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):


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.
- October 2002: Task Forces are formed to develop elements of a tiered testing approach.
- 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 redesign 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

**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
Université 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**


**COMMITTEE MEMBERSHIP**

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

Committee Presentations and Data Resources
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
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
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

產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・アウトトリーチ
  - ワークショップ、シンポジウムの計画と実施
  - 查読誌への投稿
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
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
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, Università 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
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
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
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 Als/Studies...
Queries

Sabre
Safety Assessment By
Refined Experimentation

Powered by
illuminaries
...turning Data into Information

EXIT
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
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

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

犬

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)
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
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

食品経由: 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

Pre X: 4W

X: 2W

Post X: up to 6W

P♂ & P♀

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♂ & P♀ dosing

Selected subsets F1♂ & P♀ 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（妊娠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

**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
A CSA Tier アプローチ

Tier 1: 基本試験
- 全身毒性に関する試験
- 急性毒性
- 遺伝毒性
- 代謝
- バイオアベイラビリティと薬物動態
- 皮膚浸透性
- 28日間ラット混餌投与試験
- 90日犬混餌投与試験
- 12ヶ月慢性／24ヶ月ラット発がん性試験

ライフステージに関する試験**
- F1拡大1世代繁殖試験
- ドラギ発生毒性試験

*神経毒性、免疫毒性、および内分泌系の
エンドポイントの検索を含む
** 用量設定の指標となる妊娠動物での
ADMEをオプションとして含む

曝露評価（通常モデル）

MOEは十分か？

No

Yes

MOEは十分か？

No

Yes

目標 MOE＞300～1,000

試験終了

Tier 2: 個別追加試験

下記試験もしくはその他の試験を
必要に応じて実施

作用機序に関するより詳細なエンドポイント
胎児および新生児におけるADME
追加神経毒性/免疫毒性試験
追加内分泌系試験
生涯の後期における感受性の確認
追加動物種における発生毒性試験
繁殖試験における2世代動物の追加検査
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

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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


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)
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)
- 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幾何学的毒性試験を免除する可能性

- 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

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.

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.]


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

- "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," Presentation by Dr. Drew Wagner, Organisation for Economic Cooperation and Development.
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
Hazard Characterization and Dose-Response Framework

Response

Mode of Action

Tissue Dosimetry

Exposure

Toxicodynamics

Pharmacokinetics/Toxicokinetics

Exposure

Limited information default

Qualitative Organization and Analysis

Quantitative Analysis
Dose-Response-Time

Human Exposure

Animal Testing

Dose

High

Mid

Low

Time
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...

Tox Studies

Risk?

ADME

"Basic" Tier I

"Custom" Tier II

Internal Dose

Species Differences

Mode of Action

Route-Route Animal to Human Worker Safety

"Advanced" Tier III

-Time Course -Metabolites -Bioavailability -Saturation -Recovery

-Route -Age -Species
“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:
Working through the process…

- **Tier I**
  - Time Course
  - Metabolites
  - Bioavailability
  - Saturation
  - Recovery

- **Tier II**
  - Route
  - Age
  - Species

- **Tier III**
  - Route
  - Animal to Human
  - Worker Safety

- **ADME**
  - “Advanced” Tier III
  - Internal Dose
  - Species Differences
  - Mode of Action

- **Interpret**

- **Risk?**

- **Tox Studies**

- “Custom” Tier II
  - Time Course
  - Metabolites
  - Bioavailability
  - Saturation
  - Recovery
...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.
Comparative Species PK
Working through the process...

- **Tox Studies**
  - "Basic" Tier I
    - Time Course
    - Metabolites
    - Bioavailability
    - Saturation
    - Recovery
  - "Custom" Tier II
    - Route
    - Age
    - Species

- **ADME**
  - Route
  - Route
  - Animal to Human
  - Worker Safety

- **Risk?**
  - Interpret
    - Internal Dose
    - Species Differences
    - Mode of Action

- **"Advanced" Tier III**
"Advanced" Tier III

- Route-to-Route Extrapolation
  - Dermal
    » In vitro rat/human
    » In vivo rat
  - Inhalation
- Biomonitoring
- Human clinical PK
Working through the process…

New Compound:

Tox Studies

Risk?

ADME

“Basic” Tier I

“Custom” Tier II

“Advanced” Tier III

Route-Route Animal to Human Worker Safety

- Time Course
- Metabolites
- Bioavailability
- Saturation
- Recovery

- Route
- Age
- Species

Internal Dose

Species Differences

Mode of Action
Working through the process...

Mature Compound:

Risk?

