MIXTURES PROJECT COMMITTEE

Mission

- Develop a decision-framework to advance and improve mixtures risk assessment methodology
- Design methods to prioritize those environmental chemical mixtures that should be subject to in-depth risk assessment and those that are expected to be of lesser concern

2010-2011 Participating Organizations
Bayer CropScience
Centers for Disease Control, ATSDR
Dow Corning Corporation
Eli Lilly and Company
ExxonMobil Biomedical Sciences, Inc.
Imperial College London
Procter & Gamble Company
The Dow Chemical Company
Syngenta Ltd.
U.S. Environmental Protection Agency
University of Guelph

Committee Publications
Boobis A, Budinsky R, Collie S, Crofton K, Embry M, Felter S, Hertzberg R, Kopp D, Mihlan G, Mumtaz M, Price P, Solomon K, Teuschler L, Yang R, Zaleski R. Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment. Critical Reviews in Toxicology 2011;41(5): 369-83.

Boobis A, Budinsky R, Crofton K, Embry M, Felter S, Mihlan G, Mumtaz M, Price P, Solomon K, Zaleski R. Annex B Example case study B: Tier 0 – Substances potentially detectable in surface water. Regulatory Toxicology and Pharmacology 2011

WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals Workshop Report. [Link]

HESI Project Committee Fact Scheet

Mixtures

2010-2011 Activities and Accomplishments

Committee Leader
Dr. Rosemary Zaleski
ExxonMobil Biomdedical Sciences, Inc.

HESI Manager:
Dr. Michelle R. Embry

This scientific program is committed to:

- Developing a decision-framework to advance and improve mixtures risk assessment methodology.
- Designing methods to prioritize those environmental chemical mixtures that should be subject to in-depth risk assessment and those that are expected to be of lesser concern.

Areas of scientific focus

Examining the potential application of a threshold of toxicological concern (TTC) approach to mixtures risk assessment as a screening-level, "Tier 0" approach.

Key accomplishments:

- Publication of synergy review: Prior to developing the Tier 0 TTC methodology, it was essential to know whether synergistic interactions can occur at low, environmentally relevant exposure levels. A committee-sponsored literature review was initiated and the results of this review were published in Critical Reviews in Toxicology. Due to the relevance of the review findings, there is strong international interest in this publication.
- Development of Tier 0 TTC methodology: TTC Tier 0 methodology to assess a hypothetical mixture of chemicals in surface water was developed by the Committee. This initial example was included as an example appendix within the World Health Organization/International Programme on Chemical Safety's (IPCS) Framework for Assessing Risk of Combined Exposures to Multiple Chemicals, published in Regulatory Toxicology and Pharmacology.
- Development of Tier 0 TTC case studies: The Committee developed four case examples illustrating the Tier 0 TTC approach: carbamates, commercial hexane, drinking water contaminants, and pharmaceuticals in drinking water. These examples were presented and discussed at the February 2011 World Health Organization-International Programme on Chemical Safety (WHO-IPCS)/Organisation for Economic Co-operation and Development (OECD)/HESI Workshop, included in the official OECD-led meeting report, and several will be written up for publication.
- WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals: The Committee provided funding and support of this international workshop in February 2011, whose goals were to inform participants about the WHO framework and explore application of the framework through discussion of a number of illustrative case studies. Four case examples were provided by HESI and discussed by ~60 participants representing 14 countries as well as international govern-

mental and non-governmental bodies.

- Presentations at international meetings: Representatives of the Mixtures Project Committee project have given presentations on the group's work at European Societies of Toxicology (EUROTOX)/International Congress of Toxicology (ICT) and Toxicology Forum Meetings.

What is the Committee's focus for May 2011 - April 2012

- Publication of case examples prepared for the February 2011 WHO OECD HESI Workshop.
- Presentation of Committee work at several international meetings, including the Society of Toxicology, EUROTOX, and the International Toxicology of Mixtures Conference.
- The Committee plans to sunset in Fall 2011.

Recent publications

Boobis A, Budinsky R, Collie S, Crofton K, Embry M, Felter S, Hertzberg R, Kopp D, Mihlan G, Mumtaz M, Price P, Solomon K, Teuschler L, Yang R, Zaleski R. Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment. Critical Reviews in Toxicology 2011;41(5): 369-83.

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For more information, contact the committee manager
Dr. Michelle R. Embry, membry@hesiglobal.org

Mixtures Project Committee Presentations and Data Resources

July 14, 2008: HESI Risk Assessment Methodology Committee Presentation. "Project on Risk Assessment of Chemical Mixtures." Presented at the Program Strategy and Stewardship (PSSC) Meeting, Reston, VA. Presentation by Rosemary Zaleski, Ph.D., ExxonMobil Biomedical Sciences.

