United States
Consumer Product Safety Commission
cpsc.gov | info@cpsc.gov | 800.638.2772

Guidance for Industry and Test Method Developers:

CPSC Staff Evaluation of Alternative Test Methods and Integrated Testing Approaches and Data Generated from Such Methods to Support FHSA Labeling Requirements

January 27, 2022

Introduction

Increasingly, regulatory agencies and the public desire more ethical and predictive approaches, by moving away from the use of animals in toxicological testing, toward non-animal or "new approach methods" (NAMs) for making toxicology determinations. NAMs are *in vitro*, *in chemico*, or *in silico* methods and/or integrated approaches used to test for toxicological endpoints in place of traditional animal testing. In some cases, NAMs are combined with other NAMs or existing *in vivo* (animal) data to form an "integrated approach to testing and assessment" (IATA). An alternative approach can be used, if the approach satisfies the requirements of the agency, as well as any applicable statutes and regulations.

[1] This document provides guidance to stakeholders (*i.e.*, method developers and product manufacturers) on the process by which CPSC staff assesses whether alternative toxicological methods, integrated approaches, and the resulting data are appropriate for use in hazard labeling under the Federal Hazardous Substances Act (FHSA).

The guidance includes sections that describe factors, based on current best practices, and provides definitions and discussion of key terms and concepts related to NAMs, IATAs, and the data produced using such methods. The guidance also includes an optional NAM nomination form, which can be used to organize the information about a NAM or IATA for CPSC staff to

[1] https://www.cpsc.gov/FAQ/CPSC-Policy-on-Animal-Testing

evaluate. Submitting parties can fill out the applicable portions of the form, or they can otherwise document the pertinent information and submit it to CPSC staff, using the e-mail address provided in the guidance.

The guidance is not mandatory or prescriptive. The guidance is intended to be flexible. The guidance does not present a simple blueprint into which a given set of facts may be inserted to receive a determination. Rather, staff anticipates that the evaluation of tests for different types of toxic effects may require different approaches. Application of the guidance requires expert knowledge and the use of professional judgment.

CPSC staff notes the evolving nature of NAMs and the resulting information that will be useful in prioritizing, and ultimately, developing risk assessments for products. The guidance document should be considered a dynamic, evolving document that allows consideration of the best available science.

Test developers and submitters are encouraged to review previous staff assessments of NAMs.[2,3] Several examples of these can be found in the reference section. If questions arise concerning matters not clarified by this guidance, additional guidance can be found in previous CPSC staff documents and reports found on CPSC's Policy on Animal Testing website; or from the Commission's Directorate for Health Sciences staff.

Background

Under the FHSA, 15 U.S.C. §§ 1261-1275, manufacturers must evaluate household products to determine whether they present a hazard to consumers during reasonably foreseeable handling and use, and, if so, require precautionary labeling to address the hazard. In the evaluation of hazards, the Commission has issued regulations interpreting and supplementing the definitions of the hazards that the FHSA addresses. See, for example, the definitions for "toxicity" (16 CFR § 1500.3(c)(1) and (2)), "corrosivity" (§ 1500.3(c)(3)), "irritancy" (§ 1500.3(c)(4)), and "strong sensitizers" (§1500.3(c)(5)), and test methods that may be used for toxic substances (16 CFR § 1500.40), irritant substances (16 CFR § 1500.41), and eye irritants (16 CFR § 1500.42). The regulations do not require animal testing, nor do they require any specific test methods. Often, however, manufacturers will use animal testing to evaluate hazards to satisfy those regulations. Although animal testing is still used in toxicological testing, the CPSC and most governmental agencies support reduced use of animals in testing, by promoting the acceptance of data from alternative methods.