Tox Studies

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
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.
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.
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)
- Bernhard Stahl (Bayer CropScience)
- Chuck Hastings (BASF)
- Chuck Timchalk (Pacific NW National Laboratory)
- Sesh Iyengar (Bayer CropScience)
- Robert Krieger (University of CA, Riverside)
- Larry Sheets (Bayer Corporation) – Life Stages Task Force
- Alan Boobis (Imperial College London) – Systemic Toxicity Task Force

LIAISONS:
AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

Systemic Toxicity Task Force

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

November 16, 2005
Are we stretching our technology too far?

The Comet
Are we stretching our technology too far?

The Comet

The Nimrod
Are we stretching our technology too far?

The Nimrod

The Comet

The Airbus
The Risk Assessment Matrix: Duration of Exposure

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The Risk Assessment Matrix: Life Stages

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<td>Childhood</td>
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<tr>
<td>Adult (~Systemic)</td>
<td></td>
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<td>90d dog</td>
<td>1yr dog</td>
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<tr>
<td>Elderly</td>
<td></td>
<td></td>
<td>90d rat</td>
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</table>
The Risk Assessment Matrix: Life Stages

<table>
<thead>
<tr>
<th></th>
<th>1 Day</th>
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</tbody>
</table>

- 24mth rat
- 1yr dog
- 90d dog
- 90d rat
- 1yr dog
- 24mth rat
- rabbit dev tox
- rat dev tox
- rat multigeneration
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
Is the dog necessary?

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

![Ratio of NOELS for Rat 90day v Dog 90day](image)
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
Is the 12-month dog study necessary?

Ratio of Lowest NOAELS with and without 1 Year Dog
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

<table>
<thead>
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**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

**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
Comparison of Number of Animals Required for Systemic Toxicity

<table>
<thead>
<tr>
<th>Animals</th>
<th>Current paradigm</th>
<th>New paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td>rats</td>
<td>680</td>
<td>720</td>
</tr>
<tr>
<td>mice</td>
<td>520</td>
<td>0</td>
</tr>
<tr>
<td>dogs</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>1272</td>
<td>768</td>
</tr>
</tbody>
</table>
Stepwise approach

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

- Rat is “relevant”
  - Step 5:
    - 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 1yr rat
    - Carcinogenicity from 24 month rat

- Dog is “relevant”
  - Step 5:
    - 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 1yr rat or 90 d dog
    - Carcinogenicity from 24 month rat
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
Why does the NOEL vary at different time points?

Comparison of ratios for 90 day studies in rats and dogs to longer term studies in the same species

Ratio of 90 day study NOEL to longer term NOEL (dog 12 month, rat 24 month)
Value greater than 1 indicates lower longer term NOEL
Rozman and Doull* identified the factors which underlie the toxicokinetics and toxicodynamics:

**Toxicokinetics**
- Absorption
- Elimination
- Distribution
- Biotransformation
- Excretion

**Toxicodynamics**
- Injury
- Recovery
- Adaptation
- Repair
- Reversibility

Effect depends only on current internal dose.

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

Dynamics

Resident effect

Damage and repair

Kinetics

What determines the relationship between NOELS for different exposure durations?
Effect depends only on current internal dose.

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

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

Resident effect

Damage and repair

Dynamics

What determines the relationship between NOELs for different exposure durations?

| Kinetics | | | |
| --- | --- | --- |
| Rapid elimination | Slower elimination | Accumulation |

ADI = ARfD
What determines the relationship between NOELs for different exposure durations?

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>Rapid elimination</th>
<th>Slower elimination</th>
<th>Accumulation</th>
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<tbody>
<tr>
<td>ADI = ARfD</td>
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<tr>
<td>ADI = ARfD/# doses</td>
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</table>

**Dynamics**

- Effect depends only on current internal dose.
- Effect depends on current and past internal dose — “history” effect.

**Resident effect**

- Rapid elimination
- Slower elimination
- Accumulation

**Damage and repair**
Effect depends only on current internal dose.

Effect depends on current and past internal dose -- “history” effect

Resident effect

Damage and repair

Dynamics

ADI = ARfD

ADI = ARfD/ # doses

ADI << ARfD

Rapid elimination

Slower elimination

Accumulation

Kinetics

What determines the relationship between NOELS for different exposure durations?
Effect depends only on current internal dose.

