



H E S I

HESI

ILSI Health and Environmental Sciences Institute

AGRICULTURAL CHEMICAL SAFETY ASSESSMENT

Integration of Approaches

Neil G. Carmichael, PhD
Bayer CropScience

November 16, 2005
Nice, France



H E S I

HESI

ILSI Health and Environmental Sciences Institute

Significance of the ACSA Tiered Testing Proposal

- Represents a major milestone in reaching scientific agreement across sectors on a tiered testing scheme. The development process spanned several years and involved dozens of government, academic, and industry scientists from the US, Canada, and Europe.
- 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.



H E S I

HESI

ILSI Health and Environmental Sciences Institute

Key Features of Testing Paradigm as Proposed by the HESI ACSA Technical Committee

Base Set (Tier 1)

- Integrated approach to evaluating systemic toxicity including reproductive and life stage effects
- Pivotal 28-day rat study
- Dosing based on kinetics and physiology
- Evaluation of relative sensitivity of rat v. dog
- Full utilization of animals in each study via thorough analysis of clinical chemistry, histopath, etc.
- Reduces/refines animal usage
- Concentration on effects of concern

Tier 2:

- Testing focused on endpoints identified in Tier 1
- Flexible study designs
- Mechanistic data explored



H E S I

HESI

ILSI Health and Environmental Sciences Institute

Linkage of ADME and Toxicity Studies (Systemic and Life Stages)

- Toxicity study design
 - Assist in dose selection
 - Half-life for recovery period determination
- Toxicity study interpretation
 - Absorbed dose estimates
 - Characterize fetal and pup exposure
 - Species comparisons (in vitro, in vivo)
- Risk assessment applications
 - Route extrapolation (e.g., oral to dermal)
 - Component of mode-of-action analyses (e.g., identification of active metabolites)



H E S I

HESI

ILSI Health and Environmental Sciences Institute

Tier 2: From Lists to Results-Guided Research

- The importance of the Tier 2 approach should not be overlooked. Whereas Tier 1 seeks to identify effects of concern, Tier 2 is intended to define them.
- Tier 2 is intended to promote **flexibility** to use knowledge of mode of action and kinetics to characterize the endpoints of concern. Knowledge of exposure should be used to design appropriate definitive studies for neurotox, immunotox, reprotox, hepatotox, or other toxicities.
- Studies should seek to characterize the effects which will be **relevant for risk assessment**.



HESI

ILSI Health and Environmental Sciences Institute

H E S I

“Triggers” for Tier 2 Systemic Toxicity Testing

- Second tier studies are intended to more precisely quantify toxic effects, if relevant for risk assessment
- Consider data from the 28-day rat study for indicators of neurotoxicity, endocrine modulation, and immunotoxicity to determine if second tier studies are needed to further characterize effects.



HESI

ILSI Health and Environmental Sciences Institute

H E S I

Potential Reduction in Animal Usage: Systemic Toxicity Testing

<u>Animals</u>	<u>Current Paradigm</u>	<u>New Paradigm</u>
Rats	680	720
Mice	520	0
Dogs	72	48
Total	1272	768



H E S I

HESI

ILSI Health and Environmental Sciences Institute

“Triggers” for Tier 2 Life Stages Testing

- Determine NOAELs for critical endpoints for Tier 1 studies
- Estimate Margin of Exposure (MOE) for positive findings
- If MOE is insufficient for the relevant risk assessment, consider focused Tier 2 studies
 - may include further neurotoxicity, immunotoxicity, or endocrine tests, late-in-life sensitivity, specific ADME, detailed mode-of-action endpoints
- Irrespective of the MOE, there may be important positive findings from Tier 1 that require characterization in Tier 2 (e.g., early postnatal rat pup loss could be indicative of teratogenicity)



H E S I

HESI

ILSI Health and Environmental Sciences Institute

Potential Reduction in Animal Usage: Life Stages Testing

Current testing guidelines:

• 2 species developmental tox (<i>parental</i>)	160
• 2-gen reprotox (<i>parental and offspring</i>)	2600
• developmental neurotox (<i>parental and offspring</i>)	1280
• developmental immunotox (<i>parental and offspring</i>)	<u>1280</u>
	5320

Tier 1 testing only:

