AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA) TECHNICAL COMMITTEE

The mission of the HESI Agricultural Chemical Safety Assessment (ACSA) Technical Committee was to develop a consensus across sectors (government, academia, and industry) on a credible and viable testing approach for assessing the safety of crop protection chemicals. The approach included scientifically appropriate studies that are necessary without being redundant, emphasized toxicological endpoints and exposure durations that are relevant for risk assessment, provided greater efficiency, used fewer animals, used resources more wisely, and generally included improved data for risk assessment purposes.

- Click here to download OECD Test Guideline 443 on the Extended One-Generation Reproductive Toxicity
  Study, which was based on the HESI ACSA tiered testing approach to life stages toxicity.

2007 Committee Membership

BASF Corporation
Bayer CropScience
CIIT Centers for Health Research, European Commission
Dow AgroSciences
DuPont Crop Protection
Federal Institute for Risk Assessment (Germany)
Imperial College London
INRA (France)
Johns Hopkins University Center for Alternatives to
  Animal Testing
Medical College of Wisconsin
Michigan State University
Mississippi State University
Monsanto Company
National Institute of Public Health and the
  Environment (RIVM, Netherlands)
Organisation for Economic Cooperation and Development
Pacific Northwest National Laboratory
Syngenta Ltd.
Universitá di Padua
University of California (Riverside)
University of Nottingham
University of Southampton
toXcel International Ltd.
Tox Path Inc.
US Environmental Protection Agency
  Office of Pesticide Programs
  National Center for Environmental Assessment
  National Health and Environmental Effects Research Laboratory
The Weinberg Group Inc.

Committee Publications

Four manuscripts which describe the ACSA tiered testing proposal have been published as a "Special Issue" in the journal Critical Reviews in Toxicology, Volume 36, Issue 1 (January 2006):

Carmichael, NG, Barton, HA, Boobis, AR, Cooper, RL, Dellarco, VL, Doerrer, NG, Fenner-Crisp, PA, Doe, JE, Lamb, JC, and Pastoor, TP. 2006. Agricultural chemical safety assessment: a multi-sector approach to the modernization of human safety requirements. Crit Rev Toxicol. 36, 1-7. [Details]

Barton, HA, Pastoor, TP, Baetcke, K, Chambers, JE, Diliberto, J, Doerrer, NG, Driver, JH, Hastings, CE, Iyengar, S, Krieger, R, Stahl, B, and Timchalk, C. 2006. The acquisition and application of absorption, distribution, metabolism, and excretion (ADME) data in agricultural chemical safety assessments. Crit Rev Toxicol. 36, 9-35. [Details]

Doe, JE, Boobis, AR, Blacker, A, Dellarco, VL, Doerrer, NG, Franklin, C, Goodman, JI, Kronenberg, JM, Lewis, R, McConnell, EE, Mercier, T, Moretto, A, Nolan, C, Padilla, S, Phang, W, Solecki, R, Tilbury, L, van Ravenswaay, B, and Wolf, DC. 2006. A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. Crit Rev Toxicol. 36, 37-68. [Details]

Cooper, RL, Lamb, JC, Barlow, SM, Bentley, K, Brady, AM, Doerrer, NG, Eisenbrandt, DL, Fenner-Crisp, PA, Hines, RN, Irvine, LFH, Kimmel, CA, Koeter, H, Li, AA, Makris, SL, Sheets, L, Speijers, GJA, and Whitby, K. 2006. A tiered approach to life stages testing for agricultural chemical safety assessment. Crit Rev Toxicol. 36, 69-98. [Details]

Fact Sheet

ILSI Health and Environmental Sciences Institute

TECHNICAL COMMITTEE ON AGRICULTURAL CHEMICAL SAFETY ASSESSMENT

MISSION

The mission of the HESI Agricultural Chemical Safety Assessment (ACSA) Technical Committee is to develop a consensus across sectors (government, academia, and industry) on a credible and viable testing approach for assessing the safety of crop protection chemicals. The approach will include scientifically appropriate studies that are necessary without being redundant, emphasize toxicological endpoints and exposure durations that are relevant for risk assessment, provide greater efficiency, use fewer animals, use resources more wisely, and generally include improved data for risk assessment purposes.

BACKGROUND

As biologically active molecules, crop protection chemicals undergo rigorous testing to determine their potential to cause adverse effects on human health. The testing protocols for these chemicals were initiated in the 1960s and 1970s using best practices available at the time, and were based on the premise that observed changes in animals exposed to a test chemical could be directly correlated to potential adverse health effects in humans.

Despite advances in the biological sciences in the last 20 years, as well as improved sensitivity and specificity of testing protocols, the core requirements of and rationale behind the standard toxicity testing battery for crop protection chemicals remain relatively unchanged.

OBJECTIVES

In 2000, the ACSA Technical Committee proposed to develop a tiered approach to deciding what studies should be done (and in what order) for safety assessment. The objective was to define a methodology which can be used to provide assurance that an agricultural chemical can be used without damaging human health, and which takes into account the toxicological properties and use pattern(s) of the chemicals.

ACSA PROJECT HISTORY

- January 2000: The concept is proposed at the HESI Annual Meeting.
- June 2000: The first committee meeting is held in HESI offices, Washington, DC.
- February 2001: A Steering Team is formed.
- April 2001: The Steering Team convenes a multi-sector, international scientific workshop.
- October 2002: Task Forces are formed to develop elements of a tiered testing approach.
- 2003-2004: The ADME, Life Stages, and Systemic Toxicity Task Forces develop detailed proposals.
- 2005: Manuscripts are prepared describing the proposed ACSA tiered testing approach, and are submitted to a peer-reviewed scientific journal.
- 2006: *Critical Reviews in Toxicology* accepts and publishes the papers as a "Special Issue."
- Late 2006: The ACSA Technical Committee was sunset at year end.

ACTIVITIES AND ACCOMPLISHMENTS

In 2004, the ACSA Technical Committee, a multi-sector, international group of government, academic, and industry scientists, completed the development of an improved testing scheme for assessing the safety of crop protection chemicals. Through the work of three active task forces, a proposal was developed with special emphasis on integrating metabolic and kinetic data into the safety assessment process; developing a hierarchy of

study types, endpoints, and triggers to cover vulnerable life stages; developing a tiered testing framework for endpoints such as neurotoxicity, carcinogenicity, and chronic toxicity; and evaluating the range of relevant human exposure situations in the context of experimental study design. The proposed approach provides a sound scientific basis for determining whether a given agricultural chemical poses adverse health risks in humans, taking into account the chemical's toxicological properties and use patterns.

The ACSA tiered testing proposal departs from the current standardized list of hazard studies used by many national authorities, and represents the first comprehensive effort of its kind to scientifically re-design the testing framework for agricultural chemicals. The proposal includes several important features:

- The testing strategy is driven by science.
- An integrated approach is taken to evaluating life stage effects, systemic toxicity, and kinetics.
- Testing is guided by human exposure predictions. Several durations of exposure are evaluated.
- Dosing is based on kinetics and physiology.
- Animals are fully utilized in each study via a thorough analysis of clinical chemistry, histopathology, etc.
- Animal usage is reduced and refined.
- The tiered approach provides greater flexibility for further testing and decision-making.

In late 2005, the ACSA manuscripts were completed and subject to rigorous peer review. In 2006, the papers were accepted and published as a "special issue" in *Critical Reviews in Toxicology*. Complete citations are given below.

OUTREACH

2003:

- US EPA Science Policy Council Workgroup on Toxicity Testing (Washington, DC)
- US EPA Office of Pesticide Programs (Washington, DC)
- OECD Working Group on Pesticides (Paris, France)
- EuroTox meeting (Florence, Italy)
- Society for Risk Analysis Annual Meeting (Baltimore, MD)

2004:

- Society of Toxicology Annual Meeting (Baltimore MD)
- ILSI Brasil and ANDEF (a division of CropLife Latin America) (Brazil)
- NAS/NRC Committee on Toxicity Testing and Assessment of Environmental Agents (Washington, DC)
- American Bar Association Committee on Pesticides, Chemical Regulation and Right-to-Know (Washington, DC)

2005:

- Organisation for Economic Cooperation and Development, Side Meeting to Workshop on Advancing Worksharing of Agricultural Pesticide Reviews (Washington, DC)
- US Environmental Protection Agency Science Forum (Washington, DC)
- Life World Watch Center (Japan)
- CropLife America Human Health and Risk Assessment Committee (Washington, DC)
- 42nd Congress of the European Societies of Toxicology, Eurotox 2005 (Krakow, Poland)
- National Toxicology Program Laboratory of Experimental Pathology (Research Triangle Park, NC)
- Twenty-Sixth Annual Meeting of the American College of Toxicology (Williamsburg, VA)
- HESI Workshop on Framework Approaches to Risk Assessment (Nice, France)
- International Society of Regulatory Toxicology and Pharmacology Workshop on "Progress and Barriers to Incorporating Alternative Toxicological Methods in the US" (Baltimore, MD)

2006:

- Japanese Agricultural Chemicals Inspection Station (Tokyo, Japan)
- AgChem Forum (Amsterdam, The Netherlands)
- Joint HESI / ILSI Argentina Meeting (Buenos Aires, Argentina)

FUTURE ACTIVITIES

The ACSA Technical Committee was sunset at the close of 2006.

IMPACT

Members, participants, and staff of the ACSA Technical Committee have contributed significant time and expertise to informal outreach about the proposal. The awareness level and visibility of the ACSA tiered testing approach with the international community is, as a result, much increased. Independent of the Technical Committee, proponents of the ACSA tiered testing approach at the US Environmental Protection Agency are actively working within the Agency and with the Organisation for Economic Cooperation and Development to adopt parts of the tiered testing approach in guideline form.

Notably, the National Research Council Committee on Toxicity Testing and Assessment of Environmental Agents reviewed the ACSA tiered testing proposal as part of its comprehensive review of established and emerging toxicity testing methods and strategies. In its interim report (2006), the committee indicated support for HESI's general approach.

LEADERSHIP AND INFORMATION

Chair ……..Dr. Neil Carmichael (Bayer CropScience)
Vice Chair……Dr. Timothy Pastoor (Syngenta Crop Protection)
HESI Staff..... Ms. Nancy G. Doerrer
..... Ms. Cyndi Nobles

For more information, please contact:
Ms. Nancy G. Doerrer at 202-659-3306 or
ndoerrer@hesiglobal.org

COMMITTEE MEMBERSHIP

BASF Corporation
Bayer CropScience
Dow AgroSciences
DuPont Crop Protection
Monsanto Company
Syngenta Ltd.

PUBLIC PARTICIPATION

CIIT Centers for Health Research
European Commission
Federal Institute for Risk Assessment (Germany)
Imperial College London
INRA (France)
Johns Hopkins University Center for Alternatives to Animal Testing
Medical College of Wisconsin
Michigan State University
Mississippi State University
National Institute of Public Health and the Environment (RIVM, Netherlands)
Organisation for Economic Cooperation and Development
Pacific Northwest National Laboratory
Universitá di Padua
University of California, Riverside
University of Nottingham
University of Southampton
toXcel International Ltd.
Tox Path Inc.
US Environmental Protection Agency
(EPA Office of Pesticide Programs)
(EPA National Center for Environmental Assessment)
(EPA National Health and Environmental Effects Research Laboratory)
The Weinberg Group Inc.

PUBLICATIONS

Barton, HA, Pastoor, TP, Baetcke, K, Chambers, JE, Diliberto, J, Doerrer, NG, Driver, JH, Hastings, CE, Iyengar, S, Krieger, R, Stahl, B, and Timchalk, C. 2006. The acquisition and application of absorption, distribution, metabolism, and excretion (ADME) data in agricultural chemical safety assessments. *Crit Rev Toxicol*, 36, 9-35.

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Doe, JE, Boobis, AR, Blacker, A, Dellarco, VL, Doerrer, NG, Franklin, C, Goodman, JI, Kronenberg, JM, Lewis, R, McConnell, EE, Mercier, T, Moretto, A, Nolan, C, Padilla, S, Phang, W, Solecki, R, Tilbury, L, van Ravenswaay, B, and Wolf, DC. 2006. A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. *Crit Rev Toxicol,* 36, 37-68.

Committee Presentations and Data Resources

December 11, 2009: HESI Agricultural Chemical Safety Assessment Technical Committee Presentations. Symposium Presentation (in Japanese) by Ayako Takei (HESI Scientific Advisor in Japan): "ILSI HESI ACSA Project: Outcome and Effects – Global Approaches to Future Agricultural Chemical Safety Assessment," Pesticide Regulatory Science Committee, Pesticide Science Society of Japan (Tokyo)

ILSI HESI

ACSAプロジェクトの成果とその後

新たな農薬安全性評価の枠組みを目指す国際的アプローチ

HESI サイエンティフィック・アドバイザー
武　居　綾　子

H E S I

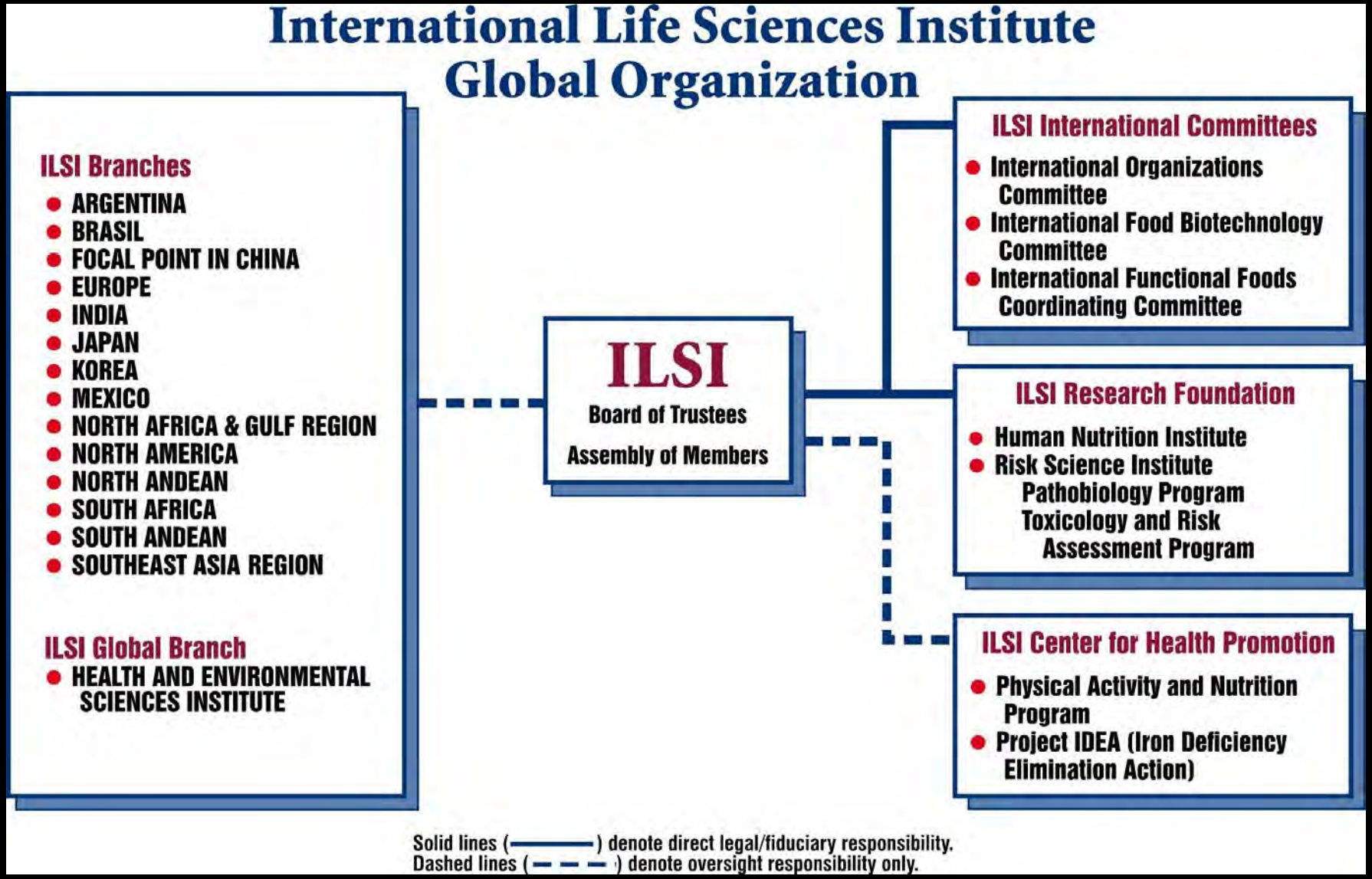
- ILSI HESIの概要：　組織と活動

- 農薬安全性評価研究委員会

  ACSA, Technical Committee for Agricultural Chemical Safety Assessment（2000-2006年）

- ACSAの成果に関連する国際的動向

International Life Sciences Institute
Global Organization



Solid lines (———) denote direct legal/fiduciary responsibility.
Dashed lines (– – –) denote oversight responsibility only.

HESIの使命

HESI = Health and Environmental Sciences Institute

環境保健科学研究所

パブリック、学術界、行政および産業界の懸念となるヒトの健康および環境に関わる問題の解決につながる科学研究と教育プログラムの推進と支援

HESIの組織

- 国際的科学研究機関　（1989年創立）
- メンバーシップによる非営利組織（NPO）：

  企業メンバーの年会費と各プロジェクト参加費で運営

  (＋*行政その他団体からの資金による援助*)
- 評議委員会：

  パブリックセクターおよび企業メンバーの代表で組織
- ワシントンDC事務局

HESI 評議委員会 (2009年）

- 30 名: 16 パブリック + 14 企業代表
  - グローバル –> ベルギー、 デンマーク、 日本、 オランダ、 スウェーデン、 スイス、 英国、米国
  - 毒性学およびリスクアセスメントの分野における著名な研究者 – 総数5,500 以上の学術論文

- 日本代表評議委員:
  - 福島昭治氏 – 日本バイオアッセイ研究センター
  - 眞鍋　淳氏 – 第一三共株式会社
  - 津田洋幸氏 – 名古屋市立大学

HESIの活動の特徴

- グローバル：
  - 北米、南米、欧州、およびアジアからの参加
- 透明性の重視:
  - 成果は全て公表
    - 査読誌への投稿論文
    - 投稿前にHESI パブリックセクター評議委員による査読実施

HESIの活動の特徴

- 多様性
  - 産官学の研究者による共同研究（*Tripartite Approach)*
    - 全プロジェクトに学術界および行政の研究者が参加
  - パブリック／私企業代表による共同リーダーシップ
  - 多様な産業界メンバーで構成される研究委員会
  - 広範な課題
    - 新規プロジェクトは国際的な産官学研究者の意見に基づき選択（*Annual Emerging Issues process)*

HESIの業績と国際的評価

- 産官学の研究者による国際的共同研究
  - ICH癌原性試験代替法国際バリデーション
  - ゲノミックス・データベースの構築
- 多彩な共同研究プログラム運営の実績
- 透明性の確保とバランスの取れたアプローチ
- 国際的コンセンサスを確立する能力
- 産官学のシナジーを生むパートナーシップの創造

HESI の活動

- 実験計画の実施
- 既存データを共有するためのフォーラム
- データベース構築
- 専門家会議
  - 著名な専門家によるフォーラム
  - 白書
- パブリック・アウトリーチ
  - ワークショップ、シンポジウムの計画と実施
  - 査読誌への投稿

メンバーシップ

- 農薬
- バイオテクノロジー
- 化学品
- 消費財
- 安全性評価に関わる受託試験機関および
  テクニカル・サービス提供機関（新規）
- 石油化学
- 医薬品

41企業（2009年7月現在）
(8カ国、3大陸)

日本企業メンバー

- アステラス製薬
- 第一三共
- エーザイ
- 田辺三菱製薬
- 住友化学工業
- 武田薬品

HESIが関与しない分野

- 企業団体としてのロビー活動
- 具体的な事業や製品の安全性に関わる問題

研究委員会（2009年）

H E S I

Technical Committees

- Application of genomics to mechanism-based risk assessment
- Cardiac safety
- Developmental and reproductive toxicology (DART)
- Immunotoxicology
- Integration of biomonitoring exposure data into the risk assessment process
- Protein allergenicity
- Risk assessment methodology (RAM)

Project Committees

- Animal alternative needs in environmental risk assessment
- Biological significance of DNA adducts
- Biomarkers of nephrotoxicity
- Development of methods for a tiered approach to assess bioaccumulation
- Relevance and follow-up of positive results from *in vitro* genotoxicity (IVGT) testing

Special Activities

- ILSI RF / HESI joint project on mode of action in risk assessment

新規研究課題（2009年）

Emerging Issues Subcommittees

- Distinguishing adverse from adaptive, non-functional and pharmacological changes in toxicology studies
- Evaluating epigenetic changes
- Identification of pharmaceuticals for validation of ToxCast
- Methodologies for intermittent / short-term exposure to carcinogens (MISTEC)

ACSA研究委員会

ACSA, Agricultural Chemical Safety Assessment Technical Committee

農薬安全性評価研究委員会

（2000 － 2006年）

使命：人為的な誤りが少なく、効率的で、かつ必要な実験動物の数を減らすことのできる、科学的に信頼性があり、実行可能な農薬の安全性評価法の開発について、産官学のコンセンサスを確立することができるフォーラムを提供する

http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3444

農薬の安全性評価要求項目

- 急性毒性（経口、経皮、吸入）
- 刺激・感作性（眼、皮膚）
- 反復投与毒性（経口、経皮；21日、28日、90日、1年）
- 神経毒性（急性、急性遅発性、反復投与遅発性、発達神経毒性）
- 発がん性
- 生殖・発生毒性
- 変異原性
- 薬理試験
- 薬物動態・代謝

評価法再検討の必要性

- 評価法の多くは1960年代や1970年代に開発
- その後40年間の毒性学および試験法における進歩
- ヒトの健康に対する影響評価の精密化の必要

  例、間歇的曝露の影響、感受性の高い集団への影響、等

- 複数のセクターにおいて、また国際的に評価プロセスの効率化と精度の向上が望まれている

国際的な産官学研究者の参加

- 産業界: (6 農薬／化学品製造企業)

  BASF, Bayer CropScience, Dow AgroSciences, DuPont Crop Protection, Monsanto, Syngenta

- 行政: (8 機関)

  Dutch RIVM, European Commission, European Food Safety Authority, German Federal Institute for Risk Assessment, Health Canada (PMRA), INRA (France), OECD, US EPA (OPP, NHEERL, NCEA)

- 学術界: (9 大学)

  Imperial College London, Johns Hopkins University Center for Alternatives to Animal Testing, Medical College of Wisconsin, Michigan State University, Mississippi State University, Universitá di Padua (Italy), University of California Riverside, University of Nottingham (UK), University of Southampton (UK)

- その他: (5 受託研究機関、コンサルタント、等)

  CIIT Centers for Health Research, Pacific Northwest National Laboratory, toXcel International Ltd., Tox Path Inc., The Weinberg Group Inc.

