DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Peer Panel Evaluation of In Vitro Pyrogenicity Testing Methods: Request for Comments, Nominations of Experts, and Submission of In Vivo and In Vitro Data

AGENCY: National Institute of Environmental Health Sciences (NIEHS), National Institutes Of Health (NIH).

ACTION: Request for comments, nominations of scientific experts, and submission of data.

SUMMARY: NICEATM, in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), is considering convening an independent peer review panel (hereafter, ''Panel'') to evaluate the validation status of five *in vitro* pyrogenicity test methods: (1) Human PBMC/IL–6 *in vitro* pyrogen test (PBMC/IL–6), (2) human whole blood/IL–1 *in vitro* pyrogen test (WB/IL–1), (3) human whole blood/IL–1 *in vitro* pyrogen test: application of cryopreserved human whole blood cryo (WB/IL–1), (4) the human whole blood/IL–6 *in vitro* pyrogen test (WB/IL–6), and (5) an alternative *in vitro* pyrogen test using the human monocytoid cell line MONO MAC–6 (MM6/IL6). NICEATM requests public comments as to the appropriateness and relative priority of this activity. In addition, NICEAM requests the nomination of expert scientists for consideration as potential Panel members in the event a Panel meeting occurs. Finally, NICEATM requests the submission of data from the rabbit pyrogenicity test, the bacterial endotoxin test (BET), and *in vitro* pyrogenicity testing with the methods listed above.

DATES: Comments, nominations of expert scientist, and data submissions should be received by January 17, 2006.

ADDRESSES: Correspondence should be sent by mail, fax, or email to Dr. William S. Stokes, NICEATM, NIEHS, P. O. Box 12233, MD EC–17, Research Triangle Park, NC, 27709, (phone) 919–541–2384, (fax) 919–541–0947, (e-mail) *niceatm@niehs.nih.gov*.

SUPPLEMENTARY INFORMATION:

Background

The European Committee on the Validation of Alternative Methods (ECVAM) conducted a validation study to independently evaluate the usefulness of five *in vitro* pyrogenicity assays (PBMC/IL–6, WB/IL–1, cryo WB/IL–1, WB/IL–6, and MM6/IL6). In June 2005, ECVAM submitted background review documents (BRDs) for these five methods to NICEATM for consideration as replacements for the currently required tests (i.e., rabbit pyrogen tests and the BET). ICCVAM and NICEATM reviewed the BRDs for completeness and concluded that these five *in vitro* test methods appear to have considerable potential for pyrogenicity testing, but the sponsors needed to provide additional information prior to a formal review by a Panel. Pending receipt and review of the requested information, ICCVAM and NICEATM will determine the priority of an evaluation of these test methods. If convened, the Panel would (1) peer review the BRDs for the test methods, and (2) determine whether the data cited in the BRDs support draft ICCVAM Test Method Recommendations regarding the proposed usefulness, limitations, and validation status of the test methods. If appropriate, the Panel might also formulate conclusions on the adequacy of any draft recommended performance standards, any proposed future validation studies, draft standardized test method protocols, and/or reference substances. In making their conclusions and recommendations, the Panel considers all available information including the scientific studies cited in the draft BRD, public comments, and any new information identified during the peer review.

Request for Public Comments and Nominations of Scientific Experts

NICEATM requests public comments on the appropriateness and relative priority of the proposed Panel review activity. In addition, NICEAM requests the nomination of scientists with relevant knowledge and experience to potentially serve on the Panel should it be convened. Areas of relevant expertise include, but are not limited to: physiology, pharmacology, immunology, pyrogenicity testing in animals, development and use of *in vitro* methodologies, biostatistical data analysis, knowledge of chemical data sets useful for validation of toxicity studies, and hazard classification of chemicals and products. Each nomination should include the person's name, affiliation, contact information (i.e., mailing address, e-mail address, telephone and fax numbers), and a brief summary of relevant experience and qualifications.

Request for Data

NICEATM invites the submission of data from standard *in vivo* rabbit pyrogen testing, the BET, and *in vitro* pyrogenicity testing using the methods detailed above. Although data can be accepted at any time, data submitted by the deadline listed in this notice would be considered during an evaluation of the validation status of the five pyrogenicity testing methods should this activity occur. Submitted data will be used to further evaluate the usefulness and limitations of *in vitro* pyrogenicity test methods and may be included in future NICEATM and ICCVAM reports and publications as appropriate. The data will also be included in a NICEATM database to support the investigation of other test methods for assessing pyrogenicity.

When submitting chemical and protocol information/test data, please reference this **Federal Register** notice and provide appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, as applicable).

NICEATM prefers data to be submitted as copies of pages from study notebooks and/or study reports, if available. Raw data and analyses available in electronic format may also be submitted. Each submission for a chemical should preferably include the following information, as appropriate:

- Common and trade name
- Chemical Abstracts Service Registry Number (CASRN)
- Chemical class
- Product class
- Commercial source
- *In vitro* pyrogenicity test protocol used
- *In vitro* pyrogenicity test results
- BET test protocol used
- BET test results
- *In vivo* rabbit pyrogen test protocol used
- Individual animal responses
- The extent to which the study complied with national or international Good Laboratory Practice (GLP) guidelines
- Date and testing organization

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that use or generate toxicological information. ICCVAM conducts technical evaluations of new, revised, and alternative methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological test methods that more

accurately assess the safety and hazards of chemicals and products and that refine, reduce, or replace animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the ICCVAM and provides scientific and operational support for ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of Federal agencies. Additional information about ICCVAM and NICEATM can be found at the following Web site: *http://www.iccvam.niehs.nih.gov.*

Dated: Decmeber 5, 2005.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP); Center for the Evaluation of Risks to Human Reproduction (CERHR); Announcement of the Genistein and Soy Formula Expert Panel Meeting; Availability of the Draft Expert Panel Reports on Genistein and Soy Formula and Request for Public Comment on the Draft Reports

AGENCY: National Institute for Environmental Health Sciences (NIEHS); National Institutes of Health (NIH).

