A Crop Protection Industry Perspective on TT21C Approaches

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Human Health Assessment

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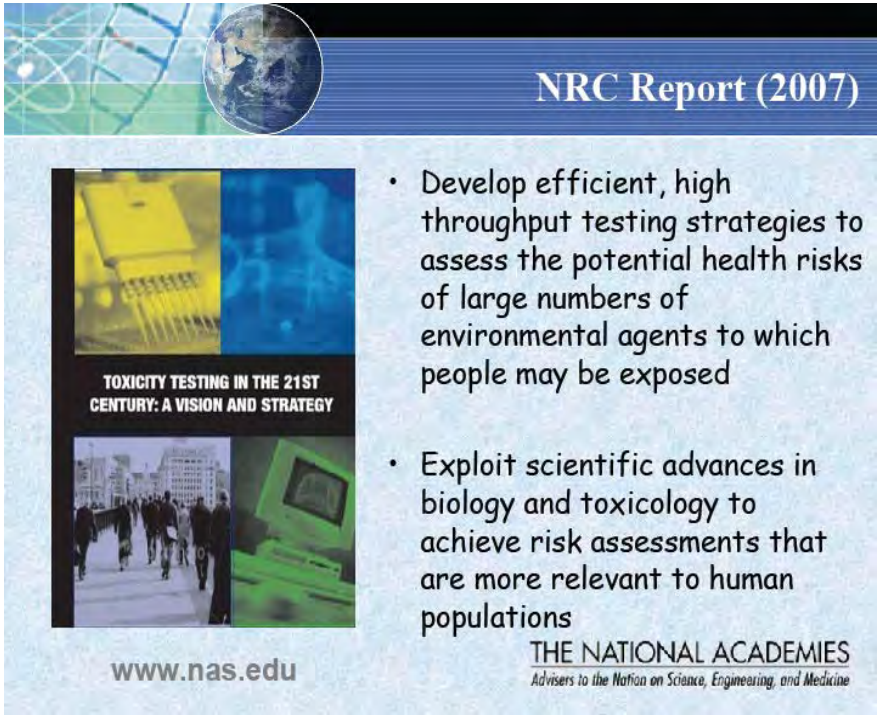
Solutions for the Growing World

Why are we undertaking this journey?

1. Provide broad coverage of chemicals, chemical mixtures, outcomes, and life stages
2. Reduce the cost and time of testing
3. Use fewer animals and minimize suffering
4. Develop a more robust scientific basis for assessing health effects of environmental agents



How do we get there?

- Recognize that it is a journey
- Appreciate and overcome challenges individually
  - Long history and level of comfort with animal-based testing
  - Need to better understand utility and applicability of new approaches
  - Need to ensure methods and data are robust, relevant and reliable
  - Need to comply with regulatory requirements (mostly animal-based)
- Don’t forget progress already made (e.g. ACSA)
- Take pragmatic steps now!

“To get through the hardest journey we need take only one step at a time, but we must keep on stepping” **Chinese Proverb**

ILSI-HESI ACSA Approach

- Carmichael, N.G., Barton, H.A., et al., (2006). Agricultural chemical safety assessment: A multi-sector approach to the modernization of human safety requirements. *Crit. Rev. Toxicol.* **36:**1–7.

- Barton, H.A., Pastoor, T.P., et al., (2006). The acquisition and application of absorption, distribution, metabolism, and excretion (ADME) data in agricultural chemical safety assessments. *Crit. Rev. Toxicol.* **36:**9–35.

- Doe, J.E., Boobis, A.R., et al., (2006). A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. *Crit. Rev. Toxicol.* **36:**37–68.

- Cooper, R.L., Lamb, J.C., et al., (2006). A tiered approach to life stages testing for agricultural chemical safety assessment. *Crit. Rev. Toxicol.* **36:**69–98.

How can we make progress?

- TT21C Goals and Vision
  1. Assess more chemicals faster for lower cost
  2. Use fewer animals (3Rs)
  3. Provide more relevant information for protection of human health
- What can we do now to make progress?
  1. Identify and eliminate studies that are redundant or have limited application to human health risk assessment
  2. Take an integrated approach - maximize amount and relevance of information obtained from each study
  3. Employ ‘new’ approaches strategically

Opportunities to Eliminate Studies (Examples)

- 1 year dog is redundant with 90-day dog study

Dellarco, V. *et al.* A retrospective analysis of toxicity studies in dogs and impact on the chronic reference dose for conventional pesticide chemicals. Critical Reviews in Toxicology 2010 40:1, 16-23.

Kobel, W. *et al.* A 1-year toxicity study in dogs is no longer a scientifically justifiable core data requirement for the safety assessment of pesticides. Critical Reviews in Toxicology 2010 40:1, 1-15.

- Immunotoxicity
  - No impact on reference doses; EPA now considering waivers
- What's next?

