

The NICEATM-ICCVAM Five-Year Plan (2008-2012)

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Prepared by the
Interagency Coordinating Committee on the
Validation of Alternative Methods (ICCVAM)
and the
National Toxicology Program (NTP) Interagency Center for the
Evaluation of Alternative Toxicological Methods (NICEATM)

National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

**This draft document is available for public review and
comment
at the ICCVAM-NICEATM Five-Year Plan Website:**

<http://iccvam.niehs.nih.gov/docs/5yearplan.htm>

Comments will be accepted at the website and via email
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On the cover

The NICEATM-ICCVAM graphic symbolizes the important role of new and alternative toxicological methods in protecting and advancing the health of people, animals, and our environment.

**The NICEATM-ICCVAM Five-Year Plan
(2008-2012)**

Draft

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1 **EXECUTIVE SUMMARY**

2 NICEATM and ICCVAM¹ prepared this five-year plan in response to requests from the
3 Appropriations Committees of the U.S. House of Representatives and the U.S. Senate.
4 Developed in conjunction with federal agency program offices, the plan describes how
5 NICEATM and ICCVAM will facilitate the research, development, translation², validation,
6 and regulatory acceptance of alternative test methods that reduce, refine, and replace the use
7 of animals in testing, while maintaining scientific quality and the protection of human health,
8 animal health, and the environment.

9 The plan addresses four key challenges. The first challenge is to identify priority areas for the
10 next five years and to conduct and facilitate activities in these areas. The second challenge
11 involves research initiatives that are expected to support the future development of
12 innovative alternative test methods. The third challenge is to foster the acceptance and
13 appropriate use of alternative test methods through outreach and communication in order to
14 reduce and replace animal use and improve animal welfare. The last challenge is to develop
15 partnerships and to strengthen interactions with ICCVAM stakeholders in order to facilitate
16 meaningful progress.

17 ***Identifying Priorities and Conducting and Facilitating Alternative Test Method Activities***

18 ICCVAM priorities emphasize alternatives for those test methods that involve significant
19 animal pain and distress and that use large numbers of animals. These priority areas include:
20 ocular toxicity, acute toxicity, biologics, dermal toxicity, immunotoxicity, endocrine
21 disruption, pyrogen testing, and chronic toxicity/carcinogenicity. Flexibility in meeting this
22 challenge is essential in order to respond to new testing needs and to take advantage of
23 advances in science and technology. Integrated testing approaches are emphasized to
24 effectively address the inherent complexity of human and animal responses to toxicants and
25 to maximize the impact of new testing alternatives on reduction, refinement, and replacement

¹ ICCVAM (The Interagency Coordinating Committee on the Validation of Alternative Methods), a permanent interagency committee administered by NIEHS under NICEATM (the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods), is composed of members designated by the heads of 15 federal agencies. ICCVAM was created under the ICCVAM Authorization Act of 2000.

² For the purposes of test method translation activities, ICCVAM considers that these are activities that are carried out to characterize if there is evidence of relevance and applicability of a test method for a specific testing purpose. If so, then the test method may be considered for evaluation in a formal validation study.

26 of animal use. NICEATM and ICCVAM will continue to facilitate research, development,
27 translation, and validation of alternative test methods by identifying critical knowledge and
28 data gaps for regulatory agencies, the scientific community, and other stakeholders.

29 ***Incorporating New Science and Technology***

30 The second challenge is to conduct research incorporating new technologies that can be
31 expected to support the future development of new test methods and approaches to reduce or
32 eliminate the need for animals. While many of these approaches will require several years to
33 develop and validate, some may be ready for use more quickly. To maximize the efficiency
34 of this process, NICEATM and ICCVAM are linking research and development activities to
35 the standardization and validation of test methods with regulatory applicability.

36 ***Fostering Regulatory Acceptance and Use of Alternative Methods***

37 The third challenge is to foster regulatory acceptance and appropriate use of alternative test
38 methods by promoting active communication and outreach efforts with both government and
39 non-government stakeholders. NICEATM and ICCVAM will provide high quality
40 comprehensive test method background review documents and the results of independent
41 scientific peer reviews to facilitate the approval of these test methods by regulatory agencies
42 and the international community. Once an alternative test method has been accepted,
43 ICCVAM will work to promote the use of the test method by sponsoring and participating in
44 training workshops.

45 ***Developing Partnerships***

46 Finally, NICEATM and ICCVAM will further develop partnerships and strengthen
47 interactions with stakeholders. The overall aims of these partnerships are to make the best
48 use of existing resources and scientific expertise, maximize the efficiency of test method
49 validation efforts and evaluations, minimize duplication of effort, and ensure an early
50 exchange of information concerning test method validation. This will facilitate national and
51 international recognition, acceptance, and implementation of scientifically valid alternative
52 test methods.

53 **INTRODUCTION**

54 This document was prepared in response to requests from the Appropriations Committees of
55 the U.S. House of Representatives and the U.S. Senate that NICEATM and ICCVAM, in
56 partnership with relevant federal agency program offices, create a five-year plan to:

- 57 • Research, develop, translate³, and validate new and revised non-animal and
58 other alternative assays for integration of relevant and reliable methods into
59 federal agency testing programs, and
- 60 • Identify areas of high priority for new and revised non-animal and alternative
61 assays or batteries of those assays to create a path forward for the
62 replacement, reduction, and refinement of animal tests, when this is
63 scientifically valid and appropriate.

64 This five-year plan will help NICEATM and ICCVAM achieve their goals and inform the
65 public of their plans and approaches to facilitate the research, development, translation, and
66 validation of alternative test methods.

67 **Background**

68 U.S. regulatory agencies are charged with protecting human and animal health and the
69 environment (**Appendix A**). As part of this mission, agencies need to determine whether
70 adverse effects may result from exposures to substances such as pesticides, consumer
71 products, medicines, workplace chemicals, food additives, or to contaminants in air, food, or
72 water. Many of the current test methods for evaluating hazards and risks from exposure to
73 such substances use laboratory animals. Federal agencies require that all test methods should
74 be based on sound science. According to the ICCVAM Authorization Act of 2000 (see
75 **Appendix E**), new, revised, and alternative test methods must be determined to be valid for
76 their proposed use before agencies adopt them for regulatory purposes. Validation is required
77 to determine if alternative test methods can provide equal or better protection of human and
78 animal health and the environment.

³ Note: For the purposes of test method translation activities, ICCVAM considers that these are activities that are carried out to characterize if there is evidence of relevance and applicability of a test method for a specific testing purpose. If so, then the test method may be considered for evaluation in a formal validation study.

(Photo of the cover of the PHS policy) Any agency or institution receiving support from the Public Health Service (PHS) for activities involving animals must comply with the requirements described in the PHS Policy on Humane Care and Use of Laboratory Animals. The agency or institution must:

- *Develop and implement an institutional program of animal care and use according to the National Research Council's Guide for the Care and Use of Laboratory Animals.*
- *Establish an Institutional Animal Care and Use Committee that will regularly evaluate the institution's animal care and use activities.*
- *Submit written assurance of compliance with the PHS Policy for review by the NIH Office of Laboratory Animal Welfare.*
- *Inform PHS about numbers of animals, species, rationale for use of animals, how animals are to be used, procedures used to minimize discomfort and injury, and methods of euthanasia.*
- *Maintain appropriate records and fulfill recording requirements.*

79

80 U.S. laws (42 USC 289d, 7 USC 2131 et. seq.) require that alternatives be considered before
81 using animals for research and testing⁴. These alternatives include new or revised test
82 methods that:

- 83 • Reduce the number of animals to the minimum required to obtain scientifically
84 valid data,
- 85 • Refine procedures to lessen or eliminate pain and distress to animals,

(Photo of the cover of the AWA and regulations book) The Animal Welfare Act and regulations apply to any institution in the United States using certain animals for testing purposes. These regulations include:

- *Registration with USDA-Animal and Plant Health Inspection Service-Animal Care, and subsequent unannounced inspections to ensure compliance with the standards and record-keeping requirements.*
- *Establishment of an Institutional Animal Care and Use Committee to assess the research facility's animal program, facilities and procedures.*
- *Submission of an Annual Report on animals used, with an assurance that each principal investigator has considered alternatives to painful procedures.*

⁴ This concept is integral to the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, which are incorporated in the Public Health Service Policy on Humane Care and Use of Laboratory Animals (<http://grants.nih.gov/grants/olaw/references/phspol.htm>).

- 86 • Replace animals with non-animal systems or one animal species with a
87 phylogenetically lower animal species

88 **The Role of ICCVAM and NICEATM**

89 ICCVAM⁵ is a permanent interagency committee administered by NIEHS under NICEATM.
90 The ICCVAM Authorization Act states that the committee is composed of members from 15
91 federal agencies (**see sidebar**).

ICCVAM Member Agencies:

- *Consumer Product Safety Commission*
- *Department of Agriculture*
- *Department of Defense*
- *Department of Energy*
- *Department of Health and Human Services*
 - *Agency for Toxic Substances and Disease Registry*
 - *Food and Drug Administration*
 - *National Cancer Institute*
 - *National Institute for Occupational Safety and Health*
 - *National Institute of Environmental Health Sciences*
 - *National Institutes of Health, Office of the Director*
 - *National Library of Medicine*
- *Department of the Interior*
- *Department of Labor*
 - *Occupational Safety and Health Administration*
- *Department of Transportation*
- *Environmental Protection Agency*

⁵ ICCVAM, a federally mandated interagency committee, provides recommendations to federal agencies about the scientific validity and usefulness and limitations of proposed test methods. Agencies are required to consider ICCVAM test method recommendations and make decisions on their acceptability. ICCVAM seeks to advance test methods that will ensure the protection of human and animal health and the environment while advancing animal welfare. It does so by facilitating the research, development, translation, and validation activities of alternative methods.

92 The mission of ICCVAM is to facilitate development, validation, and acceptance for
93 regulatory use of new, revised, and alternative test methods that reduce, refine, and replace
94 the use of animals in testing while maintaining and promoting scientific quality and the
95 protection of human health, animal health, and the environment.

96 To fulfill this mission, NICEATM and ICCVAM work with stakeholders, including federal
97 agencies, national and international validation centers, industry, academia, and the animal
98 welfare community. Many federal agencies and other organizations conduct research that
99 could ultimately result in the development and validation of an alternative test method for
100 regulatory use. Thus, ICCVAM depends on its many stakeholders to conduct and achieve
101 successful test method research, development, translation, and validation so that these test
102 methods can then be considered and potentially recommended by ICCVAM for regulatory
103 use.

*Federal agencies that have statutory authority to conduct research, development, translation,
and/or validation activities:*

- *Department of Defense*
- *Department of Energy*
- *Environmental Protection Agency*
- *Department of the Interior*
- *National Institutes of Environmental Health Sciences/National Toxicology Program*
- *Food and Drug Administration*
- *National Institute for Occupational Safety and Health*
- *Agency for Toxic Substances and Disease Registry*
- *National Institutes of Health Office of the Director*
- *National Cancer Institute*
- *Department of Agriculture*

104 The following chapters outline the NICEATM-ICCVAM five-year plan by describing the
105 ongoing and planned activities for priority areas directed at reducing, refining, or replacing
106 animal use in regulatory testing. This is followed by a summary of new science and
107 technology being pursued by ICCVAM-member agencies as promising approaches to
108 alternative test method development and testing strategies. Finally, the mechanisms for

109 fostering acceptance and appropriate use of alternative test methods and developing
110 partnerships with stakeholders are described.

