



UNITED STATES
 CONSUMER PRODUCT SAFETY COMMISSION
 4330 EAST WEST HIGHWAY
 BETHESDA, MD 20814

This document has been electronically approved and signed.

DATE: January 27, 2021

BALLOT VOTE SHEET

TO: The Commission
 Alberta E. Mills, Secretary

THROUGH: Mary T. Boyle, Executive Director
 Jennifer Sultan, Acting General Counsel*

FROM: Daniel Vice, Acting Assistant General Counsel, Regulatory Affairs
 Hyun S. Kim, Attorney, Regulatory Affairs

SUBJECT: Notice of Availability - Proposed 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

BALLOT VOTE DUE: Tuesday, February 2, 2021

Consumer Product Safety Commission (CPSC) staff drafted proposed guidance to outline the staff’s procedure for evaluating alternative test methods and integrated testing approaches in place of traditional animal testing. Such alternative test methods, if accepted by the CPSC, would be considered reliable test methods for evaluating compliance with certain labeling requirements under the Federal Hazardous Substances Act. The Office of the General Counsel prepared a draft *Federal Register* notice of availability (NOA) for the Commission’s review. The draft NOA announces the availability of the proposed guidance and asks for public comment.

Please indicate your vote on the following options:

- I. Approve publication of the attached notice in the *Federal Register*, as drafted.

 (Signature)

 (Date)

II. Approve publication of the attached notice in the *Federal Register*, with changes. (Please specify.)

(Signature)

(Date)

III. Do not approve publication of the attached notice in the *Federal Register*.

(Signature)

(Date)

IV. Take other action. (Please specify.)

(Signature)

(Date)

Attachment: Draft *Federal Register* Notice: Notice of Availability: “Proposed 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.”

*These documents were reviewed and approved by John G. Mullan in his capacity as the General Counsel before his January 18, 2021 departure.

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

[Docket No. CPSC-2021-XXXX]

Notice of Availability: Proposed Guidance on Alternative Test Methods and Integrated Testing Approaches

AGENCY: U.S. Consumer Product Safety Commission.

ACTION: Notice of availability.

SUMMARY: The Consumer Product Safety Commission (Commission or CPSC) is announcing the availability of a document titled, “Proposed 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.” The Commission requests comments on the proposed guidance.

DATES: Submit comments by [**Insert date 75 days after date of publication in the *Federal Register***].

ADDRESSES: You may submit comments, identified by Docket No. CPSC-2021-XXXX, by any of the following methods:

Electronic Submissions: Submit electronic comments to the Federal eRulemaking Portal at: <https://www.regulations.gov>. Follow the instructions for submitting comments. The CPSC does not accept comments submitted by electronic mail (e-mail), except through <https://www.regulations.gov>. The CPSC encourages you to submit electronic comments by using the Federal eRulemaking Portal, as described above.

Mail/hand delivery/courier Written Submissions: Submit comments by mail/hand delivery/courier to: Division of the Secretariat, Consumer Product Safety Commission, Room 820, 4330 East West Highway, Bethesda, MD 20814; telephone: (301) 504-7479; email: cpsc-os@cpsc.gov.

Instructions: All submissions must include the agency name and docket number for this notice. CPSC may post all comments received without change, including any personal identifiers, contact information, or other personal information provided, to: <https://www.regulations.gov>. Do not submit electronically: confidential business information, trade secret information, or other sensitive or protected information that you do not want to be available to the public. If you wish to submit such information, please submit it according to the instructions for written submissions.

Docket: For access to the docket to read background documents or comments received, go to: <https://www.regulations.gov>, and insert the docket number, CPSC-2021-XXXX, into the “Search” box, and follow the prompts. The proposed guidance is available under “Supporting and Related Material.” It is also available on the Commission’s website at: _____, and from the Commission’s Division of the Secretariat.

FOR FURTHER INFORMATION CONTACT: John Gordon, Toxicologist, Directorate for Health Sciences, U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850–3213; telephone: 301-987-2025; email: jgordon@cpsc.gov.

SUPPLEMENTARY INFORMATION:

A. BACKGROUND

The Federal Hazardous Substances Act (FHSA), 15 U.S.C. 1261-1275, requires that hazardous substances bear certain cautionary statements on their labels.

Manufacturers may perform toxicological tests to determine whether such products require cautionary labeling addressing the hazard. Although animals are still used in toxicological testing, most governmental agencies support reduced use of animals in testing, by promoting the acceptance of data from alternative test methods.