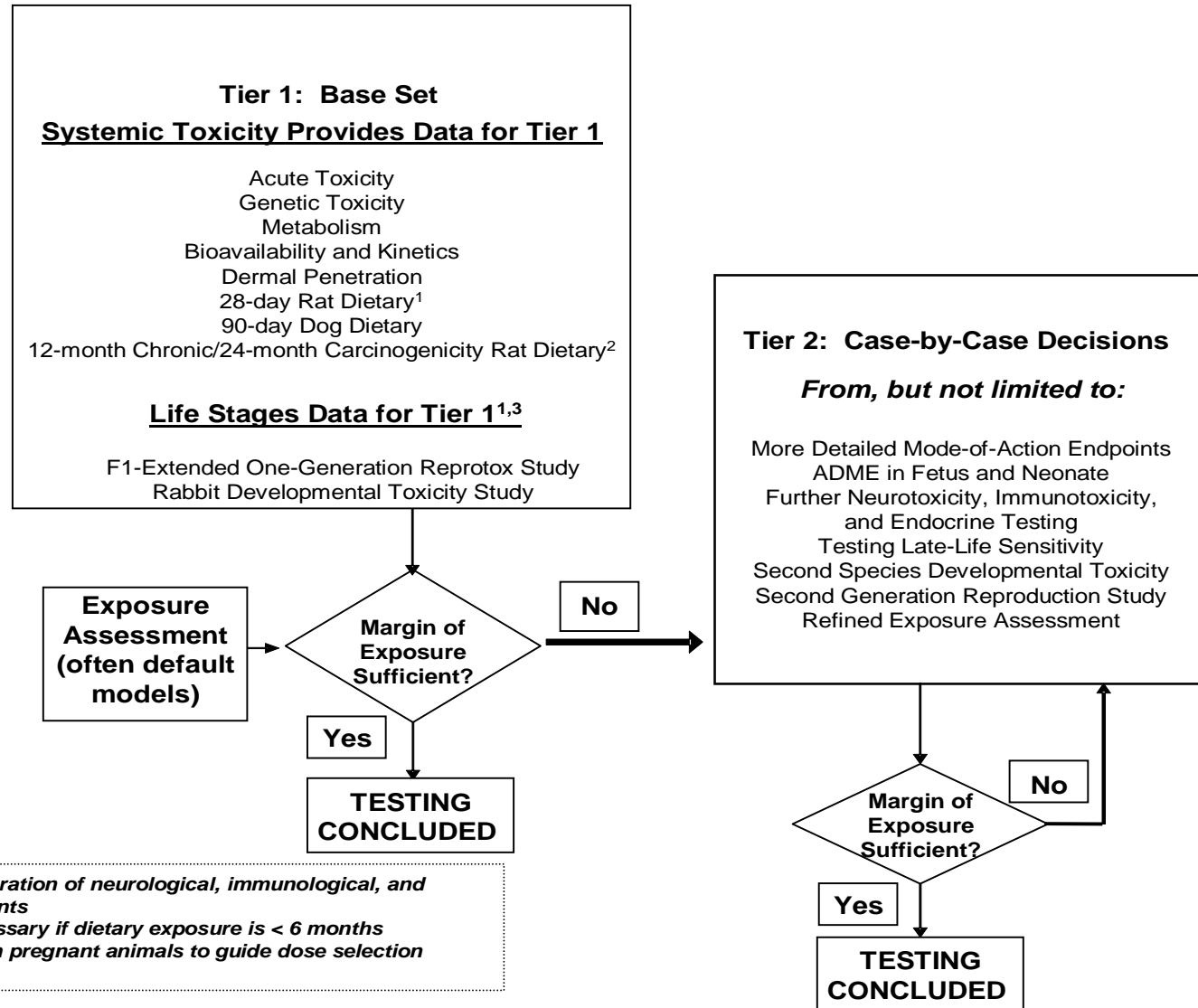
• 1 species developmental tox (<i>parental</i>)	80
• extended 1-gen reprotox (<i>parental & offspring</i>)	<u>1400</u>
	1480



HESI

ILSI Health and Environmental Sciences Institute

H E S I





HESI

ILSI Health and Environmental Sciences Institute

H E S I

Advantages of the ACSA Approach

- Tiered approach which targets endpoints that will be used for risk assessment
- Avoids generation of data which will not be relevant for risk assessment
- Contributes to at least 2 R's (reduction and refinement) in use of animals
- Promotes a dialogue on study relevance
- Reverses trend to guideline proliferation
- Forms a basis for harmonization and rationalization of requirements



HESI

ILSI Health and Environmental Sciences Institute

H E S I

Potential Reduction in Animal Usage: TOTAL

	<u>Current Paradigm</u>	<u>New Paradigm</u>
Life Stages	5320	1480
Systemic Tox	<u>1272</u>	<u>768</u>
Total	6592	2248



HESI

ILSI Health and Environmental Sciences Institute

H E S I

Broader Application of the ACSA Process?

- The ACSA process has precedent-setting potential. If viewed positively by the international community, the process gains credibility for broader application.
- HESI can bring together the right mix of international experts from government, academia, and industry to extend the application of the ACSA process beyond its targeted crop protection focus.



H E S I

HESI

ILSI Health and Environmental Sciences Institute

Next Steps and Outreach

- Publication of papers in *Critical Reviews in Toxicology*
- Discussions with EU and member states, OECD, EPA, Japan MAFF / MHW, other countries
- Data simulations from existing data sets?
- Test of new reproduction study design?