111

111 **CHAPTER 1**
112 **RESEARCH, DEVELOPMENT, TRANSLATION, AND VALIDATION ACTIVITIES**
113 **FOR PRIORITY TEST METHODS TO REDUCE, REFINES, AND REPLACE**
114 **ANIMALS IN REGULATORY TESTING**

115 Because of the different statutory mandates under which individual federal agencies operate
116 (**Appendix A**), their testing priorities often differ. ICCVAM's priorities are based on agency
117 priorities and other criteria that include:

- 118 • the potential impact that alternative test methods may have on reducing, refining,
119 or replacing the use of animals for testing, taking into consideration the severity
120 of pain and distress and numbers of animals involved;
- 121 • the applicability of testing alternatives across agencies; and
- 122 • the potential for the proposed test method(s) to provide improved prediction of
123 adverse health or environmental effects.

124 ICCVAM uses these criteria to prioritize test method nominations and submissions⁶ for
125 evaluation.

126 **Priority Activities**

127 This chapter describes ICCVAM's priority
128 areas. These priorities will likely evolve over
129 time in response to new testing needs and
130 advances in science and technology. The
131 inherent complexity of human and animal
132 responses to toxicants means that it is
133 unlikely that any single alternative test
134 method will be able to serve all regulatory needs for a specific testing area. Rather, integrated
135 approaches using batteries of two or more alternative test methods combined with other
136 information about the properties of a test substance will likely be needed to significantly
137 reduce or replace the use of animals for each type of testing. As outlined below, these
138 integrated approaches are being investigated for a number of different toxicity testing areas.

***ICCVAM Test Method Prioritization
Criteria include:***

- ***Potential impact on reducing, refining, or replacing animals for testing***
- ***Applicability to multiple agencies***
- ***Potential to improve prediction of adverse health or environmental effects***

⁶ <http://iccvam.niehs.nih.gov/SuppDocs/submission.htm>

139 Further, the development and validation
140 of alternative test methods for more
141 complex endpoints such as
142 carcinogenicity or
143 reproductive/developmental toxicity will
144 likely take longer than the five-year time
145 frame for this strategic plan.

146 **Ocular Toxicity Testing**

147 One of ICCVAM's highest priorities is
148 the evaluation and development of
149 alternatives to ocular (eye) safety testing.

150 Regulatory agencies require that ocular

151 hazards be identified to warn consumers and workers when exposure to a chemical or
152 product may cause blinding or other kinds of eye damage. However, rabbits used in tests that
153 identify such hazards can experience significant pain and distress when eye injuries occur.
154 NICEATM and ICCVAM recently evaluated and recommended *in vitro* test methods that can
155 be used to identify certain types of substances that cause permanent and severe eye damage
156 without the use of animals⁷ NICEATM and ICCVAM will carry out activities to improve the
157 usefulness and applicability of these test methods⁸. These activities include assessing the test
158 methods for their usefulness in detecting reversible and mild eye damage. NICEATM and
159 ICCVAM will also evaluate *in vitro* approaches for determining the ocular irritation
160 potential of antimicrobial cleaning product formulations. In addition, NICEATM and
161 ICCVAM will facilitate the submission of *in vivo* reference data in order to build a database
162 for use in expanding the development and applicability of new alternative ocular test
163 methods.

164 NICEATM and ICCVAM recently organized scientific symposia⁹ on “Mechanisms of
165 Chemically-Induced Ocular Injury and Recovery,” and “Minimizing Pain and Distress in
166 Ocular Toxicity Testing.” Symposia recommendations for relevant research, development,

The inherent complexity of human and animal responses to toxicants means that it is unlikely that any single alternative test method will be able to serve all regulatory needs for a specific testing area. Rather, integrated approaches using batteries of two or more alternative test methods combined with other information about the properties of a test substance will likely be needed to significantly reduce or replace animals for each type of testing.

⁷ <http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox.htm>

⁸ <http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox.htm>

⁹ <http://iccvam.niehs.nih.gov/meetings/ocumeet/sympinfo.htm>

167 and validation studies have been provided to the scientific and regulatory communities for
168 consideration. *NICEATM and ICCVAM will monitor progress for the recommended studies*
169 *and will evaluate new methods or combinations of in vitro test methods that are developed*
170 *for corrosivity and irritation testing to reduce or replace animal use. In addition, a*
171 *comprehensive review of the use of topical anesthetics and systemic analgesics for reducing*
172 *pain and distress will be conducted to determine their applicability in ocular testing.*

173 **Acute Toxicity Testing**

174 Until the recent adoption of alternative tests, a rodent acute oral test using a large number of
175 animals with death as an endpoint was used to satisfy the requirements of agencies to
176 appropriately label products that cause acute toxicity (poisoning). Since this requirement is
177 one shared by several federal agencies, acute toxicity testing has been and will remain a
178 priority. ICCVAM has made significant progress in reducing and refining acute toxicity
179 testing but more needs to be accomplished. For example, ICCVAM evaluated and
180 recommended an alternative animal test method¹⁰ that has now been adopted by regulatory
181 agencies as a replacement for the traditional acute oral toxicity test. This alternative test
182 method can reduce the use of animals for this purpose by over 70%. NICEATM and
183 ICCVAM were also involved in the development of international guidance for humane
184 endpoints that can be used as criteria to euthanize animals rather than allowing them to die
185 during the study. More recently, ICCVAM evaluated and recommended two cell culture test
186 methods that can be used to estimate the starting doses for animal studies¹¹, and thereby
187 further reduce the number of animals needed.

188 To further reduce animal use and the potential pain and distress associated with acute toxicity
189 testing, ICCVAM plans to carry out several related activities. *NICEATM will conduct a study*
190 *to determine how the two cell culture test methods can be used to set the starting dose for*
191 *mixtures, which represent a significant percentage of acute testing studies. NICEATM will*
192 *also assemble high quality rodent acute oral toxicity data (either from previous studies or, in*
193 *cooperation with industry, from future studies) and make this reference database available*

¹⁰ <http://iccvam.niehs.nih.gov/methods/acutetox/udp.htm>

¹¹ <http://iccvam.niehs.nih.gov/methods/acutetox/acutetox.htm>

194 *for the development and validation of other new in vitro tests (or batteries of tests) to more*
195 *accurately predict oral acute systemic toxicity.*

196 *In addition, NICEATM and ICCVAM will organize an international workshop to (1) identify*
197 *predictive and more humane endpoints that may be used to terminate studies earlier in order*
198 *to further reduce pain and distress, and (2) identify and standardize procedures for*
199 *collecting mechanistic information from acute oral toxicity testing that will aid in developing*
200 *batteries of predictive in vitro test methods that can further reduce and perhaps eventually*
201 *replace animals for acute toxicity testing.*

202 The ATSDR, DOI, EPA, FDA, and NIH also have ongoing or planned activities relevant to
203 the 3Rs for testing chemicals for acute toxicity. These activities include modifications to
204 current animal tests to reduce the number of animals used, as well as evaluations of *in vitro*
205 test methods to be used independently or in combination with other tests as possible
206 replacements for animal tests. *NICEATM and ICCVAM are working with these agencies to*
207 *assist in characterizing the usefulness and limitations of these methods and to foster their*
208 *appropriate use among the regulated community.*

Reduction Alternative: An ICCVAM Success Story

In 2002, ICCVAM recommended the revised Up-and-Down Procedure (UDP) as a replacement for the conventional acute oral systemic toxicity test. The UDP can reduce the use of animals for this type of testing by up to 70%. All federal regulatory agencies that require acute oral toxicity testing have accepted and adopted the revised UDP. In 2007, ICCVAM recommended that, prior to testing in animals, in vitro cytotoxicity test methods should be considered as one way to estimate the starting dose for the revised UDP. This approach is expected to further reduce the number of animals required for an acute toxicity test by up to 20%.

209

210 **Biologics/Vaccines Testing**

211 Biological products (commonly referred to as biologics) include a wide range of products
212 such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy,

213 tissues, and recombinant therapeutic proteins that are used to treat or protect humans or
214 animals. Safety and potency (strength) testing of biologics is relevant particularly to the FDA
215 and USDA. This testing is a priority because it typically requires large numbers of animals
216 that may experience significant pain and distress during testing.

217 Alternatives are under development that are targeted toward reducing and replacing animal
218 testing with *in vitro* test methods, as well as refining animal testing through modifications to
219 the current animal tests. To facilitate the development of these alternatives, ICCVAM,
220 NICEATM, and the European Centre for the Validation of Alternative Methods (ECVAM)
221 recently co-sponsored a workshop that identified activities needed to further reduce, refine,
222 or replace the use of mice for determining the effectiveness of a biologic product¹².

223 *NICEATM and ICCVAM will follow the development of alternative test methods and testing*
224 *strategies for vaccine potency testing and will facilitate the acceptance of adequately*
225 *validated test methods and humane endpoints found to be sufficiently accurate and reliable.*
226 *A priority for evaluation will be an in vitro vaccine potency test being developed by the*
227 *USDA to reduce the numbers of animals required to evaluate the potency of a common*
228 *veterinary bacterial vaccine.*

229 **Dermal Toxicity Testing**

230 Like acute ocular toxicity testing, tests for acute skin corrosivity (burns/permanent scarring)
231 and irritation are conducted to label chemicals so that consumers and workers can take
232 appropriate precautions to prevent injury.

233 Test results are also used to determine
234 appropriate packaging to minimize
235 dangerous spills during transport. These
236 tests have the potential to cause
237 significant pain and distress to animals.
238 Thus, these tests are of interest to several
239 federal agencies, and for these reasons,
240 dermal toxicity testing is a priority.

Working Towards Replacement
ICCVAM has organized independent scientific peer reviews of the usefulness and limitations of in vitro corrosivity test methods for use as alternatives to the in vivo rabbit skin and eye tests. By using these alternative methods, animal testing of substances can be avoided that would otherwise cause corrosive injuries to the skin or eyes of rabbits .