In 2012, CPSC updated its policy on animal testing to strongly encourage non-animal or alternative testing methods to support labeling requirements in the FHSA, and it codified this policy at 16 CFR § 1500.232. The policy encourages using scientifically validated alternatives

[2] Staff Response to the ICCVAM Recommendations on Four Test Method Evaluation Reports Regarding Ocular Toxicity Testing. March 2, 2011. https://www.cpsc.gov/s3fs-public/pdfs/blk_media_iccvam1.pdf
[3] Staff Response to the ICCVAM Recommendations on Revisions to the Murine Local Lymph Node Assay. January 26, 2011. https://www.cpsc.gov/s3fs-public/pdfs/foia_iccvam_0.pdf

to animal testing and using existing information, including expert opinion, prior human experience, and prior animal testing results, in the determination of a hazard under the FHSA. The FHSA does not require any specific type of testing. In introducing the updated policy on the animal testing policy website,[4] the Commission indicated that:

> The Commission's policy is to find alternatives to traditional animal testing that replace animals, reduce the number of animals tested, and decrease the pain and suffering in animals associated with testing household products. As such, the Commission and CPSC staff strongly encourage the use of scientifically validated alternatives to animal testing and the use of existing information, including expert opinion, prior human experience, and prior animal testing results, in the determination of hazard.

Accordingly, since CPSC's animal testing policy has been in place, CPSC toxicologists in the Directorate for Health Sciences have been tasked with reviewing alternative test methods and resulting data provided by manufacturers, to assess whether the data are scientifically valid and defensible to support each product's FHSA labeling.[5]

After a method is nominated for consideration, by CPSC staff, method developer, or any nominating body, CPSC staff will consider a new test method,[6] NAMs, or IATA for use in an FHSA labeling evaluation after its performance characteristics, advantages, and limitations (limits of use) have been adequately assessed for a specific purpose. Staff evaluates both the measurement of test reliability and relevance.

CPSC's designation of a test method or data as "acceptable" for a specific purpose is not irrevocable; subsequent data and experience with the test method may lead to a loss or affirmation of its acceptability status. Also, a test method could be considered accepted for a specific use, but not for other uses.

This guidance represents CPSC staff's thinking on the evaluation of NAMs, alternative test methods, and integrated testing approaches for consumer product safety, as of the date of publication. A CPSC guidance is not issued as a binding rule and is a non-mandatory statement that does not establish legally enforceable responsibilities. This guidance does not create or confer any rights for or on any person and does not operate to bind CPSC or the public. This guidance document contains recommendations only, unless specific regulatory or statutory

---

[4] CPSC. 2012. Recommended Procedures Regarding the CPSC's Policy on Animal Testing. Available at: https://www.cpsc.gov/FAQ/CPSC-Policy-on-Animal-Testing

[5] For example, under the FHSA, 15 U.S.C. §1261-1275, manufacturers must evaluate household products to determine whether they require precautionary labeling to address the hazards associated with their handling or use. When manufacturers present data from non-animal or alternative methods to CPSC in support of a FHSA labeling determination, such data is first sent to the Office of Compliance. If Compliance requires a technical evaluation, Compliance sends the information to Health Sciences for their input.

[6] Methods can be informed by integrating results from one or many methodological approaches [(Q)SAR, read-across, *in chemico, in vitro, ex vivo, in vivo*] or omic technologies (*e.g.*, toxicogenomics).

requirements are cited. An alternative approach can be used if the approach satisfies the requirements of the applicable statutes and regulations.

Submission Process

This guidance includes sections on the types of information that CPSC staff uses to evaluate NAMs, IATAs, and the data produced from such methods, as well as an optional NAM nomination form that may be used to organize the information. Submitting parties may fill out the applicable portions of the form (see Appendix A), or otherwise document the pertinent information and submit the information to CPSC staff using the e-mail address below. Submitters will be informed via e-mail of CPSC's final assessment. CPSC will post accepted NAMS to the CPSC's "Recommended Procedures Regarding the CPSC's Policy on Animal Testing" website.

Requests for CPSC evaluation of NAMs and IATAs, including supporting relevant information and data, should be submitted to the following e-mail address: AlternativeMethods@cpsc.gov.

