products of branched 4-nonylphenol, formaldehyde, and 1-dodecanethiol for use as an antioxidant in adhesives, pressure-sensitive adhesives, and repeated-use rubber articles intended for use in contact with food.

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Center for Food Safety and Applied Nutrition (HFS–215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3081.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 0B4703) has been filed by Goodyear Tire & Rubber Co., c/o Keller and Heckman LLP, 1001 G St. NW., suite 500 West, Washington, DC 20001. The petition proposes to amend the food additive regulations in § 178.2010 *Antioxidants and/or stabilizers* (21 CFR 178.2010) to provide for the safe use of acid-catalyzed condensation reaction products of branched 4-nonylphenol, formaldehyde, and 1-dodecanethiol for use as an antioxidant in adhesives, pressure-sensitive adhesives, and repeated-use rubber articles intended for use in contact with food.

The agency has determined under 21 CFR 25.32(i) that this action is of the type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Dated: November 22, 1999.

Alan M. Rulis,

Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 99–31271 Filed 12–1–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999)

SUMMARY: The National Institutes of Health (NIH) is requesting public comment on a document entitled ''Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999).'' The purpose of these draft guidelines is to recommend procedures to help ensure that NIH-funded research in this area is conducted in an ethical and legal manner. The NIH will not fund research using human pluripotent stem cells until final guidelines are published in the **Federal Register** and an oversight process is in place.

DATES: Written comments should be received by NIH on or before January 31, 2000.

ADDRESSES: The NIH welcomes public comment on the Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999), set forth below.

Comments should be addressed to: Stem Cell Guidelines, NIH Office of Science Policy, 1 Center Drive, Building 1, Room 218, Bethesda, MD 20892. Comments may also be sent by facsimile transmission to Stem Cell Guidelines at (301) 402–0280, or by e-mail to: *stemcell@mail.nih.gov.*

SUPPLEMENTARY INFORMATION: In December 1998, two different groups of scientists reported the successful isolation and culturing of human pluripotent stem cells. Such cells have the ability to develop into most of the specialized cells or tissues in the human body and can divide for indefinite periods in culture. Because of the regenerative capacity of pluripotent stem cells, a single culture of human pluripotent stem cells could supply numerous researchers.

Establishment of human pluripotent stem cell lines represents a major step forward in human biology and has generated much interest among scientists and the public, particularly among patients and their advocates, especially with regard to the ethical issues related to this research.

Because these cells can give rise to many different types of cells, such as muscle cells, nerve cells, heart cells, blood cells, and others, they are enormously important to science and hold great promise for advances in health care. For example, further research using human pluripotent stem cells may help scientists:

- Generate cells and tissue that could be used for transplantation. If human pluripotent stem cells can be stimulated to develop into many different specialized cells of the body, the resulting cells may someday be used as replacement cells and tissue to treat many diseases and conditions including Parkinson's disease, spinal cord injury, stroke, burns, heart disease, diabetes, and arthritis.
- Improve our understanding of the complex events that occur during normal human development and also help us understand what goes wrong to cause diseases and conditions such as birth defects and cancer.
- Change the way we develop drugs and test them for safety and potential efficacy. New medications could initially be tested using human pluripotent stem cells, such as liver cells or skin cells; only the drugs that are both safe and appear to have a beneficial effect would graduate to further testing, using laboratory animals and human subjects.

Human pluripotent stem cells have been isolated using two different methods. One group of scientists derived the pluripotent stem cells from early-stage human embryos in excess of clinical need and donated by people who were undergoing infertility treatment in an in vitro fertilization (IVF) clinic. Another group of scientists derived the pluripotent stem cells from human fetal tissue obtained from pregnancies that had been terminated. In both cases, the individuals gave informed consent for the embryos or fetal tissue to be used in research. Neither research project utilized Department of Health and Human Services (DHHS) funds but rather was funded by private sources.