In 1997, the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), and 13 federal agencies (including CPSC) joined to form the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM). ICCVAM sponsors scientific review of non-animal tests (known as New Approach Methodologies or NAMs) that may reduce, refine, or replace animal tests in evaluating potential hazards. Reviews from ICCVAM and other federal agencies can provide a basis for regulatory agencies, such as CPSC, to consider non-animal testing alternatives for use in regulatory decision making. In the past, CPSC staff relied upon ICCVAM's validation of new alternative testing methods, as reliable test methods to determine compliance with the labeling requirements of the FHSA. However, ICCVAM no longer formally validates test methods.

In 2012, CPSC issued a policy on non-animal or alternative testing methods to support labeling requirements under the FHSA, as codified under 16 CFR 1500.232 (Animal Testing Policy). CPSC's website lists current CPSC-accepted alternative test methods and their conditions of use.¹ Since 2012, new advancements in toxicological

¹ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

testing, and, in particular, with NAMs, have occurred. NAMs include *in vitro* (in test tube), *in chemico* (all chemical test, no biological material), or *in silico* (computer models) methods and approaches used to test for toxicological effects in place of 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” (IATAs).

Because ICCVAM no longer formally validates test methods, to assist stakeholders, including the public, manufacturers, test method developers, and test laboratories, in determining what test methods are deemed reliable for determining compliance with the labeling requirements under the FHSA, CPSC staff drafted proposed guidance clarifying staff’s informational requirements and process for evaluating NAMs and IATAs. As described in the proposed guidance, the types of information CPSC staff would use to evaluate NAMs or IATAs submitted to CPSC would include (but not be limited to): concordance and reproducibility data; false positive and false negative rates; applicability domain; test endpoint; validation studies; or any other pertinent information needed to make a determination. The proposed guidance also includes an optional NAM nomination form, which can be used to organize information about a NAM or IATA for CPSC staff evaluation. Such non-animal alternative test methods, if accepted by CPSC, would be considered reliable test methods for determining compliance with the labeling requirements under the FHSA. Additionally, CPSC would continue to list CPSC-accepted alternative test methods on CPSC’s website.

The proposed guidance is not a rule and does not establish legal requirements. The proposed guidance is intended to inform stakeholders about what information CPSC

staff uses to evaluate NAMs or IATAs for FHSA labeling determinations. The proposed guidance also informs stakeholders of CPSC staff’s process for evaluating that information. Depending on the complexity of specific NAMs or IATAs, the information discussed in the guidance may or may not apply; and in some instances, staff may need additional information not specifically described in the guidance document to make an evaluation.

The proposed guidance is available at: <https://www.regulations.gov> under docket number, CPSC-2021-XXXX, under “Supporting and Related Material” on the Commission’s website at: _____, and from the CPSC’s Division of the Secretariat, at the location listed in the **ADDRESSES** section of this notice.

B. REQUEST FOR COMMENTS

The Commission invites comments on the “Proposed 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.” The CPSC will consider all timely comments before finalizing the guidance. Comments should be submitted by [**Insert date 75 days after date of publication in the *Federal Register***]. Information on how to submit comments can be found in the **ADDRESSES** section of this notice.

Dated: _____

Alberta E. Mills, Secretary
Consumer Product Safety Commission

This document has been electronically approved and signed.



UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MARYLAND 20814

Memorandum

Date: January 27, 2021

TO: The Commission
Alberta E. Mills, Secretary

THROUGH: Jennifer Sultan, Acting General Counsel¹
Mary T. Boyle, Executive Director
DeWane Ray, Deputy Executive Director for Operations

FROM: Duane Boniface, Assistant Executive Director
Office of Hazard Identification and Reduction
John D. Gordon, Ph.D., Project Manager
Division of Toxicology and Risk Assessment, Directorate for Health Sciences

SUBJECT : Proposed Guidance on CPSC Staff's Technical Evaluation of Alternative Toxicological Testing Methods

I. Introduction

Federal regulatory agencies, the public, and other stakeholders are increasingly calling for more ethical and predictive approaches in toxicology determinations about chemicals and products. Thus, agencies and stakeholders have sought to move away from the use of animals in toxicological testing and toward establishing non-animal methods or "new approach methodologies" (NAMs).² NAMs are *in vitro* (in test tube), *in chemico* (all chemical test, no biological material), or *in silico* (computer models) methods and approaches used to test for toxicological effects in place of 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). The U.S. Consumer Product Safety Commission (CPSC or Commission) already has accepted certain NAMs for testing products for skin and eye irritation and skin sensitizers.³ This briefing package describes CPSC staff's proposed guidance for determining

¹ These documents were reviewed and approved by John G. Mullan in his capacity as the General Counsel before his January 18, 2021 departure.