Technical Information Factors for Evaluating Alternative Toxicological Test Methods and Integrated Approaches

This section describes factors that CPSC staff considers best practices for the evaluation of NAMs and IATAs. CPSC staff will consider the factors below in evaluating alternative methods and integrated approaches. Factors listed here may or may not apply to all NAMs or IATAs. Staff will not consider factors not relevant to the submitted NAM or IATA. Staff recommends that the submitting parties point out which factors do not apply and explain why those factors do not apply to their NAM or IATA. Furthermore, unforeseen factors not listed in the guidance may arise that CPSC may need in order to proceed with the NAM or IATA evaluation process. Staff will communicate any additional information needs to the submitting parties during the initial review.

An explanation of the NAM/IATA evaluation factors follows:

A. Independent scientific peer review
B. Potentially Relevant Information for Method Evaluation
    1. Selectivity
    2. Accuracy
    3. Precision
    4. Quality Control
    5. Sensitivity
    6. Reproducibility
    7. Stability

8. Robustness

C. Standard Operating Procedures and Detailed Protocols
D. Well-Defined End Point
E. Well-Defined Applicability Domain
F. Generate Data Useful for Risk Assessment
G. Limits of Use
H. Reduce, Refine, and/or Replace

Independent scientific peer review

Staff recommends that before submitting for CPSC staff evaluation, the NAM or IATA should have undergone an independent scientific peer-review process by independent scientists (*i.e.*, with no conflicts of interest), who are experts in an appropriate field (*e.g.*, toxicology, NAMs, IATAs). Conflicts of interest would include, but are not limited to, parties with a vested interest in the outcome of the studies conducted to review the NAM or IATA. Peer review can be done through several means, such as the evaluation of intra-laboratory or inter-laboratory validation studies, among other means.

Potentially Relevant Information for Method Evaluation

A submission of a NAM or IATA for CPSC staff evaluation should include a description of any intra-laboratory or inter-laboratory validation studies conducted, including whether the NAM or IATA was compared to another NAM, *in vivo* animal, or human data.

Validation can be accomplished via several different processes and involves documenting, through the use of specific laboratory investigations, that the performance characteristics of a method are suitable and reliable for the intended analytical application(s). The acceptability of data relates directly to the criteria used to validate the method. Stakeholders may contact CPSC staff at AlternativeMethods@cpsc.gov with any questions about the validation of a specific method.

A method's reliability includes reproducibility, repeatability, and robustness. In addition to the performance and applicability of the NAM/IATA, good scientific, technical, and quality practices ensure that the overall process is more efficient and effective and leads to increased confidence in the proposed method. Laboratories should retain all information necessary to operate and maintain the equipment, including equipment and software manuals, and quality and safety conformation certificates and warranties, as well as documentation of suppliers for materials, cells and reagents, if this information is relevant for evaluations of a NAM or IATA. For studies intended to be GLP-compliant, an IQ/OQ/PQ (Installation Quality/Operation Quality/Performance Quality) report for each instrument used also may be relevant.

1. Selectivity

Selectivity is the ability of an analytical method to differentiate, detect, and/or quantify the analyte of interest in the presence of other potentially interfering components in the sample. Evidence should be provided that the substance detected or quantified is the intended chemical or analyte of interest. Each blank sample should be tested for interference, and selectivity should be ensured at the lower limit of quantification (LLOQ), or limit of detection (LOD), whichever is more appropriate for the system.

Method developers should document interfering substances, which can come from critical and non-critical components of the method, including any interference with the detected signal (*e.g*., fluorescence/absorbance, luciferase, enzymatic) of the method. Interference can also come from consumables, such as certain plastics in endocrine disruptor test methods. Potential interfering substances include, but are not limited to: endogenous matrix components; metabolites; decomposition products; and other xenobiotics. If the method is intended to quantify more than one analyte, each analyte should be tested to ensure that there is no interference.

2. Accuracy

Accuracy pertains to the concordance of the assay data to known data from humans, animals, or other NAMs, and it is documented by a description of the closeness of mean test results, obtained by the method, to the known value (concentration) of the analyte. Whenever possible, well-defined reference materials can be used to check instrument response and method validity. Accuracy can be determined by replicate analysis of samples containing known amounts of the analyte (*i.e*., Quality Control samples). Quantitative measures of accuracy (*i.e*., sensitivity, specificity, positive and negative predictivity, false positive, and negative rates) should be reported.