Federal law currently prohibits DHHS from funding research in which human embryos are created for research purposes or are destroyed, discarded or subjected to greater than minimal risk. In light of this legislative restriction, the Director of the National Institutes of Health (NIH) sought a legal opinion from the DHHS Office of the General Counsel on whether NIH funds may be used for research utilizing human pluripotent stem cells.

DHHS concluded that the Congressional prohibition does not prohibit the funding of research utilizing human pluripotent stem cells because such cells are not embryos. Thus, NIH funding for research using pluripotent stem cells derived from human embryos is not legislatively prohibited. The legal opinion also clarified that human pluripotent stem cells derived from fetal tissue would fall within the legal definition of human fetal tissue and are, therefore, subject to federal restrictions on the use of such tissue. NIH funding for research to derive or utilize human pluripotent stem cells from fetal tissue is permissible, subject to applicable law and regulation.

In view of the scientific and medical benefits that may result from research using human pluripotent stem cells, it is essential that the federal government play a role in funding and overseeing the conduct of this research. Federal funding will make it possible for scientists—both privately and federally funded—to have the opportunity to

pursue this important line of research. Federal funding will provide oversight and direction that would be lacking if this research were the sole province of private sources of funding and will also help ensure that the results of research will be accessible to the public.

The NIH understands and respects the ethical, legal, and social issues relevant to human pluripotent stem cell research and is sensitive to the need to subject it to oversight more stringent than that associated with the traditional NIH scientific peer review process. In light of these issues, the NIH plans to move forward in a careful and deliberate way, prior to funding any research utilizing human pluripotent stem cells.

In an effort to ensure that any research utilizing human pluripotent stem cells is conducted appropriately, the NIH Director convened a Working Group of the Advisory Committee to the Director, NIH (ACD) to advise the ACD on guidelines and oversight for research involving human pluripotent stem cells. Specifically, the NIH Director charged the Working Group with developing appropriate guidelines governing research involving the derivation and use of human pluripotent stem cells from fetal tissue and research involving the use of human pluripotent stem cells derived from early human embryos in excess of clinical need. In an effort to ensure that a broad spectrum of viewpoints was considered, the working group was made up of individuals with varied expertise and experience, among them basic and clinical scientists, ethicists, lawyers, clinicians, as well as patients and patient advocates. On April 8, 1999, the working group held a public meeting to discuss draft guidelines. During the meeting, time was set aside for public comment; several groups came forward to speak, including the American Society of Cell Biology, the National Conference of Catholic Bishops; the Society for Developmental Biology, the Alliance for Aging Research, and the House Pro-Life Caucus. The Executive Director of the National Bioethics Advisory Commission (NBAC) also presented comments reflecting the status of the deliberations of the NBAC at that time.

The text of the draft guidelines follows.

Draft National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells (December 1999)

I. Scope of Guidelines

These guidelines apply to research applications or proposals for National Institutes of Health (NIH) funding or support involving: (1) Utilization of human pluripotent stem cells (also known as human embryonic stem cells) derived (without Department of Health and Human Services [DHHS] funding) from early human embryos, and (2) the derivation or utilization of human pluripotent stem cells from fetal tissue. For purposes of these guidelines, human pluripotent stem cells are cells derived from early human embryos or fetal tissue that can divide for indefinite periods in culture without specializing and have the potential to develop into all of the three major tissue types. NIH research funded under these guidelines will involve only human pluripotent stem cells derived either from fetal tissue or from early human embryos that are the products of in vitro fertilization in excess of clinical need, that are not implanted in a woman's uterus and that have not reached the stage when the first major tissue type is formed.

The DHHS is prohibited by appropriations law (Pub. L. 105–277, section 511,112 STAT. 2681–386) from using any appropriated funds ''for the creation of a human embryo or embryos for research purposes; or research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death. . . .'' The NIH asked the General Counsel of DHHS to clarify whether research utilizing human pluripotent stem cells is permissible under existing laws governing human embryo and fetal tissue research. After careful consideration, the DHHS concluded that, because these cells are not embryos, current law does not prohibit the use of NIH funds for research utilizing human pluripotent stem cells. In addition, it was determined that, to the extent such cells are considered human fetal tissue, they are subject to the federal requirements for fetal tissue research.

