ICCVAM Recommendations for the Routine Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints to Refine Ocular Toxicity Testing

J. Merrill,¹ M. Wind,² D. Lowther,¹ T. McMahon,³ J. Chen,³ M. Hashim,³ M. Lewis,³ W. Stokes⁴

¹U.S. Food and Drug Administration (FDA), Silver Spring, MD; ²U.S. Consumer Product Safety Commission, Bethesda, MD; ³U.S. Environmental Protection Agency (EPA), Washington, DC; ⁴National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, Research Triangle Park, NC
Abstract

eye injury is a leading cause of visual impairment in the U.S., with up to 50,000 new cases reported each year. To evaluate the potential of chemicals to cause eye irritation, the protocol most widely accepted by regulatory agencies is based on the Draize rabbit eye test method. Since current ocular test guidelines state that users must ensure that the topical anesthetic does not affect test results, pain medications are often not used. However, for over 25 years CPSC has recommended pre-application of a topical anesthetic for all rabbit eye toxicity studies. Therefore, ICCVAM recently conducted a comprehensive evaluation of the usefulness and limitations of routinely using topical anesthetics, systemic analgesics, and earlier more humane endpoints to minimize pain and distress in ocular safety testing. Following this evaluation, which included recommendations from an international independent peer review panel, ICCVAM concluded that a balanced preemptive pain management plan should always be used when the Draize rabbit eye test is conducted for regulatory safety testing. This protocol should include pre-treatment with a topical anesthetic and systemic analgesic, and routine post-treatment with systemic analgesia. ICCVAM also recommends several additional humane endpoints that should be used to end studies earlier. To ensure timely and accurate detection of humane endpoints in ocular studies, ICCVAM recommends examination with a slit-lamp biomicroscope, when considered appropriate, to characterize the nature, severity, and progression of any corneal lesions. ICCVAM also recommends routine observations for clinical signs of pain and distress at least twice daily, or more often if needed. Implementation of these ICCVAM recommendations should avoid or significantly reduce pain and distress associated with ocular safety assessments while continuing to support the protection of human health.

1The abstract has been modified slightly from the version submitted.
Introduction

- The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is charged by the ICCVAM Authorization Act of 2000 with evaluating the scientific validity of new, revised, and alternative toxicological test methods applicable to U.S. Federal agency safety testing requirements.

- ICCVAM recently evaluated the routine use of topical anesthetics, systemic analgesics, and earlier humane endpoints to avoid or minimize pain and distress during *in vivo* ocular irritation testing.

- Current U.S. and international test guidelines for the Draize rabbit eye test provide for the use of topical anesthetics only when the user demonstrates that such pretreatments do not interfere with the test results (EPA 1998; OECD 2002).
  - However, for over 25 years the U.S. Consumer Product Safety Commission (CPSC) has recommended preapplication of tetracaine ophthalmic anesthetic for all rabbit eye toxicity studies (CPSC 1984).
  - The following ocular lesions are predictive of severe irritant or corrosive injuries, and injuries that are not expected to fully reverse by the end of the 21-day observation period after treatment, and can be used as humane endpoints to terminate a study (OECD 2002)
    - Draize corneal opacity score of 4 that persists for 48 hours
      - Corneal opacity score of 4 is defined as: Opaque cornea, iris not discernable through the opacity
      - Corneal perforation or significant corneal ulceration including staphyloma
      - Blood in the anterior chamber of the eye
      - Absence of light reflex that persists for 72 hours
        - Absent light reflex corresponds to iris severity score of 2
      - Ulceration of the conjunctival membrane
      - Necrosis of the conjunctiva or nictitating membrane
      - Sloughing (separation of necrotic tissue from the living structure)

- A recent report of the National Research Council Committee on Recognition and Alleviation of Pain in Laboratory Animals emphasized the need for increased efforts to identify appropriate humane endpoints (NRC 2009).

- ICCVAM, the ICCVAM Ocular Toxicity Working Group (OTWG), and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) prepared a draft background review document (BRD) summarizing available information and data from published and unpublished studies on the use of topical anesthetics, systemic analgesics, and earlier humane endpoints in ocular toxicity testing. Draft recommendations were developed based on this information for consideration by an independent international peer review panel (see Peer Review Panel Meeting).
ICCVAM considered the report of the peer review panel, along with comments from the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) and the public. ICCVAM then developed final recommendations on the routine use of topical anesthetics, systemic analgesics, and humane endpoints for ocular safety testing.