¹² <http://iccvam.niehs.nih.gov/methods/biologics/biologics.htm>

241 *In vitro* alternatives for dermal corrosivity and irritation testing have been developed and
242 several of these test methods have been recommended and adopted as screening methods for
243 the detection of dermal corrosives¹³. In appropriate circumstances, positive results can be
244 classified and labeled as corrosives without the use of animals. *NICEATM and ICCVAM will*
245 *evaluate alternative dermal irritation test methods for their usefulness and limitations in U.S.*
246 *regulatory testing. This will include an evaluation of the utility of using a combination of in*
247 *vitro test methods for both corrosivity and irritation to reduce or replace animals. NICEATM*
248 *and ICCVAM will also evaluate non-animal methods and approaches for determining the*
249 *skin irritation potential of antimicrobial cleaning products.*

250 **Immunotoxicity Testing**

251 Regulators use skin sensitization tests to identify substances that might cause this response in
252 humans following repeated skin exposure. This type of testing is of interest to several federal
253 agencies. The Murine Local Lymph Node Assay (LLNA) is an alternative test method used
254 for skin sensitization testing, and was the first alternative test method evaluated and

Refinement Alternative: Minimizing Pain and Distress

ICCVAM recommended that the LLNA was a valid substitute to the guinea pig maximization test in many testing situations. The LLNA can substantially reduce or minimize the pain and distress in treated animals that can result from sensitizing chemicals and also requires fewer animals. Based on the recommendations of ICCVAM and an independent scientific peer review panel, the LLNA has been accepted as an alternative to the guinea pig test for assessing allergic contact dermatitis by U.S. regulatory agencies. Following an implementation workshop co-sponsored by ICCVAM and the International Life Sciences Institute (ILSI), the LLNA was incorporated into an international test guideline by the 30-member countries of the Organisation for Economic Co-operation and Development (OECD). ICCVAM will evaluate the validation status of modifications to the LLNA that may further reduce the number of animals used, expand the usefulness of the LLNA, and eliminate the need to use radioactive materials.

¹³ <http://iccvam.niehs.nih.gov/methods/dermal/corrode.htm>

255 recommended by ICCVAM. The LLNA reduces the number of animals needed, the time
256 required for testing, and can substantially reduce or minimize the pain and distress associated
257 with the traditional testing method. Based on the recommendations of ICCVAM, the LLNA
258 has been accepted by U.S. regulatory agencies and the OECD. *NICEATM and ICCVAM will*
259 *evaluate a number of modifications to the LLNA that may further reduce the number of*
260 *animals used, expand the scope of substances and mixtures for which the LLNA may be used,*
261 *and eliminate the need to use radioactive materials as part of the protocol*¹⁴.

262 Additional assays are under development that may reduce, refine, or replace the use of
263 animals in skin and respiratory sensitization testing. *Where appropriate, NICEATM and*
264 *ICCVAM will review and foster approaches to incorporate computational and in vitro*
265 *methods into laboratory testing strategies.*

266 **Endocrine Disruptor Testing**

267 A variety of substances have been shown to affect hormones, or processes involving
268 hormones, sometimes resulting in developmental or reproductive problems; these substances
269 are called endocrine disruptors. Congress has mandated the development and implementation
270 of a screening program for endocrine disruptors. NICEATM and ICCVAM recently reviewed
271 a number *in vitro* tests designed to detect chemicals that act as or interfere with male and/or
272 female hormones¹⁵. Based on this review, ICCVAM has provided recommendations for
273 future test method development and validation activities that are being implemented in
274 studies by the EPA and NICEATM¹⁶. Related test methods for detecting chemicals that act
275 like or inhibit estrogen have recently been nominated for evaluation¹⁷. *NICEATM will initiate*
276 *and complete a joint international study with ECVAM and the Japanese Center for the*
277 *Validation of Alternative Methods (JaCVAM) to evaluate the usefulness and limitations of an*
278 *in vitro test method to identify estrogen-like chemicals that does not require the use of*
279 *animals as donors for test components.*

280 *NICEATM and ICCVAM are also increasing their involvement in OECD test guideline*
281 *activities related to endocrine disruptors. This includes an early exchange of information*

¹⁴ http://iccvam.niehs.nih.gov/methods/immunotox/llnadocs/CPSC_LLNA_nom.pdf

¹⁵ http://iccvam.niehs.nih.gov/docs/endo_docs/edfinalrpt0503/edfinrpt.pdf

¹⁶ http://iccvam.niehs.nih.gov/docs/endo_docs/edfinalrpt0503/edfinrpt.pdf

¹⁷ http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm

282 concerning test method validation and, where possible, working together to best utilize
283 existing resources to maximize the efficiency of evaluation/validation efforts. These efforts
284 can be expected to facilitate national and international recognition, acceptance, and
285 implementation of scientifically valid test methods.

286 **Pyrogen Testing**

287 Products injected or implanted into the body must be appropriately shown to be free of
288 substances that could cause fever (that is, pyrogens) prior to their use in humans and animals.
289 Although these types of tests are of primary concern to the FDA, because they can require
290 large numbers of animals and may cause pain and distress to animals, pyrogen testing is
291 considered a priority. Recently, alternative pyrogenicity test methods based on the activation
292 of cultured human blood cells have been developed that take advantage of the role of these
293 cells in the fever response. ICCVAM recently evaluated five such *in vitro* test methods
294 proposed as potential replacements for the current rabbit test¹⁸. *ICCVAM will issue*
295 *recommendations on their current usefulness and future studies to advance the further*
296 *development of these methods, and will work with developers involved in carrying out these*
297 *tests. Once these additional studies have been completed, ICCVAM will revisit the validation*
298 *status of these test methods.*

299 **Chronic Toxicity/Carcinogenicity Testing**

300 Two-year studies approximating lifetime exposure in rats and mice remain the primary
301 method by which chemicals are tested for their potential to cause cancer and chronic disease
302 in humans. These methods use large numbers of animals and may involve significant pain
303 and distress from systemic effects and the cancers that may result. NIEHS and FDA continue
304 to seek alternative models that can be used to reduce the number of animals used, shorten the
305 duration of these tests, and provide more accurate predictions of adverse effects. However,
306 the development and validation of alternative test methods for this complex endpoint will
307 likely take longer than the five-year time frame for this strategic plan.

308 Federal regulatory agencies also typically require the use of tests that evaluate genetic
309 toxicity, which is the ability of chemical or physical agents to damage the DNA and/or

¹⁸ <http://iccvam.niehs.nih.gov/methods/pyrogen/pyrogen.htm>

310 chromosomes of cells, thereby potentially contributing to the cancer-causing or
311 developmental toxicity potential of a chemical. The FDA is studying the usefulness and
312 limitations of various human primary cells and cell lines for use in genetic toxicity testing.
313 *Along with ECVAM, NICEATM and ICCVAM are participating in a JaCVAM-sponsored*
314 *international validation of an alternative animal test (that is, the alkaline Comet assay) to*
315 *evaluate for the induction of DNA damage in cells of multiple organs. If the JaCVAM*
316 *validation study is successful, there are plans for the possible validation of an in vitro Comet*
317 *assay that might be incorporated into the battery of genotoxicity assays.*

318 **Other Toxicity Areas of Interest**

319 NICEATM and ICCVAM recognize that there are other areas of toxicity testing for which
320 alternative test methods are needed. Identifying alternative test methods for neurotoxicity
321 (that is, chemicals that affect the nervous system) is clearly a priority of the FDA and the
322 NIH as both agencies are involved in the development of *in vitro* methods to identify
323 biomarkers of neurotoxicity.

324 Most regulatory testing protocols for reproductive/developmental toxicity use rats, rabbits, or
325 other mammalian species. The FDA has ongoing activities towards developing *in vitro* tests
326 that could reduce the number of animals used in developmental toxicity testing.

327 *NICEATM and ICCVAM will closely follow the ongoing efforts in these areas and will work*
328 *to identify the most useful tests and facilitate their review and acceptance.*

329

329

329 **CHAPTER 2**

330 **ADVANCES IN SCIENCE AND TECHNOLOGY**

331 ICCVAM agencies are carrying out research with new technologies that is expected to
332 support the future development of new test methods and approaches to reduce or replace
333 animals. While many of these approaches will require several years of development and
334 validation, some may be ready for use more quickly. To maximize the efficiency of this
335 process, NICEATM and ICCVAM are involved in linking research and development
336 activities to the standardization and validation of acceptable test methods with regulatory
337 applicability.

338 **High Throughput Screening (HTS)**

339 The NTP promotes improvements in toxicology test methods that will enhance its ability to
340 efficiently evaluate large numbers of substances in the environment for which there is little or
341 no information about potential adverse effects. In this regard, NTP is working to identify or
342 develop rapid biochemical or cell-based tests that can be used to screen large numbers of
343 environmental substances for their potential biological activity (i.e., high throughput
344 screening [HTS]). The results of HTS experiments provide a starting point for understanding
345 the potential human and animal toxicity of the substances to be tested and might be useful in
346 setting priorities for more comprehensive testing. The NTP HTS activities are coordinated
347 with similar activities being conducted by the EPA and organizations such as ECVAM. One
348 goal of these studies is to identify batteries of HTS assays that will provide information that
349 ultimately may reduce or replace the use of animals in toxicological tests. *NICEATM and*
350 *ICCVAM are closely following these efforts and will facilitate reviews of the usefulness and*
351 *limitations of defined HTS approaches.*

352 **Other Animal Systems**

353 Both the NIEHS and the FDA are evaluating the roundworm (*Caenorhabditis elegans*) for its
354 usefulness as a more rapid method to provide information about potential adverse human
355 health effects of chemicals¹⁹. A short life cycle, easy and inexpensive maintenance and
356 culturing, and detailed knowledge of its biology has allowed for the development of rapid

¹⁹ see <http://www.nih.gov/science/models/> and <http://dir.niehs.nih.gov/dirlt/genomics.htm>

357 low-cost assays that provide information
358 potentially relevant to various types of toxicity.
359 Because many of the *C. elegans* genes are the
360 same as those of more complex animals
361 (including humans), it is likely that many of
362 the responses elicited in *C. elegans* can be
363 related to other species. *NICEATM and*
364 *ICCVAM will monitor progress with this test*
365 *model, evaluate the validation status of*
366 *promising tests with regulatory applicability,*
367 *and make recommendations for regulatory*
368 *acceptance.*

369 The EPA is developing assays to evaluate
370 various toxicity endpoints in fish and
371 amphibians, and is validating an assay to
372 evaluate the growth and development of
373 amphibians after they hatch. These efforts will
374 aid in assessing the utility of these tests to
375 predict mammalian and non-mammalian
376 effects. *NICEATM and ICCVAM will continue*
377 *to closely follow these efforts, and if*
378 *considered appropriate, will facilitate*
379 *evaluation of the validation status of these types of methods.*

380 **Computational Approaches**

381 Using data generated from a collection of high throughput bioassays that measure
382 interactions with proteins or genes (e.g. microarrays²⁰), EPA is developing computer models
383 for prioritizing chemicals for toxicology testing. This will result in a "toolbox" (referred to as
384 ToxCast) that will be used for prioritizing chemicals for toxicology evaluation. If the
385 preliminary phases are successful, the EPA will proceed to an implementation phase where



*The roundworm *C. elegans* is being evaluated as an alternative species for toxicity testing. Because the genes involved in many biological processes (for example, the stress-response) have remained essentially unchanged throughout evolution, responses elicited in *C. elegans* may be applicable to understanding similar processes in higher organisms, including humans. Testing using this organism can be adapted to automated laboratory systems, which allow for increased throughput.*

²⁰ <http://dir.niehs.nih.gov/microarray/>

386 profiles of chemicals in need of toxicological evaluation will be obtained and
387 recommendations for testing priorities provided as the final outcome.

388 ATSDR is also developing and applying computational methods to prioritize chemicals of
389 concern and to direct targeted research. Through these activities, ATSDR provides guidance
390 for efficient experimental design including the determination of appropriate doses for testing
391 chemicals and mixtures.