Risk Assessment Methodology (RAM) Technical Committee

Project on Risk Assessment of Chemical Mixtures

HESI Program Strategy and Stewardship (PSSC) Meeting
July 14, 2008
Reston, VA

Rosemary Zaleski, Ph.D.
ExxonMobil Biomedical Sciences

H E S I

Mixtures Project Participation

CHAIR
Rosemary Zaleski, Ph.D.

INDUSTRY
Bayer CropScience
The Coca-Cola Company
The Dow Chemical Company
Dow Corning
ExxonMobil Biomed. Sciences, Inc.
Pfizer, Inc.
The Procter & Gamble Company
Rohm and Haas Company
Syngenta Ltd.

GVT/ACADEMIA/OTHER
Centers for Disease Control, ATSDR
Colorado State University
Imperial College London
U.S. Food and Drug Administration
University of Guelph
U.S. Environmental Protection Agency

Mixtures Project: History

- Initiated in 2005 as part of RAM
- Aims to develop a decision-framework to advance and improve mixtures risk assessment methodology
- Current project focused at present on the potential application of a threshold of toxicological concern (TTC) approach to mixtures risk assessment as a critical "decision point."

Mixtures Project: Objective

How to prioritize those environmental chemical mixtures that should be subject to in-depth risk assessment and those that are expected to be of lesser concern?

Examine the applicability of the Toxicological Threshold of Concern (TTC) concept to chemical mixtures as a screening-level, prioritization approach

- TTC proposes that a de minimis value can be identified for many chemicals based on SAR
- When structural data are available, SAR can be used to inform TTC

TTC and Mixtures: Key Questions

- How do you combine exposure values for multi-component mixtures where interactions are possible?
- How do you deal with mixtures that contain chemicals in different Cramer classes?
- How do you evaluate mixtures where chemical structures are unknown?
- How do you handle mixtures that contain chemicals not suitable for TTC (e.g., the Cohort of Concern; aflatoxin, dioxins, etc.)

Low-Level Exposures

- Approaches to mixtures assessment
  - Common MOA: Dose addition
  - Not a common MOA: Response addition
- Synergy is possible on rare occasions
- How do you proceed in the absence of data on what is present?