評価法改善のポイント

- 柔軟性を高める – 科学 に基づく評価ストラテジー
- Tier アプローチ の導入– 基本評価試験群（Tier 1）とTier 1の結果に基づくTier 2試験群の設定
- 限られた実験動物の効率的利用
- 曝露に関する最新の理解/情報の活用

リスクアセスメントの対象となる曝露期間

- 急性
  - 24 時間以内
- 短期
  - 1 ~ 7 日
- 中期
  - 1 ~ 4 週間
- 亜急性
  - 1～ 6 ヶ月
- 慢性
  - 6 ヶ月以上
- 間歇的
  - 長期間にわたり反復される短期曝露
  - 確率的曝露モデルによる予測

ACSA タスクフォース　1

ADMEタスクフォース

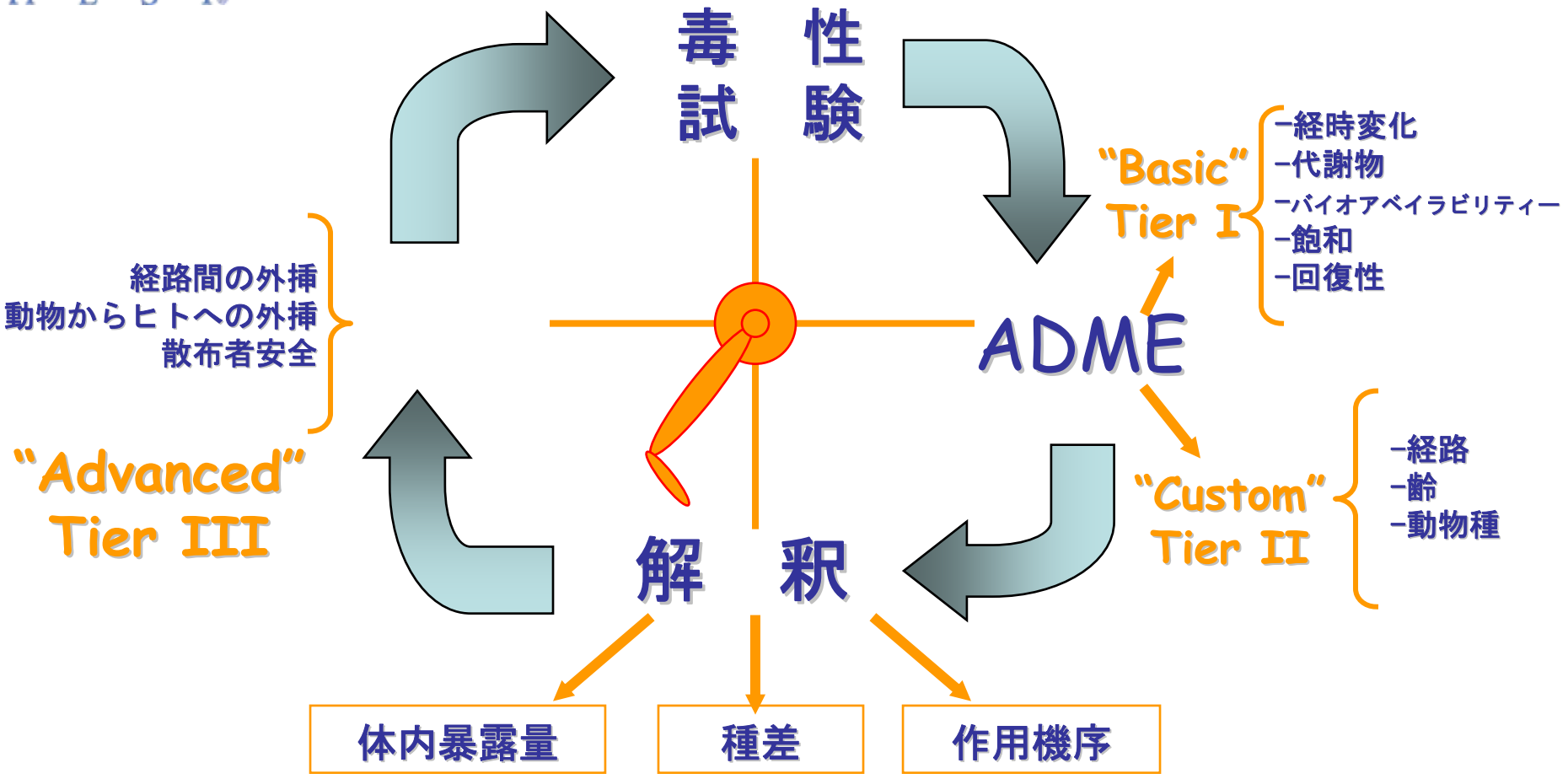
- 目的：代謝および薬物動態に関する有用なデータを農薬の毒性評価のための試験設計と解釈に活用するアプローチの開発

- リーダー：

  Dr. Hugh Barton (EPA/NHEERL)

  Dr. Tim Pastoor (Syngenta Crop Protection)

安全性評価プロセスにおけるADMEデータの活用



ACSA タスクフォース　2

❖ 全身毒性タスクフォース

- 目的：適切な毒性パラメータを全て評価することのできるアプローチを開発し、異なる試験とエンドポイントおよびTierアプローチの判断となる所見の順位を明らかにする

- リーダー：

  Dr. Alan Boobis (Imperial College London)

  Dr. John Doe (Syngenta Ltd.)

SABRE データベース

- SABRE データベース (Safety Assessment by Refined Experimentation) ：ACSAプロジェクトのために構築
- EPA/OPP農薬データベースから主要カテゴリーを代表する65農薬を選択
- RfD（参照用量、ADIに相当）設定の根拠となったかどうかについて、犬、ラット、マウスのデータを比較
- 異なる試験期間の試験についてRfD設定の根拠となったかを比較

Main Menu

ILSI-HESI ~ Systemic Toxicity Task Force

User: Admin | Technical Committee on Agricultural Chemical Safety Assessment | Version: 10.1

INPUT Study Data...

INPUT Ref. Doses...

Review AIs/Studies...

Queries

EXIT

Safety Assessment By
Refined Experimentation

Powered by
illuminaries
...turning Data into Information

SABRE データベースの解析

- ADIおよびRfDの設定に最もよく利用された試験
- 異なる試験のNOAELの関係
  （用量／エンドポイント／標的臓器）
- 異なる動物種のNOAELの関係
  （用量／エンドポイント／標的臓器）
- NOAEL、 ADI、またはRfDの設定に殆ど寄与していない試験および動物種
- ラット以外の動物種のデータがRfDの設定に利用された場合、ラットで同様の所見が観察されたか

SABREデータベースの解析結果

- 非遺伝毒性物質に関し、従来のマウス発がん性試験から安全性評価に有用な追加情報が得られることは殆どない

- 犬を用いた試験では、 90日間の試験が適切に実施されれば、12ヶ月の試験から有用な追加情報が得られることは殆どない

基本試験項目

予備試験：遺伝毒性、*in vitro* 代謝、 構造活性相関

- 主要な動物種：ラット
- 投与経路：混餌
- 投与期間：ヒトにおける曝露シナリオから決定
- 解析データ：臨床観察、完全な病理検査、血液生化学検査、血液検査を含む全てのエンドポイント
- 投与群：可逆性評価のための回復群を含む

Tierアプローチ

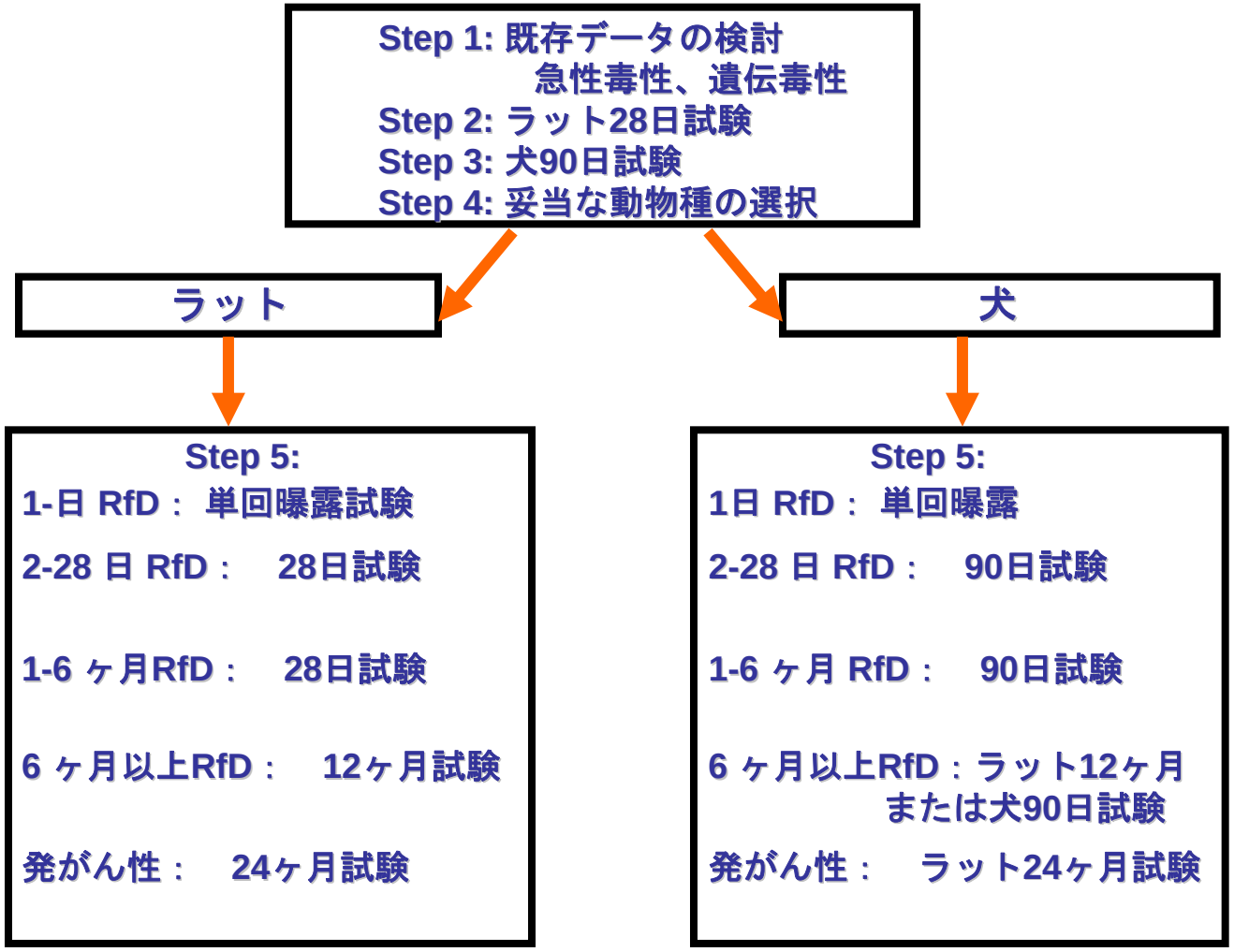
- Tier 1: 血液生化学的検査、病理検査データ等を用い、全ての臓器･組織を総合的に解析する
  - Tier 2の試験実施の判断となる特殊毒性(免疫毒性、等）の指標もTier 1の試験で評価し、陰性であった場合は、そういった特殊な有害性が発現する恐れがないことを高い信頼度で示すと判断
- Tier 2: リスクアセスメントに適用することが妥当だと考えられる影響をより詳細に定量的に評価し、作用機序の解明を試みる
- 投与量と投与経路は、薬物動態と想定される曝露に基づき決定する

用量設定

- PBTKモデルおよび体内曝露量、代謝の飽和、*in vivo*薬物動態に関するADMEの初期データに基づく用量設定

- 最高用量の設定:
  - 体重変化だけではなく、全ての有害性の兆候を含む
  - 吸収もしくは代謝の飽和を考慮する

全身毒性評価ステップ


Step 1: 既存データの検討
急性毒性、遺伝毒性
Step 2: ラット28日試験
Step 3: 犬90日試験
Step 4: 妥当な動物種の選択
ラット
犬
Step 5:
1-日 RfD： 単回曝露試験
2-28 日 RfD： 28日試験
1-6 ヶ月RfD： 28日試験
6 ヶ月以上RfD： 12ヶ月試験
発がん性： 24ヶ月試験
Step 5:
1日 RfD： 単回曝露
2-28 日 RfD： 90日試験
1-6 ヶ月 RfD： 90日試験
6 ヶ月以上RfD：ラット12ヶ月
または犬90日試験
発がん性： ラット24ヶ月試験

28日間ラット試験

- ADME
- 血液生化学的検査、血液学的検査
- 神経毒性、免疫毒性、および内分泌毒性の判断指標
- 病理検査
- 14日間回復試験

犬を用いた90日間試験

- 複数のADME評価ポイント (試験1日, 4 週、13週)
- 複数の血液生化学および血液学的検査ポイント
  （投与前、試験4週、13週）
- 生理学的検査項目（循環器、呼吸器）
- 経皮投与による ADME 評価
  (用量設定のための予備試験で実施）

ACSA タスクフォース　3

- ライフステージ・タスクフォース

  - 目的：全てのライフステージを適切に把握するアプローチを開発し、異なる試験とエンドポイントおよびTierアプローチの判断となる所見の順位を明らかにする

  - リーダー：

    Dr. Ralph Cooper (EPA/NHEERL)

    Dr. Jim Lamb (THE WEINBERG GROUP)

ライフステージ評価要求項目

米国:

- 発生毒性: 2 動物種
- 2世代繁殖試験： 1 動物種

個別要求項目:

- 発達神経毒性
- 内分泌系影響評価
- 発達免疫毒性
- (EU) ライフステージTK 評価

現行要求項目の問題点

- 個別要求項目の増加
- 高用量における所見の解釈
- 投与経路の妥当性
- 動物実験の重複
- 使用実験動物の増加
- リスクアセスメントに重要なライフステージが評価されていない

ライフステージ評価におけるTierアプローチ

リスクアセスメントから必要な試験を判断

Tier 1の目的:

- 生殖影響の評価
- 主要な毒性に対する各ライフステージ（若齢成獣を除く）の感受性の評価

Tier 1　基本項目

- ヒトにおける曝露量の推定（経路、期間、量）
- 結果の信頼性を確保する妥当な動物数の試験群
- Tier 2実施の判断となる重要な指標の評価：陰性であった場合は、有害性が発現する恐れがないことを高い信頼度で示す；陽性の場合はTier 2に進む
- リスクアセスメントの実施：十分な曝露マージン（MOE)が確保できない場合はTier 2に進む（>300～1,000）

Tier 2

- ヒトにおける曝露試験もしくはより精密な曝露推定
- 生物学的に妥当な用量域における有害性の定量化と定性化に重点を置く試験の実施
- リスクアセスメントの実施

ライフステージのリスクアセスメント

- 食物経由: 急性および慢性
  - 乳児、 1-6、7-12、 13-19、 55 歳以上
- 住居: 短期、 中期、 長期
  - 幼児、成人、 (女性 13歳以上)
- 職業曝露: 短期、中期、長期
  - 女性 13歳以上、 男性 13歳以上

Tier 1試験における 検討のポイント

- 全身毒性、ADME等、他のデータを考慮して 試験に含めるエンドポイントを精査
- ヒトにおける曝露に妥当な投与経路の選択 ：強制経口投与よりも混餌投与；摂餌量に基づき混餌濃度を調整
- ADME データで体内曝露量と薬物動態を判断
- リスクアセスメントにおいて体内曝露量と有害性の関係を評価

拡大1世代繁殖試験：P世代

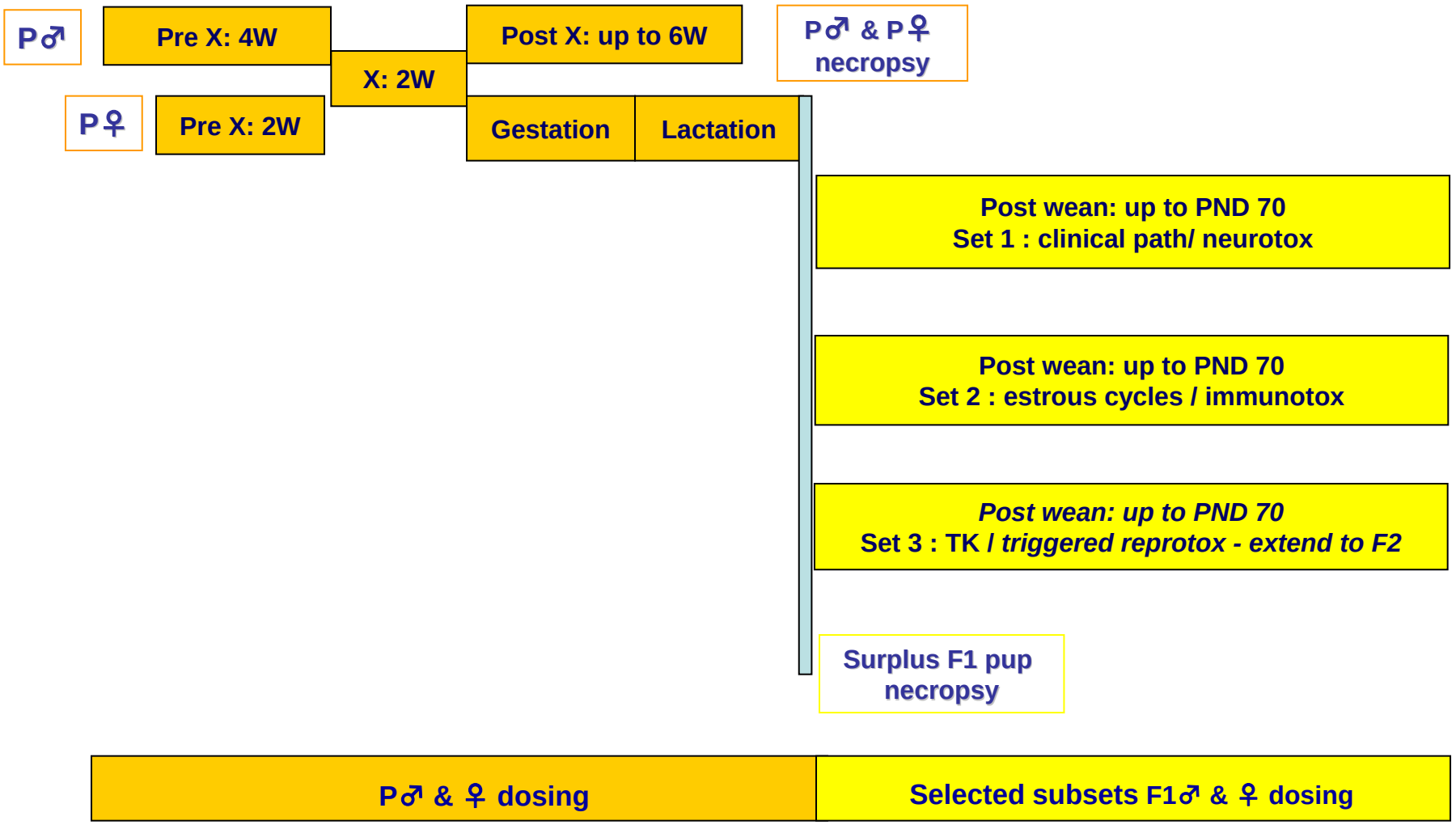
- 動物数：20腹/群に十分な匹数
- ADME / TK データの用量設定への活用
- 妊娠/授乳期間の重要なステージにおけるTK 評価
- 総合的な繁殖能評価
- サブセット群に対する詳細な病理検査
- 全身毒性評価の試験で観察された毒性所見マーカーの活用
- 予備的な*in vitro*試験を作用機序の解明およびエンドポイントの改良に利用する可能性の検討

拡大1世代繁殖試験：F1世代

生後70日まで投与

- 離乳前 (肛門性器間距離、性別、体重、臨床観察）
- 生後21日に3 サブセット選択 (雌雄各 1/腹/群、i.e., 雌雄各20/群)
  - サブセット 1: 自発運動量、機能観察バッテリー、神経病理学的検査、血液生化学的検査、血液学的検査、甲状腺ホルモン、詳細な病理検査
  - サブセット2: 発情周期、免疫毒性（SRBC抗体反応；その結果に基づくリンパ球（＋の場合）またはナチュラルキラー細胞（－の場合）に対する発現系分析
  - サブセット3: TK、内分泌系、生殖：必要であれば、生後70日以後も投与を継続し、交配、F2世代を得る
- 生後 21日の残りの児動物 (神経組織を含む臓器重量測定および病理検査)