392 The DOE is developing computer models for studying the biological effects of radiation.
393 These models will help estimate the minimum number of animals that are needed in
394 experiments dealing with low-dose radiation exposure. They may also help make decisions
395 regarding the possible use of *in vitro* models instead of live animals. However, these DOE
396 models must be adequately validated before they can gain widespread acceptance.

397 **Biomarkers of Toxicity**

398 The NIEHS and the FDA are evaluating various biomarkers that could be used in current
399 toxicology tests to predict damage to a specific organ or cause human disease or an increased
400 risk of human disease. For example, biomarkers in the blood or urine may indicate early
401 tumor development. Such biomarkers may be used as the basis for early humane euthanasia
402 to reduce or relieve the pain and distress experienced by animals with tumors or chronic
403 disease; they will also support the development of predictive *in vitro* screening tests. ATSDR
404 and the National Center for Environmental Health in collaboration with NIEHS, EPA, NCI,
405 the Armed Forces Institute of Pathology, and the International Commission for Occupational
406 Health recently organized an international conference on *Biomarkers for Toxicology and*
407 *Molecular Epidemiology*. This conference evaluated advances in biomonitoring technologies
408 and the translation of biomarker endpoints for human epidemiological studies to a number of
409 adverse health outcomes including target organ system toxicity and cancer.

410 NTP subsequently organized a workshop on *Biomarkers for Toxicology Studies*²¹ to identify
411 biomarkers related to injury or altered function of heart, lung, and lipid/carbohydrate
412 metabolism. These biomarkers could be included in toxicology tests to better understand the
413 development of environmentally-induced diseases. As a result, the NTP has begun including

²¹ <http://ntp.niehs.nih.gov/index.cfm?objectid=B743FF81-F1F6-975E-7E71E3A844E0612E>

414 serum cholesterol and triglycerides as routine measures in toxicity tests. Assays for several
415 other biomarkers are undergoing standardization and validation. The NIEHS and the FDA
416 are also exploring gene chip technologies that may allow for the identification of sets of
417 biomarkers that are more predictive of risks or benefits than a single biomarker. *NICEATM*
418 *and ICCVAM will follow the progress in these areas.*

419 **Nanomaterials Testing**

420 Nanotechnology is the control of matter at dimensions of roughly 1 to 100 nanometers (a
421 nanometer is one-billionth of a meter; a sheet of paper is about 100,000 nanometers thick),
422 and is being applied in many fields in the physical and biological sciences to create improved
423 materials, devices, and systems. The unique characteristics of nanomaterials can affect their
424 toxicity. Because hazards associated with these types of materials have yet to be
425 characterized, the applicability of current regulatory tests will have to be evaluated and new
426 tests may be required for regulatory use.

427 The number of tests needed to characterize potential hazards of nanomaterials could be very
428 large and, therefore, the HTS initiatives described above may be directly relevant to
429 nanomaterials testing. *NICEATM and ICCVAM are closely following the ongoing efforts in*
430 *this area and will work with regulators and stakeholders to identify the most useful tests,*
431 *while also addressing the 3Rs.*

432 **Toxicology Databases**

433 NIEHS is developing searchable databases of toxicological information that will be made
434 available to the general public via the Internet. Among the many advantages these databases
435 will provide is the availability of high quality animal test data that can be used as reference
436 data for comparison to new non-animal test methods. For example, NICEATM will be
437 making a database available that contains rabbit eye test data from ocular toxicity studies.
438 The database will provide the user with detailed protocol information, test substance
439 information, and animal response information. *As part of the NICEATM and ICCVAM*
440 *priority to encourage the development of new test methods, this database will also*
441 *incorporate other types of toxicity data that can be used for the development/validation of*
442 *other types of non-animal test methods (for example, dermal toxicity, in vitro cytotoxicity).*

443 The Chemical Effects in Biological Systems (CEBS) Knowledgebase²² is being developed by
444 NIEHS to promote a systems biology approach to understanding the biological effects of
445 environmental stressors. CEBS will house data derived from studies on the effects of
446 environmental chemicals on genes, proteins, and metabolism. Specifics for each study,
447 including study design details, treatment protocols, animal characteristics and toxic
448 endpoints, will be available. All of these data types can be integrated to enable data query
449 and analysis in a biologically meaningful manner. CEBS contains data from both *in vivo* and
450 *in vitro* studies, primarily in rodents, but has the potential to house data from other species
451 (for example, humans). This integration of data should improve the understanding of how *in*
452 *vitro* endpoints could be used to predict *in vivo* effects, and aid in overcoming a critical
453 barrier to the replacement of animals in testing. *NICEATM and ICCVAM will promote the*
454 *use of data from CEBS in the development of alternative test methods.*

455

²² <http://cebs.niehs.nih.gov/>

455 **CHAPTER 3**
456 **FOSTERING ACCEPTANCE AND APPROPRIATE USE OF ALTERNATIVE**
457 **TEST METHODS**

458 *NICEATM and ICCVAM will continue to promote active communication and outreach*
459 *efforts with both government and non-government stakeholders. These efforts are aimed at*
460 *encouraging the use of scientific approaches to validation that will generate the information*
461 *and data that federal agencies need in order to accept scientifically valid new and revised*
462 *alternative test methods²³. While NICEATM and ICCVAM promote and employ good*
463 *science in determining the validation status of alternative test methods, only the federal*
464 *agencies can accept these test methods and determine how they might be used in their*
465 *respective programs. Once regulatory authorities have accepted an alternative test method,*
466 *ICCVAM will work to promote its use.*

467 *NICEATM and ICCVAM will foster the use of alternative test methods by broadly*
468 *communicating the outcomes of ICCVAM review activities and/or workshops via the Federal*
469 *Register, at national or international scientific meetings, via publications, and at training*
470 *courses. The NICEATM and ICCVAM website provides information related to new test*
471 *methods and past, current, and future activities of NICEATM and ICCVAM, and will*
472 *continue to provide user-friendly access to the latest information on validation processes and*
473 *the most up-to-date status of the alternative test methods previously reviewed and those*
474 *currently under review. NICEATM and ICCVAM will use a combination of e-mail and*
475 *website announcements to inform the public of the availability of newly published Federal*
476 *Register notices, NICEATM documents, and upcoming events.*

²³ ICCVAM provides criteria for adequate validation and regulatory acceptance of test methods for its many stakeholders. These criteria and the process for achieving regulatory acceptance of scientifically valid test methods are described in the report, *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the Ad Hoc Interagency Coordinating Committee on the Validation of Alternative Methods* (http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf). Validation involves determining the usefulness and limitation of a test method for a specific purpose. This includes determining the extent that a test method will produce similar results in different laboratories around the world, and determining the extent that the test method can correctly measure or predict the biological effect of interest. ICCVAM welcomes nominations or submissions of proposed alternative or revised test methods. To aid test developers with this process, ICCVAM has published guidance on the information and data that is needed to support test method nominations and submissions in the report, *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods* (http://iccvam.niehs.nih.gov/SuppDocs/SubGuidelines/SD_subg034508.htm)

477 ICCVAM will sponsor and participate in workshops that include both government and non-
478 government stakeholders to increase the acceptance and use of new alternative test methods.
479 ICCVAM and NICEATM will actively seek
480 international participation in workshops as
481 well as international scientific partnerships on
482 validation study designs and test method
483 evaluations, such as those described in
484 Chapter 4. This will help ensure that studies
485 conducted with proposed alternative test
486 methods will facilitate international
487 acceptance of alternative test methods. This
488 international participation should also
489 streamline the validation process and avoid
490 unnecessary duplication of effort.

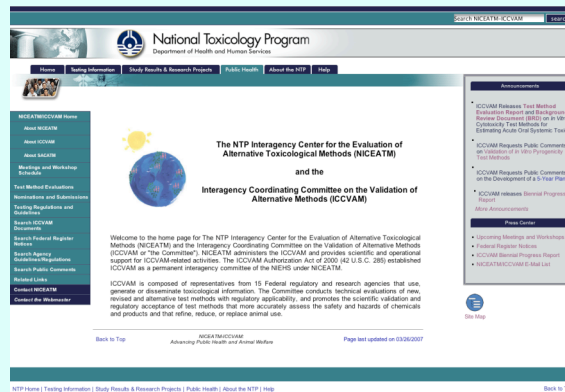
491 NICEATM and ICCVAM will promote the
492 international adoption of valid alternative test
493 methods by providing standardized protocols
494 that can be considered for adoption as OECD
495 test guidelines. NICEATM and ICCVAM will
496 provide comprehensive test method
497 background review documents and the results
498 of independent scientific peer reviews to
499 facilitate the approval of these test methods by
500 the international community.

Partnering with Stakeholders

ICCVAM co-sponsors implementation workshops to encourage interested stakeholders to use valid alternative test methods. For example, in partnership with the EPA and the International Life Sciences Institute, ICCVAM convened a training workshop on acute toxicity testing methods (<http://www.ilsa.org/file/ACF220.pdf>). The workshop provided practical information and case studies to facilitate the understanding and implementation of the UDP and other in vivo and in vitro alternative methods for acute toxicity. In addition, because calculation of dose levels to be used in the UDP test method requires complex algorithms, workshop participants were provided free software and training on its use.

The NICEATM/ICCVAM website contains background information on NICEATM and ICCVAM, current information on ICCVAM test method evaluation activities, guidance on preparing nominations and submissions to ICCVAM, details on upcoming events, and links to other sites of interest. It currently features four searchable databases:

- *NICEATM and ICCVAM publications*
- *Federal and international regulatory documents*
- *Federal Register notices relevant to NICEATM and ICCVAM activities*
- *Public comments on NICEATM and ICCVAM activities*



Please visit the website at iccvam.niehs.nih.gov.

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503 **CHAPTER 4**
504 **DEVELOPING PARTNERSHIPS AND STRENGTHENING INTERACTIONS WITH**
505 **ICCVAM STAKEHOLDERS**

506 A critical aspect of this plan is the development of partnerships and the strengthening of
507 interactions with ICCVAM stakeholders to promote research, development, translation, and
508 validation activities for alternative test methods. NICEATM and ICCVAM recognize that
509 effective interaction with stakeholders is an essential component of successfully protecting
510 human and animal health and the environment while implementing the 3Rs.

511 ICCVAM provides criteria for adequate validation and regulatory acceptance of test methods
512 for its many stakeholders²⁴. ICCVAM welcomes nominations or submissions of proposed
513 alternative or revised test methods. To aid test developers with this process, ICCVAM has
514 published guidance on the information and data that is needed to support test method
515 nominations and submissions²⁵.