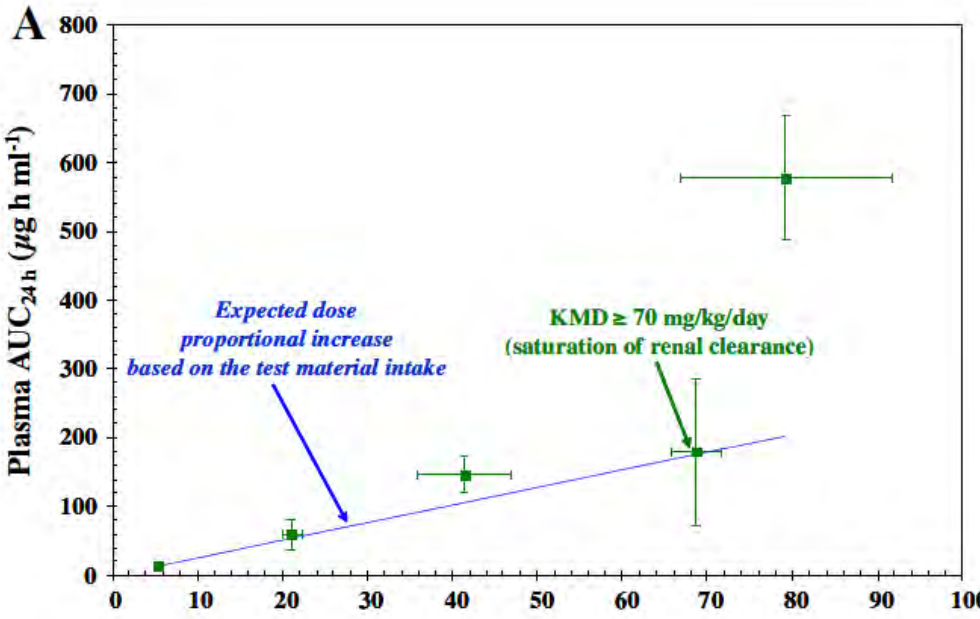
Billington, R.. *et al.* The mouse carcinogenicity study is no longer a scientifically justifiable core data requirement for the safety assessment of pesticides. Critical Reviews in Toxicology 2010 40:1, 35-49

Integrated Toxicity Testing

- In this context refers to study designs that combine multiple endpoints traditionally assessed in separate studies
- Goal = more information, better information, fewer animals
- Opportunities
  - Toxicokinetics (TK)
  - Neurotoxicity
  - Immunotoxicity
  - *In vivo* genotoxicity (MNT)
  - Mode of action
- Example
  - Separate 90-day toxicity, neurotoxicity, immunotoxicity = 200 animals
  - Combine endpoints in one study = 90 animals
  - Nearly identical information obtained!

Assessment of Kinetics in Toxicology Studies (Toxicokinetics)

- Dose levels in toxicology studies often result in saturation of absorption, distribution, metabolism or elimination = non-linear exposure kinetics
- Benefits to obtaining TK data
  - Dose-level selection; define kinetically-derived maximum dose
  - Ability to compare exposure and toxicity across studies
  - Minimize animal stress by avoiding 'overdosing'
  - Potential basis for use of internal exposure for risk assessment



Plasma AUC_{24h} of 2,4-D in male rats following 28 days of dietary exposure [Creton *et al.* (2012). Reg Tox and Pharm. 62: 241-247.]

Current Uses for 21st Century Approaches

- In general, not yet 1:1 replacement for animal studies
  - Regulatory/guideline studies still needed per regulations (e.g. part 158)
- Current Opportunities
  - Characterize mode of action and human relevance for effects in animal studies; can often be done in concert with guideline studies (hypothesis-based testing)
  - Guide early stage decision making by screening for key effects
- Future Opportunities
  - Gain greater experience with ever-improving assays
  - *In vitro* to *in vivo* extrapolation tools; understanding of ADME
  - Identify 'low hanging fruit' for replacement. Acute endpoints?

Non-Animal Approaches in Early Stage Testing

- Non-animal screens for critical effects/pathway activation can be employed during early stages of new product development
- Benefits
  - Opportunity to identify potential effects at an early stage prior to large investment or heavy animal use
  - Increased ability to make adjustments and react to data as needed
  - Increased confidence and probability of success for those molecules that move forward
- Challenges
  - Understanding relevance of alternative methods for decision making
  - Need for assays which are well understood (‘validated’)
  - How to address and follow-up on positives

USEPA Documents on Integrated Testing Approaches

- Strategic Direction for New Pesticide Testing and Assessment Approaches
- Guiding Principles for Data Requirements
- Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies
- Guidance for Selecting, Identifying and Evaluating Open Literature Studies
- Use of an Alternate Testing Framework for Classification of Eye Irritation Potential of EPA Pesticide Products
- Combining Genotoxicity Testing with Standard Repeated Dose Toxicology Testing.

Summary

- We are on a journey and progress may seem gradual at times
- We need to protect human health and comply with regulatory requirements
- We need to identify opportunities to take proactive steps now that are aligned with the overall TT21C vision
  - Eliminate studies that are redundant or provide minimal value to risk assessment
  - Take a pragmatic integrated testing approach
  - Begin implementing alternative methods for specific purposes; expand use as science dictates