² This document has not been reviewed or approved by, and may not necessarily represent the views of, the Commission.

³ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

whether alternative toxicological methods, IATAs, and the resulting data are appropriate for use in hazard labeling under the Federal Hazardous Substances Act (FHSA) (see TAB A).

This proposed guidance is intended to assist stakeholders (*i.e.*, method developers and product manufacturers) in complying with the FHSA and in developing and evaluating alternative methods. The proposed guidance is intended to inform stakeholders about what information CPSC staff uses to evaluate the utility of NAMs or IATAs in FHSA labeling determinations. Depending on the complexity of specific NAMs or IATAs, the information discussed in the guidance may or may not apply; and in some instances, staff may need additional information not specifically described in the guidance document to make an evaluation. In either case, this guidance is not intended to be mandatory or prescriptive, and it would not bind CPSC or the public in any way. The proposed guidance will serve to promote transparency in CPSC staff's assessment process, as well as demonstrate how CPSC is adapting to modern testing methods and concepts. CPSC staff's proposed guidance also will standardize staff's evaluation of alternative toxicological methods, integrated approaches, and data.

The proposed 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. CPSC staff expects that the test developers will use their professional judgment and expertise in applying the proposed guidance in their submissions. Test developers are encouraged to review previous CPSC staff briefing packages on NAMs that staff has already reviewed. Two examples of these are the ocular assays⁴ and the Local Lymph Node Assay (LLNA).⁵ Additional guidance also may be found in previous CPSC staff documents and reports, such as toxicity, exposure, and risk assessments⁶; or it may be found in data from the Commission's Directorate for Health Sciences staff.

CPSC staff expects the proposed guidance document to be a dynamic, evolving document, incorporating the best available science; staff will update the guidance document as the science evolves.

II. Background

Under the FHSA, 15 U.S.C. §1261-1275, manufacturers must evaluate household products to determine whether such products present a hazard to consumers during reasonably foreseeable handling and use; and, if so, manufacturers must provide with the products, precautionary labeling to address the hazard. The Commission has issued regulations interpreting and supplementing the definitions of the hazards that the FHSA addresses. See, for example, definitions for "toxicity" (16 CFR §1500.3(c)(1) and 16 CFR §1500.3(c)(2)), "corrosivity" (§1500.3(c)(3)), "irritancy" (§1500.3(c)(4)), and "strong sensitizers" (§1500.3(c)(5)), along with test methods that may be used to evaluate potentially toxic substances (16 CFR §1500.40),

⁴ 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

⁵ 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

⁶ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

irritant substances (16 CFR §1500.41), and eye irritants (16 CFR §1500.42). Often, manufacturers will use animal testing to evaluate hazards to satisfy those regulations. However, the regulations do not require any specific animal testing. Although animal testing is still used in toxicological testing, most governmental agencies support reduced use of animals in testing, by promoting the acceptance of data from alternative methods.

In 2012, CPSC issued an updated policy⁷ which strongly encourages 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 to animal testing and using existing information, including prior human experience, prior animal testing results, and expert judgment determining what constitutes a hazard under the FHSA.

Accordingly, since CPSC's animal testing policy has been in place, CPSC toxicologists in the Directorate for Health Sciences are tasked with reviewing alternative test methods and resulting data provided by manufacturers, to assess whether the test methods and data are scientifically valid and defensible to support each product's FHSA labeling.⁸ Alternative test methods currently accepted by CPSC; and their conditions of use, are found on CPSC's animal testing policy website.⁶

In 1997, the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), and 13 federal agencies (including CPSC) joined to form the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM). ICCVAM sponsors scientific review of non-animal tests or NAMs that may reduce, refine, or replace animal tests in evaluating potential hazards. Reviews from ICCVAM and other federal agencies, can provide a basis for regulatory agencies, such as CPSC, to consider such alternative tests for use in safety and regulatory decision making. In the past, CPSC staff relied upon ICCVAM's validation of new alternative testing methods, as well as recommendations to regulatory agencies. For CPSC, such alternatives, if accepted, were considered reliable test methods to determine compliance with the labeling requirements of the FHSA. However, as discussed below, ICCVAM has changed its processes for evaluating alternative testing methods. ICCVAM no longer formally validates test methods.

