CUMULATIVE RISK ASSESSMENT:

Experiences and Approaches in the USA

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Presentation Overview

1. History/General Background of CRA in U.S.
2. Steps in Cumulative Risk Assessment
3. Overall Experiences/Lessons Learned
4. Future Directions
5. Information Sources

EPA's Office of Pesticide Programs

- **Two Statutes:**
  - The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
  - The Federal Food Drug and Cosmetic Act (FFDCA)
- **In 1996, both were amended by:**
  - The Food Quality Protection Act (FQPA)
    - "common mechanism of toxicity"
    - "aggregation" across pathways
    - " cumulation" (combine and integrate exposure appropriately) across chemicals
    - "reasonable certainty of no harm" standard

Our legislative language defined cumulative risk under FQPA

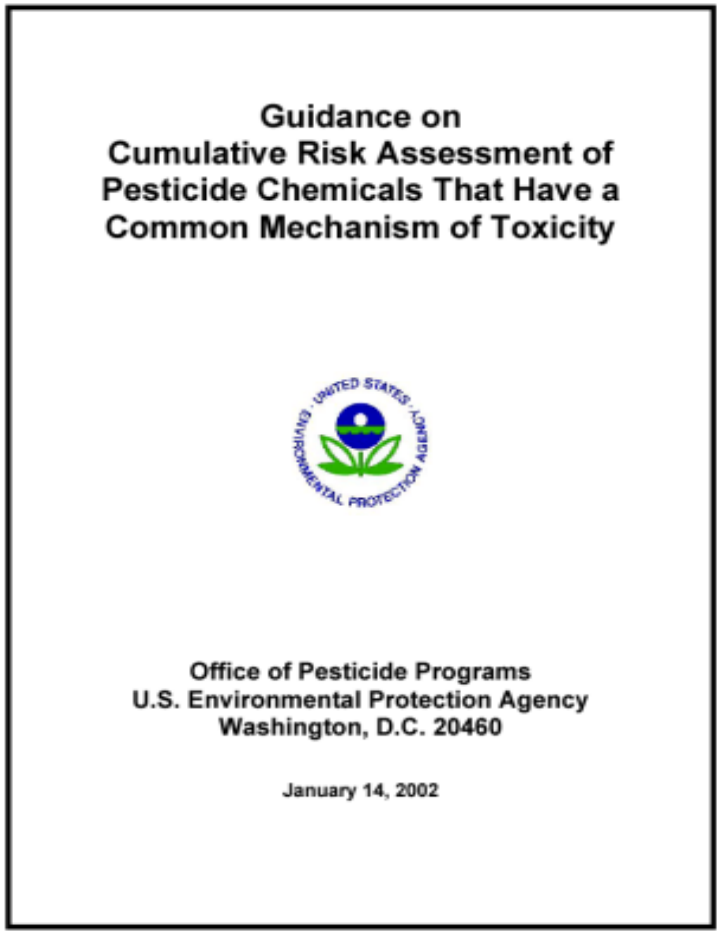
"… reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."

". . . available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity ..."

Cumulative Assessment Represents New "Paradigm"

- Required OPP to develop & implement a number of new methodologies that represented a new way of analyzing data about pesticide risks
- Clearly not just a compilation of individual chemical risks
- Different way of looking at risk
  - Different questions
  - Different methods
  - Different risk management considerations
- Why Cumulative Risk? -- It's the way people are exposed!

What had to be done to implement cumulative risk assessment


Guidance on
Cumulative Risk Assessment of
Pesticide Chemicals That Have a
Common Mechanism of Toxicity

Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460

January 14, 2002

- Interpret FQPA
  - Define Terms
- Develop guidance, methods, software
- Compile, analyze, & manage data
- Document the process & ensure transparency, public comment & peer review

Visit: http://www.epa.gov/pesticides/cumulative/

Cumulative Risk Assessment

Basic Steps

- Identify common mechanism group (CMG)
- Determine relevant exposure scenarios/pathways
- Estimate toxic potencies of common effect for each chemical
- Identify cumulative assessment group (CAG)
- Select Index Chemical, estimate Relative Potency Factors (RPFs), and convert to cumulative basis ("index chemical equivalents")
- Conduct assessment
  - Combine/integrate food, water, & residential exposures on an internally consistent manner which incorporates demographic & temporal-spatial factors

Assessing Pesticide Cumulative Risk

- Organophosphates - 31 (2006)
- Triazines – 2 (2006)
- Chloroacetanilides -2 (2006)
- N-methyl carbamates -10 (2007)
- Pyrethroids – 16 (screening) (2011)

  (currently open for public comment)

Need for Involving Public and Stakeholders in the Decision Process

LESSON LEARNED

Lesson Learned: Public Participation

- Open and transparent process with multiple opportunities for public process
  - CARAT/PPDC Workgroups
  - CRA Technical Briefings
  - Scientific Advisory Panel Presentations
    - Consultations
    - Case Studies
    - Preliminary CRA
    - Revised CRA
  - Web sites/web site updates
  - Full availability of raw data, calculation spreadsheets, etc.
  - Other Federal Agencies