3. Precision

Precision of an analytical method as it pertains to the closeness of individual measures of an analyte when the procedure is applied repeatedly to multiple aliquots of a single homogeneous volume of a given matrix is usually expressed as the coefficient of variation (CV).

It is helpful to include a description on the precision of the analytical method used and any other tests of precision, such as those assessing performance variability when different personnel use the proposed method, or when different instrumentation is used for the method, as well as participating in inter-laboratory comparison studies, when possible.

4. Quality Control (QCs)

Quality control systems (*i.e.*, charts or other performance standards) track the quality of any qualitative or quantitative process to determine if the method and its components are performing as intended. Control charts are often used for time-series data, but they may also be used for monitoring discrete data sets, such as batch-to-batch variability or operator performance. QC systems should be reported, if relevant for the submitted method or IATA.

5. Sensitivity

Sensitivity is the lowest analyte concentration that can be measured with acceptable accuracy and precision (*i.e.*, LLOQ or LOD). Response of function is the dependence of a signal on systematic change in experimental condition. If sensitivity applies to the nominated NAM or IATA, describe any systematic testing over a range of concentrations or activity with reference samples to determine the range in which the assay is sensitive.

6. Reproducibility (test method reliability)

Reproducibility is an assessment of test method reliability or repeatability and should be included with the information submitted, where applicable. Reproducibility of the method can be assessed by replicate measurements using the assay, including quality controls and possibly incurred samples. This assessment should include discussion of the rationale for the selection of the substances used to evaluate intra- and inter-laboratory reproducibility, and the extent to which they represent the range of possible test outcomes. Outlying values should be identified and discussed. A quantitative statistical analysis of the extent of intra- and inter-laboratory variability, or coefficient-of-variation analysis, should be included. Measures of central tendency and variation should be summarized for historical control data (negative, positive, and vehicle where applicable). In cases where the proposed test method is mechanistically and functionally similar to a validated test method with established performance standards, the reliability of the two test methods should be compared and the potential impact of any differences discussed.

7. Stability

Stability refers to the ability of a reagent to produce similar or acceptable results over a period of time in a given environment. The stability of a test substance, reagents, and testing apparatus (*e.g.*, plastic microplate) should be ensured to avoid interferences from degradation products and changes to the applied actual dose. Stability studies performed on any of the components should be included. The stability of any chemical mixtures or prepared samples being prepared before the day of the study should be evaluated for stability before use in development or validation studies. The chemical stability of a

given mixture or matrix under specific conditions for specific time intervals is assessed in several ways. Pre-study stability evaluations should cover the expected sample handling and storage conditions during the conduct of the study, including conditions at the test site, during shipment, and at all other secondary sites. The stability of an analyte in a particular mixture, matrix, and container system is relevant only to that mixture, matrix, and container system and should not be extrapolated to other systems. Stability testing should evaluate the stability of the analytes for long-term (frozen at the intended storage temperature) and short-term (bench top, room temperature) storage, and after freeze and thaw cycles and the analytical process. Conditions used in stability experiments should reflect situations likely to be encountered during actual sample handling and analysis. If, during sample analysis for a study, storage conditions changed and/or exceeded the sample storage conditions evaluated during method validation, stability should be established under these new conditions.

8. Robustness

Robustness is the ability of a method to be reproduced under different conditions or circumstances, without the occurrence of unexpected differences in the obtained results. Robustness testing is often used to detect changes in results from unintended variations in experimental reagents or protocols. Robustness testing is recommended for all aspects of test methods, and ranges for all parameters and measurements should be established whenever and wherever possible.

