UNITED STATES ICCVAM
Advancing alternatives to animal testing

Interagency Coordinating Committee on the Validation of Alternative Methods

ICCVAM Update

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Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration

New Vision & Direction for ICCVAM

- ICCVAM priority setting & current science focus areas:
  - Member agencies are taking a more active role in priority setting and operations of the Committee.
  - Change in approach:
    - Streamline the number of active projects where the science has advanced
      - There is a reasonable likelihood of success with a reasonable timeframe (1-5 years) for implementing into regulatory use.
    - Maintain flexibility to reorient efforts to maximize potential progress towards use of alternative approaches

Reducing Animal Use for Acute Toxicity Assessments

- NICEATM & EPA are collaborating to evaluate the relative contribution of acute and dermal toxicity tests in providing information related to labeling for pesticides

- Acute oral and dermal toxicity testing (EPA-OPP)
  - Step 1: Compile dataset(s) of oral & dermal LD50 studies
  - Step 2: Comparison analysis---How do the results of acute and dermal Lethal Dose (LD50) tests compare?
  - Step 3: Implication---Are both the oral & dermal LD50 tests needed for labelling?

Guideline	Study Type	Food Use	Non-Food Use
870.1100	Acute oral toxicity – Rat	R	R
870.1200	Acute dermal toxicity – Rat /Rabbit	R	R
870.1300	Acute inhalation toxicity – Rat	R	R
870.2400	Primary eye irritation – Rabbit	R	R
870.2500	Primary dermal irritation – Rabbit	R	R
870.2600	Dermal sensitization – Guinea Pig	R	R
870.6200	Acute neurotoxicity – Rat	R	R

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Example of OPP's use of Acute Dermal LD_{50} Data: Pesticide Handlers

- Pesticide handlers are those who mix, load and apply pesticides
- Pesticide labeling requirements describe how protective clothing, respiratory protection and engineering controls are assigned to products based on toxicity of the end use product
- Risk assessment is also used to assign protective equipment to labels in addition to these criteria

Table 1. Handler PPE for WPS Products

Route of Exposure	Toxicity Category by Route of Exposure of End-Use Product			
	I DANGER	II WARNING	III CAUTION	IV CAUTION
Dermal Toxicity or Skin Irritation Potential[1]	Coveralls worn over long-sleeved shirt and long pants	Coveralls worn over short-sleeved shirt and short pants	Long-sleeved shirt and long pants	Long-sleeved shirt and long pants
	Socks	Socks	Socks	Socks
	Chemical-resistant footwear	Chemical-resistant footwear	Shoes	Shoes
	Chemical-resistant Gloves[2]	Chemical-resistant Gloves[2]	Chemical-resistant Gloves[2]	No minimum[4]
Inhalation Toxicity	Respiratory protection device[3]	Respiratory protection device[3]	No minimum[4]	No minimum[4]
Eye Irritation Potential	Protective eyewear[5]	Protective eyewear[5]	No minimum[4]	No minimum[4]

From Chapter 10, Label Review Manual. http://www.epa.gov/oppfead1/labeling/lrm/chap-10.pdf

Oral-Dermal Hazard Classification Analyses in the Literature

- Several published studies have investigated comparability between oral and dermal acute hazard classifications to assess whether tests for both routes are needed
  - Creton et al. (2010) reported on 240 pesticide actives and 438 industrial chemicals
  - Seidle et al. (2011) reported on 1569 industrial substances and 337 pesticide actives
  - Moore et al. (2013) reported on 225 substances from the European Chemicals Agency (ECHA) database and 110 pesticide actives from Creton et al. (2010)
- These have focused on technical active ingredients & have not used the EPA-OPP categorization system.

NICEATM Oral-Dermal LD50 Data Evaluations

- In 2013, project was initiated with collaboration from EPA's Office of Pesticide Programs
- From 2013 to now, work continues
  - Studies compiled for both formulations & technical active ingredients.
  - However, the focus of current efforts is on the formulations:
    - Formulation LD50 studies are used for determining PPE for pesticide handlers.
    - Potential animal savings comes primarily from formulation acute studies
      - There are 1000's of end use products registered by EPA
    - The dermal LD50 data for the technical active ingredients are often used in ecological assessments.

Oral-Dermal LD_{50} Data Evaluation Project

- A dataset of acute & dermal LD_{50} data for formulations has been sent to NICEATM
- Current draft version includes:
  - Conventionals, antimicrobials, biopesticides
  - 12 different formulation types
    - Toxicity (particularly absorption) can be influenced by the nature of the exposure
  - Toxicity categories I, II, III, IV
  - >400 different combinations of active ingredients (single active ingredients, multiple active ingredients in various combinations)

Oral-Dermal LD_{50} Data Evaluation Project

- Acute oral and dermal toxicity testing
  - Step 1: Compile dataset(s) of oral & dermal LD_{50} studies
  - *Step 2: Comparison analysis---How do the results of acute and dermal Lethal Dose (LD_{50}) tests compare?*
  - Step 3: Implication---Are both the oral & dermal LD_{50} tests needed for labelling?
- Next Steps:
  - Discussions between NICEATM & EPA-OPP on the findings
  - Write up the project for public comment
    - Will include the dataset & the statistical analysis
  - Timeline: Goal is to have the draft analysis & summary for public comment in fall 2014

Alternative Assays

- EPA-OPP is in the early stages of collaborative project with multiple stakeholders & NICEATM
- Alternative batteries for skin sensitization, dermal irritation, skin irritation
    - Canada PMRA, animal welfare groups, & industry
    - Meetings held in May & September