Need for Representative Data

LESSON LEARNED

Consumption Data: USDA's CSFII/WWEIA

- **CSFII = USDA's Continuing Survey of Food Intake by Individuals, 1994-96/1998**
- **WWEIA = USDA's "What We Eat in America", 1999+**
- **GOAL: To provide representative food consumption data for the U.S. population**
  - Nationally Representative/Statistically-Based
    - Intakes of individuals residing in 50 states and D.C
  - 21,662 individual participants interviewed over the period
  - 2 non-consecutive days using in-person 24 hour recalls
  - Total of ca 6000 different "as eaten" foods

http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm

Residue Data : USDA's PDP Program

- **PDP = USDA's Pesticide Data Program**
- **GOAL: to provide EPA with high-quality nationally-representative data on residues in food for use in dietary risk assessment**
  - Statistically designed
  - Targets children's foods
  - Sampled from food warehouses/distribution centers
  - Foods prepared as if for consumption
  - Standardized and uniform sampling techniques
  - Common Standard Operating Procedures
  - Similar Analytical methodologies
  - Low limits of detection

http://www.ams.usda.gov/AMSv1.0/science

Need for Probabilistic Methods

(and to avoid compounding conservatisms)

LESSON LEARNED

Need for Probabilistic Methods

- **Traditional Methods** produce high-end or bounding estimates at the extremes of exposure
- **Probabilistic (Monte Carlo)** methods permit the use of the entire distribution of residue levels in crops to be combined with the distribution of food consumption

  …and allow us to more accurately estimate the complete distribution of exposures and assess their associated probabilities

Ability to “Trackback” Sources of Exposures

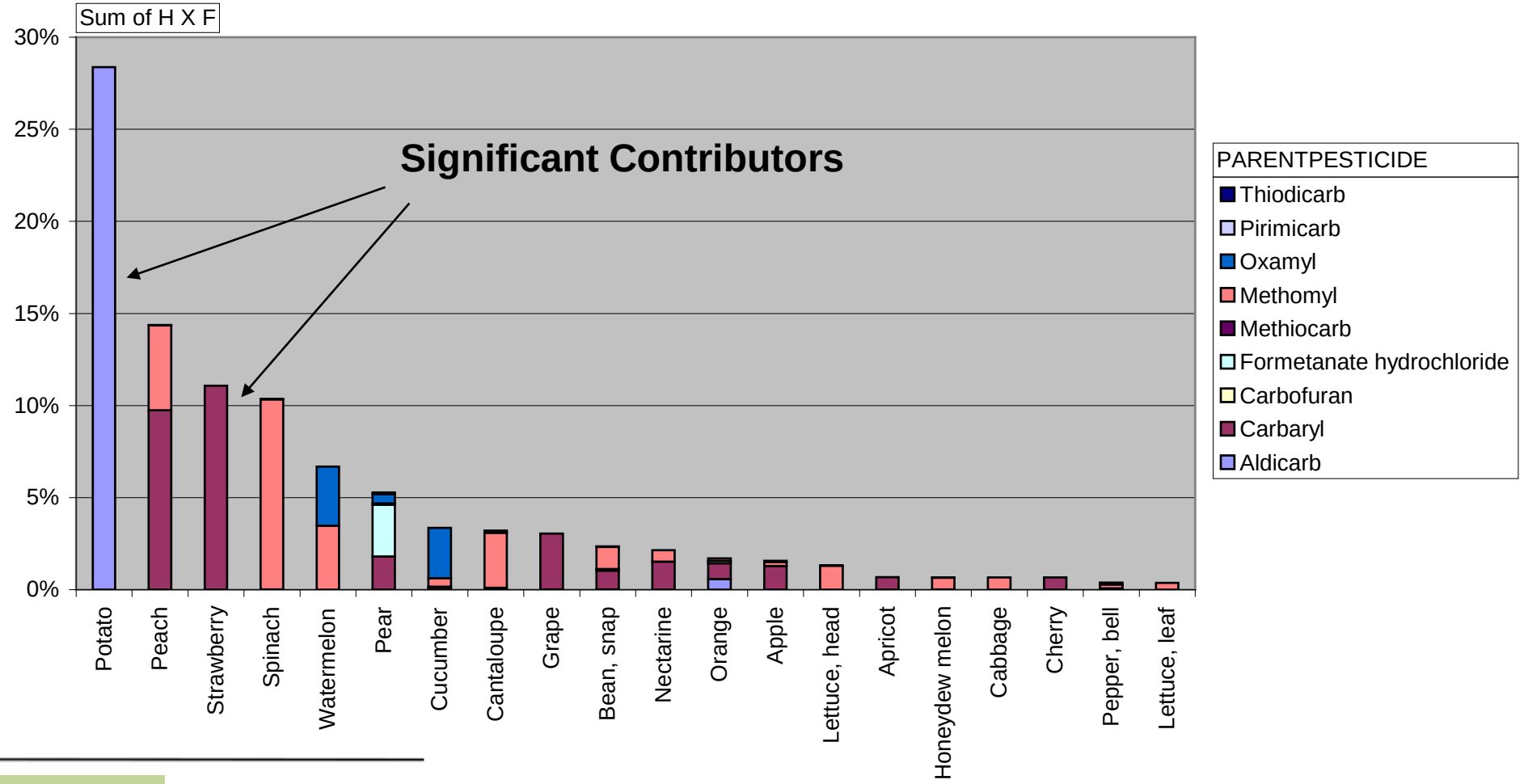
LESSON LEARNED

"Trackback"