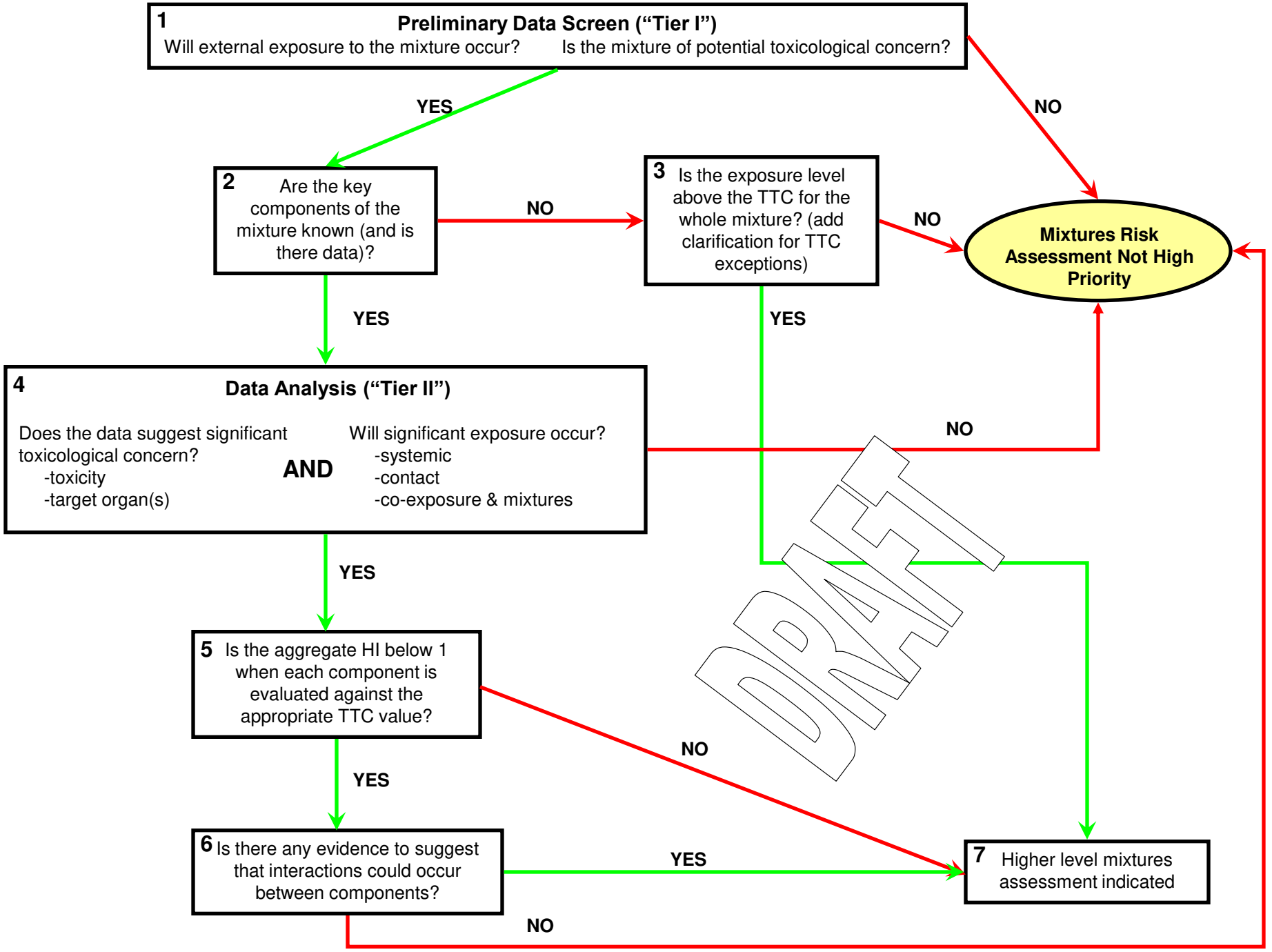
Project Plan and Scope of Work

Goal: Develop a framework for applying the TTC concept to determine if a mixture requires further assessment

- Perform a review/analysis of available synergy literature
- Analyze/review different methodologies used to calculate/determine synergy
- Define the steps of a TTC screening tool
- Develop criteria for case studies to test the TTC approach
- Select and perform case studies to illustrate the TTC approach
- Integrate findings to support, modify, or reject the TTC screening tool
- If outcome supports the approach, develop step-by-step process to integrate into the IPCS framework currently under development

Screening Approach

- Discrete activity to complement other ongoing activities
  - develop an early step for inclusion in IPCS framework
- Screening approach:
  - first tier in process
  - intentionally conservative
  - but must have discriminatory power
- HESI proposed approach based upon TTC (accepted food methodology)
- Must consider mixture-unique aspects
  - potential for interaction (synergy especially)