516 *NICEATM and ICCVAM will continue to foster interagency collaborations with federal*
517 *research and regulatory agencies, including opportunities for collaborative test method*
518 *validation activities. This also includes promoting appropriate interagency harmonization of*
519 *regulatory testing protocols that encourage reduction, refinement, or replacement of animal*
520 *test methods. Similarly, the continued involvement of representatives from multiple centers*
521 *within large agencies fosters intra-agency collaborations. Areas of mutual interest include*
522 *determining the extent to which current test methods are protecting human and animal*
523 *health, assessing the need for improved test methods or batteries of test methods to better*
524 *detect the potential adverse health effects of substances, and identifying opportunities to use*
525 *alternative test methods to match or improve the protection of human and animal health and*
526 *the environment, while implementing the 3Rs. This maximizes efficiency and avoids*
527 *unnecessary duplication of efforts among the different federal agencies.*

²⁴ Validation involves determining the usefulness and limitations of a test method for a specific purpose. This includes determining the extent that a test method will produce similar results in different laboratories around the world and that the test method can correctly measure or predict the biological effect of interest (see http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf).

²⁵ http://iccvam.niehs.nih.gov/SuppDocs/SubGuidelines/SD_subg034508.htm

528 *ICCVAM will continue to collaborate with government and non-governmental organizations*
529 *to co-sponsor workshops to evaluate the state-of-the-science related to the development and*
530 *validation of alternative toxicological test methods, and to identify high priority research,*
531 *development, translation, and validation activities necessary to advance and characterize the*
532 *usefulness of such methods. These workshops will be broadly communicated to individuals*
533 *and organizations that conduct such activities.*

534 *ICCVAM will continue to foster international collaborations by including experts from the*
535 *international community on expert panels and workshops. This ensures that the best*
536 *international scientific expertise is used to evaluate alternative test methods. It also provides*
537 *an opportunity to communicate essential aspects of the ICCVAM test method evaluation*
538 *process to the international scientific community, especially the need for transparency and*
539 *opportunity for stakeholder and public comment during the process.*

540 *NICEATM and ICCVAM will continue to collaborate with ECVAM and JaCVAM in the*
541 *design and evaluation of international independent validation studies. These collaborations*
542 *reduce duplication and streamline efforts while also facilitating the international acceptance*
543 *of those test methods found to be scientifically valid and acceptable for regulatory testing.*

544 *NICEATM and ICCVAM will continue to strengthen international relationships with other*
545 *appropriate organizations to foster the appropriate validation and evaluation of alternative*
546 *test methods. For example, NICEATM and ICCVAM will work with the U.S. National*
547 *Coordinator for the OECD Toxicity Test Guidelines Program and OECD member countries,*
548 *to implement the internationally harmonized validation and acceptance criteria provided in*
549 *OECD Guidance Document 34²⁶, and to address other issues related to validation as they*
550 *occur. NICEATM and ICCVAM will also participate in the development of performance*
551 *standards for OECD Test Guidelines. To further ensure the development of scientifically*
552 *valid international test guidelines, NICEATM and ICCVAM will seek to increase*
553 *participation of its scientists in U.S. delegations to OECD test guideline meetings, expert*
554 *consultations, and workshops. Additionally, where appropriate, NICEATM and ICCVAM*
555 *will invite representatives from international organizations such as OECD and OECD*
556 *member countries to attend and participate in relevant NICEATM and ICCVAM-sponsored*

²⁶ [http://appli1.oecd.org/olis/2005doc.nsf/linkto/env-jm-mono\(2005\)14](http://appli1.oecd.org/olis/2005doc.nsf/linkto/env-jm-mono(2005)14)

557 *workshops, peer reviews, and other scientific activities. This provides an opportunity to*
558 *promote information exchange and scientifically sound test method evaluation processes and*
559 *principles.*

560 The overall aims of these partnerships are to best utilize existing resources and scientific
561 expertise, maximize the efficiency of evaluation/validation efforts, minimize duplication of
562 effort, and ensure an early exchange of information concerning test method validation. This
563 in turn can be expected to facilitate national and international recognition, acceptance, and
564 implementation of scientifically valid test methods.

Effective Partnerships

The use of in vitro test methods is expected to continue to increase as new science and technologies are incorporated into in vitro test methods and such innovative techniques enter the regulatory arena. For this reason, ICCVAM and ECVAM have worked in conjunction to promote the international application of Good Laboratory Practices (GLPs) to in vitro systems by assisting an OECD GLP Working Group of experts from OECD member countries in the development of a guidance document. With the increasing use of non-animal testing procedures, such guidance facilitates the acceptable use of these new test methods and the proper generation and documentation of data in accordance with the requirements of GLPs. This should help ensure that in vitro data are of acceptable quality for consideration by regulatory authorities. According to ICCVAM, ECVAM, and OECD guidances, validation studies should ideally be conducted in accordance with GLPs. Thus, a user-friendly, clear, and concise document devoted to the application of GLPs to in vitro methods also could help encourage the use of GLPs for validation studies, thereby facilitating and increasing confidence in the validation of in vitro test methods.

565

566

566 **REFERENCES AND INFORMATION RESOURCES**

- 567 Animal Welfare Act, as amended. 1990. Public Law 89-544. Available:
568 <http://www.aphis.usda.gov/ac/publications/AWA/AWAINDEX.HTML> [accessed 30 April
569 2007].
- 570 Health Research Extension Act of 1985. 1985. Public Law 99-158. Available:
571 <http://grants2.nih.gov/grants/olaw/references/hrea1985.htm> [accessed 30 April 2007].
- 572 ICCVAM Authorization Act of 2000. 2000. Public Law 106-545. Available:
573 http://iccvam.niehs.nih.gov/docs/about_docs/PL106545.pdf [accessed 30 April 2007].
- 574 ICCVAM. 2003. ICCVAM Guidelines for the Nomination and Submission of New, Revised,
575 and Alternative Test Methods. NIH Publication No. 03-4508. Research Triangle Park,
576 NC: National Institute for Environmental Health Sciences. Available:
577 <http://iccvam.niehs.nih.gov/> [accessed 30 April 2007].
- 578 National Research Council. 2004. Science, Medicine, and Animals. Washington,
579 DC: National Academy of Sciences. Available:
580 http://books.nap.edu/catalog.php?record_id=10733 [accessed 30 April 2007].
- 581 NIH Revitalization Act of 1993. 1993. Public Law 103-43. Available:
582 <http://www.history.nih.gov/laws/pdf/PL103-43.pdf> [accessed 30 April 2007].
- 583 Organisation for Economic Cooperation and Development (OECD). 2005. OECD Series on
584 Testing and Assessment Number 34: Guidance Document on the Validation and International
585 Acceptance of New Test Methods for Hazard Assessment. Paris: OECD. Available:
586 www.oecd.org [accessed 30 April 2007].
- 587 Office of Laboratory Animal Welfare. 2002. Public Health Service Policy on Humane Care
588 and Use of Laboratory Animals. Bethesda, MD: National Institutes of Health. Available:
589 <http://grants2.nih.gov/grants/olaw/references/phspol.htm> [accessed 30 April 2007].
- 590 Russell WMS, Birch RL. 1959. The Principles of Humane Experimental Technique. 1st ed.
591 London: Methuen and Co.
- 592 ICCVAM. 1997. Validation and Regulatory Acceptance of Toxicological Test Methods: A
593 Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative

594 Methods. NIH Publication No. 97-3981. Research Triangle Park, NC:National Institute for
595 Environmental Health Sciences. Available: <http://iccvam.niehs.nih.gov/> [accessed 30 April
596 2007].

597 **A full listing of all ICCVAM publications can be found on the NICEATM-ICCVAM**
598 **website at <http://iccvam.niehs.nih.gov/>**

599 **Glossary of Terms**²⁷

600 **Accuracy:** (a) The closeness of agreement between a test method result and an accepted
601 reference value. (b) The proportion of correct outcomes of a test method. It is a measure
602 of test method performance and one aspect of “relevance” and is a term that is often used
603 interchangeably with “concordance”.

604 **Acute toxicity**²⁸: Adverse effects occurring within a short time (usually up to 14 days) after
605 administration of a single dose (or exposure to a given concentration) of a test substance
606 or after multiple doses (exposures), usually within 24 hours; OR the ability of a substance
607 to cause adverse effects within a short time of dosing or exposure.

608 **Assay:** The experimental system used. Often used interchangeably with “test” and “test
609 method”.

610 **Biological products or Biologics:** Includes a wide range of products such as vaccines, blood
611 and blood components, allergenics, somatic cells, gene therapy, tissues, therapeutic
612 antibodies and recombinant therapeutic proteins. Biologics can be composed of sugars,
613 proteins, or nucleic acids or complex combinations of these substances, or may be living
614 entities such as cells and tissues. Biologics are isolated from a variety of natural sources -
615 human, animal, or microorganism - and may be produced by biotechnology methods and
616 other cutting-edge technologies. Gene-based and cellular biologics, for example, often
617 are at the forefront of biomedical research, and may be used to treat a variety of medical
618 conditions for which no other treatments are available"

619 **Biomarker**²⁹: A distinctive biological or biologically derived indicator (as a biochemical
620 metabolite in the body) of a process, event, or condition (as aging, disease, or exposure to
621 a toxic substance)

622 **Chronic Toxicity:** Adverse effects following chronic exposure; OR effects which persist
623 over a long period of time whether or not they occur immediately upon exposure or are
624 delayed.

²⁷ Unless otherwise indicated, from ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods (NIH Publication No. 03-4508, September 2003, available at:

<http://iccvam.niehs.nih.gov/SuppDocs/submission.htm>

²⁸ From National Library of Medicine Toxicology Glossary ()

²⁹ From Medline Plus Medical Dictionary ()

625 **Concordance:** The proportion of all chemicals tested that are correctly classified as positive
626 or negative. It is a measure of test method performance and one aspect of “relevance”.
627 The term is often used interchangeably with “accuracy”.

628 **Endpoint:** The biological or chemical process, response, or effect assessed by a test method.

629 **Hazard:** The potential for an adverse health or ecological effect. A hazard potential result
630 only if an exposure occurs that leads to the possibility of an adverse effect being
631 manifested.

632 ***In vitro***³: outside the living body and in an artificial environment: “growth of cells *in vitro*”,
633 “*in vitro* studies”.

634 ***In vivo***³: in the living body of a plant or animal: “*in vivo* synthesis of DNA”,
635 “microorganisms are not ordinarily destroyed *in vivo* by bacteriostatic drugs

636 **Mechanistically based methods:** Methods that provide a direct relationship between the
637 biological effects observed and the biological effects of interest.

638 **Performance:** The accuracy and reliability characteristics of a test method (see “accuracy”,
639 “reliability”).

640 **Reduction alternative:** A new or modified test method that reduces the number of animals
641 required.

642 **Reference species:** The species used in the reference (or traditional) test method to which a
643 new or modified test is being compared. This may be the target species when it is also the
644 species of interest, or it may be a surrogate species when it is not possible to perform
645 testing on the target species.

646 **Reference test method:** The accepted *in vivo* test method used for regulatory purposes to
647 evaluate the potential of a test substance to be hazardous to the species of interest.

648 **Refinement alternative:** A new or modified test method that refines procedures to lessen or
649 eliminate pain or distress in animals or enhances animal well-being.

650 **Relevance:** The extent to which a test method correctly predicts or measures the biological
651 effect of interest in humans or another species of interest. Relevance incorporates

³ From Medline Plus Medical Dictionary (<http://www.nlm.nih.gov/medlineplus/mplusdictionary.html>)

652 consideration of the “accuracy” or “concordance” of a test method.