- Programmatic End Game - Ability to identify major contributors to exposure at high-end exposure tails
  - Pesticide
  - Crop or Residential Use
  - Pesticide and Crop/Use Combination
- Commodity Exposure Contribution List
  - Ability to (semi)quantitatively rank the "risk drivers"
  - Can be used to focus refinements of exposure estimates, sensitivity analyses, and risk mitigation activities on those commodities or uses which contribute most significantly to risk

"Trackback"

Pesticide-Crop Combinations Significantly Contributing to Dietary Exposure of Children 1-2 at the 99.8th Percentile of Exposure and Above



"Trackback"

- Ability to perform sensitivity analyses
  - Subtract out specific pesticides, specific crops, and specific pesticide/crop combinations
  - Examine impact of removal of a given pesticide from all forms of each of these foods from the cumulative assessment
  - Examine impact of removal of given pesticide from certain foods/food forms

Appropriate Matching and Combining

(temporal, geospatial, demographic)

LESSON LEARNED

"Appropriate Matching and Combining"

Objective: Realistic and Accurate Evaluation

- Appropriately match and subsequently combine estimates of pesticide exposures through food with estimates of pesticide exposures through residential uses and estimates of exposures through drinking water

Matching: DEEM™/Calendex™ Cumulative Assessment

- Incorporate concept of a Calendar to evaluate aggregate exposures, looking at each individual day of the year
    - Allows appropriate "temporal matching" of exposures through food, drinking water, and residential pathways.
    - Temporal aspect of exposure through residential and agricultural uses important for many pesticides due to expected seasonal use-patterns

Matching: DEEM/Calendex Cumulative Assessment

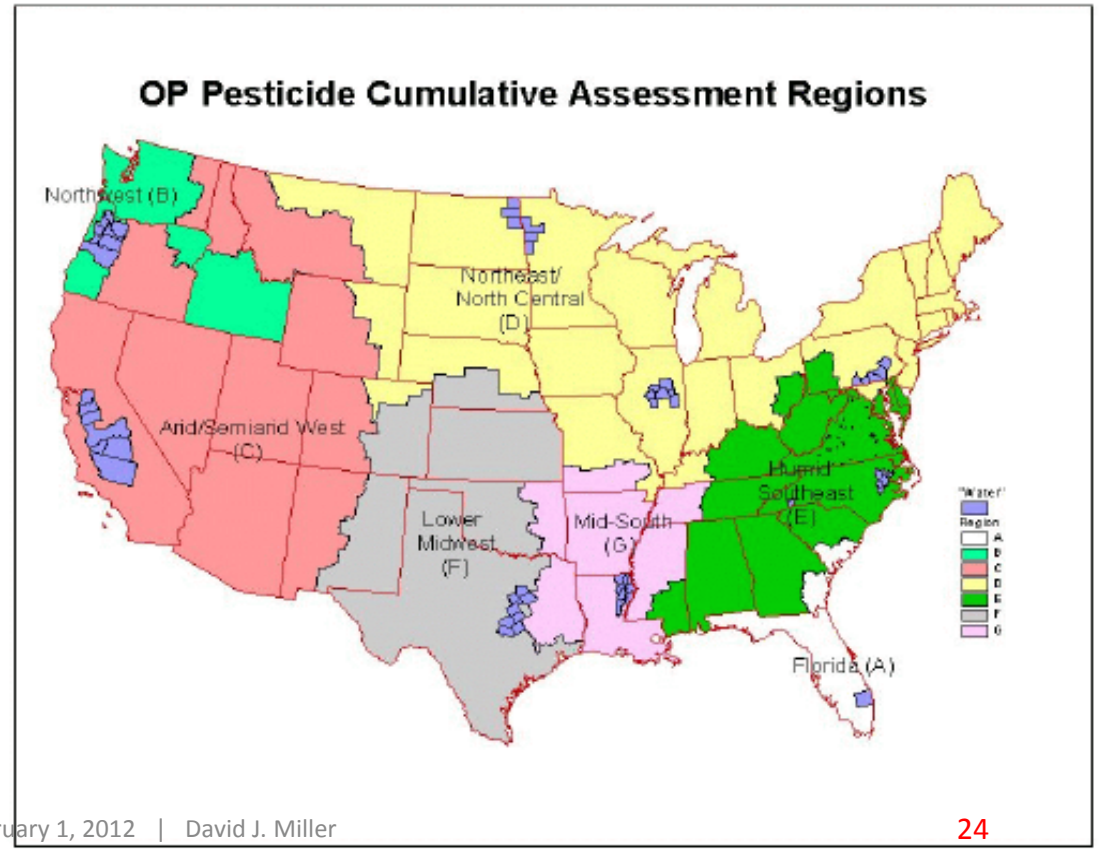
What would happen if we didn't use calendar-based approach?