For example, an incubation time of 5 minutes was established as optimal for a study, but after robustness testing, data passed all QC requirements at 5 minutes plus or minus 30 seconds. Therefore, the robustness tested acceptable incubation time would be 5 minutes ± 30 seconds. The following is a list of some, but not all, study parameters that should have an established acceptance range:

- Incubation times
- Incubation temperatures
- pH
- Sources of reagents
- Cell densities
- All experimental conditions
- Analysis software

When applicable, robustness testing for critical and non-critical reagents should also be reported. Different suppliers (whenever practical) should be tested to determine if a reagent should be purchased from one supplier or if multiple suppliers can be used.

Instrumentational robustness testing should also be conducted whenever applicable. Cross-laboratory validation often involves different brands of instruments with different

performance parameters and capabilities, which can add to the variability of the data, as well as change parameters of the method performed.

Standard Operating Procedures and Detailed Protocols.

The party submitting the NAM for review should provide a written standard operating procedure (SOP) to ensure a complete system of quality control and assurance is in place and functional. SOPs should cover all aspects of analysis. The SOPs also should include record keeping, security, and chain-of-sample custody (accountability systems that ensure integrity of test articles), sample preparation, and analytical tools, such as methods, reagents, equipment, instrumentation, and procedures for quality control and verification of results. Detailed protocols, including complete product description and formulation, test substance volume/weight, should be readily available to CPSC staff and/or in the public domain. The SOP should include the assay's ability to test the product as a whole using extracts, or explain how individual components or ingredients that make up the product were tested. Proprietary information will be handled appropriately. As part of these protocols, the submitting party should also provide a list of operating characteristics and operational criteria for judging test performance and results. Operational information and criteria for the systems may vary, but the criteria could include Quality Control (QC) charts or other performance standards for all controls, standards, and experimental groups. A description of the statistical methods used to assess the data should be included. In addition, include how experimental uncertainty, statistical uncertainty, interference, and background were assessed.

Well-Defined Endpoint

Data generated by the test method should adequately measure or predict the endpoint of interest. An example of this would be the LLNA assay giving information about a specific key event in the skin sensitization adverse outcome pathway (AOP). The data should also demonstrate a linkage between the new test method and an existing test method (*i.e.*, Guinea Pig maximization test) or between the new test method and effects in the target species. Information that defines what constitutes a positive, negative, or inconclusive result in the NAM or IATA should be included.

Well-Defined Applicability Domain

There should be adequate test method data for chemicals and/or products representative of those relevant to CPSC regulations, and for which the test is proposed. For example, a method that only has data on pesticides may not be applicable to chemicals and products relevant to CPSC and may not be sufficient for evaluation. The NAM or IATA should clearly describe the physico-chemical properties of the applicability domain. This would include any limitation of the method, such as: chemicals of a limited molecular weight

range, volatility, solubility or stability. A description of the method(s) and its/their associated data appropriateness for labeling determinations, or labeling and risk assessment, or consumer products, or mixtures, should be included, as well as whether the NAM is a standalone test, or is part of an IATA.

Generate Data Useful for Risk Assessment

The test method should generate data useful for risk assessment purposes (*i.e.*, for hazard identification, dose-response assessment, or exposure assessment) as it pertains to the FHSA. The data produced should be a direct indicator of an effect on a key event in an AOP, receptor activation or mechanism directly related to risk assessment or hazard identification. Such test methods may be useful alone or as part of an IATA.

Limits of Use

The specific strengths and limitations of the test method should be clearly identified and described. Any interference or interfering chemicals should be listed. Any chemicals or classes of chemicals that cannot be tested should be listed. Limits of use about what materials can be tested should be specifically identified.

Reduce, Refine, and/or Replace

The NAM or IATA should describe in detail how it will reduce, refine, and replace animal tests. A reduction is a method that decreases the number of animals used. A refinement is a method that reduces animal suffering. A replacement is a NAM or IATA that has been designed to fully replace a component of or an entire existing regulatory test method.

Technical Information Factors for Evaluating Data from Alternative Toxicological Methods and Integrated Approaches

CPSC staff will consider the following factors in evaluating data from alternative methods and approaches.