ACTION: Meeting announcement and request for public comment.

SUMMARY: The Center for the Evaluation of Risks to Human Reproduction (CERHR) announces availability of the two draft expert panel reports on genistein and soy formula on January 16, 2006, from the CERHR Web site (*http://cerhr.niehs.nih.gov*) or in printed text from CERHR (see **ADDRESSES** below). CERHR invites public comments on sections 1–4 of both draft expert panel reports (see **SUPPLEMENTARY INFORMATION** below). An expert panel will meet on March 15–17, 2006, at the Radisson Hotel Old Town in Alexandria, Virginia to review and revise each draft expert panel report and reach conclusions regarding whether exposure to genistein or soy formula is a hazard to human development or reproduction. The expert panel will also identify data gaps and research needs. CERHR expert panel meetings are open to the public with time scheduled for oral public comment. Attendance is limited only by the available space in the meeting room. Following the expert panel meeting and completion of the expert panel reports, CERHR will post the final reports on its website and solicit public comment on them through a **Federal Register** notice.

DATES: The expert panel meeting for genistein and soy formula will be held on March 15–17, 2006. Sections 1–4 of both draft expert panel reports will be available for public comment on January 16, 2006. Written public comments on the draft report must be received by March 1, 2006. Time will be set-aside at the expert panel meeting on March 15, 2006, for oral public comments. Individuals wishing to make oral public comments are asked to contact Dr. Michael D. Shelby, CERHR Director, by March 8, 2006, and if possible, send a copy of their statement or talking points at that time. Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, should contact 919–541–2475 voice, 919–541–4644 TTY (text telephone), through the Federal TTY Relay System at 800–877–8339, or by e-mail to *niehsoeeo@niehs.nih.gov.* Requests should be made at least 7 days in advance of the meeting.

ADDRESSES: The expert panel meeting for genistein and soy formula will be held at the Radisson Hotel Old Town, 901 N. Fairfax Street, Alexandria, Virginia 22314–1501 (telephone: 703–683–6000, facsimile: 703–683–7597). Comments on the draft expert panel reports and any other correspondence should be sent to Dr. Michael D. Shelby, CERHR Director, NIEHS, P.O. Box 12233, MD EC–32, Research Triangle Park, NC 27709 (mail), (919) 316–4511 (fax), or *shelby@niehs.nih.gov* (e-mail). Courier address: CERHR, NIEHS, 79 T.W. Alexander Drive, Building 4401, Room 103, Research Triangle Park, NC 27709.

SUPPLEMENTARY INFORMATION:

Background

Genistein (CAS RN: 446–72–0) is a phytoestrogen found in some legumes, such as soybeans and clover, or in products obtained from animals ingesting genistein-containing feed. Phytoestrogens are non-steroidal, estrogenic compounds that occur naturally in plant products. Genistein is found in food and over-the-counter dietary supplements and is the primary phytoestrogen in soy formula. Soy formula is administered to infants as a supplement or replacement for maternal breast milk or cow's milk. CERHR selected genistein and soy formula for expert panel evaluation because of (1) the availability of numerous reproductive and developmental toxicity studies in laboratory animals and humans, (2) the availability of information on exposures in infants and women of reproductive age, and (3) public concern for effects on infant or child development.

At the meeting, the expert panel will review and revise the draft expert panel reports and reach conclusions regarding whether exposure to genistein or soy formula is a hazard to human reproduction or development. Each draft expert panel report has the following sections:

1.0 Chemistry, Use, and Human Exposure
2.0 General Toxicological and Biological Effects
3.0 Developmental Toxicity Data
4.0 Reproductive Toxicity Data
5.0 Summary, Conclusions, and Critical Data Needs (to be prepared at expert panel meeting)

Request for Comments

CERHR invites the submission of written public comments on sections 1–4 of the draft expert panel reports on genistein and soy formula. Any comments received will be posted on the CERHR Web site prior to the meeting and distributed to the expert panel and CERHR staff for their consideration in revising the draft reports and preparing for the expert panel meeting. Persons submitting written comments are asked to include their name and contact information (affiliation, mailing address, telephone and facsimile numbers, e-mail, and sponsoring organization, if any) and send them to Dr. Shelby (see **ADDRESSES** above) for receipt by March 1, 2006.

Time is set-aside on March 15, 2006, for the presentation of oral public comments at the expert panel meeting. Seven minutes will be available for each speaker (one speaker per organization). When registering to comment orally, please provide your name, affiliation, mailing address, telephone and facsimile numbers, e-mail, and sponsoring organization (if any). If possible, send a copy of the statement or talking points to Dr. Shelby by March 8, 2005. This statement will be provided to the expert panel to assist them in identifying issues for discussion and will be noted in the meeting record. Registration for presentation of oral comments will also be available at the meeting on March 15, 2006, from 7:30–8:30 a.m. Persons registering at the