- For example:
  - Fall dermal exposure through lawn-use could be (incorrectly) combined with dermal exposure through spring flea treatment on pets
  - Oral hand-to-mouth exposure from spring lawn application on one day could be (incorrectly) combined with drinking water concentration characteristic of the winter season

Matching: Regional Assessment

- Regional/geospatial matching to account for differences in:
  - Climate
  - Use patterns

Figure I.D-1. OP Pesticide Cumulative Assessment Regions



Combining: the MOE equation

- Important to "integrate" or combine these route specific estimated exposures in an internally consistent manner to develop a total risk picture
  - Integrated (or Combined) Exposure = "Total MOE"
  - "Appropriate Matching and Combining"

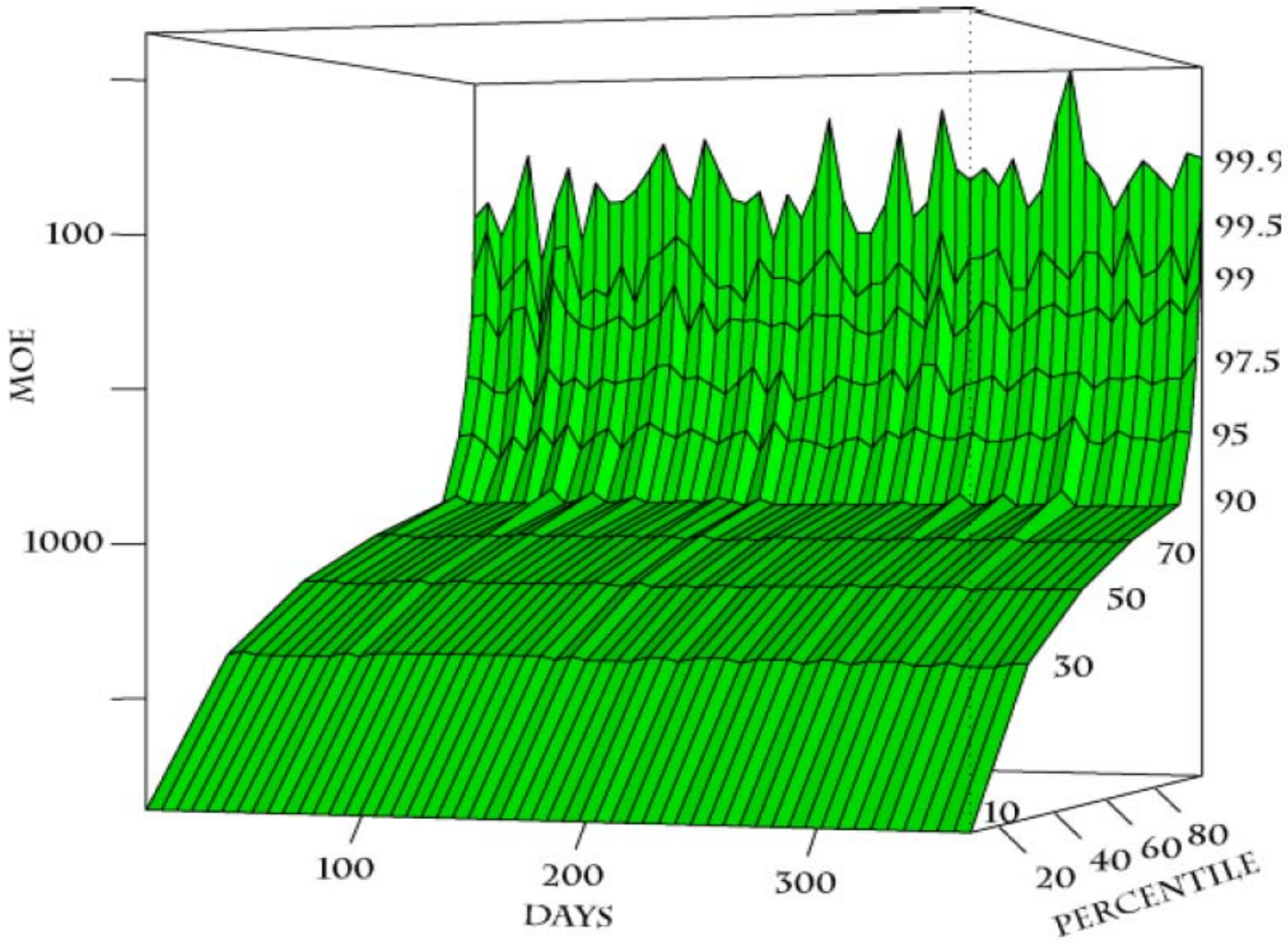
$$MOE_{dermal} = \frac{PoD}{Exposure_{dermal}}$$

$$MOE_{oral} = \frac{PoD}{Exposure_{oral}}$$

$$MOE_{inhalation} = \frac{PoD}{Exposure_{inhalation}}$$

$$MOE_{total} = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{oral}} + \frac{1}{MOE_{inhalation}}}$$

Figure I.F.1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure



Key Concept: Matching and Combining

- In summary, must track potentially exposed persons on a daily basis in a way that preserves all appropriate linkages and appropriately allows for the co-occurring exposures
  - Spatial, temporal, demographic considerations
    - All exposure events need to occur over a specified interval of time
    - All exposure events need to agree in time, place, demographic characteristics

Need for Characterization of Exposure and Risk Estimates

LESSON LEARNED

Characterization of Exposure and Risk

- Results and conclusions are clearly described, including the relative confidence in toxicity and exposure data sources and model inputs.