拡大１世代繁殖試験


P♂
Pre X: 4W
Post X: up to 6W
P♂ & P♀ necropsy
X: 2W
P♀
Pre X: 2W
Gestation
Lactation
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

発生毒性試験

ラット以外の動物種（ウサギ）を用いた発生毒性試験

- OPPTS 870.3700 / OECD 414に準ずる試験設計
- ヒトの曝露経路に妥当な投与経路：強制経口投与よりは混餌
- ADME / TK データを用量設定に活用、さらにTK測定を実施
- 病理検査を含み、他の試験で観察された有害性のマーカーを活用
- 予備的な*in vitro*試験を作用機序の解明およびエンドポイントの改良に利用する可能性の検討

ライフステージTier 2

十分なMOEが確保できない場合およびTier 1で判断指標が陽性の場合実施

- 有害性の定性化のための個別試験の実施
- 妥当な用量域（最大耐量を含まない）での試験
- 想定される試験項目：

  神経毒性、免疫毒性、内分泌系試験、高齢期感受性、胎児／新生児期ADME、作用機序の解明

- 想定される追加試験：

  2世代繁殖試験および／または他の動物種による発生毒性試験

ACSAが推奨するライフステージTierアプローチの利点

- 薬物動態と若齢動物の全身毒性データを試験設計に活用
- 出生前および出生後初期曝露の影響として若齢成獣の全身毒性を評価
- 発達神経毒性評価
- 発達免疫毒性評価
- 複数の種類の影響を共通の動物群で評価
- 実験動物数の削減

ACSAライフステージ評価の妥協点

- 交配前投与期間の短縮：現行10週から雄4週間、雌2週間に変更（妊孕性 の評価には十分であると判断）
- F1児動物を交配しF2世代を得るのは、有害性の判断指標が陽性の場合のみ
- ラットを用いた発生毒性試験は実施しない

ACSA評価法の枠組み

H E S I

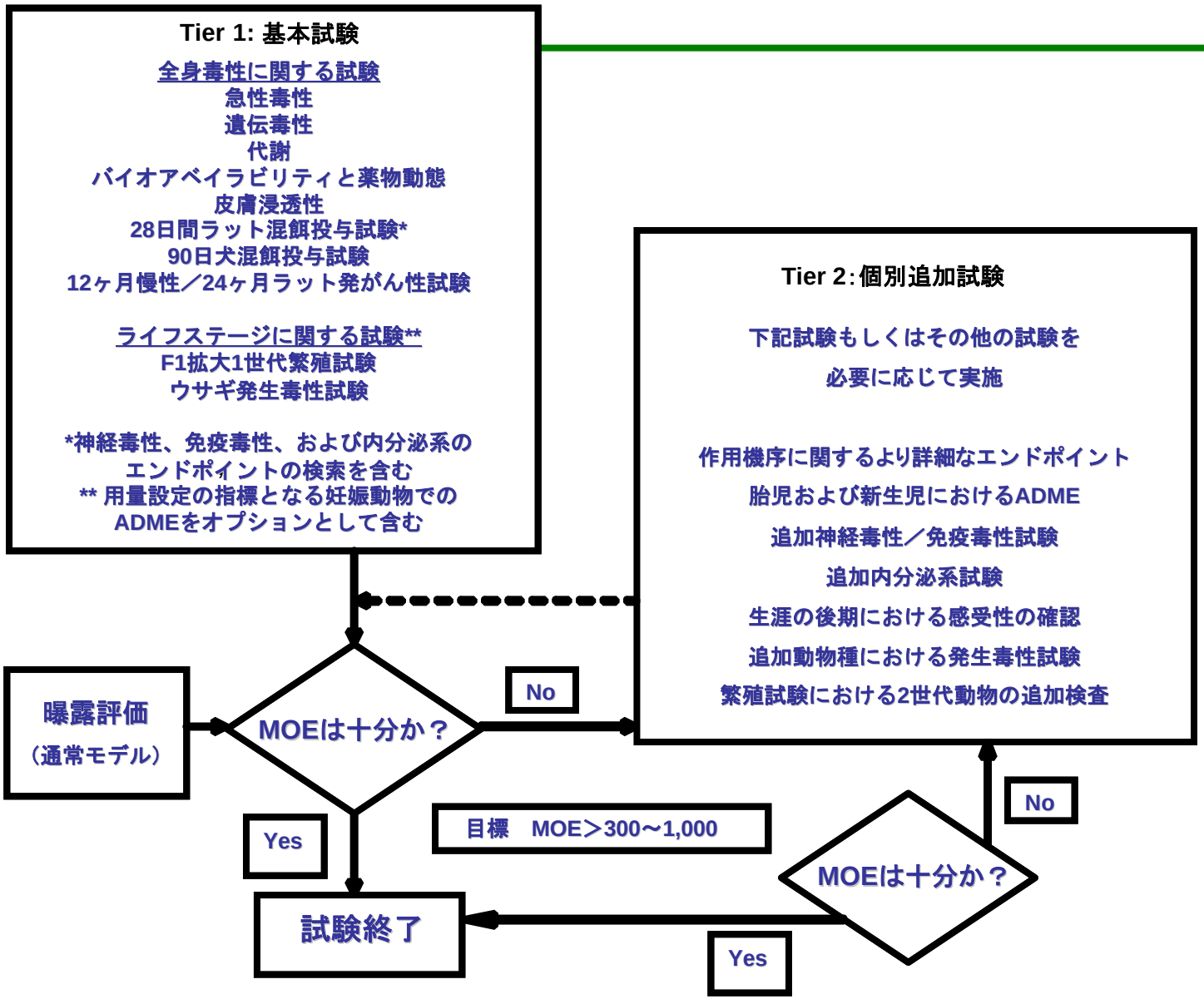
基本試験群（Tier 1）：

- 臨床症状、全身毒性、および薬物動態データを評価する総合的アプローチ
- 予想される曝露条件および包括的な28日間投与ラット試験の結果に基づく試験の実施
- 薬物動態および生理学データに基づく用量設定
- 異なる曝露期間の評価
- 臨床検査、病理検査等の完全な実施・分析によって個々の試験の実験動物を十分に活用
- 少ない実験動物の効率的活用
- 柔軟な追加試験の実施および判断

個別追加試験群（Tier 2）：

- Tier 1で検出されたエンドポイントを重視した試験の実施
- 柔軟性のある試験設計
- 作用機序の解明

ACSA　Tier　アプローチ



ACSA評価法の利点

- リスクアセスメントに適用されるエンドポイントを重視したTierアプローチ
- リスクアセスメントへの適用が妥当でないデータを創出しない
- 実験動物利用の3 R’sのうち削減と改善に貢献
- 試験の妥当性に関する検討の促進
- 試験ガイドラインの増殖に歯止め
- 要求項目のハーモナイゼーションと合理化の基礎を提供

実験動物の削減

	現行評価系	ACSA評価系
ライフステージ	5320	1480
全身毒性	1272	768
合計	6592	2248

ACSA新評価法の意義

- 米国、カナダ、欧州の行政、学術界および産業界の研究者による6年間の検討過程を経て、Tierアプローチの採用に関し、**複数のセクターの科学的同意**を得ることができた
- 多数の行政官庁が現在採用している有害性試験の**標準的リストから脱却**することができた
- 農薬の安全性評価試験の枠組みを**科学的に再構築**する初めての総合的な試み

成果の学術誌への投稿

Barton, HA, Pastoor, TP, Baetcke, K, Chambers, JE, Diliberto, J, Doerrer, NG, Driver, JH, Hastings, CE, Iyengar, S, Krieger, R, Stahl, B, and Timchalk, C. 2006. The acquisition and application of absorption, distribution, metabolism, and excretion (ADME) data in agricultural chemical safety assessments. *Crit Rev Toxicol*, 36、9-35.

Carmichael, NG, Barton, HA, Boobis, AR, Cooper, RL, Dellarco, VL, Doerrer, NG, Fenner-Crisp, PA, Doe, JE, Lamb, JC, and Pastoor, TP. 2006. Agricultural chemical safety assessment: a multi-sector approach to the modernization of human safety requirements. *Crit Rev Toxicol*, 36, 1-7.

Cooper, RL, Lamb, JC, Barlow, SM, Bentley, K, Brady, AM, Doerrer, NG, Eisenbrandt, DL, Fenner-Crisp, PA, Hines, RN, Irvine, L, Kimmel, CA, Koeter, H, Li, AA, Makris, SL, Sheets, L, Speijers, GJA, and Whitby, K. 2006. A tiered approach to life stages testing for agricultural chemical safety assessment. *Crit Rev Toxicol*, 36, 69-98.

Doe, JE, Boobis, AR, Blacker, A, Dellarco, VL, Doerrer, NG, Franklin, C, Goodman, JI, Kronenberg, JM, Lewis, R, McConnell, EE, Mercier, T, Moretto, A, Nolan, C, Padilla, S, Phang, W, Solecki, R, Tilbury, L, van Ravenswaay, B, and Wolf, DC. 2006. A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. *Crit Rev Toxicol*, 36, 37-68.

パブリック・アウトリーチ

- AgChem Forum (Amsterdam, The Netherlands)
- American College of Toxicology (Williamsburg, VA),
- CropLife America (Washington, DC)
- EuroTox (Florence, Italy; Krakow, Poland; Amsterdam, The Netherlands)
- HESI Annual Meetings
- HESI Workshop on Framework Approaches to Risk Assessment (Nice, France)
- ILSI Brasil and ANDEF (a division of CropLife Latin America) (Brazil)

パブリック・アウトリーチ(続き)

- International Society of Regulatory Toxicology and Pharmacology (Baltimore, MD)
- Japanese Agricultural Chemicals Inspection Station (Tokyo, Japan)
- Joint HESI / ILSI Argentina meeting (Buenos Aires, Argentina)
- NAS/NRC Committee on Toxicity Testing and Assessment of Environmental Agents (Washington, DC)
- National Toxicology Program Laboratory of Experimental Pathology (Research Triangle Park, NC)

パブリック・アウトリーチ(続き)

- Ochanomizu University Life World Watch Center (Tokyo, Japan)
- OECD (Paris; Washington, DC)
- Society for Risk Analysis Annual Meeting (Baltimore, MD)
- Society of Toxicology Annual Meeting (Baltimore, MD)
- US EPA (Science Policy Council, Office of Pesticide Programs, Workgroup on Toxicity Testing, Science Forum)

OECDテストガイドライン

- ACSA拡大1世代繁殖試験に基づくテストガイドライン
  - 拡大１世代繁殖試験の実施要領の詳細
  - F2世代を得る必要性を判断するためのエンドポイントのリスト
  - F1児動物の評価
    - Cohort 1:　生殖/発生エンドポイントの評価、必要な場合F2世代繁殖のために交配
    - Cohort 2:　神経系の発達への影響評価
    - Cohort 3:　免疫系の発達への影響評価
  - 2009年10月21-23日、OECD専門家グループ会合において最終案を検討
  - 2009年12月9日、最終案に対するコメント期間終了

米国および欧州での活動

- 産業界と行政の研究者が共同で犬12ヶ月試験およびマウス発がん性試験の必要性の再検討をさらに実施
- European Crop Protection Association (ECPA)が産業界と行政の研究者の共同執筆による学術論文の発表を準備中
- この活動の成果から、米国および欧州では要求事項としてのこれらの試験の位置付けに変化が期待される

今後さらに必要な検討

- ラット28日試験における毒性エンドポイントの指標（例、免疫毒性、神経毒性）
- 慢性毒性の試験要求を決定するための亜急性試験におけるラットと犬の相対的感受性
- 食物を通じた曝露が6ヶ月未満の場合、ラット慢性毒性試験を免除する可能性

受　　賞

- US Environmental Protection Agency (EPA) Scientific and Technological Achievement Award (STAA) Honorable Mention. 2007. S7HE0046 (ACSA ADME, Systemic Toxicity, and Life Stages papers). http://www.epa.gov/ncer/staa/annual/2007/2007honorable.html

- United Kingdom National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). January 2008. “Highly Commended Prize” awarded to Dr. John Doe (Syngenta) for the ACSA systemic toxicity paper.

ACSAプロジェクト/公表論文の引用例

H E S I

- Beekhuijzen, M, Zmarowski, A, Emmen, H, and Frieling, W. 2009. To mate or not to mate: A retrospective analysis of two-generation studies for evaluation of criteria to trigger additional mating in the extended one-generation design. Reprod Toxicol, 28, 203-208.
- Box, RJ, Spielmann, H. 2005. Use of the dog as a non-rodent test species in the safety testing schedule associated with the registration of crop and plant protection products (pesticides): present status. Arch Toxicol 79, 615-626.
- Cooper, RL, and Doerrer, NG. 2009. Reproductive and developmental toxicity studies. Chapter 3.17. In: *Comprehensive Toxicology*, Elsevier, United Kingdom. Submitted. [Includes section on proposed HESI ACSA extended one-generation reproductive and developmental protocol.]
- ECETOC. 2008. Workshop on Triggering and Waiving Criteria for the Extended One-Generation Reproduction Toxicity Study, 14-15 April 2008, Barza d'Ispra, Workshop Report No. 12. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels, Belgium.
- EFSA Panel on Plant Protection Products and Their Residues (PPR). 2007. Opinion of the Scientific Panel PPR related to the revision of Annexes II and III to Council Directive 91/414/EEC concerning the placing of plant protection products on the market - Toxicological and metabolism studies. European Food Safety Authority. *EFSA Journal* 449, 1-60.

ACSAプロジェクト/公表論文の引用例(続き）

- Janer, G, Hakkert, BC, Slob, W, Vermeire, T, Piersma, AH. 2007. A retrospective analysis of the two-generation study: what is the added value of the second generation? *Reprod Toxicol*. 24, 97-102.
- Joint FAO/WHO Meeting on Pesticide Residues (JMPR). October 2006. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Rome, Italy, p. 13.
- Judson R, Richard A, Dix DJ, Houck K, Martin M, Kavlock R, Dellarco V, Henry T, Holderman T, Sayre P, Tan S, Carpenter T, Smith E. 2009. The toxicity data landscape for environmental chemicals. Environ Health Perspect 117, 685-695.
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農薬安全性評価に関連するHESIの研究活動

H E S I

- Integration of biomonitoring exposure data into the risk assessment process
- Development of methods for a tiered approach to assess bioaccumulation
- Relevance and follow-up of positive results from *in vitro* genotoxicity (IVGT) testing
- Distinguishing adverse from adaptive, non-functional and pharmacological changes in toxicology studies
- Methodologies for intermittent / short-term exposure to carcinogens (MISTEC)

HESIに関する情報・お問い合わせ

Website: www.hesiglobal.org

E-mail: hesi@hesiglobal.org

E-mail: astakei@icarus-japan.com

November 16, 2005: HESI Agricultural Chemical Safety Assessment Technical Committee Presentations. Nice, France.

- "ADME," Presentation by Dr. Hugh Barton, US Environmental Protection Agency National Center for Computational Toxicology.
- "Systemic Toxicity," Presentation by Dr. John Doe, Syngenta CTL.
- "Life Stages Task Force," Presentation by Ms. Lorraine Irvine, toXcel International.
- "Integration of Approaches," Presentation by Dr. Neil Carmichael, Bayer CropScience.
- "Next Generation of Toxicology Testing Perspective," Presentation by Dr. Vicki Dellarco, US Environmental Protection Agency Office of Pesticide Programs.
- "OECD Perspective," NPresentation by Dr. Drew Wagner, Organisation for Economic Cooperation and Development.

HESI

ILSI Health and Environmental Sciences Institute

AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

ADME Task Force

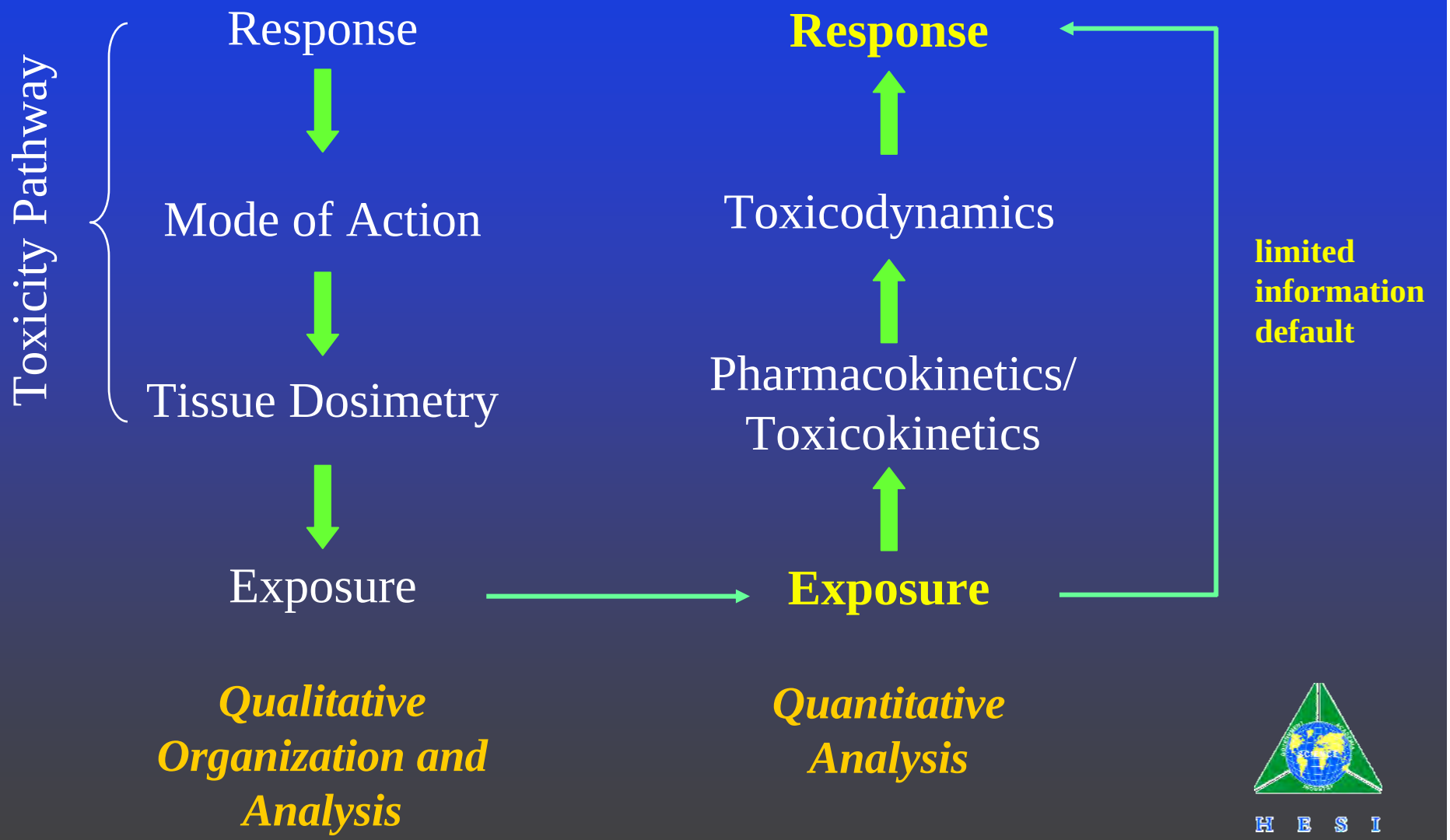
Hugh A. Barton, PhD

National Center for Computational Toxicology
Office of Research and Development
US Environmental Protection Agency
Research Triangle Park, NC

November 16, 2005

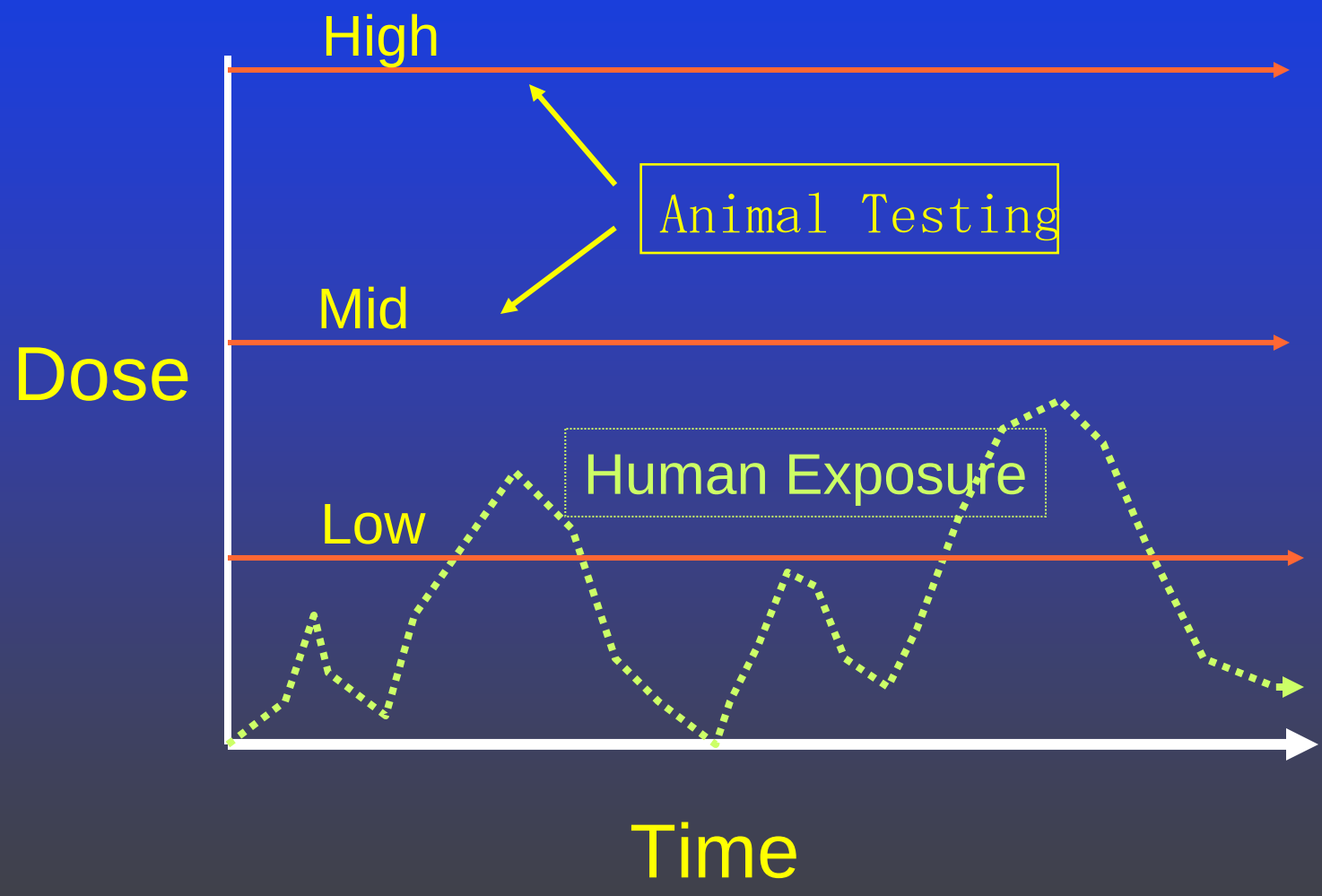
H E S I

Hazard Characterization and Dose-Response Framework



H E S I

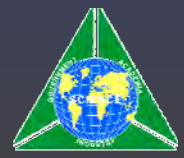
Dose-Response-Time



H E S I

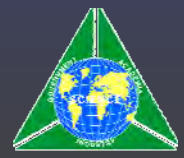
Purpose of ADME Studies

- Dose-Response: Obtain information to help determine the relationship between the concentration of free compound in plasma and the toxicological response.
- Risk: Provide data that assists in the design and interpretation of toxicity studies and the determination of risk.