III. The Proposed Guidance

The proposed guidance describes the types of information that CPSC staff uses to evaluate NAMs and IATAs for their potential use in FHSA labeling determinations. The guidance includes sections that describe current thinking for best practices, and it also provides definitions and discussion of key terms and concepts related to NAMs, IATAs and the data produced using such methods and approaches. The proposed guidance also includes an optional NAM nomination form, which can be used to organize the information about a NAM or IATA for evaluation by CPSC staff. Submitting parties may fill out the applicable portions of the form, or

⁷ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

⁸ 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.

otherwise document the pertinent information and submit the information to CPSC staff using the e-mail address provided in the guidance. CPSC staff will inform submitters of CPSC's final determinations via e-mail. CPSC will post accepted NAMS or IATAs to CPSC's "Recommended Procedures Regarding the CPSC's Policy on Animal Testing" website.

IV. Discussion

A. Need for CPSC Guidance

External developments support staff's recommendation to publish a guidance document. First and foremost, ICCVAM has changed its processes for evaluating alternative testing methods. Previously, CPSC staff relied upon ICCVAM's validation of new alternative testing methods, as well as recommendations to regulatory agencies. However, ICCVAM will no longer formally validate methods and submit recommendations to the Commission for approval. Instead, ICCVAM will work with developers and regulatory agencies to create methods that meet agency needs. Thus, CPSC staff will be required to provide, in written format, the factors CPSC staff considers in evaluating toxicology test methods and approaches so that ICCVAM and the regulated community understand staff's informational needs to complete such evaluations. A written document also would provide staff, manufacturers, and ICCVAM with greater ability and clarity in coordinating the development and validation of test methods that meet CPSC's needs for FHSA labeling evaluation.

Moreover, in response to congressional and GAO requests, ICCVAM has formed a new work group to prepare a document outlining all regulatory agencies' efforts toward their use of non-animal testing methods and associated data. Staff plans to contribute to this effort, and the proposed guidance document would aid in providing content to this ICCVAM Work Group.

CPSC staff is proposing this guidance because similar guidance from other federal agencies does not adequately meet CPSC regulatory needs. Staff has considered similar guidance documents for evaluating new methods and associated data from ICCVAM, the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), Department of Defense (DoD), and other federal agencies. These documents are informative; however, they do not address CPSC's needs completely. This is in part because these documents reflect that these agencies primarily regulate discrete chemicals, while CPSC regulates finished consumer products that often contain complex mixtures of chemicals. In addition, each agency has its own statutory and regulatory framework. Therefore, this proposed guidance document will emphasize CPSC's need to evaluate the hazards of complex mixtures and products to help shape new methods and update existing methods to meet CPSC's particular needs. CPSC staff also plans to have the guidance peer-reviewed by experts at other federal agencies and recommends that the Commission publish a Notice of Availability (NOA) for staff to receive public comments, which staff will consider before finalizing the guidance.

B. Future use of NAMs

Staff notes that tens of thousands of chemicals are in commerce and in consumer products. It is not feasible to test all of them in animals. Currently, even basic toxicological data are available for only a small percentage of chemicals in commerce. Furthermore, staff expects alternative

test methods to replace traditional animal tests in the future. For example, the EPA plans to reduce its requests for, and funding of, mammalian studies by 30 percent by 2025, and it intends to eliminate all mammalian study requests and funding by 2035. This means that, over time, animal toxicity data will become less available for staff to use in risk assessments to support regulations, label reviews, or Product Safety Assessments.

C. Impact of new advancements in toxicological testing

Staff notes that the evaluation and validation of toxicity testing methods is changing with new advancements in toxicological testing (in particular with NAMs), since the CPSC's Animal Testing Policy was codified in 2012. To date, CPSC has not provided the regulated community with a description of the types of information that CPSC staff would need, as well as the process that the staff uses, to evaluate the scientific validity and defensibility of non-animal alternative test methods to support FHSA labeling. As described in the proposed guidance, the types of information CPSC staff would use to evaluate NAMs or IATAs submitted to CPSC by interested parties would include (but not be limited to): concordance and reproducibility data; false positive and false negative rates; applicability domain; test endpoint; validation studies; or any other pertinent information needed to make a determination. The proposed guidance will facilitate product manufacturers' incorporation of NAMs as part of the company's regulatory strategy for labeling under FHSA, if CPSC outlines its informational needs. CPSC will post accepted NAMs and IATAs on CPSC's animal testing web page,⁹ allowing companies to see which NAMs are suitable for use and the limits of use for CPSC purposes. For example, CPSC currently accepts a NAM, the Local Lymph Node Assay (LLNA), for a specific key event in the skin sensitization adverse outcome pathway (AOP).