- Magnitude and direction of likely bias and the impact on the final assessment are discussed.

- Risk contributors are identified with regard to
  - pesticide(s)
  - pathway/route
  - source
  - time of year
  - impacted subpopulations (with particular attention to children)
  - kinds and quality of data available.

- Sensitivity analyses to determine those factors which are most important to final risk estimates.

Don’t sweat the small stuff

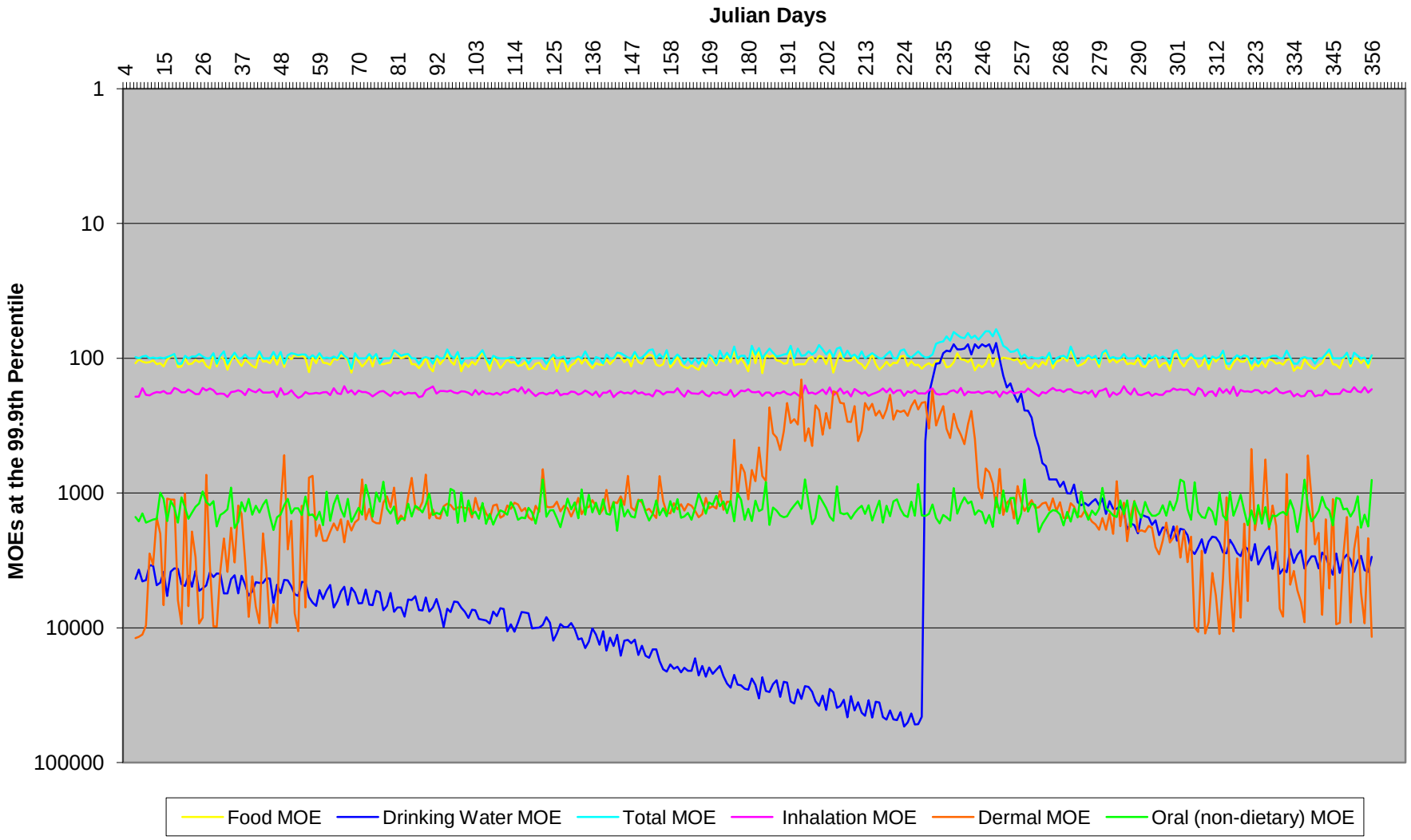
LESSON LEARNED

Eliminating Chemicals, Pathway, or Uses

- **A simple or less data-intensive method for evaluating cumulative risk may suffice when the CMG has:**
  - Small number of chemicals
  - Limited pesticide uses (e.g., no residential uses)
  - Low aggregate risks
  - Monitoring data show non-detectable levels of residues
- **The following could be removed from the quantitative cumulative risk assessment:**
  - A particular use of the pesticide
  - A route of exposure
  - A pathway of exposure (e.g., residential, drinking water)
  - An entire chemical

See p. 23-26 of http://www.epa.gov/scipoly/sap/meetings/2003/december11/cumulativeguidance2002.pdf

OP CRA Children 1-2 REGION A Surface Water (NO OXON) 6-5-06 DDVP 21 Days; MOEs at the 99.9th Percentile