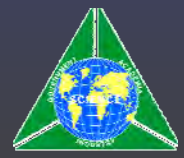
Objectives

- 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

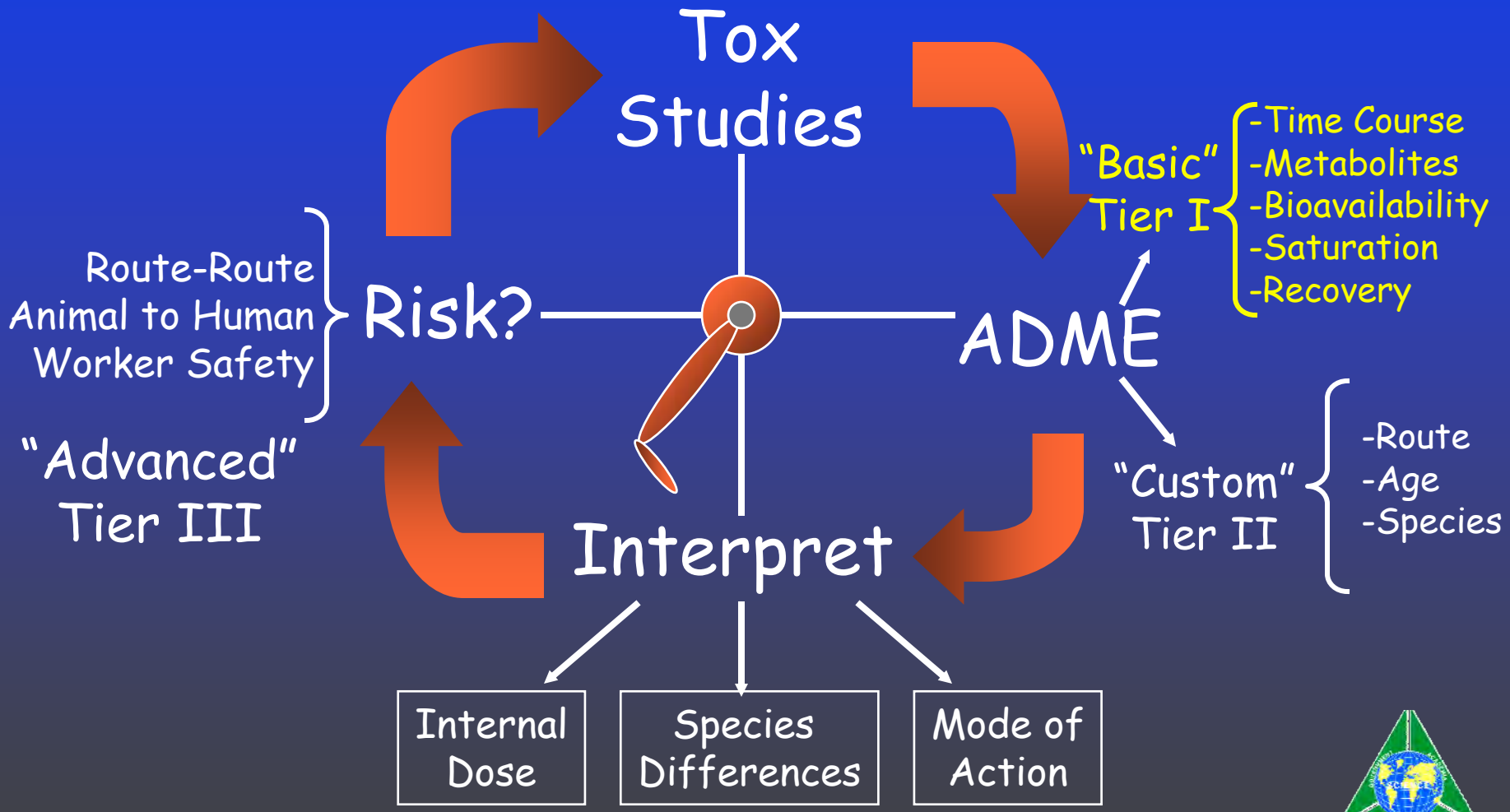


Objectives (continued)

- Provide recommendations that would help in…
  - Toxicology study design
  - Interpretation
  - Risk Assessment



Working through the process…



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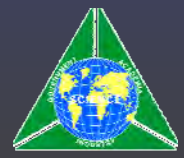
“Basic” Tier I

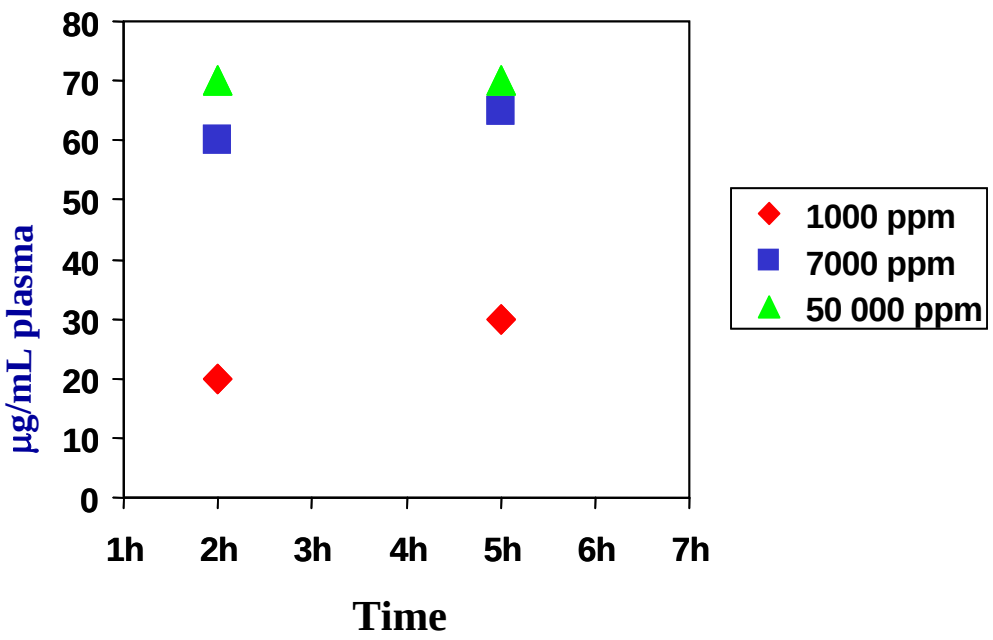
- Oral Bioavailability (iv, oral)
- Metabolism and Elimination
- Dose-Dependent PK
- Repeated-Exposure PK
- Blood levels in toxicity studies



Assisting in Dose Selection

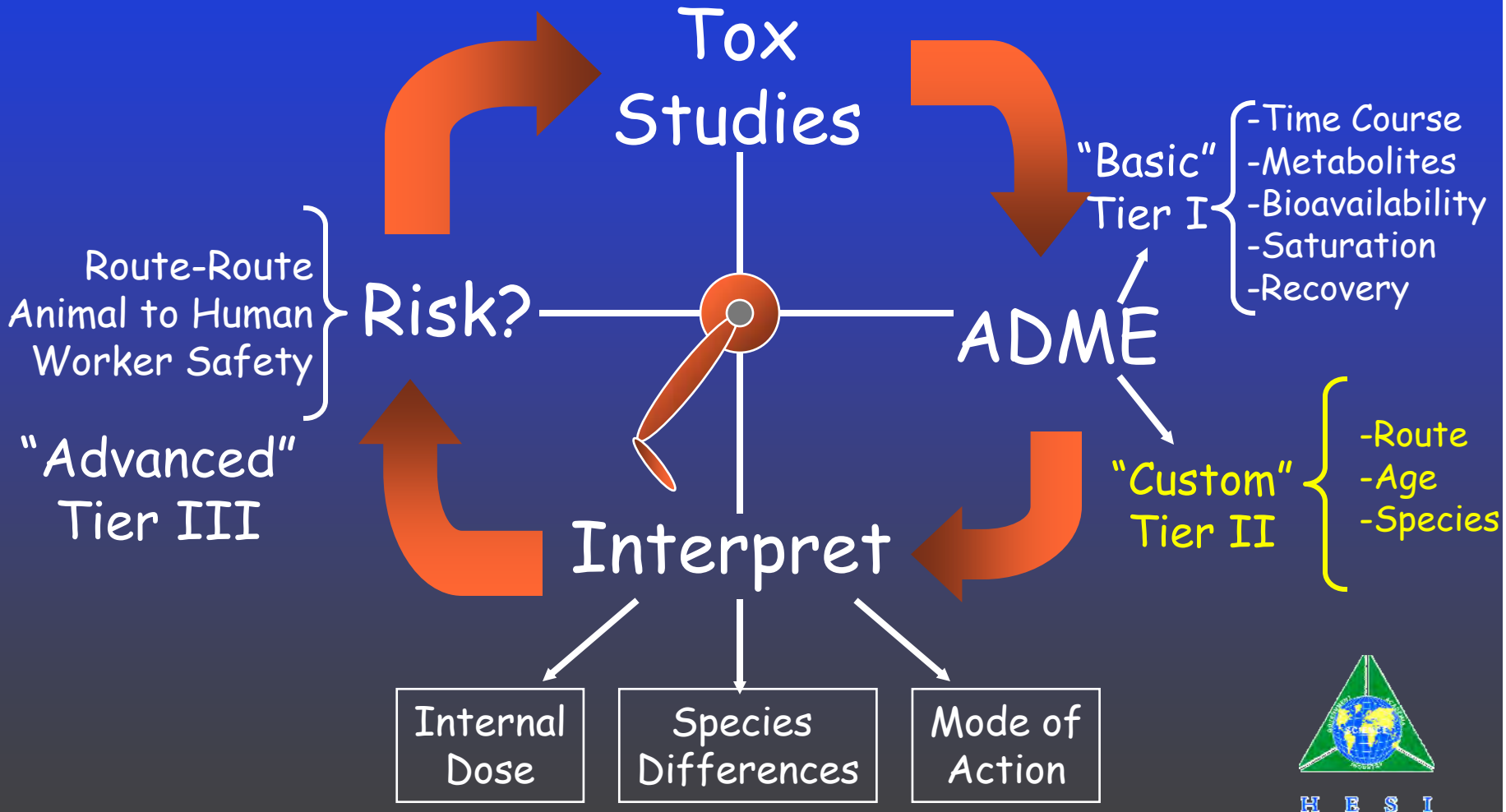
- Dose selection for chronic studies would be improved with a bioavailability assessment.
- This is an example of saturation of oral absorption at doses >7000 ppm in diet:

Plasma Time-Course: Dietary Exposure



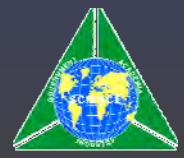
H E S I

Working through the process…



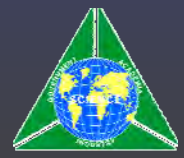
…For Interpretation

- Dose-Response
- Mode of Action
- Internal Dose



"Custom" Tier II Studies

- Non-rodent PK
- Tissue/fluid distribution (including fetus/milk)
- In vitro metabolism: rodents/humans
- Serum protein binding
- Biliary excretion/enterohepatic recirculation



Example: Species Relevance

- The dog is uniquely more sensitive to organic acids like 2,4-D.
- Renal clearance studies suggest that the dog has a low capacity to excrete organic acids.
- Allometric comparison of the pharmacokinetic parameters: volume distribution (Vd), renal clearance (Cl) and plasma half-life ($t_{1/2}$) were conducted across species (including human).
- Conclusion: the dog is an outlier.

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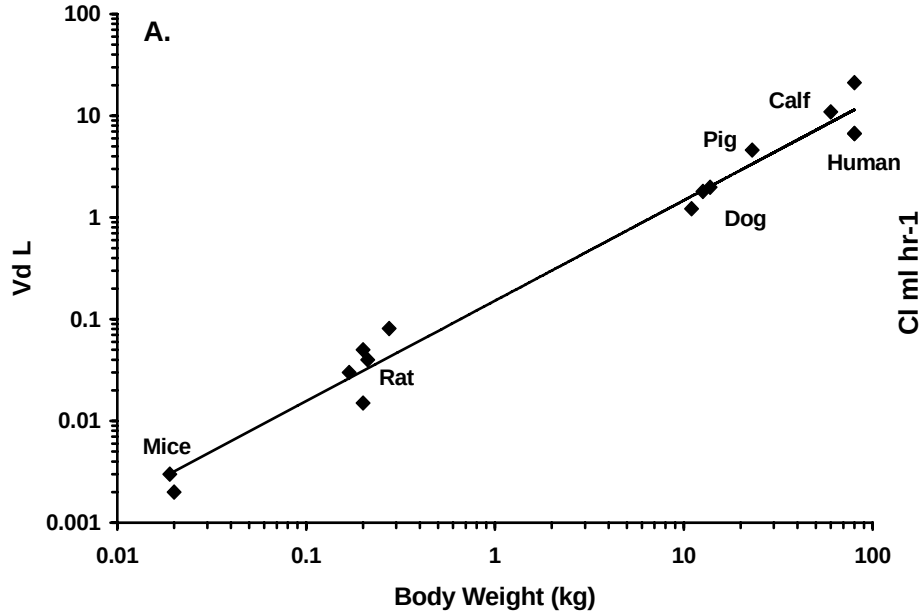
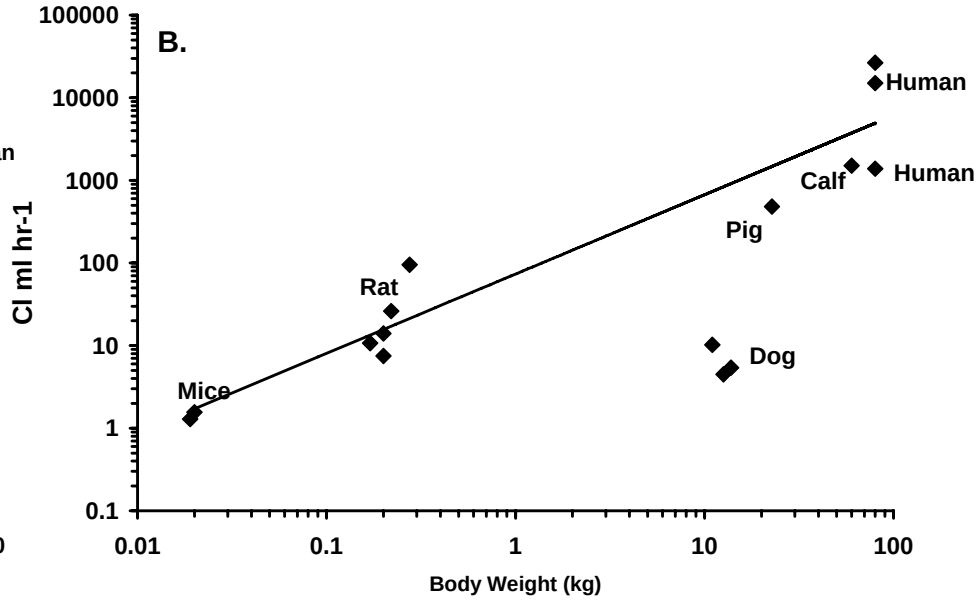
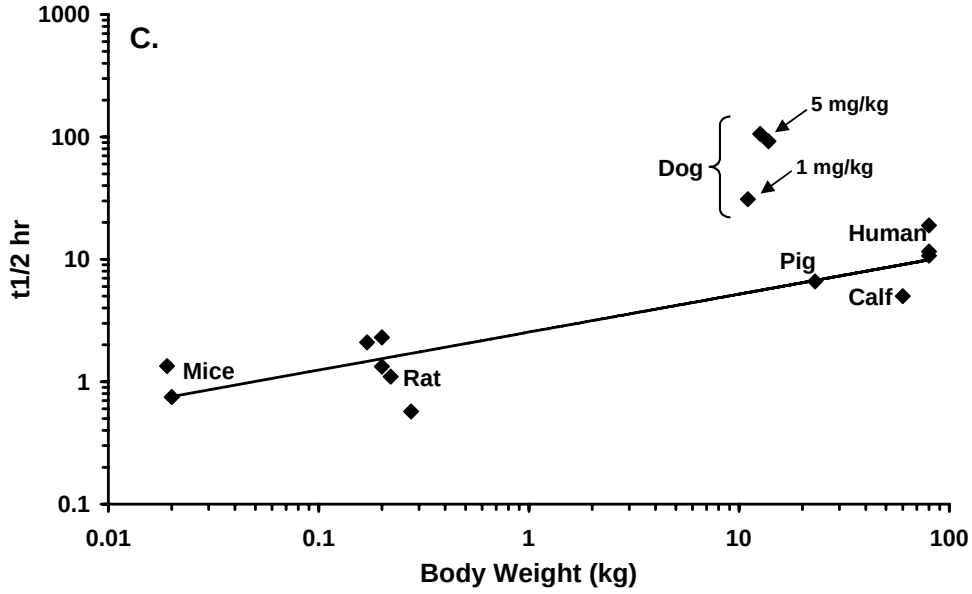
Comparative Species PK







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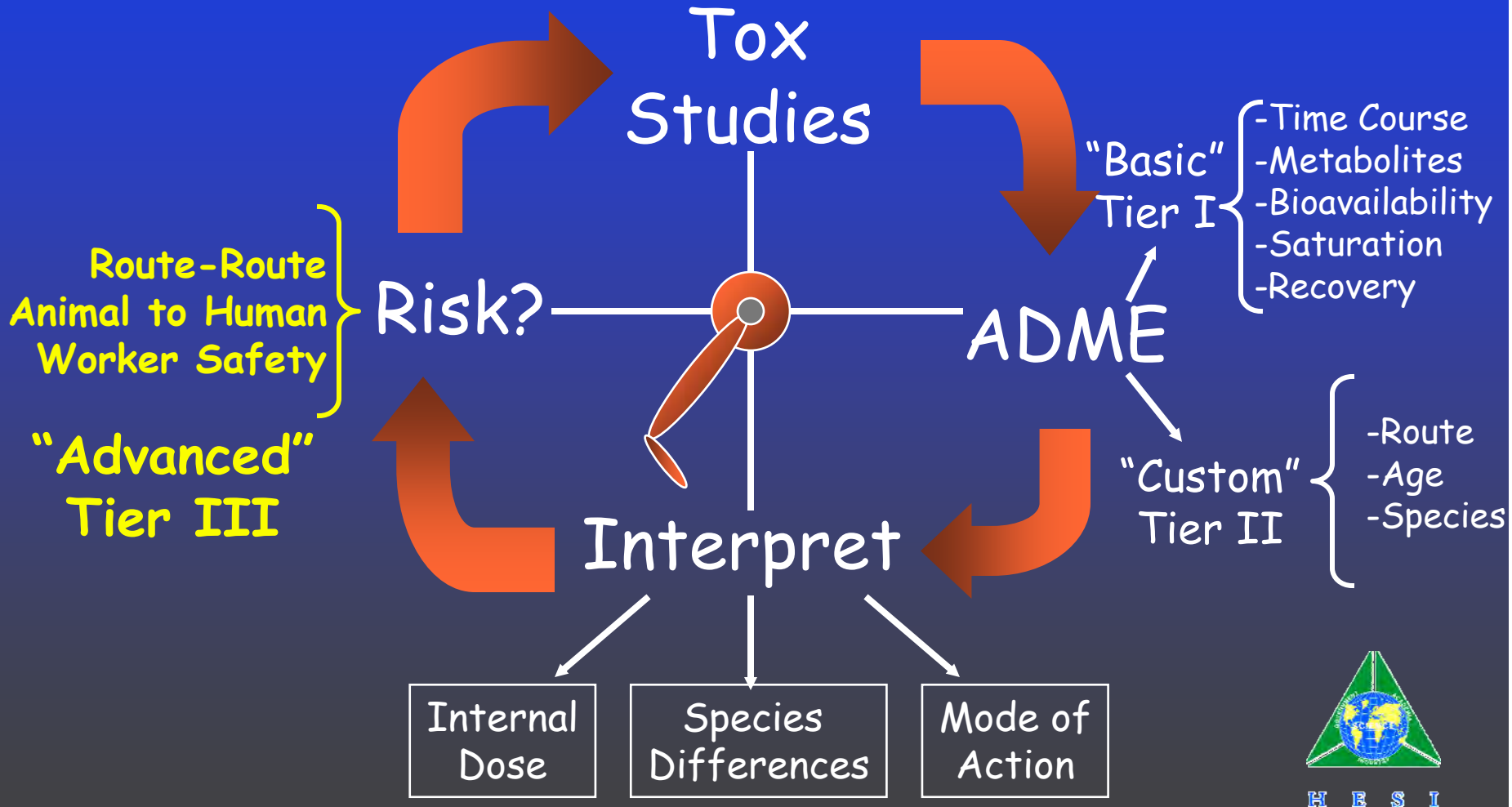
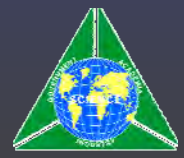
Working through the process…