Effect depends on current and past internal dose -- “history” effect

Resident effect

Damage and repair

Dynamics

ADI = ARfD

ADI < ARfD

ADI = ARfD/# doses

ADI < ARfD

ADI <<< ARfD

Kinetics

Rapid elimination

Slower elimination

Accumulation

What determines the relationship between NOELs for different exposure durations?
### Dynamics

**Resident effect**
- Effect depends only on current internal dose.

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

### Kinetics

- **Rapid elimination**
- **Slower elimination**
- **Accumulation**

<table>
<thead>
<tr>
<th>ADI = ARfD</th>
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<th>ADI = ARfD/ # doses</th>
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<td>ADI &lt;&lt;&lt; ARfD</td>
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What determines the relationship between NOELs for different exposure durations?
### Dynamics

<table>
<thead>
<tr>
<th>Resident effect</th>
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<tr>
<td><strong>Dynamics</strong></td>
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### Kinetics

<table>
<thead>
<tr>
<th>Rapid elimination</th>
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</table>

What exposures are of greatest concern?

<table>
<thead>
<tr>
<th>The highest spike</th>
<th>Highest total exposure within DT90 window (resulting in the max. internal dose)</th>
<th>Total exposure (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent spikes above a threshold</td>
<td>Highest total within a time-window whose duration is determined by DT90 and repair rate.</td>
<td>Total exposure (AUC)</td>
</tr>
</tbody>
</table>

<table>
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<th>Maximum spike</th>
<th>Highest total exposure within DT90 window (resulting in the max. internal dose)</th>
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<td>DT90 window</td>
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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.
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.

Operates for compounds across the matrix as the relationship between the RfDs will reflect their properties.
How do we deal with varying or intermittent exposures?

Dose

Time
How do we deal with varying or intermittent exposures?

- 1 day RfD
- 1-4 week RfD
- 1-6 month RfD
How do we deal with varying or intermittent exposures?

- 1-day RfD
- 1-4 week RfD
- 1-6 month RfD
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
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.
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

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“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)
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:

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<tbody>
<tr>
<td>Life Stages</td>
<td>5320</td>
<td>1480</td>
</tr>
<tr>
<td>Systemic Tox</td>
<td>1272</td>
<td>768</td>
</tr>
<tr>
<td>Total</td>
<td>6592</td>
<td>2248</td>
</tr>
</tbody>
</table>
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?
AGRICULTURAL CHEMICAL SAFETY ASSESSMENT (ACSA)

Life Stages Task Force

Lorraine Irvine, BSc, DABT
toXcel International Ltd.

November 16, 2005
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Consultant
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DuPont Crop Protection
Dr. Ann Blacker
Bayer CropScience
Dr. Angela Brady
Syngenta CTL
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US EPA NHEERL
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Dow AgroSciences
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US EPA NCEA
Dr. Herman Koeter
European Food Safety Authority
Dr. Abby Li
Exponent
Dr. Larry Sheets
Bayer Corporation
Dr. Gerrit J.A. Speijers
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


**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
• 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
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*
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
**F1-'extended': 1-Gen Study**

- **Pre X: 4W**
- **Pre X: 2W**
- **X: 2W**
- **Post X: up to 6W**
- **P♂ & P♀ necropsy**

**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**
**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 \textit{(parental)} 160
- 2-gen reprotox \textit{(parental and offspring)} 2600
- Developmental neurotox \textit{(parental and offspring)} 1280
- Developmental immunotox \textit{(parental and offspring)} 1280

\textbf{Tier 1 testing only}

- 1 species developmental tox \textit{(parental)} 80
- Extended 1-gen reprotox \textit{(parental & offspring)} 1400

\textit{(If 2\textsuperscript{nd} 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.
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

Efficient Animal Testing

Existing Data and Models
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
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

  - 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

Partitioning; Electrophilicity; Redox Cycling; Receptor Binding

Gene Activation; Cellular Function

Protein Inhibition; Protein Production; Metabolism

Systemic effects, Reproduction, Development, Cancer

Efficient Animal Testing

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

<table>
<thead>
<tr>
<th>Research</th>
<th>Papers</th>
<th>Peer Review</th>
<th>Broad Disc.</th>
<th>Test Framework</th>
<th>Guideline Dev't</th>
</tr>
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## Education & Outreach

<table>
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<tr>
<th>Experts</th>
<th>Registrants</th>
<th>Interested Stakeholders</th>
<th>All</th>
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</table>

## Policy Development

<table>
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<tr>
<th>Issue ID &amp; Data</th>
<th>Stakeholder Engagement</th>
<th>Analysis</th>
<th>Option Selection</th>
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## Implementation

<table>
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<tr>
<th>Pilot Test</th>
<th>Case-by-Case</th>
<th>Consistent Application</th>
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</thead>
</table>

## Rulemaking

<table>
<thead>
<tr>
<th>Development &amp; Analysis</th>
<th>Proposal</th>
<th>Final</th>
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</thead>
</table>
How do we get there?

Next Generation of Pesticide
Toxicology Data Requirements

Global Perspective
OECD Perspectives on Testing and Assessment
(Nice 16 November 2005)

Drew Wagner
Principal Administrator
Environment Directorate
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.