Risk assessment is a (multidimensional) story, not a number…

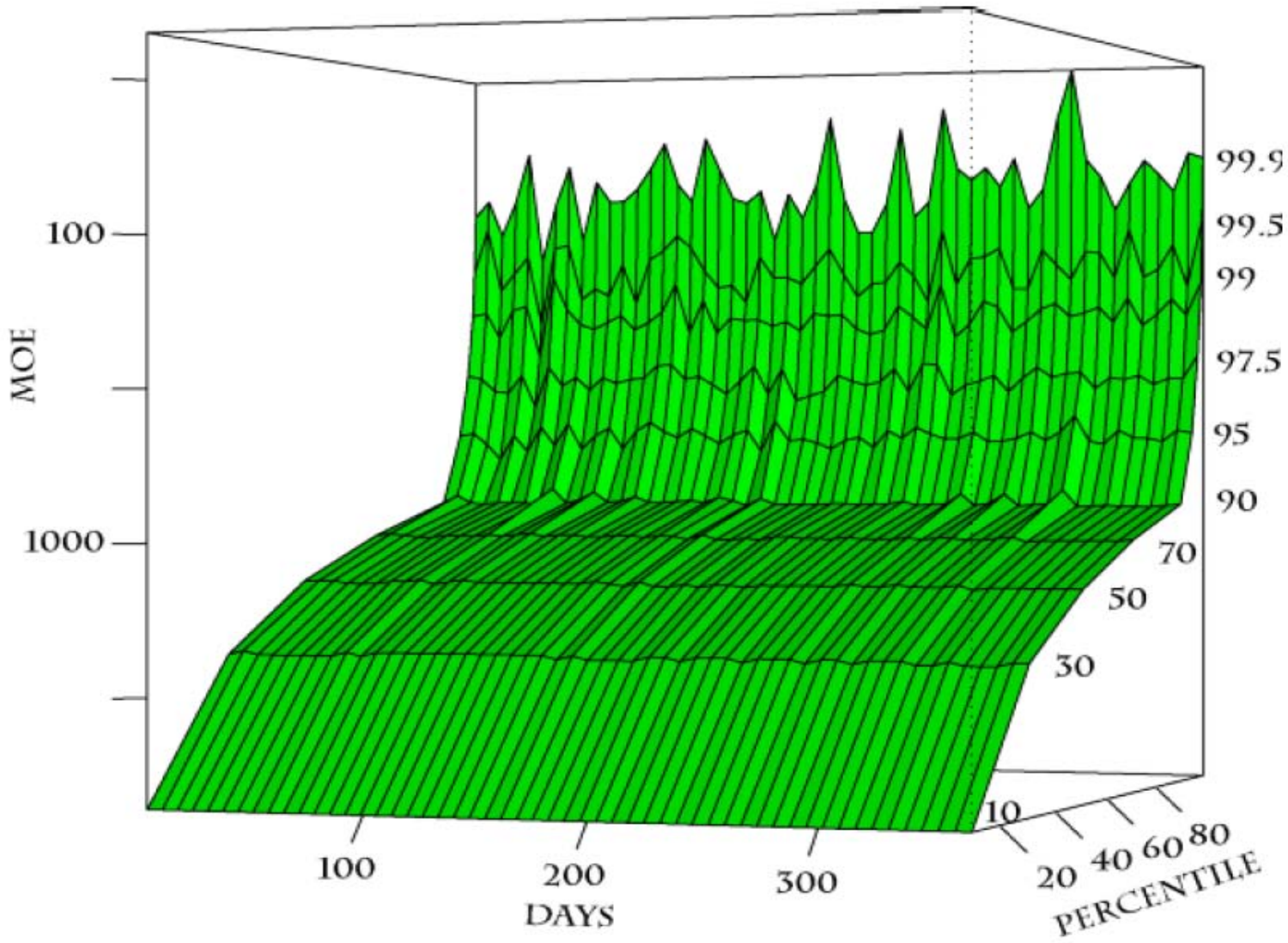
LESSON LEARNED

Risk assessment is a story, not a number…

… especially with respect to a cumulative assessment

- A series of overlays
  - By day
  - By pathway
  - By route
- No "single number" result
  - many 99.9th percentiles (e.g., ea. of 365 days)
  - Conducive to a picture and a story
- Increased emphasis on patterns in time-based "exposure profiles"

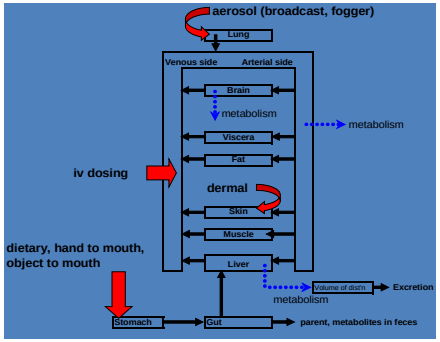
Figure I.F.1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure