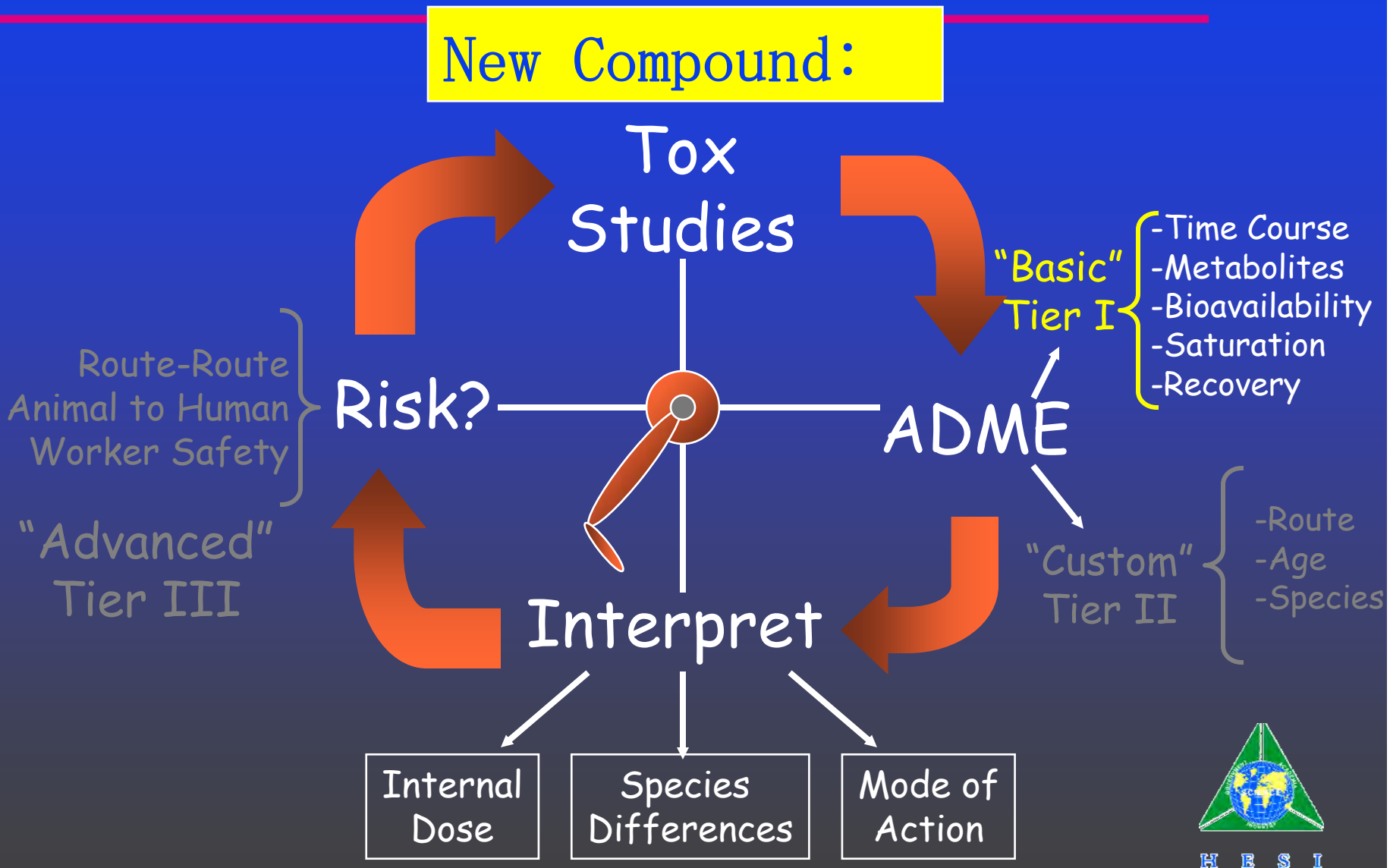


"Advanced" Tier III

- Route-to-Route Extrapolation
  - Dermal
    - » In vitro rat/human
    - » In vivo rat
  - Inhalation
- Biomonitoring
- Human clinical PK

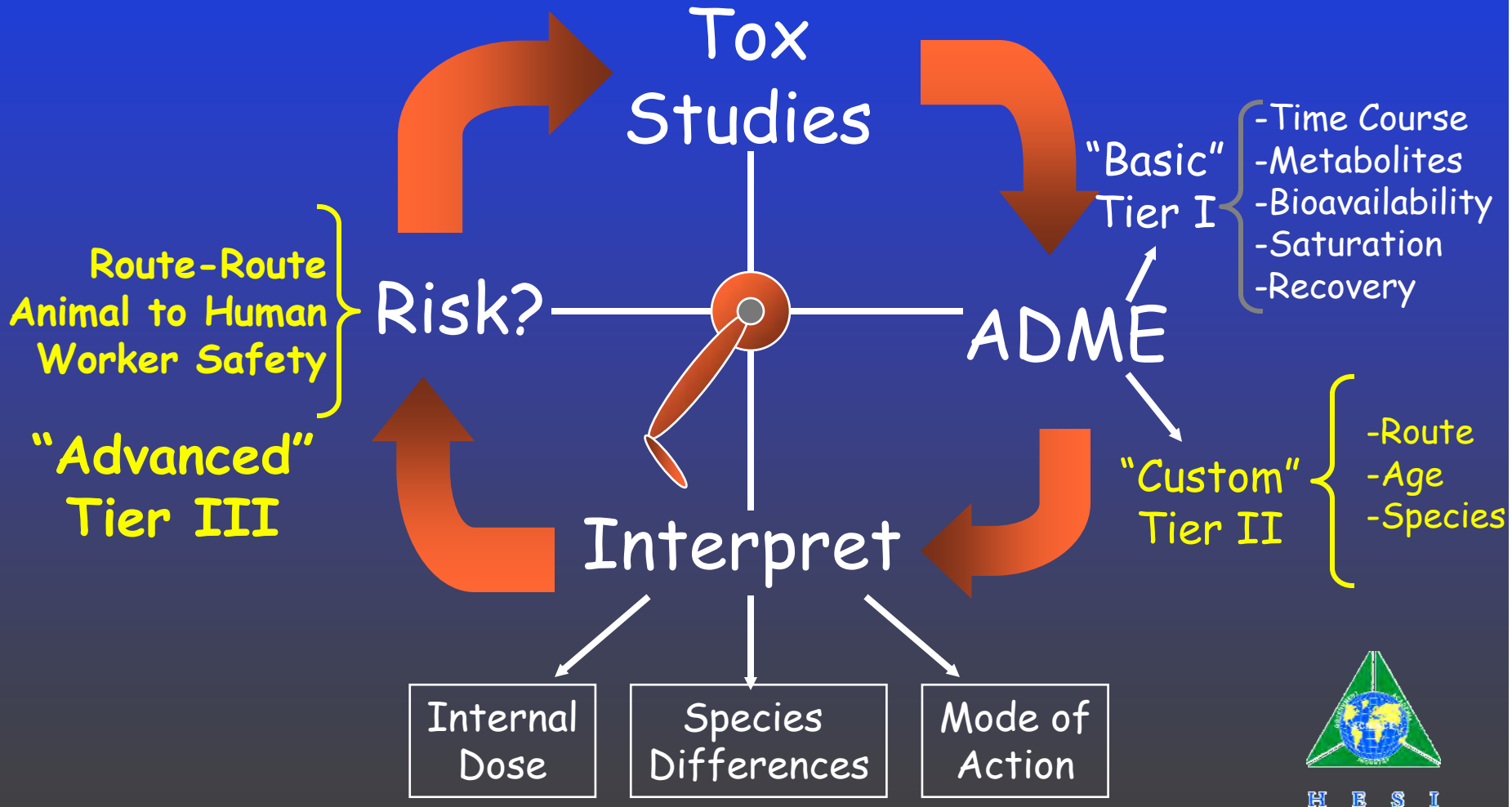


Working through the process…



Working through the process…

Mature Compound:



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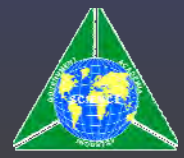
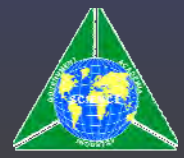
Example Tier III Study: Human dermal absorption

- Dermal is a major exposure route.
- In vitro studies can provide an initial estimate of dermal absorption.
- In vivo studies with human volunteers can establish extent of dermal absorption.
- Direct application for assessing human health risk.



Conclusions/Recommendations

- **To be useful, ADME studies need to:**
  - Help in the design of toxicity studies.
  - Help interpret results from toxicity studies.
  - Help assess risk.



Conclusions/Recommendations (continued)

- **Generalized tiered approach**
  - ***Basic*** (Tier I), which would include data that are crucial for toxicity study design including dose selection, half-life determinations for recovery period determination, and the identification of major metabolites.
  - ***Custom*** (Tier II), which would include data needed for study interpretation, absorbed dose estimates, and duration/route extrapolations.
  - ***Advanced*** (Tier III), which would include data to support the understanding of a compound's mode of action and allow the derivation of pharmacodynamic concordance.

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ADME Task Force Members

Co-Chairs: Hugh Barton (USEPA) and Timothy Pastoor (Syngenta Crop Protection)

- Karl Baetcke (US EPA)
- Jan Chambers (MS State University)
- Janet Diliberto (US EPA)
- Jeff Driver (infoscientific.com)
- Chuck Hastings (BASF)
- Sesh Iyengar (Bayer CropScience)
- Robert Krieger (University of CA, Riverside)
- Bernhard Stahl (Bayer CropScience)
- Chuck Timchalk (Pacific NW National Laboratory)

LIAISONS:

- Alan Boobis (Imperial College London) – Systemic Toxicity Task Force
- Larry Sheets (Bayer Corporation) – Life Stages Task Force

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AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

Systemic Toxicity Task Force

John E. Doe, PhD
Global Head of Health Assessment
Syngenta

November 16, 2005

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The Comet

Are we stretching our technology too far?

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Are we stretching our technology too far?

The Nimrod

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The Comet

The Airbus

Are we stretching our technology too far?

The Nimrod

The Risk Assessment Matrix: Duration of Exposure

	1 Day	2-30 days	1-6 months	>6 months

The Risk Assessment Matrix: Life Stages

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult (~Systemic)				
Elderly				

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The Risk Assessment Matrix: Life Stages

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult (~Systemic)			90d rat	24mth rat
Elderly				

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The Risk Assessment Matrix: Life Stages

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult (~Systemic)			90d dog 90d rat	1yr dog 24mth rat
Elderly				

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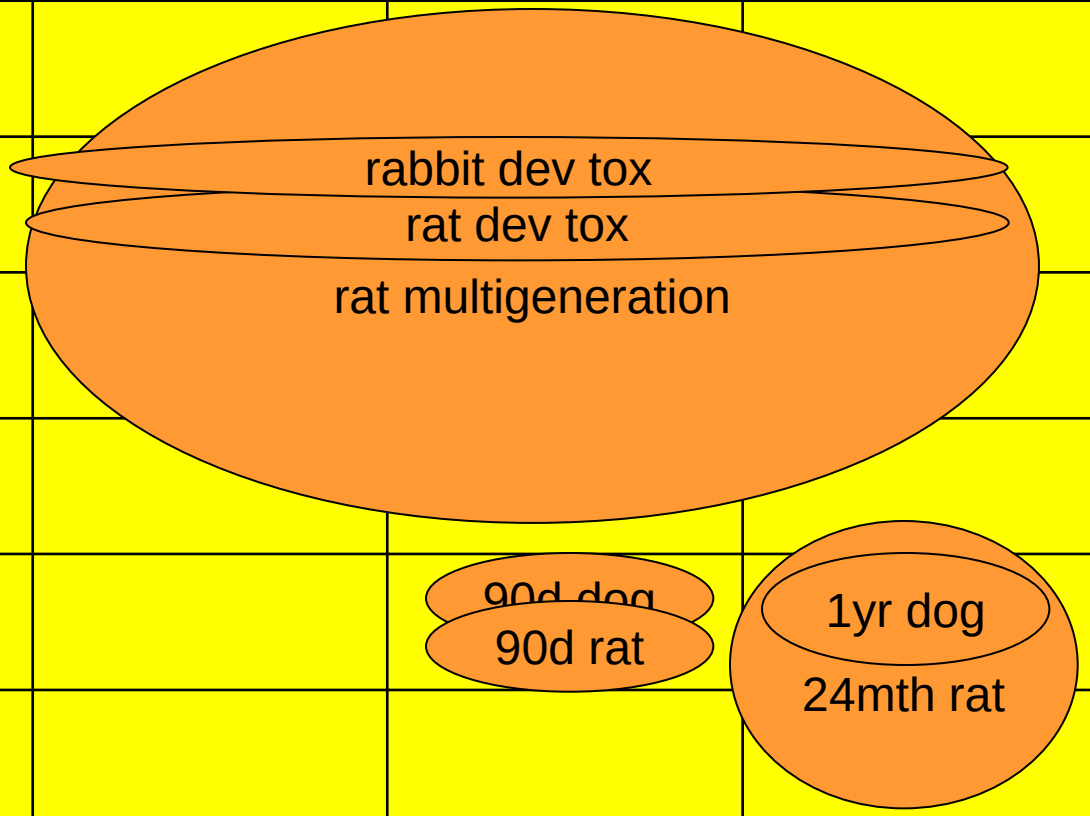
The Risk Assessment Matrix: Life Stages

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult (~Systemic)				
Elderly				



Concerns with Current Testing

- Shorter term durations of human exposure are not adequately covered
- Special endpoints such as neurotox and immunotox are not covered in the basic studies
- What is the value of the dog?
- Need more ADME and kinetic data to help with extrapolations

Systemic Toxicity Basic Principles

- Suite of studies designed to cover range of human exposure durations
- Indicators (trigger effects) in the basic studies which, if negative, give a high level of confidence of no relevant adverse effects
- Second tier studies to more precisely quantify such effects, if relevant for risk assessment

28-day study in rat

- ADME
- Clinical chemistry and hematology
- Triggers for neurotoxicity, immunotoxicity, endocrine effects
- Histopathology
- 14-day recovery group

Using the Tiered Approach - Neurotoxicity

- Evidence of neurotoxicity from FOB, motor activity, pathology
- Tier 1 very similar to current neurotoxicity protocols

and

- Low margin of exposure

then

- Design appropriate study to get more information on effect and dose response

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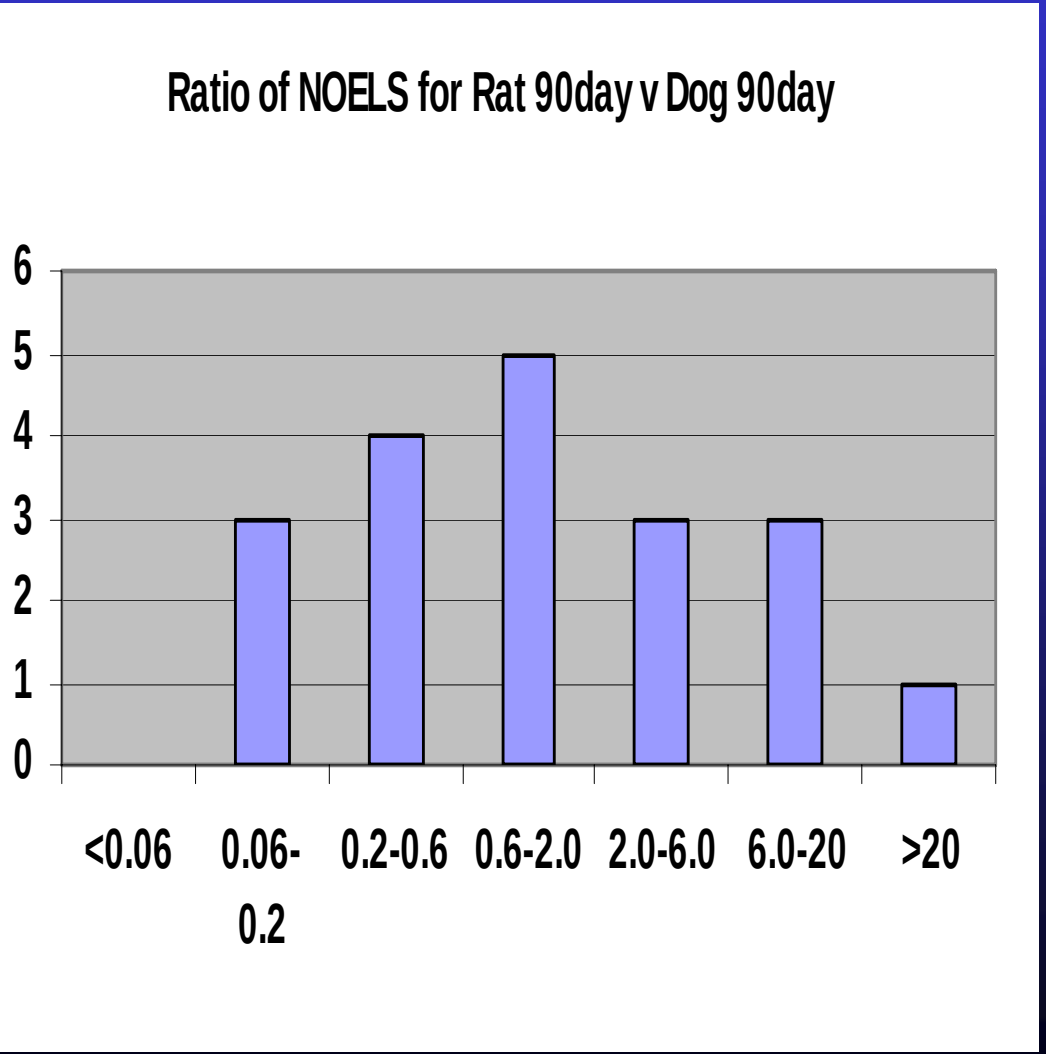
Is the dog necessary?