Data submitted

Data submitted to CPSC from NAMs and integrated testing approaches are preferably from methods accepted by CPSC or validated by agencies or organizations with strong credentials (for example, but not limited to; ICCVAM, OECD, and the International Cooperation on Alternative Test Methods (ICATM)), and are accompanied by

documentation for CPSC technical staff's evaluation of the method and data. However, CPSC staff will evaluate any data submitted for review.

Scientific and Regulatory Rationale

A statement, including the scientific and regulatory rationale for the use of the NAM or integrated testing approach, plus a clear statement of its proposed use, should be submitted with the data to CPSC. This statement should include (but not be limited to) the relationship of the test method's endpoint(s) to the biologic effect of interest. Alternative test methods may not replicate all of the metabolic processes relevant to chemical toxicity that occur *in vivo* in humans. A description of the known limitations of the test, including a description of the classes of materials (*e.g*., alcohols, metals) that the method can and cannot accurately assess, should be included. Include a description of the product tested and how it was tested. Indicate whether the product was tested as a whole product (*i.e*., an extract was made), or if the components or ingredients of the product were tested individually or grouped. Additionally, a description of false positive and false negative rates and any underlying causal effects should be included.

GLP-Compliant Data

Ideally, all data supporting the validity of a test method should be obtained and reported in accordance with Good Laboratory Practices (GLPs) or in the spirit of GLP. Aspects of data collection not performed according to GLPs should be fully described, along with their potential impacts.

References

- CPSC – CONSUMER PRODUCT SAFETY COMMISSION [CPSC Docket No. CPSC–012–0036] 16 CFR Part 1500. Hazardous Substances and Articles; Administration and Enforcement Regulations: Revisions to Animal Testing Regulations. https://www.govinfo.gov/content/pkg/FR-2012-12-10/pdf/2012-29258.pdf
- ICCVAM - Validation and Regulatory Acceptance of Toxicological Test Methods. March 1997. https://ntp.niehs.nih.gov/iccvam/docs/about_docs/validate.pdf
- ICCVAM – ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods. September 2003. https://ntp.niehs.nih.gov/iccvam/suppdocs/subguidelines/sd_subg034508.pdf
- ICCVAM – APPENDIX D: ICCVAM VALIDATION AND REGULATORY ACCEPTANCE CRITERIA. https://ntp.niehs.nih.gov/iccvam/suppdocs/subguidelines/sg034508/sgappd.pdf
- OECD Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment. August 18, 2005. https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd-gd34.pdf
- EPA – Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program. June 22, 2018. https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf
- EPA – New Approach Methods Work Plan Reducing Use of Animals in Chemical Testing. June 2020. https://www.epa.gov/sites/production/files/2020-06/documents/epa_nam_work_plan.pdf
- FDA – FDA's Predictive Toxicology Roadmap. December 2017. https://www.fda.gov/media/109634/download
- FDA – Advancing Regulatory Science at FDA. August 2011. https://www.fda.gov/media/81109/download
- Regulatory Acceptance September 22, 2008, AltTox.org. http://alttox.org/assets/files/Regulatory%20Acceptance.pdf
- Avila, M.A. et.al. (2020). An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs). Regulatory Toxicology and Pharmacology. 114. 104662. http://www.sciencedirect.com/science/article/pii/S027323002030088X
- Guidance for Industry Bioanalytical Method Validation - DRAFT GUIDANCE. September 2013. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER); Center for Veterinary Medicine (CVM). Revision 1. https://www.fda.gov/media/70858/download
- ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods – September 2003. https://ntp.niehs.nih.gov/iccvam/suppdocs/subguidelines/sd_subg034508.pdf