653 **Reliability:** A measure of the degree to which a test method can be performed reproducibly
654 within and among laboratories over time. It is assessed by calculating intra- and inter-
655 laboratory reproducibility and intralaboratory repeatability.

656 **Replacement alternative:** A new or modified test method that replaces animals with
657 nonanimal systems or one animal species with a phylogenetically lower one (e.g., a
658 mammal with an invertebrate).

659 **Risk:** The probability or degree of concern that exposure to an agent will cause an adverse
660 effect in the species of interest.

661 **Risk assessment**³⁰: Evaluation of the potential adverse health and environmental effects to a
662 target species from exposures to certain substances.

663 **Screen/screening test:** A rapid, simple test conducted for the purposes of a general
664 classification of substances according to general categories of hazard. The results of a
665 screen generally are used for preliminary decision-making and to set priorities for more
666 definitive tests. A screening test may have a truncated response range (e.g., be able to
667 reliably identify active chemicals but not inactive chemicals).

668 **Substitute method:** A new or modified test method proposed for use in lieu of a currently
669 used test method, regardless of whether that test method is for a definitive, screening, or
670 adjunct purpose.

671 **Test:** The experimental system used; used interchangeably with “test method” and “assay”.

672 **Test method:** A process or procedure used to obtain information on the characteristics of a
673 substance or agent. Toxicological test methods generate information regarding the ability
674 of a substance or agent to produce a specified biological effect under specified
675 conditions. Used interchangeably with “test” and “assay”. See also “validated test
676 method” and “reference test method”.

³⁰ Modified from Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (NIH Publication No. 97-3981, March 1997, available at: http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf)

677 **Test method nomination:** Test methods proposed to ICCVAM for review and evaluation
678 for which a complete test method submission is not available. Four examples are (1) test
679 methods for which adequate validation studies presumably have been completed but lack
680 a complete submission package; (2) test methods that appear promising based on limited
681 revalidation or validation data and are proposed for additional validation studies; (3) test
682 methods that have been developed and are proposed for revalidation or validation studies;
683 and (4) test methods that are recommended for a workshop or other activity.

684 **Test method nominator:** The organization or individual that submits a test method
685 nomination to ICCVAM for consideration.

686 **Test method sponsor:** The organization or individual that puts forward a test method
687 submission to ICCVAM for consideration.

688 **Test method submission:** A test method proposed to ICCVAM for consideration for which
689 adequate validation studies have been completed to characterize the usefulness and
690 limitations of the test method for a specific proposed regulatory testing requirement or
691 application, and adequate documentation of the scientific validity has been prepared in
692 accordance with ICCVAM test method submission guidelines.

693 **Toxicology³¹:** The study of the adverse effects of chemicals on living organisms. It is the
694 study of symptoms, mechanisms, treatments and detection of poisoning of humans,
695 animals, or the environment.

696 **Transferability:** The ability of a test method or procedure to be accurately and reliably
697 performed in different laboratories.

698 **Translation:** For the purposes of this document, ICCVAM considers translation as activities
699 that are carried out to characterize if there is evidence of relevance and applicability of a
700 test method for a specific testing purpose. If so, then the test method may be considered
701 for evaluation in a formal validation study.

³¹ Modified from Medline Plus Medical Dictionary
(<http://www.nlm.nih.gov/medlineplus/mplusdictionary.html>)

702 **Validated test method:** An accepted test method for which validation studies were
703 conducted and the demonstrated relevance and reliability were sufficient for the test
704 method's intended purpose.

705 **Validation:** The process by which the reliability and relevance of a procedure are
706 established for a specific purpose.

707

708 **Acronyms and Abbreviations**

709	3R's	Replacement, reduction and refinement alternatives in animal testing
710	ALTTOX	Alternative Toxicological Methods Evaluation Data System (NICEATM
711		database of ocular toxicity data)
712	ASTDR	Agency for Toxic Substances and Disease Registry
713	<i>C. elegans</i>	<i>Caenorhabditis elegans</i>
714	CEBS	Chemical Effects in Biological Systems
715	COLIPA	European Cosmetic, Toiletry, and Perfumery Association
716	CPSC	Consumer Product Safety Commission
717	DOD	U.S. Department of Defense
718	DOE	U.S. Department of Energy
719	DOI	U.S. Department of the Interior
720	DOT	U.S. Department of Transportation
721	DNA	Deoxyribonucleic Acid (genetic material)
722	ECVAM	European Centre for the Validation of Alternative Methods
723	EPA	U.S. Environmental Protection Agency
724	FDA	U.S. Food and Drug Administration
725	<i>FR</i>	<i>Federal Register</i>
726	GLP	Good Laboratory Practice
727	HESI	Health and Environmental Sciences Institute (global branch of the International
728		Life Sciences Institute (ILSI))
729	HTS	High Throughput Screening
730	ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
731	ILSI	International Life Sciences Institute
732	JaCVAM	Japanese Center for the Validation of Alternative Methods
733	LLNA	Murine Local Lymph Node Assay

734	NCI	National Cancer Institute
735	NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological
736		Methods
737	NIEHS	National Institute of Environmental Health Sciences
738	NIH	National Institutes of Health
739	NIOSH	National Institute for Occupational Safety and Health
740	NLM	National Library of Medicine
741	NTP	National Toxicology Program
742	OECD	Organisation for Economic Cooperation and Development
743	OSHA	Occupational Safety and Health Administration
744	PHS	Public Health Service
745	SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
746	ToxCast	Suite of computer modeling tools for prioritizing chemicals for toxicology
747		testing, developed by the U.S. EPA
748	USC	United States Code
749	USDA	U.S. Department of Agriculture
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Appendix A: Federal Agencies and Programs with Authority to Require or Use Toxicological Testing Information

Agency	Substance	Statute	Program
ATSDR	Health effects of exposure to environmental contaminants near hazardous waste sites	Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) Superfund Amendments and Reauthorization (SARA)	Division of Toxicology and Environmental Medicine
CPSC	Consumer product exposures/Household Substances	Federal Hazardous Substances Act; Consumer Product Safety Act; Poison Prevention Packaging Act	Hazard Assessment and Reduction Program and Regulated Products Program
DOI	Drug and chemical management for fisheries	Fish and Wildlife Coordination Act; Federal Insecticide and Fungicide and Rodenticide Act (FIFRA); Federal Food, Drug and Cosmetic Act (FFDCA)	Chemical-Drug Registration Program, U.S. Geological Survey
	Non-Toxic Shot Program	Migratory Bird Treaty Act	Office of Migratory Bird Management, Fish and Wildlife Service
DOT	Exposure to hazardous materials in transport	Federal Hazardous Materials Transportation Law	Pipeline and Hazardous Materials Safety Administration
EPA	Pesticides	FIFRA	Office of Pesticide Programs (OPP)
	Industrial chemicals	Toxic Substances Control Act	Office of Pollution Prevention and Toxics (OPPT)
FDA	Biologicals	FFDCA; Public Health Service Act	Center for Biologics Evaluation and Research
	Medical devices; radioactive materials	FFDCA	Center for Devices and Radiological Health
	Pharmaceuticals and Biologicals	FFDCA; Public Health Service Act	Center for Drug Evaluation and Research
	Food and color additives, cosmetics	FFDCA	Center for Food Safety and Applied Nutrition
	Veterinary drugs	FFDCA	Center for Veterinary Medicine
OSHA	Worker exposure/ Occupational materials	OSHA	Directorate of Standards and Guidance
USDA	Genetically engineered organisms	Plant Protection Act	Animal and Plant Health Inspection Services (APHIS)
	Veterinary biologicals	Virus, Serum, Toxin Act	APHIS
	Meat and Poultry products for human consumption	Federal Meat Inspection Act; Poultry Products Inspection Act	Food Safety and Inspection Service

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*OPP and OPPT can require data. In addition to these, most EPA programs can use toxicity testing data/information for regulatory and other purposes. Under the Clean Air Act, EPA's Office of Air and Radiation (OAR) can issue health effects testing requirements for fuel and fuel additives. This is done on a case-by-case basis as data needs are assessed to address specific situations.

CPSC = Consumer Product Safety Commission; DOE = Department of Energy; DOI = Department of Interior; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; OSHA = Occupational Safety and Health Administration; USDA = U.S. Department of Agriculture

759 **Appendix B: Roster of the Interagency Coordinating Committee on the Validation of**
760 **Alternative Methods (ICCVAM) and National Toxicology Program**
761 **(NTP) Interagency Center for the Evaluation of Alternative Toxicological**
762 **Methods (NICEATM)**

Agency for Toxic Substances and Disease Registry

- Moiz Mumtaz, Ph.D.

Consumer Product Safety Commission

- Marilyn L. Wind, Ph.D. (Chair)◆
- * *Patricia Bittner, M.S.*
- * *Kristina Hatlelid, Ph.D.*
- * Joanna Matheson, Ph.D.

Department of Agriculture

- Jodie Kulpa-Eddy, D.V.M. (Vice-Chair)◆
- ◇ Elizabeth Goldentyer, D.V.M.

Department of Defense

- Robert E. Foster, Ph.D.
- ◇ Patty Decot
- Harry Salem, Ph.D.

Department of Energy

- Marvin Stodolsky, Ph.D.

Department of the Interior

- Barnett A. Rattner, Ph.D.
- ◇ Sarah Gerould, Ph.D.

Department of Transportation

- George Cushmac, Ph.D.
- ◇ Steve Hwang, Ph.D.

Environmental Protection Agency

Office of Science Coordination and Policy

- Karen Hamernik, Ph.D.

Office of Research and Development

- ◇ Julian Preston, Ph.D.
- * Suzanne McMaster, Ph.D.

Office of Pesticides Programs

- * Amy Rispin, Ph.D.
- * Deborah McCall

OECD Test Guidelines Program

- * Jerry Smrcek, Ph.D.

- Principal Agency Representative
- ◇ Alternate Principal Agency Representative
- * Other Designated Agency Representatives

Food and Drug Administration

Office of Science and Health Coordination

- Suzanne Fitzpatrick, Ph.D., D.A.B.T.

Center for Drug Evaluation and Research

- ◇ Abigail C. Jacobs, Ph.D.

Center for Devices and Radiological Health

- * Melvin E. Stratmeyer, Ph.D.

Center for Biologics Evaluation and Research

- * Richard McFarland, Ph.D., M.D.
- * Ying Huang, Ph.D.

Center for Food Safety and Nutrition

- * David G. Hattan, Ph.D.
- * Robert L. Bronaugh, Ph.D.

Center for Veterinary Medicine

- * Devaraya Jagannath, Ph.D.
- * M. Cecilia Aguila, D.V.M.

National Center for Toxicological Research

- * William T. Allaben, Ph.D.

Office of Regulatory Affairs

- * Lawrence A. D'Hoostelaere, Ph.D.

National Cancer Institute

- Alan Poland, M.D.
- ◇ T. Kevin Howcroft, Ph.D.

National Institute of Environmental Health Sciences

- William S. Stokes, D.V.M., D.A.C.L.A.M.
- ◇ John R. Bucher, Ph.D., D.A.B.T.
- * Rajendra S. Chhabra, Ph.D., D.A.B.T.
- * Jerrold J. Heindel, Ph.D.