- An ICCVAM Test Method Evaluation Report (TMER) includes the updated ICCVAM-recommended test method protocols, the final BRD, and recommendations for future studies (ICCVAM 2010).
ICCVAM Ocular Toxicity Working Group

U.S. Consumer Product Safety Commission
Marilyn L. Wind, Ph.D.
Adrienne Layton, Ph.D.

U.S. Department of Defense
Harry Salem, Ph.D.

U.S. Department of Transportation
Steve Hwang, Ph.D.

U.S. Environmental Protection Agency
Office of Pesticide Programs
Meta Bonner, Ph.D.
Jonathan Chen, Ph.D.
Jack Fowle, Ph.D., DABT
Masih Hashim, D.V.M., Ph.D.
Karen Hicks
Marianne Lewis
Debbie McCall
Timothy McMahon, Ph.D.
Mark Perry
John Redden
Jenny Tao, Ph.D.

Office of Research and Development
Andrew Geller, Ph.D.

Office of Science Coordination and Policy
Karen Hamernik, Ph.D.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Paul Brown, Ph.D.
Wiley Chambers, M.D.
Abigail (Abby) Jacobs, Ph.D.
Jill Merrill, Ph.D., DABT (OTWG Chair)

Center for Food Safety and Applied Nutrition
Robert Bronaugh, Ph.D.
Donnie Lowther

Office of the Commissioner
Suzanne Fitzpatrick, Ph.D., DABT

National Institute Environmental Health Sciences
Mark F. Cesta, D.V.M., DACVP
Raymond (Buck) Grissom, Ph.D.
William Stokes, D.V.M., DACLAM

Occupational Safety and Health Administration
Surender Ahir, Ph.D.

European Centre for the Validation of Alternative Methods – Liaison
João Barroso, Ph.D.
Thomas Cole, Ph.D.
Valerie Zuang, Ph.D.

Japanese Center for the Validation of Alternative Methods – Liaison
Hajime Kojima, Ph.D.
Routine Use of Topical Anesthetics and Systemic Analgesics: Background

- Since 1984, the CPSC has recommended preapplication of tetracaine ophthalmic anesthetic in all rabbit eye toxicity studies (CPSC 1984). (illustration: Poster from NICEATM-ICCVAM/ECVAM-sponsored workshop, “Minimizing Pain and Distress in Ocular Toxicity Testing”, which took place in May 2005 at NIH headquarters in Bethesda, MD)

- In 2005, an international symposium entitled “Minimizing Pain and Distress in Ocular Toxicity Testing” evaluated the use of topical ophthalmic anesthetics and/or systemic analgesics during the conduct of the Draize rabbit eye irritation test.
  - ICCVAM, NICEATM, and the European Centre for the Validation of Alternative Methods (ECVAM) organized the symposium.
  - Scientific Experts at the workshop recommended:
    - Routine pretreatment with topical anesthetics and systemic analgesics to prevent pain
    - Treatment with systemic analgesics of animals with ocular lesions associated with painful conditions and/or clinical signs of pain or distress

- NICEATM evaluated the effects of pretreatment with tetracaine hydrochloride (0.5% w/v) on the ocular irritancy potential of 97 formulations (Choksi et al. 2007).

- Topical anesthetic pretreatment had little or no impact on:
  - The hazard classification severity category
  - The nature of the ocular irritation responses
  - The number of days for ocular lesions to clear

- A recently convened independent international scientific peer review panel recommended the routine use of topical anesthetics and systemic analgesics to prevent and minimize pain and distress during in vivo ocular irritation testing.

- A well-tested approach to balanced analgesia is to use an opioid (e.g., buprenorphine) in combination with a cycloxygenase-sparing nonsteroidal anti-inflammatory drug such as meloxicam (Roughan and Flecknell 2002; Sawyer 2008; Cooper et al. 2009).
  - Buprenorphine is an opioid agonist-antagonist analgesic that has been found to be effective in managing pain in rabbits and other small animals (Roughan and Flecknell 2002; Sawyer 2008).
  - Meloxicam has been used for postoperative or chronic pain in humans (Akarsu et al. 2004; Aoki et al. 2006) and dogs for over 10 years. Its effectiveness has been demonstrated in rabbits (Sawyer 2008; Cooper et al. 2009).
Day 1

