The ICCVAM/NICEATM Process for Developing Test Method Performance Standards

WS Stokes[1], LM Schechtman[2], A Rispin[3], RN Hill[3], K Hamernik[3], BC Blackard[4], and RR Tice[4]

[1]NTP Interagency Center for the Evaluation of Toxicological Methods (NICEATM), NIEHS, RTP, NC, [2]U.S. Food and Drug Administration, NCTR, Rockville, MD, [3]U.S. Environmental Protection Agency, Washington, DC, and [4]Integrated Laboratory Systems, Inc., RTP, NC.

Abstract

New or modified test methods proposed for regulatory testing should normally undergo validation studies to assess their reliability and relevance for specific applications. Regulatory agencies can then determine if the test method is sufficiently accurate and reliable to be accepted for a proposed specific use. The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) has established a process for developing and using performance standards (PS) to evaluate the acceptability of proposed test methods that are based on similar scientific principles and that measure or predict the same biological or toxic effect as an accepted test method. ICCVAM defined the three critical components of PS as: (1) essential test method components, i.e. the requisite structural, functional, and procedural elements of a validated test method that should be included in the protocol of a proposed mechanistically and functionally similar test method; (2) a minimum list of reference chemicals, which is used to assess the accuracy and reliability of the analogous test method; and (3) comparable accuracy and reliability values that should be achieved by the proposed test method when evaluated using the minimum list of reference chemicals. The ICCVAM also established a process for developing and recommending PS during future test method evaluations. NICEATM and an ICCVAM working group will develop proposed test method specific PS, which will be made available for public comment. An independent peer review panel will review the proposed PS for completeness and appropriateness as a part of the panel's evaluation of the proposed test method. ICCVAM will then finalize and forward recommended PS together with test method recommendations to Federal agencies and make these available to the public. The availability of PS is expected to facilitate the development and validation of test methods that are similar to previously accepted methods. ILS staff supported by NIEHS contract NO1-ES-35504. The views expressed above do not necessarily represent the official positions of any federal agency.

Performance Standards for Test Methods

- Prior to the acceptance of a new or modified test method for regulatory testing applications, validation studies are typically conducted to assess reliability and accuracy.
- The purpose of performance standards is to communicate the basis by which new proprietary (i.e., copyrighted, trademarked, registered) and nonproprietary test methods can be determined to have sufficient accuracy and reliability for specific testing purposes.
- Performance standards may be recommended by ICCVAM as part of its evaluation of the validation status of a proposed test method.
- These performance standards, based on test methods recommended by ICCVAM and/or accepted by regulatory agencies, can be used to evaluate the reliability and accuracy of other test methods that are based on similar scientific principles and that measure or predict the same biological or toxic effect.
- **The three elements of performance standards are:**
  1. **Essential Test Method Components**
  2. **Minimum List of Reference Chemicals**
  3. **Accuracy and Reliability Values**
- ICCVAM adopted and published a description of performance standards and the ICCVAM process for their development in September 2003 (ICCVAM, 2003). (Figure 1) This publication is available on the ICCVAM/NICEATM website or by request to NICEATM (NICEATM, NIEHS, 79 T. W. Alexander Drive, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709, (phone) 919-541-2384, (fax) 919-541-0947, iccvam@niehs.nih.gov)

Minimum List of Reference Chemicals

- Used to assess the accuracy and reliability of a proposed, mechanistically and functionally similar test method
- Are a representative subset of those used to demonstrate the reliability and the accuracy of the validated test method
- To the extent possible, these reference chemicals should:
  - Represent the range of responses that the validated test method is capable of measuring or predicting
  - Have produced consistent results in the validated test method and in the *in vivo* reference test method and/or the species of interest (e.g., no equivocal results)
  - Reflect the accuracy of the validated test method
  - Have well-defined chemical structures
  - Be readily available from commercial sources
  - Not be associated with excessive hazard or prohibitive disposal costs

These reference chemicals are:

- The minimum number that should be used to evaluate the performance of a proposed, mechanistically and functionally similar test method.
- Should not be used to develop the prediction model for the proposed test method.

If any of the recommended chemicals are unavailable, other chemicals for which adequate reference data are available could be substituted. To the extent possible, the substituted chemical(s) should be of the same chemical class as the original chemical(s).