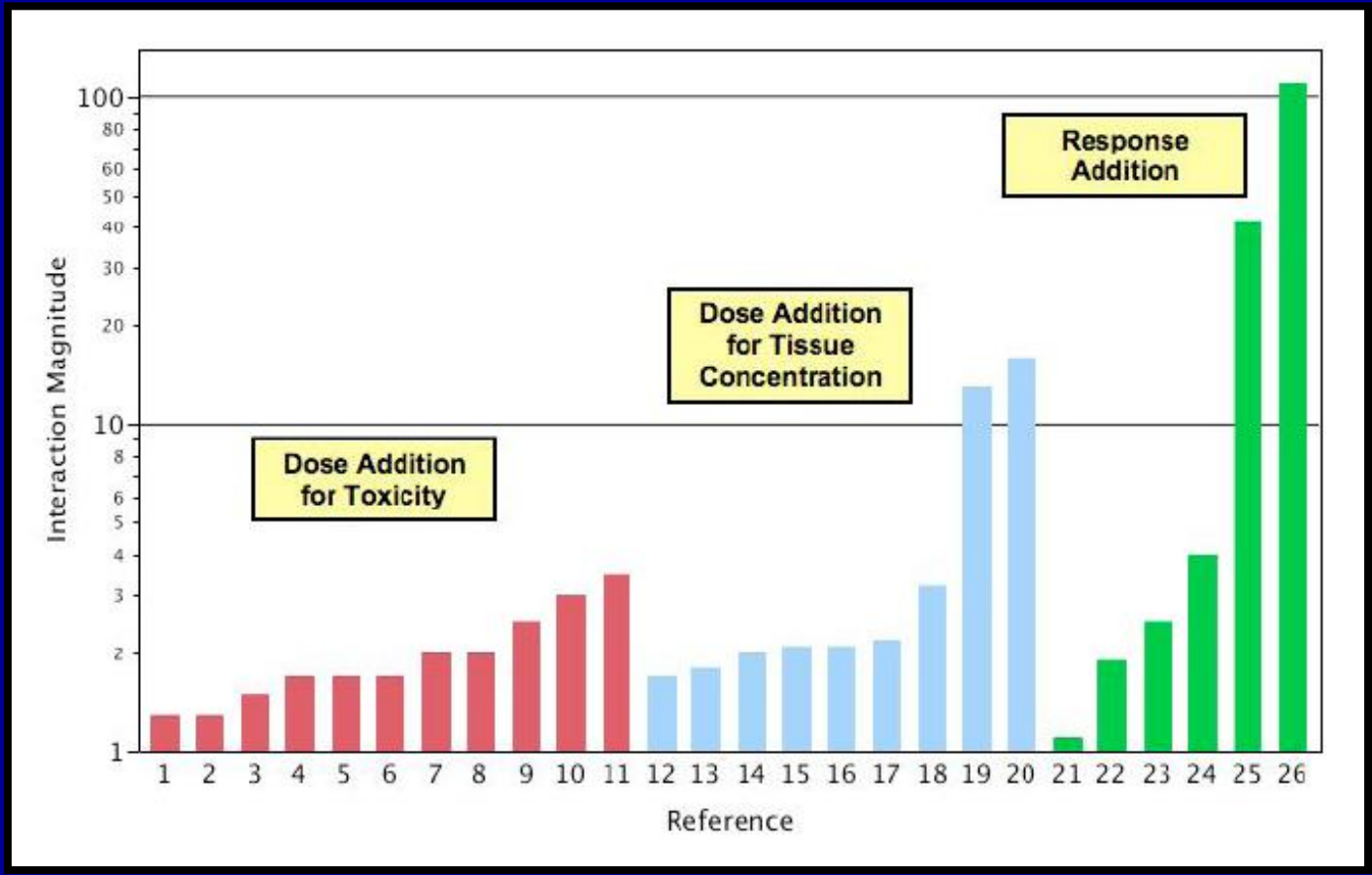

1
Preliminary Data Screen ("Tier I")
Will external exposure to the mixture occur?
Is the mixture of potential toxicological concern?
YES
NO
2
Are the key components of the mixture known (and is there data)?
NO
3
Is the exposure level above the TTC for the whole mixture? (add clarification for TTC exceptions)
NO
Mixtures Risk Assessment Not High Priority
YES
YES
4
Data Analysis ("Tier II")
Does the data suggest significant toxicological concern?
-toxicity
-target organ(s)
AND
Will significant exposure occur?
-systemic
-contact
-co-exposure & mixtures
NO
YES
5
Is the aggregate HI below 1 when each component is evaluated against the appropriate TTC value?
NO
YES
6
Is there any evidence to suggest that interactions could occur between components?
YES
7
Higher level mixtures assessment indicated
NO
DRAFT

Synergy Literature Review

- Contractors – experts in field
- Focus on:
  - low dose (at or below low or no observed effect levels)
  - mammalian toxicology
- Review included:
  - earlier mixture studies databases
  - 1990 on literature review
  - call for papers (HESI, ECETOC, IPCS, SOT mixtures specialty group)
- Database and (on contractor initiative) report
- Much external interest to date, incl. Crit Rev Tox

Results

- Few reports of quantified low-dose synergy
  - Issues with quantification – methods vary by study
- Majority of studies did not observe synergy



Next Steps

- Publication of synergy review results
- What does this mean for a TTC-based mixtures screening approach
  - How should synergy be expressed/calculated (can we agree upon a methodology?)
  - How do exposure levels compare to TTC thresholds? to effect thresholds?
  - Are there any cases where synergy patterns at low dose differ from known high dose synergy patterns?
  - Any findings about when synergy is/is not observed?
  - Where synergy is observed, what is significance (i.e., consider in vivo vs. in vitro, endpoints, test concentrations, exposure duration)

Summary of Accomplishments

- March 2007: Established a coordinated effort between the HESI project and the ECETOC Mixtures Task Force
- Spring 2007: Began coordinating with the IPCS Aggregate/Cumulative Risk Assessment Group
- September, 2007: Initiated a contractor-performed literature review on synergy to assess need for a "synergy factor" when applying the TTC concept to a mixtures screening approach ... avoid under-estimation of risk
- May 2008: Synergy review completed
- July 2008: Initiation of an outline to facilitate publication of the low-dose synergy review