1. **Sixty minutes before test substance administration**: Administer 0.01 mg/kg buprenorphine by subcutaneous injection to provide a therapeutic level of systemic analgesia

2. **Five minutes before test substance administration**: apply one or two drops of a topical ocular anesthetic to each eye.
   - 0.5% proparacaine hydrochloride or 0.5% tetracaine hydrochloride may be used
   - If the test substance is anticipated to cause significant pain and distress, consider applying more than one dose of topical anesthetic at five-minute intervals before test substance administration.
   - Users should be aware that multiple applications of topical anesthetics could increase the severity and/or extend the time required for lesions that are chemically-induced to clear.

**Box: Test Substance Administration**

*(dotted line arrow pointing to Rescue Dose Procedure box (below) is labeled “If subject shows signs of pain and distress: ADMINISTER “RESCUE DOSE”)*

**Box: Rescue Dose Procedure**

- Immediately give additional analgesia: 0.03 mg/kg buprenorphine by subcutaneous injection.
- Meloxicam would continue with the same dose and interval as described below.
- Repeat every eight hours as needed.

3. **Eight hours after test substance administration**: administer 0.01 mg/kg buprenorphine and 0.5 mg/kg meloxicam by subcutaneous injection to provide a continued therapeutic level of systemic analgesia

Days 2-21

4. **Continue until ocular lesions resolve and subject shows no clinical signs of pain and distress**: administer 0.01 mg/kg buprenorphine subcutaneously every 12 hours in conjunction with 0.5 mg/kg meloxicam subcutaneously every 24 hours.

*(dotted line arrow pointing to Rescue Dose Procedure box (above) is labeled “If subject shows signs of pain and distress: ADMINISTER “RESCUE DOSE”)*

*(end illustration)*
ICCVAM Recommendations for Routine Use of Topical Anesthetics and Systemic Analgesics

- ICCVAM recommends that balanced preemptive pain management should always be provided when the Draize rabbit eye test is conducted for regulatory safety testing.
- Pain management should include:
  1. Pretreatment with a topical anesthetic and systemic analgesic prior to test substance administration (TSA)
  2. Routine post-treatment with systemic analgesics, with additional treatments as necessary
  3. Scheduled observation, monitoring, and recording of animals for clinical signs of pain and/or distress
  4. Scheduled observation, monitoring, and recording of the nature, severity, and progression of all eye injuries
- Alternative pain management procedures may also be considered that provide as good or better analgesia and anesthesia than the recommended pain management plan.
ICCVAM Recommendations for Future Studies: Use of Topical Anesthetics and Systemic Analgesics

• ICCVAM recommends the following studies and activities to support the development of improved pain management strategies, recognizing that some involve research that would be conducted independent of regulatory safety testing.
  
  – New animal studies should only be considered when absolutely necessary in developing new pain management strategies for testing.
  
  – Detailed ocular injury and pain response data should be collected from animals used for required regulatory testing, and evaluated to assess the adequacy of the recommended pain management procedures. This data will help identify the need for modifications to dosages and dosing intervals for anesthetics and/or analgesics.
  
  – Where possible, eyes should be collected for histopathology to more thoroughly evaluate depth and area of ocular damage, as well as to provide a reference against which to compare effects produced in vitro.
  
  – Digital photographs of observed lesions should be collected for reference and to provide a permanent record of the extent of ocular damage.
  
  – Studies should be conducted to determine whether the timing and dosing of systemic analgesics together with topical anesthetics might alter the ocular defense sufficient to change the classification of test substances.
  
  – Studies should be conducted to investigate topical anesthetics that might provide longer duration of action or other advantages.
  
  – Studies should be conducted to evaluate systemic analgesics that might provide longer duration of action, improved analgesia, or other advantages.
  
  – ICCVAM encourages users to provide data generated using the recommended pain management procedures to NICEATM to create a database that can be periodically evaluated to further characterize the usefulness and limitations of such procedures for avoiding or minimizing pain and distress in ocular safety assessments.
Use of Humane Endpoints in Ocular Safety Testing: Background

- U.S. Public Health Service Policy and U.S. Department of Agriculture regulations on pain and distress in laboratory animals state that more than momentary or slight pain and distress:
  - (1) must be limited to that which is unavoidable for the conduct of scientifically valuable research or testing,
  - (2) must be conducted with appropriate pain relief medication unless justified in writing by the principal investigator, and
  - (3) will continue for only the necessary amount of time.
  - Animals suffering severe or chronic pain or distress that cannot be relieved should be humanely killed after or, if appropriate, during the procedure.