- More sensitive species assumed to be relevant
- Distribution of relative sensitivities
- Dog more sensitive c.35% cases
- Need to include the dog



90-day dog study

Repeated ADME evaluation (e.g., on day 1, weeks 4 and 13)

- Repeated Clinical Chemistry and Haematology (e.g., pre-study, weeks 4 and 13)
- Physiological evaluation (e.g., cardiovascular, respiratory)
- Dermal dosing for ADME (during preliminary study for dose-setting)

One-day human exposure

- No new study required if
  - in-life observations on day 1 in dog 90-day study from key effects

  OR

  - adequate MoE from 28-day rat and 90-day dog
- Otherwise
  - refine exposure assessment
  - consider need for acute study in rat or dog

Exposure over 6 months

- 12-month study in rat as an interim kill in 24-month carcinogenicity study
- 24-month study for carcinogenicity and for elderly life stage
- Mouse study shown to add no significant extra data apart from high dose liver tumours, usually discounted
- Compounds should be shown to be not genotoxic

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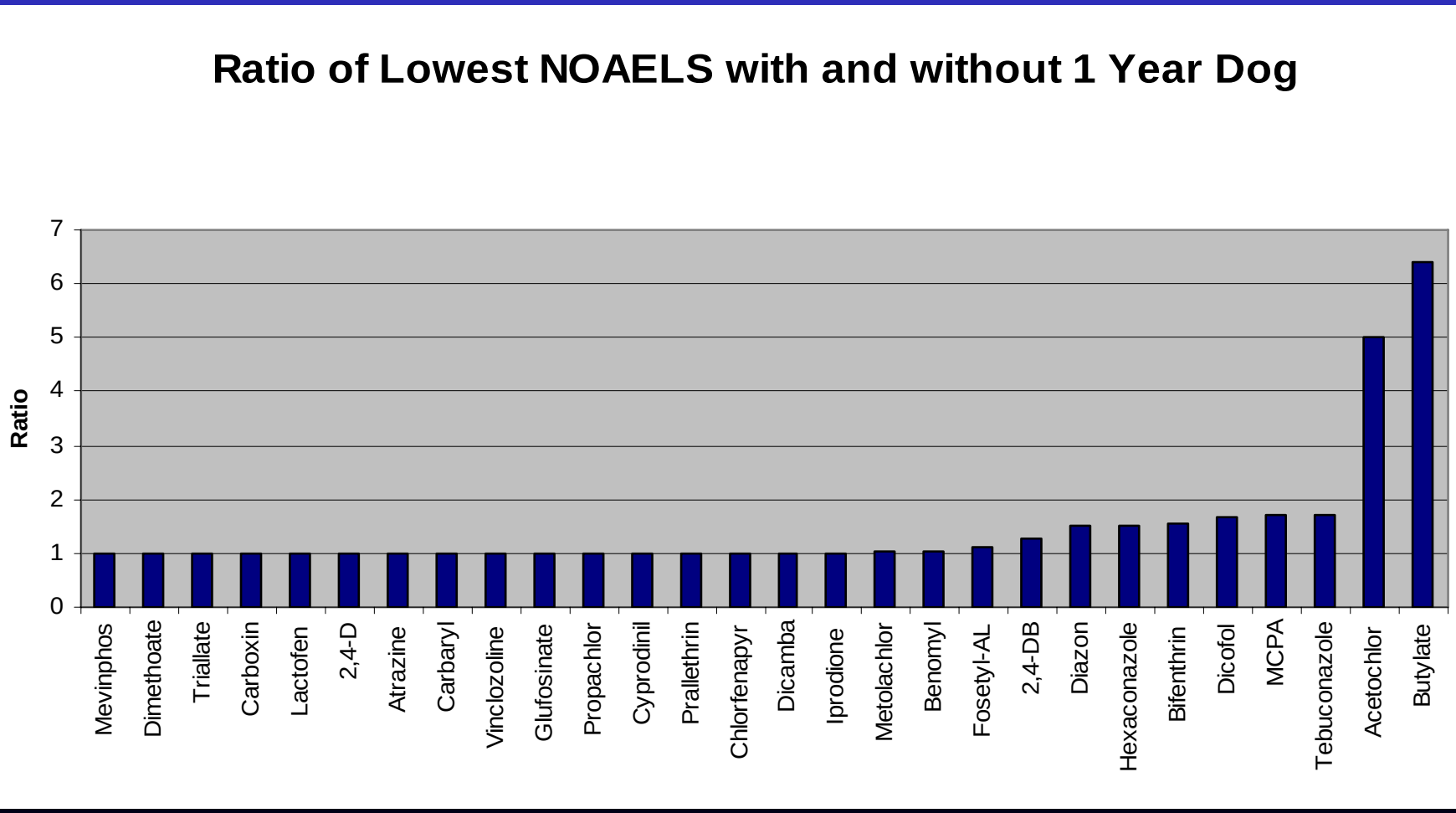
Is the 12-month dog study necessary?



Route to Route

- Understanding of “internal dose” built in to all studies from ADME
- Dermal and inhalation absorption studies
- Dermal and inhalation local toxicity studies
- Repeat dose dermal toxicity studies have dosimetric and welfare concerns

The Risk Assessment Matrix: Systemic Toxicity

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult				
Elderly				

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The Risk Assessment Matrix: Systemic Toxicity

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult		28d rat		
Elderly				

The Risk Assessment Matrix: Systemic Toxicity

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult		28d rat	90d dog	
Elderly				

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The Risk Assessment Matrix: Systemic Toxicity

	1 Day	2-30 days	1-6 months	>6 months
Preconception				
Embryo/fetal				
Newborn/ preweaning				
Childhood				
Adult	1d rat or dog	28d rat	90d dog	
Elderly				

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The Risk Assessment Matrix: Systemic Toxicity

	1 Day	2-30 days	1-6 months	>6 months
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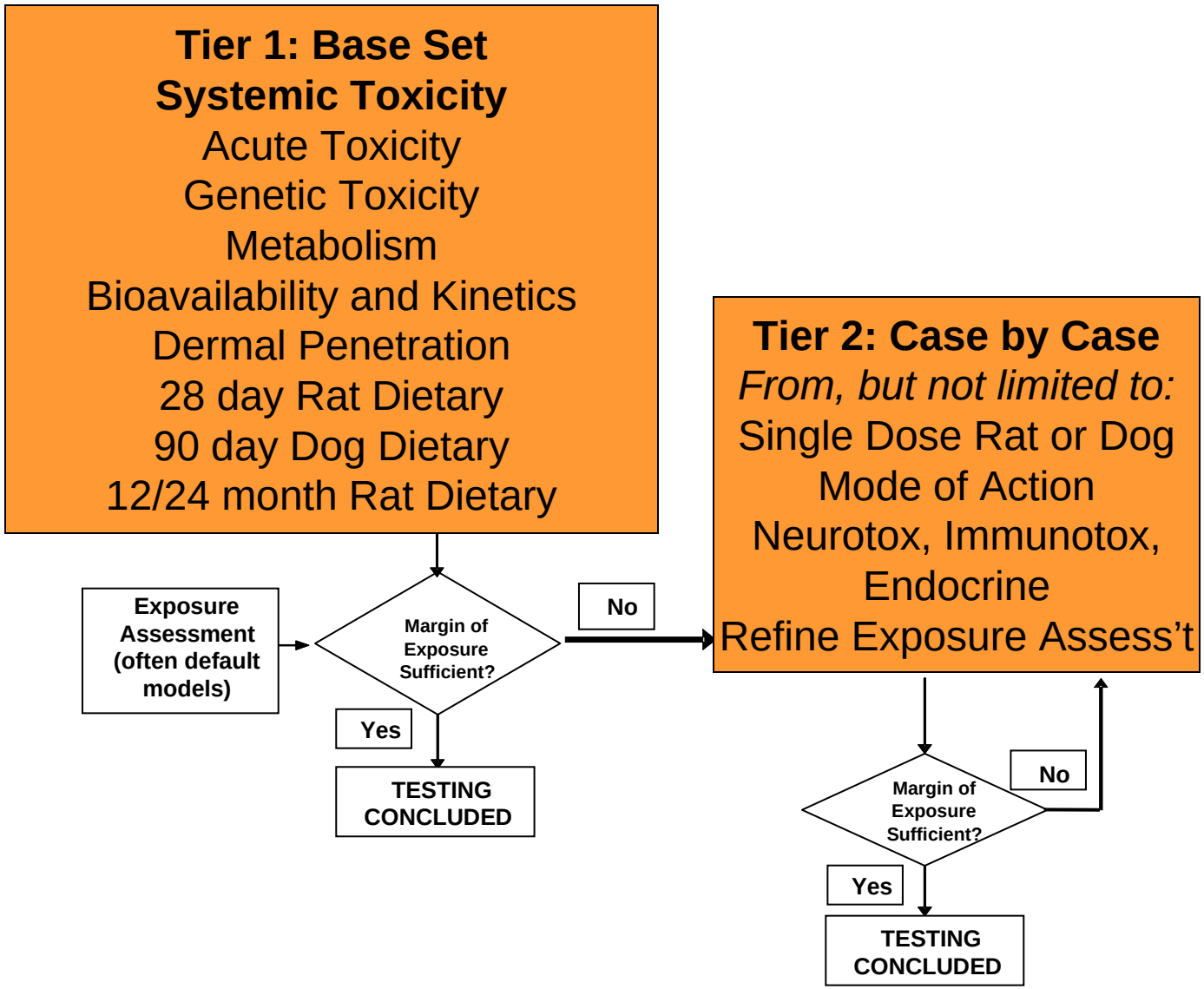
Adult	1d rat or dog	28d rat	90d dog	24mth rat
Elderly				


Tier 1: Base Set
Systemic Toxicity
Acute Toxicity
Genetic Toxicity
Metabolism
Bioavailability and Kinetics
Dermal Penetration
28 day Rat Dietary
90 day Dog Dietary
12/24 month Rat Dietary
Exposure Assessment (often default models)
Margin of Exposure Sufficient?
No
Yes
TESTING CONCLUDED
Tier 2: Case by Case
From, but not limited to:
Single Dose Rat or Dog
Mode of Action
Neurotox, Immunotox, Endocrine
Refine Exposure Assess't
Margin of Exposure Sufficient?
No
Yes
TESTING CONCLUDED

Comparison of Number of Animals Required for Systemic Toxicity

Animals	Current paradigm	New paradigm
rats	680	720
mice	520	0
dogs	72	48
Total	1272	768

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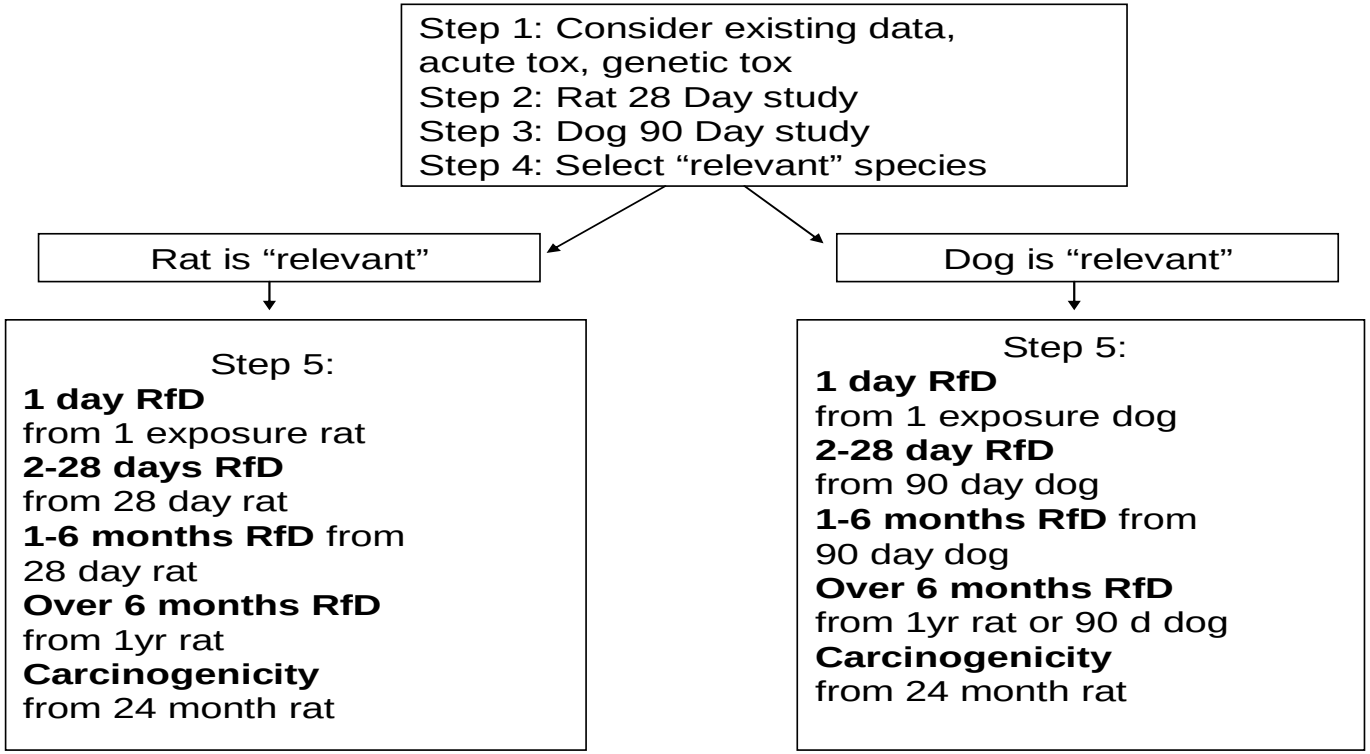
Stepwise approach



What is the output of the safety assessment?

- A qualitative and quantitative characterisation of the hazard potential of the compound
- A series of Reference Doses
- 1-day exposure
  - 28-day rat or 90-day dog or 1-day rat or dog
- 2-28 days exposure
  - 28-day rat or 90-day dog
- 1-6 months exposure
  - 90-day dog or 28-day rat
- Over 6 months exposure
  - 24-month rat or 90-day dog
- Assessment of carcinogenicity
  - Genetic toxicity and 24-month rat

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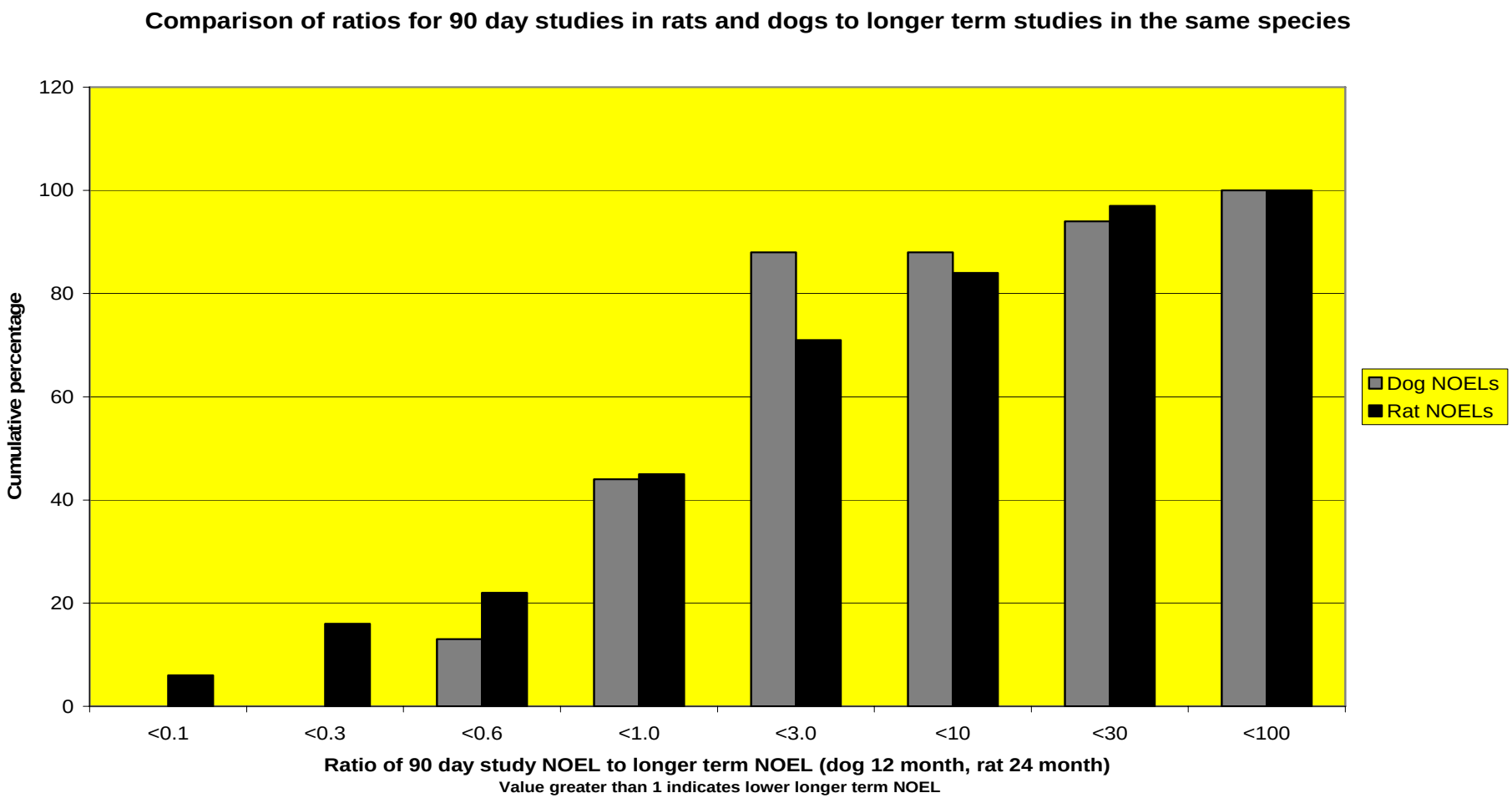
Why does the NOEL vary at different time points?



Rozman and Doull* identified the factors which underlie the toxicokinetics and toxicodynamics:

Toxicokinetics	Toxicodynamics
-Absorption	-Injury
-Elimination	-Recovery
-Distribution	-Adaptation
-Biotransformation	-Repair
-Excretion	-Reversibility

*Rozman, K.K. and Doull, J. (2000) Dose and time as a variable of toxicity. Toxicology: *144*, 169-178

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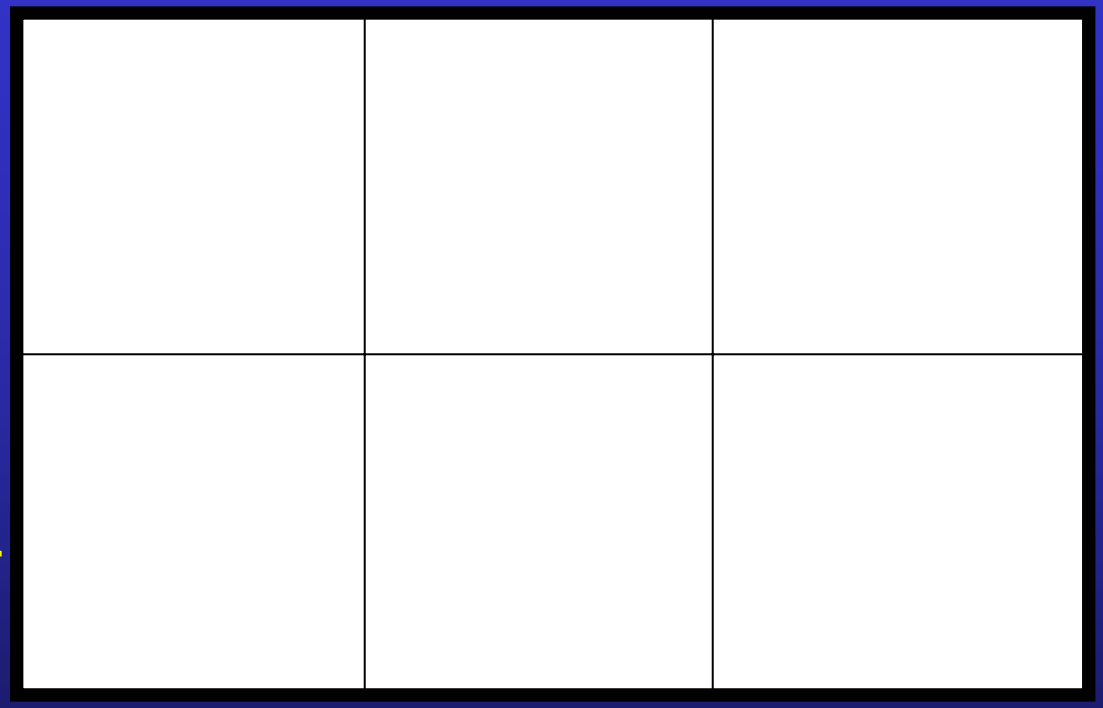
Effect depends only on current internal dose.

Resident effect

Dynamics

Effect depends on current and past internal dose -- "history" effect

Damage and repair



Rapid elimination

Slower elimination

Accumulation

Kinetics

What determines the relationship between NOELS for different exposure durations?

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H E S I

Effect depends only on current internal dose.

Resident effect

Dynamics

Effect depends on current and past internal dose -- "history" effect

Damage and repair

ADI = ARfD		

Rapid elimination | **Slower elimination** | **Accumulation**

Kinetics

What determines the relationship between NOELS for different exposure durations?

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H E S I

Effect depends only on current internal dose.

Resident effect

Dynamics

Effect depends on current and past internal dose -- "history" effect

Damage and repair

ADI = ARfD		**ADI = ARfD/ # doses**

Rapid elimination | **Slower elimination** | **Accumulation**

Kinetics

What determines the relationship between NOELS for different exposure durations?

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H E S I

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Damage and repair

ADI = ARfD		**ADI = ARfD/ # doses**
		ADI <<< ARfD

Rapid elimination | **Slower elimination** | **Accumulation**

Kinetics

What determines the relationship between NOELS for different exposure durations?

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H E S I

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Dynamics

Effect depends on current and past internal dose -- "history" effect

Damage and repair

ADI = ARfD	**ADI < ARfD**	**ADI = ARfD/ # doses**
ADI < ARfD		**ADI <<< ARfD**

Rapid elimination | **Slower elimination** | **Accumulation**

Kinetics

What determines the relationship between NOELS for different exposure durations?

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H E S I

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Resident effect

Dynamics

Effect depends on current and past internal dose -- "history" effect

Damage and repair

ADI = ARfD	**ADI < ARfD**	**ADI = ARfD/ # doses**
ADI < ARfD	**ADI << ARfD**	**ADI <<< ARfD**

Rapid elimination | **Slower elimination** | **Accumulation**

Kinetics

What determines the relationship between NOELS for different exposure durations?

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H E S I

Resident effect

Dynamics

Damage and repair

The highest spike	Highest total exposure within DT90 window (resulting in the max. internal dose).	Total exposure (AUC)
Frequent spikes above a threshold	Highest total within a time-window whose duration is a determined by DT90 and repair rate.	Total exposure (AUC)

Rapid elimination | Slower elimination | Accumulation

Kinetics

What exposures are of greatest concern?

How do we deal with varying or intermittent exposures?

The time weighted average daily dose (TWADD) for any given portion of the exposure should not exceed the relevant reference dose.

How do we deal with varying or intermittent exposures?

The time weighted average daily dose (TWADD) for any given portion of the exposure should not exceed the relevant reference dose.