These guidelines prescribe conditions that should be met before NIH funds are used to support research involving the utilization of human pluripotent stem cells derived from early human embryos or the derivation or utilization of human pluripotent stem cells from fetal tissue. DHHS funds may not be used for the derivation of human pluripotent stem cells from early human embryos. The guidelines also designate certain areas of human pluripotent stem cell research as ineligible for NIH funding.

II. Guidelines for Research Involving Human Pluripotent Stem Cells That Is Eligible for NIH Funding

A. The Utilization of Human Pluripotent Stem Cells Derived From Early Human Embryos

1. Considerations for the Utilization of Human Pluripotent Stem Cells Derived From Early Human Embryos

Studies utilizing pluripotent stem cells derived from early human embryos may be conducted using NIH funds only if the cells were derived from early human embryos that were created for the purposes of infertility treatment and were in excess of clinical need of the individuals seeking such treatment.

a. It is essential that the donation of early human embryos in excess of clinical need is voluntary. No inducements, monetary or otherwise, should have been offered for the donation of early human embryos for research purposes. Infertility clinics and/or their affiliated laboratories should have implemented specific written policies and practices to ensure that no such inducements are made available.

b. There should have been a clear separation between the decision to create embryos for infertility treatment and the decision to donate early human embryos in excess of clinical need for research purposes. Decisions related to the creation of embryos for infertility treatment should have been made free from the influence of researchers or investigators proposing to derive or utilize human pluripotent stem cells in research. To avoid possible conflicts of interest, the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not have been one and the same person.

c. To ensure that early human embryos donated for research are in excess of clinical need of the individuals seeking infertility treatment and to allow potential donors time between the creation of the embryos for infertility treatment and the decision to donate for research purposes, only frozen early human embryos should have been used to derive human pluripotent stem cells. In addition, individuals undergoing infertility treatment should have been approached about donation of early human embryos for the derivation of pluripotent stem cells only at the time of deciding the disposition of embryos in excess of clinical need.

d. Prior to the derivation of human pluripotent stem cells for use in NIH-

supported research, all identifiers associated with the early human embryos should have been removed.

e. Donation of early human embryos should have been made without any restriction regarding the individual(s) who may be the recipients of transplantation of the cells derived from the human pluripotent stem cells.

2. Informed Consent Requirements for the Utilization of Human Pluripotent Stem Cells Derived From Early Human Embryos

Informed consent should have been obtained from individuals who have sought infertility treatment who elect to donate early human embryos in excess of clinical need for research purposes. The informed consent process should have included discussion of the following information with potential donors, pertinent to making the decision whether to donate their embryos for research purposes.

a. Informed consent should have included:

(i) A statement that the early human embryos will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for human transplantation research.

(ii) A statement that all identifiers associated with the embryos will be removed prior to the derivation of human pluripotent stem cells.

(iii) A statement that donors will not receive any information regarding subsequent testing on the embryo or the derived human pluripotent cells.

(iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.

(v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development.

(vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.

(vii) A statement that early human embryos donated will not be transferred to a woman's uterus, will not survive the human pluripotent stem cell derivation process, and will be handled respectfully, as is appropriate for all human tissue used in research.

b. To ensure respect for the individuals donating early human embryo(s), protocols should have been approved by an Institutional Review Board (IRB) established in accord with 45 CFR § 46.107 and § 46.108 or FDA regulations at 21 CFR § 56.107 and § 56.108.