- During the 2005 symposium “Minimizing Pain and Distress in Ocular Toxicity Testing,” panelists recommended early adverse responses that could serve as early humane endpoints to terminate animals on study:
  - Endpoints currently accepted for study termination (OECD 2002)
  - Vascularization of the corneal surface (i.e., pannus)
  - Destruction of more than 75% of the limbus
  - No diminishment in area of fluorescein staining and/or increase in depth of injury increased over time
  - Lack of re-epithelialization 5 days after application of the test substance
  - Depth of injury to the cornea (routinely using slit-lamp and fluorescein staining) in which corneal ulceration extends beyond superficial layers of the stroma
ICCVAM Recommendations on the Routine Use of Humane Endpoints in Ocular Safety Testing

- Consistent with the Peer Review Panel, ICCVAM recommends that the following ocular lesions can be used as earlier humane endpoints to terminate studies before the end of the scheduled 21-day observation period. These lesions are considered predictive of severe irritant or corrosive injuries, and injuries that are not expected to fully reverse by the end of the 21-day observation period after treatment:
  - Endpoints currently accepted for study termination (OECD 2002; see Introduction)
  - Severe depth of injury (e.g., corneal ulceration extending beyond the superficial layers)
  - Destruction of more than 50% of the limbus, as evidenced by blanching of the conjunctival tissue
  - Severe eye infection (purulent discharge)

- A combination of the following endpoints may be useful in clinical decisions on study termination. However, these endpoints cannot be used individually to justify early study termination:
  - Vascularization of the cornea surface (i.e., pannus)
  - Area of fluorescein staining not diminishing over time based on daily assessment
  - Lack of re-epithelialization 5 days after test substance application

- ICCVAM emphasizes that, once severe effects have been identified, a qualified laboratory animal veterinarian should perform a clinical exam to determine if the combination of these effects warrants early study termination.
ICCVAM Recommendations on Changes to Ocular Safety Testing Protocols

- Ocular safety assessment studies should be conducted using the ICCVAM-recommended modifications to the current Draize rabbit eye test protocol for regulatory safety assessments of potential ocular hazards (EPA 1998; OECD 2002).

- Comprehensive evaluations for the presence or absence of ocular lesions should be conducted one hour after test substance administration, followed by at least daily evaluations
  - Animals should be evaluated once daily for the first 3 days, or more often if necessary, to ensure that termination decisions are made in a timely manner.

- Test animals should be routinely evaluated for clinical signs of pain and/or distress at least twice daily with a minimum of 6 hours between observations, or more often if necessary. Examples of relevant clinical signs include (Wright et al. 1985; NRC 2008, 2009):
  - Repeated pawing or rubbing of the eye
  - Excessive blinking
  - Excessive tearing

- Study termination based on humane endpoints should ensure that reversal is not expected and that no further useful information can be obtained from the study.

- A written record of all observations should be kept for determinations on the progression or resolution of ocular lesions.

- A slit-lamp biomicroscope should be used when considered appropriate (e.g., assessing depth of injury when corneal ulceration is present).

- Digital photographs should be taken to document ocular lesions and help assess their severity, progression, and resolution.
ICCVAM Recommendations for Future Studies: Use of Humane Endpoints in Ocular Safety Testing

*Fluorescein Staining*

- Additional data should be collected on the use of fluorescein staining to monitor wound healing.
  - Data should be evaluated to identify criteria that may be useful as humane endpoints to terminate studies.
- Guidelines should be developed for (1) the frequency of fluorescein staining that can be conducted without significant impact on wound healing that would affect classification categories and (2) the usefulness of the area and intensity, and progression/regression of fluorescein staining for identifying specific hazard classification categories.
  - Studies should be conducted to identify earlier, more predictive endpoints such as those quantifying area and intensity of fluorescein staining.