- VALIDATION AND REGULATORY ACCEPTANCE OF TOXICOLOGICAL TEST METHODS A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods – March 1997. https://ntp.niehs.nih.gov/iccvam/docs/about_docs/validate.pdf
- Anne L Plant, Laurie E Locascio, Willie E May & Patrick D Gallagher. (2014). Improved reproducibility by assuring confidence in measurements in biomedical research. Nature Methods. Vol. 11 No. 9 (September): 895-898.
- Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense. The National Academies Press. https://www.nap.edu/catalog/21775/application-of-modern-toxicology-approaches-for-predicting-acute-toxicity-for-chemical-defense
- Draft GUIDANCE DOCUMENT ON GOOD IN VITRO METHOD 2 PRACTICES (GIVIMP) FOR THE DEVELOPMENT AND IMPLEMENTATION OF IN VITRO METHODS FOR REGULATORY USE IN HUMAN SAFETY ASSESSMENT. OECD http://www.oecd.org/env/ehs/testing/OECD%20Draft%20GIVIMP_v05%20-%20clean.pdf
- Staff Response to the ICCVAM Recommendations on Four Test Method Evaluation Reports Regarding Ocular Toxicity Testing. March 2, 2011. https://www.cpsc.gov/s3fs-public/pdfs/blk_media_iccvam1.pdf
- Staff Response to the ICCVAM Recommendations on Revisions to the Murine Local Lymph Node Assay. January 26, 2011. https://www.cpsc.gov/s3fs-public/pdfs/foia_iccvam_0.pdf
- Staff Recommendation on Response to ICCVAM Revisions to the Murine Local Lymph Node Assay. March 10, 2010. https://www.cpsc.gov/s3fs-public/pdfs/foia_iccvam.pdf
- Staff Recommendation on response to ICCVAM on the use of In Vitro Basal Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing (9999). August 28, 2008. https://www.cpsc.gov/s3fs-public/pdfs/foia_invitr11.pdf
- Staff Recommendations on Response to ICCVAM on Four In Vitro Ocular Toxicity Test Methods (9999) (BALLOT VOTE). January 28, 2008. https://www.cpsc.gov/s3fs-public/pdfs/foia_ocular.pdf
- Recommended Response to ICCVAM on Acute Toxicity Testing (9999). August 28, 2003. https://www.cpsc.gov/s3fs-public/pdfs/foia_testing.pdf

Appendix A

New Approach Method (NAM) Application Form (Optional)

Use this form to organize information that may facilitate CPSC's evaluation of NAMs. Submitters may use this form, or any other suitable format, to request CPSC evaluation and provide NAM information.

1. General Information

1.1. **NAM Title/Name**:

1.2. NAM Nominating Official/Organization (with contact information):

1.3. **NAM Category** (check all that apply):

- ☐ *In chemico*
- ☐ *In silico*
  - o Analog identification
  - o Predictive model
  - o Quantitative-structure activity relationship (QSAR)
  - o Read-across
  - o Other in silico
- ☐ *In vitro*
  - o 3-D/Organotypic
  - o 2-D/Cell-based
  - o Cell-free
  - o Other in vitro
- ☐ Integrative method (e.g., Integrated Approaches to Testing and Assessment, Defined Approach)
- ☐ Other

1.4. **Description of the endpoint(s) measured, modeled, or predicted (*e.g.*, skin irritation, ocular irritation, skin sensitization, estrogen receptor signaling, ER mediated breast cancer AOP, model for systemic bioavailability)**:

2. Method Development History

2.1. **NAM Developer** (with contact information)

2.2. **NAM Development Date** (year)

2.3. **Original Method Publication** (authors, year, journal, and PubMed ID or DOI)

2.4. **Current Method Version** (number and date)

3. Method Description

3.1. Brief description of the method protocol/steps.

3.2. Type(s) of values are reported.

3.3. Calculation methods used.

3.4. For NAMs that are models, description of the feature/descriptor set and modeling method used.

3.5. Description of the throughput and resource intensity for the current version of the NAM (*i.e.*, cost per sample, samples processed per day).