FUTURE & EVOLVING DIRECTIONS

Evolving Directions

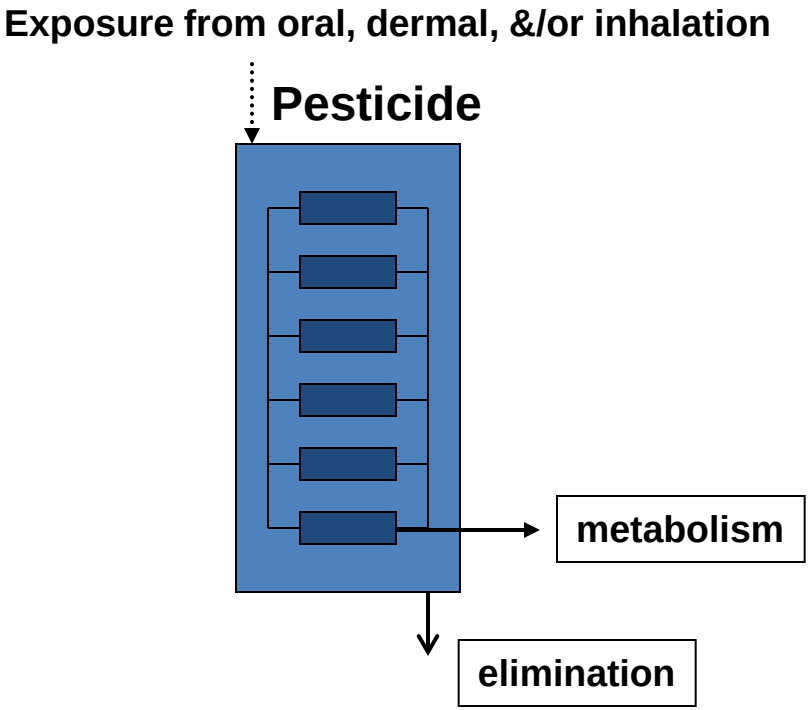
Incorporation of Physiologically Based Pharmacokinetic Models



Biomonitoring

Need for continued method & tool building & Role of New Technologies

PBPK & BBDR Models in Cumulative Risk Assessment



- **PBPK: Physiologically-based Pharmacokinetic Models**
  - Animal to human extrapolation
  - Collaborative effort by ORD-NERL, NHEERL, NCCT
    - linkage between probabilistic exposure assessment and PBPK models
    - Case study presented to SAP to link SHEDS to PBPK model in 2010
- **BBDR: Biologically-based Dose Response Model**
  - PBPK + Pharmacodynamic Component to estimate toxic outcome

Biomonitoring Data

- **Use of biomonitoring data to compare predictions of exposure**
  - NHANES CDC Biomonitoring Data
  - Assess quality of exposure assessment
    - Assumptions, data sources
    - Pathways of exposure
  - Forward and Reverse Dosimetry Calculations

Continued Model/Tool Building & New Technologies

- **Food**
  - Longitudinal studies: eating patterns over consecutive days
  - Within day exposure to foods
  - USDA CSFII=> NHANES/USDA WWEIA
  - Update pesticide residue data
- **Residential**
  - Residential Standard Operating Procedures (January 2012)
  - Update use patterns, co-occurrence, and application schedule information
- **Water**
  - Model concentrations using GIS to provide spatially-explicit drinking water assessments on a national scale
  - Model effects of drinking water treatments on concentrations
- **Toxicology**
  - Adverse Outcome Event (AEO) pathways
  - "-omics" technologies
  - Computational toxicology/bioinformatics