*Other Recommendations*

- Data should be collected during current testing to support the identification of potential earlier endpoints and to facilitate development of a database that can be used to identify useful earlier endpoints.
- Data should be collected to further evaluate pannus as a potential earlier humane endpoint. (ICCVAM did not consider the BRD data sufficient to determine the adequacy of pannus as a recommended humane endpoint for terminating a test.)
- Improved guidance on clinical signs of pain and distress in rabbits should be developed. Pain assessment training is also an important part of an effective pain management program and should be routinely provided to relevant personnel.
- Users should provide NICEATM with detailed data and observations collected from ocular safety studies that can be used to create a database to (1) further characterize the usefulness and limitations of proposed humane endpoints, and to (2) identify potential new endpoints. Such data submissions will contribute to efforts to find ways to further prevent and minimize pain and distress in ocular safety assessments.
Independent Scientific Peer Review Panel Meeting

- A public meeting of an international independent scientific peer review panel (“Panel”) organized by the ICCVAM and NICEATM was held at the U.S. Consumer Product Safety Commission Headquarters in Bethesda, MD, on May 19-21, 2009.

Charge to the Peer Review Panel

- Evaluate the extent to which the draft BRD addressed established validation and acceptance criteria.

Peer Review Panel Conclusions and Recommendations

The Panel recommended that:

- An alternative preemptive pain management plan be applied to all in vivo rabbit eye irritation tests intended for regulatory safety testing, unless there is a requirement for monitoring the pain response (e.g., pharmaceutical tolerability testing).
  - The only differences in the ICCVAM-recommended plan and the Panel’s protocol are that the ICCVAM-recommended plan (1) allows for either tetracaine or proparacaine as a topical anesthetic and (2) recommends only one dose of topical anesthetic unless there is reason to believe that this will be insufficient to relieve pain and distress, at which time additional pre-test substance applications can be considered.
  - Results from previous CPSC studies provide the basis for these differences.
- Current and proposed humane endpoints should be used routinely as humane endpoints.
- The Panel considered them predictive enough of irreversible or severe effects (i.e., EPA Category I, GHS Category 1, EU R41) that a study should be terminated as soon as they are observed.
- Test animals be examined at least daily and the presence or absence of these lesions recorded.
- For the first three days, test animals should be examined at least twice daily, or more often if necessary. The Panel emphasized the need for a slit lamp examination to ensure accurate measurement of most of the ocular endpoints.
- The Panel did not consider some of the endpoints adequate for early study termination when taken individually (e.g., pannus, area of fluorescein staining, lack of re-epithelialization). They can, however, be considered together
- The Panel emphasized that decisions to terminate a study should be based on multiple endpoints when possible.
• Only very severe endpoints (e.g., corneal perforation) would be adequate alone to terminate a study.
• The ICCVAM recommendations incorporated these Panel recommendations.
Independent Scientific Peer Review Panel

Hongshik Ahn, Ph.D.
Stony Brook University
Stony Brook, NY

Paul T. Bailey, Ph.D.
Bailey & Associates Consulting
Neshanic Station, NJ

Richard Dubielzig, D.V.M.
University of Wisconsin-Madison
Madison, WI

Henry Edelhauser, Ph.D.
Emory University School of Medicine
Atlanta, GA

Mark Evans, D.V.M., Ph.D.
Pfizer Global Research and Development
La Jolla Drug Safety Research and Development
San Diego, CA

A. Wallace Hayes, Ph.D.
Harvard School of Public Health
Andover MA

James V. Jester, Ph.D.
University of California-Irvine
Orange, CA

Tadashi Kosaka, D.V.M., Ph.D.
The Institute of Environmental Toxicology
Ibaraki, Japan

Alison McLaughlin, MSc.
Health Canada
Ottawa, Ontario
Canada

J. Lynn Palmer, Ph.D.
MD Anderson Cancer Center
Houston, TX

Robert Peiffer, Jr., D.V.M., Ph.D.
Merck Research Laboratories
Doylestown, PA

Denise Rodeheaver, Ph.D.
Alcon Research Ltd.
Dept. of Toxicology
Fort Worth, TX

Donald Sawyer, D.V.M., Ph.D.
Retired, Michigan State University
Okemos MI

Kirk Tarlo, Ph.D.
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA

Daryl C. Thake, D.V.M.
Midwest ToxPath Sciences Inc.
Chesterfield, MO

Scheffer Tseng, M.D., Ph.D.
Tissue Tech, Inc.
Miami, FL

Philippe Vanparys, Ph.D.
Cardam, Centre for Advanced Research & Development
Mol, Belgium