4. Relevance

4.1. **Intended Risk Decision Context** (check all that apply):

- ☐ Screening-level assessments
- ☐ Prioritization
- ☐ Risk evaluation
- ☐ Other (explain below)

Other:

4.2. **Relation of NAM Endpoint to Risk Decision Context** (check all that apply):

- ☐ Hazard-Human Health as it applies to FHSA rules:
  - o Acute toxicity
  - o Carcinogenicity
  - o Cardiotoxicity
  - o Developmental toxicity
  - o Epidemiology
  - o Immunotoxicity
  - o Irritation/Sensitization
- ☐ Dermal/skin
- ☐ Ocular/eye
- ☐ Respiratory/lung
- ☐ Undesignated
- ☐ Particulate overload
- ☐ Cationic binding
- ☐ Chelation
- ☐ Surfactancy
- ☐ Waterproofing
  - o Metabolism and Pharmacokinetics
  - o Mutagenicity/Genetic toxicity
  - o Neurotoxicity
  - o Reproductive toxicity
  - o Skin corrosion test
  - o Systemic toxicity
  - o Other health effect
- ☐ Physical-Chemical Properties
  - o Boiling point
  - o Dissociation constant
  - o Melting point
  - o Molecular weight
  - o Octanol water partition coefficient (log Kow)
  - o Oxidation/Reduction
  - o Physical state description
  - o Vapor pressure
  - o Water solubility
- ☐ Exposure/Monitoring
  - o General Population
  - o Workplace/Occupational

4.3. Brief description of scientific rationale linking the NAM endpoint(s) to the relevant CPSC FHSA labeling requirements, with supporting references.

4.4. Description of AOP, if the NAM endpoint(s) map to an existing adverse outcome pathway (AOP).

4.5. Description of use of the NAM endpoint(s) for qualitative evaluations (*e.g.*, hazard identification) and/or quantitative evaluations (*e.g.*, establish a point of departure for hazard) for FHSA labeling requirements.

4.6. Description of the method used (if any) to define the chemical applicability domain and limitations of the NAM.

4.7. Description of any other chemical limitations to the NAM (*e.g.*, DMSO solubility, vapor pressure, chemical classes known to produce false positive or false negative results).

5. Reliability

5.1. Controls or standards used with the NAM, with supportive literature references and/or scientific rationale.

5.2. Description of the intra-laboratory reproducibility of the NAM and how quality assurance acceptance/rejection criteria were established.

5.3. Lists of all reference or training set chemicals used to evaluate the NAM's performance with anticipated results, literature references and scientific rationale.

5.4. Descriptions of how the NAM's performance was evaluated using reference or training set chemicals with binary classifier statistics (or other appropriate metric).

5.5. Description of any uncertainties or known limitations of the NAM (*e.g.*, assay artifacts or interference, false positives/negatives, metabolic activity, dosing limits).

5.6. Description of any mathematical uncertainty in the calculations and how this uncertainty is handled.

5.7. Description of the limits of detection or quantification of the NAM.

5.8. Description of any specialized or proprietary equipment, software or data.

5.9. Description of external experience with the NAM (*i.e.*, other than the developers), including a list of external users and description of the inter-laboratory reproducibility using control/reference chemicals.

5.10. Documentation of any independent review(s) of the NAM that may have been performed (with documentation and references).

6. Documentation for Evaluation - Please provide the following documentation with the completed form for evaluation:

6.1. Any independent peer review by disinterested persons (*i.e.*, no conflicts of interest) who are experts in the field, knowledgeable of the test method, and financially (and otherwise) unencumbered by the outcome of the evaluation.

Examples of accepted groups of independent scientific peer reviewers are, but not limited to:

- Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM)
- International Cooperation on Alternative Test Methods (ICATM) partners (*e.g*., CCAAM, EURL ECVAM, JaCVAM, KoCVAM)
- Organization for Economic Co-operation and Development (OECD)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA)

6.2. Detailed test method with standard operating procedures (SOPs), a list of operating characteristics, and operational criteria for judging test performance and results.

6.3. Intra-laboratory or inter-laboratory validation studies, including description of comparison of the NAM or IATA to in vivo animal or human data, and evaluation of:

- Selectivity
- Accuracy
- Precision
- Quality Control
- Sensitivity
- Reproducibility
- Stability
- Robustness

6.4. GLP Compliance statement, including which aspects of the study were conducted under GLP or spirit-of-GLP, and which parts of the study were not performed according to GLPs, including description of potential impacts.