

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Federal Agency Responses to Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Recommendations on the Usefulness and Limitations of the LUMI-CELL® ER (BG1Luc ER TA) Test Method, An In Vitro Assay for Identifying Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals

AGENCY: Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), HHS.

ACTION: Availability of Agency Responses.

SUMMARY: The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces availability of U.S. Federal agency responses to ICCVAM test method recommendations on the usefulness and limitations of the LUMI-CELL® ER (BG1Luc ER TA) test method to identify human estrogen receptor (ER) agonist and antagonist activity of chemicals. ICCVAM forwarded the recommendations to Federal agencies and made these recommendations available to the public (77 FR 8258). ICCVAM agencies responded with their concurrence on the technical aspects of the BG1Luc ER transcriptional activation (TA) test method recommendations and their agreement that the ICCVAM BG1Luc ER TA test method is a validated screening test to identify substances with *in vitro* ER agonist activity or ER antagonist activity. The U.S. Environmental Protection Agency (EPA) responded that they regard the BG1Luc ER TA test method as an alternative to the Office of Chemical Safety and Pollution Prevention (OCSPP) 890.1300 (Organization for Economic Co-operation and Development [OECD] TG455) test guideline for transcriptional activation currently used in their Endocrine Disruptor Screening Program (EDSP). Several agencies also indicated that they would communicate the ICCVAM recommendations to stakeholders and encourage their appropriate use. Complete Federal agency responses are available at http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm. The ICCVAM recommendations are provided in the ICCVAM test method evaluation report (ICCVAM, 2011), available at: <http://iccvam.niehs.nih.gov/methods/endocrine/ERTA-TMER.htm>.

FOR FURTHER INFORMATION CONTACT: Dr. Warren M. Casey, Deputy Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2-16, Research Triangle Park, NC 27709, (telephone) 919-316-4729, (fax) 919-541-0947, (email) niceatm@niehs.nih.gov. Courier address: NICEATM, NIEHS, Room 2032, 530 Davis Drive, Morrisville, NC 27560.

SUPPLEMENTARY INFORMATION:

Background

In 2002, ICCVAM evaluated the validation status of *in vitro* ER and androgen receptor (AR) binding and TA test methods for potential use in the EPA EDSP. The evaluation indicated that no *in vitro* ER- or AR-based test methods were adequately validated for this purpose. In response to an ICCVAM request for nominations, Xenobiotic Detection Systems, Inc. (XDS, Durham, NC) nominated the *in vitro* LUMI-CELL® ER (BG1Luc ER TA) test method for an interlaboratory validation study. ICCVAM and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) recommended that the nominated method should be considered a high priority based on the lack of adequately validated test methods and the regulatory and public health need for such test methods. NICEATM led the international validation study with its partners in Japan (JaCVAM) and Europe (ECVAM), using laboratories sponsored by each validation organization. ICCVAM also proposed the development of BG1Luc ER TA test method performance standards.

Following completion of the validation study, the ICCVAM Interagency Endocrine Disruptor Working Group, working with NICEATM, prepared a draft background review document (BRD) and draft recommendations for use of the BG1Luc ER TA test method.

The draft BRD and draft ICCVAM recommendations were reviewed in a public meeting (76 FR 4113) of an international independent scientific peer review panel in March 2011. The peer review panel agreed with the draft ICCVAM recommendations that the BG1Luc ER TA test method could be used as a screening test to identify substances with *in vitro* ER agonist activity or ER antagonist activity and that the accuracy of this assay is at least equivalent to that of EPA OCSPP 890.1300, part of the EDSP Tier 1 screening battery.

The final ICCVAM recommendations are included in the *ICCVAM Test Method Evaluation Report: The LUMI-CELL® ER (BG1Luc ER TA) Test Method, An In Vitro Assay for Identifying*

Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals (NIH Publication No. 11-7850). The test method evaluation report also includes the updated ICCVAM-recommended BG1Luc ER TA test method protocol and performance standards that are applicable to functionally and mechanistically similar test methods. The final BRD, including the data and analyses on which the recommendations are based, is included as an appendix to the test method evaluation report.

Agency Responses to ICCVAM Recommendations

In February 2012, ICCVAM forwarded final test method recommendations on the BG1Luc ER TA test method to U.S. Federal agencies for consideration (77 FR 8258), in accordance with the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3). The ICCVAM Authorization Act requires member agencies to review ICCVAM test method recommendations and notify ICCVAM in writing of their findings no later than 180 days after receipt of recommendations. The Act also requires ICCVAM to make ICCVAM recommendations and agency responses available to the public. Agency responses are to include identification of relevant test methods for which the ICCVAM test method recommendations may be added or substituted and indicate any revisions or planned revisions to existing guidelines, guidances, or regulations to be made in response to these recommendations.