Maria Pilar Vinardell, Ph.D.
Universitat de Barcelona
Barcelona, Spain

Fu-Shin Yu, Ph.D.
Wayne State University
Detroit, MI

Sherry Ward, Ph.D., MBA
International Foundation for Ethical Research (IFER)
New Market, MD

Daniel Wilson, Ph.D., DABT
The Dow Chemical Co.
Midland, MI
Jan van der Valk, Ph.D.
Utrecht University
Utrecht, Netherlands
# ICCVAM Agency Representatives

* Principal agency representative  
+ Alternate principal agency representative

## Agency for Toxic Substances and Disease Registry
* Moiz Mumtaz, Ph.D.  
  Bruce Fowler, Ph.D.  
  Edward Murray, Ph.D.  
  Eric Sampson, Ph.D.

## Consumer Product Safety Commission
* Marilyn L. Wind, Ph.D. (Chair)  
+ Kristina Hatlelid, Ph.D.  
  Joanna Matheson, Ph.D.  
  Adrienne Layton, Ph.D.

## Department of Agriculture
* Jodie Kulpa-Eddy, D.V.M. (Vice-Chair)  
+ Elizabeth Goldentyer, D.V.M.

## Department of Defense
* Robert E. Foster, Ph.D.  
+ Patty Decot  
  Harry Salem, Ph.D.  
  Peter J. Schultheiss, D.V.M., DACLAM

## Department of Energy
* Michael Kuperberg, Ph.D.  
+ Marvin Stodolsky, Ph.D.

## Department of the Interior
* Barnett A. Rattner, Ph.D.  
+ Sarah Gerould, Ph.D. (to Feb. 2009)

## Department of Transportation
* George Cushmac, Ph.D.  
+ Steve Hwang, Ph.D.

## Environmental Protection Agency
Office of Pesticide Programs
* Jack Fowle, Ph.D., DABT  
+ Vicki Dellarco, Ph.D.  
+ Tina Levine, Ph.D.  
  Deborah McCall  
OECD Test Guidelines Program
Christine Augustyniak, Ph.D.  
Jerry Smrchek, Ph.D. (to July 2009)
Office of Research and Development
Suzanne McMaster, Ph.D. (to Dec. 2008)  
Julian Preston, Ph.D. (to July 2009)  
Stephanie Padilla, Ph.D. (to July 2009)
Office of Science Coordination and Policy
Karen Hamernik, Ph.D. (to July 2009)

## Food and Drug Administration
Office of the Commissioner
* Suzanne Fitzpatrick, Ph.D., DABT  
Center for Biologics Evaluation and Research
  Richard McFarland, Ph.D., M.D.  
  Ying Huang, Ph.D.
Center for Devices and Radiological Health
  Melvin E. Stratmeyer, Ph.D.  
  Vasant G. Malshet, Ph.D., DABT
Center for Drug Evaluation and Research
  + Abigail C. Jacobs, Ph.D.  
  Paul C. Brown, Ph.D.

## National Center for Toxicological Research
  + Paul Howard, Ph.D.  
  Donna Mendrick, Ph.D.  
  William T. Allaben, Ph.D. (to Jan. 2009)
Office of Regulatory Affairs
Lawrence D'Hoostelaere, Ph.D.

## National Cancer Institute
* T. Kevin Howcroft, Ph.D.  
  Chand Khanna, D.V.M., Ph.D.  
  Alan Poland, M.D. (to Oct. 2008)

## National Institute of Environmental Health Sciences
* William S. Stokes, D.V.M., DACLAM  
+ Raymond R. Tice, Ph.D.  
  Rajendra S. Chhabra, Ph.D., DABT  
  Jerrold J. Heindel, Ph.D.

## National Institute for Occupational Safety and Health
* Paul Nicolaysen, V.M.D.  
+ K. Murali Rao, M.D., Ph.D.

## National Institutes of Health
* Margaret D. Snyder, Ph.D.

## National Library of Medicine
* Pertti (Bert) Hakkinen, Ph.D.  
  Jeanne Goshorn, M.S.

## Occupational Safety and Health Administration
* Surender Ahir, Ph.D.
References
Acknowledgements

This poster was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences. The views expressed above do not necessarily represent the official positions of any Federal agency. Since the poster was written as apart of the official duties of the authors, it can be freely copied.