To expand this:

- **No single day's exposure should be above the 1-day RfD, *and***
- **The TWADD for any period of 2-28 days should not exceed the 2-28 days RfD, *and***
- **The TWADD for any period of 1-6 months should not exceed the 1-6 months RfD, *and***
- **The TWADD for any period of 6 months should not exceed the over-6 months RfD.**

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- **The TWADD for any period of 1-6 months should not exceed the 1-6 months RfD, *and***
- **The TWADD for any period of 6 months should not exceed the over-6 months RfD.**

Operates for compounds across the matrix as the relationship between the RfDs will reflect their properties.

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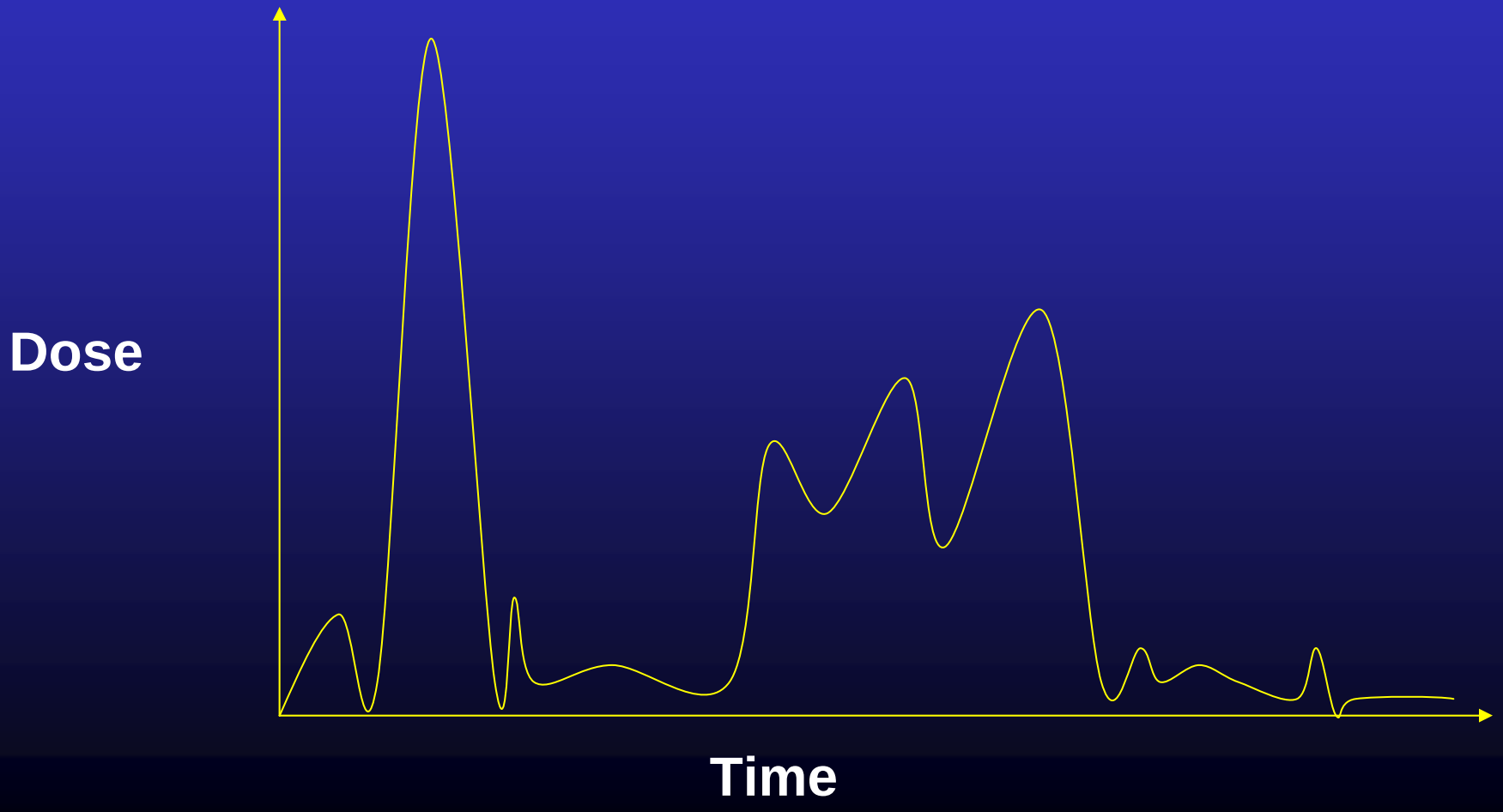
How do we deal with varying or intermittent exposures?



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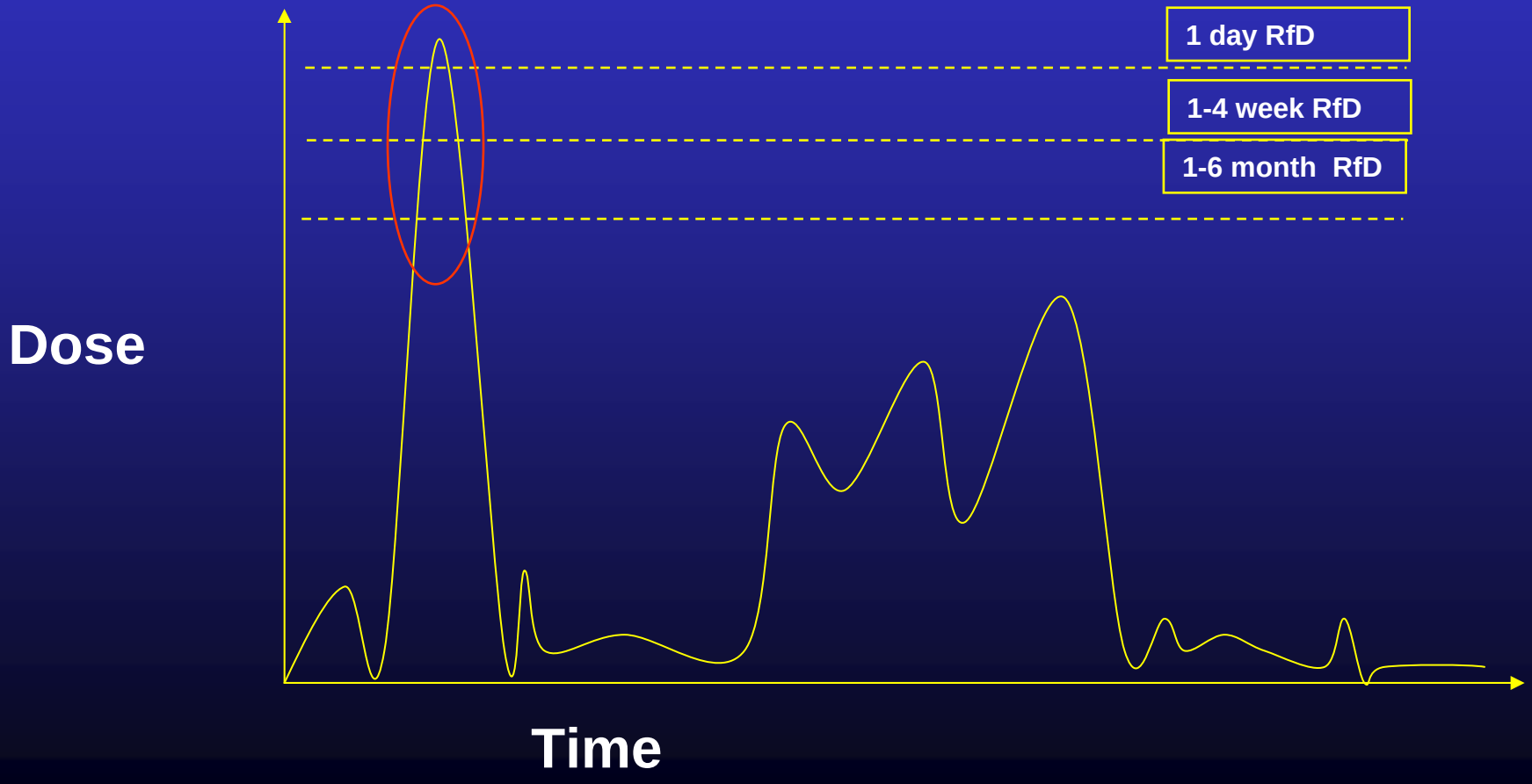

HESI

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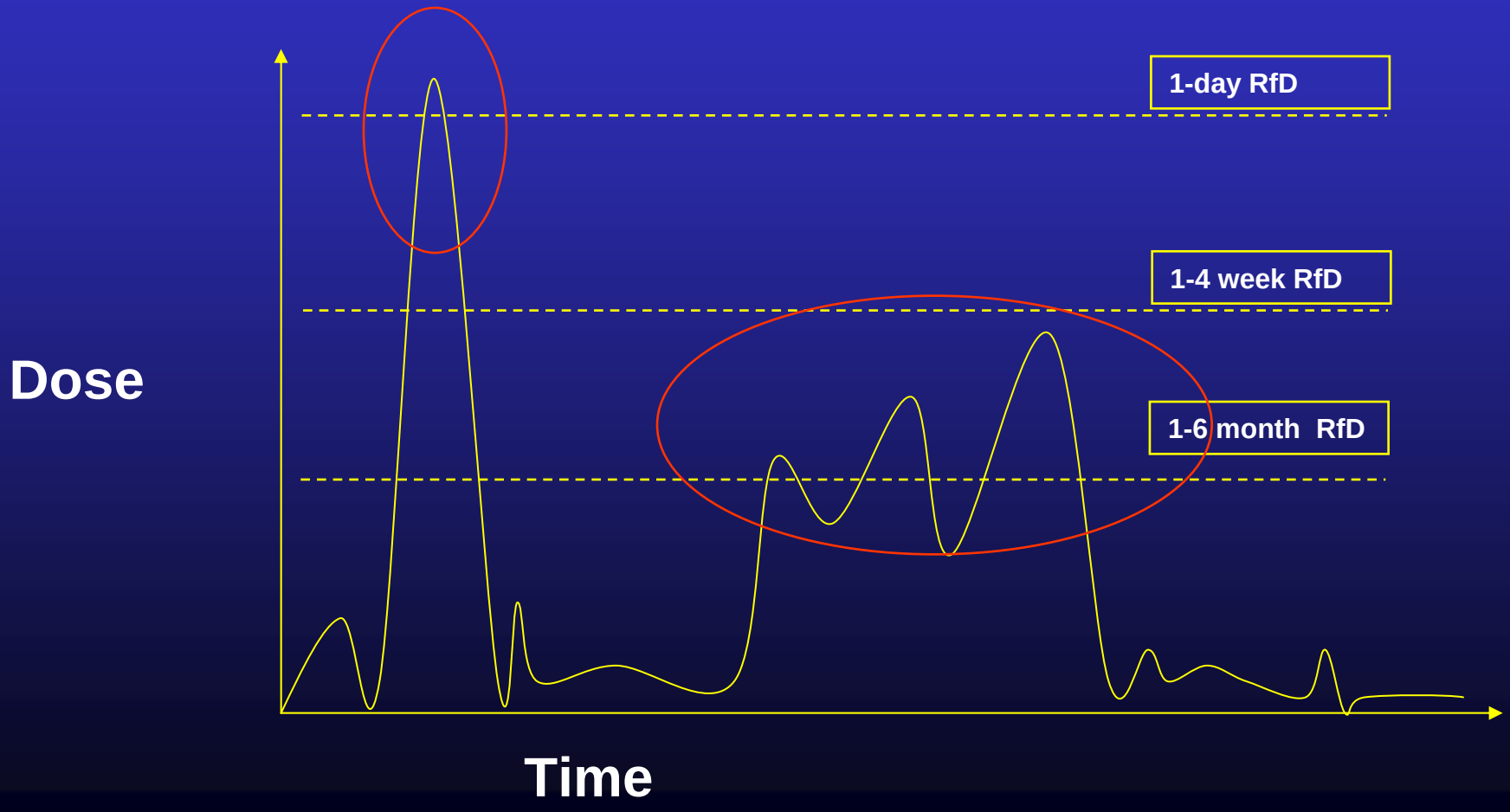

ACSA Proposal Addresses Concerns with Current Testing

- Shorter term durations of human exposure are adequately covered
- Special endpoints such as neurotox and immunotox are covered in the basic studies
- The value of the dog is to determine more sensitive species
- More ADME and kinetic data to help with extrapolations
- Reduced number of animals required
- Greater understanding of characteristics of chemical

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AGRICULTURAL CHEMICAL SAFETY ASSESSMENT

Integration of Approaches

Neil G. Carmichael, PhD
Bayer CropScience

November 16, 2005
Nice, France

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.

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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

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)

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.**

"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.

Potential Reduction in Animal Usage: Systemic Toxicity Testing

Animals	Current Paradigm	New Paradigm
Rats	680	720
Mice	520	0
Dogs	72	48
Total	**1272**	**768**

"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, immuno-toxicity, 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)

Potential Reduction in Animal Usage: Life Stages Testing

Current testing guidelines:

• 2 species developmental tox *(parental)*	160
• 2-gen reprotox *(parental and offspring)*	2600
• developmental neurotox *(parental and offspring)*	1280
• developmental immunotox *(parental and offspring)*	1280
	5320

Tier 1 testing only:

• 1 species developmental tox *(parental)*	80
• extended 1-gen reprotox *(parental & offspring)*	1400
	1480

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[1]
90-day Dog Dietary
12-month Chronic/24-month Carcinogenicity Rat Dietary[2]

Life Stages Data for Tier 1[1,3]

F1-Extended One-Generation Reprotox Study
Rabbit Developmental Toxicity Study

Exposure Assessment (often default models)

Margin of Exposure Sufficient?

No

Yes

TESTING CONCLUDED

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

Margin of Exposure Sufficient?

No

Yes

TESTING CONCLUDED

[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

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

Potential Reduction in Animal Usage: TOTAL

	Current Paradigm	New Paradigm
Life Stages	5320	1480
Systemic Tox	1272	768
Total	**6592**	**2248**

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.

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?

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AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

Life Stages Task Force

Lorraine Irvine, BSc, DABT
toXcel International Ltd.

November 16, 2005

HESI

ILSI Health and Environmental Sciences Institute

Life Stages Task Force

Dr. Ralph Cooper (Co-Chair)
US EPA NHEERL

Dr. Sue Barlow
Consultant

Dr. Karin Bentley
DuPont Crop Protection

Dr. Ann Blacker
Bayer CropScience

Dr. Angela Brady
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US EPA NHEERL

Dr. David Eisenbrandt
Dow AgroSciences

Dr. Penny Fenner-Crisp
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Ms. Lorraine Irvine
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Dr. Herman Koeter
European Food Safety Authority

Dr. Abby Li
Exponent

Dr. Larry Sheets
Bayer Corporation

Dr. Gerrit J.A. Speijers
RIVM, Natl. Inst. Public Health & Envt.

Dr. Karen Whitby
US EPA Office of Pesticide Programs

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

Conolly, R.B. et al., Stimulating research to improve the scientific basis of risk assessment. Toxicol Sci. 49: 1-4, 1999.

Goodman, J.I. The traditional toxicologic paradigm is correct: dose influences mechanism. Environ Health Perspect. 106, Suppl. 1: 285-288, 1998.

Food-use Pesticide: Current Testing

Required

- Prenatal developmental: 2 species
- 2-generation reproduction: 1 species

Conditional / Case-by-case

- Developmental neurotoxicity
- Endocrine modulation assessment
- Developmental immunotoxicity
- (for EU) TK at selected life stages

Problems with Current Testing

- 'Inevitable' progression to conditional / case-by-case studies
- High dose complications
- Relevance of route of administration
- Duplication of exposures
- Increasing use of animals
- Concern not addressing key life stages

Life Stages Review Tasks

- Reviewed existing tiered testing approaches
- Examined existing screens (including *in vitro)* and their value in risk assessment
- Considered ADME and TK needs and their integration into life stages evaluation
- Risk assessments for different life stages

Examples of Tiered Approach

Chemicals

- OECD SIDS and US EPA HPV
- NONS (92/32/EEC) or TSCA PMN

Pharmaceuticals

- ICH (human)
- VICH (veterinary drug residues)

Principle of tiered testing accepted by public/ regulators

Considerations of Life Stages Tiered Approach

Risk assessments *drive* the studies

Objectives of Tier 1

- Determine effects on reproduction
- Determine sensitivity of life stages (other than young adult) to major toxicities

Considerations of Life Stages Tiered Approach

Base set (Tier 1)

- Conduct exposure estimates (route, duration, amount)
- Consider life stages to be protected
- Use relevant group sizes for biological / statistical confidence in results
- Include key indicators (triggers) which, if negative, give a high level of confidence of no adverse effects ***If positive → Tier 2***
- Conduct risk assessment ***If low MOE → Tier 2***

Considerations of Life Stages Tiered Approach

Tier 2

- Exposure studies or refined estimates
- Focused second tier studies to quantify / characterize specific effect at biologically relevant doses
- Conduct risk assessment

Considerations of Life Stages Tiered Approach

Risk assessments involving life stages

- Dietary: acute and chronic
  - Infants, 1-6, 7-12, 13-19, >55 years
- Residential: short-term, intermediate, long-term
  - Toddlers, adults (females 13+ years)
- Occupational: short-term, intermediate, long-term
  - Females 13+ years, males 13+ years

Base Set (Tier 1) Life Stages Studies

- F1-'extended' one-generation reproduction study in one species

  (most probable = rat)

- Developmental toxicity study in second species

  (most probable = rabbit)

Considerations for Base Set (Tier 1) Testing

- Consider systemic toxicity, ADME, and other relevant data → refine toxicity endpoints for inclusion
- Administration by route of relevant human exposure (dietary preferred over gavage: adjust dosage to dietary intake)
- ADME to determine “internal dose” and kinetics
- Relate “internal dose” in risk assessment

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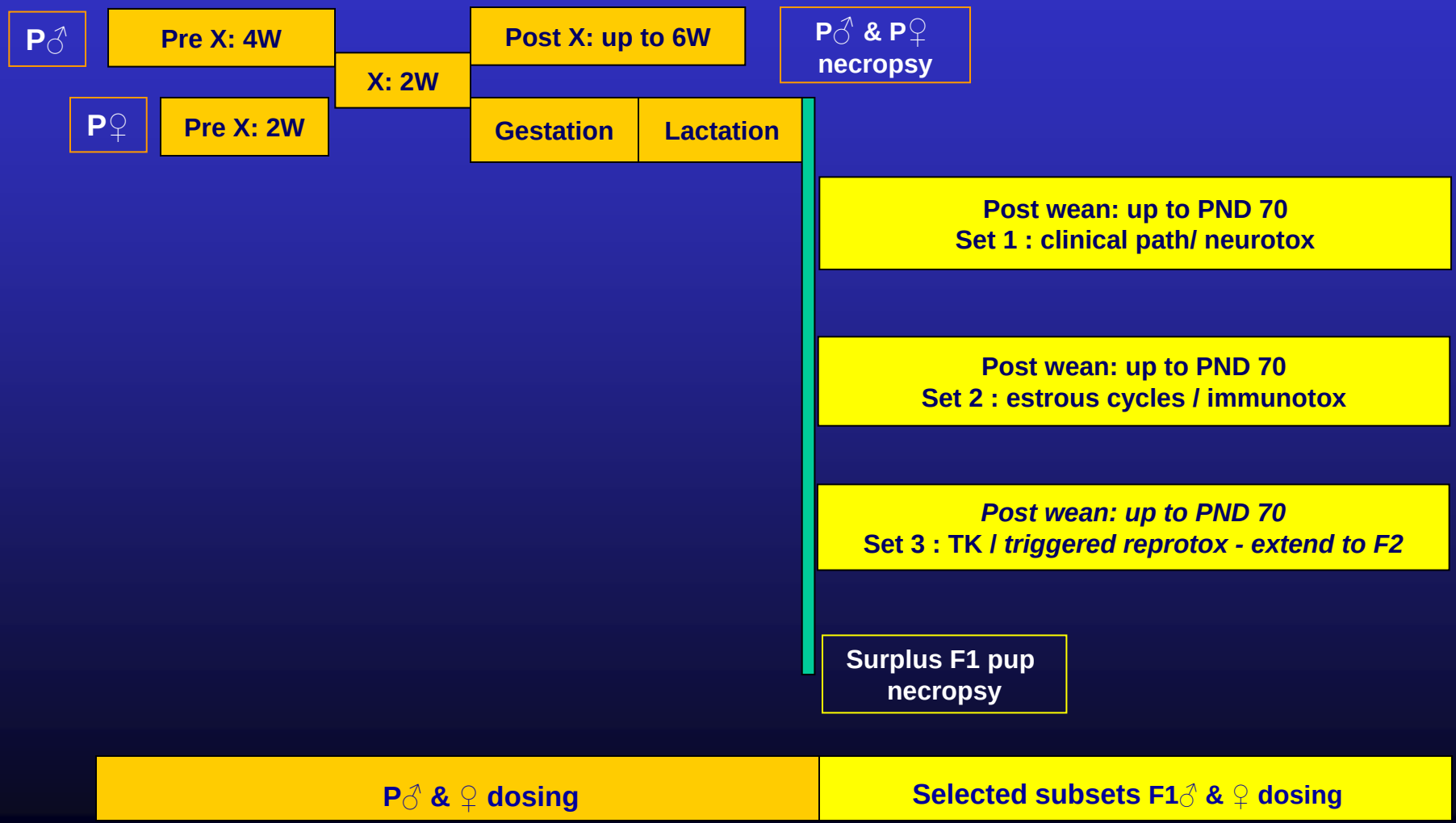
F1-'extended': 1-Gen Study



F1-'extended': 1-Gen Study

P generation

- N = sufficient for 20 litters / group
- Use ADME / TK in dose setting
- TK estimates at key stages of gestation / lactation
- Comprehensive repro evaluations
- Detailed histopathology on subset
- Use 'markers' for other toxicities identified from systemic toxicity studies
- Consider preliminary *in vitro* tests for potential mechanisms and refinement of endpoints

F1-'extended': 1-Gen Study

F1 generation (continues dosing to PND 70)

- Pre-wean (AG, sex, body weight, clinical observations)
- At PND 21, select **3 subsets** (each **1♂ and 1♀**)
- Surplus PND 21 pups (organ weight, histopathology, including neurological tissue)
- **Set 1**: Motor activity, FOB, neuropathology, clinical chemistry, hematology, thyroid hormones, detailed histopathology
- **Set 2**: estrous cycles, immunotox (SRBC antibody response; triggered phenotypic analysis of lymphocytes (if +) or natural killer cell assay (if -))
- **Set 3**: TK, endocrine, repro, and, *if triggered,* continue dosing beyond PND 70 and mate for F2 generation

Developmental Toxicity Study

Single developmental toxicity study in different species (likely rabbit)

- Design based on OPPTS 870.3700 / OECD 414
- Relevant human exposure route, but with **dietary** preferred over **gavage**
- Use ADME / TK in dose setting and measure TK
- Use ‘markers’ for toxicities identified from other studies, including histopathology
- Consider preliminary *in vitro* tests for potential mechanisms and refinement of endpoints

Potential Reduction in Animal Usage

Current testing guidelines

• 2 species developmental tox *(parental)*	160
• 2-gen reprotox *(parental and offspring)*	2600
• Developmental neurotox *(parental and offspring)*	1280
• Developmental immunotox *(parental and offspring)*	1280
	5320

Tier 1 testing only

• 1 species developmental tox *(parental)*	80
• Extended 1-gen reprotox *(parental & offspring)*	1400
	1480
(*If 2nd generation triggered*)	*(+1200)*

Considerations for Tier 2 Testing

Low MOE or triggers from Tier 1 testing lead to focused Tier 2 testing

- Case-by-case special studies to characterise effect(s)
- Conducted at relevant (*not MTD*) doses
- May include: further neurotox, immunotox, or endocrine tests, late-in-life sensitivity, fetal / neonatal ADME, detailed mode-of-action endpoints
- May include : 2-gen repro and/or second species developmental tox

Gains from Modified Approach

- Use of toxicokinetic and young adult systemic toxicity data in designing studies
- Assessment of systemic toxicity in young adults as a consequence of pre- and early postnatal exposure
- Developmental neurotoxicity assessment
- Developmental immunotoxicity assessments
- Assessment of multiple types of outcomes from the same population of animals
- Fewer numbers of animals used

Concessions under New Approach

- Shorter pre-mating exposures for males (4 weeks) and females (2 weeks) than the current 10-week period (although considered adequate for fertility assessment).
- Only mating F1 animals and producing an F2 generation *if triggered.*
- No prenatal developmental toxicity study in the rat.