3. Investigators Planning To Utilize Human Pluripotent Stem Cells Derived From Early Human Embryos Should Provide in Their Application or Proposal to NIH

a. documentation that the embryos were created for the purpose of infertility treatment;

b. documentation that the early human embryos were frozen and in excess of clinical need;

c. the protocol, including the informed consent document, used for the derivation of human pluripotent stem cells from early human embryos;

d. documentation of IRB approval of the research protocol; and

e. an assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells.

B. Derivation and Utilization of Human Pluripotent Stem Cells From Fetal Tissue

1. Considerations for the Derivation and Utilization of Human Pluripotent Stem Cells Derived From Fetal Tissue

Unlike pluripotent stem cells derived from early human embryos, DHHS funds may be used to support research to derive pluripotent stem cells from fetal tissue, as well as for research utilizing such cells. Such research is governed by federal statutory restrictions regarding fetal tissue research at 42 U.S.C. 289g–2(a) and the federal regulations at 45 CFR 46.210. In addition, because cells derived from fetal tissue at the early stages of investigation may at a later date be utilized in human fetal tissue transplantation research, it is the policy of NIH to require that all DHHS funded research involving the derivation or utilization of pluripotent stem cells from fetal tissue also comply with the fetal tissue transplantation research statute at 42 U.S.C. 289g–1.

2. Informed Consent Requirements for the Derivation and Utilization of Human Pluripotent Stem Cells From Fetal Tissue

As a policy matter, NIH funded research deriving or utilizing human pluripotent stem cells from fetal tissue should comply with the informed consent law applicable to fetal tissue transplantation research (42 U.S.C. 289g–1) and the following conditions. The informed consent process should include discussion of the following information with potential donors, pertinent to making the decision whether to donate their embryos for research purposes.

a. Informed consent should include:

(i) A statement that the fetal tissue will be used to derive human pluripotent stem cells for research, that the human pluripotent stem cells will be derived and used following these NIH guidelines, and that the cells may be used, at some future time, for transplantation research.

(ii) A statement that all identifiers associated with the fetal tissue will be removed prior to the derivation of human pluripotent stem cells.

(iii) A statement that donors will not receive any information regarding subsequent testing on the fetal tissue or the derived human pluripotent cells.

(iv) A statement that derived cells and/or cell lines, with all identifiers removed, may be kept for many years.

(v) Disclosure of the possibility that the donated material may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development.

(vi) A statement that the human pluripotent stem cell research is not intended to provide direct medical benefit to the donor.

(vii) A statement that the fetal tissue and cells will be handled respectfully, as is appropriate for all human tissue used in research.

b. To ensure respect for the individual donating tissue that results from the reproductive process, it is recommended that protocols be approved by an Institutional Review Board (IRB) established in accord with 45 CFR 46.107 and § 46.108 or FDA regulations at 21 CFR 56.107 and § 56.108.

3. Investigators Planning To Derive or Utilize Human Pluripotent Stem Cells From Fetal Tissue Should Provide in Their Application or Proposal to NIH

a. the protocol, including the informed consent document, for the derivation of human pluripotent stem cells from fetal tissue;

b. documentation of IRB approval, if any, of the research protocol; and

c. an assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells, as permitted by 42 U.S.C. 289g–2.

III. Areas of Research Involving Human Pluripotent Stem Cells That Are Ineligible for NIH Funding

Areas of research ineligible for NIH funding include:

A. The derivation of pluripotent stem cells from early human embryos;

B. Research in which human pluripotent stem cells are utilized to create or contribute to a human embryo;

C. Research in which human pluripotent stem cells are combined with an animal embryo;

D. Research in which human pluripotent stem cells are used for reproductive cloning of a human;

E. Research in which human pluripotent stem cells are derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg;

F. Research utilizing human pluripotent stem cells that were derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human or animal egg; and

G. Research utilizing pluripotent stem cells that were derived from human embryos created for research purposes, rather than for infertility treatment.

IV. Oversight

A. Requests to the NIH for the funding of research involving human pluripotent stem cells should include documentation that the human pluripotent stem cells have been or will be derived in accordance with these Guidelines.