Future Directions

- Summer / Fall 2008
  - Preparation and submission of synergy review manuscript
  - Initiation of activity on synergy calculation methodology
  - Submission of abstract for 2009 SOT poster
  - Continue development of case study criteria begun with ECETOC & IPCS

- Mid 2009:
  - Continued synergy calculation methodology analysis on available data
  - Further develop TTC screening approach, incorporating synergy review findings
    - Utilize sensitivity analysis to inform development [i.e., what does 2-fold above additive mean for risk assessment?]
  - Continued interactions with ECETOC and IPCS mixtures initiatives

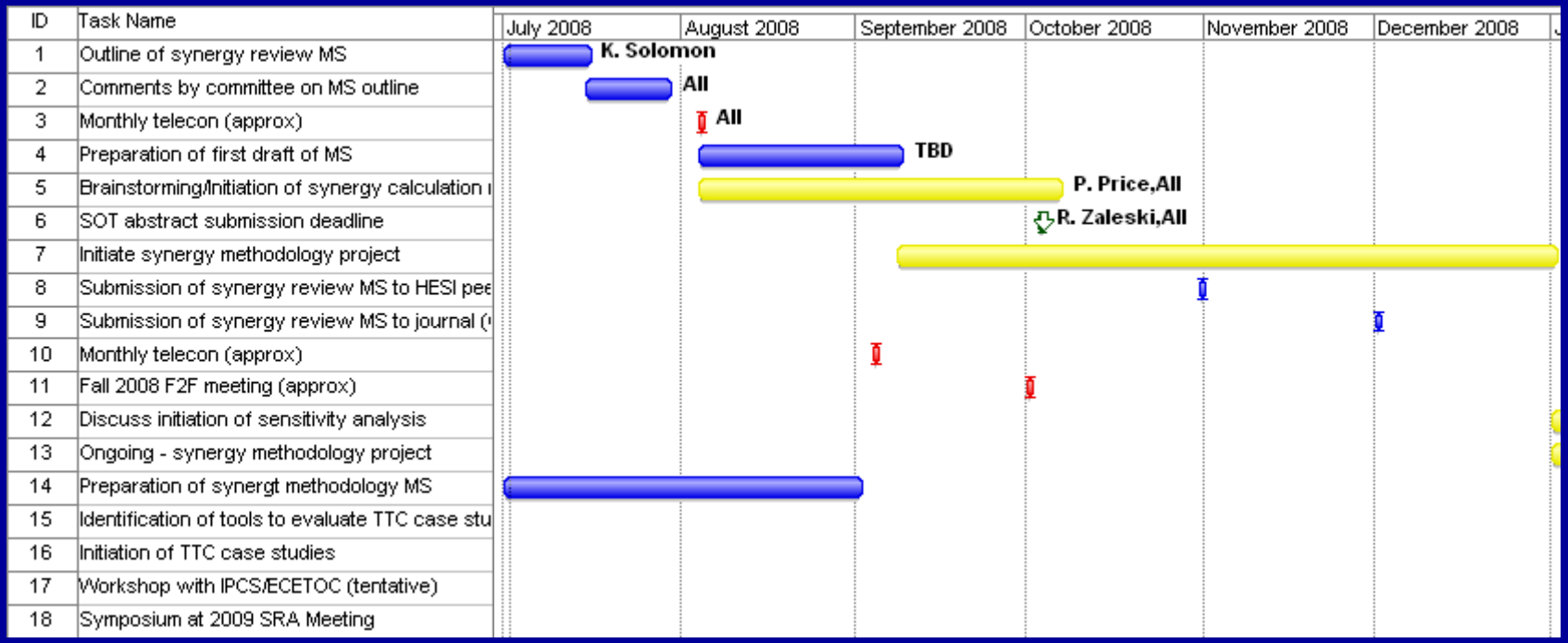
Future Directions (cont.)

- Late 2009:
  - Publication of synergy calculation methodology manuscript
  - Identification of tools to evaluate TTC case studies
  - Identification of criteria for case-studies to test the TTC approach
  - Initiation of initial TTC case-studies
  - Proceed beyond the TTC component in developing a mixtures assessment framework
  - Workshop with IPCS/ECETOC (tentative)
  - Symposium at SRA meeting

Future Directions (cont.)

- 2010:
  - Publication & presentation of TTC case studies
  - Publication of IPCS/ECETOC/HESI workshop proceedings
  - Initiation of workplan to address critical issues arising from the joint workshop and/or case studies
- 2011:
  - Broad workshop on recent developments in the mixtures arena, with a goal of identifying areas for future work
  - Wrap-up of project activities, finalization of publications, etc.

Draft Gantt Chart



Questions?