Vicki L. Dellarco, Ph.D.
Office of Pesticide Programs
US Environmental Protection Agency

Next Generation of Toxicology Testing Perspective on ACSA

Topics

- Challenges in Pesticide Health Risk Assessment
- Why Reconsider Current Data Requirements
- New ACSA Tiered Testing Approach
- Other Relevant Activities
- Next Steps

Programmatic Challenge
Areas of Increasing Emphasis

- Life stage sensitivities
- Mechanisms of toxicity
- Cumulative risk of common mechanism chemicals
- Risks associated with single or intermittent exposures
- Endocrine disruption

Programmatic Challenge

Conventional Food Use Pesticide Assessment

$15 to 20M to generate full battery of tests

$1M for the Agency to assess test results

5 to 7 years to license prior to PRIA

The Challenge of the Current Paradigm

Identifying lower risk active ingredients

Backlog in assessing inert ingredients

Difficulty in prioritizing scarce assessment resources

PRINCIPLES & GOALS OF NEXT GENERATION TOXICOLOGY TESTING PARADIGM

- Sufficient, credible amount of data for assessment & management decisions; not an overwhelming amount of data
- Reduced cost & time in data development
- Reduced cost (FTE & $) & time for EPA in reviewing & processing data
- Reduced use of animal testing
- Take full advantage of existing knowledge of pesticide database (~340 pesticide actives)

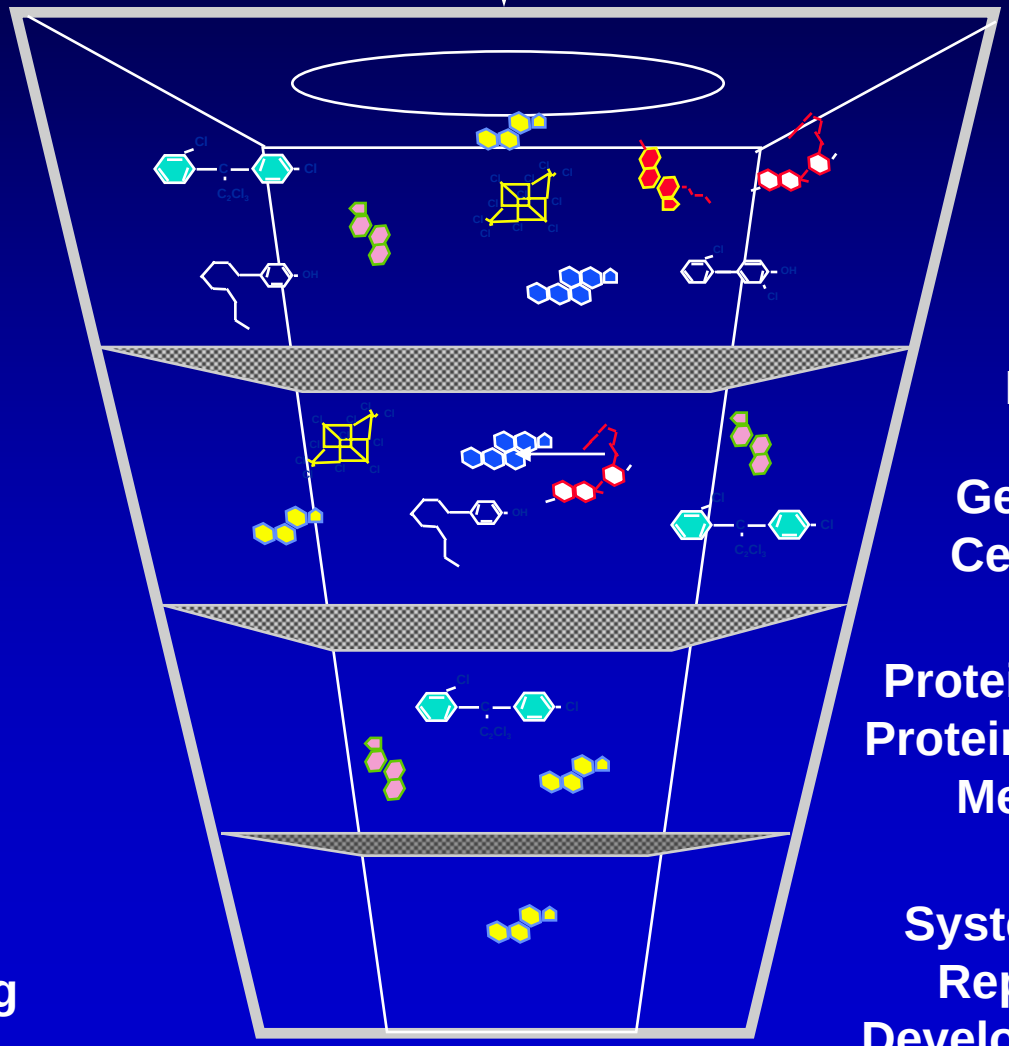
PRINCIPLES & GOALS OF NEXT GENERATION TOXICITY TESTING PARADIGM

- Take full advantage of advances in science & technology in an expeditious manner
- Credible peer-reviewed science for sound decisions
- Clarity of data requirements for all interested stakeholders & consistent application
- Transparency of transition process with full engagement of all interested parties

Goal: Identifying Toxicological Potential

Non-Animal Ranking & Prioritization; Screening

Chemical Inventories (pesticide actives, inerts, antimicrobials, high production volume chemicals,etc)



Partitioning; Electrophilicity; Redox Cycling; Receptor Binding

Gene Activation; Cellular Function

Protein Inhibition; Protein Production; Metabolism

Systemic effects, Reproduction, Development, Cancer

Existing Data and Models

Efficient Animal Testing

Next Generation of Data Requirements

Relevant Activities

- Health & Environmental Sciences Institute (HESI) Tiered Toxicology Testing Proposal for Agricultural Chemicals
- USEPA's Computation Toxicology Program
- National Academy of Sciences project on Toxicity Testing & Assessment sponsored by the USEPA
- OECD Integrative Testing & Assessment

HESI Project on Agricultural Chemical Safety Assessment

- Important Milestone & Spring Board to Next Generation of Data Requirements
  - incorporates existing knowledge
  - reduces/refines/replaces animal usage
  - optimizes study design & allows flexibility
  - better integration of metabolic & kinetic data in the safety assessment process
  - takes exposure characteristics into account, including intermittent exposures & different routes of exposure

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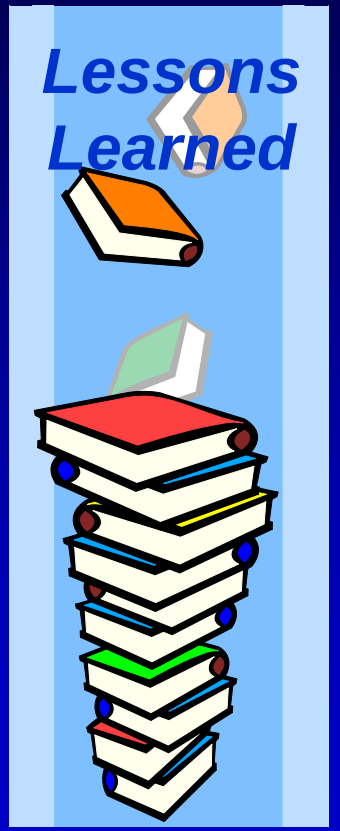
HESI Project on Agricultural Chemical Safety Assessment

Unresolved Issues

- Carcinogenicity Testing
- Triggers/criteria Used in Tiered Testing
- Consideration of Exposure
- Case Studies - Prospective Analysis

Next Generation Toxicity Testing Paradigm: Important Steps

- **Scientific Documentation**
  - **SABRE DATABASE—65 pesticides**
  - **USEPA's Retrospective Analyses--ongoing**
    - Dog toxicity studies
    - Rodent cancer studies
    - Rat Multi-generation Reproductive Studies
    - Rat Neurodevelopmental Toxicity Studies



Next Generation Toxicity Testing Paradigm: Scientific Documentation

- Dog Toxicity Studies
  - No consistent international standard regarding the treatment duration
    - EPA currently requires both a 90 day & 1 year dog toxicity study for food use pesticides
  - EPA recently review results of dog studies on pesticides from 1-2 year studies with studies of shorter duration (http://www.epa.gov/scipoly/sap/2005/may2/dogstudymay05.pdf)
    - Concluded that limiting dog studies to a duration of 13 weeks would not result in the loss of any significant toxicity information

Dog Toxicity Studies

- **May 2005 FIFRA Scientific Advisory Panel Review (**http://www.epa.gov/scipoly/sap/2005/may5/meetingminutesmay5_6_2005.pdf)
  - Generally supportive --several major recommendations
    - Analysis of additional pesticides including those where dog studies were not used to set the RfD
    - Need to ensure all chemical classes represented
    - Harmonization at international work shop

NEXT GENERATION TOXICITY TESTING PARADIGM: Important Steps

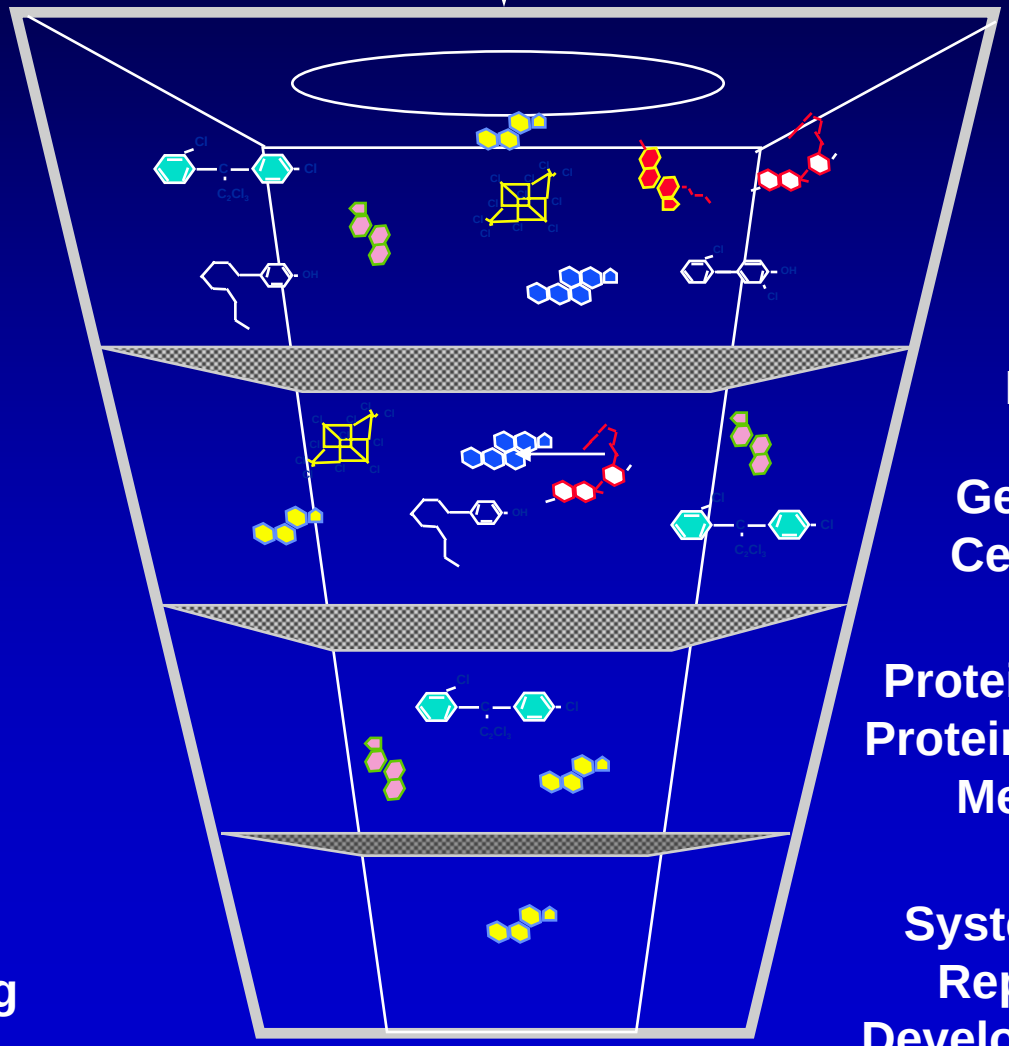
Harmonization & Consensus Building

- Work in several venues to gain international harmonization
  - EPA Outreach Efforts on ACSA
    - Jan & Jun 05 OECD meetings
    - Nov 05 Intl HESI workshop/panel discussion
    - July training of Staff on ACSA proposals (included California EPA & Health Canada)
- Started outreach with our Stakeholders
  - May workshop on our Part 158 revisions to data requirements
  - October PPDC meeting

Identifying Toxicological Potential

Non-Animal Ranking & Prioritization; Screening

Pesticide Inventories



Efficient Animal Testing

Partitioning; Electrophilicity; Redox Cycling; Receptor Binding

Gene Activation; Cellular Function

Protein Inhibition; Protein Production; Metabolism

Systemic effects, Reproduction, Development, Cancer

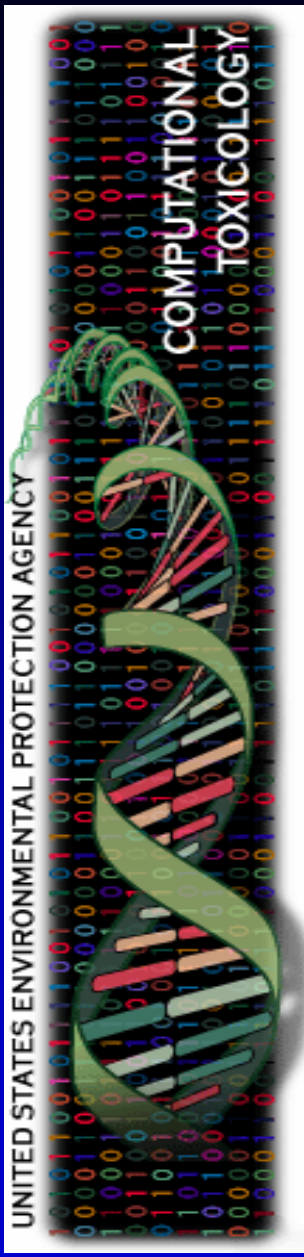
Existing Data and Models

NEXT GENERATION OF TOXICITY TESTING PARADIGM

- In summary, it will be critical to draw on several relevant activities
  - Health & Environmental Sciences Institute (HESI) Tiered Toxicology Testing Proposal for Agricultural Chemicals
  - USEPA's Computation Toxicology Program
  - National Academy of Sciences project on Toxicity Testing & Assessment sponsored by the USEPA
  - OECD Integrative Testing & Assessment

EPA's Computational Toxicology Program

Technology-based, hypothesis-driven effort to increase the soundness of risk assessment decisions build capacity to prioritize, screen & evaluate chemicals by enhancing the predictive understanding of toxicity pathways



www.epa.gov/comptox

Phases/Sequence of Integration Scheme Development

Science Development					
Research	Papers	Peer Review	Broad Disc.	Test Framework	Guideline Dev't

Education & Outreach			
Experts	Registrants	Interested Stakeholders	All

Policy Development			
Issue ID & Data	Stakeholder Engagement	Analysis	Option Selection

Implementation		
Pilot Test	Case-by-Case	Consistent Application

Rulemaking		
Development & Analysis	Proposal	Final

How do we get there?

Next Generation of Pesticide Toxicology Data Requirements

OECD Perspectives on Testing and Assessment

(Nice 16 November 2005)

Drew Wagner
Principal Administrator
Environment Directorate

OECD OCDE

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD)

- Intergovernmental Organisation
- 30 industrialised countries
  - North America
  - Europe
  - Asia/Pacific Region
- Observers from several countries with special status at the OECD
- Invited experts: industry, NGO, trade unions

OECD ROLE

- **Discuss issues of mutual concern**
- **Work together to respond to international problems**
- **Co-ordinate and harmonise policies and tools**
- **Adopt legal instruments**

(All stakeholders involved)

Chemicals Programme objectives

- **Develop high quality harmonized tools and policies for risk assessment and management**
- **Avoid duplication of work**
- **Facilitate work sharing**
- **Save time and money**
- **Avoid non-tariff trade barriers**

Hazard Assessment Tools (1)

- **In vivo/In vitro tests**
- **Structure/Activity Relationships (Principles for validation Nov. 2004, guidance document, case studies)**
- **Read Across and Categories (Manual for Existing Chemicals)**
- **Toxicogenomics (plan to improve link between fundamental research and regulatory use)**

Hazard Assessment Tools (2)

- **Initial discussions have begun on the use of integrated approaches to testing and assessment;**
- **Strong support from industry and some member countries, i.e. for pesticides;**
- **Need a better understanding of what integrated approach means to different groups;**
- **Is it a paradigm shift and revamp of overall approach to information requirements or subtle changes to existing approaches;**

Mutual Acceptance of Data (MAD)

- **Test Guidelines and Good Laboratory Practices are core elements of MAD**
- **Tests accepted by all OECD countries**
- **Council Decisions**
- **US $50-60 million saved each year**
- **Work with non-members**

Test Guidelines

- **Physical Chemical Properties (21)**
- **Effects on Biotic Systems (21)**
- **Degradation and Accumulation (12)**
- **Health Effects (48)**

Requirements for new/revised TGs

New and updated TGs should

- **improve risk management in countries and/or**
- **lead to a further reduction of animal use and improvements in animal welfare (widespread support and endorsement of the principle of the 3Rs)**

ACSA Initiative

- **Fits the rationale for developing new tests or revising existing tests**
- **Has benefits for industry, regulators, animal usage**
- **Based on robust science, but validation could be complex;**
- **Consistent with OECD discussions on more integrated approaches to testing and assessment;**
- **Performance of tests and testing strategy will be pivotal to international regulatory acceptance;**

Current Discussions on Refocusing the Test Guideline Programme

- **Simplify and streamline the process for new project proposals**
- **Transparent process to assist countries in decision-making for proposals for new or revised Test Guidelines: prior information on**
  - **Regulatory needs**
  - **Limitations**
  - **Resources**

Summary (1)

- **A large number of projects are underway in the OECD Test Guidelines Programme;**
- **These are conducted to meet the regulatory needs of the member countries and to bring a high level of harmonization in testing approaches;**
- **An integrated approach to testing and assessment is being discussed within the OECD;**

Summary (2)

- **Views of member countries, industry, NGOs and EC will be presented in Feb 06;**
- **The OECD needs to think about where this approach should be heading and what it hopes to deliver;**
- **ACSA initiative is one area of interest for the OECD;**
- **Any changes in testing approaches must meet the regulatory needs of member countries.**