National Institute for Occupational Safety and Health

- Paul Nicolaysen, V.M.D.
- ◇ K. Murali Rao, M.D., Ph.D.

National Institutes of Health

- Margaret D. Snyder, Ph.D.

National Library of Medicine

- Vera Hudson, M.S.
- ◇ Jeanne Goshorn, M.S.

Occupational Safety and Health Administration

- Surender Ahir, Ph.D.

NICEATM

- William S. Stokes, D.V.M., D.A.C.L.A.M. (Director)
- Raymond R. Tice, Ph.D. (Deputy Director)
- Debbie McCarley (Assistant to the Director)

763 **Appendix C Process for Development of the NICEATM-ICCVAM Five-Year Plan**

764 This document was prepared in response to requests from the Appropriations Committees of
765 both the U.S. House of Representatives and the U.S. Senate (**Appendices G and H**,
766 respectively) that NICEATM and ICCVAM, in partnership with relevant federal agencies,
767 create a five-year plan to:

- 768 • Research, develop, translate, and validate new and revised non-animal and
769 other alternative assays for integration of relevant and reliable methods into
770 federal agency testing programs, and
- 771 • Identify areas of high priority for new and revised non-animal and alternative
772 assays or batteries of those assays to create a path forward for the
773 replacement, reduction, and refinement of animal tests, when this is
774 scientifically valid and appropriate.

775 Consistent with all ICCVAM and NICEATM document publications, the process of
776 producing the report was planned from the outset to also allow for transparency and multiple
777 opportunities for public comment consistent with the deadline for providing the report. A
778 timeline was developed to provide five separate opportunities for public comments. This
779 included two opportunities during the early, planning stages of the report and three
780 opportunities for comment on the draft report to be considered before it was finalized.

781 The timeline also included multiple opportunities for review and comment on the plan by the
782 Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), a
783 federally chartered advisory committee for NICEATM and ICCVAM. The SACATM
784 includes members from industries (for example, pharmaceuticals, pesticides) regulated by
785 ICCVAM agencies, academic institutions, state government agencies, and at least one
786 member of a national animal protection organization. SACATM was provided two
787 opportunities for comment; one during the planning process and one following the release of
788 the draft report. These opportunities also allowed SACATM to consider public comments
789 provided prior to and during their two public meetings.

790 The process for development of the plan includes three phases (**Figure 1**). The first phase
791 involved information gathering, during which input was solicited and received from all 15 of

792 the ICCVAM agencies. Specifically, each agency was asked to provide 1) information
793 regarding research, development, translation, validation activities currently in progress or
794 planned during the next five years, and 2) areas of high priority for new and revised non-
795 animal and alternative assays or batteries of those assays to create a path forward for the
796 replacement, reduction, and refinement (reduced pain and distress) of animal tests, when this
797 is scientifically valid and appropriate. This initial phase also included requests for comments
798 from the public and SACATM.

799 During the second phase, an ICCVAM five-year plan subcommittee considered the input
800 received and, in conjunction with NICEATM, prepared an initial draft of the plan for review
801 and comment by the full ICCVAM committee and the 15 ICCVAM agencies. Following this
802 review, comments and suggestions were incorporated into a draft plan released to the public
803 for comment on May 7, 2007. A *Federal Register* notice announcing availability of the draft
804 plan and formally requesting public comment accompanied the release³². On June 11, 2007 a
805 town meeting will be held specifically to allow an opportunity for public comment. The
806 SACATM will meet on June 12 to consider and comment on the draft plan and consider
807 comments from the town meeting. The public will be provided an additional opportunity to
808 comment during the SACATM meeting.

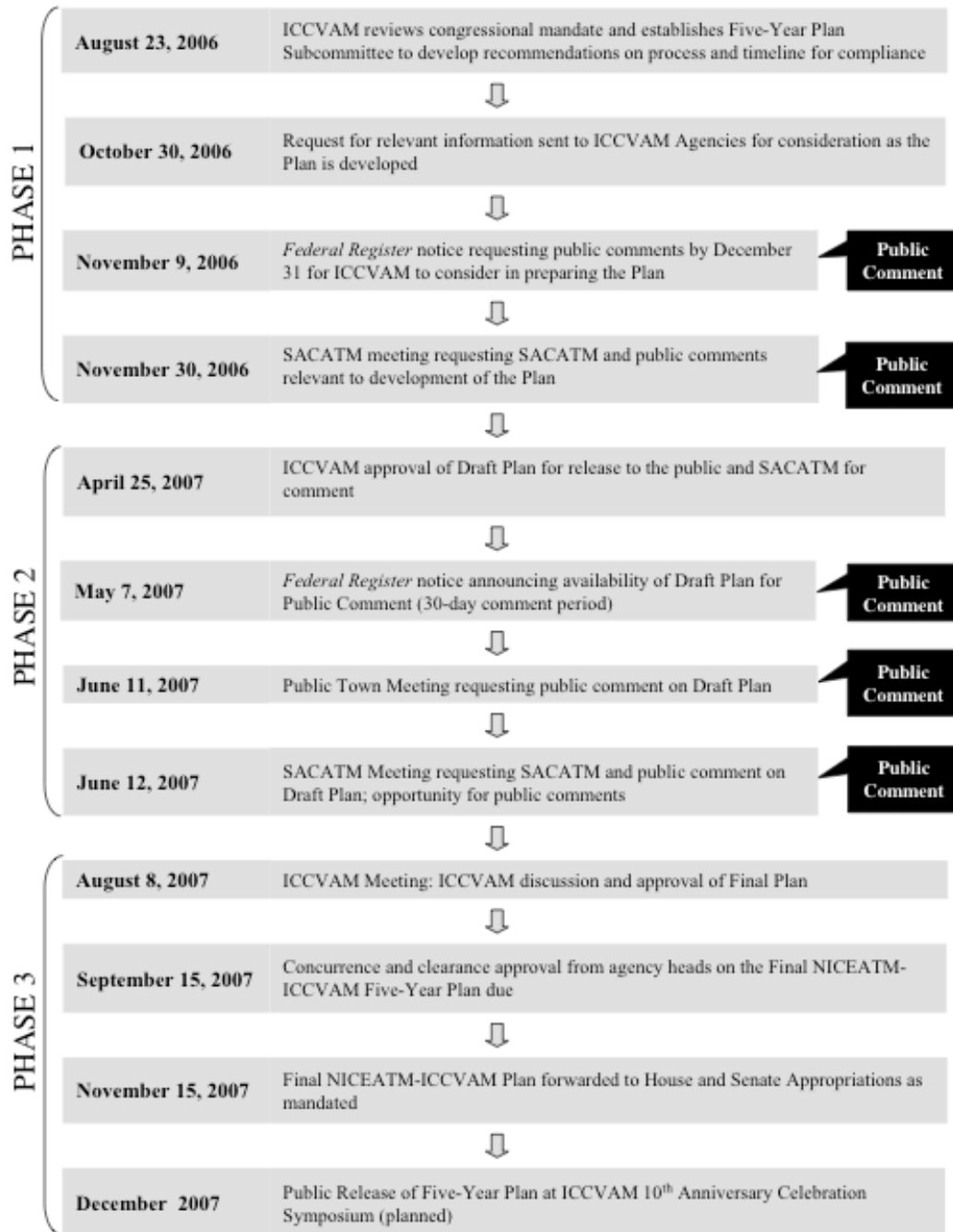
809 The final phase of the process will focus on ICCVAM and NICEATM finalizing the draft
810 plan, taking into consideration public and SACATM comments on the draft plan. The plan
811 will then be sent to ICCVAM agency heads for concurrence. NIEHS will then forward the
812 plan through NIH and DHHS to the U.S. House of Representatives and U.S. Senate
813 Appropriations Committees by the November 15, 2007 deadline. In early December 2007,
814 the plan will be released to the public and will be available at the NICEATM and ICCVAM
815 website (<http://iccvam.niehs.nih.gov/>).

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³² both available at <http://iccvam.niehs.nih.gov/docs/5yearplan.htm>

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Process Timeline for NICEATM-ICCVAM Five-Year Plan



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Appendix D U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training

U.S. GOVERNMENT PRINCIPLES FOR THE UTILIZATION AND CARE OF VERTEBRATE ANIMALS USED IN TESTING, RESEARCH AND TRAINING

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species. Whenever U.S. Government agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall be considered; and whenever these agencies actually perform or sponsor such procedures, the responsible institutional official shall ensure that these principles are adhered to:

- I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act (7 U.S.C. 2131 et. seq.) and other applicable Federal Laws, guidelines, and policies¹.
- II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.
- III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer stimulation, and *in vitro* biological systems should be considered.
- IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.
- V. Procedures with animals that may cause more than momentary or slight pain or in distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.
- VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.
- VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.
- VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in service training, including the proper and humane care and use of laboratory animals.
- IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made, with due regard to Principle II, by an appropriate review group such as an institutional animal research committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.

¹For guidance throughout these Principles the reader is referred to the Guide for the Care and Use of Laboratory Animals prepared by the National Research Council.

Published in the Federal Register, May 20, 1985, Vol. 50, No. 97, by the Office of Science and Technology Policy.

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821 **Appendix E The ICCVAM Authorization Act of 2000 (Public Law 106-545, December**
822 **19, 2000)**

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824 PUBLIC LAW 106–545—DEC. 19, 2000 114 STAT. 2721

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826 Public Law 106–545 106th Congress

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An Act

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To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness.

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Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

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SECTION 1. SHORT TITLE.

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This Act may be cited as the “ICCVAM Authorization Act of 2000”.

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SEC. 2. DEFINITIONS.

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In this Act:

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(1) ALTERNATIVE TEST METHOD.—The term “alternative test method” means a test method that—

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(A) includes any new or revised test method; and

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(B) (i) reduces the number of animals required;

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(ii) refines procedures to lessen or eliminate pain or distress to animals, or enhances animal well-being; or

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(iii) replaces animals with non-animal systems or one animal species with a phylogenetically lower animal species, such as replacing a mammal with an invertebrate.

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(2) ICCVAM TEST RECOMMENDATION.—The term “ICCVAM test recommendation” means a summary report prepared by the ICCVAM characterizing the results of a scientific expert peer review of a test method.

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SEC. 3. INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS.

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(a) IN GENERAL.—With respect to the interagency coordinating committee that is known as the Interagency Coordinating Committee on the Validation of Alternative Methods (referred to in this Act as “ICCVAM”) and that was established by the Director of the National Institute of Environmental Health Sciences for purposes of section 463A(b) of the Public Health Service Act, the Director of the Institute shall designate such committee as a permanent interagency coordinating committee of the Institute under the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods. This Act may not be construed as affecting the authorities of such Director regarding ICCVAM that were in effect on the day before the date of the enactment of this Act, except to the extent inconsistent with this Act.

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(b) PURPOSES.—The purposes of the ICCVAM shall be to—

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(1) increase the efficiency and effectiveness of Federal agency test method review;

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(2) eliminate unnecessary duplicative efforts and share experiences between Federal regulatory agencies;

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(3) optimize utilization of scientific expertise outside the Federal Government;

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(4) ensure that new and revised test methods are validated to meet the needs of Federal agencies; and

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(5) reduce, refine, or replace the use of animals in testing, where feasible.

