA 2008) (0-14 year old)
  - Deltamethrin (EPA 2010 and population excluding infants)
  - BPA (Minnesota Department of Health 2011) (1+ mg/kg per day)

Tier 2
- Grouping contaminants based on health effects/target organ
  - Deltamethrin and Deltamethrin
  - Pyrethroids
  - Neurotoxins

Group 1
- Cadmium and BPA
- Renal Effects
- Cadmium (ATSDR, 2010)
- BPA (Minnesota Department of Health 2011)

Group 2
- Cadmium and BPA
- Renal Effects
- Cadmium (ATSDR, 2010)
- BPA (Minnesota Department of Health 2011)

Group 3
- Cadmium and BPA
- Renal Effects
- Cadmium (ATSDR, 2010)
- BPA (Minnesota Department of Health 2011)