B. NIH will consider requests for funding for research utilizing human pluripotent stem cells from: (1) Awardees who want to use existing funds; (2) awardees requesting an administrative supplement; and (3) applicants or intramural researchers submitting applications or proposals.

C. NIH will consider funding requests for the derivation of human pluripotent stem cells from fetal tissue.

D. All applications shall be reviewed for scientific merit by: (1) An initial review group, in the case of new or competing continuation (renewal) applications; (2) by Institute or Center staff in the case of requests to use existing funds or applications for an administrative supplement; or (3) by the Scientific Director in the case of intramural proposals prior to submission to the HPSCRG.

E. The NIH will establish a Human Pluripotent Stem Cell Review Group (HPSCRG). This group will review documentation of compliance with the NIH Guidelines for Research Involving Human Pluripotent Stem Cells, and may, when warranted, seek further information in support of an application. The group will hold public review meetings when a funding request proposes the use of a newly derived line of human pluripotent stem cells that has not been reviewed previously by the HPSCRG in a public process or when an investigator proposes a protocol for the derivation of a new human pluripotent stem cell line from fetal tissue.

F. The HPSCRG will compile a yearly report that will include the number of applications and proposals reviewed and the titles of all awarded applications, supplements or administrative approvals for the use of existing funds, and intramural projects.

G. The HPSCRG will also serve as a resource for recommending to the Director, NIH any revisions to the NIH Guidelines for Research Involving Human Pluripotent Stem Cells.

Dated: November 29, 1999.

Harold Varmus,

Director, NIH.

[FR Doc. 99–31339 Filed 12–1–99; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute of Environmental Health Sciences National Toxicology Program; Availability and Request for Comments on the Revised Guidance Document: Evaluation of the Validation Status of Toxicological Methods: General Guidelines for Submissions to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Summary

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) prepared an initial version of the document, Evaluation of the Validation Status of Toxicological Methods: General Guidelines for Submissions to the Interagency Coordinating Committee on the Validation of Alternative Method in May 1998. It has now been updated by ICCVAM to reflect experience gained with the first two test methods reviewed by ICCVAM in 1998–1999. Further modifications are anticipated as experience accrues. The document provides guidance to test method developers on the information needed by ICCVAM to evaluate the validation status of new or revised test methods at any stage of development and after the completion of validation studies. It includes a framework for organizing the information supporting the validity of a test method. The purpose of this notice is to announce the availability of the revised guidance document and to request comments and suggestions for further improvement.

Background

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was established in 1997 as a standing collaborative effort by the National Institute of Environmental Health Sciences (NIEHS) and 13 other regulatory and research agencies. ICCVAM coordinates issues within the Federal government that relate to the development, validation, acceptance, and national/international harmonization of toxicological test methods. The Committee's functions include the coordination of interagency scientific reviews of toxicological test methods and communication with outside groups throughout the process. The focus is on new and revised test methods that are applicable to multiple Federal agencies. Emphasis is given to test methods that provide for improved prediction of adverse human health or ecological effects, and that may reduce, refine, or replace animal use.

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://ntp-server.niehs.nih.gov/htdocs/ICCVAM/iccvam.html),* various stages were identified to move a proposed test method from concept to regulatory acceptance. One stage is the communication of a proposed test method by the sponsor to ICCVAM for consideration and review. The ICCVAM review process typically involves an assessment by an ICCVAM working group comprised of government scientists, followed by an independent peer review evaluation by an expert scientific panel. Following this review, ICCVAM forwards recommendations on the usefulness and limitations of the proposed test method to regulatory agencies. Based on their specific regulatory mandates, each Federal agency then makes a determination regarding the acceptability of the test method. If the test method is accepted, appropriate actions (e.g., revision of existing regulations, guidelines, and/or guidance documents) are taken to inform the regulated community.

The following Federal regulatory and research agencies participate in this effort:

Consumer Product Safety Commission