Recommended Performance Standards for *In Vitro* Test Methods for Skin Corrosion

- A number of *in vitro* test methods have been proposed as alternatives to the standard *in vivo* rabbit skin procedure used to identify corrosive substances.
  - Generally, these test methods have involved the use of a cultured mammalian cell membrane matrix, isolated rat skin, or noncellular, membrane barrier.
  - ICCVAM previously evaluated and recommended for consideration to U.S. Federal agencies four validated test methods for assessing the dermal corrosivity hazard potential of chemicals: Corrositex®, EPISKIN™, EpiDerm™ (EPI-200), and the rat skin transcutaneous electrical resistance (TER) Assay.
- Because three of these methods were proprietary (Corrositex®, EPISKIN™, EpiDerm™ [EPI-200]), ICCVAM was asked by the U.S. Environmental Protection Agency (EPA) to develop and recommend performance standards that could be used to evaluate the acceptability of similar test methods that are based on similar scientific principles and that measure or predict the same biological or toxic effect. The EPA also asked ICCVAM to develop performance standards for the non-proprietary rat skin TER test method.
- In response, the ICCVAM Dermal Corrosivity and Irritation Working Group (DCIWG) drafted proposed performance standards based on these validated *in vitro* test methods.
  - In a *Federal Register* Notice published on July 1, 2003, NICEATM announced the availability of and invited public comment on the proposed performance standards for the three types of validated *in vitro* test methods for assessing the dermal corrosivity hazard potential of chemicals.
  - Comments were also obtained from the ICCVAM Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) and the EPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP). The public and the advisory committee's comments were considered by the DCIWG and ICCVAM during development of performance standards for *in vitro* corrosivity test methods based on membrane barrier test systems, cultured human skin model systems, or the rat skin TER test method.
  - The recommended final performance standards are expected to be available in April 2004. (Figure 2)

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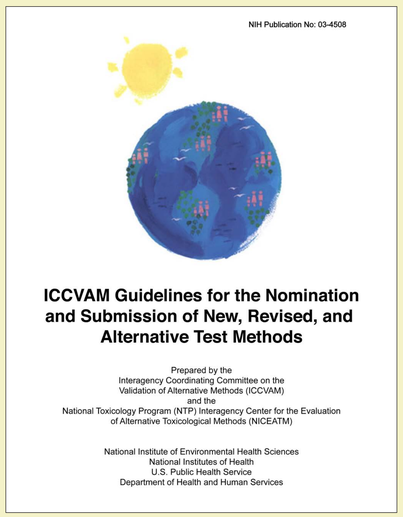
Figure 1.



Essential Test Method Components

- Essential structural, functional, and procedural elements of a validated test method that should be included in the protocol of a proposed, mechanistically and functionally similar test method.
- Unique characteristics of the test method, critical procedural details, and quality control measures.
- Adherence to essential test method components will help to assure that a proposed test method is based on the same concepts as the corresponding validated test method.

Accuracy and Reliability Values

The comparable performance that should be achieved by the proposed test method when evaluated using the minimum list of reference chemicals.

Performance parameters will normally be provided for the following:

- Accuracy
  - Sensitivity
  - Specificity
  - False positive rate
  - False negative rate
- Reliability
  - Intralaboratory Reproducibility
  - Interlaboratory Reproducibility

Note: If the test method will not be conducted in other laboratories, then an assessment of interlaboratory reproducibility may not be essential.

ICCVAM/NICEATM Process for Developing Test Method Performance Standards

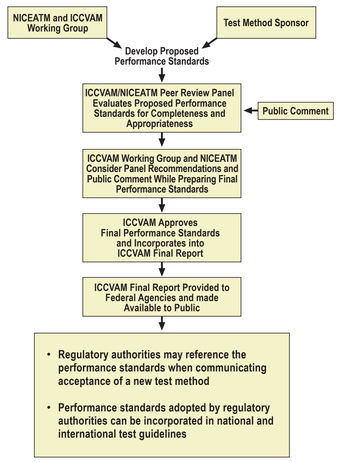
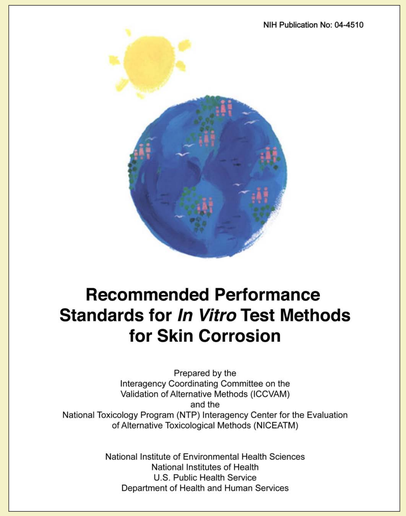


Figure 2.



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