Internally, for CPSC staff, the proposed guidance document would improve consistency, by documenting and standardizing CPSC staff's evaluation of NAMs, and additionally, provide a mechanism to update CPSC approaches based on evolving science and best practices. Thus, the proposed guidance document would assist CPSC staff in ensuring consistency in evaluations over time. For stakeholders, the proposed guidance document would inform test method developers, testing laboratories, and manufacturers, by clarifying staff's informational needs and process for determining whether non-animal alternative toxicological methods, integrated approaches, and the resulting data are scientifically valid and defensible and can be used in support of FHSA labeling determinations. Furthermore, a guidance document would promote CPSC's transparency to the public and other stakeholders, and acknowledge the need to adapt to modern testing methods and concepts.

V. Staff Recommendations

A. Notice of Availability

Staff recommends that the Commission issue a NOA and request comments on CPSC's proposed guidance document. The NOA will inform stakeholders of the CPSC proposed evaluation

⁹ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

process to assess whether alternative toxicological methods, integrated approaches, and the resulting data are scientifically defensible for use in hazard labeling under the FHSA and provide opportunity for feedback. CPSC staff will consider comments received before finalizing the proposed guidance document.

The proposed guidance will support CPSC staff's goal to use data from NAMs, in lieu of traditional animal testing, to evaluate toxics, corrosives, irritants, strong sensitizers, and other hazardous materials in products subject to the FHSA. Although staff agrees that it is preferable to avoid animal testing in the evaluation of product hazards, animal testing may be the only available approach, in the absence of reliable existing data or suitable alternative method-generated data. As discussed, the Commission has previously adopted policies intended to minimize the number of animals tested and reduce the pain associated with such tests.

B. NAM Nomination Form and Process

Staff recommends that CPSC provide with the final guidance, an optional NAM nomination form, and also establish the process for staff evaluation of nominations (Appendix A of Tab A). The draft form organizes the types of information discussed in the proposed guidance document and prompts the submitter to document applicable information for each NAM or IATA. The form, along with supporting documentation, could be submitted to CPSC staff for evaluation. The form may help organize the information from the submitting party, however, completion and submission of the nomination form is not required.

CPSC staff will inform submitters of CPSC's assessment of a NAM via e-mail. CPSC will post accepted NAMs or IATAs to the CPSC's "Recommended Procedures Regarding the CPSC's Policy on Animal Testing" website.¹⁰ CPSC will make the NAM and CPSC assessments available through this site.

¹⁰ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

TAB A: Proposed guidance document

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Proposed 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, 2021

I. Introduction

Increasingly, regulatory agencies and the public desire a more ethical and predictive approach for making toxicology determinations, by moving away from the use of animals in toxicological testing, toward non-animal or “new approach methods” (NAMs). 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 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

¹ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

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, such as toxicity, exposure, and risk assessments found on CPSC's Policy on Animal Testing website;⁴ or from the Commission's Directorate for Health Sciences staff.

II. 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 16 CFR §1500.3(c)(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). Often, manufacturers will use animal testing to evaluate hazards in an effort to satisfy those regulations. However, the regulations do not require any specific animal testing. Although animal testing is still used in toxicological testing, most governmental agencies support reduced use of animals in testing, by promoting the acceptance of data from alternative methods.

In 2012, CPSC issued an updated policy⁴ which strongly encourages 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 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. 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

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

⁴ <https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/>

whether the data are scientifically valid and defensible to support each product's FHSA labeling.⁵

CPSC staff considers a new test method⁶ for evaluation when its performance characteristics, advantages, and limitations (limits of use) have been adequately determined 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, unless specific regulatory or statutory requirements are cited. An alternative approach can be used, if the approach satisfies the requirements of the applicable statutes and regulations.

III. 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 of CPSC's final assessment via e-mail. 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.

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).

IV. 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 give an explanation of 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 to proceed with the NAM or IATA evaluation process. Staff will communicate any additional factors to the submitting parties during the initial review.