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(c) COMPOSITION.—The ICCVAM shall be composed of the heads of the following Federal agencies (or their designees):

- (1) Agency for Toxic Substances and Disease Registry.
- (2) Consumer Product Safety Commission.
- (3) Department of Agriculture.
- (4) Department of Defense.
- (5) Department of Energy.
- (6) Department of the Interior.
- (7) Department of Transportation.
- (8) Environmental Protection Agency.
- (9) Food and Drug Administration.
- (10) National Institute for Occupational Safety and Health.
- (11) National Institutes of Health.
- (12) National Cancer Institute.
- (13) National Institute of Environmental Health Sciences.
- (14) National Library of Medicine.
- (15) Occupational Safety and Health Administration.
- (16) Any other agency that develops, or employs tests or test data using animals, or regulates on the basis of the use of animals in toxicity testing.

(d) SCIENTIFIC ADVISORY COMMITTEE.—

- (1) ESTABLISHMENT.—The Director of the National Institute of Environmental Health Sciences shall establish a Scientific Advisory Committee (referred to in this Act as the “SAC”) to advise ICCVAM and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods regarding ICCVAM activities. The activities of the SAC shall be subject to provisions of the Federal Advisory Committee Act.

(2) MEMBERSHIP.—

(A) IN GENERAL.—The SAC shall be composed of the following voting members:

(i) At least one knowledgeable representative having a history of expertise, development, or evaluation of new or revised or alternative test methods from each of—

(I) the personal care, pharmaceutical, industrial chemicals, or agriculture industry;

(II) any other industry that is regulated by the Federal agencies specified in subsection (c);

and

(III) a national animal protection organization established under section 501(c)(3) of the Internal Revenue Code of 1986.

(ii) Representatives (selected by the Director of the National Institute of Environmental Health Sciences) from an academic institution, a State government agency, an international regulatory body, or any corporation developing or marketing new or revised or alternative test methodologies, including contract laboratories.

(B) NONVOTING EX OFFICIO MEMBERS.—The membership of the SAC shall, in addition to voting members under subparagraph (A), include as nonvoting ex officio members the agency heads specified in subsection (c) (or their designees).

(e) DUTIES.—The ICCVAM shall, consistent with the purposes described in subsection (b), carry out the following functions:

- (1) Review and evaluate new or revised or alternative test methods, including batteries of tests and test screens, that may be acceptable for specific regulatory uses, including the coordination of technical reviews of proposed new or revised or alternative test methods of interagency interest.
- (2) Facilitate appropriate interagency and international harmonization of acute or chronic toxicological test protocols that encourage the reduction, refinement, or replacement of animal test methods.
- (3) Facilitate and provide guidance on the development of validation criteria, validation studies and processes for new or revised or alternative test methods and help facilitate the acceptance of such

- 926 scientifically valid test methods and awareness of accepted test methods by Federal agencies and
927 other
928 stakeholders.
- 929 (4) Submit ICCVAM test recommendations for the test method reviewed by the ICCVAM, through
930 expeditious transmittal by the Secretary of Health and Human Services (or the designee of the
931 Secretary), to each appropriate Federal agency, along with the identification of specific agency
932 guidelines, recommendations, or regulations for a test method, including batteries of tests and test
933 screens, for chemicals or class of chemicals within a regulatory framework that may be
934 appropriate for scientific improvement, while seeking to reduce, refine, or replace animal test
935 methods.
- 936 (5) Consider for review and evaluation, petitions received from the public that— (A) identify a specific
937 regulation, recommendation, or guideline regarding a regulatory mandate; and (B) recommend
938 new or revised or alternative test methods and provide valid scientific evidence of the potential of
939 the test method.
- 940 (6) Make available to the public final ICCVAM test recommendations to appropriate Federal agencies
941 and the responses from the agencies regarding such recommendations.
- 942 (7) Prepare reports to be made available to the public on its progress under this Act. The first report
943 shall be completed not later than 12 months after the date of the enactment of this Act, and
944 subsequent reports shall be completed biennially thereafter.

945
946 **SEC. 4. FEDERAL AGENCY ACTION.**

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948 (a) IDENTIFICATION OF TESTS.—With respect to each Federal agency carrying out a program that
949 requires or recommends acute or chronic toxicological testing, such agency shall, not later than 180 days after
950 receiving an ICCVAM test recommendation, identify and forward to the ICCVAM any relevant test method
951 specified in a regulation or industry-wide guideline which specifically, or in practice requires, recommends, or
952 encourages the use of an animal acute or chronic toxicological test method for which the ICCVAM test
953 recommendation may be added or substituted.

954 (b) ALTERNATIVES.—Each Federal agency carrying out a program described in subsection (a) shall
955 promote and encourage the development and use of alternatives to animal test methods (including batteries of
956 tests and test screens), where appropriate, for the purpose of complying with Federal statutes, regulations,
957 guidelines, or recommendations (in each instance, and for each chemical class) if such test methods are found to
958 be effective for generating data, in an amount and of a scientific value that is at least equivalent to the data
959 generated from existing tests, for hazard identification, dose-response assessment, or risk assessment purposes.

960 (c) TEST METHOD VALIDATION.—Each Federal agency carrying out a program described in subsection
961 (a) shall ensure that any new or revised acute or chronic toxicity test method, including animal test methods and
962 alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the
963 application of such test method.

964 (d) REVIEW.—Not later than 180 days after receipt of an ICCVAM test recommendation, a Federal
965 agency carrying out a program described in subsection (a) shall review such recommendation and notify the
966 ICCVAM in writing of its findings.

967 (e) RECOMMENDATION ADOPTION.—Each Federal agency carrying out a program described in
968 subsection (a), or its specific regulatory unit or units, shall adopt the ICCVAM test recommendation unless such
969 Federal agency determines that—

- 970 (1) the ICCVAM test recommendation is not adequate in terms of biological relevance for the
971 regulatory goal authorized by that agency, or mandated by Congress;
- 972 (2) the ICCVAM test recommendation does not generate data, in an amount and of a scientific value
973 that is at least equivalent to the data generated prior to such recommendation, for the appropriate
974 hazard identification, dose-response assessment, or risk assessment purposes as the current test
975 method recommended or required by that agency;
- 976 (3) the agency does not employ, recommend, or require testing for that class of chemical or for the
977 recommended test endpoint; or
- 978 (4) the ICCVAM test recommendation is unacceptable for satisfactorily fulfilling the test needs for that
979 particular agency and its respective congressional mandate.

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SEC. 5. APPLICATION.

(a) APPLICATION.—This Act shall not apply to research, including research performed using biotechnology techniques, or research related to the causes, diagnosis, treatment, control, or prevention of physical or mental diseases or impairments of humans or animals.

(b) USE OF TEST METHODS.—Nothing in this Act shall prevent a Federal agency from retaining final authority for incorporating the test methods recommended by the ICCVAM in the manner determined to be appropriate by such Federal agency or regulatory body.

(c) LIMITATION.—Nothing in this Act shall be construed to require a manufacturer that is currently not required to perform animal testing to perform such tests. Nothing in this Act shall be construed to require a manufacturer to perform redundant endpoint specific testing.

(d) SUBMISSION OF TESTS AND DATA.—Nothing in this Act precludes a party from submitting a test method or scientific data directly to a Federal agency for use in a regulatory program.

Approved December 19, 2000.

LEGISLATIVE HISTORY—H.R. 4281 (S. 1495):

HOUSE REPORTS: No. 106–980 (Comm. on Commerce).

SENATE REPORTS: No. 106–496 accompanying S. 1495 (Comm. on Health, Education, Labor, and Pensions).

CONGRESSIONAL RECORD, Vol. 146 (2000):

Oct. 17, considered and passed House.

Dec. 6, considered and passed Senate.

1007 **Appendix F U.S. House of Representatives Appropriations Committee Request**

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1009 Excerpted from “Departments of Labor, Health and Human Services, and Education, and
1010 Related Agencies Appropriations Bill, 2007: Report of the Committee on Appropriations”

1011

1012 House of Representatives Appropriation for National Institute of Environmental Health
1013 Sciences (NIEHS), Pages 106-107

1014

1015 *National Toxicology Program Interagency Center for the Evaluation of Alternative*

1016 *Methods/Interagency Coordinating Committee on the Validation of Alternative Methods*

1017 *(NICEATM/ICCVAM).*—The Committee commends the NICEATM/ICCVAM for its leadership role

1018 in the assessment of new, revised and alternative scientifically validated methods for the federal

1019 government. The Committee also commends the National Toxicology Program (NTP) for finalizing

1020 its “Roadmap to Achieve the NTP Vision, A Toxicology Program for the 21st Century”, which

1021 commits to “develop and validate improved testing methods and, where feasible, ensure that they

1022 reduce, refine or replace the use of animals” as one of its top four goals.

1023

1024 The Committee requests that the NICEATM/ICCVAM, in partnership with the relevant federal

1025 agency program offices and the NTP, build on the NTP Roadmap to create a five-year plan to

1026 research, develop, translate and validate new and revised non-animal and other alternative assays for

1027 integration of relevant and reliable methods into the federal agency testing programs. In this five-year

1028 plan the Committee expects that federal agency program offices will identify areas of high priority for

1029 new and revised non-animal and alternative assays or batteries of those assays to create a path

1030 forward for the replacement, reduction and refinement of animal tests, when this is scientifically valid

1031 and appropriate. The Committee requests the plan by November 15, 2007. Furthermore, the

1032 Committee expects that the cost of assembling this plan will not reduce the NICEATM/ICCVAM

1033 funding base.

1034

1034 **Appendix G U.S. Senate Appropriations Committee Request**

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1036 Excerpted from “Departments of Labor, Health and Education, and Related Agencies
1037 Appropriations Bill, 2007”

1038

1039 Senate Appropriation for National Institute of Environmental Health Sciences (NIEHS),
1040 Pages 141-142

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1043 *National Toxicology Program Interagency Center for the Evaluation of Alternative*

1044 *Methods/Interagency Coordinating Committee on the Validation of Alternative Methods*

1045 *[NICEATM/ICCVAM].—*The Committee commends the NICEATM/ICCVAM for its role in the

1046 assessment of new, revised and alternative scientifically validated methods for the Federal

1047 Government. The Committee also commends the National Toxicology Program [NTP] for finalizing

1048 its “Roadmap to Achieve the NTP Vision.”

1049

1050 The Committee encourages the NICEATM/ICCVAM, in partnership with the relevant Federal

1051 agencies to build on the NTP Roadmap to create a 5-year plan to research, develop, translate and

1052 validate new and revised non-animal and other alternative assays for integration of relevant and

1053 reliable methods into the Federal agency testing programs. The Committee encourages the Federal

1054 agency program offices to identify areas of high priority for new and revised non-animal and

1055 alternative assays for the replacement, reduction and refinement of animal tests. The Committee

1056 further encourages relevant agencies to include the public when developing this plan. The Committee

1057 further requests a status report during the fiscal year 2008 budget hearings.