ILSI AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA) PROJECT:
A TIERED TESTING APPROACH

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Committee Objective:
To provide a mechanism for reaching consensus across sectors (industry, government, academia, and non-profit) on the development of scientifically credible and viable methods for assessing the safety of crop protection chemicals more efficiently, with fewer animals, and with fewer artifacts.
Technical Committee Participation

• **Chair:** Dr. Neil Carmichael (Bayer CropScience)

• **Vice-Chair:** Dr. Tim Pastoor (Syngenta Crop Protection)

• **Private Sector:** 6 agchem/chemical companies
  BASF, Bayer CropScience, Dow AgroSciences, DuPont Crop Protection, Monsanto, Syngenta

• **Academia:** 9 institutions represented
  Imperial College London, Johns Hopkins University, Medical College of Wisconsin, Michigan State University, Mississippi State University, Università di Padua (Italy), University of California Riverside, University of Nottingham (UK), University of Southampton (UK)

• **US Government:** EPA (OPP, NHEERL, NCEA)

• **Non-US Government:** 6 institutions represented
  European Commission, European Food Safety Authority, German Federal Institute for Risk Assessment, Health Canada, OECD, Dutch RIVM
ACSA TASK FORCES

**ADME Task Force**
Dr. Hugh Barton (EPA/NHEERL)
Dr. Tim Pastoor (Syngenta Crop Protection)

**Systemic Toxicity Task Force**
Dr. Alan Boobis (Imperial College London)
Dr. John Doe (Syngenta Ltd.)

**Life Stages Task Force**
Dr. Ralph Cooper (EPA/NHEERL)
Dr. Jim Lamb (THE WEINBERG GROUP)
Aims of ACSA

• Develop an efficient and accurate testing strategy
• Improve testing to provide the necessary information to assess a range of exposure scenarios
• Adverse health effects identified are relevant
• Conserve resources
• Reduce and refine animal use
Why Reconsider the Process?

- Many assessment methodologies originated in 1960s and 1970s.
- Knowledge of toxicology and testing capabilities has increased dramatically in the last 40 years.
- More sophisticated and demanding potential health impact assessments are now required (e.g., intermittent exposure, susceptible populations, etc.).
- Multi-sector, international interest exists for determining whether the process can be made more efficient and accurate.
Current CFR Part 158 Testing Requirements

- Acute toxicity battery
- 90-day feeding – rodent and nonrodent
- 21- or 28-day dermal
- Dermal penetration
- Chronic feeding – rodent and non-rodent
- Carcinogenicity – rat and mouse
- Prenatal developmental toxicity – rat and rabbit
- 2-Generation reproduction
- Bacterial reverse mutation assay
- *In vitro* mammalian gene mutation
- *In vivo* cytogenetics
- Rat metabolism
How Can Testing Be Improved?

- Introduce greater flexibility – science should drive the testing strategy.
- Incorporate the use of a tiered approach – develop a “basic” testing package (i.e., Tier 1), with subsequent tests (i.e., Tier 2) built on Tier 1 results.
- Emphasize the importance of reducing and refining animal usage.
- Integrate improved understanding of exposure.
ADME TF Objectives:

- Develop guidance for the careful, tier-wise collection of PK data that would better define dose across...
  - species
  - life stages
  - route
  - frequency and duration of exposure
ADME TF Objectives (cont’d)

• Provide recommendations that would help in…
  – Toxicology study design
  – Interpretation
  – Risk Assessment
Turning the Crank...

Tox Studies

Risk?

ADME

“Basic” Tier I

“Custom” Tier II

“Advanced” Tier III

Route-Route
Animal to Human
Worker Safety

Internal Dose
Species Differences
Mode of Action

-Time Course
-Metabolites
-Bioavailability
-Saturation
-Recovery

-Route
-Age
-Species
ADME Tiered Approach

- **Basic (Tier I):** data crucial for dose selection, half-life determinations, and identification of major metabolites.

- **Custom (Tier II):** data needed for study interpretation, absorbed dose estimates, and duration/route extrapolations.

- **Advanced (Tier III):** data to support the understanding of a compound’s mode of action and allow the derivation of pharmacodynamic concordance.
Systemic Toxicity TF Strategy

- Review how current data are used to derive risk assessments for crop protection products (CPP).
- Review toxicity parameters that currently drive tiered hazard assessments.
- Identify a hierarchy of studies, endpoints and triggers that might be used in a tiered approach.
- Incorporate exposure level, frequency and duration of potential exposure into design.
SABRE Database

- SABRE database (Safety Assessment by Refined Experimentation) constructed specifically for the HESI ACSA project.

- Includes data on 65 agrochemicals from the EPA/OPP pesticide database, representing all major classes.

- Compared dog, rat, and mouse as basis for establishing RfDs.

