



Follow Up on ICCVAM Report Recommendations

Marilyn Wind, Ph.D.
Vice-Chair, ICCVAM
U.S. Consumer Product Safety Commission

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- This talk reflects the views of the author. It has not been reviewed or approved by, and may not necessarily reflect the views of the Consumer Product Safety Commission

Planned Future Studies/Activities: *In Vitro* Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Toxicity Testing

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Recommendations: Future Studies

1. *Additional efforts should be conducted to identify in vitro tests and other methods necessary to achieve accurate acute oral hazard classification.*
 - o *Studies should be conducted to investigate the potential use of in vitro cell-based methods that incorporate mechanisms of action and evaluations of ADME (absorption, distribution, metabolism, and excretion) to provide improved estimates of acute toxicity hazard categories.*
 - o *Methods should be developed to extrapolate from in vitro toxic concentrations to equivalent doses in vivo.*

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Proposed Activity

- NICEATM and the ATWG will monitor ECVAM's progress in their A-Cute-Tox Project in which they are developing *in vitro* tests and other methods necessary to achieve accurate acute oral hazard classification.
 - Determine if any parallel and/or collaborative efforts might be beneficial to this objective
 - Maintain ICCVAM and NICEATM liaisons to the Project to facilitate communication
- Draft ICCVAM Recommended Priority: High

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Recommendations: Future Studies

2. *Standardized procedures to collect in vivo measurements and observations pertinent to an understanding of the mechanisms of lethality should be included in future rat acute oral toxicity studies.*
 - *Such information will likely be necessary to support the future development of predictive mechanism-based in vitro methods.*

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Proposed Activity

- NICEATM and ICCVAM will organize an international workshop to identify and standardize procedures for collecting information pertinent to an understanding of mechanisms of lethality in rats.
 - Will work in conjunction with the ATWG, ECVAM, JaCVAM, and various stakeholders
- The outcome of the workshop will be documented in a report
 - Recommendations provided to agencies for consideration
- Draft ICCVAM Recommended Priority: High

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Recommendations: Future Studies

3. *The in vivo database of reference substances used in this validation study should be used to evaluate the utility of other non-animal approaches to estimate starting doses for acute oral toxicity tests (e.g., widely available software that uses quantitative structure activity relationships [QSAR]).*

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Proposed Activity

- NICEATM will use available quantitative structure-activity relationship [QSAR] software and compare with the reference LD50 values determined for the validation study reference substances to estimate starting doses for acute oral toxicity testing.
 - Results will be used in computer simulations to predict both animal use/reduction in the GHS acute oral toxicity classification system
- Draft ICCVAM Recommended Priority: Medium

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Recommendations: Future Studies

4. *To supplement the high quality validation database started by this study, additional high quality comparative in vitro basal cytotoxicity data should be collected when rat oral acute toxicity testing is conducted.*
 - *However, in vivo testing should not be conducted solely to collect data to assess the usefulness of the NRU test method.*
 - *Periodic evaluations of the expanded database should be conducted to further characterize the usefulness and limitations of using in vitro cytotoxicity data as part of the weight-of-evidence approach to estimate starting doses*

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Proposed Activity

- NICEATM will identify/collect high quality comparative *in vitro* basal cytotoxicity data in tandem with *in vivo* rat acute oral toxicity testing
 - Solicit submission of data from industry
 - Data will also be identified through literature searches, searches of publicly available toxicity databases, and from secondary sources.
- *In vivo* testing will not be conducted solely to collect data to assess the usefulness of the *in vitro* basal cytotoxicity test methods.
- NICEATM will evaluate the data and compare the data to regression models developed in the validation study
- Draft ICCVAM Recommended Priority: High

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Recommendations: Future Studies

5. *An expanded list of reference substances with rat acute oral LD50 values substantiated by high quality in vivo data (including data currently held by industry) should be developed for use in future in vitro test method development and validation studies.*

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Proposed Activity

- NICEATM will identify rat oral LD50 data for the 442 RC chemicals not included in the NICEATM/ ECVAM validation study.
 - Rat oral LD50 data will be identified through literature searches, searches of publicly available toxicity databases, and from secondary sources.
- NICEATM will evaluate the data retrieved to identify the appropriate LD50 values (i.e., those using adult laboratory rats and gavage administration in the absence of anesthesia) and calculate new reference values using a geometric mean of the acceptable LD50 values
- Draft ICCVAM Recommended Priority: Medium

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Planned Future Studies/Activities for *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants

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Recommended Future Activities: *In Vitro* Ocular Toxicity Test Methods

- Histopathological evaluation of corneal tissue, using a standardized scoring system, should be included when the BCOP, IRE, or ICE test methods are conducted.
 - Create a reference atlas for the histopathology of chemically-induced ocular lesions
 - Create a standardized histological scoring system for chemically-induced ocular lesions and revised decision criteria for *In vivo* and *In vitro* methods
- Develop a targeted research grants program

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Proposed Activity: Reference Atlas

- NICEATM (in partnership with ECVAM and JaCVAM) will create an international working group to facilitate the collection of reference micrographs of chemically-induced ocular lesions in excised corneas and enucleated eyes used in an *in vitro* ocular toxicity test method (rabbit, chicken, pig, bovine) and from eyes of rabbits used in *in vivo* tests.
 - The working group will review the collection of reference micrographs of chemically-induced ocular lesions to ensure that they represent different hazard classifications, chemical classes, mechanisms of action, and other physico-chemical properties.
- These micrographs will be annotated with a standard ocular histological nomenclature and organized into an atlas, which can be used as a reference for histological evaluation of samples taken during *in vitro* and *in vivo* ocular toxicity tests.
- Data gaps in hazard classifications and pre-defined physico-chemical properties of tested chemicals, if any, will be identified during the collection of the reference micrographs.
 - A strategy to fill the data gaps will be created and implemented. This could include solicitation of additional samples of chemically-induced ocular lesions from industry and private organizations.
- Draft ICCVAM Recommended Priority: High

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Proposed Activity: Standardized Scoring Scheme and Revised Decision Criteria

- NICEATM (in partnership with the international working group) will use a detailed reference atlas of chemically-induced ocular lesions (see previous slide) to create a standardized scoring system for the evaluation of these lesions.
- Decision criteria for the BCOP, ICE, and IRE test methods will be revised to utilize histological endpoints as a component for hazard classification.
- Draft ICCVAM Recommended Priority: High

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Proposed Activity: Targeted Research Areas

- NICEATM will establish a list of high priority research areas and commercialization areas for evaluation and potential funding
- NICEATM will identify stakeholders that could work in cooperation to develop RFAs and SBIRs for the areas proposed for evaluation and commercialization, respectively
- Draft ICCVAM Recommended Priority: High

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Discussion Questions for SACATM

(Lead Discussants: Drs. Becker, Bradlaw, DeGeorge, Barile)

- Are you aware of any completed, ongoing, or planned research and development activities relevant to the planned activities?
- Do you agree with the priorities assigned to each of the ICCVAM planned activities?