ICCVAM agencies responded with their concurrence on the technical aspects of the BG1Luc ER TA test method recommendation and their agreement that the ICCVAM BG1Luc ER TA test method is a validated screening test to identify substances with *in vitro* ER agonist activity or ER antagonist activity. The EPA responded that they regard the BG1Luc ER TA test method as an alternative to the OCSPP 890.1300 test guideline for transcriptional activation currently used in their EDSP. Several agencies also indicated that they would communicate the ICCVAM recommendations to stakeholders and encourage their appropriate use. Complete agency responses are available at http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm.

Background Information on ICCVAM, NICEATM, and SACATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety

testing information. ICCVAM conducts technical evaluations of new, revised, and alternative safety testing methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological and safety-testing methods that more accurately assess the safety and hazards of chemicals and products and that reduce, refine (enhance animal welfare and lessen or avoid unrelieved pain and distress), or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM, provides scientific and operational support for ICCVAM-related activities, and conducts independent validation studies to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods and strategies applicable to the needs of U.S. Federal agencies. NICEATM and ICCVAM welcome the public nomination of new, revised, and alternative test methods and strategies applicable to the needs of Federal agencies. Additional information about NICEATM and ICCVAM can be found on the NICEATM–ICCVAM Web site (<http://iccvam.niehs.nih.gov>).

SACATM was established in response to the ICCVAM Authorization Act (42 U.S.C. 285l–3) and is composed of scientists from the public and private sectors. SACATM advises ICCVAM, NICEATM, and the Director of the NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM. SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods.

Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at <http://ntp.niehs.nih.gov/go/167>.

References

ICCVAM. 2011. ICCVAM Test Method Evaluation Report: The LUMI-CELL® ER (BG1Luc ER TA) Test Method: An *In Vitro* Assay for Identifying Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals. NIH Publication No. 11-7850. Research Triangle Park, NC: NIEHS. Available: <http://iccvam.niehs.nih.gov/methods/endocrine/ERTA-TMER.htm>.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention

Fees for Sanitation Inspections of Cruise Ships

AGENCY: Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (HHS).

ACTION: General notice.

SUMMARY: In this notice, the Centers for Disease Control and Prevention (CDC), located within the Department of Health and Human Services (HHS), announces fees for vessel sanitation inspections for Fiscal Year (FY) 2013. These inspections are conducted by HHS/CDC's Vessel Sanitation Program (VSP). VSP helps the cruise line industry fulfill its responsibility for developing and implementing comprehensive sanitation programs to minimize the risk for acute gastroenteritis. Every vessel that has a foreign itinerary and carries 13 or more passengers is subject to twice-yearly inspections and, when necessary, re-inspection.

DATES: These fees are effective October 1, 2012 through September 30, 2013.

FOR FURTHER INFORMATION CONTACT:

CAPT Jaret T. Ames, Chief, Vessel Sanitation Program, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Highway NE., MS-F-59, Atlanta, Georgia 30341-3717, phone: 800-323-2132 or 954-356-6650, email: vsp@cdc.gov.

SUPPLEMENTARY INFORMATION:

Purpose and Background

HHS/CDC established the Vessel Sanitation Program (VSP) in the 1970s as a cooperative activity with the cruise ship industry. VSP helps the cruise ship industry prevent and control the introduction, transmission, and spread of gastrointestinal illnesses on cruise ships. VSP operates under the authority of the Public Health Service Act (42 U.S.C. 264, "Control of Communicable Diseases"). Regulations found at 42 CFR 71.41 (Foreign Quarantine—Requirements Upon Arrival at U.S. Ports: Sanitary Inspection; General Provisions) state that carriers arriving at U.S. ports from foreign areas are subject to sanitary inspections to determine whether rodent, insect, or other vermin infestations exist, contaminated food or water, or other sanitary conditions requiring measures for the prevention of the introduction, transmission, or spread of communicable diseases are present.

The fee schedule for sanitation inspections of passenger cruise ships by VSP was first published in the **Federal Register** on November 24, 1987 (52 FR 45019). HHS/CDC began collecting fees on March 1, 1988. This notice announces fees that are effective for FY 2013, beginning on October 1, 2012 through September 30, 2013.

The following formula is used to determine the fees:

$$\text{Average cost per inspection} = \frac{\text{Total cost of VSP}}{\text{Weighted number of annual inspections}}$$

The average cost per inspection is multiplied by size and cost factors to determine the fee for vessels in each size category. The size and cost factors were established in the fee schedule published in the **Federal Register** on July 17, 1987 (52 FR 27060). The fee schedule was most recently published in the **Federal Register** on March 2, 2012 (77 FR 12843). The current size

and cost factors are presented in Appendix A.

Fee

The fee schedule (Appendix A) will be effective October 1, 2012 through September 30, 2013. The fee schedule has not changed since October 1, 2006. The cruise ship industry should be aware that if travel expenses for VSP

increase, the fees may need to be adjusted before September 30, 2013; travel expenses constitute a sizable portion of VSP's costs. If a fee adjustment is necessary, HHS/CDC will publish a notice 30 days before the effective date.