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

ENDPOINT	GUIDELINE	ANIMALS
Acute toxicity to fish	OECD 203	40-120
Acute lethality-oral	OECD 425	3-10
Repeat dose-28 or 90 days	OECD 407 OECD 408	40-65
Combined reproduction/ developmental screen	OECD 421	675
Combined repeat dose/ reproduction/developmental screen	OECD 422	675

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