An explanation of the NAM/IATA evaluation factors follows:

- A. Independent scientific peer review
- B. Validation Studies
 - 1. Full Validation
 - 2. Partial Validation
 - 3. Cross Validation
 - 4. Cross-Laboratory (or inter-laboratory) Validation
 - 5. Selectivity
 - 6. Accuracy
 - 7. Precision
 - 8. Quality Control
 - 9. Sensitivity
 - 10. Reproducibility
 - 11. Stability
 - 12. 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

A. 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.*, no conflicts of interest), who are experts in an appropriate field (*e.g.*, toxicology, NAMs, IATAs). This can be done through several means, such as the evaluation of intra-laboratory or inter-laboratory validation studies, as well as other means of peer review.

B. Validation Studies

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 *in vivo* animal or human data.

Validation 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.

A method's reliability includes its inter-laboratory reproducibility, intra-laboratory repeatability, and robustness. In addition to the performance and applicability of the NAM/IATA, good scientific, technical and quality practices ensure that the overall validation 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.

The following define and characterize the different types and levels of methods validation.

1. Full Validation

Full validation of analytical and bioanalytical methods is important during development and implementation of a novel NAM or IATA, for analysis of a new endpoint, or for revisions to an existing method that add new quantification. Full validation implies that all aspects of the test method have been fully evaluated using a quality system (see below).

2. Partial Validation

Partial validations evaluate modifications of already-validated methods. Typical bioanalytical method modifications or changes that fall into this category include, but are not limited to:

- Method transfers between laboratories or analysts
- Robustness testing for parameters not having proper ranges
- Change in analytical methodology (*e.g.*, change in detection systems)
- Change in mixtures or matrix
- Change in sample processing procedures
- Change in relevant concentration or concentration range
- Changes in instruments and/or software platforms

- Modifications to accommodate limited sample volume
- Rare matrices

3. Cross-Validation

Cross-validation is a comparison of validation parameters when two or more methods are used to generate data within the same study or across different studies. An example of cross-validation would be a situation in which an original validated method serves as the reference, and the revised method is the comparator. The latter method is often referred to as a “me too” method. The comparisons should be done both ways. When sample analyses within a single study are conducted at more than one site, or more than one laboratory, cross-validation with spiked mixture or matrix standards should be conducted at each site or laboratory to establish inter-laboratory reliability. Cross-validation should also be considered when data generated using different analytical techniques in different studies are included in a regulatory submission. All modifications to an existing method should be assessed to determine the recommended degree of validation.

4. Inter-Laboratory Validation

The inter-laboratory validation (sometimes referred to as cross-laboratory validation) studies generally consists of three or more laboratories at different sites, typically with the sponsor laboratory serving as the lead laboratory. Site study director and key personnel (*e.g.*, facilities manager, analyst/chemist, QA) should be identified, as needed, for each laboratory. The cross-laboratory validation will test both between-laboratory transferability (*i.e.*, can similar equipment be used at different laboratories to satisfactorily perform the assay) and between-laboratory reproducibility (*i.e.*, is similar data obtained among laboratories). It should also demonstrate the predictive capacity (accuracy) and application domain while establishing performance standards to be used in quality evaluation. Concepts that should be addressed, if relevant for the particular assay, prior to cross-laboratory validation are: selectivity, accuracy, precision, recovery, the calibration curve, sensitivity, within-laboratory reproducibility, stability, and robustness.

The analytical laboratory conducting studies for regulatory submissions should adhere to Good Laboratory Practices (GLPs) requirements or at least the spirit-of-GLP for documentation. All methods, after validation, should be capable of complying with GLP standards.

All aspects of the study should be described as they pertain to:

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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 given 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.

12. 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 \pm 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.

C. 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.

D. 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.

E. 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.

F. 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.

G. 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.

H. 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 piece or an entire existing regulatory test method.

V. 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.

A. 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 (*i.e.*, ICCVAM), 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.

B. 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*. 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. It is very informative to include a description of the product tested and how it was tested. Was the product tested as a whole product (*i.e.*, an extract was made), or were the components or ingredients of the

product tested individually or grouped. Additionally, a description of false positive and false negative rates and any underlying causal effects should be included.

C. 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.

VI. References

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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

Analog identification

Predictive model

Quantitative-structure activity relationship (QSAR)

Read-across

Other in silico

In vitro

3-D/Organotypic

2-D/Cell-based

Cell-free

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:
 - Acute toxicity
 - Carcinogenicity
 - Cardiotoxicity
 - Developmental toxicity
 - 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.