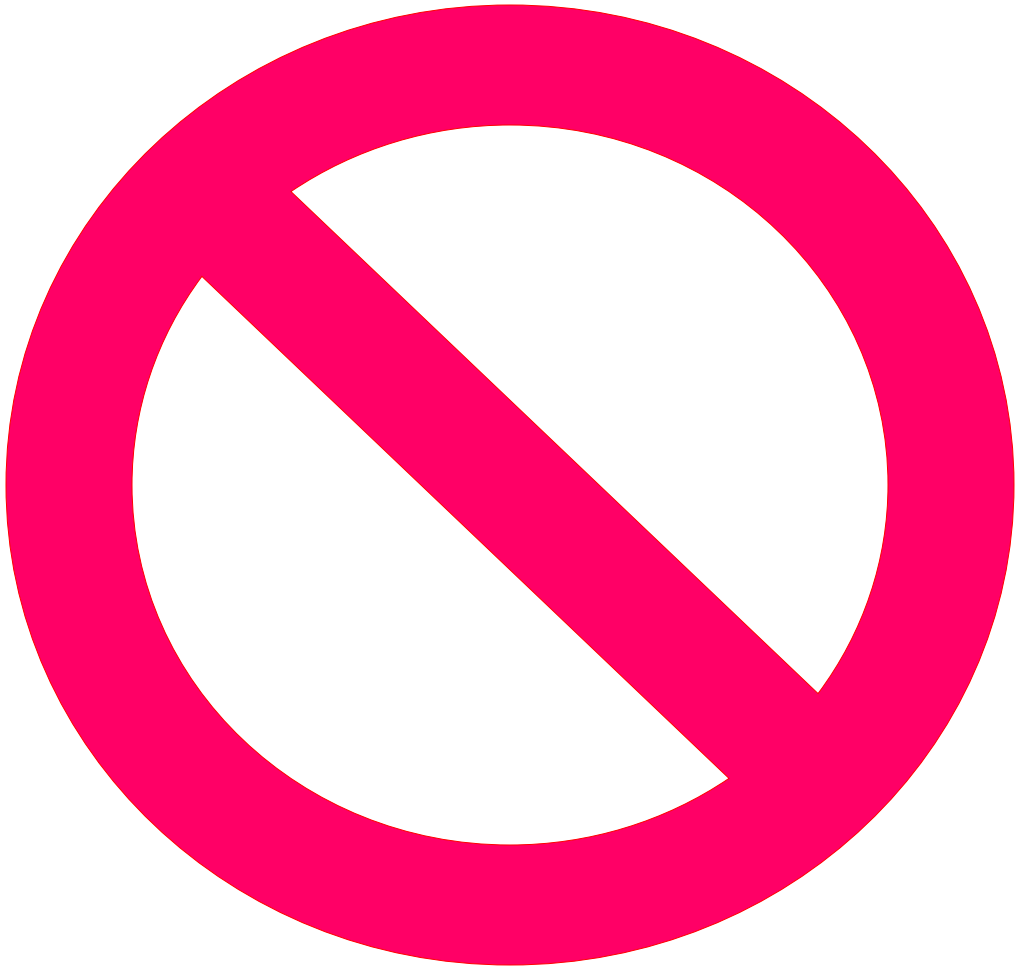
Summary: Key Principles

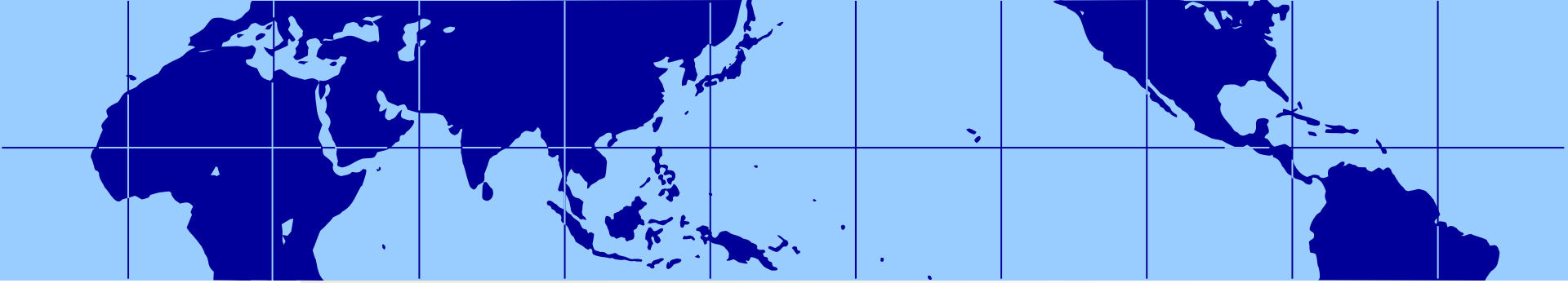
1. **Strive for Realistic & Accurate Assessments**
   - ❑ Use Representative Data
   - ❑ Probabilistic Approaches/Avoid Compounding Conservatisms
   - ❑ Appropriate "Matching and Combining"
2. **Preserve and Maintain Geographic, Temporal, & Demographic Specificity**
   - ❑ Calendar-Based, Region-specific Approach
3. **Appropriately Integrate Toxicology & Exposure Data**
   - ❑ Time-Frame Considerations
4. **Be Able to "Track Back" Sources of Exposures & Perform Sensitivity Analyses**
   - ❑ Major Risk Contributors
5. **Tell a story**
   - ❑ Patterns in time-based "exposure profiles"

Additional Key Points

- Methods and approaches to cumulative risk assessment are continuously evolving and improving
- Since data & methods vary in level of refinement and amount of uncertainty, there are no 'bright lines' in the interpretation
- Due to complexity & scope, these are highly collaborative with input from team members with variety of expertise
- Simplifications can increase efficiency but still maintain key information

THANK YOU !





Additional Information/References

A Good Place to Start:
EPA's Cumulative Website:
http://www.epa.gov/pesticides/cumulative/

Additional Sources:

U.S. EPA (2001). General Principles For Performing Aggregate Exposure And Risk Assessments
http://www.epa.gov/pesticides/trac/science/aggregate.pdf

U.S. EPA (1999) Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity.
http://www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf

U.S. EPA (2002). Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity,
http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf

On EPA's 99.9th Percentile Policy:

U.S. EPA (2000). Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern.
http://www.epa.gov/pesticides/trac/science/trac2b054.pdf

U.S. EPA (2000) Responses to Public Comments on the Office of Pesticide Program's Draft Science Policy Document: *Choosing a Percentile of Acute Dietary Exposure As a Threshold of Regulatory Concern*
http://www.epa.gov/pesticides/trac/science/trac2b055.pdf

Other Useful Weblinks:

USDA PDP Data
http://www.ams.usda.gov/AMSv1.0/science

USDA Food Consumption Survey Data
http://www.ars.usda.gov/Services/docs.htm?docid=13793

NHANES/CDC Biomonitoring Data
http://www.cdc.gov/exposurereport/
http://www.cdc.gov/nchs/nhanes.htm

EPA OPP Science Policy Website
http://www.epa.gov/pesticides/trac/science/

Or Contact…

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