- Compared studies of different duration as basis for establishing RfDs.
Sample queries conducted of the database

- Which studies were used most often to set ADIs and RfDs?
- What was the relationship between NOAELs across studies? (levels and endpoints/target organs)
- What was the relationship between NOAELs across species? (levels and endpoints/target organs)
- Which studies and species were rarely or never used to determine NOAEL, ADI, or RfD?
- When a species other than the rat was used to set a standard, were there similar effects present in the rat?
Systemic Toxicity

- **Tier 1**: comprehensive analysis of all organ systems using clinical chemistry, histopathology, etc.
  - Include indicators (trigger effects) for specialized endpoints (e.g., immunotoxicity) in Tier 1 studies which, if negative, give a high level of confidence of no relevant adverse effects.

- **Tier 2**: studies to quantify more precisely such effects if relevant for risk assessment, and explore mechanisms.

- Choice of doses and dosing regimen guided by **kinetics** and **exposure predictions**.
Systemic Toxicity Strategy

**Step 1:** Consider existing data, acute tox, genetic tox

**Step 2:** Rat 28-day study

**Step 3:** Dog 90-day study

**Step 4:** Select “relevant” species

**Step 5:**
- **Rat is “relevant”**
  - 1-day RfD from 1-exposure rat
  - 2-28 days RfD from 28-day rat
  - 1-6 months RfD from 28-day rat
  - Over 6 months RfD from 1-yr rat
  - Carcinogenicity from 24-month rat

- **Dog is “relevant”**
  - 1-day RfD from 1-exposure dog
  - 2-28 day RfD from 90-day dog
  - 1-6 months RfD from 90-day dog
  - Over 6 months RfD from 1-yr rat or 90-day dog
  - Carcinogenicity from 24-month rat
Life Stages Task Force Objectives

- Reduce / refine/ replace animal usage.
- Optimize study design / allow flexibility.
- Exposure characteristics taken into account (route, level, frequency, duration).
- Facilitate risk assessments for relevant life-stages.
- Tiered approach to testing.
Life Stages Tier I

- **F1-'extended’ one-generation reproduction study in one species (rat):**
  Dosing to PND 70 of subsets of F1 pups (with neurotox, immunotox and endocrine endpoints); study continues to a 2nd generation, if triggered.

- **Developmental toxicity study in second species (most likely the rabbit):**
  Similar to current guidelines but dietary dosing preferred and with additional key markers of maternal toxicity/exposure.
F1-’extended’ : 1-Gen Study

- Pre X: 4W
- Post X: up to 6W
- X: 2W
- Pre X: 2W
- Gestation
- Lactation
- P_ & P_ necropsy
- Post wean: up to PND 70
  - Set 1: clinical path/neurotox
- Post wean: up to PND 70
  - Set 2: estrous cycles/immunotox
- Post wean: up to PND 70
  - Set 3: TK/triggered reprotox - extend to F2
- Surplus F1 pup necropsy
- P_ & _ dosing
- Selected subsets F1_ & _ dosing
Considerations of Life Stages Tiered Approach

Tier II

- Exposure studies or refined estimates
- Focussed second tier studies to quantify / characterize specific effect at biologically relevant doses
- Conduct risk assessment
Tier 1: Base Set
Systemic Toxicity Provides Data for Tier 1

- Acute Toxicity
- Genetic Toxicity
- Metabolism
- Bioavailability and Kinetics
- Dermal Penetration
- 28-day Rat Dietary
- 90-day Dog Dietary
- 12-month Chronic/24-month Carcinogenicity Rat Dietary

Life Stages Data for Tier 1

Tier 2: Case-by-Case Decisions

From, but not limited to:

- More Detailed Mode-of-Action Endpoints
- ADME in Fetus and Neonate
- Further Neurotoxicity, Immunotoxicity, and Endocrine Testing
- Testing Late-Life Sensitivity
- Second Species Developmental Toxicity
- Second Generation Reproduction Study
- Refined Exposure Assessment

Exposure Assessment (often default models)

Margin of Exposure Sufficient?

Yes ➔ TESTING CONCLUDED

No ➔ Margin of Exposure Sufficient?

Yes ➔ TESTING CONCLUDED

No ➔ Margin of Exposure Sufficient?

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1. Includes consideration of neurological, immunological, and endocrine endpoints
2. May not be necessary if dietary exposure is < 6 months
3. Optional ADME in pregnant animals to guide dose selection
HESI ACSA Project

- **Important milestone!**
  - incorporates existing knowledge.
  - reduces/refines/replaces animal usage.
  - optimizes study design & allows flexibility.
  - better integration of metabolic & kinetic data in the safety assessment process.
  - uses a hierarchy of study types, endpoints, & triggers to ensure adequate coverage of life stages.
  - takes exposure characteristics into account, including intermittent exposures and different routes of exposure.
Significance of the ACSA Tiered Testing Proposal

- Departs from the current standardized list of hazard studies used by many national authorities.

- Represents the first comprehensive effort of its kind to scientifically re-design the testing framework for agricultural chemicals.
In Fall 2005, submitted a series of four scientific manuscripts (overview, ADME, systemic toxicity, and life stages) to *Critical Reviews in Toxicology* for publication as a “mini-monograph”
Next Generation of Pesticide Data Requirement: Important Steps

- Engage & educate broader stakeholder & scientific community.
- Work in several venues to gain international harmonization.
- Modify & refine approach based on additional input.