STRATEGIES TO REDUCE ANIMAL TESTING IN US EPA’S HIGH PRODUCTION VOLUME CHEMICAL CHALLENGE SCREENING PROGRAM (AND BEYOND)

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EPA’s High Production Volume (HPV) Program

- High production volume chemicals (>1,000,000 pounds per year)
- Assess existing hazard data
- Assess and fill data “gaps”
- No risk assessment (limited exposure considerations)
## Animal Tests Required

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>GUIDELINE</th>
<th>ANIMALS</th>
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<tbody>
<tr>
<td>Acute toxicity to fish</td>
<td>OECD 203</td>
<td>40-120</td>
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<tr>
<td>Acute lethality-oral</td>
<td>OECD 425</td>
<td>3-10</td>
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<tr>
<td>Repeat dose-28 or 90 days</td>
<td>OECD 407</td>
<td>40-65</td>
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<tr>
<td>Combined reproduction/developmental screen</td>
<td>OECD 408</td>
<td></td>
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<tr>
<td>Combined repeat dose/replication/developmental screen</td>
<td>OECD 421</td>
<td>675</td>
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<tr>
<td></td>
<td>OECD 422</td>
<td>675</td>
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**TOTAL: 750 – 800; possibly over 1000 animals; hundreds of thousands of dollars**
Examples of Current Animal Welfare Principles

- Use *in vitro* genotoxicity versus *in vivo* unless impossible
- No *repeat dose/reproductive* testing needed for closed system intermediates
- Maximize use of *existing data*
- Use *weight-of-evidence* to avoid “checklist toxicology”
- Use *SAR* to form chemical categories and extrapolate between members
Extended HPV Program

- Original program ended in 2005
- EHPV initiated in 2006
- PCRM has developed expanded Animal Welfare Guidelines based on experience from review of hundreds of HPV test plans
- Industry toxicologists and other scientists have worked with PCRM to identify opportunities to reduce animal testing and still meet the HPV data requirements
Specific Strategy Examples

1. Expanded Weight-of-Evidence Approach
   Commercial Hydroxyethylpiperazine (CHEP)

   ▪ Dermal reproductive/developmental study proposed
   ▪ (Q)SAR Modeling revealed low dermal absorption potential
   ▪ No systemic effects expected by the dermal route
   ▪ No testing conducted
   ▪ Pre-test in vitro percutaneous absorption (OECD 428) can also be used in this approach to decide whether systemic dermal toxicity testing is justified
Specific Strategy Examples

2. Expanded Weight-of-Evidence Approach
Isophthalonitrile

- No testing proposed

- Available developmental toxicity data not from traditional developmental study, but inferred from 28-day repeat dose and one-generation reproduction studies

- Scientifically sound approach accepted but more discussion of findings suggested
Specific Strategy Examples

3. Data from Analogs

Eicosenoic Acid, methyl ester, (Z)-

- Fatty Acid
  - Comments were submitted suggesting the use of data from other analogous substances
  - The sponsoring company cancelled proposed tests (which included all OECD mammalian endpoints) and used data from another fatty acid
Specific Strategy Examples

4. Rapid Hydrolysis
Triisopropyl borate (TIPB)

- Rapidly hydrolyzes to boric acid and isopropanol in aqueous environment
- Bench hydrolysis study at stomach acid pH (1.2) was proposed
- Rapid hydrolysis to well-studied products could be used to meet SIDS gaps
Specific Strategy Examples

5. Modeling based on common toxic constituent

Several Chemical Categories

- 6 chemical categories comprising several hundred chemicals
- All categories had common toxic constituent - PAH
- Modeling of toxicity across categories based on similar toxicity and level of PAH in mixtures
- Some limited animal testing may be needed to validate the model
- Ultimately may greatly reduce animal tests
Summary of Strategies

- Expand use of weight-of-evidence approach
- Use data from analogs
- Take hydrolysis or other chemical activity into account
- Model based on common toxic constituent
- Others:
  - Gases
  - Highly Reactive Materials
  - Acidic/Corrosive/Irritating Materials

- 45 chemical-specific examples and counting to reduce animal testing needed to meet HPV requirements